

**DRUGS IN PREGNANCY AND THE FIRST YEAR OF LIFE:
A PHARMACOPOEIA**

NEONATAL **FORMULARY** **4**

You are entitled to access the PDA or ebook version of *Neonatal Formulary 4* at 50% discount. Simply use a coin to scratch off the silver box on the inside front cover to reveal the code, then go to www.pda.bmjbooks.com for further details of the offer.

Visit the book website www.neonatalformulary.com for regular updates, access to abstracts of all relevant Cochrane reviews, and further commentaries on certain products

BMJ
Books

All important amendments made to this regularly revised text after the present edition went to press can be found on the web at: www.neonatalformulary.com. An annually updated electronic version of the central section of the text is also available from the publishers. Further pharmaceutical advice is available from the pharmacy staff at the Royal Victoria Infirmary in Newcastle upon Tyne, NE1 4LP, England. Please use fax or e-mail for all non urgent issues.

Telephone: +44 (0)191 282 4469

Fax: +44 (0)191 221 0081

e-mail: drug.information@trvi.nuth.northy.nhs.uk

© BMJ Publishing Group 1996, 1998, 2000, 2003

BMJ Books is an imprint of the BMJ Publishing Group

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording and/or otherwise, without the prior written permission of the publishers.

BMA House, Tavistock Square, London WC1H 9JR

First edition 1996

Second edition 1998

Third edition 2000

Indian edition 2002

Fourth edition 2003

British Library Cataloguing in Publication Data

A catalogue record for this book is available from the British Library

This compendium was originally developed for use in the north of England, and sponsored for 10 years by the Northern Neonatal Network. It continues to be compiled and edited by Dr Edmund Hey.

Pharmacy advisor Catherine Hall, MSc, MRPharmS

ISBN 0 7279 1738 2

Typeset by SIVA Math Setters, Chennai, India
Printed and bound in Spain by GraphyCems, Navarra

CONTENTS

Introduction	vii
Acknowledgements	x
Drug prescribing and administration.....	1
Terms, symbols, abbreviations, and units.....	3
Drug storage.....	4
Neonatal drug administration.....	5
Drugs and the body	9
Drugs and the law	10
The care and use of intravascular lines	11
Minimising IV infusion and drug hazards.....	15
Adverse reactions and overtreatment	17
Writing a hospital prescription	19
Body weight and surface area	21
Further reading.....	22
Making choices.....	23
Suspected bacterial infection.....	25
Clots and emboli.....	26
Managing seizures	27
Circulatory control	29
Sedation and pain relief.....	32
Maternal drug abuse.....	35
Renal failure	37
Drug monographs.....	39
Maternal medication and its effect on the baby.....	273
Useful website addresses	291
Index.....	295

**ALL SUBSTANCES ARE TOXIC;
ONLY THE DOSE MAKES A
THING NOT A POISON.**

– Paracelsus (1493–1541)

INTRODUCTION

This book has been designed to answer the growing need for compact and up to date, referenced, advice on the prescribing of drugs, and their safe and accurate nursing administration, in the neonatal period. The number of drugs used in neonates is rising rapidly, even though the manufacturers have not yet, in many cases, sought market authorisation to recommend neonatal use. One recent study in the UK found that more than 80% of neonatal prescriptions were for a product, or for a dose, formulation, or purpose, that lacked licensed endorsement from the manufacturer. The situation in the rest of Europe is not dissimilar. While a lot of general information on these drugs is given in the manufacturer's summary of product characteristics (SPC), advice on use in young children is often non-existent. Equally little information is often available regarding use during pregnancy or lactation. Since advice in the SPC is all that has been seen and approved by the UK Committee on Safety of Medicines, and since the *British National Formulary (BNF)* normally limits itself, as a matter of policy, to summarising information that has been so validated, neonatal drug use often occurs in a dangerous information vacuum. All this makes it increasingly important for midwives and nurses, as well as pharmacists and doctors, to be able to put their hands on a pocket sized reference text that summarises the scattered but extensive therapeutic and pharmacokinetic information that *is* available on the safe and appropriate use of these products. A number of other drugs that have a well authenticated, if limited, therapeutic role are also listed, even though no commercial product is currently available. Caffeine remains the most notable, but by no means the only, drug to fall into this category in the UK.

Information on placental transfer and teratogenicity, and on the extent to which each drug appears in human milk (and the degree to which this matters) is provided for each drug. Where the text merely says that treatment during lactation is safe, it can be taken that the dose ingested by the baby is likely to be less than 5% of the dose taken by the mother on a weight for weight basis, and that no reports have appeared suggesting that the baby could be clinically affected. Special attention has been paid to the rapid changes that occur in the renal and hepatic handling of some drugs in the first few weeks of life, and the impact of illness and severe prematurity on drug metabolism and drug elimination. The symptoms associated with overtreatment are summarised, and the management of toxicity is outlined. Information is also included on the best way to use the few drugs so far known to be of therapeutic benefit to the fetus.

The book provides information on the main drugs used to modify the diet of babies with congenital enzyme deficiencies ("inborn errors of metabolism"), a short monograph on breast milk fortifiers, and a monograph on the artificial milks ("formula" milks) most commonly used in the UK. However, no attempt has been made to list other dietary products, a need that is very comprehensively covered in *Medicines for Children*, published by the Royal College of Paediatrics and Child Health in London.

While the text reflects, in the main, practice in the UK, medicine is increasingly international in its scope. Every section of the text has been revised with this in mind by a wide range of local, national, and overseas collaborators. An extensive range of journals have been searched in order to make the advice given in the latest revision as comprehensive and up to date as possible, and all relevant Cochrane reviews have been consulted. Input has also been sought from colleagues with a range of professional expertise in an attempt to ensure that the text reflects a distillate of current opinion. However, in deciding what should eventually find its way into print, it was the advice of those who could provide evidence to support their approach that carried most weight. A consensus driven text could, all too easily, merely reflect what most people are doing rather than what they ought to be doing. The references cited below each entry should make it easier for readers to make up their own minds on such issues.

The **first** section of the book contains important general information on drug storage, drug licensing, and drug prescribing, with advice on drug administration, the care and use of intravascular lines, and the recognition, management, and reporting of adverse reactions. The information given on individual drugs in the third section needs to be interpreted in the light of this general advice.

The **second** section provides brief guidance on how to approach drug choice in the management of suspected infection, early renal failure, and neonatal pain. Advice is also given on the treatment of circulatory problems, vascular problems, maternal drug abuse, and the management of seizures.

The **third** (and largest) section contains whole page monographs on 219 of the drugs most often used during labour and in the neonatal period, listed in alphabetical order. Information on a number of

INTRODUCTION

blood products and vaccines is included. Each monograph lists the drug's main uses and the most appropriate dose to give, both in the term and the preterm baby. The neonatal half life is noted where known and a note made of those with an unusually large volume of distribution ($V_d > 1$ l/kg). A brief summary of the drug's discovery and development is usually included. Advice is also provided on how to measure accurately the small volumes frequently required, and how to administer bolus and IV infusions safely. The advice given can, in general, be used to guide management throughout the first year of life. Significant interactions between drugs included in the main section of the compendium are outlined. Adverse effects commonly encountered in infancy, and their management, receive attention, but the SPC should be consulted in respect of other, less common, adverse effects. All the major multicentre clinical drug trials under development, or in progress in the UK when the book went to press get a mention. Information under the heading "supply" refers to the formulation most widely used in the UK. It is important to realise that other strengths and formulations may exist, and essential to check the label on the container before giving medicine to any patient. The stated cost is the basic net price (normally quoted in the *BNF*) when the book went to press, rounded to two significant figures. This information has been included in order to make clinicians more cost conscious, but should not be interpreted as representing the pricing policy of any particular hospital. Every monograph concludes with one or more recent key references to the perinatal or neonatal literature (from which it is usually possible to identify other key reports).

The **fourth** section contains brief notes on a further 126 drugs, or groups of drugs, that are not infrequently taken by mothers during pregnancy, labour, or the puerperium. The drugs mentioned include all the more commonly used products thought to affect the baby either because of placental transfer or because of excretion in human milk. Illicit drug use and legitimate self medication both receive attention. Entries are almost always linked to two key references that can be used to access additional original studies and reports.

The **index** at the back of the compendium includes all the UK and US synonyms by which some drugs are occasionally known, and also identifies another 50 drugs referred to only in passing, within another drug monograph.

An **electronic version** of *Neonatal Formulary* suitable for use with almost any desktop PC or handheld personal digital assistant (PDA) device is also available; updates of this version are issued annually. Using this electronic version, any entry in the formulary can be accessed in no more than two "clicks". While the text is "sealed" so it cannot be copied or modified, it can be easily and flexibly annotated, and customised for local use. Those who have purchased this book can access a copy of the PDA or ebook text at a 50% discount. Simply scratch the silver box inside the front cover to reveal the code and then go to www.pda.bmjbooks.com for details of the offer. More information on the versions now available is given on the formulary website, as are details of bulk purchasing arrangements.

A **website** was launched in January 2001 (www.neonatalformulary.com). New drugs continue to come onto the market at regular intervals, and further information relating to the neonatal use of many of the drugs already contained in this book continues to appear almost monthly. As a result, the information and advice given in the text remains under semicontinuous review. The website also provides longer, more fully referenced, commentaries on some important products, and direct access to abstracts of all the relevant Cochrane reviews. The publishers plan to continue producing a new edition of the paperback book approximately once every 3 years, but the development of a website makes it possible to alert readers to all the more important changes as soon as they are issued.

IMPORTANT

While every effort has been made to check the veracity of the information in this compendium, those responsible for its compilation cannot accept responsibility for the consequences of any remaining inaccuracy.

The drugs included are, for the most part, those in current use in neonatal units in the UK, but the most recent updates have increasingly attempted to reflect international practice. Reference to a particular drug does not, however, necessarily imply any recommendation regarding its use; neither does omission necessarily imply any adverse criticism of the drug's usefulness. Indeed, a number of products are mentioned specifically to alert clinicians to some of the uncertainties or limitations associated with their use in infancy. Personal preference and past experience must inevitably influence prescribing practice, and in neonatal practice, more than any other branch of medicine, it is better to use a limited number of carefully evaluated and widely used drugs knowledgeably than to use drugs with which the prescriber is not fully familiar. It is also dangerous to go uncritically for the latest product to reach the market; too many drugs of proven value in adult medicine have been widely and indiscriminately used in pregnancy and in the neonatal period over a number of years before the potential hazards associated with their use became apparent. If diethylstilbestrol had been tested for efficacy before being given to millions of women in an effort to prevent miscarriage and premature delivery, many children would have been saved from genital tract deformity, and several hundred from developing vaginal cancer. If the pharmacokinetics of chloramphenicol and the sulphonamides had been established before these drugs were first widely used in the neonatal period some 40 years ago, many hundreds of deaths could have been avoided. Hexachlorophene baths and vitamin K injections also killed several hundred babies before anyone realised what was happening.

Neither are such inadvertent drug tragedies merely a thing of the past. Within the last 5 years, evidence has emerged that acetazolamide for posthaemorrhagic hydrocephalus can do more harm than good, and that the amount of aluminium often infused during parenteral nutrition can cause permanent neurological damage. The harm that was being done to these patients finally came to light only when these forms of treatment were exposed to controlled trial scrutiny. Concern is now starting to surface regarding the safety of sustained ante- or postnatal steroid use. Because early trials focused on short term outcomes and did not look at the child's later development we still do not know whether a drug that has now been in widespread use for more than 20 years actually does more harm than good when high dose treatment is given for more than a few days.

The simultaneous use of several drugs increases the risk of harm from drug interaction (furosemide with an aminoglycoside, or cisapride with erythromycin). It also increases the risk of erroneous drug prescription or drug administration. Almost all drugs are potentially harmful, and some of the drugs most frequently used in the neonatal period are potentially lethal when given in excess. It has been seriously suggested that every hospital drug cupboard should have the motto "Is your prescription really necessary?" pinned on the door. Sadly, such a step would probably have little effect because, although doctors are accountable for the original prescriptions, they nearly always leave the hard and responsible work of drug administration to their nursing colleagues.

Many paediatric and neonatal texts provide tabular drug lists and dosage guidelines. They can be a useful *aide mémoire*, but they encourage the false impression that all you need to know about a drug is how much to give. They should *never* be used on their own, except by somebody who is already fully familiar with all the drug's indications and contraindications, and with all aspects of the drug's pharmacokinetic behaviour (including its behaviour in the sick preterm baby). Information also becomes dated quite quickly, so any text more than 2 years old should be used with great caution.

ACKNOWLEDGEMENTS

This neonatal pharmacopoeia started life in 1978 as a looseleaf A4 reference folder of commonly used drugs for the neonatal surgical intensive care unit at the Hospital for Sick Children (Fleming Hospital) in Newcastle upon Tyne. It was prepared by Dr John Inkster, the Fleming Hospital's first Consultant Paediatric Anaesthetist, and Dr Edmund Hey, the Paediatrician from the adjoining Princess Mary Maternity Hospital. It has been updated almost annually since then, and has now expanded 10-fold, but the format and the basic layout have not changed.

The 1987 and 1989 revisions reflected practice in all the Newcastle units, and the 1991 and 1993 revisions, which drew on the accumulated experience of all the units in the region were made widely available in pocketbook format by the Northern Regional Health Authority. Both of the hospitals where this book first originated have since closed, and the Regional Health Authority is also now no more. The local Neonatal Network was pleased to find a national publisher for a new pocket version in 1996, and for further new print editions in 1998 and 2000. Since then input has become progressively more international in scope, as is reflected by the inclusion of drugs for the treatment of malaria in this new update. Nurses, midwives, and staff pharmacists have continued to play a part by asking for the inclusion of further new information, and by criticising, firmly but constructively, any lack of clarity in the text.

Change continues apace, and several important amendments make their appearance with the arrival of this latest update. The book is now available in both paper and electronic formats. An annually updated version of the central two sections is also now available for use on a wide range of desktop and hand held pocket computers. Regular updates can be found on the book's website, where an increasing range of supplementary information can also be found. The book's scope has also been expanded to include a number of drugs generally needed only in the management of tropical diseases such as malaria, and the book's contributors come from an increasing number of different countries.

Doctors, midwives, pharmacists, and nurses in the UK, Australia, Canada, the Netherlands, and New Zealand who made a significant contribution to the preparation of the two most recent editions include:

S Ainsworth, M Alam, J van den Anker, R Appleton, D Barker, P Baxter, A Bedford-Russell, I Begg, A Bint, R Bray, P Brocklehurst, C Brook, J Bunn, A Cant, T Cheetham, I Choonara, M Coulthard, S Craig, A Curley, B Darlow, T David, J Davison, D Dhawan, L Duley, D Elbourne, N Embleton, A Emmerson, N Evans, A Ewer, A Fenton, D Field, T Flood, P Fowlie, D Gardner-Medwin, D Gibb, R Gilbert, H Halliday, A Hallman, F Hampton, J Hawdon, P Heath, P Hope, D Hull, D Isaacs, K Ives, C Kennedy, S Kenyon, H Kirpalani, W Lamb, H Lambert, A Lander, P Loughnan, J Lumley, C Macpherson, J Madar, N McIntosh, P McKiernan, A McNinch, N Marlow, P Midgley, D Milligan, D Mitchell, N Modi, A Morris, M-L Newell, S Odie, A Ohlsson, S Pedler, P Powell, M Reid, J Rennie, S Richmond, M Robinson, S Robson, M Rutter, S Ryan, D Salisbury, B Schmidt, N Shaw, D Sims, S Sinha, J Skinner, J Smith, N Subhedar, A Taylor, D Taylor, G Toms, P Tookey, I Verber, P Vermeer-de Bondt, S Walkinshaw, S Wardle, M Ward Platt, U Wariyar, R Welch, B Wharton, A Whitelaw, A Wilkinson, C Wren, and J Wyllie.

Valuable dietetic advice has been provided by Caroline King and Heather Gate, and issues relating to fetal toxicity checked by Pat McElhatton.

The future of the compendium rests in the hands of those who use it; anyone spotting an error or ambiguity in the text, or identifying an important omission, is urged to contact the staff in the pharmacy in Newcastle, using one of the contact options listed on the back of the title page, so that the reference value of the various drug monographs can be sustained and further improved.

Drug prescribing and drug administration

Staff should never prescribe or administer any drug without first familiarising themselves with the way it works, the way it is handled by the body, and the problems that can arise as a result of its use. Most of the essential facts relating to use in adults are summarised by the manufacturer in the “package insert” or “summary of product characteristics”. Many are also summarised in a range of reference texts, such as the *British National Formulary* (BNF). However, manufacturers seldom provide much information about drug handling in infancy, and the BNF, as a matter of policy, summarises only the facts that have been included in the summary of product characteristics. The present book aims to supplement, but not replace, the information provided by these sources.

Neonatal and paediatric textbooks all too often offer only advice on the best dose to use in infancy – often in tabular form – and provide little or no information on the idiosyncrasies associated with neonatal use. Such dosage tables can be a useful *aide mémoire*, but they should **never** be relied upon, on their own, to help the staff decide what to use when, and to know what works best, how different drugs sometimes interact, and what potential adverse effects they need to be alert to. Access to this more detailed information is as important for the staff responsible for drug administration as it is for those prescribing treatment in the first place.

TERMS, SYMBOLS, ABBREVIATIONS, AND UNITS

Postmenstrual age: The term postmenstrual age, as used in this book, refers to the child's total age in weeks from the start of the mother's last menstrual period. Thus a 7 week old baby born at 25 weeks gestation is treated as having a postmenstrual age of 32 weeks. The complaint that, since a baby does not menstruate, it cannot logically have a postmenstrual age, is best dismissed for what it is – mere pedantry. The term “postconceptional age” is sometimes used to describe this combination of gestational and postnatal age, although, technically, of course, conception occurs about 2 weeks after the start of the last menstrual period.

Giving intravenous drugs: Intravenous (IV) drugs should *always* be given slowly, with a few notable exceptions. Because this is such universal good practice, the advice is not reiterated in individual drug monographs. The simplest way of achieving slow administration is described on pages 6 and 7. Where previous dilution or a particularly slow rate of infusion is important, this is always specified in the relevant drug monograph and the reason given. Drugs should also be given separately. Where two different IV drugs have to be given at the same time, the best way to stop them mixing is described on p. 14. Intramuscular (IM) drugs should never be mixed, except as described in the individual drug monographs.

Continuous co-infusion: Special problems arise when it is necessary to give more than one drug continuously and vascular access is limited. Here, terminal co-infusion (the mixing of two different infusates using a tap or Y connector sited as close to the patient as possible) is sometimes known to be safe. In the most frequently encountered situations where such co-infusion is safe, a comment to that effect occurs in the relevant drug monograph. In all other situations two different infusion sites will need to be used unless advice to the contrary has been obtained from the local hospital pharmacy. Note, in particular, that the advice in relation to total parenteral nutrition (TPN) relates only to formulations similar to the one described in this compendium.

Drug names: Drugs are, in general, referred to by their non-proprietary (“generic”) name, following the usage currently adopted by the *British National Formulary (BNF)*. Where, for clarity, a proprietary name has been used, the symbol[®] has been appended the first time it is used. Where the British Approved Name (BAN) or the United States Adopted Name (USAN) differ from the Recommended International Non-proprietary Name (rINN), these alternatives are also given. All synonyms are indexed.

Symbols and abbreviations: Cross references between the various monographs are marked by the Latin phrase “*quod vide*” (contracted to q.v.). Drugs vary widely in the extent to which they are distributed within the body. Some drugs accumulate only in the extracellular tissues. Others are taken up and concentrated in some or all body tissues, the total amount in the body being more than would be presumed from a measure of the amount present in the blood. This property is referred to as the drug's apparent volume of distribution, a measure summarised by the symbol V_D . References to papers reporting a randomised controlled trial are marked by the symbol [RCT]; those referring to a systematic review or meta-analysis are marked [SR]. Drugs for which the Cochrane Collaboration has produced at least one systematic review are marked with a \odot .

UNITS

1 kilogram (kg)	=	1000 grams
1 gram (g)	=	1000 milligrams
1 milligram (mg)	=	1000 micrograms
1 microgram (μg) [†]	=	1000 nanograms
1 nanogram (ng) [†]	=	1000 picograms

A 1% weight for volume (w/v) solution contains 1 g of substance in 100 ml of solution

It follows that: a 1:100 (1%) solution contains 10 milligrams in 1 ml
 a 1:1000 (1‰)[†] solution contains 1 milligram in 1 ml
 a 1:10,000 solution contains 100 micrograms in 1 ml

[†]These contractions are best avoided as they can easily be misread when written by hand

DRUG STORAGE

Storage before use: Most drugs are perfectly stable at room temperature (i.e. at between 5°C and 25°C) and do not require specialised storage facilities. Temperatures above 25°C can be harmful, however, and some drugs are damaged by being frozen, so special thought has to be given to transport and despatch. Some drugs are best protected from direct daylight, and, as a general rule, all drugs should be stored in a cupboard and kept in the boxes in which they were dispensed and despatched. Indeed, in a hospital setting, it is general policy for all drugs to be kept under lock and key.

Hospital guidelines usually specify that drugs for external use should be kept in a separate cupboard from drugs for internal use. Controlled drugs, as specified in the regulations issued under the Misuse of Drugs Act 1971, must be kept in a separate cupboard. This must have a separate key, and this key must remain under the control of the nurse in charge of the ward at all times. A witnessed record must be kept of everything placed in, or taken from, this cupboard and any loss (due to breakage etc.) accounted for. Medical and nursing staff must comply with identical rules in this regard.

Special considerations apply to the storage of vaccines. Many of these are damaged if they are not kept at between 4°C and 8°C at all times, even during transit and delivery (no mean feat in many developing countries). A range of other biological products, such as the natural hormones desmopressin, oxytocin, tetracosactide, and vasopressin, need to be stored at 4°C. So too do the cytokines, such as erythropoietin (epoetin) and filgrastim, and some surfactant products of animal origin. The only other widely used neonatal drugs that need to be kept in a refrigerator at 4°C are amphotericin, atracurium, dinoprostone, soluble insulin, lorazepam, and pancuronium, and even here the need to maintain such a temperature *all* the time is not nearly as strict as it is with vaccine storage. Many oral antibiotic preparations have only a limited shelf life after reconstitution. The same goes for a number of oral suspensions prepared for neonatal use “in house”, and for some suppositories prepared for neonatal use. The “shelf life” of all these preparations can be increased by storage at 4°C. Drugs that do not *need* to be kept in a ward refrigerator should *not* be so stored.

All the drugs mentioned in this compendium that require special storage conditions have their requirements clearly indicated in the relevant drug monograph. Where no storage conditions are specified it can be taken that no special conditions exist.

Continued retention of open vials: Glass and plastic ampoules must be discarded once they have been opened. Drug vials can generally be kept for a few hours after they have been reconstituted, as long as they are stored at 4°C but, because they often contain no antiseptic or preservative, it becomes increasingly more hazardous to insert a fresh needle through the cap more than two or three times, or to keep any open vial for more than 6–8 hours. It is, therefore, standard practice to discard all vials promptly after they have been opened (with the few exceptions specifically mentioned in the individual monographs in the third part of this compendium).

This means, of course, that 95% of the drug is often wasted because low dose vials suitable for neonatal use are not generally marketed. This can be a matter of some concern when the drug is particularly expensive. One solution is to use a Braun “Sterifix-Mini-Spike”, as first suggested by Dr de Louvois in a letter to *The Lancet* in January 1985. This makes it possible to keep certain drugs for 24 hours or even longer after reconstitution, and to draw multiple doses from one vial. Bacteriological examination has shown such a procedure to be safe as long as the vials are always stored at 4°C once they have been opened. This device is, however, itself quite expensive, it contains no sterilising filter, and it must be made clear that any such step involves a departure from the manufacturer’s strict guidelines. Given the cost of drugs, however, such expedients do have to be contemplated on occasion. Staff should follow local policy guidelines in this regard.

An alternative, safer solution designed to minimise wastage is to ask the pharmacy to draw up, seal, and label a series of loaded syringes under controlled, aseptic conditions ready for use. With certain drugs it is possible to issue enough prefilled syringes in advance to make such an arrangement practicable at weekends as well as during the working week. However, such a solution is also relatively expensive (if the administrative cost, and the cost of the pharmacist’s time, are taken into account).

NEONATAL DRUG ADMINISTRATION

Mastering the art of safe drug administration is at least as important and substantial a challenge as mastering the art of safe and effective drug prescribing. Nurses and midwives shoulder responsibilities at least as onerous as their medical colleagues.

Neonatal prescribing: It is important to consider the practicalities of drug administration when prescribing, and to avoid prescribing absurdly precise doses that cannot realistically be measured. Such problems arise with particular frequency when body weight enters into the calculation. It is difficult to measure volumes of less than 0.05 ml, even with a 1 ml syringe, and any doctor who prescribes a potentially dangerous drug without first working out how to give it must inevitably carry much of the responsibility if such thoughtlessness results in an administrative error. Guidance on this is given in the individual drug monographs, with advice on prior dilution where necessary.

Equal thought should also be given to the timing and frequency of drug administration. Because many drugs have a relatively long neonatal "half life", they need to be given only once or twice a day. More frequent administration only increases the amount of work for all concerned, and increases the risk of error creeping in. After discharge, parents are also more likely to administer what has been prescribed if they are not asked to give the medicine more than twice a day.

Length of treatment: Remembering to stop treatment can be as important as remembering to start it. Half the mothers on anticonvulsants who book into some maternity units seem to be taking medication merely because nobody ever told them they could stop. Neonatal antibiotic treatment seldom needs to be continued for very long. Treatment should always be stopped after 48 hours if the initial diagnosis is not confirmed. Babies with meningitis, osteitis, and staphylococcal pneumonia almost always need 2–3 weeks' treatment, but 10 days is usually enough in septicaemia. Few babies need to go home on treatment; even anticonvulsants can usually be stopped prior to discharge (cf. the monograph on phenobarbital). Babies are often offered respiratory stimulants like caffeine for far longer than is necessary. Few continue to need such treatment when they are of more than 32 weeks gestation; it should, therefore, usually be possible to stop all treatment at least 3 weeks before discharge. In the case of some widely used nutritional supplements (such as iron and folic acid), there was probably never any indication for starting treatment in the first place, given the extent to which most artificial milks are now fortified (cf. the monograph on milk).

Drug dilution: Many drugs have to be diluted before they can be used in babies because they were formulated for use in adults. In addition, dilution is almost always required when a drug is given as a continuous infusion. Serious errors can occur at this stage if the dead space in the hub of the syringe is overlooked. Thus, if a drug is drawn into a 1 ml syringe up to the 0.05 ml mark, the syringe will then contain between 0.14 and 0.18 ml of drug. If the syringe is then filled to 1 ml with diluent the syringe will contain **three times** as much drug as was intended.

To dilute any drug safely, therefore, draw some diluent into the syringe first, preferably until the syringe is about half full, and then add the active drug. Mix the drug and diluent if necessary at this stage by one or two gentle movements of the plunger, and then finally make the syringe up to the planned total volume with further diluent. In this way the distance between two of the graduation marks on the side of the syringe can be used to measure the amount of active drug added.

While this may be adequate for 10-fold dilution, it is not accurate enough when a greater dilution than this is required. In this situation it is necessary to use two syringes linked by a sterile three way tap. The active drug is drawn up into a suitable *small* syringe and then injected into the larger syringe through the side port of the tap. The tap is then turned so as to occlude the side port and diluent is added to the *main* syringe until the desired total volume is reached.

Detailed guidance is given in the third section of this compendium on how to reconstitute each drug prior to administration, and how to handle drug dilution whenever this is required. This can be found under the heading "Supply" or "Supply and administration" in each drug monograph.

Giving drugs by mouth: Oral medication is clearly unsuitable for babies who are shocked, acidotic, or otherwise obviously unwell because there is a real risk of paralytic ileus and delayed absorption. Babies who are well enough to take milk feeds, however, are nearly always well enough to take medication by mouth, and many drugs are just as effective when given this way. Antibiotics that can be given by mouth to any baby who is well enough to take milk feeds without detriment to the blood levels that are achieved include amoxicillin, ampicillin, cephalixin, chloramphenicol, ciprofloxacin,

NEONATAL DRUG ADMINISTRATION

co-trimoxazole, erythromycin, flucloxacillin, fluconazole, flucytosine, isoniazid, metronidazole, pyrimethamine, rifampicin, sodium fusidate, and trimethoprim. Oral administration is often quicker, cheaper, and safer than IV administration. Oral administration is also much more easily managed on the postnatal wards, and treatment can then be continued by the parents after discharge where appropriate.

Remember that if medicine is passed down an orogastric or nasogastric feeding tube much of it will be left in the tube unless it is then flushed through. It used to be standard practice to formulate drugs given by mouth so that the neonatal dose was always given in 5 ml aliquots (one teaspoonful), but this practice has now been discontinued. Dilution often reduced stability and shortened the drug's "shelf life", while dilution with a syrup containing glucose threatened to increase the risk of caries in recently erupted teeth in later infancy. Small quantities are best given from a dropper bottle (try to avoid the pipette touching the tongue) or dropped on to the back of the tongue from the nozzle of a syringe.

Additives to milk: Vitamins are often added to milk. Sodium, phosphate, and bicarbonate can also be given as dietary supplements in the same way. It is important to remember that if only half the proffered feed is taken, only half the medicine is administered. Where possible all of a day's supplements should be added to the first feed of the day, so the baby still gets all that was prescribed even if feeding is later curtailed. The giving of any such dietary supplement must be recorded either on the feed chart or on the drug prescription sheet, and, to avoid confusion, each unit needs to develop a consistent policy in this regard.

Rectal administration: This can be a useful way of giving a drug that is normally given by mouth to a baby who is not being fed. Chloral hydrate, cisapride, codeine phosphate, and paracetamol are sometimes given in this way. So are some anticonvulsants such as carbamazepine, diazepam, and paraldehyde. However, absorption is usually slower, often less complete, and sometimes less reliable than with oral administration. Suppositories have usually been used in the past (merely because that is how rectal drugs are normally given to adults) but liquid formulations are more appropriate in the neonatal period. Absorption is always more rapid and often more complete when a liquid formulation is used. It is also much easier to administer a precise, weight related dose. Half a suppository does not necessarily contain half the active ingredient even when accurately cut in two.

IV drugs: IV drugs should be given slowly and, where possible, through a secure established IV line containing dextrose and/or sodium chloride. Drugs should never be injected or connected into a line containing blood or a blood product. Since the volume of drug to be given seldom exceeds 2 ml in neonatal practice, abrupt administration can be avoided by siting a three way tap so there is only 10–25 cm of narrow-bore tubing containing about 2 ml of fluid between the tap and the patient. Give the drug over about 5 seconds as described under the heading "IV injections", but do not, except in special circumstances, flush the drug through. The adoption of this practice as a *routine* ensures that any "bolus" of drug reaches the patient slowly over a period of 5–20 minutes after being injected into the fluid line, without staff having to stand by the patient throughout the period of administration or set up a special mechanical infusion system.

On the rare occasions when a small rapid bolus injection *is* called for (as, for example, when adenosine is used in the management of a cardiac arrhythmia) the drug infusion should be followed by a 2 ml "chaser" of 0.9% sodium chloride from a second syringe in order to flush the active drug through the IV line as rapidly as possible. Do not flush the drug through by changing the basic infusion rate; several deaths have resulted from a failure to handle this manoeuvre correctly. Giving a routine chaser by hand ties up valuable senior nursing time, tends to result in overrapid administration when staff time is at a premium, and can, if repeated frequently, result in the baby getting a lot of undocumented water, sodium, or glucose.

Particular care must be taken not to mix potentially incompatible fluids. This issue is dealt with, in some detail, in the final part of the monograph on "The care and use of intravascular lines" (see p. 14). Staff must also remain alert to the very real risks of air embolism, infection, inflammation, thrombosis, and tissue extravasation (as set out in the earlier parts of that monograph). They should also be familiar with the management of anaphylaxis (see p. 135).

IV injections: The standard procedure for using a three way tap to give a slow IV "stat" dose is as follows.

- Connect the preloaded syringe to the free tap inlet.
- Turn the tap so the syringe is connected to the patient and give the injection.
- Turn the tap so the syringe is connected to the giving set, draw up about 0.2 ml of infusion fluid, turn the tap back so the syringe is reconnected to the patient, and flush this fluid through so that it just enters the giving set.

- Where two drugs are scheduled for simultaneous administration, proceed as outlined on p. 14.

While the above method is adequate for most purposes, it always results in the administration of too much medicine because it causes the baby to receive the medicine that was trapped in the hub of the syringe. A slightly more complex (and expensive) procedure that avoids this problem is preferable when the amount of drug to be given is less than 0.3 ml, and essential whenever a potentially toxic drug such as digoxin, chloramphenicol, or an aminoglycoside is given IV. Proceed as above but modify the third of the three stages listed by using a second small syringe containing water for injection or 0.9% sodium chloride, instead of fluid from the drip line, and flush just 0.2 ml of fluid through the tap. Do not give more than this or you will end up administering the drug as a relatively rapid "bolus".

Slow intermittent IV infusions: Drugs that need to be given by slow intermittent IV infusion (such as phenobarbital, sodium bicarbonate, or THAM) can, if necessary, be given by hand through a three way tap as a series of 2 ml bolus doses every few minutes, but aciclovir, amphotericin B, ciprofloxacin, co-trimoxazole, erythromycin, fluconazole, flucytosine, phenytoin, rifampicin, sodium fusidate, vancomycin, and zidovudine are best injected into an existing IV line through a three way tap using a programmable syringe pump. Slow infusion has been recommended for a range of other antibiotics without the support of any justificatory evidence. Manufacturers recommend slow aminoglycoside administration in North America, but not in Europe. Inconsistencies abound. The unquestioning acceptance of any time consuming policy of this type without a critical review of its justification limits the time staff can give to other tasks.

Continuous IV infusions: Drugs for continuous infusion such as adrenaline, atracurium, diamorphine, dobutamine, dopamine, doxapram, enoximone, epoprostenol, glyceryl trinitrate, hydrocortisone, insulin, isoprenaline, Intralipid®, labetalol, lidocaine, magnesium sulphate, midazolam, milrinone, morphine, noradrenaline, nitroprusside, prostaglandin E, streptokinase, thiopental, and tolazoline should be administered from a second carefully labelled infusion pump connected by a three way tap into the main infusion line. Remember to readjust the total fluid intake. Great care is needed to ensure that patients never receive accidentally even a brief surge of one of the vasoactive drugs, and the same is true of many inotropes. Never load the syringe or burette with more of the drug than is likely to be needed in 12–24 hours, to limit the risk of accidental overinfusion. Also check and chart the rate at which the infusion pump is actually operating by looking at the amount of fluid left once an hour. The guidelines relating to the administration of intermittent IV injections also apply when a continuous infusion is first set up.

IM administration: IM medication is more reliable than oral medication in a baby who is unwell, but drug release from the IM "depot" is sometimes slow (a property that is used to advantage during treatment with naloxone, procaine penicillin, and vitamin K). It may also be unreliable if there is circulatory shock. Bulky injections are also painful, but neither should it necessarily be assumed that permanent attachment to an IV line is without its frustrations, especially if this involves limb splinting. Prior cleaning of the skin is largely a token ritual. The main hazard of IM medication is the risk that the injection will accidentally damage a major nerve. Small babies have little muscle bulk and the sciatic nerve is easily damaged when drugs are given into the buttock, even when a conscious effort is made to direct the injection into the outer upper quadrant. The anterior aspect of the quadriceps muscle in the thigh is the **only** safe site in a small wasted baby, and this is the only site that should be used routinely in the first year of life.

Try to alternate between the two legs if multiple injections are required. Superficial injections may result in the drug entering subcutaneous fat rather than muscular tissue, causing induration, fat necrosis, delayed drug release, and a palpable subcutaneous lump that may persist for many weeks. Intradermal injections can also leave a permanent scar. IM injections should be avoided in any patient with a severe bleeding tendency. With certain drugs, such as bupivacaine, the accidental injection of drug into a blood vessel during deep tissue infiltration is toxic to the heart, and it is essential to pull back the plunger each time the needle is moved to ensure that a vessel has not been entered, and also to give any dose slowly while using a pulse oximeter to monitor for any possible adverse cardiorespiratory effect.

Intrathecal and intraventricular administration: Streptomycin was the first effective antituberculous drug. Because it does not cross the blood–brain barrier very well, a policy of repeated intrathecal injection soon evolved to cope with the scourge of tuberculous meningitis. It then quickly became common practice to treat other forms of meningitis the same way. Penicillin, in particular, was quite often injected into the cerebrospinal fluid (CSF), even though good levels could be achieved with high dose IV treatment. Such an approach is now seldom adopted because a range of antibiotics are available that penetrate CSF well. Gentamicin and vancomycin are, however, still occasionally injected

NEONATAL DRUG ADMINISTRATION

into the CSF in babies with ventriculitis, particularly if the ventricles need to be tapped diagnostically or therapeutically because of obstructive hydrocephalus. Diagnostic needling of a thick walled intracerebral abscess can also usefully be followed by the direct injection of a suitable antibiotic into the abscess cavity. The use of an intraventricular reservoir is often recommended when repeated intrathecal treatment is called for, but implanted plastic can increase the difficulty of eliminating bacterial infection because there is a strong risk of the catheter itself becoming colonised.

The intrathecal dose is always much smaller than the IV or IM dose because of the smaller volume of distribution. Gentamicin is still sometimes given into the cerebral ventricles, but the only published controlled trial suggested that children so treated actually did worse than those given standard IV treatment. Many antibiotics are irritant and the preservatives even more so. Special intrathecal preparations of benzylpenicillin and gentamicin should always be used. Dilute the preparation before use, and check there is free flow of CSF before injecting the drug.

Intraosseous administration: This can be a valuable way of providing fluid in an emergency. Any drug that can be given IV can also be given by this route. Insert the needle into the upper end of the tibia a little below the tuberosity, using a slight screwing action, until marrow is entered. Point the needle obliquely and away from the knee joint. An 18 gauge bone marrow needle is best, but success can be achieved with a 21 gauge lumbar puncture needle and stylet. The resultant fat embolisation is almost always silent; osteomyelitis is the only common complication.

Administration into the lung: Surfactant is the only drug regularly given down an endotracheal tube, but other drugs occasionally given this way include adrenaline, atropine, diazepam, lidocaine, midazolam, naloxone, propranolol, and tolazoline. Tolazoline and adrenaline are the only drugs for which a sound case has been made for such an approach. A range of drugs, including adrenaline, betamethasone, epoprostenol, furosemide, ipratropium, nitroprusside, salbutamol, and ribavirin have sometimes been administered as a fine nebulised mist. Face masks have usually been used for this in the past, but a modification of the Infant Flow[®] continuous positive airway pressure (CPAP) device is probably a better alternative. Surfactant is best delivered using a catheter inserted just beyond the end of the endotracheal tube. Other drugs should be diluted in, or followed by, a 2 ml "chaser" of sterile water. Using 0.9% saline for this purpose, or for regular endotracheal toilet, can impose an unpredictable sodium load on the baby.

Excipients: Drugs often contain preservatives, solvents, and stabilisers ("excipients"), and staff need to be aware that these can occasionally have an unpredictable effect. Such problems have occurred with particular frequency in neonatal and paediatric practice. IV benzyl alcohol can cause collapse and neonatal death ("gasping" syndrome), and the daily intake should never exceed 30 mg/kg. While amiodarone, diazepam, clindamycin, clonazepam, and lorazepam are the only products mentioned in the main section of this compendium for which the UK formulation now contains benzyl alcohol, several other US products still contain this excipient. Propylene glycol can cause seizures, hyperosmolality, and other problems (as outlined in the monograph on enoximone), especially if intake exceeds 2 g/kg per day. The UK products that contain this solvent are noted. The sulfite used in some parenteral formulations of dexamethasone is now known to be neurotoxic in mice.

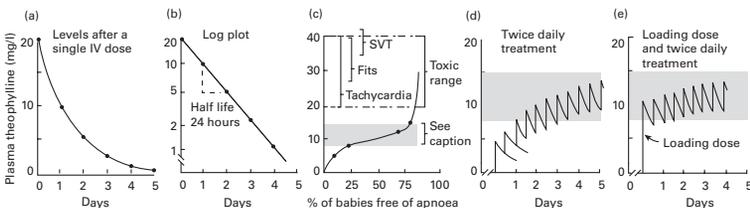
DRUGS AND THE BODY

Pharmacokinetics provides a description of the way drugs are absorbed, distributed, and excreted by the body and *pharmacodynamics* a description of how they act within it. This brief overview offers a simple introduction to some of the (*italicised*) terms and concepts most frequently encountered.

Drugs taken by mouth are effective only if absorbed, unless, like Gaviscon® or nystatin, they act on, or in, the gut. Many antibiotics are destroyed when given by mouth, although quite a small alteration in structure may be enough to change a drug like benzylpenicillin (penicillin G), which is destroyed by acid, into a drug like penicillin V, which is not. Food may reduce intestinal absorption; milk, for example, reduces the absorption of tetracycline. Delayed gastric emptying, poor peristalsis, or ileus will delay any drug's arrival in the upper small intestine, where most drug absorption occurs. Some drugs (like aciclovir) are never completely absorbed. Others, although well absorbed, also show reduced *bioavailability* because they are taken up and metabolised by the liver as they pass along the portal blood stream, before reaching the rest of the body. These are said to show extensive *first pass* metabolism. Morphine by mouth shows about 30% bioavailability for this reason. Action is also delayed by oral administration, although, if a drug is well absorbed, this delay can be circumvented by rectal (diazepam), or buccal or nasal administration (midazolam). IM administration is usually effective, but drug release from the IM "depot" may be slow (naloxone), or deliberately made slow (insulin), and may make IM treatment unpredictable (phenytoin). IV administration is usually the most reliable strategy, but drugs (like vancomycin) may need to be given slowly because even transiently high levels cause problems (such as histamine release). Consistent *side effects* like this (and the *toxic* effects of overtreatment) are easier to anticipate than less predictable *adverse reactions*. Tissue drug levels sometimes exceed plasma levels; such drugs are said to have an apparent *volume of distribution* (V_d) in litres per kilogram that exceeds 1.

Most drugs are structurally altered by oxidation, reduction, or hydrolysis within the liver, and most of the resultant products are pharmacologically inactive. However, some drugs are initially inactive and become active only after modification. Chloral hydrate is one such *prodrug*, being inert until transformed into trichloroethanol. Other drugs are "neutralised" (and rendered more water soluble) by conjugation. However, the *N*-demethylation of diazepam produces desmethyldiazepam, which then remains active in the body for longer than diazepam itself. Babies are slow to deal with many drugs because the enzyme levels controlling conjugation (such as acetylation, glucuronidation, methylation, and sulphation), are all relatively low when first brought into use after birth. *Drug interactions* can further speed up (phenobarbital) or slow down (cimetidine) the enzyme controlled transformation or elimination of other drugs by the liver.

Many drugs are eliminated by the kidneys. For some unmetabolised drugs, like gentamicin, glomerular filtration is the only means of elimination. The speed of elimination changes only slowly, therefore, in the weeks after birth. Other drugs, like the penicillins, are excreted with increasing rapidity after delivery as renal tubular secretion becomes more active. The actual dose required depends on the extent of the drug's distribution within the body, and dose frequency on its speed of elimination. This is usually proportional to the amount present, unless saturation occurs (as with phenytoin). It can be described by the time it takes for the blood level to halve (elimination *half life* or $t_{1/2}$), as shown in the figures below, a relationship (a) that is linear when plotted on a log scale (b). The challenge is to achieve and sustain levels in the safe therapeutic range. The response to the drug may improve as levels increase (c), but toxic effects may also appear, and the ratio of the toxic to the therapeutic level (*therapeutic index*) may be quite small. A drug has to be given for a time equal to four half lives before levels stabilise (d), unless a *loading dose* is given (e).



Baby with a theophylline half life of 24 hours. The therapeutic range (8–15 mg/l) is shaded.

DRUGS AND THE LAW

Licensing: While the UK laws that control the prescribing and the supply of medicines may seem complex, they actually impose few constraints on staff working in a hospital setting. The Medicines Act of 1968, passed in the wake of the thalidomide disaster, regulates the activity of the pharmaceutical industry, making it illegal for any medicine to be marketed for human use in the UK without a product licence (marketing authorisation). These are issued by the Licensing Authority (the Ministers of Health) on the advice of the Medicines and Healthcare products Regulatory Agency (MHRA). The MHRA also oversees the manufacture, promotion, and distribution of medicines, while the Committee on Safety of Medicines advises the Agency on their efficacy, quality, and safety. Although these licences are not published, the relevant provisions, including indications for use, recommended precautions, and dose ranges, are summarised in the manufacturer's summary of product characteristics (SPC). These summaries can now be assessed via the internet (www.eMC.vhn.net). Datapharm Communications also publishes the same information on a compact disc and in book format.

However, the 1968 Act was deliberately framed in such a way that it did not restrict "clinical freedom", and it exempts doctors and dentists from many of the constraints placed on drug companies. It is, therefore, perfectly in order for a doctor to recommend, or administer, a drug for which no product licence exists. The Act, and EC Directive 89/341/EEC, also make it clear that a doctor can use an unlicensed drug in clinical trials, or give an unlicensed product that has been specially prepared or imported, for a particular ("named") patient. It is also acceptable for a doctor to use, or recommend the use of, a drug in a dose, by a route, for a condition, or for a group of patients, that differs from those mentioned in the manufacturer's product licence. It is also legal for such a drug to be dispensed by a pharmacist, or administered by a nurse or midwife. Legislation in the USA, and in many other countries, has adopted a broadly similar approach.

This legal freedom places doctors under a heavy legal, moral, and professional obligation to ensure that the recommendations they make about drug use are well founded. Such problems become acute when a manufacturer offers no advice with regard to the use of a drug for children of less than a certain age, as is, for example, currently true of almost all the drugs used to manage hypotension and hypertension in childhood. Such problems can turn children into "therapeutic orphans". Manufacturers are often reluctant to bear the cost of sponsoring the trials necessary to support a change to the original marketing licence, or the cost of collating all the information published in the scientific literature after a product's first commercial launch so that the licence can be updated. Here it becomes particularly important for doctors to be sure that the use to which they are putting a product is reasonable and prudent in the light of such scientific information as is available in print. This compendium is one aid to that end. *Medicines for Children* (published by the Royal College of Paediatrics and Child Health) offers similar guidance on how to handle some of the many situations in which older children may need to be treated in ways not covered by the manufacturer's recommendations.

Prescribing: The 1968 Act classifies medicines into those available for general sale (a general sale list, or GSL, drug), those only available for retail sale through a pharmacy, and those that can be dispensed only from a pharmacy against a medical practitioner's prescription (a prescription only medicine, or POM). Additional rules apply to controlled drugs. All medicines, other than GSL drugs, have to be sold from a registered pharmacy *unless* they are being sold or supplied by a hospital or health centre, and are being administered in accordance with the directions of a doctor. The only POM products that can be dispensed by a community pharmacist without a doctor's prescription (except in an emergency) are the few products in the nurse prescribers' and dental practitioners' formularies, as listed in the BNF.

Because legislation in the UK does not yet allow nurses to prescribe medicines, alternative, more flexible, strategies have been developed in the last 5 years to enable appropriately trained staff to assume greater personal responsibility for administering a range of POM products. An "*ad hoc*" system of "group protocols" was recognised as having much merit by the Crown Report in 1998, and legislation was subsequently passed making it legal for nurses to supply and administer medicines to specific groups of patients under a formal agreement with a prescribing doctor. Pharmacists, physiotherapists, and other "paramedic" groups can be covered in a similar way. These agreements (known as patient group directions, or PGDs) need to conform to the guidance given in Health Service Circular 2000/026 in August 2000. They need to be prepared by a multidisciplinary group involving a senior doctor, pharmacist, and nurse or midwife, in consultation with the local drug and therapeutics committee, and then approved by the hospital or primary care trust. Their use is restricted to situations where such administration "offers an advantage to patient care without compromising patient safety". Vaccine administration is one area now increasingly covered by PGD guidance. The work of advanced neonatal nurse practitioners is also, increasingly, covered by such guidance.

THE CARE AND USE OF INTRAVASCULAR LINES

Intravascular lines serve a number of vital functions. They make it possible to give fluids, including glucose and a range of other nutrients, when oral nutrition is impossible or inappropriate. They also make it possible to monitor both arterial and central venous pressure directly and continuously, to collect blood specimens without causing pain or disturbance, and to give drugs reliably and painlessly.

These very real advantages have to be balanced against a range of very real disadvantages. Of these, infection due to localised vasculitis or insidious low grade septicaemia is perhaps the most common. Vascular thrombosis is a hazard, and thrombi can also shed emboli. Even reactive arterial vasospasm can cause significant ischaemia. Bleeding from an arterial line can cause serious blood loss, life threatening air embolism can occur into any central venous line, and fluid extravasation can cause severe ischaemia or chemical tissue damage with subsequent necrosis. Any baby with an intravascular line in place is at risk of sudden fluid overload if steps are not taken to make the unintentional and uncontrolled infusion of more than 30 ml/kg of fluid technically impossible (see the next main section on minimising hazards). There is also a risk of reactive hypoglycaemia if the rate of any glucose infusion is changed too abruptly.

Line care

Thrombosis: Relatively little can be done to reduce the risk of thrombosis. A small amount of heparin (q.v.) can reduce the risk of catheter occlusion, but this has little effect on the formation of mural thrombi. Whether the benefit of full heparinisation outweighs the risk remains unclear. Clinical vigilance can speed the recognition of problems when they occur, and the routine use of a lateral x-ray film to identify where any central catheter has lodged can help to ensure that the tip is optimally sited (a lateral x-ray film is more easily interpreted than an anteroposterior view). An attempt is usually made to site any central venous catheter in a major vein, or at the entrance to the right atrium. The larger the vessel the less the risk of occlusion (or extravasation), but the greater the hazard should this occur. Similarly, it is standard practice to site any aortic catheter either above the diaphragm (T_6) or below the two renal arteries (L4) to minimise the risk of a silent renal or mesenteric artery thrombosis, and there is now good controlled trial evidence that there are fewer recognisable complications associated with high placement (although there may be a marginally increased risk of necrotising enterocolitis). Case controlled studies suggest, however, that intraventricular haemorrhage may be commoner when aortic catheters are positioned above the diaphragm, and when heparin is used to prolong catheter patency. Only a very large properly conducted randomised controlled trial is likely to resolve some of these uncertainties.

Limb ischaemia is usually readily recognised, but by the time it is identified much of the damage has often been done. Thrombosis of the abdominal vessels is often silent, but may be a significant cause of renal hypertension. Central venous thrombosis is also underdiagnosed, but can cause a chylous ascites by occluding the exit of the thoracic duct. Occlusion of a small vein is seldom a problem because of the nature of the anastomotic venous plexus, but occlusion of even a small artery can cause severe ischaemia if it is an "end artery" (i.e. the only vessel supplying a particular area of the body). Even occlusion of the radial artery can sometimes cause vascular compromise if there is no significant terminal anastomosis between the radial and ulnar arteries. Every baby with an intravascular line in place should be examined regularly by the nursing staff for evidence of any of the above complications. There are good grounds for particular vigilance in the first few hours after an arterial line has been sited but, with this one exception, all lines merit equal vigilance. Treatment is reviewed on p. 26.

Vascular spasm: Arteries are particularly likely to go into spasm shortly after cannulation. This may make it necessary to withdraw the catheter, but a single small dose of tolazoline can sometimes correct the acute "white leg" seen after umbilical artery catheterisation, and a continuous low dose infusion may work when a single bolus dose is only transiently effective. Papaverine has also been used experimentally in the same way.

Extravasation: Never give a drug into a drip that has started to "tissue". Delivery cannot be guaranteed once this has happened, and some drugs (as noted in the individual drug monographs) can also cause severe tissue damage. Fluids containing calcium cause particularly severe scarring. Serious damage can also be caused by the fluids used in providing parenteral nutrition. Such problems will be noticed promptly only if every drip is so strapped that the tissue around the cannula tip can be inspected at any time. The best line of management, if extravasation is starting to cause tissue damage, involves early tissue irrigation, as outlined in the monograph on hyaluronidase on p. 130. Hot or cold compresses are of no measurable value. Neither is limb elevation.

Infection: Localised or generalised infection is probably the commonest complication of the use of intravascular lines. Indolent, usually low grade, but occasionally life threatening, blood borne infection

CARE AND USE OF LINES

(septicaemia) has been reported in more than 20% of all babies with “long lines” in some units. Infection can be devastating in the small baby, and it is a clear indictment of unit policy if the way in which a baby is cared for puts it unnecessarily at increased risk of infection. The risk of such iatrogenic infection can be minimised only by scrupulous attention to hygiene. Inadequate attention to skin sterility (see p. 227) is probably the commonest reason why cannulas and catheters later become colonised. Access should always be achieved using an aseptic approach. A gown, mask, and surgical drape should also be used whenever a long line is being inserted. The risk of infection is not reduced by the use of an antiseptic or antibiotic cream. Indeed there is evidence that such use can actually increase the risk of fungal infection. Covering the insertion site with a transparent occlusive dressing helps, even though increased humidity under such a dressing can speed the multiplication of skin bacteria. An impregnated chlorhexidine disc may help to prevent this.

Infection most frequently enters where the catheter pierces the skin. This is why most infusion related infections are caused by coagulase negative staphylococci, and why Broviac lines “tunnelled” surgically under the skin less often become infected. Bacterial colonisation of the catheter hub (where the catheter connects to the giving set) can also be the precursor of overt septicaemia. Stopcocks often become contaminated, but there is no evidence that such contamination causes catheter related infection. The risk of generalised infection is increased by the use of a long line rather than a short line. Independently of this, parenteral nutrition may, and Intralipid® certainly does, further increase the risk of systemic infection. Antibiotic treatment for this can, in turn, greatly increase the risk of life threatening fungal septicaemia. These are strong reasons for avoiding the unnecessary use of long lines, and for using parenteral nutrition only when oral feeding is impracticable. Catheters impregnated with an antimicrobial agent have started to become available, but their use is no substitute for proper attention to other aspects of catheter hygiene. Impregnation with minocycline and rifampicin seems better than impregnation with chlorhexidine and silver sulfadiazine.

It used to be thought that the risk of infection could be reduced by resiting all infusions at regular intervals, and short cannulas are still often resited in adults once every 2–3 days to reduce the risk of phlebitis and catheter colonisation. There is, as yet, no good evidence that this approach is justified in children. It also used to be said that fluids and administration sets should to be changed daily to minimise the risk of in-use fluid contamination, but this practice is *not* now endorsed by the American Centers for Disease Control in Atlanta, Georgia. Such routines generate a lot of work, increase costs and have not been shown to reduce the risk of blood stream infection. Unnecessary interference with the infusion line could actually increase the risk. Neither is there any evidence that the regular use of an in-line filter reduces these risks. There are, however, good grounds for changing the administration set each time the infusion fluid is changed (although infusion with insulin may be an exception to this generalisation as explained on p. 140). This is particularly important after any blood or blood product has been given, because the presence of a thin thrombin film increases the chance of bacteria then colonising the giving set. Lipid solutions are also particularly likely to become infected, and it is probably good practice to change these once every 48 hours. In addition, some continuously infused drugs are stable for only a limited time (as outlined in the individual drug monographs) and need to be prepared afresh once every 12–24 hours. There is no evidence that other fluids (or giving sets) need to be changed more than once every 3–4 days. The catheter *must* be removed promptly once bacteraemia is documented if complications are to be minimised (a single coagulase negative staphylococcal blood culture being the only exception to this general rule).

Air embolism: Air embolism can kill a patient very rapidly. Air is so much more compressible than blood that, once it enters the heart, it tends to stay there instead of being pumped on round the body, especially if the baby is lying flat. This air then completely stops the circulation unless immediately aspirated. Umbilical vein catheters are particularly dangerous; air can easily be drawn into the heart when the baby takes a breath if there is not a tap or syringe on the end of all catheters at all times (especially during insertion). Similarly, if air gets into a giving set (through, for example, a cracked syringe) it can easily be pumped into the blood stream.

Blood loss: Babies can easily die of blood loss. Serious loss from the cord has become rare since the invention of the modern plastic umbilical clamp, but haemorrhage can still occur if no clamp has been placed on the umbilical vessels so that they can be cannulated (especially if the baby is then wrapped up for warmth with, perhaps, a “silver swaddler”, through which telltale blood cannot seep). Death can also occur from haemorrhage if an intravascular line becomes disconnected. To minimise this latter risk all connections in any intravascular line should always have Luer-Lok® fittings.

Use of lines

There has been a lot of confused thought as to what may, and may not, be put into what sort of intravascular line. Policy varies widely from unit to unit, and all the policies cannot possibly be right. There is equal

uncertainty over who has the necessary authority to put drugs into, or take blood out of, what sort of line. True "authority" comes with training and experience, not with the mere possession of a medical qualification.

A midwife or nurse who has been trained in the care and use of intravascular catheters will often be in a better position to give **safe** care than a "qualified" but untrained and inexperienced doctor. With proper training, all qualified staff working in any neonatal unit ought to be equally competent in all aspects of intravascular catheter care and use. Anyone experienced enough to give drugs into an established line should have enough experience to sample blood from such a line, and anyone who has been trained to give drugs or sample from a venous catheter has all the knowledge necessary to use a properly inserted arterial line.

What you can safely put into a line depends not only on what sort of line it is, but also on what sort of fluid is already in the line (see below). If at all possible, nothing should be added to total parenteral nutrition whether the infusion is going in through a long line or a short line, not only because of the high risk of iatrogenic infection but also because of the risk of drug incompatibility. Where, because of limited vascular access, it does become necessary to use a single line both to give drugs and to give total parenteral nutrition, steps must be taken to separate the two infusion fluids with a separating bolus of 0.9% sodium chloride. Any line can be used for blood sampling, but care needs to be taken to clear the "dead space" first. Sodium levels can be measured from a line being infused with 0.9% sodium chloride only after a volume equal to three times the dead space has been withdrawn first. Blood glucose levels cannot be measured in a blood sample taken from *any* line through which glucose is being infused, even if the catheter dead space is first cleared by temporarily withdrawing 5 ml of blood before collecting the sample for analysis. False positive evidence of infection can also result if blood is drawn for blood culture from an already established intravascular line. When septicaemia is suspected it is always best to collect blood direct into a culture medium from a fresh venous "needle stab".

Peripheral veins: These can be used for collecting blood samples and for giving almost any drug, although care should be taken when infusing a number of vasoactive drugs (as indicated in the relevant drug monographs). Drugs such as dopamine and isoprenaline are better delivered through a central venous line. When there is no need to give a continuous infusion, a cannula can be inserted and left "stopped off" with a rubber injection "bung". There is no good evidence that these benefit from heparinisation and, in any strict interpretation of the regulations, both the drug and the heparinised flush solution would need to be prescribed, and each administration signed for separately each time (although it has not, as yet, generally been considered necessary to record the giving of every "flush" of saline or water).

Central veins: Drugs can be given safely into any central venous line once ultrasound, or an x-ray film, has shown where the catheter tip has lodged; this is the best route for giving any drug or infusion that tends to damage the vascular endothelium (such as solutions containing more than 10% glucose). Keep the tip away from the right atrium and mediastinal vessels since, if wall damage does occur, the resultant pleural or pericardial effusion will kill if not recognised promptly. Anchor the exposed end of the catheter firmly to the skin; serious complications can arise if the catheter migrates further into the body after insertion. Better still, cut the catheter to the right length before insertion. Give drugs into an umbilical vein catheter only as a last resort if the tip has lodged in a portal vein. Any midwife or nurse who has been trained to give drugs into a peripheral vein should be competent to give drugs into a central vein. However, because of the greater risk of infection when a central line is in place, such lines should not be "broken into" unnecessarily either to give drugs or to sample blood. It will often be difficult to sample blood from a central venous line because of its length and narrow bore. Furthermore, if blood is allowed to track back up a central venous catheter there is a serious risk of a clot developing and blocking the line.

Peripheral arteries: Such lines are almost always inserted in order to monitor blood pressure or to sample arterial blood. They should never be used for giving drugs. The right radial artery is the most frequently used vessel. It may be safe to use a continuous infusion of glucose saline into a peripheral artery, but it is probably best to limit any infusion to as small a volume of heparinised 0.18% (or 0.9%) sodium chloride as is compatible with maintaining catheter patency (see p. 127).

Central arteries: These will almost always be aortic catheters positioned through an umbilical artery. Such lines are usually sited in order to monitor blood pressure or sample postductal arterial blood, but they can safely be used to give glucose or total parenteral nutrition once the site of the catheter tip has been checked radiologically. Take care that this is not close to the coeliac axis, because exposing the pancreas to an infusion of concentrated glucose can cause hypoglycaemia by stimulating an excessive release of insulin. Because blood flow down the aorta is high it is also perfectly safe to give most drugs (other than some of the vasoconstrictive drugs such as adrenaline, dopamine, and isoprenaline) as a slow continuous infusion into the aorta. Bolus infusions should be avoided, however, unless there is no realistic alternative (particularly if the drug is a vascular irritant) because of the risk that an excessive amount of drug will be delivered into a single vulnerable "end artery". Severe tissue necrosis in the area served by the internal iliac artery has been documented quite frequently when drugs such as undiluted sodium bicarbonate have been administered as a bolus into an umbilical artery during emergency resuscitation after circulatory collapse.

Compatible and incompatible fluids

All the drugs mentioned in the main section of this compendium as being suitable for IV use are capable of being injected into, or pickabacked onto, any existing IV infusion containing up to 0.9% sodium chloride and/or up to 10% dextrose, unless otherwise stated (amphotericin B, enoximone, phenytoin, and erythromycin [unless buffered] being the main exceptions). Do not add drugs to any line containing blood or blood products.

Different drugs should never be mixed together, without express pharmacy approval, except as specified in the various drug monographs. Where a single infusion line *has* to be used to give more than one drug, and it is not practicable to delay the administration of the second drug for at least 10 minutes, different products must be separated by 1 ml of dextrose saline, 0.9% sodium chloride, or sterile water for injection (less will do with very narrow bore tubing). Adherence to these guidelines is particularly important where a very alkaline product such as sodium bicarbonate or THAM is being infused. Use the technique described under IV injection in the review of "Neonatal drug administration" (see p. 6), and give the separating 1 ml bolus **slowly** over at least 2 minutes to ensure that the drug already in the IV line does not reach the patient as a sudden, dangerously rapid, surge. This is particularly important if the line contains an inotrope or vasoactive product, or a drug such as aminophylline, cimetidine, phenytoin, or ranitidine, which can cause a cardiac arrhythmia if infused too fast.

Special problems arise when it is necessary to give more than one drug continuously, and IV access is limited. Here terminal co-infusion (the brief mixing of two different infusates using a T tap or Y connector sited as close to the patient as possible) is sometimes known to be safe. In this situation the two drugs are in contact for only a relatively short time (although, with slow infusion rates in a very small baby, contact may last longer than is generally appreciated). In the most frequently encountered situations where such co-infusion is thought to be safe, a statement to this effect has been added to one of the two relevant drug monographs. The documentary evidence for this practice comes (unless otherwise stated) from Trissel's *Handbook of Injectable Drugs*. Note that, even here, compatibility will have been formally assessed for only a limited range of drug concentrations.

Special considerations apply to the administration of any drug into a line containing an amino acid solution when a baby requires parenteral nutrition. Terminal co-infusion, using any product that approximates fairly closely to the formulation described in this compendium, is probably safe for certain drugs, as outlined in the various drug monographs. It is not, however, safe to assume that this is true for other formulations. **No** drug (other than Vitlipid®) should ever be added to any infusion containing emulsified fat (Intralipid), nor should lipid be co-infused with any fluid containing any other drug (other than heparin, insulin, isoprenaline, or noradrenaline). The use of a double, or triple, lumen umbilical catheter makes it possible to give drugs to a baby receiving parenteral nutrition through a single infusion site.

References

- Dann TC. Routine skin preparation before injection: unnecessary procedure. *Lancet* 1969;**ii**:96–8.
- Phillips I, Meers PD, D'Arcy PF. *Microbiological hazards of infusion therapy*. Lancaster: MTP Press, 1976.
- Moore TD, ed. *Iatrogenic problems in neonatal intensive care*. Sixty-ninth Ross Conference on Pediatric Research. Columbus, OH: Ross Laboratories, 1976.
- Burn W, Whitman V, Marks VH, et al. Inadvertent over administration of digoxin to low-birth-weight infants. *J Pediatr* 1978;**92**:1024–5.
- Leff RD, Roberts RJ. Methods for intravenous drug administration in the pediatric patient. *J Pediatr* 1981;**98**:631–5.
- MacDonald MG, Chou MM. Preventing complications from lines and tubes. *Semin Perinatol* 1986;**10**:224–33.
- Hodding JH. Medication administration via the umbilical arterial catheter: a survey of standard practices and review of the literature. *Am J Perinatol* 1990;**7**:329–32.
- Sinclair JC, Bracken MB, eds. *Effective care of the newborn infant*. Oxford: Oxford University Press, 1992. (See especially Chapter 10 pp. 188–9, Chapter 19 pp. 440–1, and Chapter 23 p. 582.)
- Fletcher MA, MacDonald MG. *Atlas of procedures in neonatology*, 2nd ed. Philadelphia, PA: Lippincott, 1993.
- Orlowski JP. Emergency alternatives to intravenous access. *Pediatr Clin North Am* 1994;**41**:1183–99.
- Salzman MB, Rubin LG. Intravenous catheter-related infections. *Adv Pediatr Infect Dis* 1995;**10**:337–68.
- American Academy of Pediatrics. Committee on Drugs. "Inactive" ingredients in pharmaceutical products: update (subject review). *Pediatrics* 1997;**99**:268–78.
- Marlow AG, Kitai I, Kirpalani H, et al. A randomised trial of 72- versus 24-hour intravenous tubing set changes in newborns receiving lipid therapy. *Infect Control Hosp Epidemiol* 1999;**20**:487–93. [RCT]
- Davies MW, Mehr S, Morley CJ. The effect of draw-up volume on the accuracy of electrolyte measurements from neonatal arterial lines. *J Paediatr Child Health* 2000;**36**:122–4.
- Benjamin DK, Miller W, Garges H, et al. Bacteremia, central catheters, and neonates: when to pull the line. *Pediatrics* 2001;**107**:1272–6.
- Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. *Pediatrics* 2002;**110**:e51.
- Trissel LA. *Handbook of Injectable Drugs*, 12th ed. Bethesda, MD: American Society of Hospital Pharmacists, 2003.

MINIMISING IV INFUSION AND DRUG HAZARDS

Occasional errors of IV fluid and drug administration are inevitable. Their reporting is important, but their occurrence should never be made the pretext for disciplinary action unless there has been obvious negligence. Medical staff sometimes share responsibility for any administrative error that does occur by prescribing in an unclear or unnecessarily complex way. Staff who are new, at all levels, frequently find themselves working under considerable pressure, and low staffing levels often impose further stress. Hospital management personnel share responsibility for protecting staff from excessive pressure, for ensuring that unit policies are such as to minimise the risk of any error occurring, and (even more importantly) for seeing that the potential danger associated with any error is minimised by the use of “failsafe” routines like those outlined below. If senior staff over-react when mistakes occur, errors may simply go unreported, increasing the risk of a recurrence.

It is, moreover, important to retain a sense of proportion in considering the issues raised by the rule that every error of drug prescribing has to be reported. While any error of **commission** is generally looked upon as a potentially serious disciplinary issue, serious errors of **omission** often go unremarked. Yet an inadvertent reduction in IV fluid administration due to tissue extravasation, failure to re-site an infusion line promptly, or failure to set up the syringe pump correctly, is more likely to put a baby at hazard (from reactive hypoglycaemia) than a transient period of excess fluid administration. Note that hypoglycaemia is particularly likely to occur when a maintenance IV infusion of dextrose saline is cut back or stopped abruptly so that blood can be given (for guidance on this see the monograph on blood transfusion). Similarly, failure to give a dose of medicine may sometimes be just as hazardous as the administration of too big a dose.

Drug prescribing and drug administration call for close teamwork between the medical, midwifery, and nursing staff. When an error does occur it is seldom one person’s sole fault; this needs to be acknowledged if disciplinary action is called for. Where it is clear that a doctor and a midwife or nurse both share responsibility for any untoward incident, natural justice demands that any necessary disciplinary action is handled in an equitable way.

Minor medication errors (i.e. any deviation from the doctor’s order as written on the patient’s hospital chart) are extremely common. Rates of between one per patient day and two per patient week have been reported in the USA. Prescribing errors are also common. Anonymous self reporting schemes have been initiated in a few hospitals, as part of a more general risk management strategy, in an attempt to identify high risk situations. Dilutional errors are particularly common in neonatal practice; the individual drug guidelines in this compendium have been carefully framed so as to minimise these.

Ten golden rules

Attention to the following 10 rules will help to minimise error and, even more importantly, ensure that when an error does occur the impact is minimised.

1. Keep the prescribing of medication to a minimum, and use once or twice daily administration where this is possible.
2. Never have more than two IV infusion lines running at the same time unless this is absolutely necessary.
3. Never put more than 30 ml of fluid at any one time into any syringe used to provide continuous IV fluid or milk for a baby weighing less than 1 kg.
4. Record the amount of fluid administered by every syringe pump by inspecting the movement of the syringe and by inspecting the infusion site once every hour. Do not rely merely on a digital electronic display.
5. In an analogous way, where the infusion of fluid from any large (half litre) reservoir is controlled by a peristaltic pump (or by a gravity operated system with a gate valve and drop counter), it is always wise to interpose a burette between the main reservoir and the control unit. Limiting the amount of fluid in the burette limits the risk of accidental fluid overload, and recording the amount of fluid left in the burette every hour speeds the recognition of any administrative error.
6. Do not change the feeding or IV fluid regimen more than once, or at most twice, a day except for a very good reason. Try to arrange that such changes that do have to be made are made during the morning or evening joint management rounds.
7. Those few drugs that have to be administered over 30 minutes or more should be given using a separate programmable syringe pump connected “pickaback” onto an existing IV line. As an extra precaution, the syringe should never be set up containing more than twice as much of the drug as it is planned to deliver. Do not adjust the rate at which the main IV infusion fluid is administered

MINIMISING HAZARDS

unless there is a serious risk of hyperglycaemia, or it is necessary to place an absolute restriction on the total daily fluid intake.

8. Do not routinely flush drugs or fluids through an established IV line except in the rare situations where this is specifically recommended in this compendium. To do so can expose the baby to a dangerously abrupt “bolus” of drug. Using fluid from the main IV line to do this can also make the baby briefly and abruptly hyperglycaemic.
9. Beware giving a small newborn baby excess sodium unintentionally. The use of flush solutions of Hepsal[®] or 0.9% sodium chloride can expose a baby to an unintended excess of IV sodium. The steady infusion of 1 ml/hour of heparinised 0.9% sodium chloride (normal saline) to maintain catheter patency is sometimes enough to double a very small baby’s total daily sodium intake; so can intratracheal sodium chloride administration during tracheal “toilet”.
10. Treat the prescribing of potentially toxic or lethal drugs (such as chloramphenicol and digoxin, etc.) with special care. There are relatively few situations where it is really necessary to use such potentially dangerous drugs.

If something *does* go wrong

Report any significant error of omission or commission promptly so that appropriate action can be taken to minimise any possible hazard to the baby. Nine times out of ten a senior member of staff with pharmacological expertise will be able to determine quite quickly that no harm has been done and offer much needed reassurance to all concerned. If malfunction of a pump or drip regulator is suspected, switch the equipment off and replace it **without touching** the setting of the rate control switches, pass the equipment to the medical electronics department for checking without delay, and record the serial number of the offending piece of equipment on the incident form.

CHECK AND DOUBLE CHECK

1. **Have you got the right drug?** *Check the strength of the formulation and the label on the ampoule as well as the box.*
2. **Has its shelf life expired?** *Check the “use by” date.*
3. **Has it been reconstituted and diluted properly?** *Check the advice given in the individual drug monograph in this compendium.*
4. **Have you got the right patient?** *Check the name band.*
5. **Have you got the right dose?** *Have two people independently checked steps 1–4 with the prescription chart?*
6. **Have you picked up the right syringe?** *Deal with one patient at a time.*
7. **Is the IV line patent? Have you got the right line?** *Is it correctly positioned? Could the line have kinked?*
8. **Is a separate flush solution needed?** *Have two people checked the content of the flush syringe?*
9. **Are all the “sharps” disposed of?** *What about any glass ampoules?*
10. **Have you “signed up” what you have done?** *Has it been countersigned?*

ADVERSE REACTIONS AND OVERTREATMENT

Adverse reactions

Any drug capable of doing good is also capable of doing harm; unwanted reactions can be very unexpected. Some of these adverse reactions are dose related, but others are idiosyncratic. Problems may relate to the drug's main pharmacological action in the body, or to some secondary action ("side effect"). The recognition of these adverse reactions is of vital importance, but their proper documentation and reporting is frequently neglected. The Medicines and Healthcare products Regulatory Agency (MHRA) operates a simple yellow lettercard reporting system in the UK, designed to make it easier for medical staff to initiate such notifications. Copies of the prepaid lettercard can be found bound into the back of each new edition of the *BNF*. The Committee has its main base in London (telephone 0800 731 6789), but there are also four other regional reporting centres, as listed at the bottom of this page.

Doctors have a professional duty to report all serious suspected reactions even if they are already well recognised, especially if they are fatal, life threatening, disabling, or incapacitating. This is necessary so that reports can be prepared comparing the risk/benefit ratio seen with other drugs of a similar class. Doctors should also report any adverse or unexpected event, *however minor*, when this could conceivably be a response to a drug that has been on the market for only a relatively short time. Pharmacists also have a responsibility to report all important adverse reactions coming to their attention. Nurses and midwives are often the first to suspect an adverse reaction; they have a duty to see that any such reaction is brought to the attention of the appropriate doctor or pharmacist, and, if necessary, to initiate a report themselves. Deaths have, by law, to be reported to the coroner.

The MHRA is interested to hear about adverse reactions caused by **any** therapeutic agent (including any drug, blood product, vaccine, dental or surgical material, x-ray contrast medium, intrauterine device, etc.). Reactions observed as a result of self medication should be reported in the same way as those seen with prescribed drugs. Drug interactions of a serious nature should also be reported. Drugs can sometimes have a delayed effect, causing later problems such as anaemia, jaundice, retroperitoneal fibrosis, or even cancer. Any suspicion of such an association should always be reported. Whenever a baby is miscarried, aborted, or is born with a congenital abnormality, doctors should always consider whether this might have been caused by an adverse drug reaction, and report all the drugs (including any self medication) taken during the pregnancy.

Adverse reactions are particularly common when drugs are given at the extremes of life. This is, in part, because the liver and the kidneys handle drugs less efficiently, both in the first weeks of life, and in old age. Nevertheless, although the MHRA receives many reports relating to drug medication in elderly people, relatively few reports are received in relation to adverse events in the neonatal period. This is not because they are uncommon, as many of the individual drug monographs in this compendium bear testimony, but because a proper tradition of reporting never seems to have become established. Yet, without such reporting, the identification of many important side effects is avoidably delayed. Because, in particular, some of the most important side effects seen in the neonatal period differ from those normally seen later in life, failure to report can also delay the recognition, and quantification, of a very real drug hazard.

Defective medicines constitute a related but different difficulty. Problems can occur either during manufacture or during distribution, rendering the product either dangerous or ineffective. Whenever such a problem is suspected it should be reported *at once* to the hospital pharmacist, who will, in turn, notify the national Defective Medicines Report Centre in London (telephone 020 7273 0574, or, out of office hours, 020 7210 5371) if the suspicions are confirmed.

UK COMMITTEE ON SAFETY OF MEDICINES

CSM Mersey, FREEPOST, Liverpool L3 3AB
CSM Northern, FREEPOST 1085, Newcastle upon Tyne NE1 1BR
CSM Wales, FREEPOST, Cardiff CF4 1ZZ
CSM West Midlands, FREEPOST SW2991, Birmingham B18 7BR
and, for all other areas,
CSM, FREEPOST, London SW8 5BR

OVERTREATMENT

Overtreatment

Identifying the right dose of medicine to give a newborn baby is never easy, and the problem is made even more difficult if kidney or liver immaturity are compounded by illness or organ failure. Progressive drug accumulation is a very real possibility in these situations. A major error can easily arise during the drawing up of the small dose needed in a small preterm baby, particularly if prior dilution is involved. Few of these events are ever widely reported. Indeed, when the baby is already ill, the cause of death may go unrecognised. Tenfold administration errors are not unknown.

Luckily, even after serious overtreatment, most babies recover with supportive or symptomatic care (although this is not always true where drugs such as atropine, chloramphenicol, digoxin, lidocaine, and potassium chloride are concerned). If the drug has been given by mouth it may be worth giving a stomach washout. A 1 g/kg oral dose of activated charcoal (repeatable every 4 hours until charcoal appears in the stool) may also be of some help, especially if it is started within 4 hours. Do not try to make the baby sick. Other forms of forced elimination such as exchange transfusion, haemoperfusion, dialysis, and forced diuresis are of only limited value for a small number of drugs taken in severe excess. Whole bowel irrigation with a polyethylene glycol electrolyte solution (such as Klean-Prep®) may occasionally be appropriate. Always seek the immediate help and advice of the nearest poisons centre (see below) if there are severe symptoms. For a limited number of drugs, specific antidotes, antagonists, or chelating agents are available; these are mentioned briefly, where appropriate, under the name of the drug for which they are of use, in the various monographs in the main section of this compendium. Specific antagonists include naloxone for opioid drugs, Digibind® for digoxin, and flumazenil for benzodiazepines. Acetylcysteine is of value after paracetamol overdose, methylene blue is used to control methaemoglobinaemia, and the chelating agent desferrioxamine mesilate is used in iron poisoning. The main components of supportive care are as follows.

Respiration: Airway obstruction is a real hazard in patients who become unconscious. Vomiting is not uncommon and inhalation is a real risk. Most poisons that impair consciousness also depress breathing, so artificial respiratory support may well be required. While specific opioid and benzodiazepine antagonists can be helpful, respiratory stimulants should not be used. Correct any serious metabolic acidosis (pH < 7.2) with sodium bicarbonate or THAM.

Fluid and glucose intake: Reduce fluid intake to a minimum and monitor urine output while retaining normoglycaemia until it is clear that kidney function is unaffected. Stop all oral feeds if there is acidosis, hypotension, and/or suspected ileus.

Blood pressure: Do not use vasopressor drugs without first getting expert advice. Cautious plasma volume expansion may help if there is serious hypotension.

Arrhythmia: Do not give drugs, especially if output is tolerably well maintained, before defining the nature of the arrhythmia and seeking advice as outlined in the monograph on adenosine. A β blocker (such as propranolol) may help to moderate the tachyarrhythmia sometimes seen with excess theophylline, chloral hydrate, quinine, amphetamine, or some of the antihistamines, and may improve cardiac output. These drugs do not seem to cause an arrhythmia in children as often as they do in adults.

Convulsions: While short lived seizures do not require treatment, prolonged seizures should be controlled, especially if they seem to be impeding respiration. A slowly infused IV dose of diazepam (preferably the emulsified formulation) is the anticonvulsant most often used in older patients, but phenobarbital is more usually used in the neonatal period. Either drug can, in itself, cause further respiratory depression.

Temperature control: Poisoning can cause both hypo- and hyperthermia. The rectal temperature should be measured to monitor deep body temperature, using a low reading thermometer if necessary so as not to miss hypothermia, and appropriate environmental measures taken.

UK NATIONAL POISONS CENTRE "HOT LINE": 0870 600 6266

MEDICINES INFORMATION CENTRES IN THE UK AND IRELAND

Belfast: 028 9089 4699

Birmingham: 0121 311 1974

Cardiff: 029 2074 2979

Edinburgh: 0131 536 2843

London: 020 7378 0023

Newcastle: 0191 232 1525

Dublin: Dublin 473 0589

WRITING A HOSPITAL PRESCRIPTION

Comprehensive guidance on how to “write up” (or transcribe) a prescription is given for those working in the UK in the introduction to the *BNF*, but many of the points in this bear repetition. Although the formal constraints that operate in the community do not apply in a hospital setting (see p. 10), the following guidelines still represent good practice.

Block capitals: Always use block capitals when prescribing drug names to ensure legibility. A poorly written prescription is, at best, discourteous to nurses, and to pharmacists who may have to spend time checking what has been written. Illegibility can also be dangerous.

Approved names: These should always be used to ensure consistency between vials, ampoules, bottles, and other labels. Proprietary names (“trade names”) should be used only for compound preparations when a generic name does not exist (for example, INFANT GAVISCON – half a dual sachet). Avoid abbreviations and contractions other than those universally used and recognised (such as THAM).

The dose: This should be given in grams (g), milligrams (mg), or micrograms. The only acceptable abbreviation for micrograms is “micro” – never mcg, ug, or µg. Units – when the dose is in “units” write this word out in full. Avoid the symbol “u” because it is too easily misread. Some drug companies still use the term “international units” (IU) but, since international agreement has now been reached as to the meaning of all such terms, this terminology is unnecessary, and best avoided.

Volumes: Volumes should always be prescribed in ml. This can be abbreviated to ml (but not to cc or cm³).

Decimal places: Carelessness here is a major cause of potentially lethal overtreatment. Decimals should be avoided where possible and, when unavoidable, always prefaced by a zero. Write 500 mg not 0.5 g. If a decimal has to be used, write 0.5 ml not .5 ml. Do not use a comma, use a stop (0.5 ml not 0,5 ml).

Time: This is best written using the 24 hour clock when prescribing for patients in hospital.

Route of administration: This must always be indicated. The following abbreviations are generally acceptable:

IV	intravenous	IM	intramuscular
NEB	nebuliser	PO	oral (<i>per os</i>)
RECT	rectal	SC	subcutaneous

All other methods of administration should be written in full (for example, intradermal, intratracheal, etc.)

Continuous IV administration: Drugs for continuous IV (or, rarely, umbilical arterial) infusion can be prescribed on an IV infusion chart and signed for on this chart in the usual way. Full details do not then need to be written up and signed for in duplicate on the main inpatient medicine chart, but the front of this chart does, as a minimum, need to be marked to show clearly what other charts are in use.

Reconstitution and dilution: Drugs often have to be reconstituted and/or diluted before they can be given to babies. It is not necessary to write down how this should be done when prescribing a drug listed in this compendium in units where all staff routinely use these guidelines because it will be assumed that reconstitution and dilution will be carried out as specified in the relevant drug monograph. Indeed, it would only cause confusion to give any instruction that was unintentionally at variance with the advice given here. Instructions *must* be given, however, where this is not the case, or if a drug is prescribed that is not in this compendium.

Limits of precision: Do not ask for impossible precision. A dose prescribed by weight will almost always have to be given to a child by volume (often after dilution, as above), and it is not generally possible to measure or administer a volume of less than 0.1 ml with any precision (as noted on p. 5).

Flexible dosage: Some drugs (such as insulin) are regularly prescribed on a “sliding scale”. Where this is the case it may not be necessary or appropriate for a doctor to write up each dose given. In the same way, detailed authorisation for hour-by-hour dose variation within a prescribed range (such as the use of labetalol or an inotrope to control blood pressure) does not require a doctor’s signature each time treatment is adjusted, as long as each change in dosage is recorded and signed for on the IV chart by the relevant responsible nurse.

Management at delivery: Drugs commonly given to a baby at birth (such as vitamin K or naloxone) do not need to be written up on a medicine chart as long as their administration is fully documented in a fixed and standardised position in the maternity notes.

WRITING A PRESCRIPTION

Emergency resuscitation: When drugs are given in an acute emergency by a doctor or nurse during cardiorespiratory resuscitation, they do not need to be recorded in duplicate on the medicine chart as long as they are accurately recorded in the narrative record in the medical notes (along with dosage and timing) when this is subsequently written up.

Blood products and vaccines: While these are not traditionally recorded on the medicine chart, their administration must be recorded somewhere in the clinical notes along with the relevant batch number.

Dietary supplements: Vitamin and other dietary supplements for which no doctor's prescription is necessary, or once daily additions to the milk formula (such as supplemental sodium), do not need to be prescribed on the medicine chart, but administration does need to be recorded each time on the child's feed chart.

Self administration: Parents should be encouraged to give certain drugs (such as eye drops) on their own, especially when they are likely to have to continue giving such treatment after the baby's discharge from hospital. This can be done by writing "self administered" in the space labelled "notes" on some medicine charts.

Midwife authorised prescriptions: In the UK, drugs given on a midwife's own responsibility must be properly recorded and "signed up" on the medicine chart. Some units ask staff to add the symbol "M" after their signature.

"As required" prescriptions: Be specific about how much may be taken, how often, and for what purpose. Specify a minimum time interval before another such dose can be given. Do not *only* write "as required" or "prn" (*pro re nata*); it will often be important to indicate a maximum cumulative daily (24 hour) dose. Patients offered analgesics "prn" often end up undertreated. A flexible prescription (see above) can often be more appropriate.

Medication on discharge: Hospitals in the UK generally instruct staff not to issue a prescription for more of any drug than the minimum needed to continue treatment until such time as the family can get a further prescription from their general practitioner, unless, as with a small minority of drugs used in the neonatal period, the drug is obtainable only from a hospital pharmacy. It should not, in other circumstances, be necessary to dispense more than 2 weeks' treatment. The same guidelines apply to the dispensing of drugs for outpatients. Drugs prescribed by a hospital doctor in the UK have to be dispensed by the hospital pharmacy except under circumstances clearly defined by the Principal Pharmacist (when form FP(10)HP may be used).

Telephone messages: Hospital rules vary. Most agree that under exceptional circumstances a telephone message may be accepted from a doctor by two nurses (one of whom must be a registered nurse and one of whom acts as witness to receipt of the message). It is not acceptable to prescribe controlled drugs in this way, and any other drug so prescribed should be given only once. The doctor must then confirm and sign the prescription within 12 hours. Faxed prescriptions should also be confirmed in writing within 72 hours.

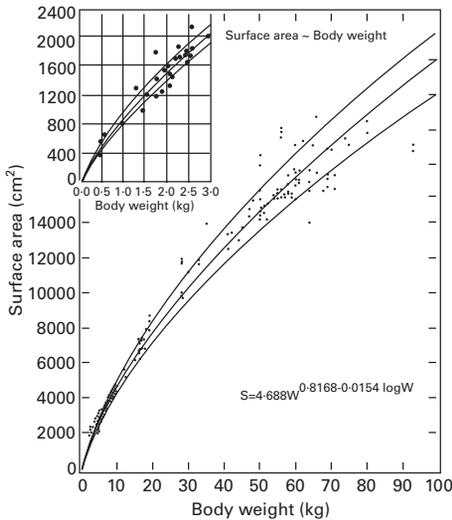
Signature: Each entry must be signed for, separately, in full, by a registered doctor (except, in the UK, as covered by the "patient group direction" (PGD) provisions outlined on p. 10). Just transcribing such a directive onto a medicine chart is *not* an act of "prescribing"; that occurred when the PGD was drawn up.

Cancellation: Drugs should not be taken for longer than necessary. Stop dates for short course treatments (such as antibiotics) can often be recorded on the medicine chart when first prescribed. The clearest way to mark the chart is to draw a horizontal line through the name of the drug, and the date, and then date and initial the "date discontinued" space. Drugs often tend to be given for much longer than is necessary.

BODY WEIGHT AND SURFACE AREA

Basal metabolic rate has a fairly fixed relationship to body surface area throughout childhood and adult life. For this reason it was once common practice to use body surface area when calculating drug dosage in childhood. However, while this works reasonably well for children more than 3 months old it is not really appropriate in early infancy because resting or "basal" metabolic rate (BMR) rises rapidly and substantially in the first 2 or 3 weeks after birth, even though little growth takes place. In addition, BMR is only one of many factors influencing drug metabolism at this time.

The graph reproduced below, taken from p. 101 of the book by Edith Boyd on *The Growth of the Surface Area of the Human Body*, which was published by the University of Minnesota Press in 1935, provides the best available experimental data on the relationship between weight and surface area. Formulas for predicting surface area from a knowledge of body length as well as body weight can be found in most paediatric textbooks, but Boyd found no evidence that the inclusion of a term for body length improved the prediction of surface area either in infancy or during childhood. Nomograms are often provided for undertaking these calculations, but studies have shown that major errors are all too easily introduced when these are used in a clinical setting (*Arch Dis Child* 1994;**71**:281). The best fit relationship for children weighing less than 10 kg is summarised in the table below. For most drugs it is perfectly acceptable to calculate the dose from a knowledge of body weight.



Relationship between body weight and surface area

Body weight (kg)	Surface area (m ²)									
	0-0	0-1	0-2	0-3	0-4	0-5	0-6	0-7	0-8	0-9
0	—	—	0-03	0-04	0-05	0-06	0-07	0-07	0-08	0-09
1	0-10	0-10	0-11	0-12	0-12	0-13	0-13	0-14	0-15	0-15
2	0-16	0-16	0-17	0-18	0-18	0-19	0-19	0-20	0-20	0-21
3	0-21	0-22	0-22	0-23	0-23	0-24	0-24	0-25	0-25	0-25
4	0-26	0-26	0-27	0-27	0-28	0-28	0-29	0-29	0-29	0-30
5	0-30	0-31	0-31	0-32	0-32	0-32	0-33	0-33	0-34	0-34
6	0-34	0-35	0-35	0-36	0-36	0-36	0-37	0-37	0-38	0-38
7	0-38	0-39	0-39	0-40	0-40	0-40	0-41	0-41	0-41	0-42
8	0-42	0-43	0-43	0-43	0-44	0-44	0-44	0-45	0-45	0-45
9	0-46	0-46	0-46	0-47	0-47	0-48	0-48	0-48	0-49	0-49

FURTHER READING

Many good books about drug use in children now exist, but detailed up to date neonatal information is harder to find. The excellent neonatal reference text published by Roberts in 1984 was never updated, while the slim US reference booklet by Young and Mangum is not widely available in the UK and covers only a limited range of drugs. The paediatric text by Taketomo *et al* is very comprehensive, and annually updated, and the formulary, *Medicines for Children*, published by the Royal College of Paediatrics and Child Health in the UK, is equally comprehensive. However, these two books include only limited information on neonatal usage, and neither text is referenced. *Martindale* remains a mine of useful information, and there is more specific information relating to pregnancy and the neonatal period available in the *BNF* than is generally realised (although this usually merely reflects the advice given in the manufacturer's summary of product characteristics). The neonatal information in Dollery's otherwise authoritative text is of very uneven quality. These books and the local formularies produced by the Hammersmith Hospital in London, by the Hospital for Sick Children in Toronto, and by the Royal Women's Hospital in Melbourne, were all consulted during the preparation of the latest edition of the present text.

British Medical Association and Royal Pharmaceutical Society of Great Britain. *British national formulary, 45th ed.* London: BMJ Books, 2003.

Dollery C, ed. *Therapeutic drugs, 2nd ed.* Edinburgh: Churchill Livingstone, 1999.

Guy's, St Thomas' and Lewisham Hospitals. *Paediatric formulary, 6th ed.* London: Guy's Hospital Pharmacy, 2001.

Isaacs D, Moxon ER. *Handbook of neonatal infections. A practical guide.* London: Saunders, 1999.

Pagliari LA, Pagliaro AM, eds. *Problems in pediatric drug therapy, 4th ed.* Hamilton, IL: Drug Intelligence Publications, 2002.

Radde IC, MacLeod SM. *Pediatric pharmacology and therapeutics, 2nd ed.* St Louis, MO: Mosby, 1993.

Roberts RJ. *Drug therapy in infants. Pharmacologic principles and clinical experience.* Philadelphia, PA: Saunders, 1984.

Royal College of Paediatrics and Child Health. *Medicines for children, 2nd ed.* London: RCPCH, 2003.

Rubin PC, ed. *Prescribing in pregnancy, 3rd ed.* London: BMJ Books, 2000.

Sweetman SC, ed. *Martindale. The complete drug reference, 33rd ed.* London: Pharmaceutical Press, 2002.

Taketomo CK, Kraus DM, Hodding JM. *Pediatric Dosage Handbook, 9th ed.* Hudson, OH: Lexi-Comp, 2002.

World Health Organization. *WHO model formulary 2002.* Geneva: WHO, 2002.

Yaffe SJ, Aranda JV. *Pediatric pharmacology. Therapeutic principles in practice, 2nd ed.* Philadelphia, PA: Saunders, 1992.

Young TE, Mangum OB. *Neofax. A manual of drugs used in neonatal care, 15th ed.* Raleigh, NC: Acorn Publishing, 2002.

Zenk KE. *Neonatal medications and nutrition. A comprehensive guide.* Santa Rosa, CA: NICU Ink, 1999.

Drug use during pregnancy and the neonatal period is now being subjected to more critical scrutiny than was usual in the past. Many drugs in common use have never been shown to achieve what is claimed for them. Others, when subjected to rigorous evaluation in a randomised controlled trial, have eventually been shown to cause unexpected adverse problems. An increasingly complete tally of such studies and overviews is now available in *The Cochrane Library*, an electronic database published for the international Cochrane Collaboration by Update Software in Oxford, and updated quarterly. For details contact Update Software, Summertown Pavilion, Middle Way, Oxford, OX2 7LG, England (tel: +44 (0)1865 513 902). A  (Cochrane Collaboration) symbol has been used to highlight those drugs or topics for which there is at least one systematic review relating to use in pregnancy or the neonatal period. Abstracts of *all* these reviews can be viewed on the Formulary website. See: www.neonatalformulary.com

For details of how to access full Cochrane reviews see the list of useful website addresses at the back of this book.

Making choices

SUSPECTED BACTERIAL INFECTION

Antibiotics are among our most valuable resources. When they first became available 50 years ago they probably made little difference to overall mortality in the neonatal period but, with the advent of prolonged intubation and intravascular catheterisation, babies are now at much greater risk of secondary bacterial infection. Modern neonatal intensive care would be impossible without antibiotics. Their effectiveness can be preserved only if they are used rationally and with great care. Irresponsible use can quickly lead to the selective appearance of organisms that are resistant to most forms of treatment.

Babies with sepsis rarely present with clear, well defined clinical features, and often deteriorate rapidly if not treated promptly. Laboratory markers of sepsis are not always present. Even complex "septic screens" utilising immature (band) neutrophil to total neutrophil cell count ratios, measurement of C-reactive protein and micro erythrocyte sedimentation rate miss nearly 7% of babies with sepsis. It is therefore hard to justify the cost of such tests and generally accepted that antibiotics should be started whenever there is a clinical suspicion of sepsis, regardless of laboratory results. Four important general principles need to be followed, however, to limit the emergence of resistant organisms.

- **Start early, stop early:** If systemic cultures are negative, antibiotics can always be stopped safely after 72 hours (after 36 hours if the baby is asymptomatic).
- **Treat sepsis, not colonisation:** Antibiotics are not indicated every time a potential pathogen is grown from a peripheral culture (for example, from an endotracheal aspirate). Treat babies, not colonising organisms.
- **Use a narrow spectrum antibiotic:** The antibiotics chosen initially need to cover all the likely organisms, but a narrow spectrum antibiotic is best once the organism is known.
- **Do not use prophylactic antibiotics:** Using an antibiotic to prevent infection, rather than treat it, is seldom of any proven value. Such an approach can easily do more harm than good. The index to this book lists those situations where prophylaxis may be of some value.

Antibiotics are potentially toxic substances and the risk of toxicity is increased when other drugs are used simultaneously. Everyone using antibiotics must make themselves aware of these potential drug interactions. Toxicity is often increased in babies with impaired renal function, as may be the case after asphyxia or extreme preterm delivery. Dose, and dose interval, may need to be modified in the light of renal function, and a knowledge of gestational and postnatal, or postconceptional age. Prolonged use makes fungal infection likely. To minimise excessive use, inexperienced staff should seek a second opinion before initiating treatment.

Rational treatment is extremely difficult if the organism cannot be isolated. Even 0.5 ml of blood will usually be enough to identify the organism if it is collected with due care to prevent skin contamination (as outlined in the monograph on skin sterility) because large numbers of bacteria are generally present in the blood stream. Taking an endotracheal aspirate before starting treatment in any baby requiring intubation on the first day of life will identify most cases of ascending intrapartum infection. Meningitis will sometimes be missed if lumbar puncture is omitted (about 15% have a sterile blood culture at presentation), but it may be advisable to secure the airway, start treatment, and initiate respiratory support before doing this (see the monograph on cefotaxime). Other components of the traditional septic workup (ear swabs, gastric aspirate, etc.) are seldom of help.

Antibiotics used alone will suffice to save only a few babies with septicaemia. Many will need ventilation and circulatory support. Hypoglycaemia may require attention, and pain relief may be necessary. Other supportive measures are under investigation. Units need a clear policy for the management of suspected infection by an, as yet, unidentified agent. A combination of penicillin and an aminoglycoside (such as gentamicin) remains the best treatment for babies becoming symptomatic in the first 48 hours of life. Use flucloxacillin and an aminoglycoside in babies with signs of late onset bacterial infection, and vancomycin when there are grounds for suspecting catheter related infection with coagulase negative staphylococci. Frequent β lactamase antibiotic use seriously increases the risk of colonisation and of infection with resistant *Enterobacter*, *Klebsiella* and *Serratia* species.

CLOTS AND EMBOLI

Clots (or thrombi) can form in any large vessel, and loose clots (or emboli) can lodge anywhere. Thromboembolism is diagnosed during about one in every 500 neonatal unit admissions, but the true incidence is almost certainly higher than this because the condition is not always considered in the differential diagnosis of seizures (neonatal stroke can go undiagnosed), respiratory distress (pulmonary emboli are seldom sought), or later renal hypertension.

Who is at risk? Thrombi form, after a while, on most intravascular lines (as x-ray angiography clearly reveals). Nobody knows what happens to these clots when the catheters are taken out. While most never cause any recognisable trouble, the presence of a "long line" greatly increases the risk of symptomatic thromboembolism. Renal vein thrombosis (where trouble first starts in the intrarenal venules) is the only condition for which this is not true. Other predisposing factors include infection, and disturbances of blood flow due to dehydration, asphyxia, and polycythaemia. Emboli from the placenta can cross into the baby around the time of birth and, since the foramen ovale and arterial duct are still open at this time, lodge in a limb or in a cerebral artery. In other circumstances the lung acts as a silent filter for small venous emboli. Hereditary thrombophilia (other than homozygous protein C deficiency, which is lethal but very rare) precipitates trouble only if other risk factors are present, but is certainly worthy of retrospective consideration.

How to make the diagnosis: Symptoms and signs of thrombosis vary, depending on the site and extent of the obstruction. A baby with renal vein thrombosis will present with haematuria and an enlarged kidney, a baby with a thrombosed iliac or femoral artery with a cool, pale, pulseless leg. When thrombosis is suspected clinically the diagnosis should be confirmed before any potentially harmful treatment is started. Doppler flow ultrasonography is the commonest imaging technique used, but its accuracy has been doubted: in a study that involved contrast angiography to validate each ultrasound examination, a significant number of false positive and false negative ultrasound diagnoses were encountered.

How to prevent thrombosis: Avoidance of known risk factors is the best possible prevention. The indication for inserting any intravascular catheter needs to be weighed against the risk incurred. Catheters need to be withdrawn as soon as they are no longer needed, or if they become infected. Low dose heparin prolongs the patency of central and peripheral lines. Heparin may also be capable of reducing the risk of catheter related vessel thrombosis and embolisation, but this is still far from certain. A much higher dose is almost certainly needed, and this may well do as much harm as good.

When to start treatment: There is no consensus on this issue, and the neonatal literature is too anecdotal to be of help. Extrapolation from the sound evidence that does exist on the management of thromboembolism in adults may not be appropriate, since all three components of "Virchow's triad" (blood flow, blood coagulability, and the vessel wall) are all very different. Because both the efficacy and the safety of neonatal treatment remain uncertain, a conservative approach is often the wisest option. Clots in the atria or in the superior or inferior vena cava clearly merit treatment since they can shed emboli. Other thrombosed veins seldom cause symptomatic emboli, but subclavian thrombi can cause thoracic duct obstruction and chylothorax. An anticoagulant *may* stop the clot getting bigger. A fibrinolytic agent is probably only appropriate where arterial occlusion is threatening to cause ischaemic damage. Surgery has rarely been of value. There is no evidence that treatment alters the long term outcome in patients with renal vein thrombosis. Uncertainty will persist until randomised trials are done.

What drugs to use: Unfractionated heparin is the most commonly used anticoagulant, although a few centres have begun to introduce low molecular weight heparin (which is given subcutaneously and is easier to monitor than standard, unfractionated heparin). Oral warfarin is best avoided in the first month of life; titrating the dose is extremely difficult, both with and without vitamin K prophylaxis at birth, and serious bleeding is a potential hazard. Streptokinase, urokinase, and tissue plasminogen activator (alteplase) have all been used to lyse thrombi, but urokinase is not readily available in some countries at present. Dose regimens have varied greatly. As no comparative studies exist, choice should be dictated by familiarity and cost.

What is the outcome? Most lesions are not life threatening, although thrombi in the heart and great vessels can be fatal. All renal lesions require follow up. Hypertension of early onset usually resolves without surgical intervention, but tubular function and concentrating capacity remain abnormal in some children with renal vein thrombosis, and a quarter develop persistent late renal hypertension.

MANAGING SEIZURES

Seizures are commoner in the neonatal period than at any other time of life. This is due both to the relative excitability of the neonatal brain and to an underdevelopment of the inhibitory system that stops seizures from spreading. Fits can occur at any time, even before delivery, but they are commonest 1–2 days after birth. They are the outward, visible sign of an inward, invisible cerebral insult, and it is usually more important to treat the cause than its outward manifestation.

Recognition and classification: Recognition can be difficult. The terminology used by neurologists can also be baffling. In what follows, an attempt has been made to define the terms most frequently encountered. Neonatal seizures are often subtle, manifesting merely as apnoea, eye deviation, or repetitive stereotypical limb movements. As a result they can be both under- and overdiagnosed. Eye manifestations include staring and lateral eye deviation. There may be repetitive, apparently compulsive, mouthing or chewing. Pedalling or boxing movements of the limbs also require documentation. Autonomic phenomena, such as salivation, drooling, and changes in skin colour, heart rate, or blood pressure, often go unrecognised. Electroencephalographic (EEG) study is of only limited value; it can be of some prognostic significance in the semicomatose baby, but even here other medication can make interpretation difficult. Electroclinical dissociation is not uncommon; a “clinical” episode may be unassociated with any “electrical” discharge. The converse can also occur. Time synchronised EEG changes are seen consistently only with clonic seizures.

Close observation is at the heart of all good nursing care, and of all reliable diagnosis. Because midwives and nurses witness seizures more often than their medical colleagues, it is vital that they should develop an ability to describe and record accurately what they see. A seizure is a paroxysm of abnormal nervous activity. It can be tonic (a generalised stiffening), clonic (a rhythmical shaking), or myoclonic (an abrupt jerk or series of jerks). It can also be focal (local) or generalised (involving the whole body). Neurologists sometimes try to differentiate further between focal and multifocal seizures. Combined tonic–clonic (also called “grand mal”) seizures are not seen in the neonatal period, probably because of the brain’s immaturity. Babies who look dazed or stuporose in the interval between their seizures (the inter-ictal period) have an encephalopathy.

Differential diagnosis: Jitteriness and benign neonatal sleep myoclonus may cause confusion. In jitteriness the dominant movement is tremor, unaccompanied by any autonomic change or eye movement. The tremor is easily provoked by movement and also easily stopped by gentle restraint in flexion (unlike seizure activity). Jitteriness is of no clinical significance; it is not even a sign of hypoglycaemia. In benign neonatal sleep myoclonus limb jerks occur only when the child is going to (or waking from) sleep; they do not involve the face and resolve spontaneously (usually within 4–8 months). No treatment is required. Hyperekplexia, a much rarer, dominantly inherited, non-epileptic disorder, may also present with sudden brief tonic spasms. There is hypertonia and an exaggerated startle response to unexpected noise or other stimuli (such as tapping the nose). Dangerous apnoea can occur. Clonazepam is an effective treatment. In both conditions the EEG is normal. Two other conditions associated with true seizures and an identifiable EEG abnormality can also be managed without drug treatment unless frequent seizures occur. In a genetic condition (benign familial neonatal seizures) seizures are usually first seen at 2–3 days after birth, and may continue to occur for a few months. In benign idiopathic neonatal seizures (“fifth day fits”) they usually first present a little later and seldom persist for more than 10 days. In both conditions the baby appears alert, well, and entirely normal except when fitting. A family history will help to distinguish the two conditions. About 10% of children with the former condition develop further fits requiring treatment in childhood.

Indications for anticonvulsant treatment: Many important questions cannot yet be answered. We still do not know if poorly controlled seizures damage the brain, compromise later intelligence, or increase the chance that the child will later develop chronic epilepsy. The answer may depend on what caused the fits in the first place. The seizures seen briefly with severe jaundice (“kernicterus”) are invariably associated with long term damage, but those with low serum sodium or calcium levels are not. There is some evidence that early anticonvulsant treatment *may* improve the long term outcome of babies with an encephalopathy 12–24 hours after birth, a condition that is often caused by lack of oxygen, (and sometimes called hypoxic ischaemic encephalopathy, or HIE), but better referred to by a neutral term like “early neonatal encephalopathy”, which does not presume a knowledge of its cause.

When seizures are caused by a biochemical disturbance it is usually necessary only to correct the underlying chemical abnormality. Some problems can be avoided by sensible anticipatory care. The fits caused by hypoglycaemia, hyponatraemia, hypocalcaemia, and hypomagnesaemia are all eminently treatable, and never call for anticonvulsant medication. Those seen in babies with the recessively inherited

abnormalities of pyridoxine or biotin metabolism respond just as rapidly once the underlying defect is recognised. Injections of lidocaine that end in the fetal scalp instead of the maternal perineum can cause seizures and a range of other symptoms that are easily confused with intrapartum asphyxia, but recovery is complete with appropriate respiratory support and there is no indication that anticonvulsant treatment improves the outcome. Restlessness can also occasionally escalate into frank seizure activity in babies born to mothers troubled by drug addiction; the logical treatment is not yet another drug but an individually tailored drug withdrawal regimen. Apnoea can sometimes be the only outward sign of seizure activity, especially in the preterm baby, but an episode of primary apnoea, if prolonged, can also precipitate an anoxic seizure if it is not terminated before severe hypoxia develops. In fits due to meningitis the only thing likely to influence the long term prognosis is the speed with which the infection is identified and treated. Once excess unconjugated bilirubin enters the brain causing kernicterus and brief seizure-like activity, irreversible damage has probably been done, and there is no evidence that any treatment is beneficial.

The case for anticonvulsant treatment is much stronger when seizures are due to underlying cerebral damage rather than a transient toxic insult. Even here, however, there is profound ignorance regarding the best way to proceed. One recent small study has suggested that the long term neurological and developmental outcome is improved by giving early high dose phenobarbital to babies with HIE *before* seizures develop, rather than starting standard medication only after they do (see the monograph on phenobarbital). More such studies are urgently required. We also need to know if such an approach has anything to offer babies with haemorrhagic lesions. Most treatment is based on the reasonable, but unproven, premise that frequent seizures are themselves damaging. Clearly, seizures should not be allowed to cause recurrent hypoxia (some would consider this an indication for ventilation), and should not be allowed to interfere with nutritional intake (IV fluids must be provided if there is any risk of hypoglycaemia).

When to start treatment: No firm consensus exists, but most clinicians would agree on the following.

- Prolonged seizures (lasting more than about 3 minutes) should be treated.
- Seizures occurring more than two or three times an hour should be treated.
- An abnormal EEG does not require treatment if the child seems normal.

What drug to use: There is no agreement as to whether a short acting drug or a longer acting drug should be given first. Few good comparative studies have yet been attempted. One approach would be to choose a short acting drug (such as rectal paraldehyde or lorazepam) when seizures are likely to be brief and there is little risk of recurrence (as, for example, with meningitis, periventricular haemorrhage, etc.), and a longer acting drug (such as phenobarbital or phenytoin) when there is a high risk of recurrent seizure activity (as, for example, with a cerebral malformation or severe HIE). In the latter condition phenobarbital may be the drug of choice. The use of multiple anticonvulsants is to be deprecated. No attempt should be made to “normalise” the EEG of a neonate who is experiencing persistent electroclinical seizures; this may be impossible and may result in excessive high dose medication. Nevertheless, semicontinuous EEG seizure activity (“status epilepticus”) is almost certainly damaging, and more needs to be done than in the past to ensure that anticonvulsant treatment does arrest this rather than merely bring clinically visible seizure activity to an end. It is usually best to give the first dose of any new drug IV. A website commentary linked to the entry on phenobarbital in this compendium offers more detailed, regularly updated information on what objective evidence there is on the best strategy to adopt when seizures fail to respond to first line treatment with phenobarbital. Phenytoin, lidocaine, and the benzodiazepines can all, in themselves, be toxic in excess.

How long to continue treatment: Little is known about the effect of prolonged anticonvulsant use on normal cerebral maturation and myelination in the first year of life. Exposure during intrauterine life is not without its long term consequences. Most babies have no further seizures if treatment is stopped as soon as there have been no seizures for 2–3 weeks. When long term treatment is called for, oral carbamazepine, vigabatrin, or lamotrigine is usually effective (although the manufacturers have, as yet, given only a limited endorsement to any use of the latter two drugs in early infancy). Valproate may occasionally be appropriate, as long as there is no evidence of hepatic dysfunction or an unexplained metabolic acidosis. One concern with high dose phenytoin is the possible development of cerebellar hypoplasia.

CIRCULATORY CONTROL

Over the last 40 years clinicians have come to a much better understanding of the changes that occur in the lung at birth, and of the things that can go wrong, especially in the preterm baby. Similar advances are now being made in the recognition and management of the many problems that can occur with circulatory adjustment in the period immediately after birth.

Monitoring the systemic circulation: Signs of circulatory stress are harder to recognise than signs of respiratory distress, and problems often go unrecognised until compensatory mechanisms start to fail. Surprisingly effective mechanisms exist to compensate for the extremely variable volume of blood present in the body when the placental circulation ceases at delivery. The body also responds to other circulatory stresses by varying cardiac output and adjusting the distribution of blood round the body, although babies have only a limited ability to increase their already high cardiac output. True hypotension (a systolic blood pressure below the 3rd centile) indicates that compensation has already failed. Circulatory failure can rapidly become a self-perpetuating problem and quickly spiral out of control. It is therefore essential to watch for early signs of stress. A range of techniques may need to be used. Deciding how invasive to be calls for good clinical judgement. Babies with severe hypoxaemia and/or asphyxia merit frequent Doppler ultrasound assessment, and continuous arterial and central venous pressure monitoring. Extreme prematurity and asphyxia are a perilous combination.

Peripheral blood flow: Skin blood flow shuts down when the circulation is under stress and the skin becomes cool. Capillary refill (the time it takes for capillaries to refill after 5 seconds of blanching pressure) is one moderately useful measure of circulatory stress; more than 3 seconds is abnormal. An increased difference between toe and deep ("core") body temperature is also a useful warning sign. Most infants who are in an incubator and have a stable temperature have a temperature difference of less than 2°C, but a changing difference is more revealing than an absolute one.

Metabolic acidosis: Circulatory failure eventually leads to metabolic acidosis as a result of lactic acid accumulation (the main byproduct of glucose metabolism when the supply of oxygen to the tissues is compromised), but another common cause of metabolic acidosis, especially in the low birth weight baby, is leakage of bicarbonate from the renal tubules. Blood gas analysis cannot differentiate between these two causes. Alkaline urine suggests a bicarbonate leak but it is better to measure arterial lactate when a rapid laboratory service is available (capillary lactate is a reasonable approximation in sick babies). Serial measurements are more useful than a single estimate, but a value of more than 2.5 mmol/l suggests circulatory failure, for whatever reason, and a value above 5 mmol/l suggests severe failure and a poor prognosis.

Arterial blood pressure: Measurements of systolic, diastolic, and mean blood pressure can be obtained from an arterial line, but invasive monitoring always entails some risk (see p. 26). Marked swings with respiration suggest hypovolaemia, tamponade, or pneumothorax. Mean pressure is often the focus of attention because this is not subject to artificial damping if the catheter is partially blocked, but that is its only particular merit. Almost equally accurate non-invasive measurements of systolic pressure can be obtained by Doppler sphygmomanometry, as long as an appropriate cuff is selected (with a width equal to at least 50% of the limb's circumference and a bladder that completely surrounds the limb). Oscillometric (Dinamap®) measurements have limited accuracy, and can give misleadingly normal results in babies who are seriously hypotensive. Systolic, diastolic, and mean blood pressure vary with weight at birth, as shown overleaf (see figure). Systolic pressure increases in the first 10 days as shown in the monograph on dobutamine. Later changes are summarised in the monograph on hydralazine.

Although there is a perfusion pressure (~20 mmHg) below which small blood vessels start to close, it is blood flow, not blood pressure, that influences oxygen supply to the tissues. Flow is directly related to pressure but inversely related to vascular resistance ($\text{flow} = \text{pressure}/\text{resistance}$), so a change in pressure will reflect flow only if resistance remains unchanged. The body's first response to both pump failure and hypovolaemia is selective vasoconstriction, which raises vascular resistance and maintains blood pressure even when output falls. Systemic pressure is maintained in this way, even when output is drastically reduced, right up to the moment when the circulation finally collapses. Furthermore, if the duct is open, this vasoconstrictive reaction only makes matters worse by increasing the left to right shunt. The isolated measurement of pressure, which is easy (but does not matter), rather than flow, which is difficult (but does), has caused much regrettable confusion of thought.

CIRCULATORY CONTROL

Doppler assessment of function: Left ventricular output can be measured in a reproducible and relatively straightforward way. It is usually about 200 ml/kg per minute. A stroke volume of less than 1 ml/kg is dangerously low. Serial measurement is particularly helpful in assessing the effectiveness of any intervention designed to increase cardiac output in babies without a large ductal shunt. However, such shunts are common in babies with respiratory failure in the first few hours of life, and left ventricular output normally rises to compensate for this. A left ventricular output of less than 150 ml/kg per minute in such a baby is perilously low, but changes in output do not always reflect changes in systemic flow because many different factors (including ventilator settings) can affect ductal flow. Assessing flow in the superior vena cava (usually 40 ml/kg per minute or more in the first 12 hours of life) can help to demonstrate the presence of low systemic cardiac output when there is ductal or intracardiac shunting.

Central venous pressure: It is possible to assess reliably the preload on the right side of the heart only by measuring central venous pressure (CVP) (with a pressure line in the right atrium); such information can be critical when managing pump failure. These measurements are particularly important in babies with so called persistent pulmonary hypertension of the newborn (PPHN) where the right ventricle has to pump blood through a high resistance pulmonary circuit, and the ventricle is often dysfunctional as a result of hypoxaemia and acidosis. Serial measurements and the dynamic response to fluid challenges will determine the best value. Ventilated term babies with PPHN often need a CVP of 4–8 mmHg, while preterm babies with respiratory failure usually have values of 1–4 mmHg. CVP reflects intrathoracic as well as right heart filling pressure, so any overdistension of compliant lungs will (like pneumothorax) raise the CVP, even though transmitted pressure is actually reducing venous return to the heart. Such problems can easily happen, particularly when high frequency oscillation is used to provide respiratory support. A catheter inserted through the umbilical vein can also be used to obtain information on central venous oxygen pressure (p_{VO_2}), as long as there is no left to right atrial shunt, because metabolic decompensation can be expected when oxygen extraction by the tissues causes venous saturation to fall below 60% (equivalent to a P_{VO_2} of about 3.6 kPa).

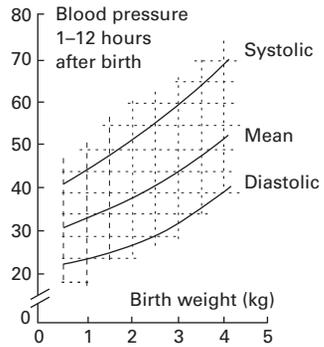
Hypovolaemia: Most hypotensive babies are not hypovolaemic. If hypovolaemia is a problem then a 10 ml/kg infusion of 0.9% sodium chloride, gelatin, or pentastarch will cause a significant rise in systemic blood pressure and a measurable increase in cardiac output. A further 10 ml/kg can be given if the first 10 ml/kg produces a measurable response. Further fluids should not be given if the first 10 ml/kg produces no response because the balance between too little and too much fluid can be critical in babies with myocardial dysfunction, and many very low birth weight babies have a degree of left ventricular dysfunction. Babies with significant hypovolaemia often have a mild tachycardia, and generally have a left ventricular end diastolic to aortic root diameter ratio (LVEDD:Ao) of less than 2. It can be important to assess right atrial filling pressure by measuring CVP in difficult cases.

Inotropes: Once hypovolaemia has been excluded, dobutamine can be used to increase ventricular output. If there is septic shock with marked peripheral vasodilatation, output can be sustained with milrinone, while a vasoconstrictive inotrope such as adrenaline or noradrenaline can be used to raise systemic blood pressure. If all else fails, vasopressin may help. Hypotension resistant to conventional treatment in the newborn preterm baby not infrequently responds to hydrocortisone. Dopamine can do harm as well as good, and low dose use does not preserve renal perfusion as is widely taught. Inotropes can also increase outflow tract obstruction in babies with hypertrophic cardiomyopathy. This diagnosis should always be considered, especially in any chubby "macrosomic" baby, and assessed by echocardiography.

Ductal problems: Echocardiography gives the definitive answer. There may be no murmur, while what sounds like a typical murmur can be due to pulmonary branch stenosis in the preterm baby. Most babies with a clinically significant ductal shunt have a left atrial to aortic root diameter ratio (LA:Ao) of more than 1.4:1, and retrograde flow during diastole in the *post*ductal aorta. If a large left to right ductal shunt is the underlying problem, ductal closure is the appropriate treatment, using indometacin, ibuprofen, or surgery. Avoid overventilation and hyperoxia because these cause pulmonary vasodilatation, increasing the shunt and reducing systemic pressure and output still further.

Hypertension: This is a serious but uncommon condition, which can present with signs of congestive cardiac failure. Its recognition and management is outlined in the monograph on labetalol.

Central cyanosis despite ventilation: Management initially consists of optimising lung expansion, and then optimising left ventricular output and systemic blood pressure before trying to reduce



pulmonary vascular resistance. Such babies require both sedation and paralysis. Many will benefit from treatment with a natural surfactant. When central cyanosis persists it is vital to have structural congenital heart disease ruled out by an experienced paediatric echocardiographer. Sequential ventilator adjustments will help to establish the mean airway pressure that provides the best balance between minimising resistance to pulmonary blood flow (see figure) while optimising alveolar ventilation.

Determine why desaturated blood is reaching the left side of the heart before instituting treatment. Blood may be passing right to left through a patent foramen ovale or a patent duct, or passing through the lung without picking up oxygen. There may be a left to right shunt between the atria and through the duct, but a right to left shunt within the lung, a situation most typically seen in very low birth weight babies with patchy atelectasis or pulmonary interstitial emphysema. Such babies seldom obtain sustained benefit from a pulmonary vasodilator.

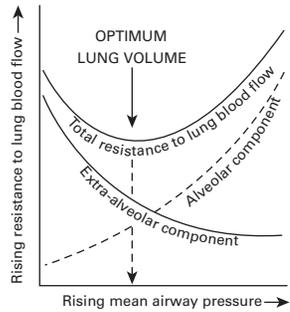
In term babies without respiratory disease (or with meconium aspiration and asphyxia) cyanosis is usually due to a persistence of the high pulmonary vascular tone normally present before birth. Blood continues to shunt right to left across the duct, and a dilated failing right ventricle causes right atrial pressure to rise, resulting in further right to left flow across the foramen ovale. A chest radiograph may suggest that pulmonary blood flow is sparse, and pulse oximetry may provide evidence of a ductal shunt with saturation in the ("productal") right arm higher than in the other limbs. This persistence of the fetal circulation is generally now called "persistent pulmonary hypertension", although the hypertension is often relative rather than absolute.

Once mean airway pressure and left ventricular function have been optimised it may be appropriate to try to manipulate pulmonary vascular tone. A physiological approach should be tried before resorting to drugs. Hypoxia, acidosis, and a high arterial pCO_2 (carbon dioxide pressure) may all need correction because they increase pulmonary vascular tone. Hyperventilation can cause volume/pressure damage to the lung and potentially harmful cerebral vasoconstriction, and it may be more appropriate to raise the pH above 7.4 by infusing base. If cyanosis persists and systemic blood pressure is satisfactory then IV tolazoline or epoprostenol (a more expensive vasodilator) should be considered. These will have some effect at once if they are going to work at all. Magnesium sulphate may also be of some value (although no comparative trials have yet been undertaken) but this seems to work more slowly. However, all these agents affect systemic as well as pulmonary vascular tone, and lower systemic as well as pulmonary arterial blood pressure. Intratracheal tolazoline and nebulised epoprostenol have been used experimentally with good effect; this approach minimises the risk of systemic vasodilatation.

Inhaled nitric oxide is generally thought to be the most effective pulmonary vasodilator in babies of more than 34 weeks gestation. Extracorporeal membrane oxygenation (ECMO) is the other option. Neither strategy should be delayed until the baby is *in extremis*. Prompt referral should be considered if the oxygenation index (OI) approaches 300, or 40 if arterial oxygen pressure (pO_2) is being measured in mmHg rather than kPa, and does not fall at least 20% after 4 hours of treatment with nitric oxide:

$$OI = \text{mean airway pressure (cmH}_2\text{O)} \times \% \text{ oxygen in inspired air/postductal arterial } pO_2 \text{ (kPa)}$$

Nitric oxide should not be used in units that lack echocardiographic expertise, and treatment with ECMO should be considered afresh if the OI is still high after nitric oxide has been given for 2–3 days. Nitric oxide use reduces the number of babies requiring ECMO but does not increase survival; more needs to be learnt about long term morbidity. Treatment cannot be stopped quickly once started; administration during interhospital transfer is not easy and babies respond badly if treatment is interrupted even briefly once started (even when there seems to have been no response to treatment). There is no evidence, as yet, that nitric oxide is beneficial in the preterm baby.



MAIN ECMO CENTRES IN THE UK

Royal Hospital for Sick Children, Glasgow: 0141 201 0000

Glenfield Hospital, Leicester: 0116 287 1471

Hospital for Sick Children, Great Ormond Street, London: 020 7813 8523

Freeman Hospital, Newcastle upon Tyne: 0191 223 1016

SEDATION AND PAIN RELIEF

Babies cry with pain, but they also cry for other reasons, even for no reason at all. This is possibly one reason why neonatal pain received so little attention for many years. Chloral hydrate was used, and was effective, at least briefly, as a *hypnotic* (i.e. as a means of inducing sleep), but was known to be no good as an *analgesic* (i.e. at relieving pain) or as an *anaesthetic* (causing loss of sensation). Short acting barbiturates calm restless babies, but do not relieve pain. Diazepam, the first of the benzodiazepines, was used in the same way, but it was recognised that its ability to relieve anxiety (its *anxiolytic* effect) was not really relevant to its use in the newborn.

Opioids like morphine were known to be good at relieving pain, but they were avoided because they depress respiration. There was also a fear of dependency. Cultural anxiety compounded these concerns. It is now recognised that, while *physical* dependency can occur, this is uncommon when morphine is being given for pain, and that addiction, or *psychological* dependency, never occurs in these circumstances (although prolonged use can cause *tolerance*, making it necessary to give a larger dose to achieve the same effect). Slow weaning can minimise the physiological changes that cause physical dependency, and the *abstinence* or withdrawal symptoms seen when treatment is stopped abruptly after more than 1 or 2 weeks of use.

The nurses and midwives practising 50 years ago recognised, instinctively, that babies felt pain but, knowing that doctors lacked any means of treating this, concentrated on protecting their charges from unnecessary pain, and on alleviating pain by non-medical means. Doctors, accepting that there was little they could do about it, but being keen to develop new ways of treating the medically or surgically ill baby, put such thoughts out of their mind. To many of them neonatal pain came as a new discovery 10 years ago. Until then it was possible to believe that neonates were so insensitive to pain that some surgeons felt able to carry out major surgery without anaesthesia. Thankfully, attitudes have changed and much thought has recently gone into preventing and treating both fetal and neonatal pain.

Even tiny babies have the nervous connections needed to perceive pain by about the 24th week of pregnancy. Doppler blood flow studies show changes in cerebral blood flow with invasive procedures as early as 18 weeks. Babies also show characteristic behavioural and physiological changes as a result of trauma after delivery. Heel pricks produce limb flexion and adduction, accompanied by crying and altered facial expressions. Acute rises in heart rate and blood pressure, together with increases in palmar sweating and falls in PaO₂, are seen. Adrenaline levels rise by 23 weeks gestation and sleep patterns may be disturbed. Babies still respond differently to pain 6 months after undergoing circumcision without anaesthesia.

Pain assessment can be difficult because babies often show an “all or nothing” response to any disturbance. The physiological expressions of pain mentioned above are non-specific and mostly transient, and the measurement of biochemical stress markers is usually impractical. Behavioural changes are more useful, but open to misinterpretation. Structured observations and scoring systems are helpful but they are time consuming to learn and use, may underscore with immaturity, and are usually impractical for everyday use. Just using present or absent characteristics, such as crying or not crying, relaxed or not relaxed, may be more realistic. The simplest and most reliable approach is to assume that anything that would be painful for us will also be painful for a baby. While this works well for procedural or postoperative pain, it may be harder to relate to a baby with peritonitis who is suffering continuous severe pain. Such a baby may be lying still because it is painful to move, in the same way as a baby with a broken clavicle (collar bone) uses its arm with reluctance. If in doubt, give an analgesic and see what happens. Even babies who are being ventilated because of primary respiratory failure, who have no overtly painful condition, can become distressed and merit sedation.

Pain needs to be anticipated. It is harder to relieve pain after it has become severe than to prevent it becoming severe in the first place. Effective management involves not only an initial assessment but also frequent reassessment to see that treatment is effective. If what “should” be adequate analgesia fails, there may have been a technical problem; the dose may have been inadequate, or there may have been a failure of delivery. Alternatively the pain may have become worse; if it has, it is important to find out why. Care *has* to be individualised; it is essential for nurses to have the training and the authority they need to adjust both the dose and its timing in response to their assessment of clinical need.

A thoughtful nursing strategy is the key ingredient. Be kind. Try to have a “baby friendly” environment, with low light levels and as little noise as possible. Monitors do not *need* to bleed continuously. Lighting should acknowledge the difference between night and day. Sleep can aid recovery, and reduce the need for analgesia and sedation. Electronic monitoring can reduce the number of times the baby is disturbed, but “non-invasive” blood pressure monitoring can all too easily disturb sleep with monotonous regularity. Observations, procedures, and tests can, with a little ingenuity, be grouped to allow the baby periods of

undisturbed sleep, and nurses need to be given the authority to ensure that this happens. Sampling from a cannula saves the baby from disturbance, but increases blood loss. A transcutaneous monitor can reduce the need for blood to be taken at all. Discourage the repeated prodding of the distended "surgical" abdomen. It may be medically fascinating, but it is also painful. Tracheal suction is also extremely unpleasant. Adults who have survived a period in intensive care complain about it bitterly. It needs to be done only when there is something there to remove. The frequency with which it is done varies so widely that some units must be making it an unnecessarily frequent routine.

Try to avoid the casual cruelty of much routine arterial and heel prick stabbing. Many blood tests are hard to justify; if they also hurt, that is quite inexcusable. Repeated attempts at venous cannulation are equally hard to justify. Difficult and complex procedures are all too often delegated to junior and inexperienced staff, an ethical issue that could do with more discussion and debate. Babies like to be snug. Gentle containment in a flexed posture can be soothing; so too can gentle stroking. Light swaddling may help, clothing can provide both comfort and warmth, and something to suck can be a useful distraction. Nevertheless, it is unrealistic, and therefore inhumane, to expect to manage severe pain without drugs. It is also ethically wrong. Children deserve, and health professionals have a duty to provide, adequate and safe pain control. A terminally ill child has even more right to pain relief, not less.

Specific issues of pain relief

Heel pricks: Small babies face innumerable pricks, and there is no doubt that the number could be reduced with a little forethought. Unfortunately, anaesthetic creams have only a marginal impact on the behavioural responses elicited by these assaults. The mixture of lidocaine and prilocaine in Emla® cream also causes vasoconstriction, which may occasionally make it more difficult to get blood, lengthening the procedure and making it more painful. Differences in technique can influence the magnitude of the response seen. Studies have shown that some staff cause more disturbance than others. A spring-loaded lance reduces the amount of distress. Offering the baby something to suck reduces the crying time, and putting something sweet in the mouth (2 ml of 30% sucrose) has an additive effect. It cannot be considered an analgesic in the conventional sense, but it does reduce the baby's reaction to procedure-related stress.

Venepuncture: This may cause less behavioural distress than a heel prick, but it becomes difficult to erect a drip in a vein that has recently been used for sampling blood. Prior preparation of the skin with an anaesthetic cream certainly makes venepuncture less painful in older children, but it has been difficult to show that this is of more than marginal benefit in babies. Tetracaine may be more effective than Emla cream, taking less time to become effective and carrying less theoretical risk of methaemoglobinaemia even in the very preterm baby. The amount used *must* be limited, it must be applied for a strictly limited time, and all excess must be wiped away afterwards. We do not yet know enough about the absorption and elimination of these powerful drugs in newborns to be in a position to recommend their use more often than once every 8–12 hours. Nor has their use been studied properly in babies of less than 30 weeks gestation. These are the babies who are subjected to the greatest number of procedures. They also have the thinnest skin, making them vulnerable to a toxic overdose. This would be a valuable area for further nursing research.

Pneumothorax drains: Quick needling may be required for a tension pneumothorax, but a local anaesthetic can always be given before any drain is inserted. Deep infiltration is necessary to relieve pain, but accidental injection into a vein could be dangerous. Aspirate, therefore, before injecting each time the needle is moved. Using lidocaine with adrenaline will delay systemic absorption and extend the period of pain relief.

Other procedures: Umbilical catheterisation may be painless, but any subsequent skin suturing is not. If more than a couple of stitches are going to be inserted it may be a kindness to infiltrate a little lidocaine first. Local anaesthesia for paracentesis and bladder tap does not seem to have been studied. Older people appreciate urethral lidocaine gel prior to bladder catheterisation. The same may well be true for nasal cannulas. There is only limited evidence that even deep lidocaine infiltration reduces the distress caused by lumbar puncture, but increasing evidence that Entonox® (50% nitrous oxide in oxygen) can relieve the pain associated with many short lasting procedures in babies more than a few months old.

Intubation and ventilation: Ketamine or propofol are valuable short acting anaesthetics that may be useful, especially where direct laryngoscopy is undertaken but there is no real call for further ventilation afterwards, although there is, as yet, very little experience of their neonatal use. Thiopental and methohexital have been used more often, although they frequently depress respiration to the point where brief hand ventilation becomes necessary. A bolus of midazolam is sometimes used during induction in older children, but it not infrequently causes brief cyanosis and seizure-like myoclonus in the preterm baby. All babies facing a period of sustained respiratory support should be offered an IV bolus dose of fentanyl or morphine prior to intubation if no other analgesia is being used. Morphine is the more logical choice when analgesia is going to be sustained for more than a few hours. Such a bolus provides analgesia within 1 minute; this deepens for the next 5–10 minutes. No anaesthetist would contemplate intubation without also paralysing the

patient, although there may be less need for this in the very preterm infant. Suxamethonium produces paralysis for a few minutes, atracurium for 20 minutes and pancuronium for 2–3 hours. There is no evidence that neonates need atropine before being given a single dose of suxamethonium. If paralysis is considered important by anaesthetists, who intubate routinely, it should not be neglected by those who are less dextrous and who intubate less often. A lidocaine spray can be used to anaesthetise the throat and larynx but it takes good judgement to give a safe yet effective dose to a small baby.

Paralysed babies should always be sedated, but sedated babies seldom need paralysis. A modest dose of morphine is normally enough, especially if this is given as a sustained infusion, and there is usually no more of an indication for continuing this after 1–2 days than in a chronically ventilated adult. High doses of morphine should be offered only to those in real pain (from surgery, peritonitis, meningitis, etc.) because this can interfere with gastrointestinal motility, setting in train a chain of other, more complex, interventions. The advent of patient sensitive ventilating systems has reduced the need for long term sedation. Where this is called for, intermittent oral chloral hydrate, alimemazine (trimeprazine), or midazolam may suffice, although none of these relieve pain, and in the only small trial undertaken to date those offered midazolam as well as morphine had worse long term outcomes than those offered only morphine.

Surgery: General (or regional) anaesthesia should be provided for all surgical procedures (including circumcision and retinal cryotherapy), even if this means the inconvenience of a trip to the operating theatre. If sick babies can be transported around the countryside, they can also be transported down the corridor, although it requires the same amount of effort. The concentration of nitrous oxide, or of any volatile agent used, should be at least the same as that needed to render an adult unconscious. Postoperative analgesia should also be planned and started before any baby leaves theatre. Apnoea is not uncommon in the first 24 hours after general anaesthesia in babies with a postconceptional age of less than 50 weeks.

Regional analgesia: Peripheral nerve blocks can provide useful postoperative analgesia. Bupivacaine is the most widely used agent, the block being carried out while the child is still under anaesthesia. Infiltrating a laparotomy or thoracotomy wound can provide significant analgesia for 8–12 hours. Central block, where the anaesthetic is injected into the intrathecal or epidural space around the spinal cord, can be offered when a skilled anaesthetist is available. A caudal epidural, using plain 0.25% bupivacaine, provides reliable analgesia for about 4 hours and can, when used with a percutaneous catheter, be topped up. It can also be used to avoid the use of general anaesthesia for herniotomy in an immature baby with chronic lung disease. An extradural opioid can be given instead of, or along with, bupivacaine (either as a bolus, or as an infusion), although this brings some risk of respiratory depression.

Systemic analgesia: Morphine remains the best studied and most effective strong analgesic. Babies quickly develop tolerance to fentanyl, and withdrawal symptoms can appear when treatment is stopped. Tolerance is less of a problem with morphine, but even here withdrawal symptoms can occur if the drug is used for more than 1–2 weeks. Both drugs depress respiration. Midazolam can be used for a baby who is restless but not in pain, but, here too, withdrawal symptoms develop after sustained use and high doses sometimes depress respiration. Intermittent injections are not the best way of controlling serious pain. Give a continuous IV analgesic, and anticipate any acutely painful procedure by giving a further small “bolus” dose. Management protocols *must* be drafted so that they avoid the need for each such dose to be specified in advance on each occasion. Pain relief will be achieved quickly only if an initial loading dose is used. No baby should ever be denied relief merely because its effective provision makes ventilatory support necessary unless local circumstances make this impracticable.

Paracetamol is a useful mild analgesic, but research has shown that the dose generally given in young children is too low to be of measurable benefit. The blood level achieved is also often subtherapeutic. Current usage often does more for the staff (who feel they are “doing something”) than it does for the patient. Early intraoperative use may reduce the need for stronger analgesia during recovery, but the evidence supporting such a strategy remains remarkably sparse. The efficacy of codeine is also poorly established and, in so far as it does work, it may do so because some is metabolised to morphine.

Conclusion: Look to a combined approach. Individualise care and complement medication with other strategies for minimising pain and distress. Stroking and containment work wonders. Even having a finger to suck can be consoling. The use of a local anaesthetic, or a systemic analgesic such as paracetamol, may reduce the need for morphine.

If in doubt, be guided by the motto: “do as you would be done by.”

MATERNAL DRUG ABUSE

Drug misuse (abuse) is common, but only a minority of misuse is associated with dependence (or addiction). Society currently displays a schizophrenic attitude to drug abuse. We seem to accept alcohol intake and smoking during pregnancy, even though we know that these drugs can be addictive and that their regular use can affect the baby. There is a puritanical (and paternalistic) streak, particularly strong amongst legislators in the USA, that would ban all alcohol intake in pregnancy, but there is no evidence that an intake of less than 10 units a week is harmful unless it is consumed in one go (one "unit" of alcohol being a single pub measure of spirits, a small glass of wine, or half a pint of ordinary strength beer or cider). In addition, smoking in pregnancy is now seen as one of those "facts of life" that the medical and midwifery professions can do little to change. The attitude to other recreational drug use is more censorious, even though we know that many UK doctors occasionally take drugs themselves, especially during times of stress in the first few years after qualification.

Opiate addiction presents the most serious challenge, and IV injection further increases the risk to the mother's health. Indeed the main reason for offering these mothers methadone is that it may help them to avoid the hazards associated with giving any drug IV. Access to oral methadone may, by limiting the woman's urge to acquire other costly drugs of doubtful purity, also help to stabilise her lifestyle. Attitudes change over time. Opium and laudanum were widely used by the middle classes in Europe and North America in the nineteenth century (especially in literary and Bohemian circles). Opium was even added to many infant "soothing syrups". Now it has been estimated that, when no legal source is available, the average UK addict gets through £20,000 worth of heroin a year. Diet may become inadequate and alcohol intake may rise. Judgemental attitudes can deter addicts from seeking help until problems escalate. Users may seem to have neglected their condition when the health services have actually, by their attitude, effectively excluded them from care. Despite this, many manage to lead apparently normal lives, running a family or holding down a job.

Few areas of maternity care are more in need of a collaborative, team based, approach. Little can be achieved until the woman's trust and confidence have been won. Antenatal care should identify the women most in need of help and support. IV drug users should always be tested, with their informed consent, for sexually transmitted infection, and for possible hepatitis B, hepatitis C, and HIV infection, both to optimise the scope for treatment and to minimise the risk that the baby will also become infected. Some units make this part of routine antenatal care. Plans for postdelivery care should also be made ahead of delivery, and the mother should know what these are.

Many heroin users also take other drugs. While the recreational use of drugs such as cannabis, LSD, phencyclidine (known as "angel dust" or PCP), amphetamine, ecstasy, or cocaine on their own do not usually cause neonatal withdrawal symptoms serious enough to require treatment, the same is not true for high dose benzodiazepine use. Transferring a mother from heroin to methadone may actually make matters worse because this does not give the immediate "high" that is obtained when heroin is smoked, heated on tin foil and inhaled ("chasing the dragon"), or taken IV. Cocaine may then be turned to for the "lift" that it gives and a benzodiazepine, such as temazepam, used to reduce the "low" that tends to follow. Fashions change, but combined addiction to heroin and temazepam is currently very common in the UK.

Most people who misuse drugs are not drug dependent. The problem becomes an addiction only if abrupt discontinuation causes serious physical and mental symptoms to appear. This is, however, what can happen to babies after birth. Those who have been exposed to opiates throughout pregnancy, or to high sustained benzodiazepine usage, often exhibit a range of symptoms (see box) 12–72 hours after birth. **None** of these, on their own, need treatment, but treatment is called for if sucking is so incoordinate that tube feeding is required, if there is profuse vomiting, or watery diarrhoea, or the baby remains seriously unsettled after two consecutive feeds despite gentle swaddling and the use of a pacifier.

Many units currently admit such babies to special care for observation and then "score" the child's condition once every 4 hours. However, experience shows that an observer's views and their "attitude" to drug misuse can influence the score awarded. Scores ask the observer to say how "severe" the symptoms are. If the nurse or doctor has not cared for such a baby before, how can they decide on the severity of the symptoms? Scoring systems, although popular, can also have the

W	Wakefulness
I	Irritability
T	Tachypnoea (≥ 60 /min)
H	Hyperactivity
D	Diarrhoea
R	Rub marks
A	Autonomic dysfunction
W	Weight loss
A	Alkalosis (respiratory)
L	Lacrymation (tears)

MATERNAL DRUG ABUSE

perverse effect of suggesting that an increasingly sedated baby is “improving” when the real need is to get the baby feeding and sleeping normally.

A better approach is to make the mother aware, before delivery, that the baby will need to be watched for a period, to involve the mother in this, and to care for mother and baby together. Most already feel guilty about their drug habit and live in constant fear of having their children taken from them. A knowledge of antenatal drug intake (even if accurate) is of only limited value in predicting whether the baby will develop symptoms, and mothers need to be aware of this. If mother and baby have been cared for together, both can be discharged home after 72 hours if no serious symptoms have developed.

If symptoms serious enough to make the baby unwell do develop then the logical approach is to wean the baby slowly from the drug to which the mother is habituated, rather than compound the problem by introducing yet another new drug. Babies of mothers taking an opiate should be weaned using a slowly decreasing dose of morphine or methadone. Morphine is widely used; the dose can be easily and rapidly adjusted up or down, but methadone may provide smoother control. Weaning should not normally take more than 7–10 days. The same approach can be used when the mother is addicted to buprenorphine, codeine, or dihydrocodeine. The use of paregoric for the baby (a variable cocktail of opium, glycerin, alcohol, and benzoic acid), or tincture of opium, lacks rational justification. Benzodiazepine dependency is harder to manage using this strategy because nearly all these drugs have such a long half life. Some clinicians use chloral hydrate in this situation but this can oversedate the baby, and chlorpromazine is probably a better choice. For the occasional mother with barbiturate dependency, phenobarbital should be considered but, while this may provide sedation, it does nothing to control gastrointestinal symptoms.

Although there have been 14 small controlled trials looking at strategies for managing neonatal withdrawal, the assessors have generally merely looked at the number of symptoms rather than how distressing and disabling they were. In addition, the assessors have usually been aware of how the babies were being treated. There is scope for some useful nursing research here.

Breastfeeding can be encouraged if the mother is on a stable dose of methadone, but it is doubtful if this should be encouraged in polydrug users since the safety of the baby cannot be assured. There is no need to place any arbitrary limit on the length of time the mother is “permitted” to breastfeed. It should, however, be explained that weaning needs to be gradual. No baby should be left in the care of anyone taking a hallucinogen, and few would condone the possible exposure of a baby to such a drug in breast milk. The place of breastfeeding in mothers taking other drugs is summarised on pages 273–290.

Screening urine, or meconium, for drugs serves little purpose unless serious thought is being given to care proceedings, since it is unlikely to influence management. If you tell the mother you plan to do this, you imply that you do not believe what she has told you about her drug history. If you tell her later, she will merely conclude that you are another person she cannot trust. The decision of any child protection conference, or court, will be influenced purely by what is best for the child, and by the mother's ability to provide that care. Drug misuse is not in itself a sufficient reason to separate mother and child.

Babies can also become addicted to opiates and benzodiazepines *after* birth. Fentanyl and midazolam are the drugs that most often cause problems. Continuous use for even a few days can produce tolerance (the need for a progressively larger dose) and dependency (addiction). Management is the same as for addiction acquired *in utero*: a slow tapered withdrawal of treatment. Perhaps we should do what we tell mothers to do, and avoid sustained use altogether.

INSTITUTE FOR THE STUDY OF DRUG DEPENDENCE

This charitable UK organisation, founded in 1968, provides an information service for professionals and for researchers. It has produced a useful series of informative booklets called ‘Drug Notes’, and a series of five short leaflets called ‘Drug Information for Women’. The Institute has recently merged with the Standing Conference on Drug Abuse (SCODA) to form DrugScope. They can be contacted at:

DrugScope, 32–36 Loman Street, London SE1 0EE. Telephone 020 7928 1771

RENAL FAILURE

Since the kidney is responsible for the elimination of most drugs from the body (either before or after inactivation by the liver) an assessment of how well the kidney is functioning is an essential part of the daily care of any patient on medication. Furthermore, kidney function can fluctuate rapidly in the neonatal period, so this is an assessment that needs to be undertaken, not only at the time treatment is first prescribed but also on a daily basis by those responsible for drug administration.

Function can deteriorate for three reasons: because blood flow has decreased (*prerenal failure*), because the kidney has suffered damage (*intrinsic renal failure*), or because the elimination of urine has been obstructed (*postrenal failure*) although both pre- and postrenal failure can also cause secondary damage to the kidney itself. Clinical examination, and a knowledge of the other problems involved, will often suggest where the problem lies. Ultrasound examination may help. In babies with normal renal function, sodium excretion is driven by intake and therefore varies widely. The proportion filtered that then appears in the urine (fractional excretion, FE_{Na}) is equally variable.

$$FE_{Na} (\%) = \frac{\text{Urinary sodium}}{\text{Plasma sodium}} \times \frac{\text{Plasma creatinine}}{\text{Urinary creatinine}} \times 100$$

Check that all concentrations are expressed in the same units. Babies with prerenal failure (who are typically oliguric and hypotensive) conserve sodium avidly under the control of aldosterone. They will have a $FE_{Na} \leq 3\%$ ($< 5\%$ when less than 32 weeks gestation and less than 2 weeks old) regardless of the intake and the plasma level, except after a large dose of furosemide. Babies with established failure have a high FE_{Na} excretion because reabsorption is impaired by tubular damage.

Weigh all ill babies at least once a day because weight change is a sensitive index of fluid balance. Babies normally lose weight for 3–5 days after birth as they shed extracellular fluid (including sodium) following the loss of the placenta through which they were “dialysed” before birth. Weight gain at this time is either a sign of excessive fluid intake or of early renal failure. Even healthy growing babies gain weight by only 2% a day. Gain in excess of this is a very useful sign of kidney failure. Urine output will vary with fluid intake, but any baby putting out less than 1 ml/kg of urine per hour is almost certainly in failure. A rising plasma creatinine or a level above 88 $\mu\text{mol/l}$ ($> 1 \text{ mg}\%$) in a baby more than 10 days old, suggests some degree of renal failure, but the plasma level should never be relied on to identify failure because it rises six times more slowly after any insult than it does in an older child or adult.

Early diagnosis is vital because the elimination of some commonly used but potentially toxic drugs, such as gentamicin, is entirely dependent on excretion in the urine. Furthermore, most acute renal failure in the neonatal period is, at least initially, prerenal in origin – often as a result of sepsis, intrapartum stress, or respiratory difficulty – and early diagnosis makes early treatment possible. Trouble can often be anticipated. The later the problem is recognised, the more difficult management

Solutions for neonatal peritoneal dialysis

Solution	Preparation	Final concentration		
		Sodium (mmol/l)	Bicarbonate (mmol/l)	Glucose (%)
A	500 ml 5% dextrose modified by removing 60 ml of fluid and adding 60 ml of 8.4% sodium bicarbonate	120	120	4.4
B	500 ml 0.9% sodium chloride	150	0	0
C	500 ml 0.9% sodium chloride modified by removing 50 ml of fluid and adding 50 ml of 50% dextrose and 1.5 ml of 30% (strong) sodium chloride	150	0	5.0
<i>Potential combinations:</i>				
1/3 A plus 2/3 B		140	40	1.47
1/3 A plus 1/2 B plus 1/6 C		140	40	2.30
1/3 A plus 1/3 B plus 1/3 C		140	40	3.13
1/3 A plus 2/3 C		140	40	4.80

RENAL FAILURE

Drugs used to combat infection, and their clearance from the body in babies with severe renal failure before or during peritoneal dialysis (PD)

Drug	Dose adjustment needed	Comment
Aciclovir	Major	Quadruple the dose interval. Removal by PD is poor
Amikacin	Measure	Judge dose interval from trough serum level. Removal by PD is slow
Amoxicillin	Some	Increase the dose interval, or give one IV dose and put 125 mg/l in the PD fluid
Amphotericin	None	Give IV treatment as normal. The drug is not removed by PD
Ampicillin	Some	Increase the dose interval, or give one IV dose and put 125 mg/l in the PD fluid
Aztreonam	Major	Halve the dose. The drug is not removed by PD
Cefotaxime	Some	Increase the dose interval, or give one IV dose and put 125 mg/l in the PD fluid
Cefoxitin	Major	Double the dose interval, or give one IV dose and put 125 mg/l in the PD fluid
Ceftazidime	Major	Double the dose interval, or give one IV dose and put 125 mg/l in the PD fluid
Ceftriaxone	Some	Reduce dose if there is both renal and liver failure. Removal by PD is poor
Cefuroxime	Major	Increase the dose interval, or give one IV dose and put 125 mg/l in the PD fluid
Chloramphenicol	None	Use with caution – metabolites accumulate. The drug is not removed by PD
Ciprofloxacin	Major	Halve the dose. Crystalluria may occur. The drug is not removed by PD
Clindamycin	Minimal	Give IV treatment as normal. The drug is not removed by PD
Erythromycin	None	Give IV as normal. The drug is not removed by PD
Flucloxacillin	Minimal	Give IV as normal, or give one dose IV and put 250 mg/l in the PD fluid
Fluconazole	Major	Double the dose interval or, in babies on PD, put 7 mg/l in the PD fluid
Flucytosine	Measure	Monitor the serum level or, in babies on PD, put 50 mg/l in the PD fluid
Gentamicin	Measure	Judge dose interval from trough serum level. Removal by PD is slow
Isoniazid	None	Give oral or IV treatment as normal. The drug is removed by PD
Meropenem	Major	Double the dose interval. It is not known if the drug is removed by PD
Metronidazole	Minimal	Give oral or IV treatment as normal. The drug is removed by PD
Netilmicin	Measure	Judge dose interval from trough serum level. Removal by PD is slow
Penicillin	Substantial	Use with caution – penicillin is neurotoxic. Removal by PD is poor
Rifampicin	None	Give oral or IV treatment as normal. The drug is not removed by PD
Teicoplanin	Moderate	Give if IV level can be measured, or give one IV dose and put 20 mg/l in PD fluid
Trimethoprim	Moderate	Halve the IV dose after 2 days. Removal by PD is slow
Vancomycin	Measure	Monitor serum level, or give one IV dose and put 25 mg/l in the PD fluid

becomes. The frequency with which it is necessary to rescue a baby from metabolic chaos by dialysis is inversely related to the promptness with which such a threat is recognised. A fluid balance strategy for minimising the need for dialysis is summarised on p. 267, and a strategy for the conservative management of hyperkalaemia on p. 225 (and p. 208).

Reduce all medication to the minimum as soon as there is evidence of definite renal failure to minimise the risk of toxic drug accumulation and of unpredictable interactions. Antibiotics should be given as indicated in the table above. Flucytosine, vancomycin, and cefuroxime are sometimes added to dialysis fluids to prevent peritonitis. A first dose of the appropriate antibiotic should always be given IV (if the baby is not already on treatment) before utilising the fluid to sustain an appropriate blood level if there are signs of systemic infection. Sustained high aminoglycoside levels are not bactericidal (see p. 121) so these drugs should not be put in peritoneal dialysis fluid. Pancuronium should be replaced by atracurium if the baby requires paralysis. Morphine may accumulate because it is renally excreted. The half life of heparin seems unaffected, but that of low molecular weight heparin is reduced. The clearance of the drugs commonly used to control arrhythmia, seizures, hypertension, and hypotension are (luckily) unaffected by renal failure.

Peritoneal dialysis is the most effective strategy in most small babies, but surgical problems may occasionally make haemodialysis necessary. Commercial dialysis fluids usually contain lactate, but some ill neonates metabolise this poorly. A flexible range of fluids can be prepared containing bicarbonate by combining three different basic solutions as outlined in the table on the previous page. Use an inline IV burette, and adjust the glucose concentration by varying ingredients B and C in order to control ultrafiltration and the removal of water. Because these dialysis fluids cannot contain calcium it is necessary to give supplemental calcium IV. Start with 1 mmol/kg a day and adjust as necessary. Magnesium may occasionally be needed. Add heparin (1 unit/ml) if the dialysis fluid is cloudy or bloodstained, to stop fibrin and clots obstructing the catheter. Watch for peritonitis by microscopy and culture of the effluent fluid daily.

Drug monographs

Use

Acetazolamide is now rarely used in the neonatal period (except to manage glaucoma) because a trial in 1998 showed that it did more harm than good when used to treat posthaemorrhagic hydrocephalus.

Pharmacology

Acetazolamide is a specific inhibitor of the enzyme carbonic anhydrase used in the treatment of glaucoma to decrease ocular fluid production. It has also been used less widely as an anticonvulsant (particularly for petit mal and complex partial seizures in children). Its first clinical use, in 1952, was as a diuretic because it increases the renal loss of bicarbonate (and hence sodium, potassium, and additional water). It is excreted unchanged in the urine with a serum half life of 4–10 hours.

The drug is not thought to cross the placenta, but high doses have been reported to cause teratogenic limb defects in animals, making its use inadvisable in the first trimester of pregnancy. Maternal treatment during lactation would result in the baby receiving only about 2% of the maternal dose on a weight for weight basis. Acetazolamide is a sulphonamide derivative, and complications such as agranulocytosis, thrombocytopenia, aplastic anaemia, skin toxicity, and crystalluria with calculus formation have all been reported on occasion, as with many of the sulphonamide drugs.

Posthaemorrhagic hydrocephalus

Trials have shown that regular tapping, to remove cerebrospinal fluid (CSF), has no measurable impact on long term disability. While it can reduce symptomatic raised intracranial pressure, it can also cause iatrogenic meningitis. As a result, oral acetazolamide (which reduces CSF production) was used with increasing frequency over a 25 year period, in the hope that it would postpone or abolish the need for surgical intervention. However a UK-based trial (using 32 mg/kg of acetazolamide once every 8 hours, and 500 micrograms/kg of furosemide twice a day) was stopped in 1998 when it was found that this did not change the number of babies requiring shunt placement, and significantly increased the number (84% v 60%) who were dead or disabled at a year. Isosorbide (q.v.) has also been used in much the same way, but has never been subject to controlled trial evaluation. If regular tapping is necessary to keep CSF pressure below 7 cmH₂O, the insertion of a ventricular reservoir should allow the atraumatic and safe removal of CSF until such time as growth and a reduction in the protein content of the CSF makes the insertion of a formal shunt possible. A new approach using alteplase (q.v.) is currently undergoing careful evaluation. If acetazolamide has any residual role in the management of such children it is when other problems make it appropriate to shunt CSF into the pleura rather than the peritoneum or right atrium.

Electrolyte imbalance

Acetazolamide can cause hypokalaemic acidosis and gastrointestinal disturbances. Give 4 mmol/kg of sodium bicarbonate prophylactically once a day by mouth with high dose treatment to reduce this risk, and monitor the child's electrolyte levels since a dangerous metabolic acidosis can occur if there is renal failure. It may also be necessary to give 1 mmol/kg per day of potassium chloride as an oral supplement.

Treatment

Seizures: Try 4 mg/kg by mouth (or, slowly, IV) once every 8 hours. Some infants only respond to two and a half times this dose.

Glaucoma: A dose of 4–10 mg/kg by mouth once every 8 hours has been used, but surgical goniotomy is usually the treatment of choice. Late recognition and inadequate treatment can cause irreversible damage to the eye.

Supply

One 500 mg vial costs £15. The dry powder should be reconstituted with 5 ml of sterile water. Take 1 ml of the resultant solution and dilute to 12.5 ml with dextrose or dextrose saline to obtain a solution for oral use containing 8 mg/ml. This solution should not be kept for more than 24 hours after reconstitution even if stored at 4°C. The same preparation can be given IV where necessary as long as it is used promptly after reconstitution. A sugar-free oral suspension with a 4 week shelf life and costing a tenth as much as this can be prepared by the pharmacy on request.

References

- Carrion E, Hertzog JH, Medlock MD, *et al.* Use of acetazolamide to decrease cerebrospinal fluid production in chronically ventilated patients with ventriculopleural shunts. *Arch Dis Child* 2001;**84**:68–71.
- Whitelaw A. Intraventricular haemorrhage and posthaemorrhagic hydrocephalus: pathogenesis, prevention and future interventions. *Semin Perinatol* 2001;**6**:135–46.
- Kennedy CR, Ayers S, Campbell MJ, *et al.* Randomized, controlled trial of acetazolamide and furosemide in posthemorrhagic ventricular dilatation in infancy: follow-up at 1 year. *Pediatrics* 2001;**108**:597–607. [RCT]
- Maertzdorf WJ, Vlies JSH, Beuls E, *et al.* Intracranial pressure and cerebral blood flow velocity in preterm infants with posthaemorrhagic ventricular dilatation. *Arch Dis Child* 2002;**87**:F185–8.

See also Cochrane reviews of ventriculomegaly 

ACICLOVIR = Acyclovir (USAN)

Use

Aciclovir is used to treat herpes simplex virus (HSV) infection. It is also used, along with varicella immune globulin (q.v.), to treat those with varicella zoster (chickenpox) who are immunoincompetent.

Pharmacology

Aciclovir is converted by viral thymidine kinase to an active triphosphate compound that inhibits viral DNA polymerase. It was first marketed in 1957. It has no effect on dormant viruses and needs to be given early to influence viral replication. Oral uptake is limited and delayed and, at high doses, progressively less complete (bioavailability 10–20%). Aciclovir is preferentially taken up by infected cells (limiting toxicity) and cleared by a combination of glomerular filtration and tubular secretion. Slow IV administration is important to prevent drug crystals precipitating in the renal tubules. Signs of central nervous system toxicity, with lethargy, tremor, and disorientation, will develop if poor renal function causes aciclovir to accumulate. The neonatal half life is about 5 hours, but 2-5 hours in adults and in children over 3 months. Aciclovir enters the cerebrospinal fluid (CSF) and ocular fluids well. Although it also crosses the placenta, and the manufacturers do not recommend use during pregnancy, there are no reports of teratogenicity. Treatment during lactation results in the baby receiving only 1% of the weight related maternal dose.

Herpes simplex infection

Neonatal illness is less common in the UK (1:50,000 births) than in North America, but can follow vaginal exposure to the HSV virus (usually HSV-2) after a variable latent period. Lesions of the skin, eyes, and mouth are usually the first signs, but an encephalitic or a generalised illness with pneumonia and hepatitis may develop without warning even, occasionally, after 4–5 weeks. The virus grows readily in cell culture, and a positive diagnosis is often possible within 2–3 days. Scrapings from a skin vesicle can be used to provide rapid diagnosis by immunofluorescence. Isolates from specimens collected >36 hours after birth suggest genuine infection rather than transient colonisation. A polymerase chain reaction (PCR) test can be used to detect viral DNA in the CSF of babies with suspected encephalitis. Congenital (transplacental) infection is rare but has been documented. Babies born to women with an active genital infection at delivery are at significant risk of infection, the risk being very much lower (well below 5%) with reactivated infection. Unfortunately, differentiation can be difficult, maternal infection is often silent, and routine cervical culture unhelpful. Caesarean delivery can prevent the baby from becoming infected, but is of limited value if the membranes have been ruptured for more than 6 hours. Only one small trial has yet assessed whether oral aciclovir (400 mg once every 8 hours from 36 weeks gestation) can reduce the need for caesarean delivery or the risk of neonatal infection in mothers becoming infected for the first time during pregnancy. Babies who survive a generalised or encephalitic illness are often disabled. Two trials of sustained oral treatment (90 mg/kg by mouth twice a day) to limit the risk of relapse are currently recruiting in North America (National Library of Medicine Nos. 6132 and 31460).

A mother with recurrent facial cold sores (labial herpes) will not infect her own baby because both will have the same high viral antibody titre. Ward staff with lesions need to apply topical 5% aciclovir cream every 4 hours as soon as the first symptoms develop (2 g quantities are available without prescription), adhere to a careful handwashing routine, and wear a mask until the lesions dry. Staff with an active herpetic whitlow should not have direct hands-on responsibility for babies.

Treatment

The standard dose is 10 mg/kg IV over 1 hour once every 8 hours for 2 weeks, but a 20 mg/kg dose given for 3 weeks improves the outcome where there is disseminated or intracranial neonatal infection. Watch and treat any absolute neutropenia with filgrastim (q.v.). The dosing interval must be at least doubled if there is renal failure. Experts do not recommend oral use in the neonatal period.

Supply and administration

Aciclovir is available in 250 mg vials of freeze dried powder costing £10-10 each. To prepare a solution for IV use reconstitute the 250 mg vial with 10 ml of water or 0.9% sodium chloride, and dilute to 50 ml with 5% dextrose to give an alkaline solution containing 5 mg/ml. Extravasation causes marked tissue damage (fluid pH 11). Do not refrigerate or keep for more than 12 hours after reconstitution. A sugar-free oral syrup containing 40 mg/ml is also available (100 ml for £29). 200 mg tablets cost 24p each.

References

- Kohl S. Neonatal herpes simplex infection. *Clin Perinatol* 1997;**24**:129–50.
- Kimberlin DW, Lin C-Y, Jacobs RF, *et al.* Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infection. *Pediatrics* 2001;**108**:230–8. (See also the linked paper on natural history, pp. 223–9.)
- Royal College of Obstetricians and Gynaecologists. Clinical Green Top Guideline. Genital herpes in pregnancy – management. (See the Good Practice guideline issued in 2002 on the College website: www.rcog.org.uk)
- Toot M, Lokiec F, Bidault R, *et al.* Pharmacokinetics of oral acyclovir in neonates and in infants: a population analysis. *Antimicrob Agents Chemother* 2001;**45**:150–7.
- Wald A. Genital herpes. *Clin Evid* 2003;**9**:1729–40 (and updates). [SR]

See also relevant Cochrane reviews 

Use

Adenosine is the drug of first recourse in the management of neonatal supraventricular tachycardia. It has also been used experimentally to lower pulmonary vascular tone.

Physiology

Supraventricular tachycardia (usually an atrioventricular re-entry tachycardia) presents with a heart rate of 260–300 bpm. It will often stop in response to vagal stimulation. One of the best ways of achieving a safe and powerful vagal stimulus is to wrap the baby in a towel, and then submerge the baby's face in a bowl of icecold water for about 5 seconds. Even a cold face flannel may occasionally suffice. There is no need to obstruct the mouth or nose as submersion will cause reflex apnoea. Always connect the child to an electrocardiograph (ECG) before starting treatment (and try to obtain a permanent *multichannel* record if at all possible). Bradycardia with nodal escape may occur for a few seconds before a normal sinus rhythm returns. This strategy is successful nine times out of ten and can be easily and safely repeated several times. Such a manoeuvre is always worth considering *before* resorting to drug treatment, especially in the neonate, unless the baby is in circulatory shock or there is a convenient IV line already in place.

Pharmacology

Adenosine is a short acting purine nucleoside with a serum half life of about 10 seconds, first marketed commercially in 1992. It has the potential to slow conduction through the atrioventricular node and suppress the automaticity of atrial and Purkinje tissues. It has no negative inotropic effects and does not cause significant systemic hypotension, and can therefore be used safely in children with impaired cardiac function or early postoperative arrhythmia. Transient flushing may occur. There is no evidence that its use is dangerous in pregnancy or lactation (although respiratory side effects may occur in mothers with asthma). It has even been given to the fetus by cordocentesis. There are also some limited animal and human data to suggest that a continuous infusion into the right atrium may, by causing pulmonary vasodilatation, occasionally be of value in babies with persistent pulmonary hypertension.

Adenosine is the drug of choice in the initial management of any supraventricular tachycardia that fails to respond to vagal stimulation. The arrival of this rapidly effective drug has greatly reduced the need for 2 joule/kg shock cardioversion, although this still occasionally remains the treatment of choice for the shocked, collapsed infant. If the problem persists or recurs, other drugs such as propranolol, flecainide, and amiodarone (q.v.) may be needed, but the true diagnosis needs confirmation first. Seek the advice of a paediatric cardiologist, and arrange, if necessary, to fax an electrocardiogram (ECG) trace for assessment. An unsynchronised DC shock remains the only effective treatment for ventricular fibrillation, but this is very rare in infancy, even in babies with congenital heart disease.

Treatment

Arrhythmia: Give 150 micrograms/kg IV (0.15 ml/kg of a dilute solution made up as specified below) as rapidly as possible, followed by a small "chaser" of 0.9% sodium chloride, while collecting at least a one channel ECG paper record for diagnostic purposes. A larger dose (300 micrograms/kg) is sometimes needed. Treatment can be repeated several times, where necessary, because the half life of adenosine is less than half a minute.

Lowering pulmonary vascular tone: Adenosine has occasionally been given as a continuous infusion into a catheter positioned in the right atrium or (preferably) the pulmonary artery, but such an approach is still entirely experimental. Start with a dose of 30 micrograms/kg per minute and double (or even treble) this if there is no response within half an hour. Treatment may need to be continued for 1–5 days.

Supply

2 ml and 10 ml vials are available containing 3 mg/ml of adenosine (costing £4 and £16 each). To obtain a dilute solution for accurate "bolus" use containing 1 mg/ml take 1 ml of this fluid and dilute to 3 ml with the 0.9% sodium chloride. To administer a continuous infusion of 30 micrograms/kg per minute give an hourly infusion of 1.8 mg of adenosine for each kilogram the baby weighs. Check the strength of the ampoule carefully because some hospitals stock non-proprietary ampoules of a different strength. Discard the ampoule once it has been opened. Do not refrigerate.

References

- Sreeram N, Wren C. Supraventricular tachycardia in infants: response to initial treatment. *Arch Dis Child* 1990;**65**:127–9.
 Paul T, Pfammatter J-P. Adenosine: an effective and safe antiarrhythmic drug in pediatrics. *Pediatr Cardiol* 1997;**18**:118–26.
 Patole S, Lee J, Buettner P, et al. Improved oxygenation following adenosine infusion in persistent pulmonary hypertension of the newborn. *Biol Neonate* 1998;**74**:345–50.
 Tanel RE, Rhodes LA. Fetal and neonatal arrhythmias. *Clin Perinatol* 2001;**28**:187–207. (See also pp. 215–20.)
 Paul T, Bertram H, Bökenkamp R, et al. Supraventricular tachycardia in infants, children and adolescents. *Pediatr Drugs* 2002;**2**:171–81.

ADRENALINE = Epinephrine (rINN)

Use

Adrenaline is widely used during cardiopulmonary resuscitation in adults, but there is very little documentary evidence to support its use during neonatal resuscitation. A continuous infusion of adrenaline or noradrenaline (q.v.) is sometimes used to treat septic shock or cardiac dysfunction.

Pharmacology

Adrenaline, first isolated in 1901, is the main chemical transmitter released by the adrenal gland. It has a wide range of α and β receptor effects, like noradrenaline. Metabolism is rapid, and the half life less than 5 minutes. It crosses the placenta. **Low** doses cause systemic and pulmonary vasodilatation, with some increase in heart rate and stroke volume. **High** doses cause intense systemic vasoconstriction; blood pressure rises as a result, but the effect on cardiac output depends on the heart's ability to cope with a rising afterload. Combined support with a corticosteroid may help, at least in the neonatal period. Adrenaline acts as a bronchodilator and respiratory stimulant; it also causes increased wakefulness, reduced appetite, and reduced renal blood flow (partly from juxtaglomerular renin release). Excessive doses cause tachycardia, hypertension, and cardiac arrhythmia. Adrenaline may be of value in the management of ventricular fibrillation, but this is excessively rare in the neonatal period. Isoprenaline (q.v.) is more widely used in the management of heart block and persistent pulmonary hypertension.

When ventricular fibrillation causes circulatory standstill (the commonest reason for "cardiac arrest" in an adult) intracardiac adrenaline should always be tried if cardiac massage on its own seems ineffective. However, when circulatory arrest due to respiratory failure (by far the commonest reason for "cardiac arrest" in infancy) proves unresponsive to immediate artificial respiration and cardiac massage, intracardiac THAM or sodium bicarbonate (q.v.) should be tried first before resorting to IV or intracardiac adrenaline (despite much published advice to the contrary). Adrenaline can also be given directly down an endotracheal tube, but the efficacy of this route remains incompletely established, and the most effective dose is unclear. It is however pointless to give *any* drug during resuscitation until oxygen has been got into the lungs and seldom necessary to give anything once it has, because, once oxygenated blood gets into the coronary artery, the heart will nearly always recover by itself. Few of the babies who *require* drugs during resuscitation survive, and most of those who do are disabled. The only reports to the contrary come from centres where drugs are used so frequently that they must have often been given unnecessarily. Inappropriate resuscitative efforts can deprive death of any dignity.

Treatment

Resuscitation: The dose usually recommended is 10 micrograms/kg (0.1 ml/kg of 1:10,000 solution), but a single dose 10 times as large as that (100 micrograms/kg, or 0.1 ml/kg of a 1:1000 solution) may be equally safe, and occasionally seems to be more effective in the term baby and older child.

Stridor or anaphylaxis: See the monograph on immunisation.

Bronchiolitis: Try 3 ml of a 1:1000 solution through a nebuliser. While length of stay is not reduced by regular use, the short term effect of 1–2 doses can reduce the number of babies judged to need admission.

Cardiac dysfunction: Continuous IV infusions of 100–300 nanograms/kg per minute, made up as described below, can increase output without causing vasoconstriction; higher doses of up to 2 micrograms/kg per minute have occasionally been used for acute hypotension.

Compatibility

It can be added (terminally) to a line containing dobutamine and/or dopamine, doxapram, heparin, midazolam, milrinone, morphine, or standard total parenteral nutrition (but not lipid).

Supply and administration

Stock 1 ml ampoules containing 1 mg of l-adrenaline (1:1000) cost 41p each. Some units also stock 100 microgram/ml (1:10,000) ampoules. To give an infusion of 100 nanograms/kg per minute, place 1.5 mg of adrenaline for each kilogram the baby weighs in a syringe, dilute to 25 ml with 10% dextrose saline, and infuse at 0.1 ml/hour. (Less concentrated solutions of dextrose or dextrose saline can be used.) Protect ampoules from light. Solutions are stable and do not need to be prepared afresh every 24 hours.

References

- Schwab KO, von Stockhausen HB. Plasma catecholamines after endotracheal administration of adrenaline during postnatal resuscitation. *Arch Dis Child* 1994;**70**:F213–17.
- Aronson JK. "Where name and image meet" – the argument for "adrenaline". *BMJ* 2000;**320**:506–9.
- Shore S, Nelson DP, Pearl JM, et al. Usefulness of corticosteroid therapy in decreasing epinephrine requirements in critically ill infants with congenital heart disease. *Am J Cardiol* 2001;**88**:591–4.
- Meates M. Does nebulised adrenaline (epinephrine) reduce admission rate in bronchiolitis? *Arch Dis Child* 2002;**87**:548–50. [SR]
- Patel H, Platt RW, Pেকেles GS, et al. A randomised, controlled trial of the effectiveness of nebulised therapy with ephedrine compared with albuterol and saline in infants hospitalized for acute viral bronchiolitis. *J Pediatr* 2002;**141**:818–24. [RCT]
- Heckmann M, Trotter A, Pohlandt F, et al. Epinephrine treatment of hypotension in very low birthweight infants. *Acta Paediatr* 2002;**91**:566–70. (See also pp. 500–2.)

See also relevant Cochrane reviews



Use

Alteplase is a fibrinolytic drug used to dissolve intravascular thrombi. Streptokinase (q.v.) is a cheaper alternative.

Pharmacology

All fibrinolytic drugs work by converting plasminogen to plasmin, which then degrades fibrin, causing the break-up of intravascular thrombi. Treatment should always be started as soon as possible after any clot has formed. Streptokinase and alteplase both have an established role in the management of myocardial infarction, but controlled trials show that benefit is limited if treatment is delayed for more than 12 hours. Alteplase, a human tissue plasminogen activator first manufactured by a recombinant DNA process in 1983, is a glycoprotein that directly activates the conversion of plasminogen to plasmin. It became commercially available in 1988. When given IV it remains relatively inactive in the circulation until it binds to fibrin, for which it has a high affinity. It is, however, rapidly destroyed by the liver, with a plasma half life of only 5 minutes. As a result, adverse effects (including excess bleeding) are uncommon in adults and usually controlled without difficulty by stopping treatment. There is little experience of use during pregnancy. The high molecular weight makes placental transfer unlikely. There is no evidence of teratogenicity, but placental bleeding is a theoretical possibility. Use during lactation seems unlikely to pose any serious problem.

Numerous uncontrolled reports have appeared of alteplase being used to lyse arterial and intracardiac thrombi in the neonatal period, but it is not clear whether it is any safer or more effective than streptokinase and the drug is considerably more expensive. There is, however, probably rather less risk of an adverse effect, and less theoretical risk of an allergic reaction. Visualise the clot and take advice from a vascular surgeon before starting treatment, remembering that ultrasound review has shown that the great majority of catheter related thrombi never give rise to symptoms. Alteplase use may speed the resolution of infective endocarditis. Bleeding is a risk, especially if the platelet count is below $100 \times 10^9/l$ or the fibrinogen level is allowed to fall below 1 g/l. Intracranial bleeding was a common complication with sustained use in neonates in one recent case series. There is a real risk, therefore, of treatment doing more harm than good. Avoid venepuncture and IM injections during treatment.

Instilling a volume of alteplase (1 mg/ml) slightly greater than the catheter dead space reopened 90% of blocked central venous catheters in one recent study, but only a few of the children were on parenteral nutrition. Alteplase (500 micrograms/kg) has also been instilled experimentally into the ventricles of babies with severe intraventricular bleeding in an attempt to reduce post-haemorrhagic hydrocephalus. Benefit was marginal in the first published study, but significantly better when treatment was started early. It should only be offered within the context of the DRIFT trial being conducted by Professor Whitelaw in Bristol.

Treatment

Give 500 micrograms/kg over 30 minutes. If ultrasound assessment shows inadequate resolution consider a second similar dose followed by a continuous infusion of 200 micrograms/kg per hour.

In the management of myocardial infarction in adults, efficacy can be optimised by giving heparin (q.v.) as well as alteplase, but it is not known whether this is also true in the management of other vascular thrombi. Combined therapy has not been used in most reports of neonatal treatment published to date.

Antidote

Give cryoprecipitate or fresh frozen plasma (q.v.) promptly if signs of a bleeding tendency develop.

Supply and administration

10 mg (5.8 mega unit) vials of powder suitable for reconstitution using 10 ml of water for injection (as provided) cost £135. The resultant solution (containing 1 mg of alteplase per ml) must be used within 24 hours of reconstitution, even if stored at 4°C. To give 200 micrograms/kg per hour, dilute the reconstituted solution with an equal volume of 0.9% sodium chloride and infuse at a rate of 0.4 ml/kg per hour. Do not dilute the reconstituted solution with anything except 0.9% sodium chloride.

References

- Edstrom CS, Christensen RD. Evaluation and treatment of thrombosis in the neonatal intensive care unit. *Clin Perinatol* 2000;**27**:623–41.
- Hartmann J, Hussein A, Trowitzsch E, et al. Treatment of neonatal thrombus formation with recombinant tissue plasminogen activator: six years experience and review of the literature. *Arch Dis Child* 2001;**85**:F18–22. (See also pp. F66–72.)
- Monagle P, Michelsen AD, Bovill E, et al. Antithrombotic therapy in children [Consensus statement]. *Chest* 2001;**119**:344–705.
- Jacobs BR, Haygood M, Hingl J. Recombinant tissue plasminogen activator in the treatment of central venous catheter occlusion in children. *J Pediatr* 2001;**139**:593–6.
- Gupta AA, Leaker M, Andrew M, et al. Safety and outcomes of thrombolysis with tissue plasminogen activator for treatment of intravascular thrombosis in children. *J Pediatr* 2001;**139**:682–8.
- Whitelaw A, Pople I, Cherian S, et al. Phase I trial of prevention of hydrocephalus after intraventricular haemorrhage in newborn infants by drainage, irrigation, and fibrinolytic therapy. *Pediatrics* 2003;**111**:759–65.

AMIKACIN

Use

Amikacin is a relatively expensive "reserve" antibiotic of use against Gram negative bacteria that are resistant to gentamicin (q.v.), as well as all the other commonly used antibiotics. Do not prescribe without first seeking the opinion of one of the hospital's consultant microbiologists.

Pharmacology

Amikacin is a semisynthetic aminoglycoside antibiotic, first developed in 1972. It is of particular use in the treatment of Gram negative bacteria resistant to gentamicin (such as certain *Enterobacter* species). Significant placental transfer occurs and, although the drug has not been documented to cause fetal damage, it would seem wise to monitor blood levels when amikacin is used in pregnancy to minimise the risk of fetal ototoxicity because drug accumulation has been documented in the fetal lung, kidney, and placenta. Only small amounts appear in cerebrospinal fluid or in human milk and absorption from the gut is minimal. The drug, like its parent compound, kanamycin, is largely excreted through the renal glomerulus. The half life is 7–14 hours in babies with a postmenstrual age of less than 30 weeks, and 4–7 hours at a postmenstrual age of 40 weeks (the adult half life being about 2 hours). Nephrotoxicity and cochlear or vestibular damage can occur if trough blood levels in excess of those generally recommended go uncorrected, as with all aminoglycosides. The risk is increased if amikacin is prescribed for more than 10 days, follows treatment with another aminoglycoside, or is given at the same time as a diuretic such as furosemide (q.v.). Amikacin is less toxic to the neonatal kidney than gentamicin or netilmicin (q.v.), however, and also probably less ototoxic. Absorption is said to be somewhat unpredictable after IM administration in very small babies. For a justification of the dose regimen recommended in this book see the monograph on gentamicin. The dosage interval should be increased in patients with renal failure and adjusted in the light of serial serum levels.

Treatment

Intermittent high dose treatment: Start by giving 15 mg/kg IV or IM once every 24 hours. If the trough serum level when the third dose was given exceeded 5 mg/l, increase the dosage interval to 36 hours and check the level again after two more doses have been given.

Conventional twice-daily treatment: Some clinicians still give term babies 10 mg/kg IV or IM once every 12 hours (once every 8 hours in babies over 6 months old). Give a 15 mg/kg loading dose first.

Blood levels

The trough level is usually all that needs to be monitored in babies on intermittent high dose treatment, and this is probably necessary as a *routine* only in babies in possible renal failure or less than 10 days old. Aim for a trough level of less than 8 mg/l (1 mg/l = 1.71 μ mol/l). The 1 hour peak level, when measured, should be 20–30 mg/l. Collect specimens in the same way as for netilmicin.

Supply and administration

2 ml (100 mg) vials containing 50 mg/ml cost £2.40. Material should not be stored after dilution. Do not mix amikacin with any other drug. IV doses do *not* need to be given slowly over 30 minutes.

References

- Prober CG, Yeager AS, Arvin AM. The effect of chronologic age on the serum concentration of amikacin in the sick term and premature infant. *J Pediatr* 1981;**98**:636–40.
- Kenyon CF, Knoppert DC, Lee SK, *et al.* Amikacin pharmacokinetics and suggested dosage modifications for the preterm infant. *Antimicrob Agents Chemother* 1990;**34**:265–8.
- Langhendries JP, Battisti O, Bertrand JM, *et al.* Once a day administration of amikacin in neonates: assessment of nephrotoxicity and ototoxicity. *Dev Pharmacol Ther* 1993;**20**:220–30.
- Giapros VI, Andronikou S, Cholevas VI, *et al.* Renal function in premature infants during aminoglycoside therapy. *Pediatr Nephrol* 1995;**9**:163–6.
- Langhendries JP, Battisti O, Bertand JM, *et al.* Adaptation in neonatology of the once-daily concept of aminoglycoside administration: evaluation of a dosing chart for amikacin in an intensive care unit. *Biol Neonate* 1998;**74**:351–62.
- Labaune JM, Bleyzac N, Maire P, *et al.* Once-a-day individualized amikacin dosing for suspected infection at birth based on population pharmacokinetic models. *Biol Neonate* 2001;**80**:142–7.

Use

Amiodarone is increasingly being used in the management of those fetal cardiac arrhythmias that are not effectively controlled by digitalisation or by flecainide (q.v.). It is also now widely used to control persisting troublesome supraventricular tachycardia in the first year of life. However, use should **always** be initiated and supervised by a paediatric cardiologist because manufacturers have not yet endorsed its use in children. Treatment can usually be discontinued after 9–12 months.

Pharmacology

Amiodarone, a class III antiarrhythmic agent first developed in 1963, is used in the management of certain congenital or postoperative re-entry tachycardias, especially where there is impaired ventricular function. It prolongs the duration of the action potential and slows atrioventricular (AV) nodal conduction. It also increases the atrial, AV nodal, and ventricular refractory periods, facilitating re-entrant rhythm suppression. Blood levels are of no value in optimising treatment or in avoiding toxicity. Combined treatment with oral propranolol (q.v.) may be needed at first, but the propranolol can usually be discontinued after a few months. Flecainide is probably a better first choice for automatic arrhythmias.

Tissue levels greatly exceed plasma levels ($V_D \sim 40\text{--}80$ l/kg). Amiodarone also has an extremely long half life (several weeks), and treatment usually has to be given for several days before a therapeutic response is achieved. IV treatment can be used, when necessary, to speed the achievement of a response as long as the consequent exposure to benzyl alcohol is judged acceptable. Most of the adverse effects associated with amiodarone treatment are reversible once treatment is withdrawn. Skin photosensitivity (controlled by using a sun block cream), skin discolouration, corneal microdeposits (easily seen with a slit lamp), liver disorders (with or without jaundice), pneumonitis, and peripheral neuropathy have all been reported, but such complications have not yet been seen in infancy.

Amiodarone is thought to be hazardous in pregnancy because of its iodine content, and the manufacturer has not endorsed the drug's use in children less than 3 years old. Such a risk may have to be accepted, however, if no other treatment can be found for maternal (or fetal) arrhythmia. For the same reason most texts recommend that patients on long term treatment should have their triiodothyronine, thyroxine, and thyroid stimulating hormone levels monitored for possible hypo- and hyperthyroidism. Such complications have not, however, been reported as yet during treatment in the first year of life. In addition, since breast milk contains a substantial amount of amiodarone, there are important reasons why a mother on treatment who wishes to breastfeed should do so only under close medical supervision. Although absorption is incomplete, experience suggests that the baby can receive, on a weight for weight basis, a dose equivalent to about a third of that taken by the mother.

Interaction with other drugs

Joint medication can prolong the half life of flecainide, digoxin, phenytoin, and warfarin (q.v.). Treatment with these drugs **must** be monitored because the dose may have to be reduced if toxicity is to be avoided.

Treatment

Intravenous: Give 5 mg/kg over 30 minutes IV when a rapid response is essential. A second similar dose can be given if the first is ineffective. Further 5 mg/kg maintenance doses can be given IV every 12 or 24 hours if necessary. Change to oral administration as soon as possible.

Oral: Give 10 mg/kg once a day for 10–14 days. Then reduce this to 7.5 mg/kg once a day unless the arrhythmia persists. If control is not achieved after 5–7 days of low dose treatment, try 15 mg/kg or even 20 mg/kg once a day, followed by half this dose once a day as soon as control has been achieved.

Supply

3 ml ampoules containing 50 mg/ml of amiodarone hydrochloride (and 20 mg/ml of benzyl alcohol) cost £1.50. To give 5 mg/kg of amiodarone IV, place 0.5 ml (25 mg) of amiodarone for each kilogram the baby weighs in a syringe, dilute to 25 ml with 5% dextrose, and give 5 ml of this dilute preparation over 30 minutes. Do not give as a continuous infusion to a child under 3 years old because it can leach the plasticiser out of an IV giving set, and do **not** dilute with sodium chloride. Prepare a fresh solution each time. An oral suspension in syrup containing 20 mg/ml amiodarone with a 14 day shelf life can be prepared on request. It must be protected from light.

References

- Figa FG, Gow RM, Hamilton RM, *et al.* Clinical efficacy and safety of intravenous amiodarone in infants and children. *Am J Cardiol* 1994;**74**:573–7.
 Fenrich AL, Perry JC, Friedman RA. Flecainide and amiodarone: combined therapy for refractory tachyarrhythmias in infancy. *J Am Coll Cardiol* 1995;**25**:1195–8.
 Perry JC, Fenrich AL, Hulse JE, *et al.* Pediatric use of intravenous amiodarone: efficacy and safety in critically ill patients from a multicenter protocol. *J Am Coll Cardiol* 1996;**27**:1246–50.
 Etheridge SP, Craig JE, Compton SJ. Amiodarone is safe and highly effective therapy for supraventricular tachycardia in infants. *Am Heart J* 2001;**141**:105–10. (See also pp. 3–5.)

AMOXICILLIN = Amoxicillin (former BAN)

Use

Amoxicillin has similar properties to ampicillin (q.v.), and there is little to choose between the two antibiotics when given IV to treat infection with *Listeria*, β lactamase negative *Haemophilus*, or *Enterococcus*.

Pharmacology

Amoxicillin is a semisynthetic broad spectrum bactericidal aminopenicillin that is active against a wide range of organisms including *Listeria*, *Haemophilus*, enterococci, streptococci, pneumococci, and many coliform organisms. It is also active against *Salmonella*, *Shigella*, and non-penicillinase-forming strains of *Proteus*. Potency can be further enhanced by also giving clavulanic acid, a compound first isolated from a streptomycete soil fungus in 1977 that has no antibiotic properties of its own but is a potent inhibitor of many β lactamase enzymes. The use of this combination (now marketed as co-amoxiclav) for women in preterm labour cannot be recommended because exposure was associated with a higher incidence of neonatal necrotising enterocolitis in the recent ORACLE trials involving more than 11,000 women.

Amoxicillin crosses the placenta readily but very little appears in human milk. The half life in full term babies is about 4 hours (although there is much unexplained variability), falling to a little over 1 hour in later infancy as renal excretion improves. The way in which the half life falls in the very preterm infant in the first few weeks of life has not yet been studied. The dosage policy recommended here is more than adequate, but designed to achieve high cerebrospinal fluid levels in the face of early subclinical meningitis, and in the knowledge that the drug is very non-toxic.

There is little to choose between ampicillin and amoxicillin when given parenterally, although amoxicillin is said to be more rapidly bactericidal at doses close to the minimum inhibitory concentration. Both antibiotics are well absorbed when taken by mouth, widely distributed in body tissues (including bronchial secretions), and rapidly excreted in the urine. Amoxicillin shows better "bioavailability" when taken by mouth, but this is seldom a consideration during neonatal use. Adverse effects are rare but similar to those seen with ampicillin, although diarrhoea may be slightly less common.

Prophylaxis

Mothers: Although ascending infection may be an occasional cause of spontaneous preterm labour, no antibiotic regimen has yet been shown to delay labour or improve outcome, although metronidazole (q.v.) may occasionally make labour less likely in a few women with heavy genital tract colonisation. See the monograph on ampicillin for a comment on antibiotic use when the membranes rupture before there are any signs of labour and pregnancy has not yet lasted at least 34 weeks.

Children: To prevent bacterial endocarditis in babies with congenital heart disease give 50 mg/kg of amoxicillin IV or IM half an hour before oral or ENT surgery. Clindamycin (q.v.) is a better alternative in babies who have had more than one dose of any of the penicillin class antibiotics in the preceding month. Teicoplanin (q.v.) is more appropriate for urogenital and other invasive procedures.

Treatment

Dose: The neonatal dose when meningitis is suspected is 100 mg/kg IV or IM. In other situations a dose of 50 mg/kg is more than adequate.

Timing: Give one dose every 12 hours in the first week of life, one dose every 8 hours in babies 1–3 weeks old, and one dose every 6 hours in babies 4 or more weeks old. Increase the dosage interval if there is severe renal failure. Treatment should be sustained for 10–14 days in proven septicaemia, for 3 weeks in babies with meningitis, and for 4 weeks in babies with osteitis. Oral medication can sometimes be used to complete a sustained course of treatment.

Supply

Stock 250 mg vials cost 34p. Add 2–4 ml of water for injection to the vial to get a solution containing 100 mg/ml and always use at once after reconstitution. A 100 mg/kg dose contains 0.33 mmol/kg of sodium. A sugar-free oral suspension (25 mg/ml) is available, which costs £1.30 for 100 ml. It can be kept at room temperature after reconstitution, but should be used within 2 weeks.

References

- Ginsburg CM, McCracken GH, Thomas ML, *et al.* Comparative pharmacokinetics of amoxicillin and ampicillin in infants and children. *Pediatrics* 1979;**64**:627–31.
- Huisman-de Boer JJ, van den Anker JN, Vogel M, *et al.* Amoxicillin pharmacokinetics in preterm infants with gestational ages of less than 32 weeks. *Antimicrob Agents Chemother* 1995;**39**:431–4.
- King J, Flenady V. Antibiotics for preterm labour with intact membranes. *The Cochrane Library*. Oxford: Update Software, 1999. [SR]
- Kenyon SL, Taylor DJ, Tarnow-Mordi W, for the ORACLE Collaborative Group. Broad-spectrum antibiotics for spontaneous preterm labour: the ORACLE II randomised trial. *Lancet* 2001;**357**:989–94. [RCT] [See also pp. 979–88 and **358**:502–4.]

See also relevant Cochrane reviews indexed under ampicillin 

Use

Amphotericin B is a valuable but potentially toxic antibiotic used in the treatment of suspected or proven systemic fungal infection. A liposomal formulation should be used if toxicity develops, but routine use is hard to justify, given the cost, since serious toxicity is relatively uncommon in infancy.

Pharmacology

Amphotericin B is a polyene antifungal derived from *Streptomyces nodosum*. It was first isolated in 1953 and has been widely used to treat aspergillosis, candidiasis, coccidioidomycosis, and cryptococcosis. It exerts its action by binding to a sterol moiety on the surface of the organism, causing cell death by increasing cell membrane permeability. The clinical response does not always correlate with the result of in vitro testing. Consider combined treatment with flucytosine (q.v.) when managing systemic fungal infection because amphotericin penetrates the cerebrospinal fluid only poorly. Fluconazole (q.v.) on its own may come to be accepted as the treatment of choice for systemic *Candida albicans* infection.

Amphotericin is a toxic drug with many common adverse effects, including a dose dependent and dose limiting impairment of renal function. Drug elimination is poorly understood, unrelated to renal function, and extremely unpredictable in the neonatal period. Significant drug accumulation is thought to occur in the liver ($V_D \sim 4$ l/kg). Glomerular and tubular damage both occur, and recovery may be incomplete, especially after exposure to a large total dose. Anaemia is common and hypokalaemia, flushing, generalised pain, convulsions, leucopenia, and anaphylaxis may occur. Fever, vomiting, and rigors can occur during or after IV infusion. Over 80% of adults given amphotericin experience renal impairment, but such problems seem less common in infancy. Rapid infusion can cause hyperkalaemia and arrhythmia, while overdose has occasionally caused death. Amphotericin crosses the placenta, but does not seem to be toxic or teratogenic to the fetus, so treatment does not need to be withheld during pregnancy. No information is available on the use of amphotericin during lactation.

Diagnosing fungal infection

Notes on the diagnosis of systemic candidiasis appear in the monograph on fluconazole.

Treatment

Standard formulation: Give 1 mg/kg IV over 4 hours once a day for 7 days, and then 1 mg/kg once every 48 hours. Incremental treatment is inappropriate, and a first "test" dose unnecessary. Halve the dose if signs of toxicity appear. Treatment is traditionally, but empirically, continued for at least 4 weeks.

Liposomal formulation: Give 2 mg/kg IV over 30–60 minutes once a day for 3–4 weeks. Doses of up to 5 mg/kg have been used uneventfully in the management of severe infection.

Supply and administration

Ready-to-use prefilled syringes (which should be stored in the dark and used within 48 hours but do not need to be protected from light during administration) can be dispensed by the pharmacy on request. Do not pass amphotericin through a <1 μm filter, or mix with any other IV drug.

Vials containing 50 mg of dry powder costing £3.70 (which should be stored at 4°C) are also available. Prepare the powder immediately before use by adding 10 ml of sterile water for injection into the vial through a wide bore needle to give a solution containing 5 mg/ml. Shake until the colloidal solution is clear. Then further dilute the drug by adding 1 ml of this colloidal solution to 49 ml of a specially prepared phosphate buffered 5% dextrose to give a solution containing 100 micrograms/ml. Buffered 5% dextrose can be prepared by adding 2 ml of an ampoule containing 0.2 mmol of phosphate per ml to 500 ml of 5% dextrose. Use no other diluent.

50 mg vials of the liposomal preparation (AmBisome®) cost £138. Add 12 ml of sterile water for injection BP to obtain a solution containing 4 mg/ml and shake vigorously until the powder is completely dispersed. Take 20 mg (5 ml) from the vial using the 5 μm filter provided, dilute to 20 ml with 5% dextrose to give a solution containing 1 mg/ml, and infuse the prescribed amount over 30–60 minutes, taking care that the product does not come into contact with **any** product other than 5% dextrose.

References

- Friedlich PS, Steinberg I, Fujitami A, *et al*. Renal tolerance with the use of intralipid-amphotericin B in low-birth-weight neonates. *Am J Perinatol* 1997;14:377–83.
- Scarcella A, Pasquareiello MB, Guigliano B, *et al*. Liposomal amphotericin B treatment for neonatal fungal infections. *Pediatr Infect Dis J* 1998;18:146–8.

AMPICILLIN

Use

Ampicillin is a widely used antibiotic with similar properties to amoxicillin (q.v.).

Pharmacology

Ampicillin is a semisynthetic broad spectrum aminopenicillin that crosses the placenta. A little appears in human milk but it can safely be given to a lactating mother because the baby is known to receive less than 1% of the weight related maternal dose. Maculopapular drug rashes are *not* a sign of serious drug sensitivity, and are relatively rare in the neonatal period. The drug is actively excreted in the urine and, partly as a result of this, the plasma half life falls from about 6 hours to 2 hours during the first 10 days of life. Penetration into the cerebrospinal fluid is moderately good, particularly when the meninges are inflamed.

Ampicillin was, for many years, the most widely used antibiotic for treating infection with *Listeria*, β lactamase negative *Haemophilus*, enterococci, *Shigella*, and non-penicillinase-forming *Proteus* species. It is also effective against streptococci, pneumococci, and many coliform organisms. Ampicillin has frequently been used prophylactically to reduce the risk of infection after abdominal surgery (including caesarean delivery), as has cefoxitin (q.v.). Ampicillin is resistant to acids and moderately well absorbed when given by mouth, but oral medication can alter the normal flora of the bowel (causing diarrhoea). The absorption and bioavailability of ampicillin when taken by mouth does not approach that achieved by amoxicillin. The arrival of ampicillin on the market before amoxicillin, after synthesis in 1961, probably explains the former's continued common use, even though most authorities now consider amoxicillin the better product because it is better absorbed and for a range of other reasons.

Preterm, prelabour rupture of membranes

Prophylactic antibiotic treatment can delay delivery enough to reduce measurably the risk of neonatal problems after birth. Ampicillin is widely used but erythromycin (q.v.) may be a better option.

Care in spontaneous preterm labour

Similar prophylaxis does *not* delay delivery, or improve outcome, when labour threatens to start prematurely before the membranes rupture, but high dose penicillin *during* delivery can reduce the risk of early onset neonatal group B streptococcal infection. Ampicillin is sometimes given instead in the hope that this will prevent coliform sepsis as well but, as such organisms are increasingly resistant to ampicillin, all women going into unexplained spontaneous labour before 35 weeks gestation are best given both IV penicillin and IV gentamicin (q.v.). Even in pregnancies more mature than this there are grounds for giving IV penicillin (q.v.) throughout labour to reduce the risk of group B streptococcal infection if the membranes are known to have ruptured more than 6 hours before labour starts. One recent study has suggested that a combination of these two strategies would result in 80% of all the babies currently dying of *any* bacterial infection of intrapartum origin (i.e. babies developing symptoms within 48 hours of birth) receiving appropriate antibiotic treatment during delivery. It means giving antibiotics to between 40 and 60 women during labour to provide optimum treatment for one baby with bacterial sepsis of intrapartum origin, but many current policies inflict such prophylaxis on many more patients than this.

Neonatal treatment

Dose: The neonatal dose when meningitis is suspected is 100 mg/kg IV or IM. In other situations, a dose of 50 mg/kg is more than adequate.

Timing: Give one dose every 12 hours in the first week of life, one dose every 8 hours in babies 1–3 weeks old, and one dose every 6 hours in babies 4 or more weeks old. Increase the dosage interval if there is severe renal failure. Treatment should be sustained for 10–14 days in proven septicaemia, for 3 weeks in babies with meningitis, and for 4 weeks in osteitis. Oral medication can sometimes be used to complete treatment even though absorption is limited.

Supply

500 mg vials cost 74p. Add 4-6 ml of sterile water for injection to the dry powder to get a solution containing 100 mg/ml and always use at once after reconstitution. A 100 mg/kg dose contains 0.3 mmol/kg of sodium. The oral suspension (25 mg/ml) costs £1.70 per 100 ml. Use within 1 week if kept at room temperature (2 weeks if kept at 4°C). No sugar-free oral suspension is available.

References

- Kaplan JM, McCracken GH, Horton L, *et al*. Pharmacologic studies in neonates given large doses of ampicillin. *J Pediatr* 1974;**84**:571–7.
- Egarter C, Leitch H, Karas H, *et al*. Antibiotic treatment in preterm and premature rupture of membranes and neonatal morbidity: a meta-analysis. *Am J Obstet Gynecol* 1996;**174**:589–97. [SR]
- Schuchat A, Zywicki SS, Dinsmoor MJ, *et al*. Risk factors and opportunities for prevention of early onset neonatal sepsis: a multicenter case control study. *Pediatrics* 2000;**105**:21–6.
- Kenyon SL, Taylor DJ, Tarnow-Mordi W, for the ORACLE Collaborative Group. Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes: the ORACLE I randomised trial. *Lancet* 2001;**357**:979–88. [RCT] (See also **358**:502–4.)

See also relevant Cochrane reviews



Use

L-Arginine is an essential nutritional supplement for patients with inborn errors of metabolism affecting the urea cycle (other than arginase deficiency). In some of these conditions it can also facilitate nitrogen excretion, together with sodium phenylbutyrate and sodium benzoate (q.v.).

Biochemistry

Arginine is a naturally occurring amino acid needed for protein synthesis. Since it is synthesised in the body by the urea cycle it is not, usually, an essential nutrient. Dietary supplementation becomes essential, however, in most patients with inherited urea cycle disorders because the enzyme defect limits arginine production, while dietary protein restriction limits arginine intake. Further supplementation also aids nitrogen excretion in citrullinaemia and argininosuccinic aciduria because excess arginine is metabolised to citrulline and argininosuccinic acid incorporating nitrogen derived from ammonia. As citrulline and argininosuccinic acid can be excreted in the urine, treatment with arginine can lower the plasma ammonia level in both these conditions.

Treatment with arginine needs to be combined with a low protein diet and supervised by a consultant experienced in the management of metabolic disease. Treatment with oral sodium phenylbutyrate and/or sodium benzoate is also usually necessary.

Treatment

Ornithine transcarbamoylase and carbamoyl phosphate synthetase deficiency: Give 25–35 mg/kg of arginine by mouth four times a day to meet the basic need for protein synthesis. Patients with acute hyperammonaemia should be given 200 mg/kg a day IV, and some authorities recommend an initial IV loading dose of 200 mg/kg of arginine given over 90 minutes.

Citrullinaemia and argininosuccinic aciduria: Up to 175 mg/kg of arginine four times a day can be given by mouth to promote nitrogen excretion. During acute hyperammonaemia 600 mg/kg can be given as a loading dose IV over 90 minutes, followed by a continuous infusion of 25 mg/kg per hour.

Monitoring

Vomiting and hypotension have occasionally been reported as a result of treatment with IV arginine. High arginine levels are thought to contribute to the neurological damage seen in arginase deficiency, and it is therefore recommended that plasma arginine levels should be kept at between 50 and 200 µmol/l. Hyperchloraemic acidosis can occur in patients on high dose IV arginine hydrochloride; pH and plasma chloride concentrations should be monitored and bicarbonate given if necessary.

Supply and administration

L-Arginine can be made available (as a free base) in powder form for oral use from SHS International; 100 g costs £7.50. This is a chemical, not a pharmaceutical, product. In the UK, regular supplies can be made available on prescription to patients with urea cycle disorders, as long as these are marked ACBS (Advisory Committee on Borderline Substances). L-Arginine is also available from Special Products Ltd as a sugar-free medicine in 200 ml bottles costing £20 each. Add 185 ml of purified water to the contents of the bottle to obtain 200 ml of a 100 mg/ml liquid that remains stable for 2 months. This can, if necessary, be mixed with milk, fruit juice, or food.

A 100 ml IV infusion pack containing 10 g of L-arginine (as the hydrochloride) is available for £12 from Special Products Ltd as are 10 ml (500 mg/ml) ampoules costing £3.

References

Brusilow SW. Arginine, an indispensable amino acid for patients with inborn errors of urea synthesis. *J Clin Invest* 1984;**74**:2144–8.
 Leonard JV. Disorders of the urea cycle. In: Fernandes J, Saudubray J-M, van den Berghe G, eds. *Inborn metabolic diseases. Diagnosis and treatment, 3rd ed.* Berlin: Springer-Verlag, 2000:214–22.
 Wraith JE. Ornithine carbamoyltransferase deficiency. *Arch Dis Child* 2001;**84**:84–8.
 Brusilow SW, Horwich AL. Urea cycle enzymes. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular bases of inherited disease, 8th ed.* New York: McGraw-Hill, 2001:1909–64.

ASPIRIN (Acetylsalicylic acid)

Use

Aspirin is now seldom given to children of any age because of evidence that use during a viral illness such as influenza or chickenpox may trigger Reye's syndrome (an acute life threatening encephalopathy with fatty liver degeneration). Aspirin is, however, still used in Kawasaki disease, to limit the risk of clot formation after cardiac surgery, and in children with severe rheumatoid arthritis.

Pharmacology

Aspirin has been better studied in pregnancy than almost any other drug. Although large trials looking into the value of low dose aspirin (~75 mg/day) in mothers at risk of pre-eclampsia failed to substantiate the hopes raised by earlier small trials, they have shown that early treatment can reduce the risk of pre-eclampsia and of perinatal death by about 15%. Its use is also remarkably safe. There is, also, some evidence that a combination of aspirin and subcutaneous heparin started shortly after conception reduces the risk of repeated miscarriage in women with phospholipid antibodies. Only small quantities of aspirin appear in breast milk, (~3% of the weight related maternal dose) and *episodic* use during lactation seems harmless. The one published report of breast milk intake causing salicylate intoxication would require the mother to have had a quite implausibly high blood salicylate level. However, because of concern over Reye's syndrome, paracetamol (q.v.) is generally considered a safer analgesic for the lactating mother. Drug elimination is usually rapid, but pathways are saturable, and little is known about the effect on the baby of regular high dose maternal use during lactation.

Kawasaki disease

Kawasaki disease is an acute febrile illness, first described by clinicians in Japan in 1967, which has now been recognised in many parts of the world, sometimes in epidemic form (making an unrecognised infection its likely cause). Most children are under 5 years and, typically, under 2 years old. Features include high fever for at least 5 days, with a variable rash, conjunctivitis, inflammation of the oral mucosa, swollen neck glands, and redness and swelling of the hands and feet with later desquamation. Other common features include abdominal pain, vomiting, diarrhoea, aseptic meningitis, arthritis, and mild liver dysfunction. Mild cases may go unrecognised, but nearly a third of children with overt disease develop serious inflammation of the coronary arteries, sometimes leading to dangerous aneurysm formation, if treatment is not started early. A high platelet count during convalescence further increases the risk of coronary thrombosis and myocardial infarction. However, more than 90% of children treated early respond to a single 2 g/kg IV dose of human immunoglobulin (q.v.) given over 12 hours, and such treatment greatly reduces the risk of secondary complications. Aspirin is also given (see below) both to reduce fever and because of the drug's known antithrombotic (platelet inhibiting) properties. Patients with severe or progressive vasculitis should be referred promptly to a paediatric cardiologist.

Treatment

Early Kawasaki disease: Give 8 mg/kg by mouth four times a day for 2 weeks to control acute symptoms. (A 30 mg/kg dose four times a day is often recommended, but there is no evidence that this higher dose further reduces the risk of cardiac complications.)

Later prophylaxis: Low dose treatment (5 mg/kg once a day by mouth) is usually given for 2 months during convalescence, and such treatment is usually maintained indefinitely when echocardiography shows continued coronary artery involvement. A similar prophylactic dose is also given for 3 months after certain forms of cardiac surgery to minimise the risk of clot formation until endothelial lining cells finally cover all postoperative scar tissue.

Monitoring

Oral absorption can be variable during the acute inflammatory phase of Kawasaki disease. It is wise, therefore, to monitor the serum salicylate level in children who are given high dose treatment, aiming for a serum level of 250 mg/l (1 g/l = 7.2 mmol/l). Levels in excess of 450 mg/l are often toxic, causing nausea, vomiting, sweating, and hyperventilation. Young children may become acidotic; IV sodium bicarbonate will correct this and aid drug elimination by helping to keep urine pH above 7.5.

Supply

To obtain a 5 mg/ml solution for oral use add one 75 mg tablet of dispersible aspirin to 15 ml of water, and use immediately. Tablets cost less than 1p each.

References

- Rai R, Cohen H, Dave M, *et al*. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). *BMJ* 1997;**314**:253–7. [RCT]
- Shingadia D, Shulman ST. New perspectives in the drug treatment of Kawasaki disease. *Pediatr Drugs* 1999;**1**:291–7.
- American Academy of Pediatrics. Kawasaki syndrome. In: Pickering LK, ed. *Red Book: 2003 report of the committee on infectious diseases*, 26th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2003:392–5.
- Kozer E, Nikfar S, Costei A, *et al*. Aspirin consumption during the first trimester of pregnancy and congenital anomalies: a meta-analysis. *Am J Obstet Gynecol* 2002;**187**:1623–30. [SR]

See also relevant Cochrane reviews



Use

Atracurium besylate is a short acting alternative to pancuronium (q.v.) when muscular paralysis is called for, but suxamethonium (q.v.) is the best drug to use when paralysis is necessary for only 3–5 minutes.

Pharmacology

Atracurium, like pancuronium, is a non-depolarising muscle relaxant. It was first developed as an analogue of suxamethonium and patented in 1977. It works by competing with acetylcholine at the neuromuscular junction's receptor site, an effect that can be reversed with anticholinesterases such as neostigmine (q.v.). No significant placental transfer occurs. Atracurium is particularly popular in anaesthetic practice because it has no vagolytic or sympatholytic properties, and is eliminated by non-enzymatic Hofmann degradation at body temperature, independently of liver or kidney function. It is non-cumulative, and effective for only about 20 minutes (30 minutes in older children). Activity is prolonged by the concomitant use of aminoglycosides, and by volatile anaesthetics such as isoflurane. The manufacturers have not yet endorsed the use of atracurium in children less than 1 month old, partly because of concern about possible increased sensitivity, but extensive clinical experience suggests that such caution is unnecessary. Unexpected sustained neuromuscular blockade is not infrequently encountered in neonates after paralysis with vecuronium (q.v.), but this does not seem to occur with atracurium.

One UK neonatal centre reported four serious adverse reactions in late 2000 after giving atracurium while preparing babies for tracheal intubation; three babies became so hypoxic, bradycardic, and unventilatable that they died, but no other unit has yet reported a similar problem. Clearly, staff should never use any muscle relaxant, except under supervision, unless they are confident that they can maintain an effective airway and sustain mask ventilation, even if intubation proves difficult, as emphasised in the commentary on suxamethonium.

Treatment

Single bolus infusion: An injection of 500 micrograms/kg IV provides almost complete muscle relaxation for about 15–35 minutes. Always flush the bolus through into the vein. A smaller dose is often enough to achieve relaxation prior to tracheal intubation.

Continuous infusion: IV infusions of 400 micrograms/kg per hour can provide sustained neuromuscular blockade in babies less than 1 month old. Older patients need 500 micrograms/kg per hour. Babies requiring paralysis should always be sedated as well.

Antidote

Most of the effects of atracurium can be reversed by giving a combination of 10 micrograms/kg of glycopyrronium (or 20 micrograms/kg of atropine (q.v.)), and 50 micrograms/kg of neostigmine, as outlined in the glycopyrronium monograph, although reversal is seldom called for given atracurium's short half life.

Compatibility

When given as a continuous infusion, atracurium can, if necessary, be given (terminally) into a line containing adrenaline, dobutamine, dopamine, fentanyl, heparin, isoprenaline, midazolam, milrinone, or morphine (q.v.).

Supply and administration

2.5 ml and 5 ml ampoules are available containing 10 mg/ml of atracurium besylate (costing £1.90 and £3.40). Multidose vials are available in North America, but they should be avoided in young children because they contain benzyl alcohol. All products need to be stored at 2–8°C. For bolus injection take 0.5 ml from a 10 mg ampoule and dilute to 5 ml with 5% dextrose or dextrose saline to obtain a preparation containing 1 mg/ml (1000 micrograms/ml) for accurate administration. To give a continuous infusion of 500 micrograms/kg per hour, draw 2.5 ml of atracurium besylate for each kilogram the baby weighs from the ampoule into a syringe and dilute to 50 ml with 10% dextrose in 0.18% sodium chloride and infuse at 1 ml/hour. A less concentrated solution of dextrose or dextrose saline can be used if appropriate.

References

Meakin G, Shaw EA, Baker RD, et al. Comparison of atracurium-induced neuromuscular blockade in neonates, infants and children. *Br J Anaesth* 1988;**60**:171–5.
 Kalli I, Meretoja OA. Infusion of atracurium in neonates, infants and children. A study of dose requirements. *Br J Anaesth* 1988;**60**:651–4.
 Piotrowski A. Comparison of atracurium and pancuronium in mechanically ventilated neonates. *Intensive Care Med* 1993;**19**:401–5.
 Martin LD, Bratton SL, O'Rourke PP. Clinical uses and controversies of neuromuscular blocking agents in infants and children. *Crit Care Med* 1999;**27**:1358–68.
 Clarkson A, Choonara I, Martin P. Suspected toxicity of atracurium in the neonate. *Paediatr Anaesth* 2001;**11**:631–2.

ATROPINE

Use

Atropine is now used less routinely prior to surgery, but it is still used during and after surgery to the eye. Ipratropium is a related compound that is used occasionally, by inhalation, as a bronchodilator.

Pharmacology

The medicinal properties of the Solanaceae have been known for many centuries, and pure atropine was first isolated from deadly nightshade root in 1833. The Venetians had called this plant "*herba bella donna*" because the ladies used water distilled from the plant as a cosmetic to beautify their eyes (by dilating the pupil). Linnaeus later gave the plant the Latin botanical name *Atropa belladonna* in recognition of its toxicity and use as a poison (Atropos being the name of one of the Greek fates who could "cut the slender thread of life"). Atropine blocks the muscarinic effects of acetylcholine on the postganglionic autonomic nerve fibres, producing a vagal block that can abolish the sudden bradycardia caused by operative vagal stimulation. The half life in adults is 4 hours, but it is longer in infancy. Use prior to anaesthesia reduces oropharyngeal secretions, but it also reduces the tone of the lower oesophageal sphincter and does nothing, directly, to reduce the risk of laryngospasm. Bronchial secretions become more viscid and less copious; gastrointestinal secretions and motility are reduced.

Atropine is moderately well absorbed by the small intestine ($V_D \sim 3$ l/kg). It crosses the placenta with ease, and has been known to affect the fetal heart rate. Small amounts are thought to appear in breast milk but no neonatal symptoms have ever been reported. It has a role in heart block caused by digoxin poisoning, and in patients with serious reflex (vagal) bradycardia. Atropine eye drops are used to achieve sustained dilatation of the pupil after ocular surgery (as described in the monograph on eye drops) but excess usage can lead to ileus and other problems, especially when the standard 1% drops are used. Its use to make surgery unnecessary in babies with pyloric stenosis merits further evaluation.

Treatment with ipratropium

Giving inhaled ipratropium with, or instead of, salbutamol (q.v.) counteracts the bronchoconstrictor effect of acetylcholine. The usual dose in babies with bronchopulmonary dysplasia is 25 micrograms/kg every 8 hours, but larger doses have been used. Protect the eye from direct exposure to avoid glaucoma. Little is absorbed systemically, making inhalational use safe during pregnancy and lactation.

Treatment with atropine

Oral premedication: Some doubt the need to use *any* drug prior to the induction of anaesthesia in most neonates as long as there is IV access. When a "premed" is judged appropriate, an IM injection can usually be avoided by giving 40 micrograms/kg of atropine by mouth 2 hours before induction as long as gut motility is normal. Glycopyrronium (q.v.) is now a commonly used alternative.

Parenteral premedication: A 10 micrograms/kg IV bolus produces an effect within half a minute that lasts at least 6 hours. A subcutaneous or IM dose will be maximally effective after 30–60 minutes.

Pyloric stenosis: A 10 micrograms/kg dose IV once every 4 hours before feeds can often check the contractile spasm of the pyloric muscle. After 5–7 days, once vomiting has ceased, treatment can be continued by giving twice this dose by mouth once every 4 hours for a further 3 weeks.

Reversing neuromuscular blockade: See the monograph on glycopyrronium.

Digoxin toxicity: Give 25 micrograms/kg IV for atrioventricular (AV) block. Ten times as much is occasionally given.

Eye drops: 0.5% drops given twice a day for 5–7 days maintain dilatation of the pupil after surgery.

Toxicity

Check the dose of atropine carefully; even a moderate overdose will cause tachycardia, flushing, and dilatation of the pupils. A severe overdose will cause respiratory depression, convulsions, and coma requiring barbiturate sedation, ventilatory support for respiratory depression, and steps to control hyperpyrexia. Neostigmine (q.v.) will counteract some of the effects of a severe overdose.

Supply and administration

1 ml 400 microgram ampoules cost 73p each. Dilute 0.1 ml of the ampoule with 0.9 ml of 0.9% saline in a 1 ml syringe to obtain a solution containing 40 micrograms/ml. Nebules of isotonic preservative-free ipratropium bromide (250 micrograms in 1 ml) cost 30p each. Take 0.1 ml for each kilogram the baby weighs and dilute to at least 2 ml with normal saline for use in a nebuliser.

References

- Shorten GD, Bissonnette B, Hartley E, *et al.* It is not necessary to administer more than 10 $\mu\text{g}\cdot\text{kg}^{-1}$ of atropine to older children before succinylcholine. *Can J Anaesth* 1995;**42**:8–11. (See also pp. 1–7.)
Bonhala S, Sparks JW, Musgrove KH, *et al.* Mydriatics slow gastric emptying in preterm infants. *J Pediatr* 2000;**127**:327–30.
Singh UK, Kumar R, Suman S. Successful management of infantile hypertrophic pyloric stenosis with atropine sulfate. *Indian Pediatr* 2001;**38**:1099–105.
Kawahara H, Imura K, Yagi M, *et al.* Motor abnormality in the gastroduodenal junction in patients with infantile hypertrophic pyloric stenosis. *J Pediatr Surg* 2001;**36**:1641–5.

See also the Cochrane review of ipratropium use 

Use

Aztreonam is useful in the management of Gram negative bacterial infections, showing few of the potentially toxic side effects seen when aminoglycosides are prescribed.

Pharmacology

Aztreonam is a narrow spectrum monocyclic β lactam ("monobactam") antibiotic, first introduced in 1985, which is only active against Gram negative aerobic bacteria. It is bactericidal, acting, like penicillin, to inhibit bacterial cell wall synthesis, and does not, like most other β lactam antibiotics, seem to induce β lactamase activity. It is particularly useful in the treatment of infection with *Pseudomonas*, a property it shares with ceftazidime (q.v.), and has sometimes been used in conjunction with an aminoglycoside in the management of infection with *Pseudomonas* because of synergy in vitro. It can also be of value in the management of *Haemophilus influenzae* (including ampicillin resistant and other penicillinase producing strains), *Enterobacter*, *Klebsiella*, *Neisseria*, and *Proteus* species. It is widely distributed in most body fluids, including bile, urine, and bronchial secretions, and diffuses into the cerebrospinal fluid relatively well when the meninges are inflamed. Aztreonam is excreted partially metabolised to an inactive metabolite, SQ-26992, which has a long half life, but is mostly excreted in the urine by a combination of glomerular filtration and tubular secretion. The half life is, in consequence, four times as long at birth as it is in adults (6.5 v 1.7 hours), changing progressively in the first few months of life.

Hypersensitivity reactions can occur, including skin rashes and urticaria. Caution should be observed in giving the drug to patients who are hypersensitive to penicillin, but there seems to be little cross reactivity with sensitivity to other β lactam antibiotics. There is no evidence of teratogenicity, but the manufacturer is not yet prepared to recommend its use during pregnancy (or its use in babies less than 1 week old). Only very small quantities of the drug appear in breast milk, and absorption from the gastrointestinal tract is, in any case, limited.

Treatment

Give 30 mg/kg IV or IM once every 12 hours in the first week of life, every 8 hours in babies 1–3 weeks old, and every 6 hours in babies older than this. The dose used should be halved in babies with renal failure.

Supply

15 ml vials containing 500 mg of aztreonam (costing £4.50) are available from the pharmacy on request. Reconstitute with 9.4 ml of water for injection to obtain a solution containing 50 mg/ml for IV administration and use promptly after reconstitution.

References

- Likitnukul S, McCracken GH, Threlkeld N, *et al.* Pharmacokinetics and plasma bactericidal activity of aztreonam in low-birth-weight infants. *Antimicrob Agents Chemother* 1987;**31**:81–3.
- Umaña MA, Odio CM, Castro E, *et al.* Evaluation of aztreonam and ampicillin vs amikacin and ampicillin for treatment of neonatal bacterial infections. *Pediatr Infect Dis J* 1990;**9**:175–80.
- Cuzzolin L, Fanoe V, Zamreri D, *et al.* Pharmacokinetics and renal tolerance of aztreonam in premature infants. *Antimicrob Agents Chemother* 1991;**35**:1726–8.

Use

BCG vaccine is used to reduce the risk of tuberculosis (TB) in children without evidence of cell mediated immunity to *Mycobacterium tuberculosis* or *M bovis*. TB is a notifiable illness.

Product

BCG vaccine contains a live attenuated strain of *M bovis* (Bacillus Calmette–Guérin). The product was developed after 13 years of research involving 200 serial subcultures. It was first used in France in 1921 and has been widely used in the international control of TB since 1950. TB is still a severe illness, especially in the first year of life, and there is clear evidence that correctly administered neonatal BCG vaccination reduces the risk of overt infection for at least 10 years without obscuring the diagnosis of active infection by intradermal testing. Immunity may wane after that, but revaccination is not recommended. Trials in later childhood have shown that BCG provides about 70% protection in the UK, but those in developing countries have been less encouraging. One recent paper has suggested that early vaccination may be more effective if it is delayed until the baby is 3 months old. BCG vaccination forms part of the World Health Organization's global immunisation programme, but vaccination is not normally offered to children in the USA at present.

Indications

In the UK, BCG vaccination is currently recommended at birth whenever there is a family history of TB (usually interpreted as any history of infection in the last 7 years in a first degree relative, grandparent, uncle, aunt, or household member). It should also be offered to any child born into a family coming from a country where community prevalence exceeds 40:100,000 (see website commentary). Prevalence is currently higher than this in many parts of Asia, India, South America, and sub-Saharan Africa. Prior tuberculin testing is not necessary before administering BCG at birth, but this should always be undertaken in children more than 3 months old. Delay administration until discharge in the preterm baby to maximise the chance of tuberculin test conversion.

Babies being cared for in a family or household where there is a patient with active tuberculosis who is on treatment should be given prophylactic isoniazid (q.v.) for 6 months from birth, and then vaccinated at 6 months unless Mantoux positive. BCG vaccination can be offered to tuberculin negative children at any time in childhood if there is a high risk of exposure due to contact or foreign travel. BCG is offered to all unimmunised tuberculin negative children in the UK when they are 10–14 years old.

Interactions

BCG can be given at the same time (but not into the same arm) as another live, or inactivated, single or combined, vaccine. Leave an interval of at least 4 weeks after giving any other live vaccine (other than the oral polio vaccine) before giving BCG. Try not to give any other vaccine into the arm used when administering BCG for 3 months in order to minimise the risk of lymphadenitis.

Contraindications

Live BCG vaccine should not be given to anyone who is immunodeficient, immunosuppressed, or on high dose corticosteroid treatment (any dose equivalent to more than 1 mg/kg of prednisolone per day, as summarised in the monograph on hydrocortisone). In countries such as the UK, where the prevalence of TB is low, BCG (unlike other live vaccines) should not be given to babies who are HIV positive (or, in the first year of life, to babies whose mothers are HIV positive). Avoid administration in any area of skin actively affected by eczema.

Administration

Babies less than 12 months old should receive 0.05 ml intradermally; older children receive 0.1 ml. Strict attention *must* be paid to the technique used if "conversion" is to be achieved and complications avoided. Injections are normally given into the left upper arm over the point where the deltoid muscle is attached to the humerus, to minimise the risk of scarring. This point is only a little above the middle of the upper arm; vaccination is often inappropriately administered higher than this (over the bulk of the deltoid muscle). Alternatively, BCG can be given into the upper lateral surface of the left thigh to minimise visible scarring, but this site should not be used in neonates. The skin needs to be cleaned first only if it is overtly dirty. If spirit is used it must be allowed to dry. Soap and water are better. Do not use an antiseptic. Use a 1 ml (Mantoux) syringe and a 25 or 26 gauge short bevel needle (with the bevel facing upwards). A separate syringe and needle must be used for each child to avoid any possibility of viral transmission. Stretch the skin between thumb and finger and insert the needle parallel with the surface about 2 mm into the superficial layers of the dermis. The tip should remain visible through the skin and a raised blanched bleb will appear if the injection has been given correctly. If no resistance is encountered the tip is almost certainly too deep. Give the injection slowly and leave the injection site uncovered to facilitate healing.

continued ...

Adverse reactions

A local reaction should be expected within 2–6 weeks. If a discharging ulcer develops this should be covered with a simple dry non-occlusive dressing (occlusive dressings can delay healing). The lesion will heal over 1–2 months and should leave only a small scar if the injection technique has been sound. Lymphadenitis may occur. For the management of anaphylaxis (a very rare occurrence) see the monograph on immunisation (q.v.). Serious local reactions should be referred to the doctor responsible for the local TB contact clinic. If disseminated infection does occur, antitubercular treatment may need to be given (the Danish strain of BCG [1331] being sensitive in vitro to isoniazid and rifampicin). Babies should become tuberculin positive within 6 weeks if vaccination has been effective.

Documentation

The identification of high risk babies is poorly organised in many maternity units at present. Parents need to be approached in the antenatal period so that babies likely to benefit can be identified before birth and agreement reached regarding the need for early vaccination. Early postdelivery discharge and the fragmentation of postnatal care have also damaged the systems that used to exist for delivering and documenting such prophylaxis reliably in many health districts. Neonatal vaccination should always be clearly documented in the child's own personal health booklet, and also in the community child health records. Failure to do this renders later interpretation of the child's tuberculin status very difficult. It is good practice to record the batch number and the expiry date, as well as the date of administration.

Tuberculin

Tuberculin (tuberculin PPD) is a purified protein made from sterile heat treated products of the growth and lysis of *M tuberculosis*. It is used as a proxy test for cellular immunity to TB. In the standard Mantoux test 0.1 ml of tuberculin PPD containing 100 units/ml is injected intradermally into the upper third of the flexor surface of the previously cleaned forearm, producing a wheal about 9 mm in diameter (see "Administration" above). Induration extending 5 mm or more at 72 hours indicates a positive response, and induration extending 15 mm or more at this time denotes a strong reaction. Start with PPD containing 10 units/ml if active TB is suspected. Patients with a strong positive reaction to 10 units of PPD should be investigated for possible active tuberculosis.

Supply

1 ml amber vials of lyophilised live BCG suitable for intradermal use (containing enough material to vaccinate 7–8 children) are manufactured by the Danish Statens Serum Institut (SSI). 2 ml vials are also available. Supplies are distributed within the UK by Farillon for the Department of Health. Vials should be stored at 2–8°C, protected from light, and used within 18 months. Do not allow the associated diluent (in vials labelled "Diluted Sauton SSI") to freeze. Reconstitute the 1 ml vials using 1 ml of this diluent. Do *not* use water for injection. Use a long needle to draw up the diluent and transfer this to the BCG vial without attempting to clean the rubber stopper with any antiseptic, detergent, or alcohol impregnated swab. Invert the vial a few times to resuspend the lyophilisate, but do not shake. Swirl the vial round gently to resuspend the material before drawing up any further dose from the same vial. Discard any material not used within 4 hours.

Supplies of a product designed for percutaneous multiple-puncture administration are still available in some countries (but not in the UK). The two products are very different, and are *not* interchangeable.

Supplies of tuberculin PPD for routine Mantoux testing (in ampoules containing 100 units/ml and costing £2.20) are available from the pharmacy. Other strengths are available on request. Ampoules must be protected from light and stored at 2–8°C. They must not be frozen.

References

- Perinatal prophylaxis of tuberculosis [Editorial]. *Lancet* 1991;**336**:1479–80.
- Ibrahim I, Sapan N, Cavosoglu B. Comparison of BCG vaccination at birth and at the third month of life. *Arch Dis Child* 1992;**67**:80–2.
- Colditz GA, Berkey CS, Mosteller F, *et al.* The efficacy of Bacillus Calmette-Guérin vaccination of newborns and infants in the prevention of tuberculosis: a meta-analysis of the published literature. *Pediatrics* 1995;**96**:29–35. [SR]
- Thilothammal N, Krishnamurthy PV, Runyan DK, *et al.* Does BCG vaccine prevent tuberculous meningitis? *Arch Dis Child* 1996;**74**:144–7.
- UK Health Departments. *Immunisation against infectious disease*. Chapter 32. London: HMSO 1996:219–41.
- Bannon MJ. BCG and tuberculosis. *Arch Dis Child* 1999;**80**:80–3.
- Thayyil-Sudhan S, Kumar A, Singh M, *et al.* Safety and effectiveness of BCG vaccination in preterm babies. *Arch Dis Child* 1999;**81**:F64–66.
- British Thoracic Society. Control and prevention of tuberculosis in the United Kingdom: code of practice 2000. *Thorax* 2000;**55**:887–901.

BETAINE

Use

Betaine is used in the management of inherited metabolic diseases associated with homocystinuria.

Biochemistry

Homocysteine is usually converted in the body either to cystathionine (by cystathionine β synthase) or to methionine (by the B_{12} dependent enzyme methionine synthase). Methionine synthase requires the methyl group donor, methyltetrahydrofolate, itself formed by methylenetetrahydrofolate reductase (MTHFR). Homocystinuria results from congenital cystathionine β synthase deficiency, disorders of cobalamin metabolism or MTHFR deficiency. Betaine (*N,N,N*-trimethylglycine) acts as an alternative methyl group donor, allowing hepatic methyltransferases to convert homocysteine to methionine. Since methionine is less toxic than homocysteine in excess, this can be beneficial in homocystinuria.

Homocystinuria

Classic homocystinuria results from cystathionine β synthase deficiency. Screening programmes are in place for the neonatal detection of this condition in some areas. Other patients present with developmental delay in the first 2 years of life, or later with dislocated lenses, skeletal abnormalities, or thromboembolic disease. Betaine is used in patients who do not respond to pyridoxine (q.v.) and who either cannot comply with, or are inadequately controlled by, a low methionine and low protein diet. Betaine lowers plasma and urine homocysteine concentrations, and usually improves symptoms such as behaviour and seizures. Women with homocystinuria should continue with treatment during pregnancy to minimise the risk of thromboembolic disease and, possibly, the risk of fetal loss.

The other causes of homocystinuria are all rare. Patients usually present with an acute neonatal encephalopathy or later with developmental delay. In defects of cobalamin metabolism homocystinuria may be accompanied by methylmalonic aciduria or megaloblastic anaemia. Betaine is probably the best available treatment for MTHFR deficiency; such patients should also be given 5 mg/day of folic acid. Betaine is also used in other defects of cobalamin metabolism if homocystinuria persists despite pharmacological doses of vitamin B_{12} (q.v.).

Treatment

Start by giving 25 mg/kg four times a day by mouth. This dose is then adjusted by monitoring the plasma homocysteine level, but doses in excess of 35 mg/kg four times a day seldom confer additional benefit.

Monitoring

Plasma methionine concentrations rise during treatment in classic homocystinuria, and monitoring is recommended to ensure that potentially toxic levels ($>800 \mu\text{mol/l}$) do not develop. Clinicians need to be aware that acute cerebral oedema has (very rarely) been reported a few weeks after starting treatment.

Supply

Most patients in the UK have, until recently, been treated with betaine hydrochloride provided by Fluka Chemicals. This company has traditionally charged £12 for 100 g of the crystalline powder, and it has been supplied on the understanding that it is a chemical, not a pharmaceutical, product. A pharmaceutical product is now available from Orphan Europe, who import it from a Food and Drug Administration approved supplier in the USA. It comes with a 1 g (1.7 ml) measuring scoop. The cost of 100 g from this supplier is £140. The powder is usually administered mixed in a drink. A palatable strawberry flavoured medicine is available as a "special" from Special Products Ltd; 100 ml costs £40. Reconstitute the dry powder with 55 ml of purified water to obtain a liquid containing 50 mg/ml; use within 28 days.

References

- Wilken DEL, Wilken B, Dudman NPB, *et al*. Homocystinuria – the effects of betaine in the treatment of patients not responsive to pyridoxine. *N Engl J Med* 1983;**309**:448–53.
- Ogier de Baulny H, Gérard M, Saudubray J-M, *et al*. Remethylation defects: guidelines for clinical diagnosis and treatment. *Eur J Pediatr* 1998;**157**(suppl 2):S77–S83.
- Rosenblatt DS. Disorders of cobalamin and folate metabolism. In: Fernandes J, Saudubray J-M, van den Bergh G, eds. *Inborn metabolic diseases. Diagnosis and treatment, 3rd ed*. Berlin: Springer-Verlag, 2000:284–98.
- Mudd SH, Levy HL, Kraus JP. Disorders of transsulfuration. In: Scriver CR, Beaudet AL, Sly WS, *et al*, eds. *The metabolic and molecular bases of inherited disease, 8th ed*. New York: McGraw-Hill, 2001:2007–56.
- Rosenblatt DS, Fenton WA. Inherited disorders of folate and cobalamin transport and metabolism. In: Scriver CR, Beaudet AL, Sly WS, *et al*, eds. *The metabolic and molecular bases of inherited disease, 8th ed*. New York: McGraw-Hill, 2001:3897–934.

Use

Maternal treatment with betamethasone accelerates surfactant production by the fetal lung, reducing the incidence of neonatal respiratory distress, a property it shares with dexamethasone (q.v.).

Pharmacology

The pharmacology of betamethasone is essentially the same as that of dexamethasone.

Indications for antenatal use

The seminal paper that first identified a strategy for preventing, rather than curing, surfactant deficiency was published more than 30 years ago. The first clue came from the observation that experimental lambs delivered prematurely failed to develop many of the respiratory problems seen in control animals if exposed to corticosteroids before delivery. A randomised placebo controlled trial in more than 1000 mothers from New Zealand (Liggins and Howie, 1972; as cited in all references given below) soon confirmed that betamethasone caused a significant reduction in the incidence of respiratory distress in babies born more than 8 weeks early, and a fall in neonatal mortality in all babies born more than 3 weeks early. A randomised controlled trial investigating if there is also a case for giving betamethasone to mothers 24–48 hours before elective caesarean section at 37 or more weeks gestation (ASTECS) continues to recruit (ring Dr Peter Stutchfield at Glan Clwyd Hospital; 01745 583910). Large trials have failed to confirm early reports suggesting that thyrotrophin releasing hormone, or protirelin (rINN), provide additional benefit.

Despite the clear evidence presented in the 1972 study, it was more than 20 years before antenatal steroid prophylaxis was widely adopted. In the interim, a further 11 trials had been done to replicate the original findings. The Cochrane overview of all the trials in 1989 concluded that antenatal treatment with 24 mg of betamethasone or dexamethasone was associated with a 40–60% reduction in the risk of neonatal respiratory distress, independent of gender. Furthermore, the benefit “appears to apply to babies born at all gestational ages at which respiratory distress syndrome may occur. Whilst the greatest benefits are seen in babies delivered more than 24 hours and less than 7 days after commencement of therapy, babies born before or after the optimum period also appear to benefit. The reduction in the risk of respiratory distress is accompanied by reductions in periventricular haemorrhage and (probably) necrotising enterocolitis. This in turn results in a reduced mortality rate, and in a reduction in the cost and duration of neonatal care”. It is hard to explain why this strategy was ignored for so long. One recent observational study has suggested that, while antenatal treatment with betamethasone may decrease the subsequent risk of periventricular leukomalacia, treatment with dexamethasone does not. There are also concerns that giving more than one course of steroids before delivery could be detrimental. Several trials to assess this are currently recruiting. For details of the UK (TEAMS) trial contact Ursula Bowler in the Perinatal Trials Service in Oxford (01865 227000).

Contraindications

While mothers with hypertension, fetal growth retardation, and rhesus isoimmunisation were excluded from most of the early trials, there is no reason to doubt that treatment benefits their babies too. The 1972 study suggested that steroids could increase the risk of stillbirth in severe pre-eclampsia, but even here the balance of evidence is now clearly in favour of treatment as long as this does not conflict with the need for urgent delivery. The use of betamethasone is also not only safe but beneficial in mothers with prelabour rupture of the membranes who are also offered prophylactic antibiotics. Pulmonary oedema has been seen in mothers taking steroids who are given ritodrine, but this is uncommon if fluid balance is supervised. The use of steroids in mothers with diabetes is less well established, and treatment could affect diabetic control.

Prophylaxis

Give the mother 12 mg of betamethasone IM and repeat this once after 24 hours; 6 mg twice a day by mouth for 2 days may be equally effective. It was long held that treatment should be repeated after 7 days if the baby remained undelivered and was still at risk, but whether this is wise is now in doubt (see above). Even though prophylaxis is of no proven benefit when delivery threatens before 24 weeks gestation, it should not be denied to those at risk of delivering at 23 weeks if they request it. See the website commentary for a review of the relevant merits of betamethasone and dexamethasone use.

Supply

4 mg (1 ml) ampoules of betamethasone sodium phosphate cost 97p each.

References

- Smith GN, Kingdom JC, Penning DH, *et al.* Antenatal corticosteroids: is more better? [Editorial] *Lancet* 2000;**355**:251–2.
- Vermillion ST, Soper DE, Newman RB. Neonatal sepsis and death after multiple courses of antenatal betamethasone therapy. *Am J Obstet Gynecol* 2000;**183**:810–14.
- Vermillion ST, Soper DE, Bland ML, *et al.* Effectiveness of antenatal corticosteroid administration after preterm premature rupture of membranes. *Am J Obstet Gynecol* 2000;**183**:925–9. [RCT]
- National Institutes of Health. Antenatal corticosteroids revisited: repeat courses. *NIH Consens Statement* 2000;**17**:1–10.

See also relevant Cochrane reviews



BIOTIN

Use

Two rare, recessively inherited, metabolic diseases respond to biotin treatment.

Biochemistry

Biotin is one of the water soluble group B vitamins. It is found in a wide range of foods, including eggs, liver, kidneys, and some vegetables. Nutritional deficiency is extremely rare. Biotin is a cofactor for four carboxylases: propionyl-CoA carboxylase, pyruvate carboxylase, 3-methyl-crotonyl-CoA carboxylase, and acetyl-CoA carboxylase. Holocarboxylase synthetase catalyses the covalent attachment of biotin to these proteins. When carboxylases are degraded, biotin is liberated by the action of biotinidase and recycled.

Indications

Deficiency of either holocarboxylase synthetase or biotinidase leads to "multiple carboxylase deficiency". Patients with holocarboxylase synthetase deficiency present as neonates or infants with feeding problems, encephalopathy, metabolic acidosis, and urinary organic acids compatible with the four carboxylase deficiencies. Lymphocytes and fibroblasts can be used to confirm the enzyme deficiency. Mothers of patients are sometimes given 10 mg of biotin a day during any subsequent pregnancy, although it is not clear whether such prenatal treatment is actually necessary. Patients with biotinidase deficiency present in the first 2 years of life, usually with seizures or developmental delay. Rashes and alopecia are common. Biotinidase can be measured in blood. In both conditions there is a good response to pharmacological doses of biotin but, if treatment is delayed, irreversible brain damage may have occurred. Screening programmes are now bringing to light cases of partial biotinidase deficiency; it is unclear whether these children require routine supplementation (although supplementation in itself seems harmless). There have been no convincing reports of benefit from biotin in patients with an isolated carboxylase deficiency.

Treatment

Patients with either holocarboxylase synthetase or biotinidase deficiency usually respond to 5–10 mg of biotin a day (irrespective of weight or age), but doses of up to 100 mg a day may be needed in a few patients. Treatment can usually be given by mouth, but a parenteral preparation is available.

Supply

The need for high dose biotin treatment is so uncommon that there is no regular pharmaceutical preparation on the market. It is possible for hospital pharmacies to obtain 5 mg tablets in packs of 20 and ampoules containing 5 mg/ml intended for IM use through John Bell and Croydon, 54 Wigmore Street, London W1H 0AU (telephone 020 7935 5555) by special request on a named patient basis from Roche Products Limited. A suspension could be prepared on request.

References

- Packman S, Cowan MS, Golbus MS, *et al.* Prenatal treatment of biotin-responsive multiple carboxylase deficiency. *Lancet* 1982;**i**:1435.
- Wastell HJ, Bartlett K, Dale D, *et al.* Biotinidase deficiency: a survey of 10 cases. *Arch Dis Child* 1988;**63**:1244–9.
- McVoy JR, Levy HL, Lawler M, *et al.* Partial biotinidase deficiency: clinical and biochemical features. *J Pediatr* 1990;**116**:78–83.
- Salbert BA, Pellock JM, Wolf B. Characterization of seizures associated with biotinidase deficiency. *Neurology* 1993;**43**:1351–5.
- Suormala T, Fowler B, Duran M, *et al.* Five patients with biotin-responsive defect in holocarboxylase formation. *Pediatr Res* 1997;**41**:667–73.
- Thuy LP, Jurecki E, Nemzer L, *et al.* Prenatal diagnosis of holocarboxylase synthetase deficiency by assay of the enzyme in chorionic villus material followed by prenatal treatment. *Clin Chim Acta* 1999;**284**:59–68.
- Baumgartner ER, Suormala T. Biotin-responsive multiple carboxylase deficiency. In: Fernandes J, Saudubray J-M, van den Bergh G, eds. *Inborn metabolic diseases. Diagnosis and treatment*, 3rd ed. Berlin: Springer-Verlag, 2000:284–98.
- Wolf B. Disorders of biotin metabolism. In: Scriver CR, Beaudet AL, Sly WS, *et al.*, eds. *The metabolic and molecular bases of inherited disease*, 8th ed. New York: McGraw-Hill, 2001:3935–64.
- Moslinger D, Stockler-Ipsiroglu S, Scheibenreiter S, *et al.* Clinical and neuropsychological outcome in 33 patients with biotinidase deficiency ascertained by nationwide newborn screening and family studies in Austria. *Eur J Pediatr* 2001;**160**:277–82 (See also **161**:167–9).

Use

Red cell concentrates, or “plasma reduced cells” (what used to be called “packed cells”) are used to correct serious symptomatic anaemia.

Products

A unit of “whole blood” (haematocrit 35–45%) contains 450 ml of donor blood added to 63 ml of anticoagulant (usually citrate phosphate dextrose with added adenine – CPD-A). Such whole blood is not routinely available. The main blood product now provided is a concentrate of about 230 ml with a haematocrit of 55–75% made by removing most of the plasma from such “whole blood”. These packs contain few functional platelets or granulocytes. The packs can be stored for 5 weeks, but blood less than 7 days old will nearly always be supplied for neonatal use because the potassium and acid load are less, there will be fewer microaggregates, and the oxygen carrying capacity will be greater (the concentration of 2,3-diphosphoglycerate in the red cells falls with time). Most clotting factors are relatively stable in storage, but factor V and factor VIII levels fall by 75% within 10 days. Red cell suspensions in optimal added solutions are sometimes issued for small “top-up” transfusions, but they should **not** be used for large transfusions. They are available in 40–45 ml “minipacks” (1 unit of donor blood usually being used to prepare six such packs).

Blood is not sterile, and viruses can be transmitted during transfusion, although the risk of cell associated virus transmission is now minimised by prior leucodepletion. Donors are screened for hepatitis B, hepatitis C, and HIV-1 antibodies, but it needs to be remembered that antibodies take some time to develop after the onset of infection. Malaria and other bloodborne parasites pose a significant risk in areas where these are endemic. Variant Creutzfeldt–Jakob disease poses what is, at the moment, a theoretical risk. There is a significant risk of neonatal cytomegalovirus (CMV) infection if an ill or preterm baby born to a mother without CMV antibodies is given CMV seropositive blood.

Matching

The laboratory needs to check the recipient’s ABO, and Rh D blood group, and to test for the existence of any irregular antibodies before donor blood is released. Maternal blood is still used for detailed matching in some districts, as long as the mother’s and baby’s ABO groups are compatible, because infants less than 4 months old rarely make antibody to red cells, and any neonatal IgG antibody will usually be derived from the mother. If unmatched group O Rh D negative blood ever needs to be used in an emergency, try to discuss this with a consultant haematologist first.

Blood for intrauterine and exchange transfusion is plasma reduced to a haematocrit of ~70% from CMV negative CPD-A blood. It is also irradiated if the baby is having, or has had, an intrauterine transfusion.

Adverse reactions

Allergic reactions with urticaria are rare in the neonatal period. Symptomatic treatment with 1 mg of chlorphenamine maleate IM (previously known as chlorpheniramine maleate) may be appropriate. Intravascular haemolysis due to ABO incompatibility is rare but potentially fatal. Immediate signs include flushing, dyspnoea, fever, hypotension, and oliguria, with haemoglobinaemia and haemoglobinuria. Stop the transfusion at once, take specimens for laboratory analysis, and watch for renal failure, hyperkalaemia, and a coagulopathy. Rhesus, Kell, Kidd (*Jk^a*), and Duffy (*Fy^a*) antibodies may cause late reticuloendothelial haemolysis with jaundice and anaemia.

Clinical factors

Intravascular blood volume almost always falls significantly during the first few hours of life as plasma leaves the intravascular compartment, but soon stabilises at 80–90 ml/kg with a haematocrit that reflects the extent and direction of any placental transfusion at delivery. Umbilical vein obstruction (as from a tight nuchal cord) can leave a baby hypovolaemic at birth. Capillary haemoglobin and haematocrit values for term babies in the first 3 months of life are shown in Figs 1 and 2 (overleaf). Replicate laboratory haemoglobin estimates from capillary samples can vary by 6 g/l, so apparent changes of 10 g/l may merely reflect sampling error. A capillary haemoglobin may also exceed the venous haemoglobin by 10 g/l. Packed cell volume (PCV) measurements using a centrifuge provide a more rapid and satisfactory way of screening for anaemia in the neonatal period. They are more reproducible, require less blood, and provide an immediate sideways answer.

Venous PCV or “haematocrit” values are shown in Fig 2. Babies of <1.5 kg weight have marginally lower values at birth, and the lower limit of the normal range 4–12 weeks after birth is 5% lower than in term babies (giving a minimum PCV of 20% instead of 25%). Capillary values exceed venous values by at least 2% (and often by 4–8% in the first few days of life). Such differences can be minimised if free flowing blood is collected from a warm, well perfused heel. Microcentrifuge measurement methods always exceed particle counting estimates by 1–2%.

continued ...

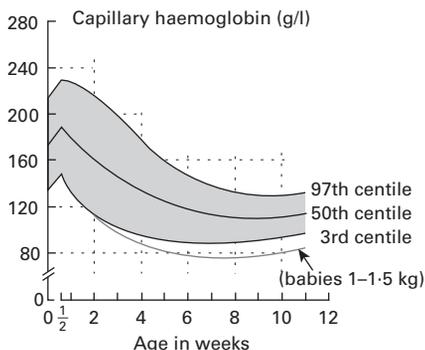


Figure 1

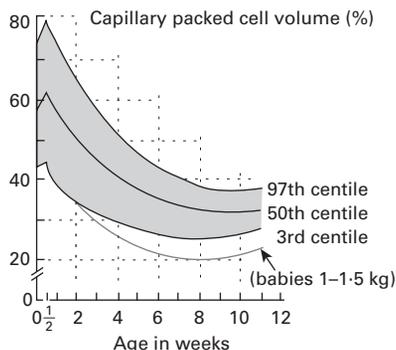


Figure 2

Indications for transfusion

Babies with a venous haematocrit of less than 45% at birth should be transfused after first collecting a generous specimen for diagnostic purposes, especially if they are symptomatic. Watch for the hypovolaemic baby with a normal haematocrit immediately after birth; haematocrit values normally rise in the first 12 hours of life, but in such babies there will be a fall. They may have lost a quarter to a half of all their blood (20–40 ml/kg). Acute loss is best managed by a prompt rapid transfusion, but chronic anaemia at birth is better managed by exchange transfusion. Since it is the fall in plasma volume rather than the fall in haemoglobin that poses the immediate threat after acute blood loss, a plasma expander such as gelatin (q.v.) should be given while waiting for blood to arrive if the patient's condition is critical.

Healthy preterm babies do not need transfusion until their haematocrit falls below 30%, but oxygen dependent babies and babies with other cardiorespiratory problems are not usually allowed to develop an untreated haematocrit below 40%. Babies who have had a lot of blood samples taken run a risk of becoming iron deficient, because four fifths of all the body's iron stores are present as molecular haemoglobin at birth. However, 10 years' research into the neonatal use of erythropoietin (q.v.) has now shown that, if blood is taken from, and given to, the very preterm baby only for carefully predefined reasons, loss from blood sampling can be kept to 0.6 ml/kg per day. Such babies seldom need to be transfused more than once or twice, or exposed to more than one donor, even if they weigh less than 1 kg at birth. Delayed cord clamping further reduces anaemia. It should be remembered that transfusing adults receiving critical care to keep their haemoglobin above 100 g/l actually *increased* mortality.

Administration

Treat anaemia with 25 ml/kg of blood over 1–2 hours. Multiple small transfusions from different donors are wasteful and put the patient at increased risk. It is not usually necessary to calculate a specific replacement volume, or give a "covering" diuretic. Give blood through a fresh giving set with a 170–200 µm filter into a line previously set up and primed with 0.9% sodium chloride. Terminal co-infusion into a line containing dextrose is also safe and does not cause measurable haemolysis as is often feared. It is better to do this than terminate the glucose infusion and precipitate reactive hypoglycaemia when it is not practicable to erect a separate IV line. Check the crossmatch particulars and the patient's name before starting any transfusion, and record the full details in the body of the case notes.

Supply

Crossmatched blood stored at 4°C is available from the local blood bank. Group O rhesus negative, CMV negative, plasma reduced blood is available for emergency use. One unit of blood costs about £55 to dispense. Do not start to use blood more than 4 hours after its removal from the fridge.

Use a minipack containing about 40–45 ml of red cell concentrate where possible, particularly if the patient is likely to require more than one transfusion within the next 7 days, in order to conserve stocks and minimise the risk of exposing the baby to a number of different donors. These cost £15.

References

Alverson DC. The physiological impact of anemia in the neonate. *Clin Perinatol* 1995;**22**:609–25. (See also pp. 657–69.)
 Jankov RP, Roy RND. Minimal haemolysis in blood co-infused with amino acid and dextrose solutions *in vitro*. *J Paediatr Child Health* 1997;**33**:250–2.
 Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999;**340**:409–17. [RCT]
 Goodman AM, Pollack MM, Patel KM, et al. Pediatric red blood cell transfusions increase resource use. *J Pediatr* 2003;**142**:123–7. (See also pp. 95–7.)

Use

Powdered products are now commercially available for modifying the nutritional content of human breast milk when this is used to feed the very preterm baby. However, the benefits have been modest to date because the variability of expressed breast milk makes "tailored" supplementation very difficult.

Immunological factors

Human milk is the ideal food for almost every baby. Although the various artificial products available seem to meet all the key nutritional needs of the term and preterm baby (as outlined in the monograph on milk formulas) feeding with unpasteurised human milk still confers a number of unique, if poorly understood, immunological advantages. Although it is now recommended that all "donor" milk should be pasteurised before use, the mother's own milk can be used without pasteurisation. Cells are damaged by storage, but the immunoprotective constituents remain stable when stored at 0–4°C for 3 days, when frozen at –20°C for 12 months, or when pasteurised at 56°C for 30 minutes.

Composition per 100 ml of human milk after fortification

	Protein (g)	Fat (g)	Carbo-hydrate (g)	Energy (kcal)	Na (mmol)	Ca (mmol)	P (mmol)	Fe (mg)	Zn (mg)	Vit D (µg)
Mature human breast milk										
Widdowson (1977)	1.3	4.2	7.4	70	0.7	0.9	0.5	0.1	0.4	<0.1
Cow & Gate Nutriprem fortifier®										
2 sachets (3 g) per 100 ml	2.5	4.0	9.0	80	1.5	2.1	1.7	0.1	0.7	≥ 5
Mead Johnson Enfamil®										
4 sachets (4 g) per 100 ml	2.0	4.2	9.7	83	1.0	3.1	1.9	0.1	1.6	5.3
Milupa Eoprotin®										
3 scoops (3 g) per 100 ml	1.9	4.2	9.5	81	1.3	1.9	1.3	0.1	0.4	< 0.1
SMA Breast milk fortifier®										
2 sachets (4 g) per 100 ml	2.3	4.4	9.8	85	1.4	3.1	2.0	0.1	0.6	7.6

Nutritional factors

All these products are designed to enhance the nutritional value of human milk. Do not insist on an arbitrary upper limit to oral intake; some preterm babies do very well on a daily intake of 220 ml/kg when 2 or 3 weeks old. The milk of a mother delivering a preterm baby usually has a relatively high protein content in the first 2 weeks of the baby's life; too high a protein intake could, theoretically, be hazardous. Fortification is best not started, therefore, until about 2 weeks after delivery and seldom needs to be continued once breastfeeding is established, or the baby weighs 2 kg.

All the products listed enhance the protein and calorie content of the milk. They also provide minerals to improve bone growth (an important requirement for all babies of less than 30 weeks gestation, as discussed in the monograph on phosphate). Human milk contains relatively little protein, and a plasma urea of less than 1.6 mmol/l may be a sign of suboptimal protein intake. Some preterm babies fed on fortified breast milk may benefit from additional sodium (either as sodium chloride (q.v.) or as some other salt) in the first few weeks of life, until their obligatory renal sodium loss decreases. Babies on Eoprotin may benefit from a further vitamin D supplement (q.v.); so may babies on Enfamil. Only the Nutriprem and Enfamil fortifiers provide added folate. Breastfed babies should get additional vitamin K (q.v.) to prevent late vitamin K deficiency bleeding, unless they are given a total "depot" supply of 1 mg IM shortly after birth. Preterm breastfed babies may need additional iron (q.v.). A few may need zinc (q.v.).

Supply

Enfamil has been widely used in the USA, but it is not commercially available in the UK. The SMA product is not yet on general release, but is available in boxes containing 50 × 2 g sachets to units stocking and using SMA low birth weight formula milk. Eoprotin is supplied in 200 g tins costing £15 each and Nutriprem fortifier in boxes containing 50 × 1.5 g sachets costing £10. The powder is best added just before the baby is fed. Do not use these products to further fortify artificial formula milks.

References

Atkinson SA. Human milk feeding of the micropremie. *Clin Perinatol* 2000;**27**:35–47.
 Greer FR. Vitamin metabolism and requirements of the micropremie. *Clin Perinatol* 2000;**27**:95–118.
 Schanler RJ. The use of human milk for premature infants. *Pediatr Clin North Am* 2001;**48**:207–19.

See also relevant Cochrane reviews



BROMOCRIPTINE

Use

Bromocriptine is used to treat galactorrhoea and cyclical benign breast disease. It was widely used for many years to suppress lactation after childbirth, but its use for this purpose is now discouraged.

Pharmacology

Bromocriptine mesilate is a semisynthetic ergot derivative that acts as a dopamine receptor agonist. It functions, therefore, like the prolactin inhibitory factor in the hypothalamus to stimulate inhibitory dopamine receptors. This results in prolactin release being inhibited and growth hormone release being modestly stimulated (although, paradoxically, it inhibits growth hormone release in acromegaly for reasons that are not entirely clear). The drug is 90% absorbed when given by mouth. It is metabolised by the liver with a half life of 2–3 days, and excreted largely in the bile. It first came into general use for the management of Parkinson's disease in 1974 (although it is now used only in patients who do not respond to levodopa). Bromocriptine is now mainly used in the treatment of prolactinoma (a pituitary tumour) and of hyperprolactinaemia causing amenorrhoea. Fertility and cyclical ovarian function are usually restored within 2 months. Multiple ovulation has not been reported. The drug should be stopped at once if pregnancy occurs (although there are no reported cases of malformation). If hyperprolactinaemia is associated with the presence of a prolactinoma there is a risk of visual field defects developing during pregnancy because of tumour enlargement.

Effect on lactation

Milk formation during late pregnancy occurs under the combined stimulus of oestrogens, prolactin (placental lactogen), and progesterone. Insulin and cortisol may also have a role. Oestrogens antagonise the effects of prolactin on milk secretion and lactation is stimulated when oestrogen levels fall after delivery.

Oestrogens were once used widely to suppress lactation in the puerperium, but they were found to be relatively ineffective and to increase the risk of potentially life threatening thromboembolism. Trials undertaken between 1972 and 1984 then showed bromocriptine to be a more effective alternative. However, most drug trials looked only at the immediate effect of drug treatment and there is some evidence that, although bromocriptine reduces pain, engorgement, and milk production 1 week after delivery more than a breast binder, the situation is reversed 2 weeks later.

More recently, reports have appeared of mothers having seizures, strokes, heart attacks, and sudden severe hypertension while taking bromocriptine to suppress lactation. It is difficult to know whether these problems were caused by the use of bromocriptine. Problems were, however, reported with sufficient frequency for the manufacturers to stop recommending its use to suppress lactation in 1994. Since discomfort is only a transient problem there can seldom be a case for using **any** drug to suppress lactation in most mothers, but its use may still, perhaps, be justified in certain situations. Continued milk production can certainly cause acute anguish to a few mothers who are coping with a stillbirth or early neonatal death. If bromocriptine is used for this purpose, treatment should certainly be stopped at once if the mother experiences any severe headache or visual disturbance.

Cabergoline is a more recently introduced analogue with a longer half life. It seems to be relatively free from the problems associated with the use of bromocriptine to suppress lactation, but that may be, in part, because it has been less widely used. Give a single 1 mg dose by mouth soon after delivery, or four 250 microgram doses at 12 hour intervals.

Treatment

Bromocriptine 2.5 mg twice a day for 2 weeks speeds the suppression of lactation, although milk production almost always increases again for a time after treatment is stopped.

Supply

2.5 mg tablets of bromocriptine (costing 18p each) are available from the pharmacy, as are 500 microgram scored tablets of cabergoline (which cost £3.70 each).

References

- European Multicentre Study Group for Cabergoline in Lactation Inhibition. Single dose cabergoline versus bromocriptine in inhibition of puerperal lactation: randomised, double-blind, multicentre study. *BMJ* 1991;**302**:1367–71. [RCT]
- Morgans D. Bromocriptine and postpartum lactation suppression. *Br J Obstet Gynaecol* 1995;**102**:851–3.
- Webster J. A comparative review of the tolerability profiles of dopamine agonists in the treatment of hyperprolactinaemia and inhibition of lactation. *Drug Safety* 1996;**14**:228–38.
- Dutt S, Wong F, Spurway JH. Fatal myocardial infarction associated with bromocriptine for postpartum lactation suppression. *Aust N Z J Obstet Gynaecol* 1998;**38**:116–19.
- Enkin M, Keirse JNC, Neilson J, et al. *A guide to effective care in pregnancy and childbirth, 3rd ed.* Oxford: Oxford University Press, 2000:467–70. [SR]

Use

Inhaled steroids are useful in the management of croup, but trials in which budesonide was given by inhalation to minimise the complications associated with systemic use to prevent or treat ventilator induced chronic lung disease have not, as yet, shown this strategy to be of more than marginal value.

Pharmacology

Budesonide (patented in 1975) and beclometasone dipropionate (called beclomethasone dipropionate in the USA) are steroids of almost equivalent potency, with strong glucocorticoid and negligible mineralocorticoid activity. Fluticasone propionate is a related compound that is about twice as potent on a weight for weight basis. These agents are widely used topically on the skin or by inhalation into the lung (as in asthma) and have little systemic effect unless high dose treatment is employed. There is no contraindication to their use during pregnancy and lactation; indeed, it is particularly important to keep asthma under stable control during pregnancy. Administration is generally from an aerosol or dry powder inhaler. Budesonide and fluticasone are also available as a suspension suitable for nebulisation, but there is no comparable preparation of beclometasone.

Inhaled steroid use in the preterm baby

Early prophylactic use: Seven trials in which ventilator dependent babies of less than 33 weeks gestation and/or weighing less than 1.5 kg were started on inhaled steroids soon after birth have failed to show that this significantly reduces the risk of the baby still being oxygen dependent at a postmenstrual age of 36 weeks, although there was a trend towards a reduced need for subsequent systemic steroid treatment. Some of these trials have so far been reported only in abstract form. The OSECT trial compared early (<3 days) versus delayed and selective (>15 days), and inhaled budesonide versus systemic dexamethasone treatment, in 570 ventilated babies of less than 30 weeks gestation using a factorial design. Inhalation seemed almost as effective as systemic treatment when started early, and less likely to cause hyperglycaemia or a rise in blood pressure. Symptomatic patent ductus was less common in babies offered early systemic treatment. Fewer babies treated early (systemically or by inhalation) were either dead or still oxygen dependent at 36 weeks (55% v 59%), but the difference was not statistically significant. Because of concern for the long term consequences of postnatal steroid use (as outlined in the monograph on dexamethasone), there is now a consensus that postnatal steroid treatment should be considered only in babies who are ill and ventilator dependent more than 1 week after birth.

Treatment of established disease: A recent overview of trial information suggests that, while aerosolised or nebulised budesonide or beclometasone can be of some help in weaning babies from ventilator support, they are not so effective as systemic steroids. Use may, however, help to reduce or abolish the need for systemic treatment in a few babies with chronic lung disease.

Inhaled steroid use in croup

Croup (the sudden onset of hoarseness, a barking cough, and distressing inspiratory stridor) is common in young children. It is mainly viral in origin, although atopy plays a part in some children. Symptoms often settle almost as fast as they arise. Brief steroid use can reduce admission, and only 1% of those admitted require intubation (once cases of bacterial epiglottitis are recognised for what they are).

Treatment

Ventilator induced chronic lung disease: 200 (or 500) micrograms of inhaled budesonide twice a day may occasionally aid extubation but this is of no other demonstrable long term benefit. The drug has usually been given from a metered dose aerosol inhaler into a rigid "aerochamber" during hand ventilation. Mask administration using a jet nebuliser after extubation can reduce the child's "symptom score" but trials have failed to show any more general clinical benefit. It may be wise to protect the eyes during mask administration. Only a tenth of the administered dose reaches the baby.

Use in croup: Two 1 mg doses of nebulised budesonide 30 minutes apart can reduce the need for hospital admission as effectively as a single 0.6 mg/kg oral (or IM) dose of dexamethasone (q.v.).

Supply

Budesonide is available in 200-dose aerosol inhalers costing £19. Each metered dose delivers 200 micrograms. 2 ml Respules[®], designed for face mask nebulisation, are also available, containing 500 micrograms or 1 mg of budesonide in an offwhite suspension (costing £1.60 or £2.20 each). Fluticasone propionate is also available in 2 ml 500 microgram Nebules[®] for use with a jet nebuliser. These cost £1 each.

References

Halliday H. Clinical trials of postnatal corticosteroids: inhaled and systemic. *Biol Neonate* 1999;**76**(Suppl 1):29–40. [SR]
 Halliday HL, Patterson CC, Halaahakoon WNL, et al. A multicenter, randomised open study of early corticosteroid treatment (OSECT) in preterm infants with respiratory illness: comparison of early and late treatment and of dexamethasone and inhaled budesonide. *Pediatrics* 2001;**107**:232–40. (See also pp. 413–15.) [RCT]
 Osmond M. Croup. *Clin Evid* 2002;**8**:319–29 (and updates). [SR]

See also relevant Cochrane reviews



BUPIVACAINE

Use

Bupivacaine is a widely used local anaesthetic. It takes rather longer than lidocaine (q.v.) to become effective and is much more toxic, but the pain relief it provides lasts four times as long.

Pharmacology

Bupivacaine is an amide local anaesthetic, like lidocaine, which blocks the conduction of nerve impulses by decreasing the nerve membrane's permeability to sodium ions. It was first developed in 1957. Sensory nerves are more readily affected than motor nerves. A small amount (~6%) is excreted unchanged in the urine, but most is metabolised by the liver, the neonatal half life being about 8 hours (at least twice as long as in adults). Tissue levels exceed plasma levels (neonatal steady state $V_D \sim 4$ l/kg). All local anaesthetic drugs are potentially toxic. Most are more toxic to the brain than the heart, causing tremor, restlessness, apnoea, and fits before they cause an arrhythmia, but the reverse is true of bupivacaine. Check the maximum dose for the baby and do not put more than this in the syringe. Have an IV line in place. Accidental injection into a blood vessel can be particularly dangerous, so aspirate before injecting. Epidural bupivacaine (with or without an opioid) provides lumbar block before surgery and during childbirth. Tissue infiltration can provide local sensory block.

Lidocaine becomes fully effective in adults within 2–4 minutes and blocks all local sensation for about 1 hour. Bupivacaine, in contrast, takes up to half an hour to become fully effective after infiltration but then blocks all sensation for 2–8 hours (probably longer than this in the neonate). Anaesthetists have used intraoperative bupivacaine nerve blocks and wound infiltration (in a dose not exceeding 2 mg/kg) to reduce postoperative pain. Epidural bupivacaine has been used during abdominal surgery to avoid the need for morphine in young children, with its attendant risk of respiratory depression. Low epidural blocks have been used, in the same way, during the surgical treatment of inguinal hernia in the preterm baby, obviating the need for a general anaesthetic.

Ropivacaine, a related aminoamide anaesthetic first introduced in 1997, has now started to be used to provide caudal and lumbar epidural block in children. Early experience suggests that it is less toxic and produces less motor block for a given degree of sensory block. The dose normally used in infancy has been 1 ml/kg of a 0.2% solution, or a continuing infusion of 200 micrograms/kg per hour of a 0.1% solution given for not more than 48 hours.

Maternal bupivacaine is systemically absorbed after epidural administration, crosses the placenta readily, and is detectable in the cord blood in a dose that is high enough to interfere transiently with auditory brain stem evoked responses. However, the amount given by the epidural route during childbirth is not high enough to induce any significant neurobehavioural changes. The same probably goes for ropivacaine. The amount excreted in human milk is negligible.

Pain relief

Infiltrative local anaesthesia: Do not exceed a dose of 2 mg/kg (0.8 ml/kg of 0.25% bupivacaine), and do not repeat this dose for 8 hours. Use a pulse oximeter (and/or ECG monitor) to detect any early adverse cardiorespiratory effect. **It is essential to avoid accidental injection into a blood vessel.**

Epidural block: Give up to 0.8 ml/kg of 0.25% bupivacaine slowly into the caudal epidural space over 1–2 minutes, aspirating intermittently to check for the presence of blood or cerebrospinal fluid. This should produce adequate anaesthesia for inguinal or perineal surgery after about 15 minutes.

Toxicity

Apnoea or a change in heart rate is usually the first sign that too much drug has entered the circulation. Immediate ventilatory support can minimise acidosis (which further augments the drug's toxicity). Hypotension may respond to dobutamine (q.v.). Thiopental (q.v.) may be needed if fits interfere with ventilation. Complete recovery can be anticipated unless an arrhythmia develops that is resistant to these measures and to a 10 micrograms/kg bolus of clonidine.

Supply

10 ml ampoules containing 25 mg of plain bupivacaine hydrochloride (i.e. 0.25% bupivacaine) cost 95p. Note that more concentrated ampoules (0.5% and 0.75%), and ampoules containing adrenaline, are also marketed. 10 ml ampoules containing 20 mg of ropivacaine hydrochloride cost £1.40.

References

- de La Coussaye JE, Bassoul B, Brugada J, *et al.* Reversal of electrophysiological and haemodynamic effects induced by high dose bupivacaine by the combination of clonidine and dobutamine in anaesthetised dogs. *Anesth Analg* 1992;**74**:703–11
- Gallagher TM. Regional anaesthesia for surgical treatment of inguinal hernia in preterm babies. *Arch Dis Child* 1993;**69**:623–4.
- Wolf AR, Hughes D. Pain relief for infants undergoing abdominal surgery: comparison of infusions of IV morphine and extra-dural bupivacaine. *Br J Anaesth* 1993;**70**:10–16.
- Ivani G. Ropivacaine: is it time for children? [Editorial] *Paediatr Anaesth* 2002;**12**:383–7.

Use

Caffeine is now preferred to theophylline (q.v.) when managing central or "mixed" apnoea after causes such as subtle seizures, sepsis, hypoglycaemia, or respiratory exhaustion have been excluded. It can speed extubation in the ventilator dependent baby and make trigger ventilation more successful.

Pharmacology

Caffeine citrate is a general stimulant that increases metabolic rate, central chemoreceptor sensitivity to CO₂, and inspiratory drive. It crosses the placenta easily, and an intake in excess of 300 mg per day (equivalent to six cups of tea or three cups of strong coffee) may be associated with some increase in the risk of abortion, stillbirth, and low birth weight (see web commentary). The quantity appearing in the breast milk of mothers on a normal diet of tea, coffee, cola, and chocolate is of no clinical significance, even though the neonatal half life (60–140 hours) is 16 times as long as it is in adults. Caffeine is well absorbed by mouth and IV treatment is seldom necessary. It is mostly excreted, unchanged, in the urine in the first month of life. Clearance rises as a result of increased liver metabolism and, in infants more than 4 months old, approaches the rate found in adults. Tachycardia and agitation are the first signs of toxicity, while a tenfold overdose causes sweating, hypertonia, severe hyperglycaemia, and heart failure. The international CAP trial continues to look into the safety of long term neonatal use.

Managing neonatal apnoea

Medication is no substitute for a sensible nursing strategy. It is better to use pulse oximetry to identify clinically significant hypoxaemia than to look for bradycardia with an electrocardiograph monitor or central apnoea with a transthoracic impedance or other movement monitor. A prone (face down) posture helps, and this, or a left lateral position, reduces the extent to which any reflux of milk from the stomach into the lower oesophagus will trigger episodic hypoxaemia. Tilting the head of the cot up 15° (preferably 30°) helps. Bolus feeding does not cause more apnoea than continuous feeding. Nasal continuous positive airway pressure (or even nasal ventilation) is occasionally required. As serious apnoea is relatively uncommon in babies with a postmenstrual age of more than 33 weeks, treatment can usually be stopped 2 weeks before discharge and any monitor removed 1 week after treatment ceases. Apnoea is a symptom not a diagnosis, and diagnosis needs to precede treatment. Doxapram (q.v.) sometimes helps if problems persist despite high dose caffeine, but stimulants seldom help when obstructive apnoea is due to reflex glottic closure or sleep associated pharyngeal hypotonia, and caffeine can make reflux worse.

Drug equivalence

1 mg of caffeine citrate contains 500 micrograms of caffeine base. To avoid ambiguity, caffeine should always be prescribed by specifying the amount of caffeine *citrate* to be administered.

Treatment

Neonatal use: The normal loading dose is 20 mg/kg of caffeine citrate IV or by mouth, followed by a maintenance dose of 5 mg/kg once every 24 hours. A minority of very preterm babies seem to do better on 10 mg/kg once every 24 hours, with or without a further loading dose. There are anecdotal reports of even higher doses being used on occasion, at least for long enough to facilitate extubation.

Later use: In the few babies with a postmenstrual age of more than 52 weeks who merit treatment it is often necessary to give a maintenance dose of 5 mg/kg four times a day.

Blood levels

The usual target plasma level is 10–20 mg/l, but a few babies may respond better to a level of 25–35 mg/l. Blood level measurement seldom influences management. Signs of toxicity occur only when the level exceeds 50 mg/l (1 mg/l = 5.14 µmol/l). Samples do not need to be collected at any set time.

Supply

Caffeine citrate is only, as yet, available as a licensed commercial preparation in the USA, but it is easily prepared in any hospital pharmacy. Many hospitals now provide 5 ml ampoules of caffeine citrate containing 10 mg/ml for IV use, at an "in house" cost of less than £1, and an inexpensive sugar-free oral preparation with a 1 year shelf life, which should be used within 4 weeks once opened. Do not freeze.

References

- Lee TC, Charles B, Steer P, *et al.* Population pharmacokinetics of intravenous caffeine in neonates with apnea of prematurity. *Clin Pharmacol Ther* 1997;**61**:628–40.
- Jenni OG, van Siebenthal K, Wolf M, *et al.* Effect of nursing in the head elevated tilt position (15°) on the incidence of bradycardic and hypoxemic episodes in preterm infants. *Pediatrics* 1997;**100**:622–5. [RCT]
- Erenberg A, Leff RD, Haack DG, *et al.* Caffeine citrate for the treatment of apnea of prematurity: a double-blind placebo-controlled trial. *Pharmacotherapy* 2000;**20**:644–52. [RCT]
- Comer AM, Perry CM, Figgitt DP. Caffeine citrate. A review of its use in apnoea of prematurity. *Paediatr Drugs* 2001;**3**:61–9.
- De Paoli AG, Davis PG, Leyre B. Nasal continuous airway pressure versus nasal intermittent positive pressure ventilation for preterm neonates: a systematic review and meta-analysis. *Acta Paediatr* 2003;**92**:70–5. [SR]

See also the relevant Cochrane reviews 

CALCIUM GLUCONATE

Use

Calcium gluconate is used orally or IV to control symptomatic neonatal hypocalcaemia, but IM magnesium sulphate (q.v.) may be preferable in babies presenting 4–10 days after birth.

Pharmacology

Calcium increases myocardial contractility and ventricular excitability and is occasionally useful in adults with profound cardiovascular collapse. It can also be used to control cardiac hyperexcitability in severe neonatal hyperkalaemia (as outlined in the monograph on the polystyrene sulphonate resins). The use of a regular 2 g daily calcium supplement in the second half of pregnancy is of some value in reducing the risk of maternal hypertension and pre-eclampsia in high risk women. Calcium is of no value during neonatal cardiopulmonary resuscitation.

Some degree of hypocalcaemia is common in the first 2 days of life, with apathy and hypotonia, especially if there is intrapartum asphyxia or respiratory distress. Late hypocalcaemia on the other hand is usually associated with increased tone, jitteriness, and multifocal seizures 4–10 days after birth in an otherwise well child. Seizures are usually associated with a serum calcium of less than 1.7 mmol/l and more specifically an ionised calcium of less than 0.64 mmol/l. Hypomagnesaemia is also often present (< 0.68 mmol/l). Most such babies have a corrected QT interval of > 0.2 seconds on electrocardiography.

There is no evidence that hypocalcaemia causes permanent neurological damage, and little evidence that an asymptomatic baby with transient hypocalcaemia requires any treatment. Calcium gluconate is probably the treatment of choice for early symptomatic hypocalcaemia, but extravasation can cause severe permanent tissue damage with IV administration, and has even made partial limb amputation necessary on occasion. IM magnesium sulphate (q.v.) may be preferable in the first line management of transient late neonatal hypocalcaemia. Calcium gluconate can also be given orally, but calcium glubionate and lactobionate (Calcium-Sandoz) is a cheaper formulation for sustained oral use. Phenobarbital is effective in controlling seizures but should not be allowed to mask symptoms in the rare baby in whom hypocalcaemia does not resolve within 48 hours. Look for evidence of parathyroid disturbance in mother and/or baby if problems persist.

Treatment

Urgent IV correction: Give 2 ml/kg (0.46 mmol/kg) of 10% calcium gluconate slowly IV over 5–10 minutes. This is more than the dose recommended in most British texts but conforms to practice in North America. Avoid intra-arterial administration. Watch for extravasation and arrhythmia. Never add calcium to any solution containing bicarbonate, sulphate, or phosphate, and never give calcium gluconate IM.

Maintenance treatment: A further 2.5 ml/kg given continuously (or in divided doses) IV over 24 hours may be necessary for 1–2 days because of the short half life of bolus infusions, but the danger of extravasation usually makes oral maintenance therapy with approximately four times this dose (4 ml/kg of the oral Calcium-Sandoz syrup per day) preferable while investigations continue into the cause of any persisting abnormality. (This is enough to double the calcium intake provided by most artificial infant milks.)

Tissue extravasation

A strategy for the early treatment of tissue extravasation due to IV administration is described in the monograph on hyaluronidase (q.v.).

Supply

One 10 ml ampoule of 10% calcium gluconate contains 1 g of calcium gluconate (or 89 mg of calcium) and costs 57p. One ml of this stock preparation, designed primarily for IV use, contains 0.22 mmol (0.46 mEq) of calcium. The product should not be used to supplement the calcium content of parenteral nutrition because of its high aluminium content. An oral syrup (Calcium-Sandoz) containing calcium glubionate and calcium lactobionate in sucrose (containing 22 mg [0.54 mmol] of calcium per ml) is available from the pharmacy on request (cost £1.20 for 100 ml).

References

- Pitkin RM. Endocrine regulation of calcium homeostasis during pregnancy. *Clin Perinatol* 1983;**10**:575–92.
Mimouni F, Tsang RC. Neonatal hypocalcaemia: to treat or not to treat? [Review] *J Am Coll Nutr* 1994;**13**:408–15.
Porcelli PJ, Oh W. Effects of single dose calcium gluconate infusion in hypocalcaemic preterm infants. *J Perinatol* 1995;**12**:18–21.

See also relevant Cochrane reviews 

Use

Captopril is of value in the management of babies with congestive cardiac failure. It is also used to control hypertension in older children, but IV labetalol followed by oral nifedipine (q.v.) offers a more secure and reliable strategy for controlling serious hypertension in infancy.

Blood pressure

The way systolic pressure normally varies with postmenstrual age in the first year of life is summarised in the monograph on hydralazine.

Pharmacology

A range of drugs used to treat heart failure and hypertension work by inhibiting the angiotensin converting enzyme (ACE) responsible for converting angiotensin I to the potent vasoconstrictor angiotensin II. These drugs are contraindicated in renovascular disease, and are fetotoxic in pregnancy, but breastfeeding is not contraindicated because the baby gets only about 0-1% of the maternal dose (on a weight for weight basis). Hyperkalaemia is a hazard in patients on potassium sparing diuretics (like spironolactone (q.v.)), or on potassium supplements. The half life of captopril is only 1-2 hours, but the clinical effect persists much longer than this, possibly because of reconversion of inactive metabolites back to active drug. The half life of enalaprilat is 1-2 days. Because the neonatal response to treatment with an ACE inhibitor is very variable, and some babies become profoundly hypotensive with even a small dose, it is essential to give a first small test dose and then increase the dose cautiously. This seems particularly true in babies under 1 month old. Adverse effects (including apnoea, seizures, and renal failure, as well as severe unpredictable hypotension) have been unacceptably common when these drugs were used to control hypertension in the first month of life. What is more worrying, such episodes have sometimes occurred unpredictably in small babies on maintenance treatment. ACE inhibitors can, however, be of help in infants with chronic congestive failure by decreasing the afterload on the heart, although babies with a left-to-right shunt seldom seem to benefit.

Treatment

Neonatal use: Start by giving 10 micrograms/kg of captopril by mouth once every 8 hours and monitor blood pressure carefully. The dose can then be increased progressively, as necessary, to no more than 100 micrograms/kg once every 8 hours.

Older children: Start by giving a 100 micrograms/kg test dose and monitor blood pressure every 15 minutes for at least 2 hours. Start treatment by giving this dose once every 8 hours, and increase the dose cautiously to no more than 2 mg/kg per dose.

Use of enalapril

Enalapril maleate is an alternative oral prodrug that is hydrolysed in the liver to the even more potent ACE inhibitor enalaprilat (enalaprilat itself being available as an IV preparation in North America, but not in the UK). The oral bioavailability of enalapril is ~60% in adults, but variably less than this in neonates. The neonatal response is very variable, as is the duration of action. As a result, the starting dose in neonates should be 10 micrograms/kg once a day. A starting dose of 100 micrograms/kg is probably safe in older children, and oral doses as high as 1 mg/kg once a day are occasionally used later in the first year of life. The dose should be titrated up slowly as required, watching for possible signs of early renal failure. The drug's main advantage over captopril is the longer half life and the availability of an IV formulation. The manufacturers have not endorsed the use of this drug in children.

Supply and administration

Captopril and enalapril both come in tablet form (and are stable only when so formulated). Various strengths are available costing between 13p and 45p each. The tablets dissolve easily in water so a 25 mg tablet dissolved in 25 ml of water gives a 1 mg/ml solution that is stable for 24 hours. A solution of captopril for oral use can also be obtained by the pharmacy from Martindale on request. The North American IV preparation of enalaprilat contains benzyl alcohol.

References

- Tack ED, Perlman JM. Renal failure in sick hypertensive premature infants receiving captopril therapy. *J Pediatr* 1988;**112**:805-10.
- O'Dea RF, Mirkin BL, Alward CT, *et al.* Treatment of neonatal hypertension with captopril. *J Pediatr* 1988;**113**:403-6.
- Perlman JM, Volpe JJ. Neurologic complications of captopril treatment of neonatal hypertension. *Pediatrics* 1989;**83**:47-52.
- Hanssens M, Keirse MJ, Vankelecom F, *et al.* Fetal and neonatal effects of treatment with angiotensin-converting enzyme inhibitors in pregnancy. *Obstet Gynecol* 1991;**78**:128-35. [SR]
- Leversha AM, Wilson NJ, Clarkson PM, *et al.* Efficacy and dosage of enalapril in congenital and acquired heart disease. *Arch Dis Child* 1994;**70**:35-9.
- Bult Y, van den Anker J. Hypertension in a preterm infant treated with enalapril. *J Pediatr Pharm Pract* 1997;**2**:229-31.

CARBAMAZEPINE

Use

Carbamazepine has been used in the management of generalised tonic clonic (grand mal) and partial (focal) epilepsy since 1963. It is a valuable (and still underused) firstline drug in the sustained, long term control of epilepsy in infancy and later childhood. It can be given only by mouth or per rectum.

Pharmacology

Carbamazepine is well but slowly absorbed from the digestive tract, and extensively metabolised in the liver before being excreted in the urine together with one of its primary active metabolites, carbamazepine-10,11-epoxide. Peak absorption is delayed when the drug is given as a tablet rather than as a liquid or chewtab. The amount offered should be increased by 25% when suppositories are used because of incomplete absorption. Carbamazepine crosses the blood-brain barrier and the placenta, and dysmorphic features develop in some babies exposed to the drug during pregnancy; more importantly, its use is associated with a 1% risk of spina bifida. A folic acid supplement (4 mg daily) is therefore recommended prior to conception and for the first 12 weeks after conception. Its use during pregnancy and lactation is further discussed in a website entry linked to the monograph on valproate (q.v.). The babies of mothers taking carbamazepine at delivery are sometimes hypoprothrombopenic, but this bleeding tendency is corrected by giving the baby 100 micrograms/kg of IM vitamin K (q.v.) at birth. Small amounts of the drug appear in breast milk but maternal treatment is not a contraindication to breastfeeding because the baby will receive only 5% of the maternal dose when intake is calculated on a mg/kg basis. Drug clearance is low at birth (half life 24 hours), but higher in infancy (3–15 hours) than in adult life. The volume of distribution in neonates is 1.5 l/kg.

Carbamazepine should always be introduced gradually. It should be avoided in children with cardiac conduction defects, and used with caution in children with a history of cardiac, hepatic, or renal disease. Its use can exacerbate myoclonic and typical absence seizures. Side effects are rare but include leucopenia and dystonia. An overdose can cause drowsiness, respiratory depression, and fits. Babies may have nausea, vomiting, urinary retention, tachycardia, and dilated pupils. One recent small study found carbamazepine to be useful in controlling the fits that occur in neonatal encephalopathy, as long as an introductory 10 mg/kg oral loading dose is given. This strategy probably deserves further study.

Drug interactions

Concurrent treatment with erythromycin, isoniazid, or valproate (q.v.) causes a rise in the serum level of carbamazepine. The use of two anticonvulsants always increases the risk of drug toxicity.

Treatment

Experience is limited. Give 5 mg/kg every 12 hours. A larger dose may be necessary in babies over 2 weeks old (maximum intake 15 mg/kg every 12 hours), but larger doses should be introduced slowly. Where oral treatment is not possible it may sometimes be appropriate to give a similar dose of the oral suspension into the rectum (although the effectiveness of such an approach may sometimes be undermined by the laxative effect that this can have).

Blood levels

The optimum anticonvulsant plasma concentration is 4–12 mg/l (1 mg/l = 4.23 µmol/l). Levels can be measured in 50 µl of plasma (or about 150 µl of heparinised whole blood). Drug levels can take a week or more to stabilise. Samples are best collected shortly before treatment is due. Levels above 30 mg/l cause severe toxicity.

Supply

A liquid, caramel flavoured, sugar-free suspension containing 20 mg/ml is available at a cost of £2.30 per 100 ml. It also contains 25 mg/ml of propylene glycol. This formulation remains stable for up to 2 weeks after dilution with an equal volume of tragacanth mucilage BPC 1973 to give a suspension containing 10 mg/ml.

References

- Morselli PL, Franco-Morselli R, Bossi L. Clinical pharmacokinetics in newborns and infants: age related differences and therapeutic implications. *Clin Pharmacokinet* 1980;**5**:485–527. (See also p. 507.)
- MacKintosh DA, Baird-Lampert J, Buchanan N. Is carbamazepine an alternative maintenance therapy for neonatal seizures? *Dev Pharmacol Ther* 1987;**10**:100–6.
- Korinthenberg R, Haug C, Hannak D. The metabolism of carbamazepine to CBZ-10,11-epoxide in children from the newborn age to adolescence. *Neuropediatrics* 1994;**25**:214–16.
- Orney A, Cohen E. Outcome of children born to epileptic mothers treated with carbamazepine during pregnancy. *Arch Dis Child* 1996;**75**:517–20.
- Singh B, Singh P, al Hfize I, et al. Treatment of neonatal seizures with carbamazepine. *J Child Neurol* 1996;**11**:378–82.
- Diav-Citrin O, Shechtman S, Arnon J, et al. Is carbamazepine teratogenic? A prospective controlled study of 210 pregnancies. *Neurology* 2001;**57**:321–3.

Use

L-carnitine is used in the management of a range of rare genetic conditions associated with carnitine deficiency.

Nutritional factors

Carnitine (3-hydroxy, 4-*N*-trimethylaminobutyric acid) is a small water soluble molecule. It is essential for the entry of long chain fatty acids into the mitochondria, where they are oxidised. Most of the body's carnitine is found in skeletal and cardiac muscle. Carnitine can be synthesised in the body from lysine and methionine, although synthetic pathways are relatively immature at birth, but most is usually provided by dietary red meat and dairy produce. Human milk and whey based formula milks all contain L-carnitine, but soya based preparations seldom do, making primary nutritional deficiency a possibility. Dialysis and defects of renal tubular reabsorption (Fanconi syndrome) can cause secondary dietary deficiency.

Pharmacology

Primary systemic carnitine transporter deficiency is an extremely rare condition resulting from a defect in the uptake of carnitine across cell membranes. It usually presents with hypoglycaemia, cardiomyopathy, or myopathy, and is generally associated with a total plasma carnitine level of less than 10 µmol/l. It is diagnosed on the basis of carnitine uptake by fibroblasts *in vitro*.

Secondary systemic carnitine deficiency occurs in fatty acid oxidation defects and organic acidaemias. In these conditions carnitine binds to accumulating intermediate metabolites and is excreted with them in the urine. The commonest fatty acid oxidation defect is medium chain acyl-CoA dehydrogenase (MCAD) deficiency, which presents with hypoglycaemic encephalopathy, sometimes in the neonatal period. Other fatty acid oxidation defects present similarly, or with cardiac or skeletal myopathy. Organic acidaemias usually present with encephalopathy, often within a few days of birth. In all these conditions treatment should be managed under the guidance of a consultant experienced in the management of metabolic disease. All are recessively inherited.

Carnitine is of proven value in primary carnitine deficiency. There are anecdotal reports of benefit in conditions associated with secondary carnitine deficiency, but objective evidence is still lacking. Carnitine is widely used in organic acidaemias (such as isovaleric, methylmalonic, and propionic acidaemia and glutaryl-CoA dehydrogenase deficiency). Its use in fatty acid oxidation defects is more controversial. Reports of supplementation in patients on dialysis, on valproate (q.v.) or with Fanconi syndrome have suggested only variable or equivocal benefit. Treatment should be with the naturally occurring L-isomer and not the racemic (DL) mixture. The main dose related adverse effects are nausea, vomiting, abdominal cramp, diarrhoea, and a fish-like smell. Women requiring carnitine supplementation should not stop treatment during pregnancy or lactation. Controlled trials have found no evidence that routine supplements are of any benefit to orally or parenterally fed preterm babies.

Treatment

Urgent IV treatment: Give 100 mg/kg (5 ml of a solution made up as described below) as a slow loading dose over 5–10 minutes, followed by a continuous infusion of 4 mg/kg per hour (0.2 ml/kg per hour of the same solution) during acute metabolic decompensation.

Oral treatment: The usual dose is 25 mg/kg four times a day by mouth.

Supply and administration

An oral preparation in sucrose, dispensed as a 30% paediatric solution (containing 300 mg/ml of L-carnitine), is available commercially costing £1.10 per ml. It can be mixed with a flavoured drink to make it more palatable. For IV use, 5 ml ampoules containing 1 g of L-carnitine, costing £12 each, are obtainable on request; to give 100 mg/kg take 1 ml of this preparation for each kilogram that the baby weighs, dilute to 10 ml with 0.9% sodium chloride, and infuse 5 ml as described above. The product is stable at room temperature for 24 hours after reconstitution in this way.

References

- Walter JH. L-carnitine. *Arch Dis Child* 1996;**74**:475–8.
- Scaglia F, Longo N. Primary and secondary alterations of neonatal carnitine metabolism. *Semin Perinatol* 1999;**23**:152–61.
- Stanley CA. Disorders of fatty acid oxidation. In: Fernandes J, Saudubray J-M, van den Berghe G, eds. *Inborn metabolic diseases. Diagnosis and treatment*, 3rd ed. Berlin: Springer-Verlag, 2000:140–50.
- Roe CR, Ding J. Mitochondrial fatty acid oxidation disorders. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular bases of inherited disease*, 8th ed. New York: McGraw-Hill, 2001:2297–326.
- Whitfield J, Smith T, Solluhub H, et al. Clinical effects of L-carnitine supplementation on apnea and growth in very low birth weight infants. *Pediatrics* 2003;**111**:477–82. [RCT]

See also relevant Cochrane reviews 

CEFALEXIN = Cephalexin (USAN and former BAN)

Use

Cefalexin is one of the few cephalosporin antibiotics that can be given by mouth. It should be used in the neonatal period only when the sensitivity of the organism under treatment is known. Cefuroxime (q.v.) is a closely related antibiotic with slightly different sensitivities that is suitable for IV or IM use.

History

Stimulated by the discovery of penicillin, many other moulds were soon studied to see if they had antimicrobial properties. This soon led Brotzu to discover *Cephalosporium acremonium* in 1948, in a sewage outlet in Sardinia, extracts of which were soon shown to be active against a range of Gram negative, as well as Gram positive, bacteria. However it took 12 years of hard work before the team working with Florey in Oxford had a product (called cephalosporin C, because it had been isolated as a pure crystalline sodium salt) ready for clinical use. Its structure was similar to that of penicillin, but it was *not* destroyed by β lactamase producing bacteria. Plans to market cephalosporin C were thwarted when Beechams brought methicillin onto the market in 1960, but a wide range of semisynthetic analogues were developed over the next 20 years. Cefalexin was one of the first in 1967. Various "second generation" products, including cefoxitin and cefuroxime (q.v.) with a wider spectrum of antibiotic activity, arrived 5 years later, and a third generation of very broad spectrum cephalosporins, including cefotaxime, ceftazidime, and ceftriaxone (q.v.), followed between 1976 and 1979.

Pharmacology

Cefalexin is a first generation cephalosporin that is reasonably active against nearly all Gram positive cocci (including group B streptococci) and most Gram negative cocci other than enterococci. Gram positive rods are relatively resistant. Although the drug is relatively resistant to staphylococcal β lactamase, it has no useful activity against methicillin resistant strains. It should not be used for infections in which *Haemophilus influenzae* is, or is likely to be, implicated, or used as an alternative to penicillin for syphilis. Although most *Bacteroides* species are susceptible to cefalexin, this is not true of *B fragilis*. Cefalexin has no useful activity against *Listeria*, *Citrobacter*, and *Enterobacter*, or against *Serratia* and *Pseudomonas* species, and it penetrates cerebrospinal fluid only poorly.

Cefalexin, unlike most cephalosporins, is acid resistant and well absorbed when taken by mouth, although absorption is delayed and incomplete when the drug is taken on a full stomach. The dose recommended here takes this into account. Oral treatment usually has only a modest effect on the balance of other bacteria in the gut. Cefalexin is actively excreted by the kidney, the plasma half life falling from 5 hours at birth to about 2.5 hours at 4 weeks. Babies more than 1 year old clear cefuroxime from their plasma almost as fast as adults (half life = 0.9 hours). Dosage intervals should be extended in babies with severe renal failure. Problems associated with treatment are uncommon but are the same as for all cephalosporins, as discussed in the monograph on ceftazidime. Only modest amounts cross the placenta and there is no evidence of teratogenicity. The baby ingests less than 1% of the weight related maternal dose when the mother takes this drug while breastfeeding.

Treatment

Give 25 mg/kg by mouth once every 12 hours in the first week of life, every 8 hours in babies 1–3 weeks old, and every 6 hours in babies older than this. The dosage interval should be increased in babies with renal failure.

Supply

Cefalexin is available as a 25 mg/ml oral suspension. Reconstitute the granules or powder with water and use the resultant suspension within 10 days. 100 ml of the sugar-free non-proprietary product costs £1.30. There are no parenteral formulations available.

References

- Boothman R, Kerr MM, Marshall MJ, *et al.* Absorption and excretion of cephalexin in the newborn infant. *Arch Dis Child* 1973;**48**:147–50.
- McCracken GH Jr, Ginsburg CM, Clahsen JC, *et al.* Pharmacologic evaluation of orally administered antibiotics in infants and children: effect of feeding on bioavailability. *Pediatrics* 1978;**62**:738–43.
- Tetzlaff TR, McCracken GH Jr, Thomas, ML. Bioavailability of cephalexin in children: relationship to drug formulations and meals. *J Pediatr* 1978;**92**:292–4.
- Creatas G, Pavlatos M, Lolis D, *et al.* A study of the kinetics of cephalosporin and cephalexin in pregnancy. *Curr Med Res Opin* 1980;**7**:43–7.
- Kefetzis D, Sifas C, Georgakopoulos P, *et al.* Passage of cephalosporins and amoxicillin into the breast milk. *Acta Paediatr Scand* 1981;**70**:285–8.
- Disney FA, Dillon H, Blumer JL, *et al.* Cephalexin and penicillin in the treatment of group A beta-haemolytic streptococcal sore throat. *Am J Dis Child* 1992;**146**:1324–9. [RCT]

Use

Cefotaxime is a broad spectrum cephalosporin largely reserved for use in the management of neonatal meningitis, with exceptional activity against most Gram negative bacteria other than *Pseudomonas*. It should not be used on its own if infection with *Listeria* is a possibility.

Pharmacology

Cefotaxime is a bactericidal antibiotic introduced into clinical use in 1976 with the same range of activity against Gram positive organisms as most other third generation cephalosporins (cf. the monograph on cefoxitin), and exceptional activity against most Gram negative organisms. Unfortunately it is not active against *Listeria monocytogenes*, enterococci, or *Pseudomonas*. Tissue penetration is good and cerebrospinal fluid (CSF) penetration is usually more than adequate when there is meningeal inflammation. Maternal use presents no problem during pregnancy; during lactation it exposes the baby to considerably less than 1% of the weight adjusted maternal dose. The neonatal half life (2–6 hours) varies with gestation and with postnatal age. The drug's primary metabolite, desacetylcefotaxime, which also displays antibiotic activity, has a neonatal half life twice as long as this. Most of the drug is excreted renally.

Cefotaxime is at present widely considered to be the antibiotic of choice in the management of most cases of Gram negative neonatal meningitis, although, for most infections, there is probably little to choose between cefotaxime and ceftazidime (q.v.). Ceftriaxone (q.v.) is sometimes used in this situation when there is no risk of jaundice. There is some limited evidence to suggest that the outcome in proven bacterial meningitis may be improved by the simultaneous early administration of dexamethasone (q.v.), although controlled trial evidence for this form of treatment is currently available only in respect of treatment for meningitis caused by *Haemophilus influenzae* in patients over 6 weeks old.

The neonatal use of the third generation cephalosporins such as cefotaxime and ceftazidime should probably be limited to the management of proven Gram negative septicaemia and meningitis because several units have reported the emergence of resistant strains of *Enterobacter cloacae* when cefotaxime is used regularly in the first line management of possible neonatal sepsis (including coagulase negative staphylococcal infection). The same potential exists with other organisms (such as *Serratia* and *Pseudomonas* species) where inducible β lactamase production is a possibility.

Diagnosing meningitis

The signs of meningitis are seldom as clear cut in the neonatal period as they are in later childhood and (since babies with meningitis do not always have a positive blood culture) the organism may be missed if a lumbar puncture (LP) is not done when blood is obtained for culture. Even if it is delayed until the baby has been stabilised, an LP should still be done (within 2 hours of initiating antibiotic treatment to be sure of isolating the organism), since diagnosis will often influence decisions regarding treatment. Flex the hips and knees, but do not bend the neck, to limit respiratory embarrassment. A Gram stain will usually reveal meningitis, but the cell count seen in normal babies overlaps with that seen in babies with early meningitis. The same is true of CSF protein and glucose levels. A combination of ampicillin and gentamicin is widely used in early onset meningitis of uncertain origin, but cefotaxime should replace ampicillin if Gram negative organisms are seen (ceftazidime being more appropriate if pseudomonas infection is suspected). Meropenem (q.v.) should be held in reserve for use when a β lactamase resistant organism is suspected. Penicillin can replace ampicillin in group B streptococcal infection. Vancomycin should be reserved for proven staphylococcal infection. Viral culture should always be undertaken if no bacteria are seen. Meningitis (whatever its cause) is a notifiable condition in the UK.

Treatment

Severe neonatal infection calls for treatment with 50 mg/kg given slowly IV (or IM) once every 12 hours in the first week of life, every 8 hours in babies 1–3 weeks old, and once every 6 hours in babies older than this. The dosage interval should be increased in babies with severe renal failure.

Supply

Stock 500 mg vials, which should be protected from light, cost £2.40. The dry powder should be reconstituted with 2.3 ml of water for injection to give a solution containing 200 mg/ml.

References

Kafetzis DA, Brater DC, Kapiki AN, *et al.* Treatment of severe neonatal infections with cefotaxime: efficacy and pharmacokinetics. *J Pediatr* 1982;100:438–9.
 Felstein TJ, Uden DL, Larson TA. Cefotaxime for treatment of gram-negative meningitis in infants and children. *Pediatr Infect Dis J* 1987;6:471–4.
 Kearns GL, Jacobs RF, Thomas BR, *et al.* Cefotaxime and desacetylcefotaxime pharmacokinetics in very low birth weight neonates. *J Pediatr* 1989;114:461–7.
 Spritzer R, Kamp HJVD, Dzoljic G, *et al.* Five years of cefotaxime use in a neonatal intensive care unit. *Pediatr Infect Dis J* 1990;9:92–6.
 de Man P, Verhoeven BAN, Verbrugh HA, *et al.* An antibiotic policy to prevent emergence of resistant bacilli. *Lancet* 2000;355:973–8.
 Heath PT, Nik usoff NK, Baker CJ. Neonatal meningitis. [Review] *Arch Dis Child* 2003;88:F173–8 (see also F179–4.)

CEFOXITIN

Use

Cefoxitin is a broad spectrum second generation cephalosporin with enhanced activity against anaerobic bacteria, used prophylactically, like ampicillin (q.v.), in patients undergoing abdominal surgery.

Pharmacology

Cephalosporins are all N-acylated derivatives of 7- β -aminocephalosporanic acid with a β lactam ring fused to a six membered dihydrothiazine ring, first found amongst the fermentation products of *Cephalosporin acremonium*. A wide range of semisynthetic products have been produced since 1948. First generation products rapidly gave way to those with greater resistance to the β lactamase enzymes that could be given parenterally. Most of these have now given way to "third generation" products with enhanced antibacterial activity, but some are still used for specialised purposes. Cefoxitin has retained its utility because of its ability to control anaerobic infection, and its better than average activity against *Bacteroides fragilis*. Most Gram positive cocci are moderately susceptible, but *Pseudomonas* species and *Listeria monocytogenes* are resistant, as are enterococci and *Enterobacter*. Cerebrospinal fluid penetration is poor and elimination is rapid in urine, the neonatal half life (3–4 hours) being nearly four times as long as in adults. Problems associated with treatment are uncommon but largely the same as for all cephalosporins, as discussed in the monograph on ceftazidime. Use can be considered safe during pregnancy and lactation. There is no evidence of teratogenicity, and the baby ingests less than 1% of the weight related dose if the mother takes the drug while breastfeeding (little of which would be absorbed anyway).

Caesarean delivery

Antibiotic prophylaxis can never be a substitute for good surgical technique and meticulous asepsis. Despite this, controlled trials have shown, quite unequivocally, that a policy of routine antibiotic prophylaxis is associated with a threefold reduction in the risk of serious postoperative infection, localised wound infection, and endometritis, as well as the much commoner risk of postoperative fever, in women undergoing caesarean delivery. Furthermore, the magnitude of the benefit seems as great for elective section as it is for section after the onset of labour. Analyses also show that, except in units with a quite exceptionally low postoperative infection rate, such a policy cuts costs. Yet, despite the combined evidence provided by more than 90 controlled trials, and the parallel evidence from other trials of prophylaxis during abdominal surgery, the adoption of routine prophylaxis remains uncommon outside North America. The cephalosporins and broad spectrum penicillins (usually ampicillin) seem to be equally effective. The use of an aminoglycoside or metronidazole (q.v.) as well as a broad spectrum penicillin and the duration of prophylaxis both deserve further study. One day of prophylaxis (starting, if necessary, after the umbilical cord has been cut) provides substantial protection. Continued treatment for several days, or the routine use of two antibiotics, have been shown further to reduce the risk of perioperative infection, but this could have a detrimental effect on the bacterial ecology of the unit and increase the risk of infection from multiresistant organisms (an issue that has received far too little attention in studies to date).

Maternal prophylaxis

Mothers who are offered prophylaxis at caesarean delivery usually receive four doses of 2 g either IV or deep IM at 6 hour intervals. It is not unreasonable to delay the first dose until the umbilical cord has been clamped.

Neonatal treatment

Babies should be given 40 mg/kg IV once every 12 hours in the first week of life, once every 8 hours when 1–3 weeks old, and once every 6 hours when older than this. The dose interval should be doubled when renal function is seriously impaired.

Supply

Vials containing 1 g and 2 g of cefoxitin sodium are available costing £4.90 and £9.80 each. For IV administration, dissolve the powder from a 1 g vial with 9.5 ml of water for injection BP and shake well to give a solution containing 100 mg/ml. For IM administration, the contents of the 1 g vial should be dissolved with 2 ml of plain 1% lignocaine hydrochloride (noting that IM treatment is not recommended in small babies). When giving 2 g IM to an adult it is best to give two separate 1 g injections.

References

- Roos R, von Hattingberg HM, Belohradsky BH, *et al*. Pharmacokinetics of cefoxitin in premature and newborn infants studied by continuous serum level monitoring during combination therapy with penicillin and amikacin. *Infection* 1980;8:301–6.
- Regazzi MBG, Chirico G, Cristiani D, *et al*. Cefoxitin in newborn infants. *Eur J Clin Pharmacol* 1983;25:507–9.
- Mugford M, Kingston J, Chalmers I. Reducing the incidence of infection after caesarean section: implications of prophylaxis with antibiotics for hospital resources. *BMJ* 1989;299:1003–6.

See Cochrane reviews of caesarean prophylaxis



Use

Ceftazidime is widely used in the management of Gram negative (including *Pseudomonas aeruginosa*) infection, although cefotaxime (q.v.) is more often used for Gram negative meningitis. However, frequent use can rapidly lead to many babies becoming colonised by resistant organisms.

Pharmacology

Ceftazidime is a valuable third generation bactericidal cephalosporin (cf. the monograph on cefoxitin) first patented in 1979. It is resistant to most β -lactamase enzymes and has good in vitro activity against a wide range of Gram negative bacteria, including *Pseudomonas aeruginosa*. It is reasonably active against group A and group B streptococci and against *Streptococcus pneumoniae*, but only has limited efficacy with most other Gram positive organisms. Ceftazidime is not effective against Enterococci, *Listeria*, *Helicobacter* or *Bacteroides fragilis*, and the widespread regular use of this (or any other) cephalosporin can result in an increasing proportion of babies becoming colonised with enterococci and with other potentially dangerous organisms. Generalised fungal infection is also a potential hazard. Ceftazidime should not, therefore, be used on its own in the management of neonatal infection due to an unidentified organism. Ceftazidime is widely distributed in most body tissues including respiratory secretions, ascitic fluid and cerebrospinal fluid (CSF), although CSF penetration is rather variable unless the meninges are inflamed. There is no clear evidence that aminoglycosides are synergistic.

Ceftazidime crosses the placenta freely, but there is no evidence of teratogenicity. Treatment during lactation is equally acceptable since this exposes the baby to less than 1% of the maternal dose on a weight-adjusted basis. The drug is not absorbed when taken by mouth and is excreted unchanged in the urine. The half life is 4–10 hours at birth, but half this in babies more than a week old. Adverse effects are not common with any of the cephalosporin antibiotics in the neonatal period, but hypersensitivity reactions are occasionally seen in older patients (sometimes overlapping with hypersensitivity to penicillin). Rashes, phlebitis, and leucopenia have all been reported. Diarrhoea can progress to pseudomembranous colitis, due to an overgrowth of antibiotic-resistant bowel organisms, such as *Clostridium difficile* and, if this is not recognised and treated with metronidazole (q.v.), this could prove fatal. A very high blood level, usually because of a failure to reduce dose frequency when the patient is in renal failure, can cause CNS toxicity and fits (as is true of all the β -lactam antibiotics). Bleeding due to hypoproteinaemia (easily reversed by giving vitamin K) has been associated with the prolonged use of cephalosporins in malnourished patients. Ceftriaxone is, on theoretical grounds, the cephalosporin most likely to cause such a problem of the products listed in this compendium.

Some 5% of patients given a cephalosporin develop a transient positive Coombs' test (and this can interfere with the cross matching of blood), but frank haemolytic anaemia is extremely uncommon. Tests may wrongly suggest that there is glucose in the urine because of interference with the alkaline copper reduction test, and interference with the Jaffé reaction may affect the measurement of creatinine (giving a false high reading that can be particularly misleading when renal failure is a concern).

Treatment

Give 25 mg/kg of ceftazidime IV or deep IM once a day in the first week of life, once every 12 hours in babies 1–3 weeks old, and once every 8 hours in babies older than this. Doses of 50 mg/kg should be used in the treatment of suspected or proven meningitis. The dosage interval should be increased in babies with renal failure.

Supply and administration

Ceftazidime is supplied as a powder in 250 mg vials under reduced pressure costing £2.40 each. For intramuscular administration add 0.75 ml of water to provide a solution containing 250 mg/ml. Reconstitute for intravenous use with 2.25 ml of water for injection to produce a solution containing 100 mg/ml. Ceftazidime should not be put in the same syringe, or administered in a giving set at the same time, as vancomycin or an aminoglycoside.

References

Tessin I, Trollfors B, Thringner K, et al. Concentrations of ceftazidime, tobramycin and ampicillin in the cerebrospinal fluid of newborn infants. *Eur J Pediatr* 1989;148:678–81.
 de Louvois J, Dagan R, Tessin I. A comparison of ceftazidime and aminoglycoside based regimens as empirical treatment of 1316 cases of suspected sepsis in the newborn. *Eur J Pediatr* 1991;151:876–84.
 van den Anker JN, Schoemaker RC, Hop WCJ, et al. Ceftazidime pharmacokinetics in preterm infants: effects of renal function and gestational age. *Clin Pharmacol Ther* 1995;58:650–9.
 van den Anker JN, Hop WCJ, Schoemaker RC, et al. Ceftazidime pharmacokinetics in preterm infants: effect of postnatal age and postnatal exposure to indomethacin. *Br J Clin Pharmacol* 1995;40:439–43.
 Bègué P, Michel B, Chasalette JP, et al. Etude clinique multicentrique et pharmacocinétique de la ceftazidime chez l'enfant et le nouveau-né. *Pathol Biol* 1996;34:525–9.

CEFTRIAZONE

Use

Ceftriaxone is a cephalosporin antibiotic that needs to be given only once a day. Seek the advice of a microbiologist before using this drug in the neonatal period for anything other than gonococcal infection.

Pharmacology

Ceftriaxone is a β lactamase resistant, "third generation" cephalosporin first patented in 1979 that is active, like cefotaxime and ceftazidime (q.v.), against some important Gram positive and most Gram negative bacteria. Because of good cerebrospinal fluid penetration, even in the absence of marked meningeal inflammation, it has been used as an alternative to cefotaxime in the treatment of early neonatal meningitis due to organisms other than *Listeria monocytogenes* and faecal streptococci (enterococci). It is also used to treat infection with *Salmonella typhi* in countries where this organism is becoming resistant to chloramphenicol (q.v.), and to treat gonorrhoea (infection with *Neisseria gonorrhoea*). The drug is excreted unaltered almost equally in bile and urine, so treatment does not normally require adjustment unless there is both renal and hepatic failure. It has a longer half life than other cephalosporins, the plasma half life falling from 15 hours at birth to a value only a little in excess of that found in adults (7 hours) over 2–4 weeks. It crosses the placenta and also appears in amniotic fluid. There is no evidence of teratogenicity in animals, but only limited information regarding its safety during human pregnancy. Very little appears in breast milk; the baby of any mother treated during lactation would be exposed to less than 1% of the maternal dose on a weight adjusted basis, and little of this would be absorbed.

Ceftriaxone displaces bilirubin from its plasma albumin binding sites, thereby increasing the amount of free, unconjugated bilirubin. For this reason the manufacturers do not recommend its use in babies who are less than 6 weeks old, and the drug should be used in babies at risk of developing unconjugated hyperbilirubinaemia only if a lower than usual threshold is adopted for starting phototherapy (q.v.). A dose of more than 50 mg/kg can also cause a precipitate to form, which obstructs the bile duct. Ceftriaxone has occasionally caused severe neonatal erythroderma ("red baby" syndrome). Severe, potentially lethal haemolysis has developed after a time on rare occasions. Other problems are uncommon but the same as for all cephalosporins, as discussed in the monograph on ceftazidime.

Gonorrhoea

The incidence of this sexually transmitted disease, which can cause vaginal discharge, dysuria, and heavy or intermenstrual bleeding, varies greatly in different parts of the world. A single 125 mg IM dose of ceftriaxone is widely used to treat maternal infection. If it is not possible to test for possible co-infection with *Chlamydia*, it may be appropriate to give a single 1 g dose of azithromycin by mouth as well. The risk of reinfection is high unless sexual partners are also seen and treated. There is a 30–50% risk that the baby will become infected at birth, and a 4% chance of severe eye infection developing in the absence of prompt prophylaxis (as outlined in the monograph on eye drops). The eyes become increasingly purulent and inflamed, and sight can be put at risk if treatment is not started promptly. The untreated eye discharge can also cause cross infection. The presence of intracellular Gram negative diplococci on a conjunctival Gram stain is virtually diagnostic. Generalised septicæmia can occur, and may cause a destructive septic arthritis if early signs are not sought with diligence.

Treatment

Gonococcal eye infection: This is notifiable. Irrigate the eyes with saline drops, and give 50 mg/kg of ceftriaxone made up in 1% lidocaine IM once a day. A single dose is effective in uncomplicated early infection. Consider giving erythromycin (q.v.) as well for possible chlamydial co-infection.

Other sepsis: Give 50 mg/kg IV once a day for 7 days. Use with caution where there is neonatal jaundice. A dose of 75 mg/kg has been used to treat meningitis in term babies more than 4–6 weeks old. The manufacturers recommend that IV doses of more than 50 mg/kg should be given slowly over 30 minutes.

Supply

250 mg vials are available costing £2-80. For IV administration dissolve the powder from one 250 mg vial in 5 ml of water for injection to give a solution containing 50 mg/ml. To make IM (but not IV) injections less painful, dissolve the powder from the vial in **only** 2 ml of plain 1% lidocaine hydrochloride. This gives a solution containing 125 mg/ml. 1g of ceftriaxone contains 3.6 mmol of sodium.

References

- Mulhall A, de Louvois J, James J. Pharmacokinetics and safety of ceftriaxone in the neonate. *Eur J Pediatr* 1986;**144**:179–82.
- Laga M, Naamara W, Brunham RC, *et al*. Single-dose therapy of gonococcal ophthalmia neonatorum with ceftriaxone. *N Engl J Med* 1986;**315**:1382–5.
- World Health Organization. *Conjunctivitis of the newborn; prevention and treatment at the primary health care level*. Geneva: WHO, 1986.
- Robertson A, Fink S, Karp W. Effect of cephalosporins on bilirubin–albumin binding. *J Pediatr* 1988;**112**:291–4.
- Moran J. Gonorrhoea. *Clin Evid* 2003;**9**:1754–62 (and updates). [SR]

See also the Cochrane review of gonococcal treatment



Use

This non-toxic broad spectrum antibiotic was quite widely used for some years in the prophylactic management of babies considered to be at increased risk of intrapartum infection.

Pharmacology

Cefuroxime is a β lactamase resistant second generation cephalosporin first patented in 1973, which is active against most Gram positive organisms (including group B streptococci and penicillin resistant staphylococci) and a wide range of Gram negative organisms. It is reasonably active against *Haemophilus influenzae* and *Neisseria gonorrhoeae*, but inactive against *Listeria*, enterococci and *Bacteroides*, and *Pseudomonas* species. It penetrates cerebrospinal fluid poorly, but has sometimes been used prophylactically, like cefoxitin (q.v.), in neonates undergoing abdominal surgery. Coagulase negative staphylococci are increasingly resistant to this antibiotic. It was advocated for some years for use (on its own) at birth in asymptomatic babies who were thought to be at risk as a result of prolonged rupture of membranes, maternal pyrexia, or meconium aspiration, because of its broad spectrum and low potential toxicity. However, controlled trial evidence to support this strategy does not yet exist, and such use has declined in recent years. Although prophylactic treatment is certainly simplified by using a single broad spectrum antibiotic administered once or twice a day, there are very few situations in which prophylactic treatment has ever been shown to be of clinical value in the neonatal period.

Cefuroxime is ineffective when given by mouth (less than 1% is recovered in the urine), but about a third of the administered dose is absorbed when the drug is given as the lipophilic acetoxyethyl ester, cefuroxime axetil. There are no published reports of the use of this formulation in children aged less than 3 months, but it has been widely used to treat otitis media and other respiratory infections in children older than this. It is just as effective as treatment with co-amoxiclav, and less likely to cause troublesome loose stools. Alternative oral cephalosporins include cefalexin (q.v.), and cefixime.

Cefuroxime is largely excreted by the kidney. Little crosses the placenta and only negligible amounts are found in breast milk. On a weight for weight basis, the baby will be exposed to less than 1% of the maternal dose. The plasma half life falls from 6 hours at birth to about 3 hours at 2 weeks. Babies more than 1 month old clear cefuroxime from the plasma almost as fast as adults (half life 1 hour). Dosage intervals should be extended in babies with severe renal failure. Toxic adverse effects are rare but oral treatment does sometimes cause nausea and vomiting, and a change in stool frequency. Pseudomembranous colitis has been reported. Other problems are uncommon but much the same as for all cephalosporins (as discussed in the monograph on ceftazidime).

Lyme disease

Lyme disease, like syphilis, is caused by a spirochete (*Borrelia burgdorferi*), human infection being caused by the bite of an infected animal tick. Illness is rare in the UK, but not uncommon in much of Europe and North America. While a migrating annular skin lesion (erythema migrans) is the classic presentation, symptoms are very variable. Fetal infection was first recognised in 1985, and it is now realised that the risk to the fetus is comparable to that from congenital syphilis. While tetracycline (q.v.) (or doxycycline) is generally considered the treatment of choice, sustained high dose treatment with cefotaxime (q.v.) is generally preferred in pregnancy and childhood. Mothers should be given 2 g of cefotaxime IV three times a day for 2–4 weeks, and babies treated as indicated below for 2–4 weeks.

Treatment

Systemic: Give 25 mg/kg IM or IV once every 12 hours in the first week of life, every 8 hours in babies 1–3 weeks old, and every 6 hours in babies older than this. Double this dose when treating Lyme disease in a baby aged <4 weeks. The dosage interval needs to be increased if there is serious renal failure.

Oral: Give 20 mg/kg once every 12 hours. There is no experience of use in babies under 3 months old.

Supply

250 mg vials of the dry powder cost 84p each. They can be reconstituted by adding 2.4 ml of sterile water to the vial to obtain a solution containing 100 mg/ml. A 25 mg/ml suspension of cefuroxime axetil is available as a powder for oral use after reconstitution with water; 100 ml costs £7.70.

Reference

de Louvois J, Mulhall A, Hurlley R. Cefuroxime in the treatment of neonates. *Arch Dis Child* 1982;**57**:59–62.
 Donn KH, James NC, Powell JR. Bioavailability of cefuroxime axetil formulations. *J Pharm Sci* 1994;**83**:842–4.
 Gooch WM, Blair E, Puopolo A, et al. Effectiveness of five days of therapy with cefuroxime axetil suspension for treatment of acute otitis media. *Pediatr Infect Dis J* 1996;**15**:157–64. [RCT]
 Smith J, Finn A. Antimicrobial prophylaxis [Commentary]. *Arch Dis Child* 1999;**80**:388–92.
 Gardner T. Lyme disease. In: Remington JS, Klein JO, eds. *Infectious diseases of the fetus and newborn infant, 5th ed.* Philadelphia, PA: Saunders, 2001:519–641.

CHLORAL HYDRATE

Use

Chloral hydrate has been widely used as a short term sedative and hypnotic drug for more than a century. It is of no use in controlling pain.

Pharmacology

Chloral hydrate was synthesised in 1832 and first used as a hypnotic in 1869. Its chemical resemblance to chloroform led early workers to believe that it may work by liberating chloroform in the blood stream. It is rapidly and effectively absorbed from the stomach and then metabolised by liver enzymes to trichloroacetic acid and the active hypnotic metabolite trichloroethanol (TCE). Further conjugation results in the drug's eventual excretion in the urine as a glucuronide. The half life of TCE in babies (about 30 hours) is at least three times as long as that in adults and toddlers. It is rather variable and may be further increased in preterm babies, and in babies with hepatic or renal disease, making drug accumulation a potential hazard with repeated administration. Hypotension and respiratory depression have been described. Long term use has also, on occasion, been thought to cause jaundice and an increased metabolic acidosis in the neonate. The main adverse effects of oral administration (nausea, vomiting, and gastric irritation) can be minimised by giving the drug with a small amount of milk or fruit juice; this also serves to disguise the drug's unpleasant taste. An overdose can be dangerous.

Triclofos sodium, which causes less gastric irritation, has the same hypnotic and sedative action as chloral hydrate. Like chloral hydrate it is also rapidly hydrolysed to TCE; 75 mg of triclofos is therapeutically equivalent to 45 mg of chloral hydrate.

Adult insomnia

Chloral hydrate is a good short term nocturnal sedative for adult patients who find it difficult to sleep while in hospital. It is probably potentially less addictive than the widely used short acting benzodiazepine temazepam. The usual adult dose of chloral hydrate is 1 g given well diluted with water, and the usual dose of temazepam is 20 mg. Both these drugs appear in human milk but there is no published evidence of their short term night use by a nursing mother causing overt neonatal sedation. Chloral hydrate does not seem to be teratogenic, but there is some concern that sustained benzodiazepine use could be.

Infant sedation

Single dose treatment: A single dose of 45 mg/kg usually produces about 1 hour's deep sleep after about 30 minutes. In term babies a dose of 75 mg/kg is occasionally used prior to computed tomographic scanning, etc.; such babies should be monitored because this dose can produce mild hypoxaemia. Rectal administration is sometimes used. A single dose of 100 mg/kg is probably safe in later infancy, but only if a pulse oximeter is employed and the child is kept under close surveillance.

Sustained sedation: A sedative dose of 30 mg/kg by mouth, repeatable every 6 hours, has been used as an alternative to 400 micrograms/kg of diazepam every 6 hours for 1–2 days in the management of babies with cerebral irritation. It has also been used in some centres to sedate babies requiring respiratory support, but drug accumulation can occur, especially with repeated use in ill and preterm babies.

Antidote

Flumazenil (as described in the monograph on midazolam) may be effective in the management of an overdose, but propranolol may be needed to control any arrhythmia.

Supply

An oral elixir of chloral hydrate in glucose (Welldorm®) containing just under 30 mg/ml (143 mg per 5 ml) is available, costing less than 2p per ml. Stocks may be stored at room temperature (5–25°C). 125 mg and 250 mg suppositories of chloral hydrate can be obtained from Novo on request.

A solution of triclofos in syrup (costing £11.50 for 100 ml) is available containing 100 mg/ml. It should be used within 7 days if further diluted. Midwives in the UK have the little known right to supply chloral hydrate and triclofos to women on their own authority in the course of their professional practice.

References

- American Academy of Pediatrics Committee on Drugs and Committee on Environmental Health. Use of chloral hydrate for sedation in children. *Pediatrics* 1993;**92**:471–3.
- McCarver-May DG, Kang J, Aothmany M, *et al*. Comparison of chloral hydrate and midazolam for sedation of neonates for neuroimaging studies. *J Pediatr* 1996;**128**:573–6. [RCT]
- American Society of Anesthesiologists Task Force. Practice guidelines for sedation and analgesia by non-anesthesiologists. *Anesthesiology* 1996;**84**:459–71.
- Sury MRJ, Hatch DJ, Deeley T, *et al*. Development of a nurse-led sedation service for paediatric magnetic resonance imaging. *Lancet* 1999;**353**:1667–71.

Use

Chloramphenicol is used for infection with *Salmonella* (the cause of notifiable typhoid and paratyphoid fever), and occasionally to control meningitis and ventriculitis (because of good cerebrospinal fluid (CSF) penetration). It is also used for sepsis and pneumonia in countries where the alternatives are prohibitively expensive.

History

Chloramphenicol came into widespread neonatal use soon after it first became available in 1949. Then, early in 1959, came a report describing three babies who suffered a "fatal cardiovascular collapse". It was not, however, until the result of a prospective controlled trial was published in December of that year that the potential toxicity of treatment with 100–150 mg/kg per day (the dose then normally recommended) was generally accepted. Coming only 4 years after it was realised that sulphonamides could cause kernicterus and death in the jaundiced preterm baby (as described in the monograph on sulfadiazine), neonatologists had to accept that two widely used drugs had killed many hundreds of babies over a 10 year period. That most had been given antibiotics only to prevent infection added to the anguish. The drug's potential toxicity seems to be a lesson that each new generation of clinicians has to learn afresh, because more deaths from dosing errors were reported in 1983.

Pharmacology

Chloramphenicol kills *Haemophilus influenzae*, and *Neisseria* species, and stops the growth of rickettsiae and most bacteria. It penetrates all body tissues well; the CSF concentration averages 60% of the serum level, while brain levels are said to be nine times higher because of the high lipid solubility. Despite this, cefotaxime (q.v.) has now become the drug of choice in the management of suspected or proven Gram negative meningitis (partly because 2–5% of all strains of *Haemophilus influenzae* are resistant to chloramphenicol). Marrow toxicity means that the drug should be used only for severe infection. Haemolysis can occur if there is glucose-6-phosphate dehydrogenase (G6PD) deficiency. The parenteral drug (chloramphenicol succinate) becomes biologically active only after hydrolysis and, because this can be delayed in the neonate, levels of the active antibiotic can be very unpredictable. Levels should therefore be monitored. The oral drug (chloramphenicol palmitate) also requires prior hydrolysis by pancreatic enzymes, which makes it unwise to give the drug by mouth when first starting treatment in early infancy. Much of the inactive ester is excreted by the renal tubules (especially in children), and most of the active drug is first metabolised to the inactive glucuronide, so the dose does not usually need to be modified when there is renal failure. Excretion and metabolic inactivation are, however, influenced by postnatal age. The half life decreases from a mean of 27 hours in the first week of life to 8 hours by 2–4 weeks, and 4 hours in children over 4 months old. There is no evidence of teratogenicity. Although the baby of a mother on treatment receives only about 5% of the weight related maternal dose, breastfeeding is to be discouraged because of the drug's slow neonatal metabolism. Alternative strategies are, in any case, almost always available.

Drug interactions

Cotreatment with phenobarbital or rifampicin tends to lower the plasma chloramphenicol level. The effect of phenytoin is more variable, but chloramphenicol can slow the elimination of phenytoin.

Treatment

Neonatal IV treatment: Give a loading dose of 20 mg/kg and then 12 mg/kg 12 hourly IV in babies less than 1 week old. Babies 1–4 weeks old should have further doses every 8 hours in the absence of renal failure or liver damage. **Check the dose given carefully; an overdose can be fatal.**

Older children: Children over 4 weeks old can usually be started on 25 mg/kg every 8 hours. The first doses should be given IV or IM in any child who is ill, but further treatment can then be given by mouth.

Eye drops: See the eye drops monograph.

Blood Levels

Aim for a peak serum concentration of 15–25 mg/l (1 mg/l = 3.1 μmol/l). Levels over 35 mg/l may cause transient marrow suppression. Levels over 50 mg/l can cause cardiovascular collapse.

Supply

1 g vials of chloramphenicol succinate cost £1.40. Add 9.2 ml of water to give a solution containing 10 mg in 0.1 ml. No oral suspension of the palmitate salt is now commercially available in the UK, but a sugar-free suspension with a 4 week shelf life can be provided on request.

References

- Rojchgot P, Prober CG, Soldin S, *et al.* Initiation of chloramphenicol therapy in the newborn infant. *J Pediatr* 1982;101:1018–21.
Smith AL, Weber A. Pharmacology of chloramphenicol. *Pediatr Clin North Am* 1983;30:209–36.
Mulhall A, de Louvois J, Hurley R. Chloramphenicol toxicity in neonates: its incidence and prevention. *BMJ* 1983;ii:1424–7.
Weber MW, Gatchalian SR, Ogunlesi O, *et al.* Chloramphenicol pharmacokinetics in infants less than three months of age in the Philippines and The Gambia. *Pediatr Infect Dis J* 1999;18:896–901.

CHLOROQUINE

Use

Chloroquine is still used to prevent and treat malaria in those parts of the world where parasites remain sensitive to this drug. Quinine (q.v.) is usually used for treatment if chloroquine resistance is likely.

Pharmacology

Chloroquine (a 4-aminoquinoline developed during the second world war) is well absorbed, widely distributed in body tissues, slowly metabolised by the liver, and only very slowly cleared from the body. It crosses the placenta, making high dose treatment unwise during pregnancy; but weekly prophylaxis is safe and also advisable during pregnancy, in areas where disease is endemic. Use during lactation exposes the baby to under 10% of the weight adjusted maternal dose, which is not enough to protect the baby from infection. In areas where chloroquine resistance is common, efficacy is enhanced by also giving children over 6 months old simultaneous high dose chlorphenamine (2 mg by mouth once every 8 hours).

Malaria

Malaria, caused by four closely related parasites spread by the bite of the night feeding female *Anopheles* mosquito, currently kills 2 million people in the tropics each year, most of them children. Residents develop considerable immunity over time, but pregnancy makes women more vulnerable, and infection during pregnancy increases the risk of anaemia, miscarriage, stillbirth, and prematurity. Transplacental spread is uncommon but infection sometimes occurs during delivery, although florid symptoms (including fever, jaundice, an enlarged liver and spleen, and a low platelet count) usually manifest themselves 2–8 weeks later. Diagnosis of infection, however acquired, depends on recognising the intracellular parasite in a thick smear of stained blood on a microscope slide. Parasite numbers rise every 2–3 days as the fever peaks, infection being considered severe if there is shock, acidosis, hypoglycaemia, or cerebral symptoms, or if more than 5% of red cells are involved. Treatment with chloroquine can leave organisms dormant in the liver unless primaquine is then given (see below).

Drug resistance

World Health Organization advice on travel, and the prevalence of drug resistant organisms in different parts of the world, can be found on www.who.int/ith/english/index.htm

Advice from the Centers for Disease Control in the USA is available on www.cdc.gov/travel/index/htm

Similar advice can also be found in the *BNF*.

Prophylaxis

See the monograph on mefloquine for a discussion of strategies for prevention and prophylaxis.

Treatment

Prevention: Children should take 5 mg/kg of chloroquine *base* once a week.

Cure: Give a 10 mg/kg loading dose of chloroquine *base* IV or by mouth, and then three 5 mg/kg doses (given at 24 hour intervals) starting 6 hours after the loading dose was given.

Eradicating liver organisms

Give 250 micrograms/kg of primaquine *base* by mouth once a day for 3 weeks (or 500 micrograms/kg once a week for 8 weeks if there is glucose-6-phosphate dehydrogenase (G6PD) deficiency) *after* completing treatment with chloroquine.

Toxicity

Excess chloroquine is toxic to the heart and is a central nervous system depressant. Prompt high dose diazepam (2 mg/kg daily) and ventilation seem beneficial. Gastric lavage may be appropriate once the airway has been protected, and activated charcoal may reduce gut absorption. IV adrenaline helps to control hypotension. Acidosis must be corrected. Phenytoin or a β blocker is the only safe treatment for arrhythmia.

Supply

A syrup exists containing 10 mg/ml of chloroquine *base* (13.6 mg/ml of chloroquine sulphate); 100 ml of this syrup costs £2.80; 5 ml ampoules containing 200 mg of chloroquine *base* (272.5 mg of chloroquine sulphate) suitable for IV use cost 76p each; and tablets containing 155 mg of chloroquine *base* (250 mg of chloroquine phosphate) cost 6p each. 7.5 mg tablets of primaquine *base* cost 63p each. A 3 mg/ml suspension can be prepared, which retains its potency for at least 1 week if stored at 4°C.

References

- World Health Organization. Practical chemotherapy for malaria. *WHO Tech Rep Ser* 1990;**805**:1–141.
- Souwmni A, Oduola AMJ. Comparative efficacy of chloroquine/chlorpheniramine combination and mefloquine for treatment of chloroquine-resistant *Plasmodium falciparum* malaria in Nigerian children. *Trans R Soc Trop Med Hyg* 1997;**91**:689–93. [RCT]
- Goodman CA, Coleman PG, Mills AJ. Cost-effectiveness of malaria control in sub-Saharan Africa. *Lancet* 1999;**354**:378–85.
- Souwmni A, Fehintola FA, Adedede AA, *et al.* Comparative efficacy of chloroquine plus chlorpheniramine alone and in a sequential combination with sulfadoxine-pyrimethamine, for the treatment of acute, uncomplicated, falciparum malaria in children. *Ann Trop Med Parasit* 2000;**94**:209–17. [RCT]
- Kramer MH, Lobel HO. Antimalarial chemoprophylaxis in infants and children. *Paediatr Drugs* 2001;**3**:113–21.

See also relevant Cochrane reviews



Use

Chlorothiazide is a thiazide diuretic used to control the pulmonary oedema seen in preterm babies with chronic ventilator induced lung disease. It is also used in the control of fluid retention in congestive heart failure, preferably in combination with spironolactone (q.v.). Furosemide (q.v.) is a useful short term alternative in both conditions when oral treatment is not possible or a rapid response is required.

Pharmacology

Chlorothiazide is a diuretic that was first developed commercially in 1957. It crosses the placenta but shows no definite evidence of teratogenicity, although there is one study suggesting some increased risk associated with its use in the first trimester of pregnancy. Diuretic use is, nevertheless, generally considered unwise in pregnancy, except in women with heart disease, because it alters the course of pre-eclampsia and may decrease placental perfusion. Chlorothiazide is moderately well absorbed when taken by mouth and excreted unchanged into the lumen of the proximal straight tubule, where it acts by inhibiting the absorption of sodium and chloride from the urine in the distal tubule, doubling the excretion of potassium, and causing a fivefold increase in sodium excretion. The plasma half life (about 5 hours in the preterm baby) is much shorter than the functional half life. It increases when there is renal failure, making drug accumulation possible. Kernicterus is a theoretical possibility in the very jaundiced baby because the drug competes with bilirubin for the available plasma albumin binding sites.

Hydrochlorothiazide is an alternative, closely related, thiazide with very similar properties. Since the usual dose of hydrochlorothiazide is only 1.5 mg/kg twice a day by mouth, it is important not to confuse the two products. Chlorothiazide and hydrochlorothiazide are both excreted in breast milk, but the baby receives less than 2% of the maternal dose on a weight for weight basis. Reports that use during lactation can cause thrombocytopenia are unsubstantiated, as are suggestions that thiazide diuretics suppress lactation.

Diuretics are routinely used in patients with heart failure. They can also improve lung compliance in babies with chronic lung damage and pulmonary oedema, but further studies are needed to confirm whether sustained thiazide treatment really reduces the need for supplemental oxygen (as suggested by one small trial). Diuretics often stimulate increased aldosterone secretion, and the addition of spironolactone, which counteracts the sodium retaining and potassium excreting effect of aldosterone on the distal tubule, is thought to enhance the response to thiazide use. Combined treatment with spironolactone does, however, cause urinary calcium loss of a magnitude similar to that incurred by furosemide use, and this can cause serious bone demineralisation in the preterm baby. It can also cause nephrocalcinosis detectable on ultrasound (but not, usually, on x-ray examination), although this appears to resolve in later infancy when treatment is stopped. While there are good grounds for giving spironolactone to babies with heart failure (as outlined in the monograph on that drug), it is not yet clear whether such treatment does more good than harm in the preterm baby with chronic lung damage.

Treatment

Heart failure: Give 10 mg/kg of chlorothiazide and 1 mg/kg of spironolactone twice a day by mouth. Babies that fail to respond to a standard dose sometimes respond to twice this dose. Potassium supplements are not usually necessary with such combined treatment.

Chronic lung disease: Babies with chronic ventilator induced lung damage may benefit from a similar dose of chlorothiazide. Whether they should also receive spironolactone requires further study.

Supply

Chlorothiazide is available commercially, to special order, as a suspension containing 50 mg/ml (costing about £12.80 for 100 ml), but this formulation has to be imported from the USA at present. This formulation contains sucrose and saccharin. A sugar-free suspension could be prepared, but any such suspension would have a reduced shelf life. A similar oral suspension of hydrochlorothiazide could be prepared if required.

References

Atkinson SA, Shah JK, McGee G, *et al.* Mineral excretion in premature infants receiving various diuretic therapies. *J Pediatr* 1988;**113**:540–5.
 Albersheim SG, Solimano AJ, Sharma EK, *et al.* Randomised double blind trial of long term diuretic therapy for bronchopulmonary dysplasia. *J Pediatr* 1989;**115**:615–29. [RCT]
 Engelhardt B, Blalock A, DanLevy S, *et al.* Effect of spironolactone-hydrochlorothiazide on lung function in infants with chronic bronchopulmonary dysplasia. *J Pediatr* 1989;**114**:619–24. [RCT]
 Wells TG. The pharmacology and therapeutics of diuretics in the pediatric patient. *Pediatr Clin North Am* 1990;**37**:463–504.
 Kao LC, Durand DJ, McCrea RC, *et al.* Randomised trial of long-term diuretic therapy for infants with oxygen-dependent bronchopulmonary dysplasia. *J Pediatr* 1994;**124**:772–81. [RCT]

See also the relevant Cochrane reviews



CHLORPROMAZINE

Use

Chlorpromazine hydrochloride is a widely used antipsychotic or "neuroleptic" drug. It was first used in 1952 for the treatment of schizophrenia, but has also been widely used in the short term management of severe anxiety. It is still used as a short term tranquilliser in patients of all ages.

Pharmacology

Chlorpromazine hydrochloride is a phenothiazine used to reduce agitation without causing respiratory depression. The phenothiazines have an antihistaminic effect and are sometimes used to combat nausea. They have also been used to reduce peripheral and pulmonary vascular resistance and were so used for a few years in the 1980s in the management of neonatal respiratory distress. Although chlorpromazine was initially most frequently offered to psychiatric patients, the drug soon became even more widely used in the 1950s as an adjunct in preoperative medication, and as a joint agent in sedation anaesthesia because of the way it potentiates the hypnotic, narcotic, and analgesic effects of other drugs. Such use has now diminished.

Chlorpromazine is well absorbed by mouth, although absorption is said to be occasionally unpredictable. Deep IM injection is generally considered preferable to IV administration, although this is sometimes painful. It is metabolised by the liver into a number of different breakdown products with a half life of about 30 hours in adults and a half life twice as long as this at birth. Attempts to correlate plasma levels with the clinical effects of treatment have been largely unsuccessful, probably because tissue drug levels greatly exceed those in plasma ($V_d > 8$ l/kg). The drug crosses the placenta and unpredictable maternal hypotension has been reported following use during labour, but there is no evidence of teratogenicity. The baby receives only about 3% of the weight related maternal dose during lactation, and there is only a single unevaluable report of this making a baby drowsy. Extrapyramidal signs have occasionally been suspected for a few days after delivery in babies born to mothers on long term high dose antenatal medication. Use in babies less than 1 year old has not yet been endorsed by the manufacturer, and very few reports have been published relating to its use in the neonatal period. It is, however, sometimes used in the management of babies born to non-opioid drug abusing mothers. It is also very good for sedating babies with chronic respiratory problems who become seriously agitated and distressed after weeks of care on a ventilator. There is one unconfirmed report of naloxone (q.v.) being an effective antidote after an overdose.

Neonatal abstinence syndrome

Many different drugs provoke similar withdrawal symptoms in the baby after birth. Restlessness, irritability, and excessive wakefulness are the commonest problems seen. Autonomic dysfunction can include sneezing, yawning, sweating, and temperature instability. Feeding can prove difficult. Symptoms can be very unpleasant and occasionally, if particularly severe, dangerous. Those that persist after feeding, swaddling, and the use of a dummy or pacifier should be managed with a tapering dose of methadone or morphine (q.v.) if the mother has been taking a narcotic (opioid) drug. Phenobarbital (q.v.) is probably helpful for mixed dependency; chlorpromazine is an understudied alternative. With amphetamine and most opiate abuse, serious symptoms usually present within 1–2 days, peak early, and subside fairly rapidly, because these drugs have a fairly short half life. Symptoms present more insidiously with other drugs, such as diazepam (q.v.) and the barbiturates, which have a particularly long neonatal half life. Some illicit drugs, such as marijuana (cannabis), seldom cause symptoms. For a fuller discussion see the methadone website commentary.

Treatment

Start by offering 1 mg/kg by mouth every 8 hours. Most authorities suggest that the *total* daily dose should not exceed 6 mg/kg.

Supply

An oral syrup containing 5 mg/ml of chlorpromazine hydrochloride (costing 90p for 100 ml) is available. It can be diluted 10-fold for accurate administration by the pharmacy on request, but the diluted preparation has only a 2 week shelf life. A 1 ml ampoule containing 25 mg of chlorpromazine hydrochloride (costing 60p) is available for IM use.

References

- Nielsen HC, Wiriyathian S, Rosenfeld CR, *et al.* Chlorpromazine excretion by the neonate following chronic *in utero* exposure. *Pediatr Pharmacol* 1983;**3**:1–5.
- Chasnoff IA, ed. Chemical dependency in pregnancy. *Clin Neonatal* 1991;**18**:1–191.
- McElhatton PR. The use of phenothiazines during pregnancy and lactation. *Reprod Toxicol* 1992;**6**:475–90.
- Theis JGW, Selby P, Ikizler Y, *et al.* Current management of neonatal abstinence syndrome: a critical analysis of the evidence. *Biol Neonat* 1997;**71**:345–66.
- Yoshida K, Smith B, Craggs M, *et al.* Neuroleptic drugs in breast-milk: a study of pharmacokinetics and of possible adverse effects in breast-fed infants. *Psychol Med* 1998;**28**:81–91.

See also relevant Cochrane reviews



Use

Cimetidine inhibits gastric acid secretion. Rather fewer side effects have been reported for the closely related drug ranitidine (q.v.).

Pharmacology

Cimetidine is a safe and widely used drug, a low dose formulation of which is now available "over the counter" without prescription for the short term management of indigestion and heartburn in adults. The drug, first synthesised in 1972, was designed to work by blocking the H₂ histamine receptors in the stomach that control the release of gastric acid, thereby also reducing pepsin output. High dose treatment has been shown to speed the healing of peptic ulcers in the oesophagus, stomach, and duodenum, and low dose maintenance treatment can be used to prevent a recurrence in vulnerable patients. Omeprazole (q.v.) may be effective when cimetidine is not. Cimetidine and ranitidine have also been widely used to treat acute non-specific gastrointestinal bleeding, especially in patients undergoing intensive care (where acute haematemesis is often seen to be a sign of stress ulceration), but such haemorrhage frequently stops rapidly without specific treatment, and the 27 trials that have been carried out in adult patients fail to show clear evidence of benefit. Only one small trial has yet been attempted in the neonatal period.

Cimetidine is rapidly absorbed when taken by mouth and mostly excreted unchanged in the urine, the plasma elimination half life being about 2 hours in adults, but rather more than this in the neonatal period. Side effects are rare, although dizziness, somnolence, and fatigue have been reported. Arrhythmia has been seen both in adults and in neonates, especially with rapid IV administration. Cimetidine has mild, dose related, antiandrogenic properties and reversible gynaecomastia has been reported.

Cimetidine crosses the placenta and should be used with caution in early pregnancy, although teratogenicity has not been reported. It has been widely used in mothers during delivery (as discussed in the monograph on ranitidine) without adverse effects being noted in the neonate. Use during lactation will result in the baby receiving (on a weight for weight basis) a dose equivalent to 5–7% of the maternal dose. This does not seem to have caused problems. There is not enough experience with its use for the manufacturers to recommend the use of this drug in children under 1 year old.

Drug interactions

Cimetidine (unlike ranitidine) binds very strongly to cytochrome P450, inhibiting the breakdown of those drugs that are metabolised by this enzyme in the liver. Erythromycin, lidocaine, midazolam, nifedipine, phenytoin, suxamethonium, theophylline (or aminophylline), and warfarin are amongst the drugs most notably affected.

Treatment

Give 5 mg/kg by mouth every 6 hours if there is evidence of active ulceration. Half this dose may be adequate when the drug is given prophylactically. Treatment can be given IV when necessary, but **must** be given slowly over at least 10 minutes. A continuous infusion of ranitidine may be preferred. Dosage must be halved or treatment stopped when there is renal failure.

Supply

2 ml ampoules for IV or IM use containing 200 mg of cimetidine cost 36p. The IV preparation must be diluted at least fivefold, and is most conveniently diluted 10-fold, before use. Take 1 ml of cimetidine from the ampoule and dilute to 10 ml with 0.9% sodium chloride to provide a preparation containing 10 mg/ml suitable for IV (or oral) use. Rapid IV administration can cause arrhythmia. An oral syrup containing 40 mg/ml of cimetidine is also available from the pharmacy (100 ml costs £4.70) and this can be diluted with syrup BP to give a preparation containing 10 mg/ml on request.

References

- Somogyi A, Gugler R. Cimetidine excretion into breast milk. *Br J Clin Pharmacol* 1979;**7**:627–9.
- Ziemiak JA, Wynn RJ, Aranda JV, et al. The pharmacokinetics and metabolism of cimetidine in the premature newborn. *Dev Pharmacol Ther* 1984;**7**:30–8.
- Lloyd CW, Martin WJ, Taylor BD, et al. Pharmacokinetics and pharmacodynamics of cimetidine and metabolites in critically ill children. *J Pediatr* 1985;**107**:295–300.
- Collins R, Langman M. Treatment with histamine H₂ antagonists in acute upper gastrointestinal hemorrhage: implications of randomised trials. *N Engl J Med* 1985;**313**:660–76. [RCT]
- Vandenplas Y, Sacre L. The use of cimetidine in newborns. *Am J Perinatal* 1987;**4**:131–3.
- Lambert J, Mabassaleh M, Grand RJ. Efficacy of cimetidine for gastric acid suppression in pediatric patients. *J Pediatr* 1992;**120**:474–8.

Use

Ciprofloxacin is a quinolone antibiotic with broad spectrum activity against a wide range of infectious organisms. Discussion with a consultant microbiologist should normally precede the use of this drug in children.

Pharmacology

Ciprofloxacin is a fluoroquinolone, first patented in 1982, with broad spectrum activity against many Gram positive and Gram negative bacteria, and against other organisms such as *Chlamydia* and the rickettsiae. It is particularly useful in the management of *Enterobacter* and other infections resistant to all cephalosporins and all the widely used aminoglycosides. Because it can be given by mouth (oral bioavailability 70%) it is particularly useful in the treatment of pulmonary infection with *Pseudomonas aeruginosa* and systemic infection with *Salmonella*. IV administration can be painful, and can cause local erythema and phlebitis unless a slow rate of infusion is used. Ciprofloxacin crosses the placenta and diffuses well into most body fluids. Very adequate levels have also been documented in the cerebrospinal fluid (> 1.0 mg/l) in infants with ventriculitis. It is partly metabolised in the liver but largely excreted unchanged in the urine (where crystalluria may occur if fluid intake is not maintained). The half life does not seem to have been studied in babies less than 1 month old, but it seems to be much the same throughout childhood as in adult life (4–5 hours). Dosage requires review only where there is serious renal or liver dysfunction.

Although the use of this drug was initially discouraged in children because studies had shown lasting damage to the cartilage of weightbearing joints during growth in animals, no reports of any such complication have appeared following its use in childhood. Nalidixic acid (the first widely used quinolone antibiotic) caused similar cartilage damage to growing animals, but was never shown to cause a comparable problem in children. One isolated report has suggested that the drug may stain the primary dentition green. Nevertheless, although the drug should not be used in the neonatal period when other alternative treatment strategies are available, its use has sometimes proved extremely effective in the treatment of severe septicaemia or meningitis, even though the manufacturers have no licence to recommend its use in young children. The dose quoted here seems safe, and is in line with US advice, but it is higher than usually recommended in the UK. Half the dose quoted here may well be curative in the neonate. There is some suggestion that the drug can cause seizures in patients with an underlying epileptic tendency, and some risk of haemolytic anaemia in babies with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Lingering reservations regarding its use in children should be explained before the drug is given to any mother who is breastfeeding, even though such use exposes the baby to less than 3% of the maternal weight related dose.

Drug interactions

Ciprofloxacin treatment increases the half life of theophylline and (to a lesser extent) caffeine. The dose of theophylline may need to be halved if toxic side effects are to be avoided.

Treatment

Dose: Give 10 mg/kg IV over 30–60 minutes when treating severe infection. Oral treatment with a marginally higher dose (12 mg/kg) may well suffice when treating pulmonary infection.

Timing: Give one dose every 12 hours in the first six months of life, and one dose every 8 hours in babies older than this. Treatment is usually continued for 10–14 days.

Supply

Ciprofloxacin lactate for IV use is available in 50 ml bottles containing 100 mg of ciprofloxacin (costing £8-60) from the pharmacy. A 10 mg/kg dose contains 0.76 mmol/kg of sodium. Bottles must be discarded promptly after they have been opened; capped syringes can be prepared for IV use by the pharmacy on request to minimise drug wastage. A sugar free oral suspension of ciprofloxacin hydrochloride containing 50 mg/ml is available (100 ml costs £15).

References

- Schaad EB, Salam MA, Aujard Y, *et al.* Use of fluoroquinolones in pediatrics: consensus report of the International Society of Chemotherapy Commission. *Pediatr Infect Dis J* 1995;**14**:1–9.
- Peltola H, Ukkonen P, Saxén H, *et al.* Single-dose and steady-state pharmacokinetics of a new oral suspension of ciprofloxacin in children. *Pediatrics* 1998;**101**:658–62.
- van den Oever HLA, Verteegh FGA, Theweesen EAPM, *et al.* Ciprofloxacin in preterm neonates: case report and review of the literature. *Eur J Pediatr* 1998;**157**:843–5.
- Singh UK, Sinha RK, Prasad B, *et al.* Ciprofloxacin in children: is arthropathy a limitation? *Indian J Pediatr* 2000;**67**:386–7.

Use

Cisapride seems to be of use in the treatment of severe gut immotility (including postoperative ileus), but there is only meagre controlled trial evidence to support its use in the management of gastro-oesophageal reflux in children, and none in the neonate. It is no longer on general sale in the UK or the USA.

Pharmacology

Cisapride is a substituted benzamide that increases gut motility without stimulating gastric secretion, probably by increasing the release of acetylcholine within the nerve plexus of the gut wall. It was first patented in 1983. It has been shown to increase the tone of the gastro-oesophageal sphincter, accelerating gastric emptying and reducing the incidence of gastro-oesophageal reflux in children but, despite widespread use, there is little controlled trial evidence that it is of value in the management of most neonatal reflux. One controlled trial, in babies 2–18 months old, also found that *Gaviscon*[®] (q.v.) and a thickening agent at feed time usually produced rather more symptomatic benefit than the administration of cisapride half an hour before feeds. Cisapride and erythromycin (q.v.) both normally decrease transit time through the small and large bowel, but neither seems to reduce the time it usually takes for full enteral feeding to be achieved in the preterm baby. This is not, however, to deny the drug a role in the management of babies with stubborn immotility of the small gut, especially after surgery.

Cisapride is readily absorbed when taken by mouth, and undergoes rapid first pass metabolism in the liver and gut wall. The metabolites are then excreted in the urine and faeces (the adult plasma elimination half life being 7–10 hours). Bioavailability is approximately halved when the drug is given rectally. The commonest sign of an overdose in adults is abdominal cramp and intestinal hurry, although headache, dizziness, tachycardia, and convulsions have been reported. Drug accumulation can cause a serious arrhythmia. Avoid in hypokalaemia or hypomagnesaemia. Start with a low dose in patients with kidney or liver failure. Little is known about use in pregnancy, and high doses may be fetotoxic, but the baby is exposed to less than 1% of the maternal dose on a weight for weight basis during lactation. The manufacturers never had a licence to recommend its use in children less than 12 years old, either in the UK or the USA, but it soon came to be widely used by paediatricians on both sides of the Atlantic. Both the manufacturers and the UK Committee on Safety of Medicines issued warnings regarding neonatal use because too little was known about the drug's metabolism, and it was eventually withdrawn from sale in the USA, and suspended from sale in the UK, in July 2000. Continued use, in the end (where it is available), must depend on an individual assessment of the possible risks and the potential benefits.

Drug interactions

Patients taking amiodarone, doxapram, erythromycin, spiramycin, or any of the systemic imidazole or triazole antifungal agents (such as fluconazole) should **never** be given cisapride; all these drugs interfere with the metabolic inactivation of cisapride and can prolong the QT interval, causing ventricular arrhythmia.

Treatment

By mouth: Try 200 micrograms/kg once every 8–12 hours. Do not exceed 800 micrograms/kg per day.

Rectally: 1 mg/kg, given once every 12 hours, has been shown to be of benefit in the treatment of severe postoperative ileus, especially in babies with gastroschisis or malrotation.

Monitoring for toxicity

Electrocardiographic measurement of the QT and RR intervals should be used to watch for potential overtreatment, especially in the preterm baby. Use lead II for consistency. The *corrected* QT interval ($QT_c = QT/RR$) averaged over 5–10 beats should not exceed 0.45, or rise by more than 10% on treatment.

Supply

Cisapride monohydrate suspension contains the equivalent of 1 mg/ml of anhydrous cisapride, plus sucrose and parabens (100 ml costs £3.70). It can be given rectally when necessary. A more dilute suspension is stable for 7 days. The drug is now only available in the UK on a "named patient" basis.

References

- Lander A, Redkar R, Nicholls G, *et al.* Cisapride reduces neonatal postoperative ileus: a randomised placebo controlled trial. *Arch Dis Child* 1997;**77**:F119–22. [RCT]
- Vandenplas Y, Belli DC, Benatar A, *et al.* The role of cisapride in the treatment of pediatric gastroesophageal reflux. *J Pediatr Gastroenterol Nutr* 1999;**28**:518–28. (A European Society of Pediatric Gastroenterology, Hepatology and Nutrition statement.)
- Lander A, Desai A. The risks and benefits of cisapride in premature neonates, infants and children. *Arch Dis Child* 1998;**79**:469–70.
- Khosho V, Edell D, Clarke R. Effect of cisapride on the QT interval in infants with gastroesophageal reflux. *Pediatrics* 2000;**105**:e24.
- Gilbert R, Augood C, MacLennan S, *et al.* Cisapride treatment for gastro-oesophageal reflux in children: a systematic review of randomised controlled trials. *J Paediatr Child Health* 2000;**36**:524–9. [SR]
- Tréluyer J-M, Rey M, Sonnier M, *et al.* Evidence of impaired cisapride metabolism in neonates. *Br J Clin Pharmacol* 2001;**52**:419–25.

See also relevant Cochrane reviews

CLINDAMYCIN

Use

Clindamycin is used in the prophylaxis and treatment of anaerobic infections, and to protect against bacterial endocarditis and intrapartum group B streptococcal infection in people who are allergic to penicillin.

Pharmacology

Clindamycin hydrochloride is an antibiotic related to lincomycin that has a mainly bacteriostatic effect on Gram positive aerobes and a wide range of anaerobic bacteria. It acts by inhibiting protein synthesis in much the same way as erythromycin (q.v.). It was originally isolated from the soil fungus *Streptomyces lincolnensis*, and first synthesised in 1967. It is rapidly absorbed when given by mouth, and penetrates most tissues well, although cerebrospinal fluid penetration is poor. The drug is metabolised by the liver with an adult half life of 2–3 hours. The dose given does not normally need to be changed when there is renal failure because only a little is excreted unmetabolised in the urine. The half life is long, and troublesomely variable (3–15 hours) in the preterm baby, falling to adult values by 2 months. The manufacturers do not recommend IV use in babies less than 4 weeks old. The risk of diarrhoea, and of occasionally fatal antibiotic related pseudomembranous colitis (characterised by bloody diarrhoea and abdominal pain), has limited the neonatal use of this antibiotic. Treatment must be stopped at once if this adverse reaction is suspected. Oral vancomycin (q.v.) (15 mg/kg every 8 hours) and parenteral nutrition (q.v.) are often used to treat this colitis, which seems to be due to the toxin of *Clostridium difficile*. Other adverse effects include skin rashes and other hypersensitivity reactions, blood dyscrasias, and disturbances of hepatic function. The drug is still sometimes used as an alternative to sodium fusidate (q.v.) in the management of resistant staphylococcal osteomyelitis, and to control the anaerobic sepsis associated with necrotising enterocolitis (although the only controlled trial raised the possibility that clindamycin may increase the risk of late stricture formation). Clindamycin is occasionally used in the management of protozoal infection (including malaria and toxoplasmosis). It is also being used to treat bacterial vaginosis. There is no evidence of teratogenicity, and treatment during lactation exposes the baby to only about 3% of the maternal dose on a weight for weight basis. There is one anecdotal report of a baby who passed two bloody stools while being breastfed by such a mother.

Prophylaxis

Short courses of clindamycin are used prophylactically during dental and ENT procedures to prevent endocarditis in children and adults with heart defects who are allergic to penicillin, or who have received more than a single dose of penicillin in the past 4 weeks. Give 20 mg/kg of clindamycin by mouth 1 hour before the procedure is due.

Prophylactic maternal clindamycin (900 mg IV once every 8 hours) can also be used instead of penicillin (q.v.), or erythromycin, where there is a risk of intrapartum group B streptococcal infection. Oral clindamycin (300 mg twice a day for 5 days) reduced the risk of preterm birth in one recent controlled trial in women with an abnormal vaginal flora or frank bacterial vaginosis.

Treatment

Neonates: Give 5 mg/kg by mouth or (slowly) IV once every 8 hours to manage severe staphylococcal infection, or the anaerobic septicaemia sometimes associated with neonatal necrotising enterocolitis. Babies more than 2 weeks old with normal liver function may benefit from one dose every 6 hours.

Older children: Give infants with severe infection over 2 months old 10 mg/kg IV once every 6 hours.

Supply

300 mg (2 ml) ampoules of clindamycin phosphate (containing 0.9% w/v benzyl alcohol) cost £5. To obtain a solution containing 5 mg/ml for accurate administration, first dilute the contents of the 300 mg ampoule to 15 ml with 5% dextrose, and then take 0.25 ml (5 mg) of this solution for each kilogram that the baby weighs, dilute this with 0.75 ml/kg of 5% dextrose, and infuse over at least 10 minutes. Clindamycin palmitate is also available in some countries as an oral suspension that is stable for 2 weeks at room temperature after reconstitution.

References

- Bell MJ, Shackelford P, Smith R, *et al.* Pharmacokinetics of clindamycin phosphate in the first year of life. *J Pediatr* 1984;**105**:482–6.
- Koren G, Zarfin Y, Maresky D, *et al.* Pharmacokinetics of intravenous clindamycin in newborn infants. *Pediatr Pharmacol* 1986;**5**:187–92.
- Faix RG, Polley TZ, Grasela TH. A randomised, controlled trial of parenteral clindamycin in neonatal necrotising enterocolitis. *J Pediatr* 1988;**112**:271–9. [RCT]
- Dejani AS, Taubert KA, Wilson W, *et al.* Prevention of bacterial endocarditis: recommendations by the American Heart Association. *JAMA* 1997;**277**:1794–801.
- Ugwamadu A, Manyonda I, Reid F, *et al.* Effect of early oral clindamycin on late miscarriage and preterm delivery in asymptomatic women with abnormal vaginal flora and bacterial vaginosis: a randomised controlled trial. *Lancet* 2003;**361**:983–8. [RCT]

Use

Clonazepam, like lorazepam (q.v.), is sometimes used in the neonatal period to control severe continuous seizure activity resistant to routine anticonvulsant treatment, despite increasing concern that its sedative effect may sometimes mask the fact that cortical seizure activity has not been suppressed.

Pharmacology

Clonazepam is a benzodiazepine that is completely and readily absorbed from the gastrointestinal tract, peak plasma levels occurring after 60–90 minutes. Steady state tissue levels exceed plasma levels ($V_d \sim 3$ l/kg). Clonazepam is extensively metabolised to inactive compounds, but the neonatal half life is 24–48 hours. It may be given IV if a rapid onset of action is required. Clonazepam has been used since the mid 1970s as an anticonvulsant in various types of epilepsy, but is now mostly used in the management of panic attacks and the treatment of myoclonic and absence seizures. It crosses the placenta but no adverse fetal effects have been noted. It has also been used in late pregnancy without causing any obvious sedation of the infant after birth, but it appears in breast milk in the same way as other benzodiazepines. Babies so exposed need to be monitored for signs of drowsiness, and apnoea is a theoretical possibility.

Clonazepam has often been given as a slow, continuous, IV infusion in the neonatal period, but this approach is of no particular benefit since it is only slowly cleared from the brain (unlike diazepam (q.v.)). In addition, its onset of action will be seriously delayed if an initial loading dose is not given. There are no good controlled trial data on the use of clonazepam in the control of neonatal seizures. Drug tolerance becomes a problem if treatment is continued for any extended period, and increasing seizure activity may occur if the serum level exceeds 125 $\mu\text{g/l}$. See the phenobarbital website for a discussion of how best to control seizures resistant to phenobarbital and phenytoin.

Major adverse effects are drowsiness, ataxia, and behavioural changes. Bronchial hypersecretion and salivation are said to be a problem in infancy, particularly if there is neurological dysfunction with impaired swallowing. As with all benzodiazepine anticonvulsants, withdrawal of clonazepam should be gradual (over 3–6 weeks if medication has been used for any length of time) in order to reduce the risk of withdrawal (rebound) seizures.

Drug interactions

Concurrent treatment with phenytoin or carbamazepine (q.v.) reduces the half life of clonazepam.

Treatment

Try 100 micrograms/kg IV as a slow bolus injection once every 24 hours for 2–3 days in babies resistant to routine anticonvulsant medication.

Antidote

Flumazenil is a specific antidote (as described in the monograph on midazolam).

Blood levels

Plasma levels are usually 30–100 $\mu\text{g/l}$ (1 $\mu\text{g/l} = 3.16$ nmol/l), but levels do not always correlate with clinical efficacy.

Supply and administration

Stock ampoules containing 1 mg in 1 ml of solvent costing 68p each come supplied with a further 1 ml ampoule of water for injection. The content of *both* ampoules should be drawn into a syringe *immediately* before use, and then diluted to 10 ml with 10% dextrose saline to give a solution that contains 100 micrograms/ml suitable for slow bolus IV administration. Such a solution should **not** be used to give a continuous IV infusion. Each 1 ml ampoule contains 30 mg of benzyl alcohol and a significant (but unspecified) amount of propylene glycol.

References

- André M, Boutroy MJ, Dubruc C, *et al*. Clonazepam pharmacokinetics and therapeutic efficacy in neonatal seizures. *Eur J Clin Pharmacol* 1986;**30**:585–9.
André M, Boutroy MJ, Bianchetti G, *et al*. Clonazepam in neonatal seizures: dose regimes and therapeutic efficiency. *Eur J Clin Pharmacol* 1991;**40**:193–5.

CODEINE PHOSPHATE

Use

Codeine is an opioid analgesic frequently given by mouth to adults together with aspirin or paracetamol (q.v.). Paracetamol on its own is more often used to provide oral analgesia in young children.

Pharmacology

Codeine was first isolated in 1832 from the opioid juices left over after morphine had been extracted from poppy juice. The name chosen came from the Greek word *codeia* meaning a poppy capsule. Codeine is only a mild narcotic but it is probably as effective an antitussive (cough suppressant) as morphine. When given by mouth its analgesic effect starts to become apparent after 30 minutes and peaks at 2 hours. Absorption is as rapid but less complete after rectal administration, making a larger dose necessary. Few pharmacokinetic studies have yet been done in early infancy. Tissue levels exceed plasma levels ($V_D \sim 3$ l/kg). The drug is partly metabolised by the liver (morphine being one of the metabolites), and it is increasingly thought that metabolism to morphine probably explains much of the drug's analgesic effect. The extent to which this occurs seems to depend on which genetic variant of the CYP2D6 cytochrome P450 enzyme the child has inherited, making the exact analgesic effect of any given dose hard to predict except in a child who has taken the drug before. Contrary to general belief, it certainly seems to cause as much nausea, vomiting, constipation, and ileus as a dose of morphine of similar analgesic potency. It also causes as much respiratory depression and hypotension (due to histamine release). Much is finally excreted after conjugation with glucuronic acid in the urine, making repeated, or high dose, administration hazardous where there is renal or liver failure. Little has been published relating to the use of codeine in babies less than 3 months old.

Excess medication can cause somnolence and respiratory depression, and death has been reported as a result of accidental ingestion. Some cough medicines contain quite a lot of codeine. Children as old as 5 years have died after taking more than 5 mg/kg of codeine a day in this way. For this reason the *BNF* strongly discourages the use of any cough mixture containing codeine in children less than 1 year old. Codeine is also an ingredient of many of the compound analgesic preparations routinely available in the UK (including a range of preparations that are available "over the counter") even though it is a schedule 2 controlled drug, a fact that those travelling abroad need to bear in mind.

Codeine crosses the placenta but there is no evidence of teratogenicity. Tolerance develops with repeated usage and withdrawal symptoms have been documented, even in infancy. Heavy maternal usage in the period immediately before delivery has even, rarely, caused neonatal symptoms of opiate withdrawal 1–2 days after delivery. Codeine, and its active metabolite morphine, are excreted into breast milk, but the highest blood levels achieved in the baby seem to be less than a third of the lowest therapeutic blood level. As a result, most authorities consider codeine use to be safe during lactation.

Treatment

Dose: Give 1 mg/kg by mouth, or IM, or 1.5 mg/kg rectally. Never give the drug IV because of the risk of anaphylactoid hypotension.

Timing: Never give a dose more than once every 6–8 hours in the first 3 months of life, or once every 4–6 hours in children older than that, and never give repeat medication without monitoring for possible respiratory depression.

Antidote

An overdose causes drowsiness, pinpoint pupils, hypotension, and dangerous respiratory depression. Naloxone (q.v.) is a specific antidote for all the opiate drugs.

Supply

A sugar-free linctus containing 5 mg/ml of codeine phosphate is available on request (100 ml costs 90p). It can be further diluted if requested. An IM preparation is also available, but it is hard to envisage a situation in the neonatal period where treatment with IM codeine phosphate would be preferred to an equivalent dose of morphine (q.v.). Rectal suppositories are available in some hospitals, but the linctus can also be used to give a more accurate measured dose.

References

- Meny RG, Naumburg EG, Alger LS, et al. Codeine and the breastfed neonate. *J Hum Lactation* 1993;9:237–40.
- Zhang WY, Li Wan Po A. Analgesic efficacy of paracetamol and its combination with codeine and caffeine in surgical pain – a meta-analysis. *J Clin Pharm Ther* 1996;21:261–82. [SR]
- Magnani B, Evans R. Codeine intoxication in the neonate. *Pediatrics* 1999;104:e75.
- McEwan A, Sigston PE, Andrews KA, et al. A comparison of rectal and intramuscular codeine phosphate in children following neurosurgery. *Paediatr Anaesth* 2000;10:189–93. [RCT]
- Williams DG, Hatch CJ, Howard RF. Codeine phosphate in paediatric medicine. *Br J Anaesth* 2001;86:413–21.
- Williams DG, Patel A, Howard RF. Pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability. *Br J Anaesth* 2002;89:839–45.

Use

Co-trimoxazole is used to treat cholera (infection with *Vibrio cholerae*) and to prevent and treat infection with *Pneumocystis carinii*. It is also sometimes used in the management of neonatal meningitis because of good tissue and CSF penetration. Trimethoprim (q.v.) on its own is now usually used for most respiratory and urinary tract infections because of the side effects associated with the sulphonamide component of co-trimoxazole.

Pharmacology

Co-trimoxazole is a 5:1 mixture of two different antibiotics that inhibit folic acid synthesis in protozoa and bacteria (and, to a lesser degree, in humans). It was first marketed in 1969. The bacteriostatic effect of the long acting sulphonamide (sulfamethoxazole) is augmented by the synergistic effect of trimethoprim. In combination, these two drugs are active against most common pathogens except *Pseudomonas* and *Mycobacterium tuberculosis*. Both drugs are well absorbed by mouth, and actively excreted by the kidney with half lives of about 12 hours. Both drugs also cross the placenta with ease. Drug levels in the cerebrospinal fluid approach half those in the plasma, while the levels in bronchial and vaginal secretions, and in the urine, exceed those in plasma. The amount in breast milk is small.

Because both drugs are folate antagonists, the manufacturers still caution against their use during pregnancy, but teratogenicity has been encountered only in folate deficient animals and the drug has now been in widespread clinical use for more than 30 years. The manufacturers have also declined to recommend its use in babies less than 6 weeks old, but there is no specific reason for this caution other than the risk of haemolytic anaemia in babies with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and the risk of kernicterus (although sulfamethoxazole competes for the protein binding sites usually available to bilirubin in babies with jaundice less than most of the other sulphonamide antibiotics). Caution is understandable, however, given the unnecessary deaths caused by the prophylactic use of sulphonamide drugs in the early 1950s (as outlined in the monograph on sulfadiazine). Rapid IV administration can cause an allergic reaction or anaphylaxis. Other adverse effects, which can be fatal, are usually seen only in elderly patients, or following high dose treatment in patients with AIDS. Nevertheless, since the problems (including rashes, erythema multiforme, and marrow depression) are almost certainly due to the sulphonamide component, trimethoprim is now increasingly prescribed on its own.

Drug interactions

Treatment with co-trimoxazole increases the plasma half life of phenytoin.

Prescribing

Specify the *total* amount of active drug in milligrams. Thus 20 mg/kg of sulfamethoxazole and 4 mg/kg of trimethoprim are prescribed as 24 mg/kg of active drug.

Prophylaxis

Give babies with asplenia, or with possible combined immune deficiency or HIV, 24 mg/kg by mouth once a day to reduce the risk of bacterial infection, and of fungal *Pneumocystis carinii* pneumonia. Such prophylaxis is usually continued for 12–15 months, but a shorter period may be wise in countries where pyrimethamine (q.v.) and sulfadoxine are used to treat malaria to limit the risk of developing drug resistance.

Treatment

Dose: Treat severe systemic infection with 24 mg/kg of active drug by mouth (or IV, if oral treatment is impracticable). Avoid in babies with limited renal function, unless the plasma sulfamethoxazole trough level is kept below 120 mg/l (1 mg/l = 3.95 mmol/l), and in babies with serious unconjugated jaundice.

Timing: Give once a day in the first week of life, and once every 12 hours after that. Treat *Pneumocystis* once every 6 hours in babies over 4 weeks old, even if the blood level exceeds 120 mg/l.

Supply and administration

The sugar-free paediatric oral suspension with 48 mg of active drug per ml costs £2.60 per 100 ml. 5 ml ampoules for IV use containing 96 mg/ml (costing £1.60 per ampoule) are also available. To give the standard neonatal dose (24 mg/kg) dilute 0.25 ml/kg of the contents of the ampoule into at least 15 times the same volume of 10% dextrose in 0.18% sodium chloride and then infuse this over 2 hours. The IV preparation contains 45% w/v propylene glycol. Avoid IM use in small children. More concentrated solutions have been given using a central line.

References

- Sobel KG, Braidberg A. Treatment of meningitis and septicemia in infancy with a sulphamethoxazole/trimethoprim combination. *Acta Paediatr Scand* 1975;**64**:25–32.
- Springer C, Eyal F, Michel J. Pharmacology of trimethoprim-sulfamethoxazole in newborn infants. *J Pediatr* 1982;**100**:647–50.
- Graham SM. Prophylaxis against *Pneumocystis carinii* pneumonia for HIV-exposed infants in Africa. *Lancet* 2002;**360**:1966–8.

Use

The use of a single 2 day course of dexamethasone or, preferably, betamethasone (q.v.) to accelerate surfactant production in the fetal lung *before* birth is known to be safe, but the safety of sustained high dose use in the weeks *after* birth remains extremely uncertain.

Pharmacology in pregnancy

Dexamethasone, a potent glucocorticoid steroid that is well absorbed by mouth, was developed in 1958. It crosses the placenta and has a half life of about 3 hours. It appears to be as effective as betamethasone, the drug first used for this purpose, in accelerating surfactant production by the preterm fetal lung, reducing the risk of death from respiratory distress. Renal maturation is also marginally enhanced. Treatment can control virilisation in fetuses with congenital adrenal hyperplasia. Anecdotal reports suggest that 4 mg/day may improve cardiac function if maternal lupus erythematosus causes fetal heart block. Maternal steroid treatment alters fetal heart rate and its variability. It is not known if treatment during lactation affects the baby but treatment with prednisolone (q.v.) is known to be safe.

Pharmacology in the neonate

Dexamethasone can speed extubation in a minority of babies with laryngeal oedema. It can also reduce the amount of time that preterm babies with ventilator scarred lungs (so called bronchopulmonary dysplasia or BPD) need to spend on a ventilator or in oxygen after extubation. Steroids should not be given lightly, however, because their use is associated with a 50% increase in the risk of secondary infection, while protein catabolism also affects growth. The associated rise in blood pressure and blood glucose rarely calls for intervention, and the marked hypertrophy of the ventricular myocardium seen in a minority is reversible, but steroid use increases the risk of nephrocalcinosis in babies on diuretics. Gastrointestinal haemorrhage and perforation can occur, while continuous treatment for over 10 days can also cause adrenal suppression for 2–4 weeks. If steroids are going to be beneficial, some improvement will almost always be seen within 48 hours.

Increased survival, rather than time in oxygen, is, however, what matters. Improved survival free from evidence of chronic lung disease at 36 weeks postmenstrual age has been seen only when treatment is given to babies who are still ventilator dependent and in substantial oxygen 7–14 days after birth. Intervention outside this “time window” seems to have no measurable impact on survival. Even more worrying, the results from 11 trials involving 1388 children who were followed up after discharge show, when combined, much more disability among the steroid treated children (although frequent steroid treatment in control children in some studies complicates any analysis). Although this does not mean that steroid treatment is unsafe, it does show that the high dose used in almost all these studies was unsafe.

Unfortunately, despite 15 years of widespread use, we still know little about the best dose to use, or the optimum length of treatment. Inhaled steroids have not proved as effective as was hoped, as the monograph on budesonide makes clear. Neither have short, 3 day “pulses” of treatment proved an advance. However, Durand’s low dose regimen (see below) has been shown to improve pulmonary function in the first week of treatment as effectively as the regimen used in the past, while reducing corticosteroid exposure by two thirds. The short term outcome of the Australian DART trial may provide important information here (since no other strategy has yet emerged for treating serious lung damage once it has occurred) even though it had to close early (see web commentary). In the end, however, any *short* term benefit seen may only be worth having if the *long* term outcome is equally reassuring.

One recent study has suggested that a tapering three-week course of hydrocortisone (60 mg in total) may be as effective as standard high dose dexamethasone treatment, and generate fewer adverse effects. Some will read this as evidence that the standard dose of dexamethasone is excessive, others that it may be worth studying the efficacy of a different corticosteroid more fully.

Drug equivalence

4 mg of dexamethasone base is equivalent to 4.8 mg of dexamethasone phosphate or 5 mg of dexamethasone sodium phosphate. Minimise confusion by prescribing the amount of *base* to be given.

Prophylaxis

Congenital adrenal hyperplasia: Adrenal suppression can reduce virilisation in the affected female fetus if the mother is given 7 micrograms/kg of dexamethasone *base* every 8 hours from as early in pregnancy as possible (preferably before 8 weeks), but such treatment remains experimental and its long term consequences have been inadequately assessed. The dose should be reduced in the third trimester of pregnancy, especially if adverse maternal effects develop. Hydrocortisone (q.v.) is used once diagnosis is confirmed after birth.

Fetal lung maturation: Give 12 mg of dexamethasone *base* IM to the mother and repeat once after 24 hours if there is a risk of preterm delivery. Oral treatment (four 6 mg doses once every 12 hours) is sometimes preferred, although one small trial has suggested that the outcome is marginally less satisfactory. One important observational study suggests that betamethasone may be better.

Early BPD: Early postnatal use can no longer be justified except as part of a formal controlled trial.

continued ...

Meningitis: 300 micrograms/kg of dexamethasone *base* twice a day IV, IM, or by mouth for 2 days started *early* can reduce the risk of subsequent deafness in young children with early haemophilus or pneumococcal meningitis (possibly by moderating the toxic effect of the rapid bacterial lysis caused by treatment with cefotaxime). It did not improve outcome when used in a recent large trial in Africa.

Treating chronic lung disease

Ventilated preterm babies who are still seriously oxygen dependent 7–10 days after birth are at serious risk of developing chronic lung disease. Although parents may understandably want treatment with dexamethasone tried if it is starting to look as though a progressive lung disease problem may jeopardise survival, it remains uncertain which, if any, of the following treatment strategies is best:

Traditional BPD regimen: 250 micrograms/kg of dexamethasone *base* orally or IV twice a day for 7 days has been, until recently, the most widely used regimen. A second course is occasionally given.

Current Durand regimen: 100 micrograms/kg of dexamethasone *base* IV twice a day for 3 days, and then 50 micrograms/kg twice a day for 4 days (a total of 1 mg/kg over 7 days).

DART trial BPD regimen: 60 micrograms/kg of dexamethasone *base* twice a day IV (or orally), on days 1–3, 40 micrograms/kg twice a day on days 4–6, 20 micrograms/kg twice a day on days 7–8, and 8 micrograms/kg twice a day on days 9–10 (a total of 712 micrograms/kg over 10 days). This 10 day course can be repeated once if necessary.

Treating other conditions

Hypotension: A single 250 micrograms/kg dose IV will sometimes “cure” inotrope resistant hypotension in the preterm neonate. Double this dose twice a day for 2–3 days may sometimes be necessary. Low dose hydrocortisone is equally effective.

Treatment for postintubation laryngeal oedema: Three 200 micrograms/kg doses of dexamethasone *base* orally or IV at 8 hourly intervals starting 4 hours before extubation may aid extubation in a minority of babies with an oedematous or traumatised larynx. Viral croup in later infancy responds just as well to a single oral 600 micrograms/kg dose of dexamethasone as to IM treatment.

Surgical stress: To cover possible adrenal suppression, babies on dexamethasone, or who last completed a course of dexamethasone lasting more than 1 week less than 4 weeks previously, should receive 1 mg/kg of hydrocortisone IV prior to surgery and then every 6 hours IV or IM for 24–48 hours.

Supply

Several products exist. Stock 1 ml vials containing 4 mg of dexamethasone phosphate (costing £1) contain 3.3 mg of dexamethasone *base*. *Avoid products with a sulphite preservative* (for reasons outlined in the website commentary). Draw 0.3 ml of fluid from the vial into a syringe and dilute to 10 ml with 5% dextrose to get a solution containing 100 micrograms/ml of *base* for IV or oral use. A cheap sugar-free 1 mg/ml oral solution with a 3 month shelf life is available, which can be further diluted immediately before use if necessary, as are scored 500 microgram tablets (costing 3p each).

References

See also relevant Cochrane reviews

- Egerman RS, Mercer BM, Doss JL, *et al.* A randomised, controlled trial of oral and intramuscular dexamethasone in the prevention of neonatal respiratory distress syndrome. *Am J Obstet Gynecol* 1998;**179**:1120–3. [RCT]
- O’Shea TM, Kothadia JM, Klinepeter KL, *et al.* Randomised placebo-controlled trial of a 42-day tapering course of dexamethasone to reduce the duration of ventilator dependency in very low birth weight infants: outcome of study participants at 1-year adjusted age. *Pediatrics* 1999;**104**:15–21. [RCT]
- Gaissmaier RE, Pohlant F. Single-dose dexamethasone treatment of hypotension in preterm infants. *J Pediatr* 1999;**134**:701–5. [RCT]
- Ausejo M, Saenz A, Pham B, *et al.* The effectiveness of glucocorticoids in treating croup: meta-analysis. *BMJ* 1999;**319**:595–600. [SR]
- Kopelman AE, Moise AA, Holber D, *et al.* A single very early dexamethasone dose improves respiratory and cardiovascular adaptation in preterm infants. *J Pediatr* 1999;**135**:345–50. [RCT]
- Stoll BJ, Temprosa M, Tyson JE, *et al.* Dexamethasone therapy increases infection in very low birth weight infants. *Pediatrics* 1999;**104**:e63.
- Brook CGD. Antenatal treatment of a mother bearing a fetus with congenital adrenal hyperplasia. *Arch Dis Child* 2000;**82**:F176–8. (See also associated commentaries pp. 178–81.)
- Doyle LW, Davis PG. Postnatal steroids in preterm infants: systematic review of effects on mortality and motor function. *J Paediatr Child Health* 2000;**36**:101–9. [SR]
- Finer NN, Craft A, Vaucher YE, *et al.* Postnatal steroids: short term gain: long term pain [Commentary]. *J Pediatr* 2000;**137**:9–13.
- American Academy of Pediatrics. Committee on Fetus and Newborn. Postnatal corticosteroids to treat or prevent chronic lung disease in preterm infants. *Pediatrics* 2002;**109**:330–8. (See also pp. 1168–9.) [SR]
- Armstrong DL, Penrice J, Bloomfield FH, *et al.* Follow up of a randomised trial of two different courses of dexamethasone for preterm babies at risk of chronic lung disease. *Arch Dis Child* 2002;**86**:F102–7. [RCT]
- Durand M, Mendoza ME, Tanivit P, *et al.* A randomised trial of moderately early low-dose dexamethasone therapy in very low birth weight infants: dynamic pulmonary mechanics, oxygenation, and ventilation. *Pediatrics* 2002;**109**:262–8. [RCT]
- Molyneux EM, Walsh AL, Forsyth H, *et al.* Dexamethasone treatment in childhood bacterial meningitis in Malawi: a randomised controlled trial. *Lancet* 2002;**360**:211–18. (See also p. 183.) [RCT]
- van der Heide-Jalving M, Kamphuis PJGH, van der Laan, *et al.* Short- and long-term effects of neonatal glucocorticoid therapy: is hydrocortisone an alternative to dexamethasone? *Acta Paediatr* 2003;**92**:827–35.

DEXTROSE (Glucose)

Use

Dextrose given IV prevents and corrects hypoglycaemia, and provides calories for babies who are too ill to be fully fed by mouth. It is a key component of parenteral nutrition (q.v.).

Pharmacology

Dextrose is the naturally occurring D-isomer of glucose. A 5% solution is isotonic with blood. More concentrated solutions can cause thrombophlebitis due, in part, to the fact that autoclaved solutions have a relatively low pH; indeed, 50% dextrose has been used to sclerose varicose veins. A "long line" with its tip in a large vessel is, therefore, best for any solution containing more than 10% dextrose.

Hypoglycaemia: This is common shortly after birth, but monitoring is not necessary during the first postnatal hours because the brain is protected by a range of fuels. Subsequently, a laboratory estimated whole blood glucose level of <2.5 mmol/l is unusual in a baby maintained prophylactically on a sustained infusion of 8 ml/kg per minute of 10% dextrose, and hyperinsulinism should be suspected if the requirement exceeds 12 mg/kg per minute. Much asymptomatic hypoglycaemia is caused by delayed feeding, compounded by an inadequate (and frequently interrupted) glucose infusion rate. Never give oral dextrose; milk is the best prophylaxis, and the best treatment, for any baby who is not too ill to absorb what is offered by mouth, since milk has a calorie content 50% higher than that of 10% dextrose. Reagent strip measurements should not be used. The HemoCue®, or Ames Glucometer®, can offer "point of care" measurement with a precision comparable to any laboratory estimate, but even these are not very precise. Results obtained by different, but equally well validated, techniques may vary by as much as ± 30 (95% confidence interval). Sluggish homeostasis can cause a "rebound" that makes it difficult to interpret any measurement made shortly after an infusion is stopped or reduced. Mild asymptomatic hypoglycaemia may respond to IM glucagon (q.v.), making IV dextrose unnecessary. Sustained hypoglycaemia due to hyperinsulinism may respond to diazoxide (q.v.) or octreotide. Hydrocortisone is of no proven value.

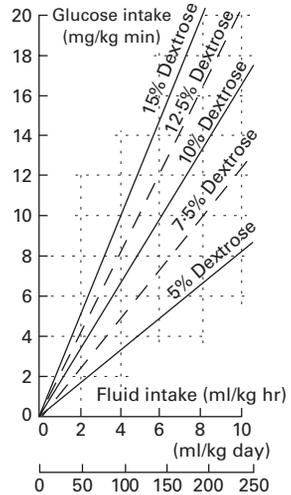
Hyperglycaemia: Although most healthy babies can metabolise at least 14 mg/kg of dextrose per minute, small babies of under 1 kg are often relatively intolerant at first, and all babies spill small amounts of glucose in their urine for several days, especially after any period of stress. Uptake saturation is best dealt with by reducing the rate of glucose infusion by 75% for 6–12 hours. Insulin (q.v.) is seldom needed. There is *no* good evidence that blood levels of up to 15 mmol/l are dangerous, or that urinary loss can cause an osmotic diuresis (as is often feared) until the urine contains at least 1% glucose. Sudden hyperglycaemia in a previously stable baby may be caused by pain, infection, necrotising enterocolitis, or an intracranial bleed. Very high plasma levels raise serum osmolality.

Treatment of hypoglycaemia

Starting a 5 ml/kg per hour infusion of 10% dextrose will raise the blood sugar level out of the hypoglycaemic range within 10 minutes in 9 babies out of 10. A loading dose of 2.5 ml/kg over 5 minutes will speed the control of hypoglycaemic stupor or fits. The infusion must then be continued at a steady rate and reduced only slowly as the milk intake is increased. Avoid bolus injections of any strength; they only destabilise the body's regulatory mechanisms. A maintenance infusion containing more than 10% dextrose may be necessary when water intake has to be kept below 100 ml/kg per day.

Supply

Half litre bags containing 5%, 10%, and 15% dextrose, 4% dextrose in 0.18% sodium chloride and 10% dextrose in 0.18% sodium chloride are available as stock, and cost 48p to £1.60 each. 25 ml ampoules of 25% glucose (costing £2.60 each) and 50 ml bags of 5% dextrose are available on request. Use the graph to compute intake in mg/(kg.min) from the infusion rate in ml/(kg.hr).



References

Lilien LD, Grajwer LA, Pildes RS. Treatment of neonatal hypoglycaemia with continuous intravenous glucose infusions. *J Pediatr* 1977;**91**:779–82 (see also 1980;**97**:295–8).
Williams AF. Hypoglycaemia of the newborn – a review. *Bull WHO* 1997;**75**:261–90.
Hawdon JM. Blood glucose monitoring in the newborn. *MIDIRS Midwifery Digest* 1999;**9**:493–6.
Coulthard MG, Hey EN. Renal processing of glucose in well and sick neonates. *Arch Dis Child* 1999;**81**:F92–8.
Cornblath M, Hawdon JM, Williams AF, et al. Controversies regarding definition of neonatal hypoglycaemia. Suggested operational thresholds. *Pediatrics* 2000;**105**:1141–5.

Use

Diamorphine has been used to control neonatal pain, but morphine (q.v.), which has been more fully evaluated, is equally effective. The monograph on methadone has a discussion of maternal addiction.

Pharmacology

Diamorphine hydrochloride is a potent semisynthetic opioid analgesic. Because it is all converted, within minutes, to morphine and 6-monoacetylmorphine in the body, almost all the drug's properties and adverse effects, including reduced peristalsis, urinary retention, and respiratory depression, are essentially the same as for morphine. It is well absorbed by mouth, but bioavailability is reduced by rapid first pass liver metabolism. Some enters the central nervous system after bolus IV administration, causing intense euphoria, and it is this that probably makes the drug so addictive. Clearance is very variable, inversely related to gestational age, and essentially the same as for morphine. High solubility is the drug's only clinical advantage, because this makes it possible to give a large IM dose in a small volume injection, but this is of no relevance to its use in infancy. Indeed there are *no* good reasons for using diamorphine rather than morphine in young children, and parents can be very disconcerted to discover, possibly by chance, that their child is on heroin. It was first manufactured on a commercial basis in 1898, but eventually banned in the USA in 1924 after its full addictive potential became apparent. Many other countries have since introduced similar bans. Placental transfer is rapid, but there is no reason why a mother given diamorphine in labour should not breastfeed. The baby, however, may be too drowsy to latch on or suckle vigorously for several hours after delivery, unless offered naloxone (q.v.).

Maternal addiction

Although there have been suggestions that diamorphine could be teratogenic, the malformations reported conform to no discernible pattern, and all the mothers in the studies reported had been taking heroin of uncertain purity as well as other drugs during pregnancy. Fetal growth is often reduced, and there may be an increased risk of fetal death. Mothers in the UK who admit to opiate addiction are usually placed on methadone (q.v.) during pregnancy, and the same drug can then be used to control any neonatal withdrawal symptoms appearing after delivery. Other centres use morphine to control the baby's symptoms. It probably helps to give phenobarbital (q.v.) as well. Many think chlorpromazine (q.v.) helps if the mother is also taking other illicit drugs. The use of paregoric (a variable cocktail of opium, glycerin, alcohol, and benzoic acid) lacks rational justification. Some assessment scales have the perverse effect of suggesting that an increasingly sedated baby is improving, but the main aim of treatment must be to improve the baby's ability to feed normally as well as sleep normally, and an unnecessarily complex weaning strategy merely serves to delay discharge. Mothers are sometimes discouraged from breastfeeding but lactation can be used as part of a controlled weaning strategy as long as they are not also taking other serious drugs of abuse, since the baby receives, on a weight for weight basis, only about 5–10% of the maternal dose.

Pain relief

Give ventilated babies in serious pain a loading dose of 180 micrograms/kg IV followed by a maintenance infusion of 15 micrograms/kg per hour (or 6 ml/hour **for 1 hour**, followed by 0.5 ml/hour of a solution made up as described below). This dose may well cause respiratory depression in a "trigger" ventilated baby. Sedation requires only 9 micrograms/kg per hour IV (0.3 ml/hour).

Antidote

Naloxone is a specific antidote for all the opioid drugs.

Supply and administration

10 mg ampoules of diamorphine (costing £1.40) can be provided on request. The ampoule should be reconstituted with 1 ml of water to give a solution containing 10 mg/ml. To set up a continuous infusion, dilute this reconstituted liquid to 10 ml with 0.9% sodium chloride; place 1.5 ml of this diluted preparation for each kilogram the baby weighs in a syringe, dilute to 50 ml with 10% dextrose saline, and infuse at a rate of 0.5 ml/hour in order to provide a continuous infusion of 15 micrograms/kg per hour. The drug is stable in solution, so it is not necessary to change the infusate daily.

Storage and administration of diamorphine is controlled under Schedule 2 of the UK Misuse of Drugs Regulations 1985 (Misuse of Drugs Act, 1971).

References

- Barker DP, Simpson J, Barrett DA, *et al.* Randomised double blind trial of two loading dose regimens of diamorphine in ventilated newborn infants. *Arch Dis Child* 1995; **73**:F22–6. [RCT]
- Barrett DA, Barker DP, Rutter N, *et al.* Morphine, morphine 6 glucuronide and morphine 3 glucuronide pharmacokinetics in newborn infants receiving diamorphine infusions. *Br J Clin Pharmacol* 1996; **41**:531–7.
- Bauer CR. Perinatal effects of prenatal drug exposure. Neonatal aspects. *Clin Perinatol* 1999; **26**:87–106.
- Siney C, ed. *Pregnancy and drug misuse*. Hale: Books for Midwives Press, 1999.

See also relevant Cochrane reviews 

DIAZEPAM

Use

Diazepam may control seizures where phenobarbital (q.v.) fails, but a more sustained anticonvulsant effect is obtained by using the newer benzodiazepines lorazepam or clonazepam (q.v.).

Pharmacology

Diazepam is primarily an anxiolytic, but it is often used to control status epilepticus, although drug accumulation, toxicity, and increasing tolerance make the drug of limited value for long term use. It was first marketed in 1963 and widely used for many years in the UK in the treatment of pre-eclampsia, although evidence for its efficacy was always limited, and its sedative effect did nothing to control maternal blood pressure. Its use declined after large international trials showed that magnesium sulphate (q.v.) was much better at controlling convulsions in mothers with eclampsia and preventing convulsions in mothers with severe pre-eclampsia. The drug has a long half life (20–60 hours) in adults and a longer half life in late pregnancy, while the drug and its pharmacologically active metabolite, *N*-desmethyl diazepam, accumulate in both maternal and fetal tissues ($V_D \sim 1.3$ l/kg). Some (but not all) reports suggest that high dose exposure in early pregnancy could be teratogenic. All benzodiazepines cause a reduction in fetal heart rate and its variability, inducing what appears to be an extension of the normal fetal sleep state. Treatment during lactation results in the baby receiving only about a tenth of the maternal dose (on a weight for weight basis), but there are reports of sedation and poor weight gain, particularly in babies who had also been exposed to diazepam before delivery.

The half life in the neonatal period is even longer than in adults. As a result, a maternal dose of 30 mg or more in the 15 hours before delivery can cause severe hypotonia, respiratory depression, and feeding difficulties, as well as temperature instability, particularly in babies of short gestation. Chronic low dose maternal medication may possibly have a similar effect because the drug seems to accumulate in the fetus. Withdrawal symptoms with jitteriness and hypertonia have also been reported. Artificial ventilation may even be necessary for 24–48 hours because of severe hypotonia and respiratory depression in some babies whose mothers receive high doses of diazepam for eclampsia. Unpredictable respiratory depression has also been reported occasionally when diazepam is used to terminate uncontrolled seizure activity in children. While rectal diazepam will stop most neonatal seizure activity at least briefly, the drug's anticonvulsant effect is poorly sustained because diazepam is rapidly cleared from the brain and accumulates progressively in body fat. A multicentre trial to see whether buccal midazolam (q.v.) provides as safe and effective a strategy for controlling tonic clonic convulsions in young children, particularly where IV access proves difficult, is currently nearing completion in the UK. For details contact Richard Appleton in Liverpool (tel: 0151 252 5851/5375).

Drug interactions

Concurrent treatment with phenytoin or carbamazepine may reduce the half life of diazepam.

Treatment

IV administration: The amount necessary to control status epilepticus in the neonatal period can be extremely variable (0.1–2.7 mg/kg in one published series). 200 micrograms/kg is a common starting dose. High doses can cause respiratory depression. Prolonged infusions are not recommended.

Rectal administration: The drug is rapidly absorbed when administered as a rectal solution (achieving good plasma levels after 5 minutes, and a peak level after 15 minutes). The usual starting dose in the neonatal period is 500 micrograms/kg, but this can be repeated safely at least once after 10 minutes if seizures persist or recur. It is not easy to administer small doses accurately.

Antidote

Flumazenil is a specific antidote (as described in the monograph on midazolam).

Supply

The emulsified IV oil in water formulation (Diazemuls®) is to be preferred for neonatal use; 2 ml (10 mg) ampoules cost 76p. Other IV formulations are more irritant, and potentially toxic, because they contain benzyl alcohol (15–55% w/v). Some also contain 40% w/v propylene glycol. A rapidly absorbed rectal preparation (Stesolid®) is also available in 2.5 ml tubes containing 2.5, 5 or 10 mg of diazepam per tube (costing between 90p and £1.60 each). Because of slow and incomplete absorption, diazepam should not be given IM.

References

- Smith BT, Masotti RE. Intravenous diazepam in the treatment of prolonged seizure activity in neonates and infants. *Dev Med Child Neurol* 1971;13:630–4.
- Cree JE, Meyer J, Harley DM. Diazepam in labour: its metabolism and effect on the clinical condition and thermogenesis of the newborn. *BMJ* 1973;iv:251–5.
- Rainbow J, Browns GJ, Lam LT. Controlling seizures in the prehospital setting: diazepam or midazolam? *J Paediatr Child Health* 2002;38:582–6.

See also relevant Cochrane reviews



Use

Diazoxide is used to treat intractable hypoglycaemia due to persisting hyperinsulinism.

Pharmacology

Diazoxide has been used to control severe hypertension in pregnancy, but prolonged use can affect neonatal glucose homeostasis. Long term outcomes have not been reported. High dose (75 mg) bolus use can cause dangerous maternal hypotension while use during labour it may affect uterine tone and delay labour unless oxytocin is prescribed as well. Its use during lactation has not been studied.

In infancy, diazoxide is used to control hypoglycaemia associated with hyperinsulinism. Insulin secretion by pancreatic β cells is controlled by adenosine triphosphate (ATP) sensitive potassium (K_{ATP}) channels. In the presence of glucose the channels close, leading to depolarisation of the cell membrane, an influx of calcium ions, and insulin secretion. Diazoxide inhibits insulin secretion by opening K_{ATP} channels.

Neonatal hyperinsulinism sometimes resolves within 1–2 days (e.g. infants of diabetic mothers), when drug treatment is unnecessary. In other babies, hyperinsulinism can persist for 2–4 weeks (usually following intrauterine growth retardation or perinatal asphyxia); diazoxide can be helpful in these patients. Persisting hyperinsulinaemic hypoglycaemia of infancy ("nesidioblastosis") is a heterogeneous condition, but most cases appear to result from genetic defects. Diazoxide is most often effective in relatively mild cases. Severely affected patients require partial pancreatectomy (for focal adenomatous islet cell hyperplasia), or subtotal pancreatectomy (for diffuse β cell hyperplasia).

For the treatment of hyperinsulinism, diazoxide should generally be given orally, as it is well absorbed by mouth and has a long half life (10–20 hours). In patients who are thought to have transient hyperinsulinism, fasting tolerance should be monitored about 5 days after diazoxide is withdrawn, to ensure that there is no longer a risk of hypoglycaemia. Complete resolution is less likely in babies with hyperinsulinism persisting beyond the neonatal period, but the severity of the problem decreases with time and it is often possible to withdraw diazoxide after the age of 5–6 years. Excessive hair growth is almost inevitable if treatment is continued for more than a few months. Blood dyscrasias have been seen with prolonged use. Giving 100–200 micrograms/kg of oral nifedipine (q.v.) once every 6 hours may help. Although diazoxide is a thiazide derivative, it has an antidiuretic effect. Chlorothiazide (10 mg/kg twice daily) prevents fluid and salt retention and helps to raise glucose concentrations.

Treatment

Try 5 mg/kg of diazoxide orally or IV twice a day in the management of persistent hypoglycaemia. Avoid IV administration where possible and watch for possible tissue extravasation. Doses in excess of 15 mg/kg per day seldom confer any additional benefit.

Concurrent use of octreotide

Babies who cannot be weaned from IV glucose with diazoxide are likely to require subtotal pancreatectomy, but, while this step is being contemplated, may be stabilised by the use of 5 micrograms/kg of octreotide (a synthetic octopeptide analogue of the natural hypothalamic hormone somatostatin) given subcutaneously every 6–8 hours. Rarely, doses of as much as 7 micrograms/kg may be required every 4 hours. Such treatment should be contemplated only under the direct supervision of a consultant paediatric endocrinologist. There is no animal evidence to suggest that octreotide is fetotoxic or teratogenic and, since the drug is ineffective when given by mouth, there is no realistic likelihood of maternal use being hazardous during lactation.

Supply

Ampoules of diazoxide (300 mg in 20 ml) cost £30 each. They should be protected from light. A sugar-free oral suspension that is stable for 1 week can be provided on request.

1 ml single dose ampoules containing 50 micrograms of octreotide (costing £3.50 each) are available, as are 5 ml multidose vials containing 200 micrograms/ml (costing £65). Ampoules and vials are best stored at 4–8°C, but they are stable at room temperature for 2 weeks. Multidose vials can be kept for 2 weeks once open.

References

- Michael CA. Intravenous labetalol and intravenous diazoxide in severe hypertension compromising pregnancy. *Aust NZ J Obstet Gynaecol* 1986;**26**:26–9. [RCT]
- Cresto JC, Abdenur JP, Bergada I, et al. Long term follow up of persistent hyperinsulinaemic hypoglycaemia of infancy. *Arch Dis Child* 1998;**79**:440–4.
- Schwitzgebel VM, Gitelman SE. Neonatal hyperinsulinism. *Clin Perinatol* 1998;**25**:1015–38.
- de Lonray-Debeney P, Poggi-Travert F, Fournet J-C, et al. Clinical features of 52 neonates with hyperinsulinism. *N Engl J Med* 1999;**340**:1169–75.
- Aynsley-Green A, Hussain K, Hall J, et al. Practical management of hyperinsulinism in infancy. *Arch Dis Child* 2000;**82**:F98–F107.

DIGOXIN

Use

Digoxin is still sometimes used in supraventricular tachycardia. It is less certain whether it still has any real value in the management of other cardiac problems in the newborn period.

Pharmacology

William Withering's description in 1785 of the value of the foxglove leaf as a herbal remedy for "dropsy" (or cardiac failure) is well known. The active ingredient, digoxin, is still sometimes used to control supraventricular tachycardia in utero, because placental transfer is relatively brisk after maternal digitalisation. Aim for a level at the top of the therapeutic range. It is by no means universally effective, however, especially in the hydropic fetus, and flecainide (q.v.) may be a better first option. Quinidine sulphate (starting with 200 mg every 6–8 hours) has occasionally been of benefit in fetuses with atrial flutter after prior digitalisation. Adenosine (q.v.) is the most appropriate first line treatment for this arrhythmia after birth. Digoxin is present in breast milk but this excretion can be ignored when considering clinical management. Digoxin is largely eliminated by the kidney without prior degradation (clearance exceeding glomerular filtration rate). Marked tissue binding occurs, the myocardial levels being linearly related to (and some 20 times) the serum concentration, and twice as high in infancy as in adults, while the neonatal serum half life (55–90 hours) is nearly three times as long as in adults ($V_d \sim 9$ l/kg). Clearance is not affected by the serum level, so doubling the dose will double the serum concentration.

Drug interactions

Patients on indometacin (q.v.), may need a lower dose. The same is occasionally true with erythromycin (q.v.). Arrhythmias have been reported when digitalised patients are given pancuronium or suxamethonium (q.v.).

Treatment

The conventional starting dose in micrograms/kg is:

Weight (kg)	Total slow IV loading dose	Total oral loading dose	Daily oral maintenance dose
< 1.5	20	25	5.0
1.5–2.5	30	35	7.5
> 2.5	35	45	10.0

Seek consultant advice. Give half the total loading dose immediately, and a quarter of the total dose after 8 and 16 hours. Digoxin is rather erratically absorbed IM and bioavailability when given by mouth is only 80% of that achieved by IV administration (as reflected above). Use a reduced dose in babies with renal failure and monitor the blood level. **Check each dose carefully.** An overdose can cause serious arrhythmia and a life threatening reduction in cardiac output without warning.

Toxicity

While electrocardiographic signs may appear when the neonatal serum level exceeds 2 µg/l (2.5 nmol/l), *clinical* symptoms (with partial AV block or a PR interval of >0.16 seconds) appear only when the level exceeds 3 µg/l. Serum levels are not the best way to define toxicity. Control hyperkalaemia with salbutamol (q.v.). Give atropine for AV block, and lignocaine or (if this fails) phenytoin (q.v.) for tachyarrhythmia. Severe bradycardia or block may require transvenous pacing. Ventricular fibrillation will respond only to a DC shock. Control severe toxicity by infusing digoxin specific antibody fragments (F (ab)) marketed by Wellcome as Digibind® after first contacting the local poisons centre for advice.

Blood levels

Levels can take 10 days to stabilise because of the 2–4 day half life. Collect at least 0.2 ml of serum or plasma 6 or more hours after the last dose was administered. (1 µg/l = 1.28 nmol/l).

Supply

Each 1 ml (100 microgram) ampoule costs £5.20. The oral elixir (Lanoxin PG®) containing 50 micrograms/ml costs 9p per ml. Both products contain 10% v/v ethanol; the ampoules contain 40% and the oral syrup 5% v/v propylene glycol. Digoxin should not be given as an IM injection. Digibind is available in vials costing £83 each.

References

- Hastreiter AR, John EG, van der Horst RL. Digitals, digitalis antibodies, digitalis-like immunoreactive substances, and sodium homeostasis: a review. *Clin Perinatol* 1988;15:491–522.
- Azancot-Benisty A, Jacqz-Aigrain E, Guiris NM, *et al.* Clinical and pharmacological study of fetal supraventricular tachyarrhythmias. *J Pediatr* 1992;121:608–13.
- Oudijk MA, Ruskamp JP, Ambachtsheer BE, *et al.* Drug treatment of fetal tachycardias. *Pediatr Drugs* 2002;4:49–63.

See also relevant Cochrane reviews



Use

Dobutamine can increase cardiac output in babies with poor ventricular function. Milrinone (q.v.) should be tried if this proves ineffective, remembering that cardiac output matters more than blood pressure.

Physiology

The normal relationship between systolic blood pressure and gestation at birth is shown in Fig. 1. Pressures rise significantly during the first week of life and then more slowly after that; 95% of babies will have a systolic value within $\pm 35\%$ of the relevant mean shown in Fig. 2 during the first 10 days of life. Thus, the most likely value for a 6 day old baby of 25 weeks gestation is 50 mmHg, and most will have a systolic pressure of between 33 mmHg and 67 mmHg (95% confidence intervals).

Pharmacology

Dobutamine hydrochloride is a synthetic inotropic catecholamine developed in 1973 by the systemic alteration of isoprenaline with a view to reducing some of the latter's unwanted adrenergic effects (i.e. chronotropism, arrhythmias, vascular constriction). It has to be given IV because of rapid first pass metabolism. Dobutamine is a β_1 agonist like dopamine, but in high doses its β_2 effects can decrease rather than increase peripheral resistance. For a brief summary of how drug receptors act see the monograph on noradrenaline. Dobutamine is about four times as potent as dopamine in stimulating myocardial contractility in low concentration, and of proven value in increasing left ventricular output in the hypotensive preterm neonate, but it has less effect than dopamine on blood pressure because it has little effect on systemic vascular resistance. Clearance is very variable in children, so the right dose to use needs to be *individually assessed* (something that can be done after 10–15 minutes because of the drug's short half life). Tachycardia may occur, and increased pulmonary blood pressure leading to pulmonary oedema has been reported. In general, however, side effects are rare as long as the dose does not exceed 10 micrograms/kg per minute. Note that the use of the drug in children has not yet been endorsed by the manufacturers.

Treatment

Start with 5 micrograms/kg per minute (0.5 ml/hour of a solution made up as described below). Adjust this dose as necessary after ~20 minutes because of the drug's variable half life (see above), accepting that a few babies need three times as much. Prepare a fresh solution every 24 hours.

Compatibility

Dobutamine is compatible with noradrenaline (q.v.), and with the same drugs as for dopamine (q.v.). Do not mix with sodium bicarbonate (q.v.).

Supply and administration

20 ml vials of dobutamine hydrochloride costing £8.30 each contain 12.5 mg/ml of dobutamine. To give 10 micrograms/kg of dobutamine per minute place 2.4 ml (30 mg) of this solution for each kilogram that the baby weighs in a syringe, dilute to 50 ml with 10% dextrose or dextrose saline, and infuse at a rate of 1 ml/hour. Less concentrated solutions of dextrose or dextrose saline can be employed.

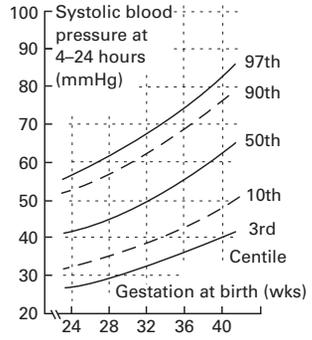


Figure 1

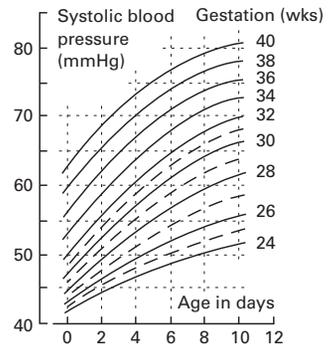


Figure 2

References

Martinez AM, Padbury JF, Thio S. Dobutamine pharmacokinetics and cardiovascular responses in critically ill neonates. *Pediatrics* 1992;**89**:47–51.
 Steinberg C, Notterman, DA. Pharmacokinetics of cardiovascular drugs in children: inotropes and vasopressors. *Clin Pharmacokinetics* 1994;**27**:345–67.
 Northern Neonatal Nursing Initiative. Systolic blood pressure in babies of less than 32 weeks gestation in the first year of life. *Arch Dis Child* 1999;**80**:F38–F42.
 Kluckow M, Evans N. Low systemic blood flow in the preterm infant. *Semin Perinatol* 2001;**6**:75–84.
 Osborn D, Evans N, Kluckow M. Randomised trial of dobutamine versus dopamine in preterm infants with low systemic blood flow. *J Pediatr* 2002;**140**:183–91. [RCT]

See also relevant Cochrane reviews



DOMPERIDONE

Use

The main recognised use for this drug in children is in the short term management of severe nausea in patients undergoing chemotherapy and radiotherapy. However, the drug's effect on upper gastrointestinal motility is also leading to increased postoperative use, and to use in the management of severe gastro-oesophageal reflux, although there is, as yet, little controlled trial evidence of efficacy.

Pharmacology

Domperidone is a dopamine D_2 receptor antagonist used to relieve nausea and vomiting, which works by stimulating gastric and upper intestinal motility as well as by acting on the chemoreceptor trigger zone. It would also seem, like metoclopramide (q.v.) to *increase* gastro-oesophageal, and *decrease* pyloric sphincter tone. It first came into clinical use in 1978, largely as a potent antiemetic. Because of its effect on prolactin excretion it was, at one time, given to women with premature babies in order to stimulate their milk yield. Dystonic and extrapyramidal reactions are much rarer than with metoclopramide, probably because only a little of the drug crosses the blood-brain barrier. Domperidone is rapidly metabolised by the liver after absorption into the portal vein following oral administration and, because of this "first pass" metabolism, systemic bioavailability is quite low (15%). The volume of distribution in adults is high ($V_d \sim 5.5$ l/kg) and the elimination half life is about 7 hours, most of the drug being excreted in the bile and the urine, mainly as inactive metabolites. No pharmacokinetic studies seem to have been undertaken into the drug's use in infancy or childhood. Sustained use for more than 12 weeks is not recommended even in adults, and the manufacturers have not, as yet, made any recommendation concerning its use in children, except to control the nausea and vomiting caused by cytotoxic drugs and by radiotherapy. The drug is still available only for "investigational purposes" in the USA.

Few formal studies have been undertaken into the use of domperidone in children. One small controlled trial found only marginal benefit in the treatment of gastro-oesophageal reflux. Little is known about its use during pregnancy, but the drug is not teratogenic in animals. Breastfeeding is not contraindicated because the baby will receive less than 1% of the maternal dose when intake is calculated on a weight for weight basis. Indeed, a 10 mg dose taken three times a day has recently been reported to augment the milk supply of some mothers who have just delivered a preterm baby.

Treatment

The usual dose is 300 micrograms/kg by mouth, repeatable every 4–8 hours as necessary. There is relatively little experience of sustained use, and no published data on the drug's use in babies less than 1 month old.

Supply

Domperidone is available as a 1 mg/ml sugar-free suspension (100 ml costs 90p). Small quantities (packs containing not more than twenty 10 mg doses) are available "over the counter" in the UK to treat flatulence, epigastric discomfort, and heartburn in adults.

References

- O'Meara A, Mott M. Domperidone as an antiemetic in pediatric oncology. *Cancer Chemother Pharmacol* 1981;**6**:147–9.
- Hofmeyr GJ, van Iddekinge B. Domperidone and lactation. *Lancet* 1983;**i**:647.
- Hofmeyr GJ, van Iddekinge B, Blott JA. Domperidone: excretion in breast milk and effect on puerperal prolactin levels. *Br J Obstet Gynaecol* 1985;**92**:141–4.
- Grill BB, Hillemeier AC, Semeraro LA, et al. Effects of domperidone therapy on symptoms and upper gastrointestinal motility in infants with gastroesophageal reflux. *J Pediatr* 1985;**106**:311–16.
- Bines JE, Quinlan J-E, Treves S, et al. Efficacy of domperidone in infants and children with gastroesophageal reflux. *J Pediatr Gastroenterol Nutr* 1992;**14**:400–5. [RCT]
- Da Silva OP, Knoppert DC, Angelini MM, et al. Effect of domperidone on milk production in mothers of premature newborns: a randomized, double-blind, placebo-controlled trial *CMAJ* 2001;**164**:17–21. [RCT]

Use

Dopamine hydrochloride has been widely used to control neonatal hypotension, but it has a variable, unpredictable, and dose dependent impact on vascular tone. Its use too often fails to recognise that adequate tissue perfusion, rather than supply pressure *per se* must be the primary aim of treatment. Studies suggest that hydrocortisone (q.v.) is sometimes better at raising neonatal blood pressure. A dobutamine or adrenaline (q.v.) infusion should be used if low cardiac output is the primary problem.

Pharmacology

Dopamine is a naturally occurring catecholamine precursor of noradrenaline (q.v.) that was first synthesised in 1910 and shown to be a neurohormone in 1959. **Low** dose infusion (2 micrograms/kg per minute) normally causes dopaminergic coronary, renal, and mesenteric vasodilatation, but there is little evidence that this is clinically beneficial, and good controlled trial evidence that such treatment does *not* protect renal function in adults with septic shock. **High** doses cause vasoconstriction, increase systemic vascular resistance, and eventually decrease renal blood flow. Although there is good evidence that moderate doses increase myocardial contractility and cardiac output in adults and older children, they often cause an increase in systemic resistance, a fall in gut blood flow, and a *reduction* in cardiac output in the neonate. The response of individual patients is hard to predict. The use of this drug in children has not yet been endorsed by the manufacturer. There are no known teratogenic effects.

High doses, in particular, should be used with caution after cardiac surgery, or where there is coexisting neonatal pulmonary hypertension, because the drug can cause a detrimental change in the balance between pulmonary and systemic vascular resistance. Doses of more than 15 micrograms/kg per minute can cause tachycardia and arrhythmia in adults, but some have claimed benefit from high dose neonatal use. Correct any acidosis first, and look to see if there is a reason for the hypotension before just treating the symptom itself. Lack of response may suggest vasopressin (q.v.) exhaustion. Most side effects are easily controlled by stopping the infusion because the neonatal half life is only 5–10 minutes.

Drug interactions

There are reports of phenytoin and tolazoline (q.v.) causing severe hypotension in patients on dopamine.

Hazards

Extravasation can cause dangerous ischaemia. It has been traditional to manage this by immediate infiltration with not more than 5 mg of phentolamine mesilate (Rogitine®) in 5 ml 0.9% sodium chloride using a fine needle, but 1 inch (16 mg) of topical 2% glyceryl trinitrate ointment (q.v.) may prove a simpler and equally effective strategy. Because limb ischaemia has been reported even in the absence of extravasation, the infusion should be stopped at once if significant blanching appears along the side of the vein. Many units infuse high doses only through a long line threaded into a major vein.

Treatment

Start with a low dose infusion (3 micrograms/kg per minute, or 0.3 ml/hour of a solution made up as described below), and increase as indicated with ultrasound assessment if possible. The response (like the drug's blood level) varies greatly. Prepare a fresh infusion daily. Stop high dose treatment slowly.

Compatibility

Dopamine is inactivated by alkali but can be added (terminally) to a line containing standard total parenteral nutrition when absolutely necessary, and to a line containing fentanyl, lidocaine, midazolam, milirone, or morphine. It can also be put in the same syringe as dobutamine to simplify nursing supervision when both drugs are being infused simultaneously at an unvarying rate. See also the monograph on heparin.

Supply and administration

One stock 5 ml (200 mg) ampoule (pH 2.5–4.5) costs £3.90 To give an infusion of 1 microgram/kg per minute of dopamine, place in a syringe 0.75 ml (30 mg) of the concentrate for each kilogram the baby weighs, dilute to 50 ml immediately before use with 10% dextrose saline and infuse at a rate of 0.1 ml/hour. (A less concentrated solution of dextrose or dextrose saline can be used where necessary.)

1 ml ampoules containing 10 mg phentolamine mesilate cost £1.70 each.

References

- Wong AF, McCulloch LM, Sola A. Treatment of peripheral tissue ischaemia with topical nitroglycerin ointment in neonates. *J Pediatr* 1992;**121**:980–3.
- Rozé JC, Tohier C, Maingueneu C, *et al.* Response to dopamine and dobutamine in the hypotensive very preterm infant. *Arch Dis Child* 1993;**69**:59–63. [RCT]
- Seri I. Cardiovascular, renal and endocrine actions of dopamine in neonates and children. *J Pediatr* 1995;**126**:333–44.
- Zhang J, Penny DJ, Kim NS, *et al.* Mechanisms of blood pressure increase induced by dopamine in hypotensive preterm neonates. *Arch Dis Child* 1999;**81**:F99–104.
- ANZICS Clinical Trials Group. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. *Lancet* 2000;**356**:2139–43 (see also pp. 2112–30). [RCT]

See also relevant Cochrane reviews



DOXAPRAM

Use

Oral or IV doxapram can be useful in preterm babies who continue to have troublesome apnoea despite treatment with caffeine (q.v.). The effects of caffeine and doxapram appear to be additive.

Pharmacology

Doxapram (first developed commercially in 1964) stimulates all levels of the cerebrospinal axis, and respiration appears to be stimulated at doses that cause little general excitation. A plasma concentration of 2 mg/l doubles the minute volume in healthy adults, but there is no evidence of any additive benefit from raising the plasma level above 1 mg/l in babies. High doses cause convulsions, and subconvulsive doses can still cause tachycardia, hypertension, hyperpyrexia, jitteriness, laryngospasm, and vomiting.

Oral caffeine is usually considered the drug of choice in the management of idiopathic neonatal apnoea but adding doxapram can sometimes bring additional benefit. The drug is usually given as a continuous infusion, but oral treatment is often very effective as long as the dose is doubled to compensate for poor absorption. Developmental delay is not uncommon in survivors and, while severe apnoea may merely be the first sign of some existing cerebral dysfunction that later manifests as developmental delay, a drug related effect cannot be ruled out until an appropriately designed trial is done. Nasal continuous positive airway pressure (CPAP) may make tracheal intubation and ventilation unnecessary.

Doxapram is metabolised by the liver, the half life in babies (about 7 hours) being double that seen in adults. It is longer still in the first week of life. Significant tissue accumulation occurs ($V_D \sim 6$ l/kg), and some of the metabolic breakdown products are also potentially metabolically active. The optimum respiratory response is usually seen with a plasma level of 2–4 ng/ml, but the dose needed to achieve this plasma level varies. Adverse effects are increasingly common when the level exceeds 5 ng/ml. The dose recommended in certain neonatal texts (2.5 mg/kg per hour) is almost certainly potentially toxic in some babies, (especially if there is evidence of an intraparenchymal cerebral bleed or an existing seizure disorder). Watch for adverse effects (including hyperexcitability, atrioventricular heart block, and a rise in blood pressure if more than 1 mg/kg per hour has to be infused for more than 36–48 hours), remembering that doxapram's use in children has not yet been endorsed by the manufacturers.

Treatment

IV administration: Start with 2.5 mg/kg as a loading dose over at least 5–10 minutes, followed by a maintenance infusion of 300 micrograms/kg per hour (0.3 ml/hour of a solution made up as described below) and increase the dose cautiously as required. Babies over 1 week old sometimes respond only to a continuous infusion of 1 or even 1.5 mg/kg per hour. Tissue extravasation can cause skin damage.

Oral administration: Babies who respond to IV doxapram can usually be transferred to oral maintenance treatment. Take half the total daily dose found to be effective IV and give this once every 6 hours by mouth, diluted in a little 5% dextrose. High dose oral treatment sometimes slows gastric emptying. Such problems can usually be resolved by reverting to IV treatment.

Postanaesthetic use: A single 1 mg/kg IV bolus dose will sometimes rouse the postoperative preterm baby.

Compatibility

Doxapram can probably be added (terminally) into a line containing standard total parenteral nutrition (but not lipid) when absolutely necessary.

Supply and administration

5 ml (100 mg) ampoules cost £2.10. To give an infusion of 1 mg/kg per hour of doxapram, place 2.5 ml of the concentrate for each kilogram the baby weighs in a syringe, dilute to 50 ml with 10% dextrose saline, and infuse at 1 ml/hour. (A less concentrated solution of dextrose or dextrose saline can be used where necessary.) Doxapram is stable in solution, so IV lines do not require changing daily, nor does material prepared for oral use. The US formulation contains 0.9% benzyl alcohol.

References

- Kumita H, Mizuno S, Shinohara M, *et al.* Low-dose doxapram therapy in premature infants and its CSF and serum concentrations. *Acta Paediatr Scand* 1991;**80**:786–91.
- Aranda JV, Lopes JM, Blanchard P, *et al.* Treatment of neonatal apnoea. In: Rylance G, Harvey D, Aranda JV, eds. *Neonatal clinical pharmacology and therapeutics*. Oxford: Butterworth-Heinemann, 1991:95–115.
- De Villiers GS, Walele A, Van der Merwe P-L, *et al.* Second-degree atrioventricular heart block after doxapram administration. *J Pediatr* 1998;**133**:149–50.
- Huon C, Rey E, Mussat P, *et al.* Low-dose doxapram for treatment of apnoea following early weaning in very low birthweight infants: a randomised double-blind study. *Acta Paediatr* 1998;**87**:1180–4. [RCT]
- Poets CF, Darraj S, Bohnhorst B. Effect of doxapram on episodes of apnoea, bradycardia and hypoxaemia in preterm infants. *Biol Neonate* 1999;**76**:207–13.
- Sreenan C, Etches PC, Demianczuk N, *et al.* Isolated developmental delay in very low birth weight infants: association with prolonged doxapram therapy of apnea. *J Pediatr* 2001;**139**:832–7. (See also 2002;**141**:296–7.)

See also relevant Cochrane reviews



Use

IV enoximone is sometimes used in the short term management of heart failure that fails to respond to other forms of treatment. Milrinone (q.v.) is an easier drug to administer.

Pharmacology

Enoximone (patented in 1980) is a selective phosphodiesterase inhibitor that acts mainly on the myocardium as an inotrope. It is, however, also a mild vasodilator. Long term oral use seems to be associated with an increase in mortality in adults with congestive failure, and the drug is now used only in the short term IV management of patients in whom a low cardiac output persists despite treatment with a catecholamine such as dobutamine (q.v.). Preoperative monitoring has certainly shown enoximone to be of short term benefit in restoring myocardial function after bypass surgery. It seems to work by increasing the intracellular concentration of cyclic AMP. This could explain why the drug's effectiveness seems to be enhanced by the simultaneous use of a catecholamine to stimulate the cardiac β receptors. Enoximone is excreted in the urine, but is also partially metabolised in the liver, the half life in healthy adults being about 90 minutes. Its use could be hazardous in patients with outlet obstruction or hypertrophic cardiomyopathy (as with any inotrope). There is no published evidence relating to the use of enoximone in pregnancy, and it is not known whether the drug is excreted into breast milk. There is no animal evidence of teratogenicity. The manufacturers have not yet endorsed the use of enoximone in children.

Treatment

Give 600 micrograms/kg of enoximone over 15 minutes (0.24 ml of a solution made up as described below for each kilogram the baby weighs). Continuing this same infusion at a rate of 0.24 ml/kg per hour then provides a maintenance infusion of 10 micrograms/kg per minute. Maintenance doses of up to 20 micrograms/kg per minute have sometimes been used for short periods, but drug accumulation could be a hazard where there is renal failure. The benefits seen at the start of treatment seem to wane with time. Treatment following corrective cardiac surgery is seldom continued for more than 1 or 2 days. Prepare a fresh solution once every 24 hours.

Propylene glycol toxicity

Enoximone contains 41.3% w/v of propylene glycol, and sustained high dose administration is known to have caused severe hyperosmolality. Some propylene glycol is metabolised by the liver, but much is excreted unmetabolised in the urine. Renal failure would, therefore, increase the risk of toxicity.

Propylene glycol is widely used as a solvent in IV drugs, and is also a component of many topical pharmaceutical creams. Although it is relatively non-toxic, excess intake can certainly be harmful. The first sign of accumulation is usually an otherwise unexplained rise in osmolality. Symptoms have included stupor, seizures, and lactic acidosis. Arrhythmias have developed in animals.

Supply and administration

20 ml ampoules containing 5 mg/ml cost £15. Dilute immediately before use with an equal volume of water for injection to obtain a solution containing 2.5 mg/ml, and prepare a fresh solution once every 24 hours. (Enoximone should not be co-infused with any other drug. It is incompatible with dextrose, and dilution with 0.9% sodium chloride imposes a relatively large obligatory sodium load on the baby. The manufacturers are not even prepared to say that it is safe to infuse enoximone through a terminal Y connector into a line containing glucose because solubility problems cause rapid crystal formation.) Troublesome crystal deposition can even narrow, and occasionally block, a narrow IV line even when the drug is infused in saline. Make sure that the solution is still a clear yellow colour prior to administration. Keep ampoules at below 20°C (they are conveniently stored at 4°C).

References

- Huggon I, James I, Macrae D. Hyperosmolality related to propylene glycol in an infant treated with enoximone infusion. *BMJ* 1990;**301**:19–20.
Vernon MW, Heel RC, Brogden RN. Enoximone: a review of its pharmacological properties and therapeutic potential. *Drugs* 1991;**42**:997–1017.
Hausdorf G, Friedel N, Berdjis F, et al. Enoximone in newborns with refractory postoperative low-output states (LOS). *Eur J Cardiothorac Surg* 1992;**6**:311–17.
Innes PA, Frazer RS, Booker PE, et al. Comparison of the haemodynamic effects of dobutamine with enoximone after open heart surgery in small children. *Br J Anaesth* 1994;**72**:77–81.

EPOPROSTENOL (Prostacyclin)

Use

Epoprostenol has not lived up to its early promise as a treatment for babies with persistent transitional circulation, but there have been a few reports of IV (or nebulised) administration improving oxygenation in the term baby even, occasionally, when treatment with nitric oxide (q.v.) proved ineffective.

Pharmacology

Epoprostenol (PGI₂) is a prostaglandin-like substance first discovered in 1976. It is an extremely powerful inhibitor of platelet aggregation sometimes used during renal dialysis and in the management of haemorrhagic meningococcal purpura. Epoprostenol produces rapid dose related decreases in pulmonary arterial pressure and pulmonary vascular resistance, and came to be used experimentally, therefore, in the management of babies with persistent pulmonary hypertension or cyanosis due to a persisting transitional circulation. The drug is not metabolised during passage through the lungs, but it has only a 3 minute half life, making continuous infusion necessary. The drug's rapid action makes efficacy easy to judge but it can also leave the baby very drug dependent. Tolazoline (q.v.) is much less expensive, but has a much longer half life.

Early experience was encouraging, but a multicentre trial in the 1980s was discontinued because the results were so disappointing, and most experience since then has been equally discouraging. Systemic hypotension can also be a serious problem because of marked systemic vasodilatation. However, since it seems likely that persistent pulmonary hypertension can be caused in a number of different ways, and triggered by different factors, it remains possible that epoprostenol could help an occasional baby. More recently there have been three reports describing the management of seven babies in whom aerosolised epoprostenol improved oxygenation *without* affecting systemic blood pressure. A reduction in intrapulmonary shunting seemed to account for much of the improvement.

Treatment

Inhaled: Try giving 20 nanograms/kg per minute using a SPAG-2 aerosol generator. Double this dose has also been used with apparent safety. Tail off treatment gradually.

Intravenous: Try a continuous IV infusion of 12 nanograms/kg per minute of epoprostenol (0.3 ml/hour of a solution made up as specified below) to stimulate pulmonary artery vasodilatation, and watch carefully for systemic hypotension. If there is no response it is worth trying a 20 nanograms/kg per minute dose at least briefly. Even higher doses have been used anecdotally.

Supply and administration

Vials containing 500 micrograms of powder (costing £69), with 50 ml of glycine diluent buffer for reconstitution, are available from the pharmacy. Vials and diluent must be stored at 2–8°C, protected from light, and discarded promptly after use. To prepare epoprostenol for use draw 10 ml of sterile diluent (pH 10.5) into a syringe, inject into the epoprostenol vial, and dissolve the contents completely. Draw the epoprostenol back into the syringe and reunite the contents of the syringe with the residue of the original 50 ml of diluent. A filter is provided for use when drawing up the concentrate. Take 6 ml of the filtered concentrate for every kilogram the baby weighs, dilute to 25 ml with 0.9% sodium chloride, and infuse at 0.5 ml/hour to infuse 20 nanograms/kg per minute of epoprostenol. Do not dilute the concentrate more than 1 in 6, or with any fluid other than 0.9% sodium chloride. Make up a fresh supply once every 24 hours (the manufacturer recommends once every 12 hours but potency falls only 5% in this time). Watch for tissue extravasation, and tail off any infusion over a number of hours.

References

- Lock JE, Olley PM, Coceani F, *et al.* Use of prostacyclin in persistent fetal circulation. *Lancet* 1979;**i**:1343.
- Kaapa P, Koivisto M, Ylikorkala O, *et al.* Prostacyclin in the treatment of neonatal pulmonary hypertension. *J Pediatr* 1985;**107**:951–3.
- Hammerman C, Yousefzadeh D, Choi J-H, *et al.* Persistent pulmonary hypertension in the newborn. *Clin Perinatol* 1989;**16**:137–56.
- Bindl I, Fahrenstick H, Peukert U. Aerosolised prostacyclin for pulmonary hypertension in neonates. *Arch Dis Child* 1994;**71**:F214–16.
- Eronen M, Pohjavouri M, Andersson S, *et al.* Prostacyclin treatment for persistent pulmonary hypertension of the newborn. *Pediatr Cardiol* 1997;**18**:3–7.
- Soditt V, Aring C, Gronceck P. Improvement in oxygenation in a preterm infant with persistent pulmonary hypertension of the newborn. *Intensive Care Med* 1997;**23**:1275–8.
- Kelly LK, Porta NFM, Goodman DM, *et al.* Inhaled prostacyclin for term infants with persistent pulmonary hypertension refractory to inhaled nitric oxide. *J Pediatr* 2002;**141**:830–2.

Use

Erythromycin is used to treat neonatal *Chlamydia*, *Mycoplasma*, and *Ureaplasma* infection and to reduce whooping cough cross infection. It marginally, but usefully, delays delivery in a few women with preterm prelabour rupture of membranes (pPROM), and helps some babies with gut motility problems.

Pharmacology

This broad spectrum macrolide antibiotic, first isolated in 1952, does not enter the cerebrospinal fluid. A little crosses the placenta but the amount ingested in breast milk exposes the baby (weight for weight) to only 1% of the maternal dose. Erythromycin (1 g IV every 8 hours) can be given in labour to women who are allergic to penicillin and at risk of intrapartum group B streptococcal infection (see penicillin monograph). Giving mothers with pPROM 250 mg by mouth four times a day reduced delivery within 48 hours by 15% in the large ORACLE trial, but reduced neonatal postdelivery problems only enough for some differences to become statistically significant in singleton pregnancy (which was not a prespecified trial outcome). Only follow up will establish whether these statistical differences are of clinical importance. A single 1 g dose of the related drug azithromycin clears maternal genital infection due to *Chlamydia trachomatis*.

Erythromycin is well absorbed by mouth and IV treatment is seldom necessary. The oral preparation (erythromycin ethylsuccinate) has to be hydrolysed to the active base after absorption, and the ester occasionally causes reversible liver toxicity. Sudden arrhythmia has occurred when the drug has been given IV too rapidly, while vomiting and diarrhoea (occasionally caused by pseudomembranous colitis) have been reported in older children, but the drug is, in most respects, one of the more innocuous antibiotics in current use. The serum half life is short (2–4 hours), is unaffected by renal function, and changes little during the neonatal period. Some of the drug appears in bile and urine but most is unaccounted for. Erythromycin is a motilin receptor agonist, with advantages over cisapride (q.v.), but early and high dose use must be balanced against a knowledge that this increases the risk of pyloric stenosis.

Chlamydial infection

Chlamydiae are small intracellular bacteria that need living cells to multiply. Genitourinary infection with *Chlamydia* is sexually transmitted and particularly common in young women who have had a new sexual partner in the last 12 months and are not using barrier contraception. Some 5% of women of childbearing age are infected, but two thirds have no symptoms and, since infection is responsible for two thirds of all tubal infertility and nearly half of all tubal pregnancies, screening should be available to all high risk groups. It should certainly be offered to all women requesting an abortion, and to all women aged under 25 who are booking for antenatal care. Babies of infected mothers frequently develop infective conjunctivitis at delivery, and a few develop an afebrile pneumonitis. Failure to recognise that this is due to *Chlamydia*, and to refer as appropriate, exposes the mother to all the risks associated with progressive unchecked pelvic inflammatory disease.

Drug interactions

Erythromycin increases the half life of midazolam, theophylline, and carbamazepine, producing potential toxicity. Its effect on the half life of caffeine has not yet been clarified. Increased oral bioavailability can also cause toxicity in a minority of patients on digoxin. Erythromycin also seems to potentiate the anticoagulant effect of warfarin. **Never** give erythromycin to a baby taking cisapride.

Treatment

Systemic infection: Give 10 mg/kg every 6 hours by mouth, or infuse IV over 1 hour (to avoid the risk of arrhythmia) as described below. There is no satisfactory IM preparation.

Conjunctivitis: Treat chlamydial conjunctivitis with oral erythromycin and with an eye ointment 5–6 times a day for 2 weeks (as outlined in the monograph on eye drops).

Neonatal gut dysmotility: Some studies have used a low oral dose (3 mg/kg once every 6 hours).

Supply and administration

1 g vials of the IV (lactobionate) salt cost £9.40. When made up with 20 ml of water for injection (not saline), the resultant stock solution contains 50 mg/ml. Individual doses containing 5 mg/ml can be prepared by drawing 5 ml of the stock solution into a syringe and diluting this to 50 ml with non-buffered 0.9% sodium chloride (or with buffered dextrose previously prepared by adding 5 ml of 8.4% sodium bicarbonate to a 500 ml bag of 10% dextrose or dextrose saline). Give IV doses within 8 hours of preparation. The sugar-free oral suspension of erythromycin ethylsuccinate (25 mg/ml) costs 1p per ml and can be kept for up to 2 weeks after being reconstituted from the dry powder if stored at 4°C.

References

- Kenyon SL, Taylor DJ, Tarnow Mordi W for the ORACLE Collaborative Group. Broad-spectrum antibiotics for preterm prelabour rupture of fetal membranes: the ORACLE I randomised trial. *Lancet* 2001;**357**:979–88. [RCT] (Also see pp. 973–4, **358**:502–4 and 1184–5.)
Ng PC, So KW, Fung KSC, et al. Randomised controlled study of oral erythromycin for treatment of gastrointestinal dysmotility in preterm infants. *Arch Dis Child* 2001;**84**:F177–82. [RCT]
Low N, Cowan F. Genital chlamydial infection. *Clin Evid* 2003;**9**:1721–8 (and updates). [SR]

See also relevant Cochrane reviews

ERYTHROPOIETIN = Epoetin (rINN)

Use

Erythropoietin stimulates red cell production, but its impact on the need for neonatal blood transfusion is negligible if steps are taken to eliminate unnecessary blood sampling.

Pharmacology

Erythropoietin is a natural glycoprotein produced primarily in the kidneys, which stimulates red cell production, particularly when there is relative tissue anoxia. During fetal life it is mostly produced in the liver (which is presumably why babies with renal agenesis are not anaemic). Two commercial versions (epoetin alfa and epoetin beta), both synthesised using recombinant DNA technology, became available in 1986. They have identical amino acid sequences, but different glycosylation patterns. Epoetin alfa is the product most widely used in the USA, but epoetin beta is the product the manufacturer has been authorised to recommend for use in infancy in Europe. Progressive hypertension is the most serious adverse effect seen in adults, but this has not been reported in neonates to date. The platelet count may rise. Erythropoietin does not seem to cross the human placenta, and it would be destroyed in the digestive tract of the baby even if it were excreted in breast milk. Women should not be denied treatment, therefore, merely because they are pregnant or breastfeeding.

Numerous randomised and blinded, or placebo controlled, trials have now shown that early and sustained treatment with erythropoietin can stimulate red cell production in the very preterm baby, as long as supplemental iron is also given. However, large doses have to be given because clearance and the volume of distribution are both 3–4 times as high as in adult life. Treatment certainly has a place in the early care of vulnerable babies born into families who are reluctant to sanction blood transfusion on religious grounds. Nevertheless, although treatment reduces the need for replacement transfusion, especially in the smallest babies, it seldom eliminates it, and no response to treatment is generally seen for 1–2 weeks. In two recent well conducted controlled trials involving 391 babies weighing 1 kg or less at birth, high dose treatment only marginally reduced the number of transfusions given (1.86 v 2.66 in one study). Attention to reducing blood loss into the placenta and loss from unnecessary blood sampling, together with a more structured approach to transfusion policy, can be at least as effective as treatment with erythropoietin in reducing the need for blood transfusion. As long as the safety of donor blood can be assured, and care is taken to minimise the number of donors used using the strategies outlined in the monograph on blood, cost reduction is limited. Since treatment has to be started early to be effective and, since it is difficult to predict within a few days of birth which babies will later become anaemic, all high risk babies need treating, further limiting the drug's cost effectiveness.

Treatment

Give 400 units/kg by subcutaneous injection into the thigh three times a week for at least 3 weeks (treatment was continued for 6 weeks in many of the clinical trials).

Supplementary iron

Erythropoietin will fail to stimulate sustained red cell production if iron deficiency develops. A minimum of 3 mg/kg of elemental iron a day seems to be necessary in the neonatal period, which is more than in any UK formula milk (q.v.). It is common practice to give twice as much as this. For very low birth weight babies, supplementation can conveniently be achieved by giving 1 ml of oral sodium feredetate (5.5 mg of elemental iron) once a day, as outlined in the monograph on iron.

Compatibility

Erythropoietin seems equally effective when given as a continuous (but not as a bolus) infusion in parenteral nutrition (q.v.), together with 1 mg/kg a day of parenteral iron if oral iron cannot be given.

Supply

500 unit vials of recombinant human erythropoietin (epoetin beta) cost £4.20. Reconstitute with 0.5 ml of water (as supplied). Vials should be stored at 4°C. Do not freeze or shake. Discard once opened. The larger multidose vials, which contain benzyl alcohol, should not be used when treating babies.

References

- Maier RF, Sonntag J, Walka MM, *et al.* Changing practices of red cell transfusions in infants with birth weights less than 1000 g. *J Pediatr* 2000;**136**:220–4.
- Franz AR, Pohlant F. Red cell transfusions in very and extremely low birthweight infants under restrictive transfusion guidelines: is exogenous erythropoietin necessary? *Arch Dis Child* 2001;**84**:F96–100.
- Ohls RK. Human recombinant erythropoietin in the prevention and treatment of anemia of prematurity. *Pediatr Drugs* 2002;**4**:111–21.
- Garcia MG, Hutson AD, Christensen RD. Effect of recombinant erythropoietin on "late" transfusions in the neonatal intensive care unit: a meta-analysis. *J Perinatol* 2002;**22**:108–11. [SR]
- Maier RF, Obladen M, Muller-Hansen I, *et al.* Early treatment with erythropoietin β ameliorates anemia and reduces transfusion requirements in infants with birth weights below 2000 g. *J Pediatr* 2002;**140**:8–15.
- Ohls RK. Erythropoietin treatment in extremely low birth weight infants: blood in versus blood out [Editorial]. *J Pediatr* 2002;**141**:3–6.

Use

Ethamsylate was widely given for many years in an attempt to reduce the incidence of periventricular haemorrhage in babies weighing <1.5 kg in the first week of life. Use has now declined.

Pharmacology

Ethamsylate (diethyl ammonium 2,5-dihydroxybenzene sulphonate) is a water soluble non-steroidal drug that has been used for several decades to reduce capillary bleeding in adults during surgery. It is thought to work principally by maintaining capillary integrity, probably by promoting polymerisation of mucopolysaccharide in vessel walls. It may also inhibit the action of prostacyclin in adrenaline induced platelet aggregation. After systemic administration, the mean bleeding time is significantly reduced without any effect on cell counts, fibrinolysis, prothrombin time, or clotting time. The drug is excreted unchanged, mainly in the urine. It is known to cross the placenta and some also appears in breast milk but there is no evidence that such exposure constitutes any risk to the baby. Adults sometimes experience nausea; transient headaches and skin rashes have also been reported on occasion.

A double blind, placebo controlled, multicentre trial of prophylactic treatment in babies weighing <1.5 kg in the first 4 days of life in the UK in 1986 has been interpreted as showing that ethamsylate can reduce the incidence of ultrasound diagnosed intraventricular and periventricular haemorrhage by a third. Such a clearcut benefit could be identified, however, only by excluding from analysis those children who died and those who had evidence of haemorrhage when first examined shortly after birth. A more recent European trial completed in 1994 found no such benefits. Treatment was said to be associated with a modest but statistically significant improvement in outcome in survivors as assessed using the McCarthy ability scales in the UK trial, but only an abstract of these research findings has yet appeared in print. No such benefit was seen in the subsequent European trial. Recent work suggests that ethamsylate may modify prostaglandin biosynthesis, and this may help to explain the apparent reduction in symptomatic patent ductus in ethamsylate treated babies in the UK trial. No systematic overview of the various neonatal studies undertaken has yet been published.

Strategies for preventing periventricular haemorrhage

Other strategies that have been tried include giving phenobarbital or vitamin K (q.v.) before birth or fresh frozen plasma, ibuprofen, indometacin, phenobarbital, or vitamin E (q.v.) after birth. Even prophylactic ibuprofen and indometacin, the most successful strategies studied to date, have not yet been shown convincingly to improve long term outcome, even though they do reduce the number of babies developing ultrasound evidence of serious periventricular bleeding. Many of the early trials were launched before it became clear that long term disability is seldom seen in survivors unless there has been parenchymal haemorrhage (haemorrhage into the brain substance) or posthaemorrhagic hydrocephalus as well as intraventricular or subependymal bleeding. More recently it has become clear that ischaemia, rather than bleeding, causes most of the perinatal brain damage seen in babies of less than 32 weeks gestation, and that reduced cerebral perfusion shortly after birth (as documented by measuring superior vena caval blood flow) is an important marker for this. Blood flow, rather than blood pressure, would seem to be what counts, but flow (unfortunately) cannot be measured as easily as pressure.

Prophylaxis

A small number of units in the UK still offer "at risk" babies prophylactic ethamsylate. The regimen used is 12.5 mg/kg IV or IM within 1 hour of birth, and further IV doses every 6 hours for the first 4 days of life (i.e. a total of 200 mg/kg over 4 days).

Supply

2 ml ampoules containing 250 mg of ethamsylate could be ordered by the pharmacy on special request. They cost 78p per ampoule. This gives a preparation containing 12.5 mg in 0.1 ml.

References

- Benson JWT, Drayton MR, Hayward C, *et al*. Multicentre trial of ethamsylate for prevention of periventricular haemorrhage in very low birthweight infants. *Lancet* 1986;**ii**:1297–300. (see also *Lancet* 1987;**i**:623–4). [RCT]
- Schulte JF, Benson JWT, Cooke RWI, *et al*. The follow-up study of the multicentre trial of ethamsylate for prevention of periventricular haemorrhage [Abstract]. *Proceedings of the Annual Meeting of the British Paediatric Association*: April 1991. [RCT]
- The EC Ethamsylate Trial Group. The EC randomised controlled trial of prophylactic ethamsylate for very preterm neonates: early mortality and morbidity. *Arch Dis Child* 1994;**70**:F201–5. [RCT]
- Sanghi KP, Merchant RH, Karnik A, *et al*. Role of ethamsylate in preventing periventricular-intraventricular hemorrhage in premature infants below 34 weeks of gestation. *Indian Pediatr* 1999;**36**:653–8. [RCT]
- Elbourne E, Ayers S, Dellagrammaticas H, *et al*. Randomised controlled trial of prophylactic ethamsylate: follow up at 2 years of age. *Arch Dis Child* 2001;**84**:F183–7. [RCT]

EYE DROPS (and ointments)

Use

Antibiotic eye drops are used to treat acute bacterial conjunctivitis (ophthalmia neonatorum), and saline eye drops (or fresh tap water) are used to treat chemical conjunctivitis. Cyclopentolate and phenylephrine (or atropine (q.v.)) eye drops are used to dilate the pupil, proxymetacaine provides surface anaesthesia, and hypromellose eye drops ("artificial tears") are used to moisten the cornea when tear production is inadequate, or if the baby is paralysed or unconscious.

Pharmacology

Because penetration is limited and rather variable when antibiotics are prescribed topically as drops, a systemic antibiotic should always be given as well if there is serious deep seated infection. Tropicamide should be used to dilate the pupil because, unlike atropine, the effect lasts only for hours rather than days. (Adverse systemic effects, and even ileus, have been seen with long acting drugs given in excess.) The response is enhanced by using phenylephrine, an α adrenergic sympathomimetic, simultaneously. Proxymetacaine is a local anaesthetic of the ester type (like procaine) that acts by diminishing sensory nerve conduction. Hypromellose is a mixed ether of cellulose that forms a clear viscous, slightly alkaline, colloidal solution in water. Steroid eye drops (such as betamethasone) with or without antibiotic (such as neomycin) are used to minimise inflammation and the risk of infection after ocular surgery.

Microbiology

Credé pioneered in 1881 the prophylactic use of silver nitrate drops at birth to prevent blindness from gonococcal infection, and some states in the USA still have laws mandating its use. Unfortunately it is not effective against chlamydial infection, which is now commoner. In addition, it also causes a mildly irritating chemical conjunctivitis. Many of the "sticky" eyes seen soon after birth seem to be no more than a response to irritating vernix, and these are best managed by bathing the eyes regularly with fresh clean tap water. Povidone iodine provides a cheaper and more effective strategy to use in countries where routine prophylaxis is judged appropriate. The routine collection of swabs for bacteriology is expensive and rarely influences management, but swabs *should* be collected to identify the causative agent when an eye infection develops in a baby already on treatment. Their collection in babies with unusually severe or persistent inflammation will also help to identify gonococcal or chlamydial infection, and point to the need for parental treatment.

Chloramphenicol eye drops are still widely used to deal with low grade conjunctivitis (especially where this seems to be due to staphylococcal or coliform infection) except in the USA, where an unsubstantiated fear of aplastic anaemia, especially after prolonged use, has influenced prescribing. Gonococcal infection is best treated with chloramphenicol eye drops and systemic penicillin (q.v.) for 7 days. Chlamydial infection causing inclusion conjunctivitis (or, very rarely, if not treated, trachoma) should be managed with oral erythromycin (q.v.) and ointment for 2 weeks. Infection with *Pseudomonas*, which is potentially very dangerous but luckily very rare, except in the colonised preterm baby, should be treated with gentamicin eye drops and appropriate systemic antibiotics under the supervision of a consultant ophthalmologist. Look for keratitis or a corneal ulcer using fluorescein if in any doubt, after first anaesthetising the cornea. Herpes conjunctivitis as a first manifestation of generalised neonatal herpes infection requires equally expert management with topical and systemic aciclovir (q.v.). **Any** infection causing ophthalmia neonatorum is notifiable.

Swabs

Stop the use of antibiotic eye drops for a few hours before taking specimens for bacteriology and wash the eye with saline before swabbing the conjunctiva. Swabs of the purulent exudate may give negative results because the pus itself contains few viable organisms. Taking a second conjunctival swab and placing this in the transport medium provided by the Public Health Laboratory virology service will increase the chance of chlamydial infection being recognised. Smears can also be collected onto two plain glass slides for Gram stain testing to search for gonococci, and to look, by immunofluorescence, for *Chlamydia*, if the diagnosis proves elusive.

Differential diagnosis

It is important to differentiate conjunctivitis from orbital cellulitis associated with underlying ethmoiditis or maxillary osteomyelitis requiring urgent systemic treatment. A chronic watery discharge is usually due to congenital nasolacrimal duct obstruction (a very common condition that almost always cures itself and seldom needs treatment unless overt infection supervenes). The main need is to exclude congenital glaucoma, keratitis, or uveitis. Pain, photophobia, corneal clouding, and conjunctival injection are warning signs. Probing is called for only if problems persist for more than 1 year.

Contacts

The mother should always be seen and treated as well when venereally acquired neonatal gonococcal or chlamydial infection is encountered. It may also be important to trace the mother's contacts.

continued ...

Application

Wait if possible until the baby is awake (e.g. immediately before a feed). Wash your hands before handling the baby and again afterwards if the eye is infected. Confine the baby's hands with a blanket or wrap the baby up. Start by using a fresh tissue moistened with clean tap water or normal saline to wipe away any accumulated discharge starting at the inner corner of the eye. Then place one drop of medication in the inner angle of the open eye. If the eyes do not open spontaneously it may be necessary to hold them open gently. Always treat **both** eyes unless expressly told not to do so. Finally, wipe away any excess medication, if present, using a fresh swab or tissue for each eye. Make sure the drops do not themselves become infected by letting the pipette actually touch the eye when using a multidose container. Some authorities recommend the use of a separate bottle for each eye (but this is of more relevance after ophthalmic surgery than in the case of the otherwise healthy infant).

Eye ointment should be squeezed as a thin ribbon into the gap between the lower lid and the white of the eye while the lower lid is held slightly everted. It is not enough to put ointment on the eyelid.

Treatment

0.5% tropicamide and 2.5% phenylephrine eye drops are used to aid ophthalmic examination. One drop of each should be placed in each eye 30 and 60 minutes before examination is due. Do not be put off by the vasoconstrictive blanching seen in the skin round the eye.

0.5% atropine (q.v.) is used as an eye drop twice a day to keep the pupil dilated after surgery to the eye.

0.5% proxymetacaine hydrochloride drops provide corneal anaesthesia. Three drops provide local anaesthesia after about 5 minutes that lasts for an hour or more.

0.3% hypromellose eye drops (one drop in each eye every 6–8 hours while general care is being given) can help to prevent corneal damage in the unconscious or paralysed patient. Hypromellose eye drops do not need a doctor's prescription.

Antibiotic eye drops should normally be instilled 6–8 times a day, although more frequent administration may sometimes be indicated for the first 24 hours. It is often convenient to give the drops when the baby wakes for feeding and it is perfectly acceptable to leave the medication in the mother's possession so she can learn how to give the drops herself (a point of some importance if further treatment is going to be necessary after discharge) as long as the drops are kept in a secure place. Mark the medicine chart appropriately.

Steroid eye drops with or without an antibiotic (such as Betnesol-N®) are given once every 6 hours for 5–7 days after ocular surgery to minimise inflammation and the risk of infection.

Saline (0.9% sodium chloride) eye drops (as minims) do not need a doctor's prescription. However they cost 25p each and their use is hard to justify in babies with a mild (probably chemical) conjunctivitis. Such eyes merely need to be bathed periodically with clean fresh tap water.

Supply

0.9% sodium chloride, 0.5% tropicamide, 2.5% phenylephrine, and 0.5% chloramphenicol are available as single dose Minims costing between 25p and 30p each. 0.3% hypromellose BPC eye drops should be stocked routinely in units undertaking intensive care (10 ml bottles costing 75p), while 0.5% atropine sulphate drops, 0.3% gentamicin drops, 0.5% proxymetacaine drops, 1% fluorescein drops and Betnesol-N eye drops (a combination of 0.1% betamethasone sodium phosphate and 0.5% neomycin), 3% aciclovir eye ointment, and 0.5% erythromycin eye ointment are available from the pharmacy. It is not normally necessary to use a different dropper bottle for each eye (except after surgery), but it is unnecessarily hazardous for two patients to share the same bottle.

Chloramphenicol minims are best stored at 2–8°C but they are stable for 1 month at room temperature. Other Minims do not need to be stored at less than room temperature.

References

- Hammerschlag MR, Cummings C, Roblin PM, *et al.* Efficacy of neonatal ocular prophylaxis for the prevention of chlamydial and gonococcal conjunctivitis. *N Engl J Med* 1989;**320**:769–72. [RCT]
- O'Hara MA. Ophthalmia neonatorum. *Pediatr Clin North Am* 1993;**40**:715–25. (See also pp. 767–76.)
- Isenberg SJ, Apt L, Wood MA. A controlled trial of povidone-iodine as prophylaxis against ophthalmia neonatorum. *N Engl J Med* 1995;**332**:562–6.
- Wiholm B-E, Kelly JP, Kaufman D, *et al.* Relation of aplastic anaemia to use of chloramphenicol eye drops in two international case-control studies. *BMJ* 1998;**316**:666. (See also p. 667.)
- Dunn PM. Dr Carl Credé (1819–1892) and the prevention of ophthalmia neonatorum. *Arch Dis Child* 2000;**83**:F158–9.

See also relevant Cochrane reviews 

FENTANYL

Use

Fentanyl is widely used to provide perioperative pain relief. A continuous infusion causes tolerance to develop and exposes babies to symptoms of opiate withdrawal. Morphine (q.v.) is better in this regard.

Pharmacology

Fentanyl citrate is a synthetic fat soluble opioid first developed as an analogue of pethidine and haloperidol in 1964, which is now widely used to provide rapid shortlived pain relief during surgery. It is also widely used during epidural anaesthesia in childbirth. Few haemodynamic effects are seen even when large doses are used. The drug is therefore seen as having a wide safety margin, and as providing an effective way of inhibiting the haemodynamic and metabolic effects of surgical stress. Administration can sometimes cause muscle rigidity requiring a muscle relaxant. Although it is absorbed from the gastrointestinal tract, bioavailability is limited by rapid liver metabolism. Alfentanil may, on theoretical grounds, be a useful alternative, because less tissue accumulation occurs, but muscle rigidity is even more common and the shorter half life seen in adults is not replicated in infancy.

Fentanyl's reputation as a "short acting" narcotic has tended to obscure the general recognition of its prolonged elimination half life. Significant doses rapidly cause respiratory depression. The drug's ability to limit pain after "bolus" IV infusion may last for only 30 minutes, because of its rapid redistribution into fat and muscle "depots" round the body (neonatal $V_D \sim 17$ l/kg). Sustained use is, therefore, associated with all the problems seen in prolonged thiopental infusion (q.v.). Drug elimination follows more slowly as a result of N-dealkylation and hydroxylation and excretion in the urine (half life = 4 hours), and elimination takes at least twice as long as this at birth. The elimination half life (like that of morphine) varies only slightly with gestation at birth. It is much more rapid in babies over 2 months old, and may be even more rapid during infancy than it is in adults. Unfortunately, it is not possible to use this information to say how the dose used needs to vary if fentanyl is used to provide sustained analgesia in early childhood, because the dose needed to provide adequate analgesia may also change.

Continuous infusions cause tolerance to develop. A higher plasma level becomes necessary, and a higher dose has to be given. Serious withdrawal symptoms can then occur when the drug is stopped, with extreme irritability, tremor, myoclonus, ataxia, and choreoathetosis. Although this can be reduced by gradual dose reduction, such problems make the long term use of fentanyl unwise in infancy. The drug crosses the placenta moderately well, but fetuses of more than 20 weeks gestation are best offered a direct 15 micrograms/kg injection (estimated fetal weight) if subjected to any potentially painful in utero procedure. Breastfed babies ingest about 3% of the maternal dose on a weight for weight basis.

Pain relief

Short term use: A 5 micrograms/kg IV dose depresses respiration and provides good brief analgesia; twice this dose is effective for 1 hour. A smaller dose (2 micrograms/kg) is more often given, with a volatile agent such as isoflurane, as part of a "balanced" general anaesthetic.

Sustained use: Give 10 micrograms/kg and then 1.5 micrograms/kg per hour for not more than 3 days.

Antidote

Bradycardia after excess administration may respond to atropine (q.v.). Muscle rigidity will respond to muscle relaxants. Naloxone (q.v.) is an effective fentanyl antidote.

Compatibility

Fentanyl can be added (terminally) to a line containing midazolam, milrinone, or standard TPN.

Supply and administration

2 ml and 10 ml ampoules containing 50 micrograms of fentanyl per ml (costing 24p and £1.20 each) are available. Take 0.2 ml (10 micrograms) and dilute to 1 ml with 5% dextrose to obtain a solution containing 10 micrograms/ml for accurate low dose administration. Storage and use are controlled under Schedule 2 of the UK Misuse of Drug Regulations (Misuse of Drugs Act, 1971).

References

- Arnold JH, Truog RD, Scavone JM, *et al.* Changes in the pharmacodynamic response to fentanyl in neonates during continuous infusion. *J Pediatr* 1991; **119**:639–43. (See also pp. 588–9.)
- Frank LS, Vilardi J, Durand D, *et al.* Opioid withdrawal in neonates after continuous infusions of morphine or fentanyl during extracorporeal membrane oxygenation. *Am J Crit Care* 1998; **9**:364–9.
- Saarenmaa E, Huttunen P, Leppäluoto J, *et al.* Advantages of fentanyl over morphine in analgesia for ventilated newborn infants after birth: a randomised trial. *J Pediatr* 1999; **134**:144–50. (See also pp. 127–9.) [RCT]
- Fahrenstich H, Steffan J, Kau N, *et al.* Fentanyl-induced chest wall rigidity and laryngospasm in preterm and term infants. *Crit Care Med* 2000; **28**:836–9.
- Saarenmaa E, Neuvonen PJ, Fellman V. Gestational age and birth weight effects on plasma clearance of fentanyl in newborn infants. *J Pediatr* 2000; **136**:767–70.
- Fisk NM, Gitau R, Teixeira JM. Effect of direct fetal opioid analgesia on fetal hormonal and hemodynamic stress response to intrauterine needling. *Anesthesiology* 2001; **95**:828–35.

Use

Fibrin glue, made by mixing bovine or human thrombin and fibrinogen (or cryoprecipitate), can secure haemostasis during surgery when blood oozes uncontrollably from multiple pinpoint sites on a large raw surface. The glue has also been used experimentally in a few patients with intractable pneumothorax in order to achieve pleurodesis.

Product

Thrombin is currently available as a sterile freeze dried powder prepared from bovine prothrombin by interaction with thromboplastin. Its main use is in the **topical** control of minor bleeding (as, for example, after dental treatment). It must not be injected or allowed to enter a large blood vessel because it could cause extensive, potentially lethal, intravascular clotting. Impregnation of a gelatin sponge (such as Sterispon) has occasionally been used to staunch extensive capillary bleeding. A commercial spray kit is also marketed.

Fibrin glue is made from fibrinogen and thrombin mixed in equal parts. The thrombin converts the fibrinogen to fibrin within 10–15 seconds, depending on the concentration of thrombin employed. While the extrinsic and intrinsic coagulation mechanisms are bypassed by this approach, the final common coagulation pathway is faithfully and physiologically replicated. A coagulopathy caused by antibody development has occurred on rare occasions when bovine thrombin was used. Anaphylaxis has also been reported. These hazards could be avoided by the use of human thrombin but no such commercial preparation is currently available in the UK. The use of human fibrinogen also brings with it all the theoretical hazards associated with the use of a non-sterilised human product (as outlined in the monograph on fresh frozen plasma). The available products do not have a specific licence for use in children.

Treatment of pneumothorax

Pulmonary air leaks usually respond to drainage and expectant management within 2–3 days, but high frequency ventilation, selective ventilation of a single lung, and surgical exploration are occasionally required. As a last resort, if all else fails, approximately 2 ml of reconstituted thrombin can be instilled into the pleural cavity followed, after 2 minutes, by 2 ml of fibrinogen or cryoprecipitate. The pleural drains need to be clamped for 3–5 minutes during this procedure. Such a strategy should not be adopted without first discussing the patient with a paediatric or thoracic surgeon. Tetracycline and talc have been used successfully in much the same way to minimise the risk of a recurrence in adults. Some would have reservations over using either of these options in the neonate.

Supply and administration

Supplies of bovine thrombin could be made available by the pharmacy (as long as the request has first been authorised by a consultant), and commercial combination kits containing both bovine thrombin and fibrinogen in separate 2 ml vials (sold by Immuno for £140) for use on a "named patient" basis could be obtained by the pharmacy on request. Stocks must be stored at 4°C. The material should be reconstituted as described in the package insert and used within 4 hours. Reconstitution requires access to a water bath maintained at 37°C.

References

- Moront MG, Katz NM, O'Donnell J, *et al.* The use of topical fibrin glue at cannulation sites in neonates. *Surg Gynecol Obstet* 1988;**166**:358–9.
Atrah HI. Fibrin glue. Topical use for areas of bleeding large and small. *BMJ* 1994;**308**:933–4.
Kuint J, Lubin D, Martinowitz U, *et al.* Fibrin glue treatment for recurrent pneumothorax in a premature infant. *Am J Perinatol* 1996;**13**:245–7.
Cunnington J. Spontaneous pneumothorax. *Clin Evid* 2002;**8**:1575–82 (and updates). [SR]

FILGRASTIM (and lenograstim)

Use

Filgrastim (and lenograstim) enhance the production and release of white blood cells from bone marrow. Whether these cytokines can be effective, either prophylactically or therapeutically, in combating neonatal bacterial and fungal infection, remains to be established.

Pharmacology

Marrow colony stimulating factors are naturally occurring glycoprotein growth promoters (cytokines) that stimulate the proliferation and differentiation of red and white blood cell precursors in the bone marrow. A number of these factors (including erythropoietin (q.v.)) have been produced by recombinant DNA technology and brought into clinical use in the last 10 years. Filgrastim (like lenograstim), is a recombinant version of the human granulocyte colony stimulating factor (G-CSF), while molgramostim (q.v.) is a recombinant version of the granulocyte-macrophage colony stimulating factor (GM-CSF). Both enhance the production and release of neutrophil white blood cells from bone marrow, and filgrastim is now being widely used to prevent chemotherapy induced neutropenia and to accelerate neutrophil recovery after bone marrow transplantation. Subcutaneous rather than IV use doubles the elimination half life to about 3 hours, increases therapeutic efficacy, and minimises the risk of toxicity associated with high peak blood levels. Adverse effects, including fever, dyspnoea, nausea, and vomiting, seem to have been uncommon with neonatal use. Use during pregnancy is associated with increased fetal death in primates. Use during lactation has not been studied but it seems unlikely, on theoretical grounds, to pose any serious risk.

Both G-CSF and GM-CSF have been shown to abolish the postnatal neutropenia, and the sepsis induced neutropenia, seen in preterm neonates, and to augment neutrophil function. However, prophylactic use has not yet been shown to reduce the incidence of later infection in the only neonatal trials completed to date, and the only trials of treatment have not yet been large enough to show whether it can convincingly improve outcome in babies with overt infection. They are, nevertheless, likely to result in the wider use of G-CSF in the low birth weight baby with septicaemia and moderate or severe neutropenia. The one very small head-to-head neonatal trial undertaken to date suggests that treatment with G-CSF generates a faster neutrophil response than treatment with GM-CSF. It was much too small to detect any difference in true therapeutic efficacy.

Normal neutrophil levels

The neutrophil count varies widely in the first week of life, as outlined in the monograph on molgramostim.

Treatment

Give 10 micrograms/kg of filgrastim (or lenograstim) subcutaneously once a day for 3 days (0.1 ml/kg of either of the products made up as described below). Inject the cytokine subcutaneously into alternate thighs using a 1 ml syringe and a 26 or 27 French gauge needle.

Supply and administration

Two very similar G-CSF products are available. Lenograstim is glycosylated; filgrastim is not. Almost all the neonatal studies reported to date have used filgrastim, but the related product, lenograstim, comes in low dose vials that can be more economical to use. The manufacturers have not yet endorsed the use of lenograstim in children less than 2 years old, or the use of filgrastim in neonates.

Filgrastim: Add 2 ml of 5% dextrose to a 300 microgram (30 million unit) 1 ml vial of filgrastim (costing £74), to obtain a preparation containing 100 micrograms/ml. Store all vials at 4°C, and do not keep material for more than 24 hours once the vial has been opened, even if it is still stored at 4°C.

Lenograstim: 105 microgram (13.4 million unit) 1 ml vials cost £42. Dissolve the lyophilisate with 1 ml of water for injection (as supplied). Agitate gently, but do not shake. Vials can be stored at room temperature. Reconstituted material should not be kept for more than 24 hours even if stored at 4°C.

References

- Goldman S, Ellis R, Dhar VF, *et al.* Rationale and potential use of cytokines in the prevention and treatment of neonatal sepsis. *Clin Perinatol* 1998;**25**:699–710.
- Schibler KR, Osborne KA, Leung LY, *et al.* A randomized, placebo-controlled trial of granulocyte colony-stimulating factor administration to newborn infants with neutropenia and clinical signs of early-onset sepsis. *Pediatrics* 1998;**102**:6–13. [RCT]
- Modi N, Carr R. Promising stratagems for reducing the burden of neonatal sepsis. *Arch Dis Child* 2000;**83**:F150–3.
- Bedford Russell AR, Emmerson AJB, Wilkinson N, *et al.* A trial of recombinant human granulocyte colony stimulating factor for the treatment of very low birth weight infants with presumed sepsis and neutropenia. *Arch Dis Child* 2001;**84**:F172–6. [RCT]
- Miura E, Procianny RS, Bittor C, *et al.* A randomised double-masked placebo-controlled trial of recombinant granulocyte colony-stimulating factor administration to preterm infants with the clinical diagnosis of early-onset sepsis. *Pediatrics* 2001;**107**:30–5. [RCT]
- Bernstein HM, Pollock BH, Calhoun DA, *et al.* Administration of recombinant granulocyte colony-stimulating factor to neonates with septicemia: a meta-analysis. *J Pediatr* 2001;**138**:917–20. [SR]
- Ahmad A, Laborada G, Bussel J, *et al.* Comparison of recombinant granulocyte colony-stimulating factor, recombinant granulocyte-macrophage colony-stimulating factor and placebo for treatment of septic preterm infants. *Pediatr Infect Dis J* 2002;**21**:1061–5. [RCT]

Use

Flecainide is increasingly replacing digoxin (q.v.) in the control of fetal and neonatal supraventricular arrhythmia. Amiodarone (q.v.) will usually work when flecainide does not. Because the manufacturer has not yet endorsed the use of either of these drugs in children, they should be used only under the direct supervision of a paediatric cardiologist.

Pharmacology

Flecainide is a relatively new class 1 antiarrhythmic agent that functions as a sodium channel blocker. It is a fluorinated derivative of procainamide, first synthesised in 1975. The drug is well absorbed by mouth, extensively metabolised to a range of non-active breakdown products in the liver, but also partly excreted by the kidneys. There is one isolated report suggesting that diarrhoeal illness may actually cause blood levels to rise owing to altered absorption. The half life in adults is about 14 hours, and such evidence as there is suggests that the half life is shorter than this in infancy. Tissue levels greatly exceed plasma levels ($V_d \sim 10$ l/kg).

The drug crosses the placenta and can be used to control any fetal supraventricular arrhythmia that does not respond to digitalisation. Indeed, it is increasingly being used from the outset for hydrops. It suppresses most re-entry tachycardias, and is also effective in atrial ectopic and bundle of His tachycardia. Most children with tachycardia first manifesting itself in the perinatal period become symptom free within 1 year. Where problems persist, or return 5–8 years later, radiofrequency catheter ablation of the offending pathways is becoming a progressively more effective long term solution.

Teratogenic effects have been reported with high dose treatment in laboratory animals; the relevance of this to the drug's use in early pregnancy remains to be established. The drug causes slowing of atrial, AV nodal, and infranodal conduction, increasing the atrial and ventricular muscle's refractory period. The drug exerts little effect on sinus node function, but it increases the PR interval and the duration of the QRS complex. Few extracardiac adverse effects have been noted to date. Some caution should be exercised when the drug is used during lactation because the baby will receive 5–10% of the maternal dose when intake is calculated on a mg/kg basis.

The β blocker sotalol (q.v.) has sometimes been used as an alternative strategy for controlling supraventricular arrhythmia, but such comparative information as there is suggests that flecainide is probably the better drug to use both before and after birth. Sotalol may, however, be a better drug to use in the management of atrial flutter (a rare, and potentially lethal, fetal arrhythmia with an excellent long term prognosis if identified in time).

Treatment

Oral treatment: There is only limited information on the use of flecainide in children. Start by giving 2.5 mg/kg by mouth once every 8 hours. Dosing is unpredictable and blood levels may need monitoring 4 days after treatment is started. The ECG should also be monitored until a satisfactory treatment regimen is established (since a broad P wave, widened QRS, and prolonged PR interval provide early signs of toxicity).

IV treatment: When other strategies fail, a single 1–2 mg/kg dose given IV over about 10 minutes may successfully arrest a dangerous arrhythmia. Oral treatment should then be started promptly.

Blood levels

The therapeutic plasma range in children is 0.25–0.75 mg/l (which is lower than the level sometimes needed in adults) (1 mg/l of flecainide acetate = 2.10 μ mol/l). Trough drug levels can be measured by the Toxicology Unit at New Cross Hospital, Avonley Road, London SE15, on request (telephone 020 7771 5361). For further details of the service provided by this unit see: www.medtox.org.uk

Supply

15 ml ampoules containing 10 mg/ml of flecainide acetate cost £4.70 each. An oral liquid containing 5 mg in 1 ml is available for "named" patients from Penn Pharmaceuticals. It should *not* be refrigerated.

References

- Perry JC, Garson A Jr. Flecainide acetate for treatment of tachyarrhythmias in children: review of world literature of efficacy, safety and dosing. *Am Heart J* 1992;124:1614–21.
- Ito S, Magee L, Smallhorn J. Drug therapy for fetal arrhythmias. *Clin Perinatol* 1994;21:543–72.
- Fenrich AL, Perry JC, Freidman RA. Flecainide and amiodarone: combined therapy for refractory tachyarrhythmias in infancy. *J Am Coll Cardiol* 1995;25:1195–8.
- O'Sullivan J, Gardiner H, Wren C. Digoxin or flecainide for prophylaxis of infant supraventricular tachycardia. *J Am Coll Cardiol* 1995;26:991–4.
- Paul T, Bertram H, Bökenkamp R, et al. Supraventricular tachycardia in infants, children and adolescents. *Paediatr Drugs* 2000;2:171–81.

FLUCLOXACILLIN = Floxacillin (USAN)

Use

Flucloxacillin is usually the drug of choice for penicillinase resistant staphylococcal infection.

Pharmacology

Flucloxacillin is a non-toxic, semisynthetic, acid resistant, isoxazolyl penicillin similar to methicillin that was first developed in 1970. It has a side chain that protects the β lactam ring from attack by staphylococcal (and some other) penicillinases. Flucloxacillin is closely related to cloxacillin, nafcillin, and oxacillin, which are the products most often used in the USA. None is as well absorbed by mouth, but the dose when given IV or IM is the same as for flucloxacillin. Flucloxacillin is the only product commercially available in the UK, but cloxacillin is the product most widely available elsewhere.

Placental transfer is poor and little of the drug appears in breast milk (1 mg/l). The drug is well absorbed by mouth and mostly inactivated within the body, although a third may appear in the urine. Because it is also very non-toxic the dose used needs to be reduced only when there is profound renal failure. Bioavailability approaches 50% when the drug is given by mouth to both babies and adults, although the presence of food in the stomach delays absorption. The half life is only 1 hour in adults. It is five times longer than this at birth, but the half life falls rapidly during the first month of life. Drug penetration into the meninges and into bone is limited but, because of its lack of toxicity, high dose treatment can be used safely in these situations. Anaphylaxis can occur (as with all penicillins) and patients who are hypersensitive to one product are often sensitive to others, but anaphylaxis is extremely uncommon in the neonatal period. Transient diarrhoea is quite common with oral flucloxacillin. The Committee on Safety of Medicines have noted an association with severe, delayed (and occasionally lethal) cholestatic jaundice in adults, particularly after treatment for more than 2 weeks. No such problem has yet been recognised with neonatal use.

Maternal mastitis

The main problem, especially in the early days, is usually local engorgement, and this can be overcome by relieving the obstruction and "emptying" the breast. Recurrent trouble is almost always due to poor positioning, as is confirmed by the fact that the affected breast is nearly always on the side that the mother less instinctively holds her baby. A red, swollen, tender area is *not* always a sign of bacterial infection, even if the temperature and pulse are raised, or rigors occur, although this possibility always merits maternal treatment with oral flucloxacillin if symptoms persist, even if infection is only a secondary consequence of engorgement. Since infection is almost always staphylococcal in origin, the most appropriate treatment is oral flucloxacillin 250 mg once every 6 hours by mouth. Antibiotics are, however, no substitute for dealing with the engorgement and reviewing the mother's feeding technique. Never stop feeding just because antibiotics have been started; feed more often, offering the affected breast first. Ibuprofen (q.v.) may help both the pain and the inflammation. Localised *nipple* pain is usually traumatic, but can be due to infection with *Candida*, as discussed in the monograph on nystatin.

Treatment

Dose: A dose of 100 mg/kg IV or IM is the one usually recommended when treating staphylococcal osteitis, meningitis, or a cerebral abscess, but 50 mg/kg is adequate for most other purposes. These doses are higher than those usually recommended. A dose of 25 mg/kg by mouth is more than adequate when managing most minor infections.

Timing: Give one dose every 12 hours in the first week of life, one dose every 8 hours in babies 1–3 weeks old, and one dose every 6 hours in babies 4 or more weeks old. Treatment should be sustained for 2 weeks in proven septicaemia, for at least 3 weeks in babies with infections of the central nervous system, and for 4 weeks in babies with osteitis or proven staphylococcal pneumonia. Oral medication can often be used to complete a course of treatment, and the dosage recommended here allows for the fact that treatment may well need to be given to a baby who has recently been fed.

Supply

Stock 250 mg vials cost £1 each. Add 2-3 ml of sterile water for injection to obtain a solution containing 100 mg/ml. Vials should be discarded after use and never kept for more than 24 hours after reconstitution. A 100 mg/kg dose contains 0.23 mmol/kg of sodium. The stock oral suspension in syrup (25 mg/ml) costs £3.20 for 100 ml. Sustained IV treatment often causes a reactive phlebitis.

References

- Hengren L, Ehrnebo M, Broberg U. Pharmacokinetics of free and total flucloxacillin in newborn infants. *Eur J Clin Pharmacol* 1987;**32**:403–9.
Bergdahl S, Eriksson M, Finkel Y. Plasma concentration following oral administration of di- and flucloxacillin in infants and children. *Pharmaceutical Toxicology* 1987;**60**:233–4.
Inch S, Fisher C. Mastitis: infection or inflammation? *Practitioner* 1995;**239**:472–6.

Use

Fluconazole is an antifungal agent that is increasingly used, instead of amphotericin B and flucytosine (q.v.), in the management of neonatal infection with *Candida albicans*. Prophylactic use remains more controversial.

Pharmacology

Fluconazole is a potent, selective, triazole inhibitor of the fungal enzymes involved in ergosterol synthesis. The drug is reasonably effective against most *Candida* species, other than *C. krusei* and *C. glabrata*. It is also of value in the treatment of cryptococcal infection (although in this condition treatment needs to be sustained for several weeks). It was first synthesised and patented in 1982. It is water soluble, well absorbed by mouth, and largely excreted unchanged in the urine. Penetration into the cerebrospinal fluid (CSF) is good. It crosses the placenta but its use in pregnancy is probably safe, although malformations have been seen in a few babies whose mothers had high dose treatment (> 400 mg/day) in early pregnancy (and in animals exposed to toxic doses). Fluconazole is probably the best antifungal to use when *Candida* infects the mother's milk ducts during lactation (the baby receiving only ~10% of the weight adjusted maternal dose), although it is not recommended by the manufacturer for this purpose.

Fluconazole is increasingly used in the treatment of babies with **invasive** (systemic) *Candida albicans* infection. Studies suggest that it is less toxic, and at least as effective as amphotericin B. Liver function tests sometimes show a mild self correcting disturbance, and rashes can occur, but serious drug eruptions have been seen only in immunodeficient patients. The half life is about 70 hours in the preterm baby at birth, but 20 hours throughout infancy and childhood, and 30 hours in adults. Oral fluconazole is also widely used to treat **superficial** (topical) infection in adults, and is now starting to be used for this purpose in babies. There is no advantage in combined treatment with amphotericin B. Although trials of neonatal prophylaxis have been conducted, it may be wiser to use nystatin (q.v.) for this purpose, to minimise the risk of fluconazole resistant strains of *Candida* proliferating.

Diagnosing systemic candidiasis

Systemic candidiasis is difficult to diagnose, but it is rare in the absence of superficial infection. The isolation of *Candida* from blood should never be ignored, especially if the patient is receiving TPN or has a long line in place, even if the child seems well. Unfortunately, blood cultures may reveal evidence of infection only after more than 1 week and can sometimes be misleadingly negative, but *Candida* has a predilection for the urinary tract and the presence of budding yeasts or hyphae in freshly voided urine should lead to an immediate search for further evidence of infection. Examination of the blood's buffy coat may show budding yeasts within phagocytic leucocytes. The CSF should also be examined if systemic candida infection is suspected. A suprapubic tap can be used to collect urine for microscopy and fungal culture to clinch any diagnosis, and to prove that treatment has been effective. Treatment should not necessarily await the outcome of laboratory studies. Congenital infection from ascending vaginal infection can occur. Tracheal colonisation frequently precedes systemic infection. Fungal and bacterial infection can coexist.

Drug interactions

Never give fluconazole to a patient on cisapride (q.v.). Fluconazole use greatly increases the half life of midazolam (q.v.).

Prophylaxis

One neonatal trial used 3 mg/kg IV once every 3 days for 2 weeks, and then once every other day.

Treatment

Dose: 6 mg/kg by mouth or, slowly, IV. Superficial infection needs only half this dose. A 12 mg/kg dose has occasionally been used to treat deep seated fungal infection in babies over 1 month old.

Timing: Once every 3 days in the first week of life, once every 2 days in babies 1–2 weeks old, and once a day in babies older than this. Extend the treatment interval after two doses if renal function is poor.

Supply

25 ml bottles containing 2 mg/ml of fluconazole are available for IV use. They cost £7-30. A 6 mg/kg dose contains 0.46 mmol/kg of sodium. Oral absorption is excellent, even in infancy, and a pack, which, when reconstituted, contains 35 ml of a solution containing 10 mg/ml, costs £16-60. Do not dilute further, or keep more than 2 weeks after reconstitution. The product contains sucrose.

References

- Driessen M, Ellis JF, Cooper PA, et al. Fluconazole vs amphotericin B for the treatment of neonatal fungal septicaemia: a prospective randomised trial. *Pediatr Infect Dis J* 1996;**15**:1107–12. [RCT]
- Huttova M, Hartmanova I, Kralinsky K, et al. *Candida* fungemia in neonates treated with fluconazole: report of forty cases, including eight with meningitis. *Pediatr Infect Dis J* 1998;**17**:1012–15.
- Schwarze R, Penk A, Pittrow L. Administration of fluconazole in children below 1 year. *Mycoses* 1998;**42**:3–16. [SR]
- Kauffman D, Boyle R, Hazen KC, et al. Fluconazole prophylaxis against fungal colonization and infection in preterm infants. *N Engl J Med* 2001;**345**:1660–6. [RCT]

See also relevant Cochrane reviews



FLUCYTOSINE

Use

Flucytosine has been used to treat systemic or respiratory fungal infection due to *Candida* or cryptococci. Microbiologists always recommend simultaneous treatment with amphotericin (q.v.). Time may show that fluconazole (q.v.) is a better alternative. Topical infections are more appropriately managed with nystatin or miconazole (q.v.).

Pharmacology

Flucytosine (previously called 5-fluorocytosine) is useful in the treatment of systemic infections due to *Candida* and, because of its good cerebrospinal fluid (CSF) penetration, is often prescribed jointly with amphotericin. Amphotericin and flucytosine are almost certainly synergistic, and joint use may make it possible to use less toxic doses of amphotericin. Flucytosine has been used successfully on its own in the management of candidal infection of the renal tract, but resistant strains have been reported with worrying frequency in some units. Such strains are best treated with amphotericin B, despite its greater toxicity. Drug resistance to flucytosine is generally said to be present in candidal infection when the minimum inhibitory concentration (MIC) exceeds 100 µg/ml, and in cryptococci when the MIC exceeds 12.5 µg/ml.

Flucytosine is a fluorinated pyrimidine first developed in 1957, which acts as a competitive inhibitor of uracil metabolism. The drug is well absorbed by mouth and more than 90% is excreted unchanged in the urine. Renal clearance is about three quarters of that achieved for creatinine. The half life in the neonatal period is *very* variable, but usually about 8 hours. The drug is distributed widely throughout body tissues, including the CSF. It has been given on occasion in pregnancy without causing any apparent harm to the baby, although the risk of teratogenicity cannot be discounted. Dose related leucopenia and thrombocytopenia can occur, while reversible liver function changes have also been reported. Vomiting and diarrhoea can occur. It is not known whether the drug appears in breast milk.

Diagnosing fungal infection

Notes on the diagnosis of systemic candidiasis appear in the monograph on fluconazole.

Treatment

Neonatal use: Give 50 mg/kg by mouth or IV once every 12 hours for at least 10 days. Start with 50 mg/kg once every 24 hours if there is evidence of renal failure. Any IV infusion should be given using a 15 µm in-line filter to trap any drug crystals. The manufacturers also recommend slow infusion over at least 20 minutes, although they offer no reason for this recommendation.

Older children: A dose of 50 mg/kg every 6 or 8 hours is normally used in older children. Always check the blood level after 1–2 days if a dose as high as this is used in a young baby.

Blood levels

Always check the serum level when the fourth dose is given, to guard against drug accumulation if renal function is impaired, aiming for a peak serum level of 50–75 mg/l (1 mg/l = 7.75 µmol/l). Take at least 0.5 ml of blood, after prior consultation with the local laboratory, 60 minutes after *all* the most recent dose has been infused. Aim to keep the trough level above 25 mg/l.

Supply

A 250 ml bottle containing 10 mg/ml suitable for oral or IV use (costing £35-70) is stocked by the pharmacy. A 50 mg/kg dose contains 0.69 mmol/kg of sodium. Prefilled and sealed single dose syringes can be dispensed on request. The reserve stock should be protected from light, and kept at room temperature. Do not refrigerate. The IV preparation can be infused (terminally) into a line containing dextrose or dextrose saline. There is no IV product on the market in the USA.

References

- Smith H, Congdon P. Neonatal systemic candidiasis. *Arch Dis Child* 1985;**60**:365–9.
- Butler KM, Baker CJ. *Candida*: an increasingly important pathogen in the nursery. *Pediatr Clin North Am* 1988;**35**:543–63.
- Loke HL, Verber I, Szymonowicz W, *et al.* Systemic candidiasis and pneumonia in preterm infants. *Aust Paediatr J* 1988;**24**:138–42.
- Baley JE, Meyers C, Klegmann RM, *et al.* Pharmacokinetics, outcome of treatment, and toxic effects of amphotericin B and 5-fluorocytosine in neonates. *J Pediatr* 1990;**116**:791–7.
- Baley JE. Neonatal candidiasis: the current challenge. *Clin Perinatol* 1991;**18**:263–80.

Use

Folic acid is necessary to prevent megaloblastic anaemia. Supplementation prior to conception can decrease the risk of the fetus developing various defects such as anencephaly or spina bifida.

Nutritional factors

Folic acid was first synthesised in 1945. It is almost certainly the factor first identified in 1930 by the obstetrician Wills as the cause of prematurity and "tropical macrocytic anaemia" among malnourished women in Bombay. Tetrahydrofolic acid, the metabolically active form of folic acid (one of the water soluble B vitamins) participates in DNA synthesis and red cell maturation. Peas, beans, green vegetables (such as sprouts and spinach), yeast extract, Bovril®, and fortified cereals are the best dietary sources. Liver is a rich source of folate but this should be avoided in pregnancy because of its high vitamin A content. Excessive folate intake does not appear to be dangerous.

Serum and red cell folate levels are higher in the infant than the mother at birth, and deficiency is seen only in the babies of grossly deficient mothers. Folate is actively excreted in breast milk and well absorbed in the duodenum and jejunum. Cows' milk contains as much as human milk (3–6 micrograms/100 ml) but folic acid is heat labile. All preterm formula milks in the UK contain 43–50 micrograms/100 ml. It is often claimed that folate requirements in infancy are as high as 20–50 micrograms/day (4–10 times the adult requirement). This is more than most babies get by mouth for some months after birth. However, although serum and red cell folate levels fall after delivery, especially in babies of low birth weight, and urinary losses are high, symptomatic deficiency has not been observed in the absence of chronic infection, malabsorption (e.g. coeliac disease), or diarrhoea, and supplementary folic acid fails to produce any rise in haemoglobin in the absence of megaloblastic anaemia, even in babies with severe haemolytic disease.

Maternal prophylaxis

Serum folate levels fall significantly during pregnancy but red cell levels (which probably reflect tissue levels) fall very little and the increased risk of megaloblastic anaemia during pregnancy correlates poorly with serum folate levels. A 400 microgram daily supplement does not increase the risk of miscarriage (or prevent recurrent abortion, premature labour, or abortion), but preconceptional use does make the birth of a baby with a neural tube defect 2–5 times less likely. An earlier UK trial, published in 1991, showed that 4 mg a day is equally protective in women who have already had one such pregnancy. The risk of facial clefting and conotruncal heart defects may also be reduced. Tablets containing 5 mg are available on prescription, but the cost of a 12 week course (about £3) is less than the standing charge for an NHS prescription. For most women therefore, it is cheaper to request a private prescription and then get this dispensed. All women who are planning to become pregnant should be advised to start taking 400 micrograms/day *before conception*. Suitable tablets are now available to the general public "over the counter" without prescription; the cost for a 3 month course of Preconceive® is less than £4. Some cereals are now heavily fortified, but the Food Safety Act of 1990 renders the making of any medicinal claim for these products illegal. The effective elimination of spina bifida in the UK is probably going to require the routine fortification of all bread or flour (as in the USA), but a recommendation that each 100 g of flour should be fortified with 240 mg of folic acid was blocked by the UK Food Standards Agency in May 2002.

Neonatal prophylaxis

Preterm babies fed heat treated human milk may benefit from a 500 microgram supplement once a week if a suitable breast milk fortifier (q.v.) is not used. Supplementation has no impact on the risk of anaemia developing in other term or preterm breast or formula fed babies.

Treatment

Diagnosed megaloblastic anaemia in infancy, in the absence of vitamin B₁₂ (q.v.) deficiency, is usually treated with 1 mg folic acid daily by mouth, but should respond rapidly to physiological doses of folic acid (50 micrograms/day) if folate deficiency is the true cause of anaemia.

Supply

A sugar-free oral suspension containing 500 micrograms/ml of folic acid is available. A 150 ml bottle costs £9.70.

References

- Ehrenkranz RA. Iron, folic acid and vitamin B₁₂. In: Tsang RC, Lucas A, Uauy R, *et al*, eds. *Nutritional needs of the preterm infant*. Baltimore, MD: Williams and Williams, 1993:187–9.
- Hall J, Solehdin F. Folic acid for the prevention of congenital anomalies. *Eur J Pediatr* 1998;**157**:445–50.
- Botto LD, Moore CA, Khoury MJ, *et al*. Neural-tube defects [Review]. *N Engl J Med* 1999;**341**:1509–19. (See also pp. 1485–90.)
- Lumley J, Watson L, Watson M, *et al*. Modelling the potential impact of population-wide periconceptual folate/multivitamin supplementation on multiple births. *Br J Obstet Gynaecol* 2001;**108**:937–42.
- Ray JG, Meier C, Vermeulen MJ, *et al*. Association of neural tube defects and folic acid fortification in Canada. *Lancet* 2002;**360**:2047–8.

See also relevant Cochrane reviews 

FRESH FROZEN PLASMA (FFP)

Use

Fresh frozen plasma (FFP) and cryoprecipitate can be used to treat symptomatic coagulation factor deficiency. Safer (and cheaper) products such as gelatin, pentastarch, or plasma albumin (q.v.) can be used to expand plasma volume. An exchange transfusion with freshly donated blood may sometimes be a better way of controlling early coagulation failure.

Product

Standard 200–250 ml packs of fresh plasma containing albumin, immunoglobulin, and stable clotting factors are prepared and frozen at minus 30°C within 6 hours of collection from a single donation of whole blood. Cryoprecipitate, the precipitate formed during controlled thawing of fresh pooled frozen plasma, later resuspended in plasma, contains an eightfold concentrate of fibrinogen together with a range of other coagulation factors (especially factor VIII) in 20 ml packs. Since most products are not sterilised, transfusion can transmit any HIV, hepatitis, or cytomegaloviruses not detected by routine donor screening. A range of commercial solvent/detergent treated (virally inactivated) products are now starting to become available that make HIV and hepatitis C transmission unlikely. They are, however, prepared from donor pools, and could still transmit human parvovirus (B₁₉) and hepatitis A infection.

Early reports suggesting that the prophylactic use of FFP immediately after birth could reduce the risk of intraventricular haemorrhage in babies of less than 32 weeks gestation have *not* been confirmed by a multicentre trial involving more than 750 babies. A specific product of fraction III, plasminogen, was shown to reduce mortality from respiratory distress in a trial reported in 1977 (as briefly described in the monograph on urokinase), but no other studies of this strategy have appeared since then. Immunoglobulin concentrates (q.v.) may help when there is sepsis.

Assessment

The assessment of any bleeding tendency requires a knowledge of normal test ranges. At birth, healthy babies have values in the range shown in the table below. The normal prothrombin and activated partial thromboplastin times both decrease by about 10% in the first month of life. While D-dimer levels are usually below 250 µg/l, normal babies occasionally have values as high as 1000 µg/l.

Coagulation screening tests (95% confidence intervals)

Test	Gestation (weeks)		
	24–29	30–36	37–41
Prothrombin time (seconds)	12.2–21.0	10.6–16.2	10.1–15.9
International normalised ratio (INR)	–	0.61–1.70	0.53–1.62
Activated partial thromboplastin time (seconds)	43.6–>101.0	27.5–79.4	31.3–54.5
Thrombin clotting time (seconds)	–	19.2–30.4	19.0–28.3
Fibrinogen (g/l)	0.69–4.12	1.50–3.73	1.67–3.99
Platelets (platelets × 10 ⁹ /l)	100–350	100–350	150–350

Treatment

Infuse 20 ml/kg of blood group compatible FFP over 30–60 minutes. The use of plasma from a group A rhesus negative donor is not likely to be accompanied by a transfusion reaction in the neonatal period, but such a departure from standard practice is seldom justifiable. Hypoglycaemia is possible if any existing glucose infusion is stopped during the administration of FFP.

Supply

Stocks of FFP and cryoprecipitate from the local blood bank cost £20 to prepare and dispense. 50 ml “minipacks” are sometimes available. The packs should be thawed by the blood bank staff immediately prior to issue and used within 6 hours. Hold the material at 2–6°C if there is any unavoidable last minute delay in administration. A filter is not necessary. Commercial virus inactivated products cost £45.

References

- Buchanan GR. Coagulation disorders in the neonate. *Pediatr Clin North Am* 1986;**33**:203–20.
Cohen H. Avoiding the misuse of fresh frozen plasma. *BMJ* 1993;**307**:395–6.
Seguin JH, Topper WH. Coagulation studies in very-low birthweight infants. *Am J Perinatol* 1994;**11**:17–19.
NNNI Trial Group. Randomised trial of prophylactic early fresh frozen plasma or gelatin or glucose in preterm babies: outcome at 2 years. *Lancet* 1996;**348**:229–32. [RCT]

See also relevant Cochrane reviews 

Use

Furosemide is a valuable, powerful, and rapidly acting diuretic that can be particularly useful in the management of acute congestive cardiac failure. Alternatives (such as chlorothiazide (q.v.) with or without spironolactone (q.v.)) are cheaper and preferable for maintenance treatment.

Pharmacology

Furosemide was first marketed commercially in 1962. It crosses the placenta and increases fetal urine flow, but there is no good evidence that furosemide is teratogenic. It is also excreted into breast milk, but no adverse effects have ever been reported. There is the remote possibility, however, that its use in a nursing mother may inhibit lactation by causing maternal fluid depletion.

Furosemide is protein bound in the plasma (but normal doses do not significantly influence bilirubin binding capacity). It is both filtered by the glomerulus and actively excreted by the proximal renal tubule. The filtered drug then works from within the tubule, inhibiting active chloride reabsorption and, as a result, passive sodium reabsorption, from the thick ascending limb of the loop of Henlé and the distal tubule (hence the term "loop" diuretic). While this can result in a sixfold increase in free water clearance in adults, its efficacy in the preterm baby remains less clearly quantified. Sustained use increases urinary sodium and potassium loss and can cause hypokalaemia. Urinary calcium excretion triples in the preterm baby, causing marked bone mineral loss, and renal and biliary calcium deposition.

Furosemide stimulates renal synthesis of prostaglandin E₂ (q.v.), thus enhancing, and modifying, renal blood flow. Early use is associated with some increase in the incidence of a symptomatic patent ductus in babies requiring ventilation for respiratory distress, and this may be due to increased prostaglandin production. Furosemide also has a direct effect on lung fluid reabsorption. Aerosol administration can transiently improve lung function, and sustained IV or oral use can improve oxygenation in babies over 3 weeks old with chronic lung disease, but there is no evidence, as yet, of sustained clinical benefit.

The half life is about 8 hours in the term baby at birth, but it approaches adult values (2 hours) within a few months. It may be as long as 24 hours at first in the very preterm baby, making progressive drug accumulation (and ototoxicity) possible with repeated use. The related diuretic bumetanide may be less ototoxic but neonatal use has not yet been fully evaluated; it may also be more effective in renal failure, because entry into the tubular lumen is less dependent on glomerular filtration and clearance is less dependent on renal excretion. The usual dose of bumetanide in infancy is 20 micrograms/kg IV or IM once every 6 hours but, because of reduced clearance, drug accumulation must be a possibility if treatment is repeated more than once every 12 hours in the first month of life.

Drug interactions

Concurrent furosemide use significantly increases the risk of aminoglycoside ototoxicity. Precipitation will occur if furosemide is injected into an IV line containing milrinone.

Treatment

Use as a diuretic: Try 1 mg/kg IV or IM or 2 mg/kg by mouth, repeatable after 12–24 hours. The drug should not be given more than once every 24 hours to babies with a postmenstrual age of less than 31 weeks. Patients on long term treatment with furosemide may require 1 mmol/kg per day of oral potassium chloride (q.v.) to prevent hypokalaemia.

Renal failure: Give a single 5 mg/kg dose IV as soon as renal failure is suspected, to lower the metabolic activity of the chloride pump, minimise the risk of ischaemic tubular damage, and reduce the shutdown in glomerular blood flow that follows on from this. Consider giving 10 ml/kg of pentastarch or 5% albumin as well if hypovolaemia could be a contributory factor (as outlined in the monograph on water).

Chronic lung disease: 1 mg/kg of the IV preparation added to 2 ml of 0.9% sodium chloride (q.v.) and given by nebuliser once every 6 hours may temporarily improve lung compliance (and therefore tidal volume) in some ventilator dependent babies, without affecting renal function.

Supply and administration

2 ml (20 mg) ampoules of furosemide cost 84p. The IV preparation can be given by mouth after dilution, but a cheaper sugar free oral preparation containing 1 mg/ml is available (150 ml costs £3.80). Precipitation can occur when furosemide is mixed with any IV fluid (such as dextrose and dextrose saline) with a pH of < 5.6, so it should *always* be separated by a 1 ml bolus of 0.9% sodium chloride or water when given IV. 2 ml (1 mg) ampoules of bumetanide cost 40p.

References

- Wells TG. The pharmacology and therapeutics of diuretics in the paediatric patient. *Pediatr Clin North Am* 1990;**37**:463–504.
 Sullivan JE, Witte MK, Yamashita TS, et al. Dose-ranging evaluation of bumetanide pharmacodynamics in critically ill infants. *Clin Pharmacol Ther* 1996;**60**:424–34.
 Pai VB, Nahata MC. Aerosolised furosemide in the treatment of acute respiratory distress and possible bronchopulmonary dysplasia in preterm neonates. *Ann Pharmacother* 2000;**34**:386–92. [SR]

See also other relevant Cochrane reviews 

GANCICLOVIR

Use

Ganciclovir is a toxic antiviral agent being used experimentally in the management of neonatal cytomegalovirus (CMV) infection, otherwise known as human herpes virus 5 (HHV-5).

Pharmacology

Ganciclovir is a synthetic nucleoside with similar pharmacological properties to aciclovir (q.v.) that accumulates after phosphorylation in CMV infected cells, inhibiting virus replication. It was first developed in 1980 and is much more toxic than aciclovir, frequently causing neutropenia and thrombocytopenia. Regular haematological monitoring is therefore essential. Concurrent treatment with zidovudine (q.v.) increases the drug's toxicity. It is very poorly absorbed by mouth, and rapidly excreted by the kidney, with an adult half life of 3 hours. It crosses the placenta and is known to be teratogenic in animals. Male and female fertility may be affected. Animal studies suggest that the drug is also a potential mutagen and carcinogen. Breastfeeding is not advisable.

CMV infection

Fifty per cent of all women of childbearing age in the UK have already had an asymptomatic CMV infection (often in early childhood) before the start of pregnancy, but primary or reactivated infection is thought to cause congenital or perinatal infection in about one in every 300 UK pregnancies. Most of these babies show few signs of overt infection, but about 5% develop disseminated cytomegalic inclusion disease with thrombocytopenic petechiae, hepatitis, chorioretinitis, intracranial calcification, and/or microcephaly. Cerebral palsy can occur, and severe progressive deafness may develop even after an apparently asymptomatic infection. Overt cytomegalic inclusion disease can also result from neonatal cross infection, or exposure to CMV infected blood or human milk; such babies often develop pneumonia as well as many of the symptoms listed above. Proof that infection was congenital requires the collection of a positive culture or polymerase chain reaction (PCR) test to be obtained within 2 weeks of birth. Handwashing is important to prevent congenitally infected babies causing iatrogenic cross infection. Staff are at little increased risk of personal infection as long as proper precautions against cross infection are observed.

There is no evidence, as yet, that any antiviral agent can alter the course of congenitally acquired infection, but ganciclovir can transiently eradicate virus excretion in a congenitally infected baby. Trials are currently being conducted in the USA on babies with perinatally or neonatally acquired infection. Foscarnet sodium (60 mg/kg once every 8 hours) has been used instead of ganciclovir (mostly in immunocompromised adults) when there is chorioretinitis; it causes less marrow suppression but does cause reversible renal toxicity. There is too little experience for the manufacturers to recommend the use of either ganciclovir or foscarnet in the management of neonatal infection.

Treatment

Seek expert advice and explain to parents that treatment is still under evaluation and seldom eliminates the virus. Give symptomatic babies with neonatally acquired disease 6 mg/kg IV of ganciclovir (5 ml of the solution made up as described below) over 1 hour, once every 12 hours for 2 weeks. Maintain hydration and watch for neutropenia. Increase the dosage interval if there is renal impairment. Then give 10 mg/kg once every other day for 3 months if initial treatment seems to have been of benefit.

Supply

500 mg vials cost £34 each. The freeze-dried powder must be reconstituted with 9.7 ml of water for injections BP to give a solution containing 50 mg/ml (water containing a bacteriostatic such as para-hydroxybenzoate may cause precipitation). Shake to dissolve, and use promptly; do not use the vial if there is any particulate matter still present. To give 6 mg/kg of ganciclovir take 1.2 ml of this solution for each kilogram the baby weighs, dilute to 50 ml with 10% dextrose or dextrose saline, and infuse 5 ml over 1 hour. Since the undiluted product is very caustic (pH ~ 11) gloves and goggles should be used during reconstitution. Use soap and water immediately to wash any accidental contamination of skin.

Bottles containing 6 g of foscarnet for IV infusion cost £31. They cannot be kept once opened, but the pharmacy may be in a position to prepare several individually dispensed daily aliquots of diluted foscarnet from one bottle on request, because the product remains stable after dilution.

References

- Nigro G, Scholz H, Bartmann U. Ganciclovir therapy for symptomatic congenital cytomegalovirus infection in infants: a two regimen experience. *J Pediatr* 1994;**124**:318–22.
- Nelson CT, Demmler GJ. Cytomegalovirus infection in the pregnant mother, fetus and newborn infant. *Clin Perinatol* 1997;**24**:151–60.
- Whitley RJ, Cloud G, Gruber W, et al. Ganciclovir treatment of symptomatic congenital cytomegalovirus infection: results of a Phase II study. *J Infect Dis* 1997;**175**:1080–6.
- Stagno S. Cytomegalovirus. In: Remington JS, Klein JO, eds. *Infectious diseases of the fetus and newborn*, 5th ed. Philadelphia, PA: Saunders, 2001:389–424.
- Revello MG, Gerna G. Diagnosis and management of human cytomegalovirus infection in the mother, fetus, and newborn infant. *Clin Microbiol Rev* 2002;**15**:680–715. [SR]

Use

Gaviscon is used to control gastro-oesophageal reflux (GOR). It also acts as an antacid.

Pharmacology

A range of antacid preparations containing magnesium salts (which have a mild laxative effect) and aluminium salts (which have the opposite tendency) are commercially available "over the counter". There is no contraindication to their use during pregnancy or lactation. Magnesium trisilicate and magnesium or aluminium hydroxide, being relatively water insoluble, are commonly chosen because they are retained rather longer in the stomach. Alginates are often added when reflux is thought to be a problem, because they react with gastric acid to form a viscous gel or "raft" that then floats to the top of the stomach, acting as a mechanical barrier to any reflux of gastric fluid back into the oesophagus. The commercial product most widely used in early infancy is Infant Gaviscon. Each sachet contains 225 mg of sodium alginate and 87.5 mg of magnesium alginate, with colloidal silica and mannitol (q.v.). The drug has been suspected of occasionally forming a solid intragastric mass or "bezoar", a problem usually ascribed to its (now discontinued) aluminium content. Gaviscon is specifically contraindicated in the treatment of gastroenteritis and of suspected intestinal obstruction; even the infant formulation has a high sodium content (21 mg or 0.9 mmol/dose) that can cause hyponatraemia if there is dehydration or poor renal function. Other formulations contain even more sodium.

Gastro-oesophageal reflux

Art plays a larger role than science in the feeding of the small preterm baby, and experienced neonatal nurses are the acknowledged artists. Many babies "posset" a few mouthfuls of milk quite regularly, and some swallow quite a lot of air while feeding and then bring back milk when winded. Most small babies regurgitate some milk back into the lower half of the oesophagus after feeding because of poor sphincter tone, but only a few aspirate, and very few develop a chemical oesophagitis because milk is an excellent antacid. Nevertheless, silent reflux can cause serious lung damage, and babies with a postconceptional age of less than 35 weeks have no effective cough reflex. Reflux must be distinguished from vomiting, which is characterised by reflex contraction of the stomach. One sign of reflux, especially in the preterm baby, may be intermittent episodic apnoea. Placing the baby prone (face down), or on its left side, sometimes helps. Tilting the head of the cot up 30° may help, but this may increase abdominal pressure. One trial suggests that a semiupright posture may actually make matters worse. Gaviscon can be helpful when oesophagitis is suspected, or when recurrent reflux is interfering with nutrition. The use of thickened feeds remains poorly evaluated. There is no evidence that cisapride (q.v.) is of help. While severe symptoms may merit oesophageal pH monitoring, it is usually enough to test oropharyngeal secretions for acid with blue litmus paper once every 6–8 hours. Painful oesophagitis, which can provoke apnoea, vomiting, and/or food aversion, may require ranitidine or (rarely) omeprazole (q.v.).

Treatment

Term babies: Babies weighing under 5 kg should be offered one dose of Infant Gaviscon with feeds. Babies over 5 kg may be offered a double dose (i.e. both sections of a paired sachet) with each feed.

Preterm babies: The manufacturer does not recommend the use of Infant Gaviscon for preterm babies, but it may, on occasion, be appropriate to give a proportionate dose (see below) regularly with each feed.

Supply and administration

Infant Gaviscon powder comes made up in paired sucrose free and lactose free sachets; each paired sachet contains enough powder for **two** standard doses of Gaviscon. Paired sachets cost 16p each. They can be purchased from community pharmacists without a doctor's prescription, but such use is not to be encouraged. Infant Gaviscon is one of the few commercial products marketed specifically for use in the treatment of reflux vomiting in infancy that can be prescribed on the NHS.

Take the powder from one section of a paired sachet of Infant Gaviscon, mix with 5 ml (one teaspoonful) of fresh tap water and add 1 ml of this thin paste to each 25 ml of artificial milk. Breastfed babies can be offered a similar quantity on a spoon after each feed. Do not give the liquid formulation to babies.

References

- See also Cochrane review of GOR 
- Greally P, Hampton FJ, MacFadyen UM, *et al.* Gaviscon and carobel compared with cisapride in gastro-oesophageal reflux. *Arch Dis Child* 1992;**67**:618–21. [RCT]
- Ewer AK, James ME, Tobin JM. Prone and left-lateral positioning reduce gastro-oesophageal reflux in preterm infants. *Arch Dis Child* 1999;**81**:F201–5.
- James ME, Ewer AK. Acid oro-pharyngeal secretions can predict gastro-oesophageal reflux in preterm infants. *Eur J Pediatr* 1999;**158**:371–4.
- Carroll AE, Garrison MM, Christakis DA. A systemic review of nonpharmacological and nonsurgical therapies for gastroesophageal reflux in infants. *Arch Pediatr Adolesc Med* 2002;**156**:109–13. [SR]
- Kumar Y, Saranathan R. Gastro-oesophageal reflux in children. *Clin Evid* 2003;**9**:496–507 (and updates). [SR]

GELATIN

Use

A range of plasma substitutes can be used to expand intravascular volume in patients with shock or impending shock. The National Blood Service recommends their use in preference to 4-5% human albumin (q.v.) because these "less expensive synthetic products are readily available and equally effective".

Pharmacology

Gelatin is a purified protein obtained by the partial hydrolysis of BSE-free bovine collagen. A sterile saline solution (Gelofusine®) containing 40 g/l of modified gelatin has the same properties and uses as dextran 40 (a polymer of glucose), but gelatin, unlike dextran, does not interfere with subsequent blood grouping and compatibility testing procedures. Gelatin is also used as a haemostatic film or sponge (Sterispon®) in surgical procedures. The gelatin in Gelofusine, with an average molecular weight (30,000) almost half that of human plasma albumin, has only a 4 hour half life and is rapidly excreted unchanged in the urine. Anaphylactic reactions have been described, but seem rare in young children. Immediate and delayed-type hypersensitivity reactions have sometimes occurred, however, after immunisation with vaccines containing gelatin in presensitised children. The trivalent measles (MMR) vaccine is the only UK vaccine to contain gelatin. Prior exposure to Gelofusine may nevertheless make a reaction to this vaccine marginally more likely.

Pentastarch and hexastarch are artificial colloids derived from starch, with a much higher mean molecular weight (200,000). The glucagon-like polymerised glucose units are of variable size. While the smaller molecules are rapidly excreted in the urine, the larger molecules remain in the blood stream for some days, undergoing slow enzymatic degradation. Although use is thought to cause a sustained expansion of the intravascular volume (even when endothelial damage causes increased capillary permeability, allowing smaller molecules (such as plasma albumin) to leak rapidly out of the intravascular space), use of this product rather than gelatin was associated with an *increased* risk of transient renal failure in adults with septic shock in one recent trial. Large volumes reduce platelet aggregation, lower factor VIII level, and increase the bleeding time. Hexastarch is a related product with an even higher molecular weight (450,000). The manufacturers stress that little is known about the use of any of these products during pregnancy or childhood.

Indications for use

A major systematic review has suggested that the indiscriminate use of *any* colloid in the management of hypovolaemia actually does more harm than good. However, this may be because the product is being used inappropriately rather than because it is inherently dangerous. Gelatin can be used to reconstitute packed red cells. It may also be the best colloid to use during routine surgery because this has the least effect on *in vitro* tests of coagulation, but 20 ml/kg is the largest dose known to have been used in any one day in the neonatal period. Naturally, when blood has been lost, it will often be more appropriate to replace this as soon as practicable. Early neonatal hypotension without hypovolaemia is more appropriately treated with dobutamine and/or dopamine, or hydrocortisone (q.v.), while fresh frozen plasma (q.v.) should be used where there is a significant clotting factor deficiency.

Treatment

20 ml/kg of Gelofusine infused over 5–15 minutes should correct all but the most severe hypovolaemia. The effect of giving more than a total of 30 ml/kg in the first week of life has not been studied.

Supply

500 ml bags of 4% gelatin (Gelofusine) in 0.9% sodium chloride cost £4-60. 500 ml bags of 6% pentastarch in 0.9% sodium chloride cost £10-50. Both products contain 154 mmol/l of sodium. They should not be kept once they have been opened because they contain no preservative. Do not use any material that looks cloudy or turbid.

References

- Gold MS, Russo J, Tissot M, *et al.* Comparison of hetastarch to albumin for perioperative bleeding in patients undergoing abdominal aortic aneurysm surgery: a prospective, randomised study. *Ann Surg* 1990;**211**:482–5. [RCT]
- The NNNI Trial Group. A randomised trial comparing the effect of prophylactic early fresh frozen plasma, gelatin or glucose on early mortality and morbidity in preterm babies. *Eur J Pediatr* 1996;**155**:580–8. [RCT]
- Hope P. Pump up the volume? The routine early use of colloid in very preterm infants [Commentary]. *Arch Dis Child* 1998;**78**:F163–5.
- Roberts JS, Bratton SL. Colloid volume expanders. Problems, pitfalls and possibilities. *Drugs* 1998;**55**:621–30.
- Shierhout G, Roberts I. Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: a systematic review of randomised trials. *BMJ* 1998;**316**:961–4. [SR]
- Schortgen F, Lacherade J-C, Bruneel F, *et al.* Effects of hydroxyethylstarch and gelatin on renal function in severe sepsis: a multicentre randomised study. *Lancet* 2001;**357**:911–6. [RCT] (See also **358**:581–3.)

See also relevant Cochrane reviews



Use

Gentamicin is widely used to treat Gram negative bacterial infection but it is of variable efficacy (and not the treatment of choice) for known staphylococcal sepsis. The indigenous flora makes netilmicin (q.v.) a better aminoglycoside antibiotic for unidentified infection in some units.

Pharmacology

Gentamicin is currently the most widely used aminoglycoside antibiotic (streptomycin having been the first aminoglycoside to come into use). It is a naturally occurring substance, first isolated in 1963 and, like kanamycin and neomycin, consists of a mixture of closely related compounds. It does not, therefore, have a single quotable molecular weight. Its pharmacology is as outlined in the monograph on netilmicin.

Cerebrospinal fluid (CSF) penetration is not good and lumbar injection may do more harm than good in the treatment of meningitis. However, it may *rarely* be appropriate to give 1–2 mg of the **intrathecal** preparation once every 24–48 hours as a direct intraventricular injection, and to monitor the CSF drug level (aim for 5–10 mg/l) when treating chronic ventriculitis, especially when this complicates shunt surgery. Ceftazidime, cefotaxime, co-trimoxazole, and chloramphenicol (q.v.) all achieve better CSF penetration when given IV.

Therapeutic strategy

Aminoglycosides become effective against some common bacteria only when the serum level is high enough to be potentially toxic. A high peak level (at least eight times the minimum inhibitory dose) enhances the drug's bactericidal effect, but Gram negative organisms stop taking up the drug after 1 hour, and only do so again 2–10 hours after exposure is over ("adaptive resistance"). Repeat treatment during this time is ineffective. However, serious toxicity is normally seen only with treatment lasting more than 7–10 days, a sustained high drug serum level (i.e. a high trough level), and/or coexposure to other ototoxic drugs (such as furosemide). These features suggest that the treatment of adults with normal renal function will be optimised, and adverse effects minimised, by giving treatment once a day (a "high peak, low trough" policy). Such controlled trial evidence as exists supports this conclusion. Aminoglycosides undergo no change in the body, leaving through the kidney by passive filtration, so neonatal treatment must reflect the changes in glomerular filtration that occur with increasing gestational and postnatal age. When aminoglycosides are given more than once a day in babies with a postmenstrual age of less than 60 weeks the serum level will remain subtherapeutic for many hours if an initial loading dose is not given (because of the large V_d). Babies less than 1 week old and under 30 weeks gestation are often best treated once every 36 hours; babies with renal failure may need treatment only once every 48 hours.

Prophylaxis

Several small controlled trials have suggested that prophylactic **oral** administration of an aminoglycoside (typically 2.5 mg/kg of gentamicin every 6 hours) for 7–10 days can reduce the risk of necrotising enterocolitis in high risk babies if started before feeds are begun. A larger trial is needed before this policy can be recommended and the risk that aminoglycoside resistant organisms will start to proliferate taken into account.

Treatment

Intermittent high dose treatment: Start by giving 5 mg/kg IV or IM once every 24 hours. If the trough serum level when the third dose was given exceeded 2 mg/l, increase the dosage interval to 36 hours and check the level again after two more doses have been given. A slow 30 minute infusion is *not* necessary.

Conventional twice daily treatment: Some clinicians still give term babies 3.5 mg/kg IV or IM once every 12 hours (once every 8 hours in babies over 6 months old). Give a 5 mg/kg loading dose first.

Blood levels

Monitor the level, as outlined in the monograph on netilmicin, aiming for a trough level of about 1 mg/l. Extend the dosage interval if the trough level exceeds 2 mg/l. The 1 hour peak level, when measured, should be 8–12 mg/l. See the web commentary for a more detailed discussion.

Supply

2 ml (20 mg) vials costs 65p, and 1 ml (5 mg) intrathecal ampoules cost 77p.

References

- Barclay ML, Begg EJ. Aminoglycosides – 50 years on. *Br J Clin Pharmacol* 1995;**39**:587–603.
- Ali MZ, Goetz MB. A meta-analysis of the relative efficacy and toxicity of single daily dosing versus multiple daily dosing of aminoglycosides. *Clin Infect Dis* 1997;**24**:797–809. (See also pp. 816–23.)
- Lundergan FS, Glasscock CF, Kin EH, et al. Once-daily gentamicin dosing in newborn infants. *Pediatrics* 1999;**103**:1228–34.
- de Hoog M, Mouton JW, van den Anker JN. The use of aminoglycosides in the newborn. *Paediatr Perinat Drug Ther* 1999;**2**:48–56.
- Miron D. Once daily dosing of gentamicin in infants and children. *Pediatr Infect Dis J* 2001;**20**:1169–73. [SR]
- Lannigan R, Thomson A. Evaluation of 22 neonatal gentamicin dosage protocols using a Bayesian approach. *Paediatr Perinat Drug Ther* 2001;**4**:92–100. [SR]

See also Cochrane review of prophylaxis

GLUCAGON

Use

Glucagon can be useful in the management of neonatal hypoglycaemia.

Pharmacology

Glucagon is a polypeptide hormone produced by pancreatic α cells with a natural half life of about 5 minutes. It used to be extracted from animal pancreatic islet cell tissue, but was synthesised in 1967. A recombinant product is also now available. Glucagon mobilises hepatic glycogen and increases hepatic glucose and ketone production, causing increased amino acid uptake and free fatty acid flux. It is also known to stimulate growth hormone release. Glucagon activates the adenylyl cyclase system even when the β adrenoreceptors are blocked, and a continuous infusion is of proven value in the management of unintentional overtreatment with β blockers such as atenolol, labetalol, and propranolol (q.v.). Isoprenaline (q.v.) may be of value if glucagon is not effective. Glucagon does not cross the placenta, so there is no reason to suppose that its use would be hazardous during pregnancy. It is not known whether it appears in breast milk. However it is difficult to see how maternal administration during lactation could have any effect on the baby because the drug has a very short half life and is also inactivated when taken by mouth.

Glucagon is also useful in the management of hypoglycaemia. A single bolus injection can sometimes increase the blood glucose level enough to make further treatment unnecessary. It is not clear how this effect is achieved, but glucagon may act by inducing key gluconeogenic enzymes in the period immediately after birth. A subcutaneous or IM injection is sometimes used to counteract accidental hyperinsulinism in patients with diabetes. An IM injection can also be used as a temporary expedient to reduce the risk of reactive hypoglycaemia in an infusion dependent baby when an IV drip suddenly "tissues" and proves difficult to resite. Continuous infusions are not recommended by the manufacturer, but have sometimes been used in light-for-dates babies with persisting neonatal hypoglycaemia, despite a substantial infusion of IV dextrose (q.v.). They have also been used in the initial short term management of babies with endogenous hyperinsulinism, sometimes in conjunction with octreotide (as outlined in the monograph on diazoxide), since glucagon can itself stimulate insulin production. High dose infusion can cause nausea and vomiting.

Treatment

Single dose treatment: Give 200 micrograms/kg of glucagon subcutaneously, IM, or as a bolus IV. This can sometimes raise the blood glucose level permanently out of the hypoglycaemic range in the first few days of life (maybe even making it unnecessary to erect an IV drip).

Continuous IV infusion: Start with 300 nanograms/kg per minute (0.3 ml/hour of a solution made up as described below) and increase this, if necessary, to a dose of not more than 900 nanograms/kg per minute. Prepare a fresh solution if treatment needs to be continued for more than 24 hours.

Supply and administration

Vials containing 1 mg of powder (1 mg = 1 unit), suitable for single dose administration, are available, costing £20 each. Reconstitute with the diluent provided to obtain a solution containing 1 mg/ml. To give a continuous infusion, reconstitute with water for injection and **not** with the usual diluent because of its phenol content. To give an infusion of 100 nanograms/kg per minute, take 300 micrograms (0.3 ml) of this reconstituted material for each kilogram the baby weighs, dilute this to 5 ml with further 5% dextrose to obtain a solution containing 60 micrograms/kg per ml, and infuse this at a rate of 0.1 ml/hour. Vials should be stored at 4°C and reconstituted immediately before use. The fluid has a pH of 2.5–3.0. Do not use the reconstituted solution unless it is clear.

References

- Mehta A, Wootton R, Cheng KL, *et al*. Effect of diazoxide or glucagon on hepatic glucose production rate during extreme neonatal hypoglycaemia. *Arch Dis Child* 1987;**62**:924–30.
- Carter PE, Lloyd DJ, Duffy P. Glucagon for hypoglycaemia in infants small for gestational age. *Arch Dis Child* 1988;**63**:1264–5.
- Hawdon JM, Aynsley-Green A, Ward Platt MP. Neonatal blood glucose concentrations: metabolic effects of intravenous glucagon and intragastric medium chain triglyceride. *Arch Dis Child* 1993;**68**:255–61.
- Stevens TP, Guillet R. Use of glucagon to treat neonatal low-output congestive heart failure after maternal labetalol therapy. *J Pediatr* 1995;**127**:151–3.
- Miralles RE, Lodha A, Perlman M, *et al*. Experience with intravenous glucagon infusions as a treatment for resistant neonatal hypoglycemia. *Arch Pediatr Adolesc Med* 2002;**156**:999–1004.
- Charsha DS, McKinley PS, Whitfield JM. Glucagon infusion for treatment of hypoglycaemia: efficacy and safety in sick preterm infants. *Pediatrics* 2003;**111**:220–1.

Use

The main neonatal use of glyceryl trinitrate is in the management of low output cardiac failure. Topical use to counteract tissue ischaemia is discussed in the monograph on dopamine (q.v.).

Pharmacology

The main use of glyceryl trinitrate (other than as an explosive) is in the treatment of coronary heart disease. When it was first used for angina in 1879 it was presumed that it had a direct effect on the coronary arteries, but it is now recognised to have other systemic effects that help to reduce cardiac oxygen requirements. **Low** doses (between 500 nanograms and 3 micrograms/kg per minute) decrease ventricular filling pressure ("preload") by reducing venous tone. This decreases pulmonary artery pressure and increases cardiac output. It also improves coronary artery perfusion and decreases myocardial oxygen consumption, making secondary cardiac ischaemia less likely. **Moderate** doses (4–6 micrograms/kg per minute) cause pulmonary and systemic arteriolar dilatation, while **high** doses (7–10 micrograms/kg per minute) eventually cause hypotension and secondary tachycardia.

Glyceryl trinitrate is taken up avidly by vascular smooth muscle. Nitric oxide (q.v.) is then liberated, causing a marked decrease in venous and arterial tone. It is also quickly metabolised (half life 1–4 minutes) by glutathione-organic nitrate reductase in the liver and must, therefore, be given by continuous infusion. Therapy can be complicated by methaemoglobinaemia (an oxidation byproduct of the reaction between nitric oxide and haemoglobin) but this has not been described in neonates and children. It can also produce raised intracranial pressure, although this has also not been described in the newborn. Nevertheless, its use in children has not yet been endorsed by the manufacturers. There is no proof of teratogenicity, and there is growing evidence that it can be used as a safe, rapid onset, short acting, tocolytic agent (one 100 microgram bolus IV) to manage placental retention or fetal entrapment during caesarean section or vaginal twin delivery, or to control uterine tone during external cephalic version. Transdermal patch treatment (used as a nitric oxide "donor") is not an effective way of arresting preterm labour, and can cause headache. Local vasodilatation of the skin can be achieved by topical application of a cream or ointment. No information is available on its use during lactation.

Treatment

Continuous IV infusions are usually used, as indicated above, in the management of patients with systemic or pulmonary venous congestion. Start with a low dose and increase as necessary. It is important to exclude hypovolaemia and often appropriate also to use an inotrope.

Compatibility

Glyceryl trinitrate can be added (terminally) to an IV line containing atracurium, dobutamine, and/or dopamine, midazolam, milrinone, and nitroprusside.

Supply and administration

Ampoules containing 0.5, 1, or 5 mg/ml of glyceryl trinitrate are available. The cost of non-proprietary IV products is about 25p per mg. Most formulations contain some propylene glycol (a maximum of 30% v/v). To give an infusion of 1 microgram/kg per minute, draw up 15 mg of glyceryl trinitrate for each kilogram the baby weighs, dilute to 25 ml with 10% dextrose or saline, and infuse at a rate of 0.1 ml/hour (a less concentrated solution of dextrose or dextrose saline can be used if necessary). Ampoules should be protected from strong light, discarded if the fluid is discoloured, and disposed of promptly after use. Check the strength of the ampoule carefully before use. Glyceryl trinitrate is absorbed by polyvinyl chloride and should be given using only syringes (Gillette Sabre®, BD Plastipack®, Monoject® disposable) and tubing (such as Vygon Lectrocath®) made of polyethylene. A fresh solution should be prepared every 24 hours. An ointment containing 2% glyceryl trinitrate (60 g costing £10.50) can be obtained on request. Transdermal patches are used in adult coronary heart disease.

References

- Artman M, Graham TP. Guidelines for vasodilator therapy of congestive heart failure in infants and children. *Am Heart J* 1987;**113**:994–1004.
- Keeley SR, Bohn DJ. The use of inotropic and afterload-reducing agents in neonates. *Clin Perinatol* 1988;**15**:467–89.
- Tamura M, Kawano T. Effects of intravenous nitroglycerin on hemodynamics in neonates with refractory congestive heart failure or PFC. *Acta Paediatr Jpn* 1990;**32**:291–8.
- Wong AF, McCulloch LM, Sola A. Treatment of peripheral tissue ischaemia with topical nitroglycerin ointment in neonates. *J Pediatr* 1992;**121**:980–3.
- Black RS, Lees C, Thompson S, et al. Maternal and fetal cardiovascular effects of transdermal glyceryl trinitrate and intravenous ritodrine. *Obstet Gynecol* 1999;**94**:572–6.

See also relevant Cochrane reviews

GLYCINE

Use

Glycine is used in the management of isovaleric acidaemia, a rare, autosomal recessive, inborn error of metabolism.

Biochemistry

Glycine is a naturally occurring amino acid. When isovaleric acid, and other toxic metabolites of leucine metabolism, accumulate in excess due to a deficiency of the enzyme isovaleryl-CoA dehydrogenase, the administration of additional glycine greatly speeds the conversion of isovaleryl-CoA to isovalerylglycine, which is then excreted in the urine. Additional L-carnitine (q.v.) may also facilitate this. Aspirin (q.v.) should be avoided as it is a competitive substrate for one of the essential metabolic steps involved.

Isovaleric acidaemia

Isovaleric acidaemia is a rare inherited metabolic condition caused by a deficiency of the enzyme isovaleryl-CoA dehydrogenase, which controls an early irreversible step in the metabolism of the essential branch-chain amino acid leucine. A range of metabolites, including isovaleric acid, then accumulate. Glycine becomes conjugated to isovaleric acid (see above) and this is then excreted in the urine. Toxicity can be avoided by adhering to a low protein (or low leucine) diet, and by taking additional glycine by mouth. Some patients present soon after birth (often within 3–6 days) with poor feeding, vomiting, and drowsiness. Tremor, twitching, and seizures may be seen before the child lapses into coma and death. Other patients present for the first time when rather older, with similar symptoms precipitated by intercurrent illness. Symptoms are often accompanied by acidosis, ketosis, and a high blood ammonia level (sometimes $> 500 \mu\text{mol/l}$), and this can lead, wrongly, to a disorder of the urea cycle being suspected. There may be neutropenia, thrombocytopenia, and hypo- or hyperglycaemia when the condition first presents in the neonatal period. High isovaleric acid levels may give rise to a characteristic unpleasant odour, which has been likened to that of "sweaty feet". Patients present, very occasionally, with progressive generalised developmental delay. The condition is most easily diagnosed by detecting excess isovalerylglycine (and 3-hydroxyisovaleric acid) in the urine, or abnormal acylcarnitines in the blood. The prognosis, with early diagnosis, glycine supplementation, and careful dietary supervision, can be good, but many patients suffer neurological damage prior to diagnosis. Symptomatic disturbance becomes less common in later childhood, and the condition is compatible with normal adult life (including a normal uneventful pregnancy). There is no reason to think that lactation would be unwise while the mother herself remains well.

Treatment

Acute illness: Withdraw all protein from the diet, and give IV dextrose to minimise catabolism. Urgent haemodialysis may be indicated if there is severe hyperammonaemia ($>500 \mu\text{mol/l}$) when the patient first presents. Start treatment with oral glycine (see below).

Maintenance care: The usual maintenance dose is 50 mg/kg of glycine three times a day, although, during acute illness, the amount given can be increased to 100 mg/kg six times a day. The normal maintenance dose may need to be modified if there is liver or kidney impairment, and stopped if there is anuria. Long term management involves dietary protein restriction supervised by someone experienced in the management of metabolic disease. L-carnitine may also be given routinely, or as an additional detoxifying agent, orally or IV, if a metabolic crisis occurs.

Supply and administration

Glycine is available as a powder from SHS International, and a stable solution containing 50 mg/ml or 100 mg/ml can be provided on request. 100 g of powder costs £5. No IV preparation is available, but glycine can be given by nasogastric tube, and the likelihood of vomiting can be reduced by giving small frequent doses.

References

- Cohn RM, Yudkoff M, Rothman R, *et al.* Isovaleric acidemia: use of glycine therapy in neonates. *N Engl J Med* 1978;**299**:996–9.
- Shih VE, Aubry RH, DeGrande G, *et al.* Maternal isovaleric acidemia. *J Pediatr* 1984;**105**:77–8.
- Dixon MA, Leonard JV. Intercurrent illness in inborn errors of intermediary metabolism. *Arch Dis Child* 1992;**67**:1387–91.
- Ogier de Baulny H, Saudubray J-M. Branched-chain organic acidurias. In: Fernandes J, Saudubray J-M, van den Berghe G, eds. *Inborn metabolic diseases. Diagnosis and treatment*, 3rd ed. Berlin: Springer-Verlag, 2000:195–212.
- Sweetman L, Williams JC. Branched chain organic acidurias. In: Scriver CR, Beaudet AL, Sly WS, *et al*, eds. *The metabolic and molecular bases of inherited disease*, 8th ed. New York: McGraw-Hill, 2001:2125–63.

Use

Glycopyrronium, like atropine (q.v.), can be used to combat vagal bradycardia and to control salivation and tracheal secretions during general anaesthesia. It is also given to control the muscarinic effect of neostigmine (q.v.) when this drug is used to reverse the effect of a non-depolarising muscle relaxant.

Pharmacology

Glycopyrronium bromide is a quaternary ammonium drug with peripheral antimuscarinic effects similar to those of atropine that is rapidly redistributed into the tissues after IV or IM injection. It was first introduced into clinical use in 1960. Oral absorption is poor. The full effect of IM administration is seen after only 15 minutes, and vagal blockade lasts for about 3 hours. The plasma half life is only 5–10 minutes during childhood and adult life, with almost half the drug being excreted in the urine within 3 hours. The way that babies handle this drug when less than 1 month old has not yet been studied. Anaesthetists increasingly prefer glycopyrronium to atropine and the other belladonna alkaloids, partly because very little glycopyrronium crosses the blood–brain barrier. Transplacental passage is also less than for atropine, and the amount detected in umbilical cord blood after its use during caesarean delivery is small. Rapid plasma clearance makes it extremely unlikely that use during lactation would pose any problem. A 50 micrograms/kg dose of glycopyrronium 2–3 times a day has been given by mouth with some success to control drooling in older children with severe cerebral palsy.

Glycopyrronium, given with neostigmine, achieves an excellent controlled reversal of the neuromuscular blockade seen with the competitive muscle relaxant drugs such as pancuronium (q.v.), but it may take at least 30 minutes to effect the full reversal of deep blockade. A 1:5 drug ratio seems to minimise any variation in heart rate. The risk of dysrhythmia is lower with glycopyrronium, and the lack of any effect on the central nervous system speeds arousal after general anaesthesia.

Treatment

Premedication: The usual dose is 5 micrograms/kg IV shortly before the induction of anaesthesia. Oral premedication with 50 micrograms/kg 1 hour before surgery was not as effective as a 20 micrograms/kg oral dose of atropine at controlling the bradycardia associated with anaesthetic induction.

Reversing neuromuscular block: 10 micrograms/kg of glycopyrronium and 50 micrograms/kg of neostigmine (0.2 ml/kg of a combined solution made up as described below), given IV, will reverse the muscle relaxing effect of pancuronium, (and, where necessary, atracurium, rocuronium, and vecuronium (q.v.)).

Alternatives

Neuromuscular blockade can be reversed just as effectively with atropine and neostigmine if glycopyrronium is not available. Give 20 micrograms/kg of atropine IV followed by a 40 micrograms/kg dose of IV neostigmine.

Toxicity

There are, as yet, few published reports of the effect of an excessive dose, but presentation and management would be the same as for atropine.

Supply and administration

Combined 1 ml ampoules containing 2.5 mg of neostigmine and 500 micrograms of glycopyrronium bromide are available costing £1. Take the contents of the 1 ml ampoule, dilute to 10 ml with 0.9% sodium chloride, and give 0.2 ml/kg of this diluted solution to reverse the neuromuscular block caused by non-depolarising muscle relaxant drugs. Plain 1 ml ampoules simply containing 200 micrograms of glycopyrronium bromide are also available for 60p. Dispersible 1 mg and 2 mg tablets for oral use could be imported into the UK on request.

References

- Mirrkakur RK, Shepherd WFI, Jones CJ. Ventilation and the oculocardiac reflex. Prevention of oculocardiac reflex during surgery for squints: role of controlled ventilation and anticholinergic drugs. *Anaesthesia* 1986;**41**:825–8. [RCT]
- Goldhill DR, Embree PB, Ali HH, *et al.* Reversal of pancuronium. Neuromuscular and cardiovascular effects of a mixture of neostigmine and glycopyrronium. *Anaesthesia* 1988;**43**:443–6.
- Ali-Melkkilä T, Kaila T, Kanto J, *et al.* Pharmacokinetics of glycopyrronium in parturients. *Anesthesia* 1990;**45**:634–7.
- Cartabuke RS, Davidson PJ, Warner LO. Is premedication with oral glycopyrrolate as effective as oral atropine in attenuating cardiovascular depression in infants receiving halothane for induction of anaesthesia? *Anesth Analg* 1991;**73**:271–4. [RCT]
- Rautakorpi P, Ali-Melkkilä T, Kaila T, *et al.* Pharmacokinetics of glycopyrrolate in children. *J Clin Anesth* 1994;**6**:217–20.
- Bachrach SJ, Walter RS, Trzeinski K. Use of glycopyrrolate and other anticholinergic medications for sialorrhoea in children with cerebral palsy. *Clin Pediatr* 1998;**37**:485–90.

HAEMOPHILUS INFLUENZAE (Hib) VACCINE

Use

This vaccine provides protection from type b *Haemophilus influenzae* (Hib) infection. It is made from protein conjugated capsular polysaccharides. Serious adverse reactions are rare.

Haemophilus infection

Infection with *Haemophilus influenzae* can be an important cause of morbidity and mortality in young children. Most infections are caused by encapsulated strains. Six strains (a–f) exist, but 99% of the strains from invasive disease are type b. Infection is rare before the age of 3 months, peaks at 1 year, and becomes less common in school age children. Non-encapsulated strains, although uncommon, make up an increasing proportion of the cases now being reported, although there has been no increase in their absolute number. Meningitis (60%), epiglottitis (15%), and septicaemia (10%), along with septic arthritis, osteomyelitis, cellulitis, and pneumonia, are the illnesses most commonly encountered. Hib meningitis is a notifiable disease in the UK, but other manifestations of Hib disease are not. Five per cent of infected children die and 10% are left impaired. In Finland, the first country to take the Hib vaccine into routine use, there were 203 cases of childhood infection in 1986 but only 1 case in 1992. This decline has now been replicated in several other countries, but vaccine failure has been encountered with increasing frequency since 1998 in term babies in the UK. Preterm babies are also known to mount a less vigorous immune response to primary immunisation at 2–4 months. However, no decision has yet been taken to give all children a further booster dose in the second year of life (as is the policy in some countries). UK clinicians are urged to continue reporting *all* cases of invasive *H influenzae* disease to Mary Ramsay (MRamsay@phs.org.uk) so that trends can be monitored.

Indications

All children should be offered immunisation against *Haemophilus* (Hib), preferably at the same time as they are immunised against meningococcus (MenC) and against diphtheria, tetanus, and pertussis (DTP).

Contraindications

Immunisation should not be offered to a child who is acutely unwell, or who has had a serious reaction to a previous injection. Minor infection unassociated with fever is not a reason to delay immunisation, however, and the contraindications associated with the use of a live vaccine (cf. measles) do not apply.

Administration

Children under 1 year old: Give three 0.5 ml doses by deep IM injection into the anterolateral aspect of the thigh at monthly intervals. Use the combined Hib/DTP vaccine when simultaneous protection against diphtheria, tetanus, and pertussis is also being offered. Use a different thigh when giving the group C meningococcal vaccine simultaneously. There is increasing evidence that a booster dose may be appropriate for very preterm babies at 12–15 months.

Older children: Give other previously unimmunised children aged under 4 years a single 0.5 ml injection when opportunity arises. There is no contraindication to simultaneous immunisation with other routine vaccines when using a different injection site. Older children merit immunisation only if they have sickle cell disease, asplenia, or congenital or acquired immunodeficiency, because serious infection is uncommon.

Anaphylaxis

The management of anaphylaxis (which is very rare) is outlined in the monograph on immunisation.

Documentation

Inform the district immunisation coordinator (see monograph on immunisation) when any child is immunised in hospital, and complete the relevant section of the child's own personal health booklet.

Supply

Two companies make 0.5 ml vials of the monovalent Hib vaccine; these products can be drawn up into the same syringe as the same company's DTP vaccine and given as a single 1 ml injection. A combined DTP and Hib vaccine is available in a dual chamber syringe from Pasteur Mérieux, and as a powder for reconstitution, from SmithKline Beecham. Vaccines must be stored at 2–8°C, but not frozen.

References

- UK Health Departments. *Immunisation against infectious disease*. Chapter 16. London: HMSO, 1996:77–84.
- Kirmani KI, Lofthus G, Pichichero ME, et al. Seven-year follow-up of vaccine response in extremely premature infants. *Pediatrics* 2002;**109**:498–504.
- Tanner K, Fitzsimmons G, Carrol ED, et al. Haemophilus influenzae type b epiglottitis as a cause of acute upper airways obstruction in children. *BMJ* 2002;**325**:1099–100. (See also **326**:284–5.)
- Claire P, Powell PJ, Goldblatt D, et al. Effect of a fourth *Haemophilus influenzae* type b immunisation in preterm infants who received dexamethasone for chronic lung disease. *Arch Dis Child* 2003;**88**:F58–61.
- Garner D, Weston V. Effectiveness of vaccination for *Haemophilus influenzae* type b. *Lancet* 2003;**361**:395–6. (See also pp. 360–1.)
- Heath PT, Booy R, McVernon J, et al. Hib vaccination in infants born prematurely. *Arch Dis Child* 2003;**88**:206–10.
- McVernon J, Andrews N, Slack MPE, et al. Risk of vaccine failure after *Haemophilus influenzae* type b (Hib) combination vaccines with acellular pertussis. *Lancet* 2003;**361**:1521–3. (See also 1523–4.)

Use

Heparin is used during cardiovascular surgery and, prophylactically, to maintain catheter patency. Low molecular weight heparins are used, in adults, to prevent and manage venous thromboembolism.

Pharmacology

Heparin is an acid mucopolysaccharide of variable molecular weight (4000–40,000 Daltons) that was first obtained from liver (hence its name) in a form pure enough to make clinical trials possible in 1935. Although it has some thrombolytic action it is mostly used to prevent further blood clot formation rather than to lyse clots that have already formed. The higher molecular weight heparins also inhibit platelet activity. Heparin works *in vitro* by activating plasma antithrombin inhibitor, which then deactivates thrombin and factor Xa. It is metabolised by N-desulfation after IV administration and then rapidly cleared from the body. The half life of conventional unfractionated heparin is dose dependent, increasing as the plasma level rises. It averages 90 minutes in adults, but may be less at birth. Fractionated low molecular weight (4000–6000 Daltons) heparins, such as enoxaparin, have a much longer half life. They cause less osteopenia, show much greater bioavailability when given subcutaneously, and are mostly excreted by the kidneys. All products occasionally cause an immune mediated thrombocytopenia, most commonly 5–10 days after the start of treatment. Because any such response can, paradoxically, cause a major thromboembolic event, the platelet count *must* be monitored during treatment with heparin. Heparin does not cross the placenta, and can be given with complete safety during lactation. The same is true for all the low molecular weight heparins.

Women at high risk of thromboembolism because of immobility, obesity, high parity, previous deep vein thrombosis, or an inherited thrombophilia, are now increasingly given prophylactic low molecular weight heparin during pregnancy (treatment being switched to IV heparin shortly before delivery). Prophylaxis is probably even more important in the period immediately after birth. Warfarin (q.v.) continues to be used to anticoagulate women with pulmonary vascular disease, and patients with an artificial heart valve or atrial fibrillation, but time may show that they, too, can be protected with enoxaparin.

Indications for neonatal use

There is controlled trial evidence that even a small (0.5 unit/ml) dose of heparin can help to sustain the patency of neonatal monitoring lines, especially when it is given as a continuous infusion, but there is no evidence that this reduces the risk of thromboembolism or arterial occlusion. Although one small study has suggested that full heparinisation may reduce the formation of arterial thrombi, the effect of any such approach on the risk of intraventricular haemorrhage remains uncertain. Three observational studies (one so far reported only in abstract) even suggest a correlation between total heparin exposure and the risk of intraventricular haemorrhage in babies of under 1.5 kg in the first week of life. However, this may merely mean that some babies were given more heparin because they were already less well. No adequate sized trials have ever been done. Although adverse effects of heparin are rare, heparinised babies can bleed unpredictably. The use of heparin is probably contraindicated, therefore, in babies with intracranial or gastrointestinal haemorrhage. Uncorrected thrombocytopenia ($< 50 \times 10^9/l$) is also a contraindication, and IM injections should not be given to any heparinised patient. Lumbar puncture can also be hazardous. Alteplase or streptokinase (q.v.) are more appropriately used to lyse clots that have already formed.

Prophylactic strategies

Monitoring lines: Intravascular catheters are often used to monitor blood pressure and to make blood sampling possible without disturbing the patient. A steady 0.5 ml/hour or 1.0 ml/hour infusion containing 1–2 units of heparin for each ml of fluid prolongs catheter patency. Glucose shortens the line's life and makes it impossible to monitor blood glucose levels. The use of 0.18% rather than 0.9% sodium chloride reduces the risk of sodium overload. Clear the 1 ml catheter "dead space" carefully after sampling, and consider using water rather than dextrose or saline for this in order to avoid sudden swings in blood glucose and the infusion of further unmeasured quantities of sodium chloride. It is not necessary to add further heparin to the fluid used to flush the dead space.

"Stopped off" cannulas: It has long been common practice to use 2 ml of "normal" saline containing 10 units/ml of heparin to flush "stopped off" cannulas after use, but the addition of heparin to the flush solution does nothing to prolong patency and exposes these babies to an uncertain and undocumented amount of additional heparin. Using water instead of 0.9% sodium chloride decreases the sodium load.

Cardiac catheterisation: A 100 unit/kg IV bolus at the start of the procedure greatly reduces the risk of symptomatic thromboembolism.

Intravascular infusions: Adding heparin to the infusate prolongs the patency of arterial catheters in *adults*. Peripheral venous catheter patency is also probably prolonged. However, the only controlled trials done to date have *not* been large enough to show that the addition of 1 unit/ml of heparin increases the length of time that peripherally inserted central venous lines remain patent in the *neonate*.

continued ...

HEPARIN (continued)

Full anticoagulation

The indications for this in the neonate remain unclear. There is no good evidence that anticoagulation reduces the risk of an existing clot enlarging, fragmenting, and shedding emboli, or reforming after lysis. Neither is heparinisation called for in most cases of disseminated intravascular coagulation. If treatment is indicated, start by giving a loading dose of 75 units/kg IV over 10 minutes (a loading dose of 50 units/kg may be safer in babies with a postmenstrual age of less than 35 weeks). Maintenance requirements vary: start with a continuous IV infusion of 25 units/kg per hour and assess the requirement by monitoring the activated partial thromboplastin time (APTT) after 4 hours.

Dose monitoring

The anticoagulant dose used during extracorporeal membrane oxygenation and to lyse thrombi is one that raises the APTT to 1.8–2.0 times the normal level. Never take blood for this test from a heparinised intravascular line; sufficient quantities of heparin will remain to invalidate the laboratory result even if the line is flushed through first. Normal neonatal APTT times are given in the monograph on fresh frozen plasma.

Antidote

Protamine sulphate is a basic protein that combines with heparin to produce a stable complex devoid of anticoagulant activity. The effect of heparin can, therefore, be neutralised by giving 1 mg of protamine sulphate IV over about 5 minutes for every 100 units of heparin given in the previous 2 hours. Excess protamine is dangerous because it binds platelets and proteins such as fibrinogen, producing, in itself, a bleeding tendency.

Compatibility

It is known that adrenaline, amphotericin (but not the liposomal formulation), atracurium, fentanyl, isoprenaline, midazolam, milrinone, morphine, noradrenaline, ranitidine, streptokinase, TPN (the standard formulation with or without lipid), and urokinase (q.v.) can be added (terminally) to a line containing heparin. The same is true for dopamine (q.v.), but there are reports suggesting that, although heparin is compatible with dobutamine when suspended in 0.9% sodium chloride, precipitation may occur (somewhat unpredictably) when the two drugs are mixed, even briefly, in a dextrose solution.

Supply and administration

Stock multidose 5 ml vials containing 1000 units/ml of standard, unfractionated heparin sodium and preservative (costing 47p each) are stable for up to 3 years. To prepare a solution containing 1 unit/ml, add 0.5 ml from the vial to a 500 ml bag of IV fluid. It is stable in solution and does not need to be prepared afresh every day. 5 ml preservative-free Hepsal[®] ampoules containing 0.75 mmol of sodium and 50 units of unfractionated heparin cost 25p each. All these preparations can be stored at room temperature (5–25°C). There is, as yet, too little experience of the use of the low molecular weight products to recommend their use in early infancy.

5 ml ampoules of protamine sulphate containing 10 mg/ml cost 96p each.

References

- Rajani K, Goetzman BW, Wennberg RP, *et al.* Effect of heparinisation of fluids infused through an umbilical artery catheter on catheter patency and frequency of complications. *Pediatrics* 1979;**63**:552–6. [RCT]
- McDonald MM, Hathaway WE. Anticoagulant therapy with continuous heparinisation in newborn and older infants. *J Pediatr* 1982;**101**:451–4.
- Horgan MJ, Bartoletti A, Polansky S. Effect of heparin infusates in umbilical arterial catheters on frequency of thrombotic complications. *J Pediatr* 1987;**111**:774–8.
- Hecker JF. Potential for extending survival of peripheral intravenous infusions. *BMJ* 1992;**304**:619–24. [SR]
- Ginsberg JS, Barron WM. Pregnancy and prosthetic heart valves [Editorial]. *Lancet* 1994;**344**:1170–2.
- Mocclair A, Bates I. The efficacy of heparin in maintaining peripheral infusions in neonates. *Eur J Pediatr* 1995;**154**:567–70. [RCT]
- Andrew M. Indications and drugs for anticoagulation therapy in children. *Thromb Res* 1996;**81**:561–573.
- Silvers KM, Darlow BA, Winterbourn CC. Pharmacological levels of heparin do not destabilise neonatal parenteral nutrition. *J Parenteral Enteral Nutr* 1998;**22**:311–14.
- Randolph AG, Cook DJ, Gonzales CA, *et al.* Benefit of heparin in peripheral venous and arterial catheters: systematic review and meta-analysis of randomised controlled trials. *BMJ* 1998;**316**:969–75. [SR]
- Monagle P, Michelson AD, Bovill E, *et al.* Antithrombotic therapy in children. *Chest* 2001;**119**:344–70S. [SR]
- Royal College of Obstetricians and Gynaecologists. *Clinical Green Top Guideline. Thromboembolic disease in pregnancy and the puerperium.* (See the Good Practice guideline issued in 2001 on the College website: www.rcog.org.uk)
- Kamala F, Boo NY, Cheah FC, *et al.* Randomised controlled trial of heparin for prevention of blockage of peripherally inserted central catheters in neonates. *Acta Paediatr* 2002;**91**:1350–6. [RCT]

See also relevant Cochrane reviews



Use

Hepatitis B vaccine provides active lasting immunity to the hepatitis B virus; a specific hepatitis B immunoglobulin (HBIG) can be used to provide immediate, short lasting passive immunity.

Hepatitis B

Hepatitis B is a major worldwide problem. Illness starts insidiously and is of variable severity. Infection can result from sexual contact, contaminated blood, or a needle contaminated with blood. Some 2–10% of the adults so infected become chronic carriers, and nearly a quarter of these eventually develop chronic disease (with possible cirrhosis or hepatocellular carcinoma). Infection can also pass from mother to child. Transplacental passage is rare, but 80% of babies become infected during delivery, and 90% of those so infected become chronic carriers. Universal early immunisation is the policy recommended by the World Health Organization, but maternal screening and selective neonatal immunisation remains the policy still in place in Scandinavia and the UK. The present vaccine contains 20 micrograms/ml of hepatitis B surface (Australian) antigen (HBsAg) adsorbed onto an aluminium hydroxide adjuvant. Hepatitis B, at any age, like any form of hepatitis, is a notifiable infection.

Indications

Babies born to mothers who develop hepatitis B during pregnancy, and to mothers with hepatitis B surface (s) antigen (HBsAg) in their blood, are at high risk and should be offered active immunisation within 24 hours of birth. Since this takes time to become effective, they also need "bridging" protection with HBIG unless they are known to have antibodies to the core (e) antigen (i.e. to have HBeAg antibodies). The UK's current policy of selective immunisation can be made to work only if there is universal antenatal screening and a failsafe "call back" system so that those identified receive all the recommended treatment. Active immunisation is also offered to all healthcare staff, and to all children on haemodialysis, requiring frequent or large blood transfusions, or repeated factor concentrates.

Contraindications

Side effects of immunisation (other than local soreness) are rare, and contraindications to immunisation almost non-existent (although vaccination should be delayed in the face of intercurrent illness). Vaccination should not be withheld from a high risk woman because she is pregnant because infection in pregnancy can result in severe illness and chronic infection in the baby.

Administration

Universal vaccination: Three doses of vaccine are normally given (as below). In countries where the first dose is usually given at birth, babies who are preterm probably benefit from a fourth dose.

Selective vaccination: Babies at risk need a first IM injection of hepatitis B vaccine (10 micrograms in 0.5 ml) within 24 hours of birth, and "booster" injections 1 and 4–6 months later. Babies at high risk, as specified above, also need 2 ml (200 units) of HBIG into the other thigh within 24 hours of birth. Such a policy offers 95% protection. Breastfeeding can continue safely.

Anaphylaxis

The management of anaphylaxis (which is very rare) is outlined in the monograph on immunisation.

Supply

0.5 ml, 10 microgram, thiomersal free, £9.80 vials of hepatitis B vaccine (Engerix B[®] from SmithKline Beecham) are available from the pharmacy. Aventis-Pasteur produce a similar product (HBvaxPRO[®]); the recommended dose is different. Store at 2–8°C but do not freeze. Shake before use. *Always* record administration in the child's personal health record.

Ampoules containing 200 units or 500 units of HBIG prepared by the Blood Products Laboratory are available in the UK from the local public health laboratory on request. HBIG is expensive and only limited supplies are available. Store all ampoules at 4°C.

References

- UK Health Departments. *Immunisation against infectious disease*. Chapter 18. London: HMSO, 1996:95–108.
- Kane MA. Hepatitis viruses and the neonate. *Clin Perinatol* 1997;**24**:181–91.
- Larcher VF, Bourne J, Aitken C, *et al*. Overcoming barriers to hepatitis B immunisation by a dedicated hepatitis B immunisation service. *Arch Dis Child* 2001;**84**:114–18. (See also commentary pp. 118–19).
- MacIntyre CR. Hepatitis B vaccine: risks and benefits of universal neonatal vaccination. *J Paediatr Child Health* 2001;**37**:215–19.
- Whittle H, Jaffar S, Wansbrough M, *et al*. Observational study of vaccine efficacy 14 years after trial of hepatitis B vaccination in Gambian children. *BMJ* 2002;**325**:569–72 (See also **326**:105.)
- Arora NK, Ganguly S, Agadi SN, *et al*. Hepatitis B immunisation in low birthweight infants: do they need an additional dose? *Acta Paediatr* 2002;**91**:995–1001.
- Lin Y-C, Chang M-H, Ni Y-H, *et al*. Long-term immunogenicity and efficacy of universal hepatitis B virus vaccine vaccination in Taiwan. *J Infect Dis* 2003;**187**:134–8.

HYALURONIDASE

Use

Extravasation can cause severe tissue injury when irritant fluid leaks from a vein during infusion. Hyaluronidase can be used to minimise such damage, facilitating fluid dispersal during tissue irrigation.

Pharmacology

Hyaluronidase is a naturally occurring enzyme that has a temporary and reversible depolymerising action on the polysaccharide hyaluronic acid present in the intercellular matrix of connective tissue. It can be used to enhance the permeation of local anaesthetics, subcutaneous infusions, and IM injections into the body tissues. It can also aid the resorption of excess tissue fluid. The product that has been in general use since 1980 is a purified extract of beef or sheep semen. The dose recommended here (the dose usually employed in the UK) is nearly 10 times the dose generally considered adequate in the USA. Hyaluronidase was initially used on its own in an attempt to disperse damaging extravasated fluid, but such an approach appears to be of limited value. Reports now suggest that immediate irrigation (after prior infiltration with hyaluronidase) with a view to washing away any irritant fluid may be a much more effective strategy.

Infiltration with phentolamine mesilate or the use of a glyceryl trinitrate ointment (as described in the monograph on dopamine) is a more appropriate strategy for preventing the dermal necrosis that is likely to follow the accidental extravasation of vasoconstrictive drugs.



Reproduced with permission from Davies *et al* (1994).

Treatment

Clean the damaged area of skin and then infiltrate it immediately with up to 0.3 ml/kg of 1% lidocaine (q.v.). (Bupivacaine (q.v.) could, alternatively, be used to provide more sustained pain relief, although it takes longer to become effective.) Then inject 500–1000 units of hyaluronidase into the subcutaneous tissues under the area of damaged skin. While the simplest approach is merely to inject some hyaluronidase into the cannula through which extravasation occurred (if this is still in place), it is almost certainly better, with large lesions, to make three or four small “incisions” into the skin with a sharp scalpel round the edges of the area to be treated, insert a blunt Verres needle into each incision in turn, inject the hyaluronidase, and then irrigate the damaged tissue with 25–100 ml of 0.9% saline using the needle and threeway tap (i.e. a total of 100–400 ml of irrigating fluid in all, depending on the size of the lesion). Saline should flow freely out of the other incisions (see figure). Excess fluid can be massaged out of the incisions by gentle manipulation. The damaged area is then covered with a paraffin gauze (tulle gras) dressing for 24–48 hours.

Supply

Ampoules containing 1500 units of hyaluronidase injection BP cost £7.60 each. Dissolve the contents in 1.5 ml of water for injection to give a solution containing 1000 units/ml immediately before use. The product is not, at present, commercially available in North America.

Verres needles are obtainable in the UK from Downes Surgical Ltd, Sheffield. They are widely used to insufflate air during laparoscopy.

References

- Razka WV, Kueser TK, Smith FR, *et al*. The use of hyaluronidase in the treatment of intravenous extravasation injuries. *J Perinatol* 1990;**10**:146–9.
- Davies J, Gault D, Buchdahl R. Preventing the scars of neonatal intensive care. *Arch Dis Child* 1994;**70**:F50–51
- Camp-Sorrell D. Developing extravasation protocols and monitoring outcomes. *J Intraven Nurs* 1998;**21**:232–9.
- Kassner E. Evaluation and treatment of chemotherapy extravasation injuries. *J Pediatr Oncol Nurs* 2000;**17**:135–48.

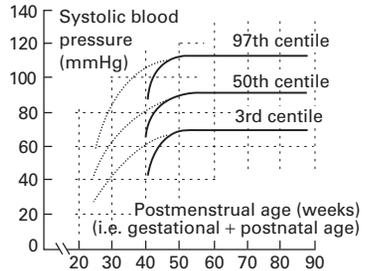
Use

Hydralazine has been used in the long term management of chronic neonatal hypertension, together, if necessary, with propranolol (q.v.). IV labetalol (q.v.) is more effective in the initial urgent control of any acute hypertensive crisis, and nifedipine (q.v.) may provide better long term control.

Hypertension

Systolic blood pressure at rest varies with postmenstrual (that is gestational plus postnatal) age during the first year of life as shown in the figure. Dark lines show the level usually seen in the term baby, and dashed lines the normal range for a baby of 24–26 weeks gestation at birth. Systolic pressure in those less immature than this seldom exceeds that shown for a 24–26 week gestation baby. See the monograph on labetalol for general guidance on the measurement of blood pressure.

Serious hypertension is rare in the neonatal period, but can present with signs of congestive cardiac failure. The cause is most often renal in origin and can follow silent embolic arterial damage (hypertension due to renal vein thrombosis usually occurs only after a longer latent phase). Hydralazine, with or without propranolol, was often used for maintenance in the past, once any acute crisis was under control, but nifedipine is now increasingly the preferred option. The response to captopril (q.v.) and enalapril is too unpredictable to make either of these drugs easy to use. Unilateral nephrectomy occasionally merits consideration.



Pharmacology

Hydralazine became the first effective oral antihypertensive when it was patented in 1949. The drug crosses the placenta but there is no evidence of teratogenicity in humans. It is well absorbed by mouth but rapid metabolism within the liver as the drug passes up the portal vein halves bioavailability when it is given by mouth. Hydralazine is eliminated by acetylation at a very variable rate ("fast acetylation" being an inherited characteristic). The drug causes vasodilatation; drug retention in the vascular wall making it unnecessary to prescribe the drug more than once every 8–12 hours, despite a variable plasma half life. Vomiting, diarrhoea, and postural hypotension are relatively common adverse effects in older patients but little is known about the side effects associated with treatment in the first year of life. Reflex tachycardia is sometimes a problem but this can be controlled with a β blocker drug such as propranolol. Salt and water retention, as a result of increased renal medullary blood flow, can be counteracted by prescribing a diuretic. Hepatitis, oedema, and paralytic ileus have occasionally been reported after long term administration. Hydralazine appears in human milk but, weight for weight, a breastfed baby ingests only about 1% of the maternal dose. The manufacturer has not endorsed the use of hydralazine in children.

Drug interaction

Severe hypotension has been described when a patient on hydralazine is given diazoxide.

Treatment

Oral treatment: Start with 500 micrograms/kg of hydralazine once every 8 hours by mouth to control hypertension; increase this, as necessary, to a maximum of 2–3 mg/kg every 8 hours. A dose as high as 4 mg/kg every 8 hours has been used in older children, but not documented in the neonatal period.

IV treatment: The appropriate dose is about half the oral dose.

Supply and administration

Ampoules containing 20 mg of hydralazine are available for IV use. They cost £1.50 each. Dissolve the powder in 1 ml of sterile water, draw all the fluid from the ampoule into a syringe and dilute to 20 ml with 0.9% sodium chloride to obtain a solution containing 1 mg/ml. This preparation can also be given by mouth. A sugar-free oral suspension with a 3 month shelf life is also available.

References

- Fried R, Szeinherz LJ, Levin AR, *et al.* Use of hydralazine for intractable cardiac failure in childhood. *J Pediatr* 1980;**97**:1009–11.
- Beekman RH, Rocchini AP, Rosenthal A. Haemodynamic effects of hydralazine in infants with a large ventricular septal defect. *Circulation* 1982;**65**:523–8.
- Adelman RD. The hypertensive neonate. *Clin Perinatol* 1988;**15**:567–85.
- Rasoulpour M, Marinelli KA. Systemic hypertension. *Clin Perinatol* 1992;**19**:121–37.
- Northern Neonatal Nursing Initiative. Systolic blood pressure in babies of less than 32 weeks gestation in the first year of life. *Arch Dis Child* 1999;**80**:F38–42.
- Watkinson M. Hypertension in the newborn baby [Review]. *Arch Dis Child* 2002;**86**:F78–81.

See also relevant Cochrane reviews

HYDROCORTISONE

Use

Hydrocortisone is used in the management of adrenal insufficiency due to hypopituitarism or congenital adrenal abnormality. Many preterm babies with hypotension also respond to IV hydrocortisone.

Pathophysiology

The adrenal cortex normally secretes hydrocortisone (cortisol), which has glucocorticoid activity and weak mineralocorticoid activity. It also secretes the mineralocorticoid aldosterone. Physiological replacement in adrenal insufficiency is best achieved by a combination of hydrocortisone and the artificial mineralocorticoid fludrocortisone but, where the problem is secondary to pituitary failure, mineralocorticoid replacement is seldom necessary because aldosterone production is mainly controlled by the renin–angiotensin system. Hydrocortisone first became available in 1949.

Congenital adrenal hyperplasia can result from a number of different recessively inherited enzyme deficiencies. Nearly 95% of cases are due to 21-hydroxylase deficiency; most of the others are caused by 11-hydroxylase deficiency. Salt loss is a problem in the former condition but not usually in the latter. Diagnosis is relatively easy in girls because of virilisation and sexual ambiguity, but less easy in boys until the child presents with vomiting, failure to thrive, and (ultimately) circulatory collapse. Some boys are initially misdiagnosed as having pyloric stenosis. A 17-hydroxyprogesterone (17-OHP) measurement, an urgent karyotype, pelvic imaging, and a urinary steroid profile confirm the diagnosis. Functional adrenal hypoplasia can also present in a similar manner, or with hypoglycaemia. It is diagnosed by the lack of a significant response to tetracosactide (q.v.) and a normal 17-OHP level.

Drug	Equivalent activity (mg)		Biological half life (h)
	Glucocorticoid	Mineralocorticoid	
Fludrocortisone	0	20	–
Cortisone acetate	25	0.8	8–12
Hydrocortisone	20	1	8–12
Prednisolone	5	<1	12–36
Betamethasone	0.75	0	36–54
Dexamethasone	0.75	0	36–54

Treatment

Early neonatal hypotension: Hydrocortisone often increases blood pressure as effectively as dopamine (q.v.), and may work when a catecholamine does not. A 2 mg/kg dose IV and then 1 mg/kg every 8–12 hours often causes a rapid and obvious improvement in tissue perfusion. Such babies usually show a normal pituitary but blunted adrenal response to tetracosactide. Withdraw treatment over 2–3 days. Such use may increase the risk of candidiasis. Dexamethasone (q.v.) may also be effective.

Addisonian crisis: This requires IV glucose and a 10 mg bolus followed by a continuing 100 mg/m² per day infusion of hydrocortisone. Rapid fluid replacement may be necessary with 0.9% sodium chloride. The high serum potassium almost always corrects itself, but 2 ml/kg of 10% calcium gluconate (q.v.) and/or an infusion of glucose and insulin (q.v.) may be needed if a cardiac arrhythmia develops.

Congenital adrenal hyperplasia: Adrenal suppression with 5–7 mg/m² of hydrocortisone once every 8 hours, plus at least 100 micrograms of fludrocortisone once a day, provides a good starting point for neonatal care. Babies with 21-hydroxylase deficiency usually need an additional 2–4 mmol/kg of sodium a day. Long term care should be supervised by a paediatric endocrinologist.

Adrenal hypoplasia: Production of cortisol normally averages 6–9 mg/m² per day and, making allowance for absorption, 10–12 mg/m² of hydrocortisone by mouth will meet normal replacement needs (although need may rise 10-fold during any acute illness).

Supply

100 mg vials of hydrocortisone (as the sodium succinate powder) cost 92p each. Reconstitute with 2 ml of water. Oral suspensions of hydrocortisone and of fludrocortisone acetate in sucrose can be provided.

References

- Miller WL. The adrenal cortex and its disorders In: Brook CGD, Hindmarsh PC, eds. *Clinical paediatric endocrinology*, 4th ed. Oxford: Blackwell Science, 2001:321–76.
- Ng PC, Lam CWK, Fok TF, et al. Refractory hypotension in preterm infants with adrenocortical insufficiency. *Arch Dis Child* 2001;**84**:F122–4.
- Seri I, Tan R, Evans J. Cardiovascular effects of hydrocortisone in preterm infants with pressor-resistant hypotension. *Pediatrics* 2001;**107**:1070–4.

Use

Ibuprofen is an effective alternative to indometacin (q.v.) in the management of patent ductus arteriosus, and can be used instead of paracetamol (q.v.) to control fever in babies over 3 months old.

Pharmacology

Aspirin (q.v.) is the most widely used non-steroidal anti-inflammatory drug (NSAID), but many other drugs with similar properties are now marketed. Different drugs seem to suit different patients best, but ibuprofen (patented in 1964) seems, in general, to have been associated with the fewest reported adverse effects when used in adults with rheumatoid arthritis. Gastrointestinal complications are the most common problem, and occur often enough to make NSAID treatment inappropriate in any patient with a history of peptic ulceration.

Ibuprofen (another commonly used NSAID) is generally well absorbed when taken by mouth and is excreted partly metabolised in the urine. The half life is extremely variable at birth (10–80 hours) but is similar to that seen in adults (~90 minutes) within 3 months. Oral ibuprofen has a useful role in the management of postoperative pain in childhood, but the very variable half life precludes its use as a neonatal analgesic. Ibuprofen is the most widely used NSAID in children with rheumatoid arthritis, but the manufacturers do not recommend its use for *any* reason in children weighing less than 7 kg.

All NSAIDs inhibit prostaglandin synthesis to some degree. There is, therefore, at least a theoretical risk that the use of high doses in the third trimester of pregnancy could cause premature closure of the ductus arteriosus before birth, prolong or delay labour, or affect postdelivery pulmonary vascular tone. Although there may be a slight increase in the risk of miscarriage, there is no evidence of teratogenicity in humans. Manufacturers, however, remain reluctant to recommend the use of any NSAID in pregnancy and information on recently introduced products is limited. The amount present in breast milk is undetectably small, and is no contraindication to maternal use during lactation.

The NSAID indometacin has been used for nearly 30 years to induce ductal closure in preterm babies, precisely because of its ability to inhibit prostaglandin synthesis. However, indometacin also causes a fall in cerebral blood flow, a property that it does not share with other NSAIDs, and also a transient fall in neonatal renal and gut blood flow. There is no evidence that any of these changes are of clinical significance. Nevertheless, because it is equally good at effecting duct closure and does not cause other changes in regional blood flow, ibuprofen is now being used instead of indometacin to effect duct closure in some parts of Europe. Prophylactic treatment, before persisting patency has been documented, reduces the number of very preterm babies eventually requiring duct ligation (just as indometacin does). There is, however, no good evidence that the early use of either drug improves the long term prognosis for survivors. Ibuprofen, in the dose recommended here, has a negligible effect on renal function, although there may be a small fall in sodium excretion. Gut problems are uncommon.

Treatment

Patent ductus: Give 10 mg/kg IV, followed by 5 mg/kg 24 and 48 hours later. Oral treatment may turn out to be equally effective. The effect of giving further doses if patency persists has not yet been studied.

Fever: An oral dose of between 5 mg/kg and 8 mg/kg, repeatable after 6 hours, is widely used to control fever in children more than 3 months old (and seems to be as effective as paracetamol).

Supply

The IV preparation used in all the published trials to date was obtained by asking a local pharmacy to make a solution containing 10 mg/ml by reconstituting with 23.4 ml of water for injection one of the 300 mg vials of the lysine salt marketed by Merckle in Germany for IM use. Such vials cost £1.75 each. Other formulations containing lidocaine cannot be substituted safely for this product. Orphan Europe has an IV product, trometamol, under development (2 ml, 5 mg/ml ampoules cost £62), but the safety of prophylactic use remains to be assessed. A sugar-free 20 mg/ml oral suspension is available "over the counter" from community pharmacists without prescription (100 ml costs £1.90).

References

- McIntyre J, Hull D. Comparing efficacy and tolerability of ibuprofen and paracetamol in fever. *Arch Dis Child* 1996;**74**:164–7. [RCT]
- Van Overmeire B, Smets K, Lecoutere D, et al. A comparison of ibuprofen and indomethacin for closure of patent ductus. *N Engl J Med* 2000;**343**:674–81. (See also pp. 728–30.) [RCT]
- Van Overmeire B, Touw D, Schepens PJG, et al. Ibuprofen pharmacokinetics in preterm infants with patent ductus arteriosus. *Clin Pharmacol Ther* 2001;**70**:336–43.
- Lago P, Bettiol T, Salvadori S, et al. Safety and efficacy of ibuprofen versus indomethacin in preterm infants treated for patent ductus arteriosus: a randomised controlled trial. *Eur J Pediatr* 2002;**161**:202–7. [RCT]
- Van Overmeire B, Casaer A, Allergaert K, et al. Multicentre randomized double-blind placebo-controlled trial of ibuprofen prophylaxis in very preterm infants [Abstract]. *Pediatr Res* 2002;**51**:379A. [RCT]
- Gournay V, Savagner C, Thiriez G, et al. Pulmonary hypertension after ibuprofen prophylaxis in very preterm infants. *Lancet* 2002;**359**:1486–8. [RCT] (See also: commentary p. 1449; letters **360**:492; and pp. 1023–4.)

IMIPENEM

Use

Imipenem is a useful reserve antibiotic that is active against a very wide range of bacteria. Cilastatin is always administered as well. Meropenem (q.v.) is more appropriate when meningitis is suspected, has fewer adverse effects, and is easier to administer, but little information on neonatal use is yet available.

Pharmacology

This β lactam antibiotic, developed in 1983, is active against a very wide range of Gram positive and Gram negative aerobic and anaerobic bacteria. Some methicillin resistant staphylococci, group D streptococci, and *Pseudomonas* species are resistant to imipenem. The drug acts synergistically with the aminoglycosides *in vitro*, and is sometimes prescribed with an aminoglycoside in the treatment of infection with *Pseudomonas* in order to prevent the emergence of drug resistance. Imipenem is a valuable reserve antibiotic that should be used only on the advice of a consultant microbiologist.

Because imipenem can cause renal toxicity, and because it is partially inactivated within the kidney, it is always given in combination with cilastatin, a specific dehydropeptidase enzyme inhibitor, which blocks imipenem's renal breakdown. Imipenem is widely distributed in many body tissues and crosses the placenta, but cerebrospinal fluid levels are low and the drug is not recommended for central nervous system (CNS) infection. Both imipenem and cilastatin are rapidly eliminated by a combination of glomerular filtration and tubular secretion into the urine in adults, the plasma half life being under 1 hour. Less is known about drug handling in the neonatal period; the half life of imipenem is increased threefold but that of cilastatin is increased 11-fold in the first week of life. As a result, any dose regimen that is appropriate for the bactericidal ingredient, imipenem, will result in the progressive accumulation of cilastatin when the standard product containing equal amounts of both ingredients is used. Whether this matters is not known. A 4:1 imipenem:cilastatin formulation may be better. In its absence, prolonged, or high dose, treatment should be employed with caution. Both drugs are rapidly cleared from the body during haemodialysis.

Adverse effects include localised erythema and thrombophlebitis. Neurotoxic reactions, including a progressive encephalopathy with seizures, have been seen, sometimes preceded by myoclonic twitching, especially in patients with an existing CNS abnormality. Rapid infusion may cause nausea and vomiting. Diarrhoea can occur and this may, on occasion, be the first sign of pseudomembranous colitis. Superinfection with a non-susceptible organism is an ever present possibility. The manufacturers have advised against the use of imipenem with cilastatin in pregnancy because of increased embryonic loss in animal studies, and have not, as yet, been ready to recommend their use in children less than 3 months old. Substantial placental transfer occurs, but there is no evidence of teratogenicity. Treatment during lactation also seems safe since the baby receives less than 1% of the weight-related maternal dose and the drug is largely inactivated in the gut.

Drug prescribing

The drug should technically be referred to as "imipenem with cilastatin", but omitting the words "with cilastatin" is unlikely to cause misunderstanding, since all commercial preparations contain both drugs. Record merely the dose of imipenem required.

Treatment

Give 20 mg/kg of imipenem IV over 30 minutes once every 12 hours in the first week of life, every 8 hours in babies 1–3 weeks old, and every 6 hours in babies 4 or more weeks old. Use with caution in patients with a suspected CNS abnormality. Dosage frequency should be reduced if there is any evidence of renal failure, and treatment stopped altogether if there is anuria, unless dialysis is instituted.

Supply and administration

Vials suitable for IV use contain 500 mg of imipenem monohydrate, with an equal quantity of the sodium salt of cilastatin, as a powder ready for reconstitution. Vials cost £12 each. Dilute the contents of the 500 mg vial with 100 ml of 10% dextrose saline immediately before use, to obtain a solution containing 5 mg/ml. (The drug can be prepared using a less concentrated solution of dextrose, or dextrose saline can be used where necessary.) Shake the vial well until the powder is all dissolved and then infuse the prescribed dose slowly over 30 minutes. Discard the remaining unused solution promptly. Avoid IM use in young children. A 20 mg/kg dose contains 0.07 mmol/kg of sodium.

References

- Reed MD, Kleigman RM, Yamashita TS, *et al.* Clinical pharmacology of imipenem and cilastatin in premature infants during the first week of life. *Antimicrob Agents Chemother* 1990;**34**:1172–7.
- Stuart RL, Turnidge J, Grayson ML. Safety of imipenem in neonates. *Pediatr Infect Dis J* 1995;**14**:804–5.

Aim

A national policy exists in the UK to provide protection against a range of potentially serious infectious illnesses. Separate monographs are available in this reference manual for BCG vaccination (against tuberculosis (TB)), and for immunisation against: hepatitis B; *Haemophilus influenzae*; meningococcal infection; polio; measles, mumps, and rubella (MMR: see monograph on rubella vaccine); and diphtheria, tetanus, and pertussis (DTP: see monograph on whooping cough vaccine). All the above products (other than hepatitis B vaccine) are supplied free of charge by the UK Departments of Health.

Basic schedule

In order to improve uptake and achieve greater immunity against *Haemophilus* and whooping cough at a younger age, immunisation schedules in the UK were revised in 1990 so that basic immunity is achieved within 4 months of birth. Immunisation in preterm babies should not be delayed because of the child's prematurity or low body weight. Protective immunisation should therefore be started before discharge in all babies spending more than 7 weeks in hospital after delivery.

At birth	BCG and hepatitis B	selectively
2 months	Diphtheria, tetanus, pertussis (whooping cough), haemophilus (Hib), meningococcus (MenC), and polio	} first dose second dose third dose
3 months		
4 months		
12–15 months	Measles, mumps, and rubella (MMR)	single dose
4–5 years	Diphtheria, tetanus and <i>acellular</i> pertussis, plus MMR and polio	booster
15–18 years		

BCG should be administered at 10–14 years if not given in infancy

Foreign travel

Advice on immunisation prior to foreign travel is summarised in a UK Departments of Health leaflet obtainable from pharmacies, GPs' surgeries, post offices, and travel agents, or by telephoning 0800 555 777. See also the Department's website: www.fitfortravel.scot.nhs.uk. More detailed advice on this, and on malaria prophylaxis, is also given in the *BNF* and in the UK Health Departments' publication *Health Information for Overseas Travel*, published in 2001.

Reactions to immunisation

Most reactions to immunisation are not serious. Older children sometimes faint and a few hyperventilate. Even quite young infants sometimes respond to pain or sudden surprise with a syncopal attack. Blue breathholding attacks, in which a child cries and then stops breathing, turning limp and unconscious, can occur and can end with a seizure. Attacks of stiffness and pallor, with self limiting bradycardia or asystole (reflex anoxic seizures), are less common but well documented. Infants prone to these reactions may also have a seizure if they become feverish after immunisation. The sudden brief loss of consciousness and body tone a few hours after vaccination for pertussis is another well described, but poorly understood, clinical entity. Such events should *not* be interpreted as anaphylactic or encephalopathic. Loss of consciousness should last only 5–10 minutes, and recovery is complete without treatment. Episodes should be managed as though they were a fainting attack.

True anaphylactic reactions after immunisation are *very* rare and seldom severe. When urticaria or slowly progressive peripheral oedema is all that develops, give 200 micrograms/kg of the H₁ histamine antagonist chlorphenamine maleate (chlorpheniramine maleate [former BAN]) promptly IM (even though the manufacturers have not yet endorsed its use in children). If there is stridor or progressive angio-oedema give 10 micrograms/kg of deep IM adrenaline (q.v.); some also give 0.4 ml/kg of a 1 mg/ml (1:1000) solution of L-adrenaline by nebuliser. Then give 100 micrograms/kg of chlorphenamine IM or, preferably, IV diluted in 5 ml of 0.9% sodium chloride. Give oxygen (q.v.) and take whatever steps are necessary to ensure that the airway can be secured should this become necessary. The dose of nebulised adrenaline can be repeated after 30 minutes. Wheeze and bronchospasm (seen particularly in patients with a past history of asthma) respond best to nebulised salbutamol (q.v.); 4 mg/kg of IV hydrocortisone (q.v.) may also be of benefit. Send for help, but never leave the patient unattended.

Severe anaphylactic shock, with hypotension, tachycardia, and rapid cardiovascular collapse, can cause death, but there has not been a single death using any of these products in the UK since formal monitoring began 22 years ago (during which time 280 million doses have been issued). IM (but not subcutaneous) adrenaline is probably of some help, but it is no panacea. Such patients also need IV chlorphenamine and IV hydrocortisone, and may need urgent volume expansion with gelatin, pentastarch or plasma albumin (q.v.). Notify all untoward events to the Committee on Safety of Medicines.

continued ...

Problems in the preterm baby

Irrespective of weight or gestation at birth, every baby should be started on a course of primary immunisation when 8 weeks old. Immunising these babies before they reach a postmenstrual age of 40 weeks may trigger an increased incidence of self limiting apnoea for 2–3 days, but this is not a reason for postponing protection, or for insisting that the baby is admitted for immunisation.

Some very preterm babies mount a less vigorous antibody response to early immunisation, and those on dexamethasone (q.v.) for chronic lung disease mount a particularly limited response to the pertussis vaccine. Interpretation is difficult since the antibody level necessary for protection is unknown; this is a worry because these are among the babies at greatest risk of serious illness if exposed to whooping cough infection. The response to the Hib vaccine, and to the serotype 3 element of the polio vaccine, can also be blunted. The best strategy to adopt in this situation remains uncertain. Until more is known some recommend giving all babies of less than 29 weeks gestation a fourth injection of the DTP, Hib, and MenC vaccines at 1 year, together with a fourth dose of the oral live (or IM inactivated) polio vaccine. Babies who are on steroids when immunisation is started probably merit similar treatment.

HIV infection

Babies with suspected or proven HIV infection need the normal protection from diphtheria, measles, mumps, rubella, tetanus, and whooping cough, and from haemophilus, meningococcal and pneumococcal infection. They should have the inactivated rather than the live (oral) polio vaccine. Do not give BCG. They also need co-trimoxazole prophylaxis (q.v.).

Patients with sickle cell disease or no spleen

Babies with *situs ambiguus* and certain cardiac syndromes are often born without a spleen, making them dangerously prone to infection. While haematological features (Howell–Jolly bodies, etc.) are suggestive, imaging is essential for diagnosis. Giving either co-trimoxazole or amoxicillin (125 mg twice a day) regularly for 5 years from birth will reduce the risk of fatal septicaemia. All the usual vaccines should also be given. These babies should also be offered both the available pneumococcal vaccines (q.v.). Do the same for children with homozygous (SS or Sb0Thal) sickle cell disease.

Babies with chronic lung disease

Consider winter prophylaxis against respiratory syncytial virus (RSV) infection with palivizumab (q.v.). Influenza can also be devastating in babies with a serious pulmonary or cardiac problem. However, while two 0.25 ml IM doses of vaccine 4 weeks apart provide substantial protection in infancy, parents need to know that safety and efficacy are still uncertain in babies less than 6 months old. Vaccinating the close family may offer added winter protection. Avoid this vaccine if there is hypersensitivity to egg.

Consent

Time must be taken to ensure that parents have had all their questions answered. A record of any issues raised, and of any verbal consent given, should then be placed in the case notes. Prior written consent implies general agreement to the child's inclusion in an immunisation programme, but does not address the issue of current fitness and is no substitute for the presence and involvement of a parent when any vaccine is actually administered, especially in a hospital setting.

Documentation

Inform the relevant district immunisation coordinator each time any immunisation procedure is undertaken in a hospital inpatient or outpatient setting. A national list of contact addresses is available at the back of the Department of Health's book *Immunisation Against Infectious Disease* (the "Green Book"). Complete the relevant section of the child's own personal health booklet at the same time.

Districts differ in the arrangements they make for recording neonatal BCG administration. A signed entry should always be made in the case notes, recording the BCG batch number. Many districts also arrange for this information to be passed to staff at the local TB contact clinic.

References

- Working Party of the British Committee for Standards in Haematology. Clinical Haematology Task Force. Guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen. *BMJ* 1996;**312**:430–4.
- Bedford H, Elliman D. *Childhood immunisation: a review for parents and carers*. London: Health Education Authority, 1998.
- Mayon-White R, Moreton J. *Immunising children. A practical guide*. Oxford: Radcliffe Medical, 1998.
- Project Team of the Resuscitation Council (UK). The emergency medical treatment of anaphylactic reactions. *J Accid Emerg Med* 1999;**16**:243–9.
- UK Health Departments. *Health Information for Overseas Travel*. London: HMSO, 2001.
- Kirmani KI, Lofthus G, Pichichero ME, et al. Seven-year follow-up of vaccine response in extremely premature infants. *Pediatrics* 2002;**109**:498–504.

Use

An immediate IV dose of immunoglobulin (Ig) may reduce mortality in severe early neonatal infection.

Physiology

Immunoglobulin antibodies help to ward off infection. Babies produce few antibodies until they are 3–4 months old, although they acquire maternal gammaglobulin transplacentally in the last 3 months of pregnancy. Preterm babies have low levels at birth, which can decline further, and this seems to be one reason why they are at particular risk of nosocomial (hospital acquired) infection in the first few weeks of life. Large trials have shown that the benefit of **prophylaxis**, (often 700 mg/kg Ig IV every 2 weeks), although significant, reduces the risk of infection by only 3–4%. However, a meta-analysis of a number of small trials suggests that the same dose used **therapeutically** may reduce mortality in babies with clinical evidence of severe early sepsis. The neutrophil white cells are of equal importance in defending the body against infection, but whether the prophylactic or therapeutic use of the marrow stimulating factors filgrastim or molgramostim (q.v.) is of any value in the neutropenic preterm baby is not yet clear.

Pharmacology

Normal human immunoglobulin for IV use (IVIG) contains immunoglobulin G (IgG) prepared from pooled human plasma collected during blood donation. It contains antibodies against a range of common infectious diseases including measles, mumps, varicella, hepatitis A, and other common viruses, and can be used to provide immediate but short lasting passive immunity to a range of viral and bacterial illnesses. Products vary in potency. Special products such as rhesus and varicella zoster immunoglobulin (q.v.) also exist. Donor screening, heat treatment, and alcohol fractionation combine to make IVIG safer than fresh frozen plasma (q.v.) or cryoprecipitate. The process also removes IgM, the main source of anti T antibody that can cause haemolysis in necrotising enterocolitis (NEC) and *Clostridium difficile* infection.

A large MRC funded trial (the International Neonatal Immunotherapy Study – INIS) is currently testing whether normal polyclonal immunoglobulin can really reduce neonatal mortality and brain damage in neonatal sepsis. For details contact Christine Chan-Fook at the National Perinatal Epidemiology Unit in Oxford (+ 44 (0) 1865 226 683).

Oral prophylaxis

An IgA-rich immunoglobulin reduced NEC in vulnerable low birth weight babies in one trial. 600 mg was given by mouth once every 8 hours for 20 days to all babies not offered breast milk. Igabulin® (the product used) is no longer available, and products containing only IgG are ineffective.

Treatment

Fetal thrombocytopenia: Some treat severe alloimmune disease by giving the mother 1 g/kg of IV human immunoglobulin weekly. Very severe disease may make fetal platelet transfusions necessary.

Neonatal thrombocytopenia: Babies with immune thrombocytopenia (ITP) who fulfil the criteria given in the monograph on platelets should be given 400 mg/kg of human immunoglobulin IV once a day for 1–3 days. Oral prednisolone (2 mg/kg every 12 hours for 4–6 days) may marginally improve the response.

Rhesus haemolytic disease: 500 mg/kg of human immunoglobulin given IV over 2 hours reduces the need for phototherapy and exchange transfusion, but increases the likelihood that the baby will need a “top up” transfusion.

Neonatal sepsis: Give an immediate 500 mg/kg dose of human immunoglobulin IV to babies with signs of severe sepsis, and another dose after 1–2 days if the serum IgG level is still less than 5 g/l (a second dose after 48 hours is a standard part of the INIS treatment protocol).

Supply and administration

A range of IV preparations are available. A 2.5 g or 3 g pack typically costs about £35; other pack sizes are also produced. Storage at 4°C is recommended for some products. Preparations designed for IM use, although cheaper, must **not** be given IV. Reconstitute where necessary by adding 20 ml of 0.9% sodium chloride or diluent (as provided) to each gram of lyophilisate immediately before use to obtain a preparation containing 50 mg/ml. Do not shake. Wait until the solution is clear. Start to infuse at a rate of 30 mg/kg per hour (i.e. at 0.6 ml/kg per hour when using the 50 mg/ml solution), and double the rate twice at half hourly intervals to a maximum rate of 120 mg/kg per hour, unless there is a systemic reaction (usually vomiting or hypotension). Discard all unused material. Centres recruiting to INIS are being provided with free supplies of IVIG and placebo for trial purposes.

References

- Eibl MM, Wolf HM, Fürnkranz H, *et al.* Prevention of necrotising enterocolitis in low-birth-weight infants by IgA-IgG feeding. *N Engl J Med* 1988;**319**:1–7. [RCT]
- Bussel JB, Berkowitz RL, Lynch L, *et al.* Antenatal management of alloimmune thrombocytopenia with intravenous γ -globulin: a randomised trial of the addition of low-dose steroid to intravenous γ -globulin. *Am J Obstet Gynecol* 1996;**174**:1414–23. [RCT]
- Gottstein R, Cooke RWI. Systematic review of intravenous immunoglobulin in haemolytic disease of the newborn. *Arch Dis Child* 2003;**88**:F6–10. [SR]

See also relevant Cochrane reviews

Use

Indometacin causes effective patent ductus arteriosus closure, as does ibuprofen (q.v.).

Pharmacology in pregnancy

Indometacin is an inhibitor of prostaglandin synthesis widely used as an analgesic anti-inflammatory drug in rheumatoid arthritis and gout. It is normally well absorbed by mouth, but neonatal oral absorption is sometimes unpredictable. The neonatal half life averages 16 hours (nearly seven times the half life in adults). Indometacin crosses the placenta and is excreted in the urine. There is no evidence of teratogenicity. Maternal treatment (25 mg by mouth every 6 hours after a loading dose of 50 mg) can be used to treat polyhydramnios, but use of a similar dose to control premature labour has declined because of fetal and neonatal complications. Problems include reversible fetal duct closure, necrotising enterocolitis, and focal gut perforation, particularly in babies of over 31 weeks gestation. Maternal use can also increase the risk of the baby developing a treatment resistant patent ductus after birth. Breastfeeding is quite safe because the baby gets less than 1% of the weight adjusted maternal dose.

Pharmacology in the neonate

Indometacin was first used experimentally to effect ductal closure in 1976, and some still use the dose used in the early studies (three 200 microgram/kg doses 12 hours apart). This dose is of proven value in the **treatment** of symptomatic patent ductus, especially when used within 2 weeks of birth, but sustained low dose treatment seems measurably more effective in the very preterm baby (where the risk of treatment failure is highest). A first loading dose may further help to optimise the chance of closure. A left atrium to aortic root (LA:Ao) ratio of 1.5 or more, a ductal diameter on colour Doppler of over 1.4 mm, and descending aortic flow reversal in diastole on ultrasound after the first 2 days of life, all suggest the presence of a haemodynamically significant duct. Babies offered early **prophylaxis** show less ultrasound evidence of serious intraventricular haemorrhage, but cerebral palsy and other sensorimotor disability is *no* less common, neither is bronchopulmonary dysplasia. However, for every 20 babies of under 1 kg so treated, five will avoid prolonged duct patency and one will avoid duct ligation. Evaluation at school entry has failed to confirm an earlier report that early prophylaxis reduces the number of survivors with speech and language problems. Nor, however, is there any evidence that early low dose use increases the risk of necrotising enterocolitis or ischaemic brain damage, an issue of real concern that even slow infusion causes a transient fall in cerebral, renal, and gut blood flow.

Serious coagulation problems are considered to be a contraindication to neonatal treatment because of the effect of indometacin on platelet function, as is necrotising enterocolitis, but jaundice is not a contraindication. The decrease in urine flow is transient with the dose regimen suggested here, and cotreatment with furosemide (q.v.) is not indicated. For this reason indometacin can still be given, even when there are early signs of renal failure, and *no* adjustment needs to be made in the dosage of other renally excreted drugs. Focal ischaemic gut perforation is the most dangerous complication, and gastrointestinal haemorrhage the commonest (even with IV administration), possibly because of the inverse correlation between local prostaglandin production and gastric acid secretion.

Treatment options

Early pre-emptive treatment: Give babies of under 28 weeks gestation three 100 microgram/kg doses IV (traditionally over 20 minutes) at daily intervals starting 12 hours after birth (as in the TIPP trial).

Haemodynamically significant ducts: Give 200 micrograms/kg IV once (as a loading dose) and then five further doses of 100 micrograms/kg IV (or by mouth) at daily intervals. Treatment can be stopped early if there is good ultrasound evidence that total closure has been achieved. In *very* preterm babies there is a case for treating any duct still patent at 3 days, even if the LA:Ao ratio is normal.

Supply

1 mg stock vials of the IV preparation cost £7.50. They should be reconstituted immediately before use with 2 ml of sterile water for injection to give a solution containing 500 micrograms/ml. The IV formulation can also be given by mouth.

References

- Merrill JD, Clyman RI, Norton ME. Indomethacin as a tocolytic agent: the controversy continues. *J Pediatr* 1994;**124**:734–6.
- Schmidt B, Davis P, Moddemann D, *et al.* Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight babies. *N Engl J Med* 2001;**344**:1966–72. (The TIPP Trial) [RCT]
- Knight DB. The treatment of patent ductus arteriosus in preterm infants. A review and overview of randomised trials. *Semin Perinatal* 2001;**6**:63–73. [SR]
- Dumas de la Roque E, Fayon M, Babre F, *et al.* Minimal effective dose of indomethacin for the treatment of patent ductus arteriosus in preterm infants. *Biol Neonate* 2002;**81**:91–4.
- Quinn D, Cooper B, Clyman RI. Factors associated with permanent closure of the ductus arteriosus: a role for prolonged indomethacin therapy. *Pediatrics* 2002;**110**:e10.
- Vohr BR, Allan WC, Westerveld M, *et al.* School-age outcomes of very low birth weight infants in the indomethacin intraventricular hemorrhage prevention trial. *Pediatrics* 2003;**111**:e340. [RCT]

See also relevant Cochrane reviews 

Use

Inositol deserves further investigation as a prophylactic nutritional supplement that can be used to reduce the severity of respiratory distress due to surfactant deficiency. Evidence that it may reduce the severity of retinopathy of prematurity also calls for more energetic study.

Nutritional factors

Myo-inositol (inositol), a six carbon sugar alcohol, is at least as abundant as glucose in the body. It is a precursor of various cell membrane phospholipids. High levels potentiate the glucocorticoid induced acceleration of lung surfactant production. Breast milk and colostrum are rich in inositol, but artificial milk contains much less, and the fluids used to provide parenteral nutrition are totally deficient. Serum concentrations are high during fetal life, and later fall. Neonatal inositol levels rise when there is anuria, presumably because of reduced catabolism or excretion. There have been reports suggesting that some folate resistant neural tube defects may be prevented by inositol supplementation (at least in the laboratory mouse).

Serum levels of inositol rise after birth in babies who are fed breast milk, whereas in infants receiving TPN they tend to fall. Inositol is well absorbed by mouth but can also be given IV. Two controlled trials conducted in the 1980s in Helsinki, involving 295 babies, suggested that ventilator dependent babies of less than 2 kg who are offered oral or IV inositol supplementation require less mechanical ventilation, are less likely to suffer a pneumothorax, and are less likely to require long term supplemental oxygen than placebo matched controls. Mortality is also reduced. In one trial there was also a reduced incidence of severe retinopathy of prematurity. Whether inositol is of any additional benefit in babies also offered exogenous surfactant, and whether early inositol supplementation can reduce the need for exogenous surfactant, remains to be established. Neither is it yet known whether inositol is of any measurable additional benefit when steroids have also been given antenatally. Plans for a further, much larger, trial of inositol were formulated a few years ago by neonatologists in Canada, but are currently "on hold".

Treatment

In the larger of the two trials alluded to above, babies were given 80 mg/kg of inositol IV over 5 minutes twice a day for 5 days. In the earlier trial the healthier babies were given inositol by mouth. Treatment was suspended if there was anuria or evidence of renal failure. A second course was given after 2 weeks in those babies who were still largely parenterally fed.

Supply

No commercial preparation is currently available but material suitable for oral use could be obtained by the local pharmacy on request, and a sterile preparation suitable for IV use could be prepared on request at moderate cost (the ingredients would not cost as much as £1 per dose). There is nothing to stop its use on a "named patient" basis (as with other unlicensed drugs) but its use in the context of a clinical trial would require the prior issue of an exemption certificate by the Medicines Control Agency.

References

- Hallman M, Järvepää A-L, Pohjavouri M. Respiratory distress syndrome and inositol supplementation in preterm infants. *Arch Dis Child* 1986;**61**:1076–83. [RCT]
- Hallman M, Bry K, Hopper K, *et al.* Inositol supplementation in premature infants with respiratory distress syndrome. *N Engl J Med* 1992;**326**:1233–9. [RCT]
- Friedman CA, McVey J, Borne MJ, *et al.* Relationship between serum inositol concentration and development of retinopathy of prematurity: a prospective study. *J Pediatr Ophthalmol Strabismus* 2000;**37**:79–86. [RCT]

See the relevant Cochrane review

INSULIN

Use

Insulin has been used to increase glucose uptake in very preterm babies requiring TPN, and to control acute hyperkalaemia. Small doses may also be needed in transient neonatal diabetes.

Pathophysiology

Women with diabetes mellitus need to be told of the importance of optimising glucose homeostasis over the time of conception to minimise the risk of fetal abnormality, aiming for a glycosylated haemoglobin (HbA_{1c}) level below 7.5%. Insulin, first isolated as a hormone from pancreatic islet β cells in 1922, is the drug to use during pregnancy because it does not cross the placenta or appear in human milk.

Newborn babies are relatively intolerant of glucose and the response of the pancreas to an IV load is relatively sluggish. The infusion of 10% dextrose at a rate appropriate to normal fluid and calorie needs may sometimes exceed the very preterm child's ability to metabolise glucose, or to turn glucose into glycogen, especially in the first week of life. Such intolerance usually resolves rapidly if the rate of glucose infusion is reduced for 6–12 hours, but it is important to remember that a sudden rise in blood glucose can also be the first sign of illness or sepsis. Insulin is not needed for transient intolerance, but it can be used if plasma glucose levels persistently in excess of 12 mmol/l limit parenteral feeding. Glycosuria can be ignored unless the blood glucose level exceeds 15 mmol/l.

Arrhythmia due to sudden unexplained neonatal hyperkalaemia (K^+ > 7.5 mmol/l) is occasionally seen in very preterm babies, especially in the first 3 days of life. Continuous infusions of glucose and insulin have been widely employed to control such hyperkalaemia, and may work quicker than a polystyrene sulphate resin (q.v.), but nebulised or IV salbutamol (q.v.) may be the treatment of choice, at least initially. Where continuous IV insulin has been employed in the past the dose has seldom exceeded 0.5 units/kg per hour; whether more can be given is unclear.

Treatment

Parenteral nutrition: Start with 0.05 units/hour and increase as tolerated. While an infusion of up to 0.5 (rarely even 1.0) units/hour can increase glucose tolerance in babies of < 1 kg by 30%, it is not clear that a glucose uptake of more than 14 mg/kg per minute is actually desirable. The true blood glucose level *must* be monitored regularly. Terminal co-infusion with TPN is acceptable and often convenient.

Hyperkalaemia: Combine IV glucose with between 0.3 and 0.6 units/kg per hour of IV insulin.

Neonatal diabetes: This rare condition presents with acidosis, dehydration, and hyperglycaemia (usually > 20 mmol/l) but little ketosis. Such babies respond well to very low levels of insulin; as little as 0.5–3.0 units/kg per day has usually been adequate. Start with a continuous infusion before moving to once or twice daily subcutaneous injections. Treatment can usually be tailed off within 4–6 weeks.

Compatibility

Insulin can be added (terminally) to a line containing dobutamine (but not dopamine), glyceryl trinitrate, midazolam, milrinone, morphine, or nitroprusside.

Supply and administration

10 ml multidose vials of human soluble insulin containing 100 units/ml cost approximately £10 each. They are best stored at 4°C, but contain m-cresol as a preservative and can be kept for 1 month at room temperature. Do not freeze. Any short acting soluble product (such as Humulin S[®]) can be used for IV or subcutaneous administration. These products should not be used if the fluid appears hazy or coloured. Long acting, slow release products containing a cloudy crystalline zinc suspension (such as Humulin Zn[®]), or isophane protamine (such as Humulin I[®]), are suitable only for subcutaneous use.

For accurate administration, take 0.25 ml (25 units) from the vial and dilute to 50 ml with 0.9% sodium chloride to obtain a preparation containing 0.5 units/ml. Insulin adheres to plastic and consistent IV delivery will not be achieved for several hours unless the delivery tubing is flushed with at least 20 ml of fluid before use. Delivery is more constant if the set is also left with fluid in it for 1 hour before being flushed through. While such priming is less essential when treatment is first started because the initial infusion rate is likely to be determined by the response achieved, failure to prime any *replacement* set could well destabilise glucose control. The IV solution is stable and does not need to be changed daily.

References

- Comblath M, Schwartz R. *Disorders of carbohydrate metabolism in infancy, 3rd ed.* Chapter 6. Boston, MA: Blackwell, 1991:225–46.
- Collins JW, Hoppe M, Brown, et al. A controlled trial of insulin infusion and parenteral nutrition in extremely low birthweight infants with glucose intolerance. *J Pediatr* 1991;**118**:921–7. [RCT]
- Mitamura R, Kimura H, Murakami Y, et al. Ultralente insulin treatment of transient neonatal diabetes mellitus. *J Pediatr* 1996;**128**:268–70.
- Hewson MP, Nawadra V, Oliver JR, et al. Insulin infusions in the neonatal unit: delivery variations due to adsorption. *J Paediatr Child Health* 2000;**36**:216–20.
- Metz C, Cavé H, Bertrand AM, et al. Neonatal diabetes mellitus: chromosomal analysis in transient and permanent cases. *J Paediatr* 2002;**141**:483–9.

See also relevant Cochrane reviews



Use

Interferon alfa-2 has been used to induce the early regression of life threatening, corticosteroid resistant haemangiomas of infancy.

Vascular birth marks

Haemangiomas are common in infancy. Seldom noticed at birth, they grow rapidly for 6–9 months and then gradually involute during early childhood. Bleeding is uncommon. Usually solitary and superficial, they are most often found on the head and neck. They are particularly common in preterm babies, and occur in almost a quarter of babies of less than 28 weeks gestation. Superficial dermal haemangiomas are fleshy and bright red ("strawberry naevi"), but deeper ones show only surface telangiectasia or a bluish hue. Lesions around the eye can cause amblyopia (a "lazy eye"), while sublingual lesions can cause serious bidirectional stridor as they grow. Children with multiple lesions sometimes have visceral haemangiomas. Large lesions can cause thrombocytopenia from platelet trapping (the Kasabach-Merritt syndrome) and high output heart failure. Treatment should be considered only for lesions causing airway or visual obstruction, facial distortion, or thrombocytopenia; 3 mg/kg of prednisolone once a day for 2 weeks benefits a third of these children, and may be worth continuing for longer if there is some response in 2 weeks. Pulsed dye laser treatment of skin lesions is of very limited value.

Other vascular malformations, in contrast, do not generally increase disproportionately in size after birth. Although, by definition, congenital, they may not be noticed for some months. Capillary and venous malformations lose their colour on compression (unlike strawberry naevi). Most capillary malformations ("port-wine stains") are flat and sharply demarcated. The paler salmon coloured patches, often seen on the forehead, nose, and eyelids, always fade with time, although patches on the nape of the neck ("stork bites") sometimes persist. Lymphatic and mixed malformations are usually noticed within a few months of birth. Venous and arteriovenous lesions are seldom suspected at birth.

Pharmacology

Interferons are proteins or glycoproteins produced by the body in response to viral and other stimuli. Interferon alfa is derived from leucocytes, interferon beta from fibroblasts, and interferon gamma from stimulated T lymphocytes. Human interferon alfa was first manufactured artificially from bacteria in 1980 using recombinant DNA technology (as indicated by the use of the suffix "rbe"). It has since been used to treat chronic hepatitis B and C, and certain types of leukaemia, myeloma, and lymphoma. Flu-like symptoms and fever are the only common problems seen, but nausea, lethargy, and depression can occur with high dose treatment. Motor problems have been seen with use in young children, but these usually seem to resolve when treatment is stopped. Little is known about use during pregnancy, but it does not seem to pose a toxic or teratogenic threat. Only small amounts appear in breast milk. The unexpected observation that interferon alfa is of benefit in the management of Kaposi's sarcoma, an endothelial cell tumour associated with HIV infection, has led to its successful use in suppressing the endothelial proliferation that forms the cellular basis of other haemangiomatous lesions.

Treatment

Serious haemangiomatous lesions that fail to respond to prednisolone should be treated with interferon alfa-2a. The usual dose is 3 million units/m² subcutaneously once a day (i.e. 600,000 units for an average baby of 3 kg). Side effects of such treatment seem to be rare, even though treatment may need to be continued for several months.

Supply

A range of products are available. A good product for neonatal use is IntronA® (interferon alfa-2b (rbe)), which is available as a powder in vials containing 1 million units costing £5-20. Vials should be stored at 4°C, but *not* frozen, and reconstituted with 1 ml of water for injection immediately before use. Agitate gently to speed dissolution. The alternative product, Roferon-A® (interferon alfa-2a (rbe)), is best avoided when treating babies because it contains benzyl alcohol as an excipient.

References

- Fishman SJ, Mulliken JB. Hemangiomas and vascular malformations of infancy and childhood. *Pediatr Clin North Am* 1993;**40**:1177-200.
- Soumekh B, Adams GL, Shapiro RS. Treatment of head and neck hemangiomas with recombinant interferon alpha 2b. *Ann Otol Rhinol Laryngol* 1996;**105**:201-5.
- Lopriore E, Markhorst DG. Diffuse neonatal haemangiomatosis: new views on diagnostic criteria and prognosis. *Acta Paediatr* 1999;**88**:93-9.
- Dubois J, Hershon L, Carmant L, *et al.* Toxicity profile of interferon alfa-2b in children: a prospective evaluation. *J Pediatr* 1999;**135**:782-5.
- Gruinwald JH, Burke DK, Bonthius DJ, *et al.* An update on the treatment of hemangiomas in children with interferon alfa-2. *Arch Otolaryngol Head Neck Surg* 1999;**125**:21-7.
- Batta K, Goodyear HM, Moss C, *et al.* Randomised controlled trial of early pulsed dye laser treatment of uncomplicated childhood haemangiomas: results of a 1-year analysis. *Lancet* 2002;**360**:521-7. (See also **361**:348-9.) [RCT]

Use

Intralipid is the most widely studied of the lipid products used to give fat (and the associated essential fatty acids) to children requiring parenteral nutrition (q.v.). No other IV fluid is as calorie-rich.

Pharmacology

Intralipid is an emulsion of soy bean oil stabilised with egg phospholipid. It is approximately isotonic, and is available as a 10% solution providing 1.1 kcal/ml and as a 20% solution providing 2 kcal/ml (1 kcal = 4.18 kJ). It contains 52% linoleic acid, 22% oleic acid, 13% palmitic acid and 8% linolenic acid (and so lacks the best linoleic:linolenic ratio for brain growth). Metabolism is the same as for chylomicrons. When first introduced it was often only infused for 4–20 hours a day, so that lipaemia could 'clear', but continuous infusion has been shown to improve tolerance and seems more 'physiological'. The 20% product is tolerated better than 10% Intralipid, possibly because the phospholipid content is lower. Infection with *Malassezia* can occur, and this lipid dependent fungus may escape detection if specific culture techniques are not used, but the fungaemia usually clears if administration is stopped. Intralipid can cause the blood glucose level to rise. It can also cause a 10-fold increase in the risk of coagulase-negative staphylococcal bacteraemia. The amount given is often limited in babies with serious unconjugated jaundice, but there is no evidence that use interferes with the protein binding of bilirubin. Early use does not increase the risk of chronic lung disease developing.

Nutritional factors

The use of Intralipid enhances protein utilisation, and considerably increases calorie provision in babies receiving Total Parenteral Nutrition (TPN). The co-infusion of 0.8 ml/kg of 20% Intralipid per hour with an infusion of 6 ml/kg per hour (i.e. 144 ml/kg per day) of an amino acid solution containing 10% glucose increases total calorie intake from 60 to 100 kcal per kg per day. By way of comparison, 160 ml/kg per day of one of the high-calorie preterm-milk formulas provides an intake of 130 kcal/kg per day (if no allowance is made for incomplete intestinal absorption). An infusion of 0.1 ml/kg hour (half a gram per kilogram a day) is the minimum needed to meet essential fatty acid needs.

Intake

Policies vary widely (a sure sign that there is much uncertainty), but it seems quite safe to start infusing 0.4 ml/kg of 20% Intralipid (0.08 g of fat) per hour through a peripheral, central or umbilical line within a few hours of birth once it is clear that the baby is stable. There is no evidence that stepped introduction improves tolerance, but good evidence that many babies develop hyperlipidaemia when intake exceeds 0.8 ml/kg per hour (3.8 g/kg of fat a day). Babies less than a week old, or less than 28 weeks gestation at birth, may be marginally less tolerant. Septic, acidotic and postoperative babies should probably not be offered more than 2 g/kg a day. Adhere to unit practice where a fixed local protocol exists.

Administration

1.2 µm lipid filters exist, but Intralipid cannot be infused through the 0.2 µm filter normally used for TPN, and it should only be allowed to mix with TPN just before it enters the baby. Consider protecting the lipid line from light during phototherapy to limit hydroperoxide production. Some units change the syringe and giving set daily because of concern that Intralipid can leach the chemical plasticiser out of syringes.

Blood levels

Serum triglycerides can be measured in 50 µl plasma (~150 µl of heparinised whole blood). A level much above 2 mmol/l (the highest level seen in the breast fed baby) suggests early lipid overload. Plasma turbidity is a much less satisfactory test. Re-emergent lipaemia may suggest early sepsis.

Supply

Stock 100 ml bags of 20% Intralipid (0.2 grams of fat per ml) cost £5.85, and 10 ml ampoules of Vitlipid N® infant cost £1.70. Store below 25°C, but do not freeze. Children requiring sustained parenteral nutrition should have Vitlipid N infant (containing vitamins A, D₂, E, and K₁) added to their Intralipid by the pharmacy prior to issue (as outlined in the monograph on multiple vitamins), and material so primed should then be used within 24 hours. Never add anything else to Intralipid, or co-infuse it with a fluid containing any drug other than heparin, insulin or isoprenaline. Discard all open bags.

References

- Haumont D, Richele M, Deckelbaum RJ, *et al.* Effect of liposomal content of lipid emulsions on plasma lipid concentrations in low birth weight infants receiving parenteral nutrition. *J Pediatr* 1992;**121**:759–63. [RCT]
Cairns PA, Wilson DC, Jenkins J, *et al.* Tolerance of mixed lipid emulsion in neonates: effect of concentration. *Arch Dis Child* 1996;**75**:F113–6. [RCT]
Avila-Figueroa C, Goldman DA, Richardson DK, *et al.* Intravenous lipid emulsions are the major determinant of coagulase-negative staphylococcal bacteraemia in very low birth weight newborns. *Pediatr Infect Dis J* 1998;**17**:10–77.
Matlow AG, Kitai I, Kirpalani H, *et al.* A randomised trial of 72- versus 24-hour intravenous tubing changes in newborns receiving lipid therapy. *Infect Control Hosp Epidemiol* 1999;**20**:487–93. [RCT]

Use

Oral iron is used to prevent iron deficiency anaemia during growth in breastfed babies weighing under 4 lb (1.8 kg) at birth. It is also used after birth to correct the iron loss that a few babies suffer as a result of chronic fetal blood loss before birth.

Nutritional factors

Iron is a major constituent of the haemoglobin molecule and routine supplementation is traditional in pregnancy, although the scientific basis for this is far from convincing and the practice is now actively discouraged. Even when nutrition is poor, the effect of a micronutrient supplement can be complex and unpredictable. Tablets can pose a very real hazard to young children because they are often mistaken for sweets, and the ingestion of as little as 3 g of ferrous sulphate can kill a small child. Maternal iron deficiency anaemia does not result in neonatal anaemia or iron deficiency during infancy except in the most exceptional circumstances, but all babies need an intake of 0.4–0.7 micrograms of iron a day to maintain their body stores because the circulating blood volume triples during the first year of life.

Haemoglobin and haematocrit levels change rapidly during the first 2–4 weeks of life, as outlined in the monograph on blood, but these changes are not due to iron deficiency and cannot be influenced by iron supplementation. There is now good evidence that “anaemia of prematurity” can be reliably modified using recombinant human erythropoietin (q.v.) as long as the baby is also given supplemental iron (at least 3 mg/kg per day), but it is doubtful whether such treatment is justified except in a small minority of very low birth weight babies, given the current cost. Most commonly, anaemia in the neonatal period is iatrogenic, resulting from doctors taking blood for laboratory analysis. Such babies should be offered a replacement transfusion of blood (q.v.); they do not respond to supplemental iron.

Babies have substantial iron stores at birth, even when born many weeks before term (and even in the face of severe maternal iron deficiency), but these stores start to become depleted unless dietary intake is adequate by the time the child's blood volume has doubled. Microcytosis (mean corpuscular volume $< 96 \mu\text{m}^3$) at birth is **never** a sign of iron deficiency, but it can be due to a haemoglobinopathy (usually some form of thalassaemia). The iron in breast milk is extremely well absorbed (as long as the baby is not also being offered solid food), but absorption from artificial feeds is less than a tenth as good, and the use of unmodified cows' milk in the first 6 months of life is particularly likely to cause iron deficiency anaemia. It used to be thought that this could be due to iron loss as a result of occult gastrointestinal bleeding, but recent studies have failed to confirm this. It is possible that the high phosphate and low protein content of whole cows' milk may interfere with iron absorption.

The fortification of artificial feeds with 0.6 mg iron/100 ml is enough to prevent iron deficiency in babies of normal birth weight and it is now clear, despite official advice to the contrary, that this is also enough for the preterm baby. Almost all the commonly used formula milks in current use contain at least as much iron as this (as outlined in the monograph on milk formulas), making the widespread practice of further supplementation quite unnecessary. There is rather more uncertainty as to how well the iron in most fortified infant cereal foods is absorbed. Bran and tannates bind iron and prevent absorption. The most easily assimilated form of iron is haem iron. Some vegetarian diets, therefore, may increase the risk of iron deficiency. Children on a poor diet often become anaemic during the second year of life, especially if they are given cows' milk rather than a fortified formula, but randomised controlled trials have not confirmed early reports suggesting that iron deficiency can cause psychomotor delay or increase vulnerability to infection, although there may be a marginal increase in diarrhoea.

Breastfed babies weighing less than about 1.8 kg (4 lb) at birth are, however, at some risk of developing iron deficiency anaemia at 2–3 months, as a result of the rapid expansion of their circulating blood volume with growth; these babies benefit from supplemental iron started within 4–6 weeks of birth. There is no good reason for starting supplemental iron before this because there is some doubt whether the gut absorbs iron in excess of immediate requirements, and some reason for believing that the iron binding protein, lactoferrin, present in milk (and particularly in breast milk), inhibits bacterial growth only when not saturated with iron. Early supplementation of breast milk with iron in the preterm baby may also unmask latent vitamin E deficiency.

Assessment

A serum ferritin level of less than 10 ng/ml is considered diagnostic of iron deficiency in infancy. Send 1 ml of blood in a plain tube or an EDTA tube to the haematology department. Most anaemia in early infancy is not due to iron deficiency. In some recent neonatal trials of the use of erythropoietin an attempt has been made to keep the serum ferritin level above 100 ng/ml.

continued ...

Prophylaxis and treatment

Normal babies: Breastfed babies require supplementation only if no other source of iron is introduced into the diet by about 6 months. Term babies who are fed one of the standard, artificially fortified, neonatal milk formulas (q.v.) never require further supplementation.

Low birth weight babies (<1.8 kg): Iron deficiency anaemia in the low birth weight **breastfed** baby of under 4 lb (1.8 kg) can be prevented by giving one dose of sodium ferredetate (Sytron®) each day after discharge from hospital until mixed feeding is established. The precise dose of Sytron necessary to meet the nutritional guideline is 0.4 ml/kg (2.2 mg/kg of elemental iron) once a day, but for most babies over 3 kg it is probably enough to tell the parents to give half a teaspoon (2.5 ml) once a day. Although it is traditional to offer all preterm babies further supplemental iron after discharge, this prophylaxis is a "hang over" from the days when the powdered artificial milks used for infant feeding were not specially fortified. There is, in fact, no good evidence that **formula** fed babies benefit from further supplementation after discharge (unless they are still on Osterprem®) and excess intake can have disadvantages.

Babies with anaemia at birth (Hb <12 g/dl): Babies who have suffered *chronic* blood loss from fetomaternal bleeding or twin-to-twin transfusion benefit from supplemental iron once their initial deficit has been corrected by transfusion. Babies with anaemia due to *acute* blood loss at birth do not usually become iron deficient; neither do babies with haemolytic anaemia.

Babies on parenteral nutrition: Babies unable to tolerate even partial enteral feeding by 3 months benefit from 100 micrograms/kg of iron a day IV (most conveniently given as iron chloride). Babies on erythropoietin (q.v.) also need IV supplementation if they cannot be given oral iron.

Toxicity

The stomach should be emptied without delay if oral ingestion is suspected, and vigorous lavage organised. Activated charcoal is of no value, but an attempt should be made to identify the amount ingested and treatment started by giving 15 mg/kg of desferrioxamine mesilate (desferoxamine mesilate) per hour IV for 5 hours if the ingested dose is thought to exceed 30 mg/kg. No universally agreed treatment protocol exists and advice should be sought from the local poisons centre. Acute toxicity can be expected if the serum iron level exceeds 90 µmol/l 4 hours after ingestion. A leucocytosis of more than $15 \times 10^9/l$, or a blood glucose of more than 8.3 mmol/l, also suggests serious toxicity. Early symptoms include diarrhoea and vomiting, followed, after 12–48 hours, by lethargy, coma, convulsions, intestinal bleeding, and multiorgan failure. Survivors may develop intestinal strictures 2–5 weeks later.

Supply

A variety of commercial liquid iron preparations are available. There are some arguments in favour of using a stable sugar-free preparation that does not require dilution for accurate administration to small babies. The most suitable preparation is probably sodium ferredetate (previously known as sodium ironedetate). Each 5 ml of the commercial elixir (Sytron) contains 190 mg of sodium ferredetate, which is equivalent to 27.5 mg of elemental iron. This comes in 500 ml bottles costing £5, although smaller volumes can be dispensed on request. Parents can obtain supplies from any community pharmacist without a doctor's prescription. 10 ml ampoules of iron chloride for IV use containing 1 g (17.9 micromol) of iron are obtainable through the pharmacy at the Queens Medical Centre, Nottingham.

Vials containing 500 mg of desferrioxamine mesilate powder (costing £3.70) suitable for reconstitution with 5 ml of water for injection could be provided by the pharmacy on request.

References

- Barrett JFR, Whittaker PG, Williams JG, *et al.* Absorption of non-haem iron from food during normal pregnancy. *BMJ* 1994;**309**:79–82.
- Griffin IJ, Cooke RJ, Reid MM, *et al.* Iron nutritional status in preterm infants fed formulas fortified with iron. *Arch Dis Child* 1999;**81**:F45–9. [RCT]
- Morley R, Abbott R, Fairweather-Tait S, *et al.* Iron fortification follow on formula from 9 to 18 months improves iron status but not development or growth: a randomised trial. *Arch Dis Child* 1999;**81**:247–52. [RCT]
- Franz AR, Mihatsch WA, Sander S, *et al.* Prospective randomised trial of early versus late enteral iron supplementation in infants with a weight of less than 1301 grams. *Pediatrics* 2000;**106**:700–6. [RCT]
- Friel JK, Andrews WL, Aziz K, *et al.* A randomized trial of two levels of iron supplementation and developmental outcome in low birth weight infants. *J Pediatr* 2001;**139**:254–60. [RCT]
- Griffin IJ, Abrams SA. Iron and breastfeeding. *Pediatr Clin North Am* 2001;**48**:401–14.
- Gera T, Sachdev HPS. Effect of iron supplementation on incidence of infectious illness in children: systematic review. *BMJ* 2002;**325**:1142–4. (See also p. 1125.) [SR]
- Christian P, Khatry SK, Katz J, *et al.* Effects of alternative micronutrient supplements on low birth weight in rural Nepal: double blind randomised community trial. *BMJ* 2003;**326**:571–4. [RCT]
- Juurlink DN, Tenebbin M, Koren G, *et al.* Iron poisoning in young children: association with the birth of a sibling. *CMAJ* 2003;**168**:1539–42.

See also relevant Cochrane reviews



Use

Isoniazid is used in the primary treatment and retreatment of tuberculosis (TB), which remains a notifiable disease. Its main use in the neonatal period is in the prophylactic management of babies being cared for in a house where a person with active TB is under treatment.

Pharmacology

Isoniazid was first isolated in 1912. It was found to be bacteriostatic and, in high concentrations, bactericidal against *Mycobacterium tuberculosis* in 1952. It is active against intracellular and also extracellular tubercle bacilli. Resistance develops rapidly when isoniazid is given on its own, so other antituberculous drugs are always given as well. Isoniazid has no significant activity against other micro-organisms. There is no evidence that isoniazid is teratogenic, but treatment with isoniazid increases the excretion of pyridoxine (vitamin B₆) and to counter the risk of peripheral neuropathy, all women should take 10 mg of pyridoxine (q.v.) once a day if pregnant or breast feeding. Malnourished children deserve a similar dose, especially when given isoniazid in the first year of life. Treatment during lactation will result in the breastfed baby receiving about a fifth of the maternal dose (and of the drug's main metabolite) on a weight for weight basis, but toxic symptoms have not been seen.

Isoniazid is rapidly metabolised prior to renal excretion, the half life being between 2 and 5 hours, except in the neonatal period. Adverse effects are uncommon in children and appear to be related to hypersensitivity to the use of large doses; patients who are slow inactivators of the drug may experience a greater incidence of toxicity. The drug is contraindicated, however, in drug induced liver disease and porphyria. Peripheral neuropathy may occur; convulsions, optic neuritis and skin rashes have been reported; haemolytic anaemia and agranulocytosis, metabolic acidosis, and hyperglycaemia can also occur. A lupus-like syndrome, liver damage, and gynaecomastia have been reported in adults.

Tuberculosis

Mothers found to have TB during pregnancy need expert management. They usually receive a 10 month course of isoniazid and rifampicin (q.v.), along with pyrazinamide for 6 months. Some may need 2 months' treatment with ethambutol. Fetal infection is likely only if the mother has an extrapulmonary infection, but the baby is vulnerable to infection after birth from any caregiver with open untreated pulmonary disease, and remains at risk of serious generalised ("miliary") infection. Patients are not likely to pass infection to others after they have been on effective treatment for at least 2 weeks, so babies born into such a household need prophylactic isoniazid only as indicated below. Where there is a real possibility that the baby has become infected, give 5 mg/kg of isoniazid and 10 mg/kg of rifampicin once a day for at least 6 months. Pyrazinamide should also be given under expert supervision for the first 2 months (30 mg/kg once a day), especially if there is a possible non-pulmonary focus of infection. Possible meningeal involvement calls for at least 1 year's expert treatment using four drugs.

Drug interactions

Isoniazid can potentiate the effect of carbamazepine and phenytoin to the point where toxicity develops.

Prophylaxis

Give babies exposed to possible infection 5 mg/kg once a day by mouth. Dose adjustment is not necessary for poor renal function. If tests after 3 months show the baby to be tuberculin negative, treatment can be stopped and BCG (q.v.) given. It is *not* necessary to use an isoniazid resistant strain of BCG. Prophylaxis should be continued for a further 3 months if the tuberculin test is positive.

Toxicity

Giving over 30 mg/kg in error can cause seizures due to pyridoxine (q.v.) loss. Treat by giving 1 mg of pyridoxine IV (or by mouth) for every mg of excess isoniazid ingested. Control seizures, acidosis, and respiration as necessary.

Supply

An inexpensive sugar-free oral elixir of isoniazid containing 10 mg/ml is available, as are 2 ml ampoules containing 25 mg/ml (costing £7-10 each) that are suitable for IM or IV injection. A sugar-free suspension of pyrazinamide for oral use, with a 4 week shelf life, can be provided at low cost on request.

References

- Roy V, Tekur U, Chopra K. Pharmacokinetics of isoniazid in pulmonary tuberculosis – a comparative study at two dose levels. *Indian Pediatr* 1996;**33**:287–91.
- Romero JA, Kuczeler FJ. Isoniazid overdose: recognition and management. *Am Fam Physician* 1998;**57**:749–52.
- Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1999;**53**:536–48.
- American Academy of Pediatrics. Tuberculosis. In: Pickering LK, ed. *Red Book: 2003 report of the committee on infectious diseases*, 26th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2003:642–60.

ISOPRENALINE = Isoproterenol (USAN)

Use

Isoprenaline is a sympathomimetic drug sometimes used in the management of haemodynamically significant bradycardia or heart block.

Pharmacology

Isoprenaline is a synthetic sympathomimetic related to noradrenaline (q.v.) with potent β adrenergic receptor activity that was first brought into clinical use in 1951. This adrenergic agonist has virtually no effect on α receptors. Gastrointestinal absorption is unpredictable, but sublingual administration is effective and, in the 1960s, the drug was widely given by aerosol as a bronchodilator for asthma. Continuous IV infusion can increase cardiac output through its inotropic and chronotropic action, and an increase in cardiac venous return. It has more effect on heart rate than on stroke volume and little effect on peripheral vascular resistance, renal blood flow, or blood pressure. While the drug seems to be of some value in the management of low cardiac output with or without pulmonary hypertension in older children and adults, it is said to be of less value in the neonatal period. High doses cause tachycardia and cardiac arrhythmia but these toxic effects subside fairly rapidly when treatment is stopped.

Treatment

Start with a continuous IV infusion of 20 nanograms/kg per minute (0.2 ml/hour of a solution made up as described below), and increase as necessary. Use the lowest possible effective dose and never use a dose of more than 200 nanograms/kg per minute (2 ml/hour of the standard dilution recommended below).

Compatibility

Isoprenaline can be added (terminally) into a line containing standard TPN (with or without lipid) when absolutely necessary, and into a line containing dobutamine, heparin, or milrinone. Isoprenaline is stable only in acid solutions, and should never, therefore, be infused into the same line as sodium bicarbonate.

Supply and administration

2 ml ampoules containing 2 mg of isoprenaline cost £2.70 each. Protect the ampoules from light prior to use. To give an infusion of 10 nanograms/kg of isoprenaline per minute, place 300 micrograms (0.3 ml) of isoprenaline for each kilogram the baby weighs in a syringe, dilute to 50 ml with 10% dextrose saline, and infuse at a rate of 0.1 ml/hour. (A less concentrated solution of dextrose or dextrose saline can be used when necessary). The drug is relatively stable in solutions with a low pH such as dextrose and does not need to be prepared afresh every 24 hours.

References

- Drummond WH. Use of cardiotoxic therapy in the management of infants with PPHN. *Clin Perinatal* 1984;11:715–28.
Driscoll DJ. Use of inotropic and chronotropic agents in neonates. *Clin Perinatal* 1987;14:931–49.

Use

Isosorbide has been used intermittently for some years on an experimental basis to control hydrocephalus in infancy in order to prevent or delay the need for shunt surgery.

Pharmacology

Isosorbide is an inert sugar (1,4,3,6-dihydrosorbitol) that acts as an osmotic agent when given IV in much the same way as mannitol (q.v.). It is thought to be capable of reducing the formation of cerebrospinal fluid (CSF) without inducing an excessive diuresis. Hypernatraemia may occur, especially if the fluid intake is inadequate. Many children dislike the taste (particularly at first). Possible adverse effects (all of which are reversible on stopping the drug) include hypernatraemia, acidosis, weight loss, vomiting, and diarrhoea, but much experience suggests that, with the dose recommended here, such problems are uncommon.

Lorber first suggested, in 1981, that isosorbide may delay or abolish the need for shunt surgery in some children with congenital hydrocephalus with or without spina bifida, as long as the condition is not deteriorating rapidly and the cerebral mantle is at least 15 mm thick. He also published a preliminary report suggesting that it is of value in at least delaying the need for shunt surgery in children with posthaemorrhagic hydrocephalus. No controlled study of its use in the management of such children has yet been published, and the only formal trial of its role in the management of children with spina bifida has concluded that, although it can delay the need for shunt placement for 2–3 months, it makes no clear long term difference to the number finally requiring shunt placement. Nevertheless, this study was not large enough to rule out some reduction in the number needing surgery, and such lasting benefit may arguably be more readily expected in children with acquired posthaemorrhagic hydrocephalus. In the USA, oral glycerol, or a combination of acetazolamide (q.v.) with or without furosemide (q.v.), was rather more widely used in the first line management of posthaemorrhagic hydrocephalus, until a recently completed UK trial cast serious doubt on the wisdom of such treatment.

Treatment

The standard starting dose is 8 g/kg per day by mouth, given in divided doses every 4–8 hours. The sugar has a slightly bitter aftertaste and is best given, therefore, with feeds. Lower doses can sometimes be used for maintenance purposes, but doses of up to 12 g/kg per day have been used for a few weeks without side effects. Medication is usually withdrawn gradually (unless there is a shunt capable of relieving any acute change in CSF pressure).

Supply

Pharmacies can prepare a solution containing 1 g/ml with a 1 year shelf life for a basic in-house cost that should not exceed £40 per 100 ml.

References

- Salfield AN, Lorber J, Lonton T. Isosorbide in the management of infantile hydrocephalus. *Arch Dis Child* 1981;**56**:806–7.
Lorber J, Salfield S, Lonton T. Isosorbide in the management of infantile hydrocephalus. *Dev Med Child Neurol* 1983;**25**:502–11.
Liptak GS, Gellerstedt ME, Klionsky N. Isosorbide in the medical management of hydrocephalus in children with myelodysplasia. *Dev Med Child Neurol* 1992;**34**:150–4.

Use

Ketamine is a short acting general anaesthetic like propofol (q.v.), usually administered IV.

Pharmacology

Ketamine is a versatile general anaesthetic. It was first developed in 1970, but its mode of action is complex and still unclear. IV administration produces an immediate feeling of dissociation, followed, after 30 seconds, by a trance-like state that lasts 8–10 minutes. It produces marked amnesia but is devoid of hypnotic properties. The eyes often remain open and nystagmus may develop. Functional and electrophysiological dissociation seem to occur between the brain's cortical and limbic systems. Respiration is not depressed, but salivation may increase and laryngeal stridor is occasionally encountered. Muscle tone increases slightly, and random limb movements occasionally require restraint. Serious rigidity is sometimes seen in adults. Tachycardia, systemic hypertension, and increases in pulmonary vascular resistance have been reported in adults, but such problems have not been encountered in children whose breathing was controlled. Analgesia persists for a sustained period after the anaesthetic effect has worn off. These characteristics make ketamine a particularly useful drug to give during painful but short lasting procedures that do not require muscle relaxation. Intubation is not usually necessary. Full recovery can take 2–3 hours, and signs of distress and confusion are sometimes seen in adults during this time. Nightmares and hallucinations have been reported. Midazolam (q.v.) may help in this situation, but such problems are uncommon in children and there is no evidence that routine combined use is beneficial. Nausea and vomiting are the commonest problems.

Oral administration has been used in older children requiring multiple invasive procedures. Bioavailability by this route is low (~16%), but plasma levels peak within 30 minutes. A 10 mg/kg oral dose is recommended. Ketamine is rapidly redistributed round the body after IV administration ($V_D \sim 2.5$ l/kg) and then cleared from the plasma with a terminal half life of 3 hours. Clearance is similar in children and adults, but neonatal clearance has not been studied. Ketamine undergoes extensive metabolism in the liver before excretion in the urine. Some of the metabolic products cause CNS depression. An overdose may make respiratory support necessary, but will have no adverse long term consequences. Doses lower than those quoted here are adequate when a volatile anaesthetic is also administered. While ketamine crosses the placenta, when given in induction doses, its use during caesarean delivery does not sedate the baby. There are no clear reports of teratogenicity or suggestions that ketamine is incompatible with lactation.

Anaesthesia

"Bolus" IV administration: A 2 mg/kg IV dose administered over at least 1 minute will provide about 10 minutes of surgical anaesthesia after about 30 seconds. Premedication with atropine (q.v.) should be considered if the patient is not already intubated.

Sustained IV administration: Give a loading dose of 1 mg/kg IV followed by an infusion of 500 micrograms/kg per hour (2 ml of the dilute preparation described below, followed by 1 ml/hour). Four times this dose can be used to produce *deep* anaesthesia when few other options exist.

IM administration: 4 mg/kg given IM in a syringe also containing 10 micrograms/kg of atropine will provide dissociative anaesthesia for about 15 minutes after a latent 5–10 minute period. Recovery will usually be complete after 2–3 hours.

Precautions

There are few reports of neonatal use (see website commentary). Complications are uncommon in older children, but stridor and laryngospasm can be encountered, perhaps as often as once in every 200 procedures. Because of this, ketamine should be given *only* by an experienced intensivist ready and equipped to take immediate control of the airway should this prove necessary (and any such clinician may prefer some other anaesthetic option). Monitoring is essential until recovery is complete.

Supply

Ketamine is available in 20 ml vials containing 10 mg/ml costing £3.50 each. To give a continuous infusion of 500 micrograms/kg of ketamine per hour, take 0.5 ml of the 10 mg/ml preparation for each kilogram the baby weighs, dilute to 10 ml with 5% dextrose or dextrose saline, and infuse at a rate of 1 ml/hour. Multidose vials containing 50 mg/ml and 100 mg/ml are also manufactured.

References

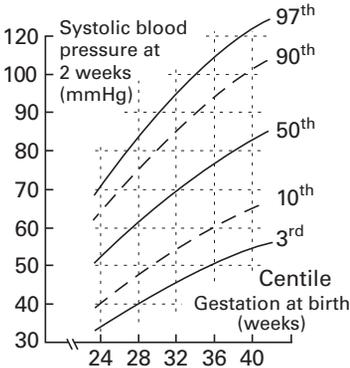
- Green SM, Johnson NE. Ketamine sedation for pediatric procedures. *Ann Emerg Med* 1990;**19**:1033–46. (See also pp. 1024–31). [SR]
Cote CJ. Sedation for the pediatric patient: a review. *Pediatr Clin North Am* 1994;**41**:31–58.
Wathen JE, Roback MG, Mackenzie T, et al. Does midazolam alter the clinical effects of intravenous ketamine sedation in children? A double-blind, randomised, controlled emergency department trial. *Ann Emerg Med* 2000;**36**:579–88. [RCT]
Tashiro C, Matsui Y, Nakano S, et al. Respiratory outcome in extremely premature infants following ketamine anaesthesia. *Can J Anaesth* 1001;**38**:287–91.

Use

Labetalol is the best drug for achieving quick but safe control over high blood pressure in infancy.

Pathophysiology

Judge the need for treatment by measuring the systolic blood pressure in a quiet baby, using a Doppler flow probe or stethoscope, a close fitting cuff that is as wide as possible, and an inflatable section that more than surrounds the arm. Resting systolic pressure at two weeks varies with gestation at birth as shown below, and rises to stabilise at a mean of 92 mm Hg (95% CI 72–112 mm Hg) at a postmenstrual age of 46 weeks (as summarised in the monograph on hydralazine).



Graded maintenance schedule for IV labetalol.

Measure systolic blood pressure at least twice an hour.

Give X mg/kg (X ml/hr) of labetalol IV while this pressure is in the target range of Y to Z mmHg.

Double the dose if this pressure exceeds, and halve the dose if it falls below, this range.

Stop the infusion if this pressure falls below Y mmHg while the labetalol infusion is only 0.5 ml/hr.

Call the resident **at once** if this pressure is more than 15 mmHg above or below the above target range.

Serious hypertension is an emergency, but can be difficult to treat. Overtreatment can cause dangerous hypotension and potentially lethal β blockade. Treatment should always be discussed with a consultant therefore, and with a paediatric nephrologist where possible, because the cause is often renal.

Pharmacology

Labetalol is a non-selective α blocker (causing some decrease in peripheral vascular tone) with additional β blocking properties like propranolol (q.v.). It was patented in 1971. It is rapidly effective, but rapidly metabolised by the liver (adult half life 4–8 hours), so any reactive hypotension quickly corrects itself once the infusion is stopped even though tissue levels exceed plasma levels ($V_d \sim 9$ l/kg). The neonatal half life may be longer, making reactive hypotension more hazardous. Glucagon (q.v.) may be of help following an overdose. The benefit achieved by controlling hypertension usually outweighs the risk of use in cardiac failure. Oral nifedipine (q.v.) is normally used for maintenance once the acute situation is under control. Hydralazine (q.v.), with or without propranolol, was used for this in the past. Labetalol is irritant to veins and should be diluted for infusion. It crosses the placenta and can cause bradycardia, transient hypoglycaemia, and mild hypotension after delivery, while sustained maternal use can cause fetal cardiac hypertrophy. Use during lactation only exposes the baby to 1% of the maternal dose on a weight for weight basis. The manufacturers have not yet endorsed the drug's use in children.

Treatment

Start by infusing 0.5 mg/kg of labetalol per hour (0.5 ml/hr of the dilute solution described below). Measure systolic pressure at least once every 15 minutes, and double the dose once every 3 hours until the blood pressure has been reduced to an acceptable level. The maximum safe dose is 4 mg/kg per hour (4 ml/hr). Define the target range (Y and Z in the box above), and then prescribe a sustained infusion of this dose (X ml/hr) using a graded infusion schedule, while continuing to measure systolic blood pressure at least twice an hour. Modify the treatment schedule daily, aiming to take 3 days to bring the pressure down to normal, as discussed in the website commentary, unless hypertension is known to be of very recent onset. Start an oral drug and wean from labetalol as soon as practicable.

Supply and administration

20 ml ampoules containing 5 mg/ml of labetalol cost £2.80. Take 10 ml of labetalol for each kilogram the baby weighs from several such ampoules and dilute to 50 ml with 10% dextrose saline to give a solution containing 1 mg/kg per ml of labetalol. Then pickaback this infusion into an IV glucose line. The drug is stable in solution and does not need to be prepared afresh every 24 hours.

References

Bunchman TE, Lynch RE, Wood EG. Intravenously administered labetalol for treatment of hypertension in children. *J Pediatr* 1992;**120**:140–4.
Deal JE, Barratt TM, Dillon MJ. Management of hypertensive emergencies. *Arch Dis Child* 1992;**67**:1089–92.
Crooks BNA, Deshpande SA, Hall C, *et al*. Adverse neonatal effects of maternal labetalol treatment. *Arch Dis Child* 1998;**79**:F150–1.

LAMIVUDINE

Use

Lamivudine is used, in combination with other antiviral drugs, in the control of HIV infection.

Pharmacology

Lamivudine (or 3TC) is an antiviral drug, first introduced in 1992, which works, like zidovudine (q.v.), after intracellular conversion to the triphosphate, as a nucleoside reverse transcriptase inhibitor (NRTI) to halt retroviral DNA synthesis. Resistance quickly develops if it is used on its own to treat HIV infection, and it is unclear whether sustained low dose treatment is any better than interferon alfa (q.v.) in the management of chronic hepatitis B infection. Oral uptake is good and is not reduced (although it is delayed) by ingestion with food. Bioavailability seems, nevertheless, to be rather lower in children than in adults. Most of the drug is rapidly excreted, unchanged, in the urine (half life ~ 2 hours in children), making dosage reduction necessary when there is serious renal failure. Adverse effects include nausea, vomiting and diarrhoea, malaise, muscle pain, and a non-specific rash. Neuropathy and pancreatitis is uncommon, except in children with advanced disease who are on many other drugs. Lamivudine crosses the placenta but does not seem to be teratogenic. Not enough information exists to exclude the possibility that it could be embryotoxic if taken at the time of conception. It passes freely into breast milk. Whether this reduces the risk of a baby becoming infected from virus infected milk is not known.

Didanosine (or ddI) is a related NRTI with many similar properties and for which there is rather more clinical experience (except in babies under 3 months old). The neonatal dose is 50 mg/m² by mouth twice a day (90 mg/m² in babies over 3 months old). Didanosine is quite rapidly hydrolysed and inactivated by stomach acid, and bioavailability is also reduced if the drug is taken with or after food. Serious adverse effects include retinal depigmentation, optic neuritis, peripheral neuropathy, and pancreatitis, all of which can be difficult to detect in a young child. The dose needs to be reduced when renal function is impaired. Didanosine crosses the placenta, but did not seem toxic to the embryo or fetus in animal studies. Information in humans is currently limited. Nothing is known about excretion into breast milk.

Managing overt HIV infection in infancy

New information on optimum management becomes available so frequently that anyone treating this condition *must* first familiarise themselves with the latest information posted on the National Institutes of Health website: www.AIDSinfo.nih.gov

Diagnosis and management must also be discussed with, and supervised by, someone with extensive experience of this condition. Treatment will be influenced by any prior treatment that the mother has received, but will normally include zidovudine and lamivudine together with a protease inhibitor (such as nelfinavir or ritonavir (q.v.)) or nevirapine (q.v.). Other drug strategies are often difficult to employ in young babies because suitable liquid formulations are not available.

Ritonavir is usually given twice a day, and nelfinavir three times a day. Little is known about the use of either of these drugs in babies less than 1 month old, and treatment should *never* be started until the manufacturer's guide sheet has been studied, because competition for metabolism by the liver's cytochrome P450 enzyme system can precipitate a serious drug interaction. Treatment for HIV must be sustained, and can be burdensome, so, since most of the other drugs recommended here need to be taken only twice a day, it may be appropriate, in this situation, to give zidovudine as a 180 mg/m² dose once every 12 hours.

Treatment

The standard dose is 4 mg/kg by mouth twice a day. In the rare situation where treatment is called for in the first month of life, give 2 mg/kg.

Supply

150 mg tablets of lamivudine cost £2.70 each; oral syrups containing 5 mg/ml and 10 mg/ml sucrose are also available, costing £9 and £18 per 100 ml respectively. 150 mg tablets of didanosine cost £2.20 each, but the drug is also available as a 10 mg/ml suspension, buffered in an antacid, on a "named patient" basis. Neither of these drugs can be given IV or IM.

References

- Mueller BU, Butler KM, Stocker VL, *et al.* Clinical and pharmacokinetic evaluation of long term therapy with didanosine in children with HIV infection. *Pediatrics* 1994;**94**:724–31.
- Moodley J, Moodley D, Pillay K, *et al.* Pharmacokinetics and antiretroviral activity of lamivudine alone or when coadministered with zidovudine in human immunodeficiency virus type 1-infected pregnant women and their offspring. *J Infect Dis* 1998;**178**:1327–33.
- Johnson MA, Moore KHP, Yuen GJ, *et al.* Clinical pharmacokinetics of lamivudine. *Clin Pharmacokinetics* 1999;**36**:41–66.
- De Martino M, Tovo P-A, Balducci M, *et al.* Reduction in mortality with availability of antiretroviral therapy for children with perinatal HIV-1 infection. *JAMA* 2000;**284**:190–9.
- American Academy of Pediatrics. Human immunodeficiency virus infection. In: Pickering LK, ed. *Red Book: 2003 report of the committee on infectious Diseases, 26th ed.* Elk Grove Village, IL: American Academy of Pediatrics, 2003:360–82.

Use

Lamotrigine is increasingly used to improve seizure control in children who are already taking one anticonvulsant drug, but experience with use in young children is still very limited. The fact that treatment has to be introduced gradually is often seen as something of a disadvantage.

Pharmacology

Lamotrigine is a phenyltriazine, and structurally unrelated to any other established antiepileptic drug. It first came into clinical use in 1987. It may work as a sodium channel blocker, or by inhibiting excitatory (glutamate) neurotransmitter release. It is well absorbed when taken by mouth and mostly metabolised by the liver. The half life in adults who are taking no other drug is 24–36 hours. It is significantly less than this in children. Tissue levels are high ($V_D > 1.2$ l/kg). The drug should not be used in patients with liver failure, and only used with caution in patients with renal failure. A measles-like skin rash is the commonest adverse effect, occurring most often 10–20 days after treatment is started, especially if the dose given is increased too quickly. Treatment is always best stopped gradually (to minimise the risk of increased seizure activity) unless there is a severe toxic skin reaction.

Lamotrigine has been formally approved only for "adjunctive" use in children with refractory partial and general tonic clonic seizures who are also taking some other anticonvulsant, but it is also known to be effective in controlling infantile spasms, myoclonic jerks, and absence seizures. It also seems to be effective in Lennox–Gastaut syndrome (a severe form of epilepsy in early childhood, associated with multiple seizure types in which the waking ECG shows inter-ictal slow spike wave activity). Lamotrigine on its own may be as effective as treatment with carbamazepine (q.v.) in children with typical absence epilepsy, and in adults with partial and generalised tonic clonic seizures. Manufacturers are encouraging wider use in pregnancy, although evidence concerning safety is, as yet, limited. There is nothing to suggest that it renders the baby vitamin K deficient. Use during lactation results in the baby developing a blood level that is about a third of that present in the mother, but adverse effects have not been documented.

Drug interactions

All the drugs that increase liver enzyme activity (such as carbamazepine, phenobarbital and phenytoin (q.v.)) greatly speed the elimination of lamotrigine. The dose given often needs to be *increased* as a result. Combined treatment with carbamazepine may increase the risk of toxicity. Combined treatment with valproate (q.v.) (which may confer synergistic benefit), in contrast, doubles the half life, probably because both drugs compete for glucuronidation in the liver. Consequently, a *lower* dose needs to be used, especially when treatment is first started. The valproate dose will also need adjusting down.

Treatment

Monotherapy: Start by giving 300 micrograms/kg once a day by mouth for 2 weeks, and then twice a day for a further 2 weeks. Treatment can then be further "titrated" upwards, as necessary, to maximise seizure control, to a dose that should not, initially, exceed 2 mg/kg twice a day.

Adjunctive (combined) therapy: Children taking other enzyme inducing drugs (see above) often require double the usual dose, while those on valproate usually need only half the usual dose.

Blood levels

A knowledge of the blood level does not help to optimise management, but it may reveal failure to take medicine as prescribed. Effective levels are usually 1–4 mg/l (1 mg/l = 3.9 μ mol/l) but can be higher.

Case notification

A voluntary, confidential, UK based register is currently collecting *prospective* information on anticonvulsant use during pregnancy. For further information ring 0800 389 1248.

Supply

Scored 5 mg tablets of lamotrigine cost 30p each. They are only semisoluble but small doses can be given with reasonable accuracy by adding a tablet to 10 ml of water; 1 ml of liquid will then contain approximately 500 micrograms of lamotrigine as long as the particulate matter is kept in suspension. A stable suspension with a 4 week shelf life can be prepared, but it has a very unpleasant taste.

References

- Walker MC, Li LM, Sander JWAS. Long term use of lamotrigine and vigabatrin in severe refractory epilepsy: audit of outcome. *BMJ* 1996;**313**:1184–5.
- Frank LM, Enlow T, Holmes GL, *et al.* Lamictal (lamotrigine) monotherapy for typical absence seizures in children. *Epilepsia* 1999;**40**:973–9. [RCT]
- Öhman I, Vitols S, Tomson T. Lamotrigine in pregnancy: pharmacokinetics during delivery, in the neonate, and during lactation. *Epilepsia* 2000;**41**:709–13.
- Tennis P, Eklidridge RR. International lamotrigine pregnancy registry scientific advisory committee. Preliminary results on pregnancy outcomes in women using lamotrigine. *Epilepsia* 2002;**43**:1161–7.

LEVOTHYROXINE SODIUM

Use

Thyroid extracts have been used to treat hormone deficiency since 1890.

Pathophysiology

Thyroid stimulating hormone (TSH) produced by the pituitary regulates the release of levothyroxine (T_4) and (to a lesser extent) liothyronine (T_3) from the thyroid gland. T_4 is then converted to T_3 in the tissues. Significant amounts of maternal T_4 (but not TSH and T_3) cross the placenta – explaining the relatively normal appearance of the baby at birth. Inadequately treated maternal hypothyroidism may increase the risk of spontaneous abortion and impact on long term growth and development. Antithyroid drugs and maternal thyroid receptor antibodies can cross the placenta causing fetal hypo- and hyper-thyroidism. Fetal goitre can now be detected by antenatal ultrasound. The mother can be offered an anti-thyroid drug if the fetus is thyrotoxic, while hypothyroidism has, occasionally, been managed by putting 250–500 micrograms of thyroxine into the amniotic cavity once every 10–14 days (so it can be swallowed by the fetus). There is no reason why mothers taking thyroxine should not breast feed. The management of neonatal thyrotoxicosis is discussed in the monograph on propranolol.

Hypothyroidism at birth

Congenital hypothyroidism occurs in about 1 in 3500 babies, and is due to thyroid dysgenesis (~85%) and dyshormonogenesis (~15%). There is considerable biochemical heterogeneity, but treatment needs to be started within two weeks of birth if outcome is to be optimised. Babies in the UK are, therefore, screened (by the Guthrie test) both for hypothyroidism and for phenylketonuria when they are a week old. Confirmation requires the demonstration of a high TSH and, usually, also a low T_4 . This screening programme has been very successful, but thyroid function should still be measured if hypothyroidism is suspected because false negatives can occur and because hypothyroidism can evolve.

The normal TSH surge and the rise in T_3 and T_4 levels after birth are much less marked in the preterm infant. These babies often have low thyroid hormone levels, and this tendency may be exacerbated by exposure to the iodine in antiseptics and x-ray contrast media. The risk of developmental delay and cerebral palsy also seems to be increased in preterm babies who had transient low thyroxine levels after birth. Trials have not been able to show that correction improves the long term outcome, but there remains a case for a further trial to assess intervention in babies of less than 27 weeks gestation.

Guthrie screening

TSH screening for hypothyroidism is generally performed on dried (Guthrie) blood samples. Quantitative TSH assays are undertaken by the UK Supra-Regional Assay Service on 200 μ l of serum (c. 600 μ l of whole blood). T_4 assays can be undertaken on 50 μ l of serum (c. 150 μ l of whole blood).

Treatment

Neonatal treatment: The usual starting dose is 10 micrograms/kg of levothyroxine by mouth (or 8 micrograms/kg IV or IM) once a day. Monitor the thyroid hormone and TSH levels after 2 and 4 weeks and then every 1–2 months during the first year of life, aiming for a TSH in the normal range and a free T_4 level in the upper part of the normal range. Because hypothyroidism is occasionally transient it is usual to reassess the requirement for continued treatment when the child is two or three years old.

Older children: In older children a starting dose of 100 micrograms/m² a day has been suggested.

Blood levels

Early levels vary, but TSH levels above 10 mU/l are rare after the first 3 days, and the free T_4 level by immunoassay in the term baby more than a month old should be 10–25 pmol/l (1 pmol/l = 0.7 ng/l).

Supply

25, 50, and 100 microgram tablets of levothyroxine cost 2 to 3p each. A sugar-free suspension, which is stable for 3 months, can be provided on request. If treatment has to be given IV or IM, and no suitable T_4 product is available (as in the UK), treatment with a 2 microgram/kg dose of liothyronine twice a day should be considered (although experience with such an approach is very limited).

References

- Thorpe-Beeston JG, Goitre. In: *Fetal Therapy*. Fisk NM, Moise KJ, eds. Cambridge: Cambridge University Press, 1997:252–60.
- Fisher DA. Thyroid function in premature infants. *Clin Perinatol* 1998;**25**:999–1014.
- Bongers-Schokking JJ, Koot HM, Wiersma D, et al. Influence of timing and dose of thyroid hormone replacement on development in infants with congenital hypothyroidism. *J Pediatr* 2000;**136**:292–7.
- Fisher DA, Nelson JC, Carlton EL, et al. Maturation of human hypothalamic-pituitary-thyroid function and control. *Thyroid* 2000;**10**:299–34.
- Hindmarsh PC. Optimisation of thyroxine dose in congenital hypothyroidism. *Arch Dis Child* 2002;**86**:73–5.
- Hrytsiuk I, Gilbert R, Logan S, et al. Starting dose of levothyroxine for the treatment of congenital hypothyroidism. *Arch Pediatr Adolesc Med* 2002;**156**:485–91. [SR]
- Biswas S, Buffery J, Enoch H, et al. A longitudinal assessment of thyroid hormone concentrations in preterm infants younger than 30 weeks' gestation during the first 2 weeks of life and their relationship to outcome. *Pediatrics* 2002;**109**:222–7.

See also relevant Cochrane reviews



Use

Lidocaine is a widely used local anaesthetic. A short infusion can sometimes stop neonatal fits that are resistant to phenobarbital (q.v.) and the benzodiazepines, and it is occasionally used to control arrhythmia.

Pharmacology

Systemic and subcutaneous use: Lidocaine hydrochloride is a local anaesthetic of the amide group with effects on the central nervous system (where it acts as a sedative in low doses and a stimulant in high doses), on peripheral nerves (where it decreases conduction), and on the heart (where it shortens the duration of the action potential). It was first marketed in Sweden in 1948. Lidocaine is metabolised by the liver, but some of the intermediary breakdown products are metabolically active as well as potentially toxic; up to a third is excreted unchanged by the neonatal kidney. Oral administration fails to produce adequate blood levels because of rapid first pass liver metabolism. The terminal half life is about 100 minutes in adults, and at least twice as much as this in the newborn. IV infusion produces high drug concentrations in those organs with a high blood flow, with later redistribution throughout the body. This volume of distribution is particularly high in the neonatal period ($V_d > 1$ l/kg). Drowsiness is a common side effect, while over-treatment can cause irritability and fits. Lidocaine is occasionally used in adults and older children to treat acute ventricular tachycardia. Lidocaine crosses the placenta but the amount required to cause neonatal depression is above the therapeutic level required to treat arrhythmia. Maternal treatment is not a contraindication to breastfeeding.

Analgesic cream: Plain (30%) lidocaine ointment is ineffective when applied to the skin, but a eutectic mixture of 2.5% lidocaine and 2.5% prilocaine as a cream (Emla[®]) provides good surface anaesthesia for 1–2 hours in children if applied under an occlusive dressing at least 1 hour in advance of venepuncture. Unfortunately, it seems less effective in babies, and does little to modify their response to venepuncture or heel lancing. Rapid drug clearance from the skin may be part of the explanation. Tetracaine gel (q.v.) may provide better pain relief for venepuncture in infancy. The manufacturers have been reluctant to endorse the use of Emla cream in children less than 1 year old, but the prilocaine it contains does not cause significant methaemoglobinemia (at least in babies of 30 or more weeks gestation with a reasonably mature epidermis) as had once been feared.

Treatment

Local surface anaesthesia: Apply 1 g of Emla cream to a 2 × 2 cm area of undamaged skin, and cover with an occlusive dressing for 1 hour. Tetracaine gel may be a better product to use.

Mucosal anaesthesia: Use no more than 0.1 ml/kg of a 4% lidocaine spray or 0.3 ml/kg of a 2% lidocaine gel on mucosal surfaces. Experience with the spray is very limited in small children.

Infiltrative local anaesthesia: 0.3 ml/kg of 1% plain lidocaine provides excellent anaesthesia for 1–2 hours 1–2 minutes after infiltration. Take care not to inject anything into a blood vessel and give no further lidocaine for 4 hours. A 0.6 ml/kg dose of 1% lidocaine in adrenaline will offer pain relief for 3 hours. Bupivacaine (q.v.) can provide pain relief for at least 6 hours, but only after a half hour latent period.

Fits and arrhythmia: Try a 4 mg/kg dose (0.4 ml/kg of a 1% solution of adrenaline free lidocaine IV over 1 hour), followed by a maintenance infusion of 2 mg/kg per hour if the initial dose has the desired effect. Always tail off treatment after 12–36 hours. A maintenance infusion twice as high as this (4 mg/kg) may work when a lower dose does not, but it may produce a potentially toxic blood level after 12 hours. A 5 mg/kg IM injection will, in an emergency, give an effective blood level in 15 minutes.

Toxicity

Accidental infiltration of the fetal scalp during the injection of lidocaine into the maternal perineum can cause toxic apnoea, bradycardia, hypotension, and fits, a cluster of features that can be mistaken for intrapartum asphyxia. Some affected babies have required ventilatory support, but most have made a complete recovery. Arrhythmia is uncommon. An excessive IV dose can also be very dangerous. Management is as discussed in the monograph on bupivacaine.

Supply

Ampoules of adrenaline free 1% (10 mg/ml) lidocaine cost between 11p and 41p each. 20 ml ampoules of 1% lidocaine with adrenaline (10 mg of lidocaine and 5 micrograms of adrenaline per ml) cost 69p. 5 g tubes of Emla cream cost £1.70. Anhydrous lidocaine as a 2% gel is available in 20 g tubes costing £1 each. A 4% lidocaine jetspray (IMS) delivery system for use during laryngoscopy costs £5.

References

- Hellström-Westas L, Svenningsen NW, Westgren U, *et al.* Lidocaine for treatment of seizures in newborn infants – II Blood concentrations of lidocaine and metabolites during intravenous infusion. *Acta Paediatr* 1992;**81**:35–9.
- Brisman M, Ljung BML, Otterborn I, *et al.* Methaemoglobin formation after the use of Emla cream in term neonates. *Acta Paediatr* 1998;**87**:1191–4.
- Gradin M, Eriksson M, Holmqvist G, *et al.* Pain reduction at venepuncture in newborns: oral glucose compared with local anesthetic cream. *Pediatrics* 2002;**110**:1053–7. [RCT]

See also relevant Cochrane reviews



LINEZOLID

Use

This expensive new antibiotic should be reserved for treating methicillin resistant staphylococcal and vancomycin resistant enterococcal infection. It should be used only after obtaining microbiological advice. There is, as yet, little published information on neonatal use and none on use in the preterm baby.

Pharmacology

Linezolid is an oxazolidinone antibiotic, first marketed in 2000, which inhibits bacterial protein synthesis in a new and unique way. The drug is active against a range of Gram positive bacteria, including methicillin resistant (and glycopeptide intermediate) *Staphylococcus aureus*. It is also active against vancomycin resistant enterococci, and strains of *Streptococcus pneumoniae* resistant to a range of other antibiotics. It also shows activity against some anaerobes, including *Clostridium perfringens*, *C difficile*, and *Bacteroides fragilis*. However, enterobacteriaceae and *Pseudomonas aeruginosa* are not susceptible to linezolid. The drug is rapidly and completely absorbed when given by mouth, and it penetrates the meninges well when these are inflamed. Thirty per cent of the drug is excreted, unchanged, in the urine; the remainder is excreted as inactive metabolites (which could accumulate in severe renal failure). The half life is shorter in children aged 1 week to 10 years (3 hours) than it is in adult life.

Generally reversible thrombocytopenia can occur when treatment is given for more than 10–14 days. More serious temporary marrow depression, similar to that seen with chloramphenicol (q.v.), has also (rarely) been reported, and a full blood count should probably be performed once a week if sustained treatment becomes necessary. There is also concern that prolonged low dose use could lead to the development of bacterial resistance (especially with *Enterococcus faecium*). Linezolid is a weak, reversible, non-selective, monoamine oxidase (MAO) inhibitor, and it has been suggested that this makes unwise its use at the same time as (or within 2 weeks of treatment with) an MAO antidepressant. Similarly, combined use with a range of other antidepressants could cause "serotonin syndrome", with hyperpyrexia and cognitive dysfunction.

No information is available as yet on use during pregnancy, but placental transfer is to be expected because the drug has a low molecular weight. Indeed, for the moment, it should be used during pregnancy only when no other good option exists because, although there is no evidence of teratogenicity, increased embryo death, decreased litter size, decreased fetal weight, and costal cartilage abnormalities were reported during drug testing in mice. Nothing is known about its use during lactation either but, based on extrapolated animal data, a baby could be expected to ingest a little under 10% of the weight related maternal dose. Manufacturers have not yet recommended its use in children less than 18 years old.

Drug interactions

Use with care, and monitor blood pressure during co-administration with any sympathomimetic drug (such as dopamine or dobutamine).

Treatment

Give 10 mg/kg IV once every 8 hours for 2 weeks. The manufacturers recommend that adults should receive an IV infusion over at least 30 minutes, but this is because the volume of fluid involved is considerable. Oral absorption is good in adults but this has not yet been studied in children. No IM preparation is available.

Supply and administration

300 ml bags containing 2 mg/ml of linezolid suitable for IV administration cost £33 each. Do not mix linezolid with, or infuse it into the same line as, any other drug. Do not dilute further before administration. Bags should be stored at room temperature, protected from light during storage in the foil overwrap provided, and inverted gently 2–3 times before use. The fluid slowly turns yellow with time, but this does not affect potency. An oral suspension containing 20 mg/ml is available on request.

References

- Kearns GL, Abdel-Rahman SM, Blumer JL, *et al.* Single dose pharmacokinetics of linezolid in infants and children. *Pediatr Infect Dis J* 2000;**19**:1178–84.
- Chien JW, Kucia ML, Salata RA. Use of linezolid, an oxazolidinone, in the treatment of multidrug-resistant Gram-positive bacterial infections. *Clin Infect Dis* 2000;**30**:146–51.
- Clemett D, Markham A. Linezolid. *Drugs* 2000;**59**:815–27.
- Perry CM, Jarvis B. Linezolid. A review of its use in the management of serious Gram-positive infections. *Drugs* 2001;**61**:525–51. [SR]
- Graham PL, Ampofu K, Saiman L. Linezolid treatment of vancomycin-resistant *Enterococcus faecium* ventriculitis. *Pediatr Infect Dis J* 2002;**21**:798–800.
- Jungbluch GL, Welshman IR, Hopkins NK, *et al.* Impact of gestational and postnatal age on linezolid disposition in neonates and young infants [Abstract]. *Pediatr Res* 2002;**51**:465A.

Use

Lorazepam is mostly used as a sedative and anxiolytic. Although it seems to be better than diazepam (q.v.) at bringing acute seizure activity under sustained control, its use in the neonatal period not infrequently causes hypotension, respiratory depression, and abnormal tonic clonic movements.

Pharmacology

Sales of chlordiazepoxide (or Librium®) rose so fast when Hoffman-La Roche put the first benzodiazepine on the market in 1960 that many other products soon followed. Diazepam, a structurally simpler analogue, was licensed in 1963, and lorazepam was synthesised 1 year later. These, and a range of other products, have been widely used to treat anxiety, but it is now generally accepted that such use should always be limited to the lowest possible dose for the shortest possible time. Dependence can become a serious problem, even with careful prescribing, particularly in patients with a history of alcohol or drug abuse, and in patients with a serious personality disorder. Diazepam is more rapidly cleared from the brain than most of the other products after IV administration, sometimes making it necessary to give a continuous infusion to contain serious persisting seizure activity ("status epilepticus").

Lorazepam crosses the placenta, but there is no clear evidence of teratogenicity. Respiratory depression, hypothermia, lethargy, and poor feeding have all been observed, however, when a mother is given high dose medication shortly before delivery. Breastfeeding may further sedate the neonate in the period immediately after birth, even though the baby receives only 5–10% of the maternal dose on a weight for weight basis, but sustained lactation does not seem to cause noticeable drowsiness. The drug is well absorbed when taken by mouth, conjugated to an inactive glucuronide in the liver, and then excreted in the urine by glomerular filtration. The half life in the neonatal period is 30–50 hours (2–3 times as long as in adult life). Tissue drug levels slightly exceed plasma levels ($V_D \sim 1.3$ l/kg).

Benzodiazepines are of limited value in the treatment of epilepsy, but can have a role in acute seizure management. Which one is best is far from clear. Midazolam (q.v.) has recently become more popular than diazepam for seizure control in children, but lorazepam or clonazepam (q.v.) is more commonly used to control seizures that fail to respond to phenobarbital in the neonatal period. There is, however, increasing concern that, while sedation may abolish the abnormal movements that are the outward sign of cerebral seizure activity, the seizures themselves may sometimes continue unchecked. Administration can also precipitate hypotension, respiratory depression, and abnormal seizure-like movements in up to one baby in seven, especially in response to the first dose given. For a review of the various treatment options see the website commentary linked to the monograph on phenobarbital.

Treatment

There is only limited information on the use of this drug in the neonatal period. Try 100 micrograms/kg once every 24 hours IV, IM, or by mouth for 2–3 days in babies resistant to routine anticonvulsant medication. The drug's very long neonatal half life makes a continuous infusion quite unnecessary.

Antidote

Flumazenil is a specific antidote (as described in the monograph on midazolam).

Supply

1 ml ampoules containing 4 mg of lorazepam cost 40p each. The ampoules contain 1 ml of propylene glycol and 0.02 ml of benzyl alcohol. They should be stored at 4°C and protected from light. To make a solution suitable for neonatal IV use, draw the contents of the ampoule into a large syringe and dilute to 40 ml with dextrose saline to obtain a solution containing 100 micrograms/ml. A sugar-free oral suspension can be provided on request. The drug should be given only IM in an emergency because release from the injection site is slow even after dilution: take the contents of the ampoule and dilute to 4 ml with 0.9% sodium chloride to obtain a solution containing 1 mg/ml for IM use.

References

- Maytal J, Novak GP, King KC. Lorazepam in the treatment of refractory neonatal seizures. *J Child Neurol* 1991;**6**:319–23.
- McDermott CA, Kowalczyk AL, Schritler ET, et al. Pharmacokinetics of lorazepam in critically ill neonates with seizures. *J Pediatr* 1992;**120**:479–83.
- Cronin CMG. Neurotoxicity of lorazepam in a premature infant. *Pediatrics* 1992;**89**:1129–30.
- Lee DS, Wong HA, Knoppert DC. Myoclonus associated with lorazepam therapy in very-low-birth-weight infants. *Biol Neonate* 1994;**66**:311–15.
- Appleton R, Sweeney A, Choonara I, et al. Lorazepam versus diazepam in the acute treatment of epileptic seizures and status epilepticus. *Dev Med Child Neurol* 1995;**37**:682–8.
- Sexson WR, Thigpen J, Stajich GV. Stereotypic movements after lorazepam administration in premature neonates: a series and review of the literature. *J Perinatol* 1995;**15**:146–9.
- Ng E, Klinger G, Shah V, et al. Safety of benzodiazepines in newborns. *Ann Pharmacother* 2002;**36**:1150–5.

See also relevant Cochrane reviews



MAGNESIUM SULPHATE

Use

Magnesium sulphate is now widely used to prevent or control eclamptic convulsions. It is also used to treat neonatal hypocalcaemia and hypomagnesaemia. It does *not* prevent preterm labour, and trials of this strategy have been associated with increased infant mortality.

Pharmacology

Maternal treatment (4 g of magnesium sulphate IV over 15 minutes followed by 1 g/hour IV for up to 24 hours) is the treatment of choice for eclampsia, and for *pre*-eclampsia severe enough for urgent delivery to be contemplated. It prevents seizures and almost certainly lowers maternal mortality, but does nothing to lower blood pressure or reduce perinatal mortality. Low dose aspirin (q.v.) marginally reduces the risk of toxoemia developing in high risk women, as does added calcium. A high dose antioxidant (vitamin C and E) trial (DAPIT) is currently recruiting among pregnant women with diabetes in the UK. Treatment with magnesium sulphate has been very widely used in North America to inhibit preterm labour, but there is no controlled trial evidence of benefit. Long term use may affect fetal bone growth and even cause congenital rickets. Even short term use increases the fetal, as well as the maternal, plasma magnesium level, causing hypotonia, reduced gastrointestinal motility, and mild respiratory depression; treatment with gentamicin (q.v.) after birth could exacerbate this hypotonia. Trials are nearing completion in Australia and the USA to see if short term maternal treatment lowers the risk of cerebral palsy in surviving preterm babies. A still unpublished trial undertaken more than 5 years ago in the UK failed to show any evidence that use *after* delivery was of benefit in babies with features suggestive of an intrapartum asphyxial insult. Breastfeeding does not need to be discouraged because of maternal treatment.

Magnesium levels above 4 mmol/l are sedative, causing muscle relaxation and significant pulmonary and systemic vasodilatation. Following a number of encouraging observational studies, continuous infusions are now sometimes used in ventilated babies with persistent pulmonary hypertension that is unresponsive to tolazoline (q.v.). No controlled trial of this strategy has yet been mounted. Improvement is variable, and babies showing no sustained response should be managed in a unit able to offer treatment with nitric oxide (q.v.).

Symptomatic hypocalcaemia (a serum calcium less than 1.7 mmol/l) is now rare, and usually associated with hypomagnesaemia. Empirical data suggest that children treated with IM magnesium sulphate improve more quickly than those given calcium gluconate (q.v.).

Treatment

Hypocalcaemia: 100 mg/kg of magnesium sulphate (0.2 ml/kg of a 50% solution) deep IM on two occasions 12 hours apart will control most cases of symptomatic late neonatal hypocalcaemia. One further dose may be necessary in a minority of babies.

Hypomagnesaemia: The same dose every 6–12 hours can also be used for primary neonatal hypomagnesaemia however caused (normal plasma level 0.75–1.0 mmol/l). It is usually given IV or IM because it is a purgative (like Epsom Salts) when given by mouth.

Persistent pulmonary hypertension: Give a loading dose of 250 mg/kg of magnesium sulphate IV over 10–15 minutes. If a clinical response is obtained once the serum magnesium level exceeds 3.5 mmol/l, give between 20 mg/kg and 75 mg/kg per hour for 2–5 days, while maintaining a blood level of between 3.5 mmol/l and 5.5 mmol/l. This strategy has not yet been subjected to controlled trial evaluation.

Supply and administration

Magnesium sulphate is conventionally prescribed as the heptahydrate. Non-proprietary 2 ml ampoules of 50% magnesium sulphate contain 1 g (4.1 mmol) of magnesium. They cost £2-70. For IV administration in ventilated babies with pulmonary hypertension, draw 1 g of magnesium sulphate (2 ml of the 50% solution) for each kilogram the baby weighs into a syringe, dilute to 20 ml with 10% dextrose saline to obtain a solution containing 50 mg/kg per ml, and give 5 ml of this solution over 5–10 minutes. Follow this with a continuous infusion of 0.4 ml/hour (20 mg/kg per hour) as appropriate, and monitor the serum level every 12–24 hours.

References

- Turner TL, Cockburn F, Forfar JO. Magnesium therapy in neonatal tetany. *Lancet* 1977;**i**:283–4. [RCT]
- Tolsa J-F, Cotting J, Sekarski N, *et al.* Magnesium sulphate as an alternative and safe treatment for severe persistent pulmonary hypertension of the newborn. *Arch Dis Child* 1995;**72**:F184–7.
- Rajaduria VS, Nqiam N, Agrawal P, *et al.* Magnesium sulphate infusion for the treatment of persistent pulmonary hypertension of the newborn [Abstract]. *Pediatr Res* 1999;**45**:316A.
- The Magpie Trial Collaborative Group. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. *Lancet* 2002;**359**:1877–90. [RCT]
- Duley L. Pre-eclampsia and hypertension. *Clin Evid* 2003;**9**:1584–60 (and updates). [SR]

See also relevant Cochrane reviews 

Use

Mannitol is now recognised as having a valuable role in preventing and minimising the damage caused by acute cerebral trauma. Its utility in managing postanoxic cerebral oedema is less clearly established. Mannitol is sometimes used in adults to induce the forced diuresis of renally excreted poisons.

Pharmacology

Mannitol is a relatively inert hexahydric alcohol related to mannose and isomeric with the sugar sorbitol. It is rapidly excreted in the urine; very little is metabolised. Nothing is known about its use during pregnancy or lactation. A recent large trial has shown that the early infusion of a large dose to all patients prior to surgical decompression, whatever their initial clinical condition, significantly decreased the amount of residual disability seen 6 months later, and it now seems clear that it works more by decreasing the viscosity of the blood than by setting up an osmotic gradient to counter cerebral oedema. Mannitol works by diluting the blood and increasing the deformability of the red cells, increasing cerebral blood flow, initiating autoregulatory vasoconstriction of cerebral arterioles, and decreasing intracerebral blood volume and intracranial pressure. Prompt bolus administration is therefore the strategy of choice in all patients with an acute traumatic subdural haematoma. Urinary losses should also be replaced; it is inappropriate to allow dehydration and haemoconcentration to occur. A similar strategy was equally effective in the preoperative management of patients undergoing surgical evacuation of traumatic temporal lobe contusion.

Hypoxic/ischaemic brain injury

While mannitol can undoubtedly reduce intracranial pressure it is increasingly clear that the rise in pressure sometimes (but not always) seen as a result of cerebral oedema is a sign that develops only after severe damage has already occurred. One small trial of early intervention with phenobarbital (q.v.) before seizures occurred seemed to show evidence of benefit, but another did not, and a study using thiopental (q.v.) showed equally little evidence of benefit. No other drug has yet been shown to influence long term outcome. Some combination of sedation, paralysis, ventilation, anticonvulsant treatment, and a controlled lowering of body temperature to 33–35°C for 2–3 days *may* be beneficial, and several controlled trials of this are now under way. For details of the TOBY trial in the UK contact Dr Denis Azzopardi in London (020 8383 3174). However, such treatment is experimental and should *not* be contemplated except within the context of a properly structured randomised controlled trial. Treatment probably needs to be started within 3 hours to stand any real chance of success. Continuous amplitude integrated electroencephalographic analysis using a cerebral function monitor may be the best way to identify babies who justify such intervention. Term babies with a flat trace or continuous low voltage pattern who survive are currently nearly always left with severe spastic quadriplegia. The same is true when a burst suppression pattern persists for more than 24–36 hours. A single early 8 mg/kg IV dose of theophylline (q.v.) seems to reduce some of the adverse renal consequences of perinatal asphyxia.

Treatment

Give 1–4 g/kg (7 ml/kg of a 20% solution) of mannitol IV over 10–20 minutes through a filter to trap any small crystals that may have formed in an existing infusion of dextrose or dextrose saline.

Supply and administration

Bags containing 500 ml of 20% mannitol in water, costing £3.20 each, are stocked in the pharmacy. They should be stored at 20–30°C to prevent crystallisation; if this does occur the bag should be warmed to 60°C and allowed to cool to blood temperature before use. Do not mix mannitol with any other drug.

References

- Marchal C, Costagliola P, Laveau P, *et al.* Traitement de la souffrance cérébrale néonatale d'origine anoxique par le mannitol. *Rev Pediatr* 1974;**9**:581–9.
- Levene MI, Evans DH, Forde A, *et al.* Value of intracranial pressure monitoring of asphyxiated infants. *Dev Med Child Neurol* 1987;**29**:311–19.
- MacLennan A for the International Cerebral Palsy Task Force. A template for defining a causal relation between acute intrapartum events and cerebral palsy: international consensus statement. *BMJ* 1999;**319**:1054–9.
- Groenendaal F, de Vries LS. Selection of babies for intervention after birth asphyxia. *Semin Neonatal* 2000;**5**:17–32. (See also pp. 61–73.)
- Cruz J, Minoja G, Okuchi K. Improving clinical outcomes for acute subdural hematomas with the emergency preoperative administration of high doses of mannitol: a randomized trial. *Neurosurgery* 2001;**49**:864–71. [RCT]
- Laptook AR, Corbett RJT. The effect of temperature on hypoxic-ischemic brain injury. *Clin Perinatol* 2002;**29**:623–49.
- Shankaran S. The postnatal management of the asphyxiated term infant. *Clin Perinatol* 2002;**29**:675–92.
- Cruz J, Minoja G, Okuchi K. Major clinical and physiological benefits of early high doses of mannitol for intraparenchymal temporal lobe hemorrhages with abnormal pupillary widening: a randomised trial. *Neurosurgery* 2002;**51**:628–37. [RCT]

MEFLOQUINE

Use

Although a weekly dose of chloroquine (q.v.) has been widely used to prevent malaria, mefloquine now has to be used in those parts of the world where most parasites have become resistant to chloroquine. Mefloquine is also sometimes used, instead of quinine (q.v.), to treat overt infection.

Pharmacology

Mefloquine hydrochloride is an amino alcohol with a half life of 2–3 weeks, which is concentrated in the red cells. It was developed by the US military as an antimalarial in the 1960s and became generally available in 1986. High dose treatment can provoke nausea, vomiting, loose stools, headache, abdominal pain, and somnolence, symptoms that can be hard to distinguish from malaria itself. It is also teratogenic in animals and high dose use should be avoided during pregnancy. Low dose prophylactic use seems safe, at least in the second and third trimesters, and little of the drug seems to appear in breast milk. It is doubtful whether the baby is exposed to more than 10% of the weight adjusted maternal dose during lactation, but the long half life makes prediction difficult and more information is needed. The manufacturer has not yet felt able to recommend its use during pregnancy or lactation, or to offer advice on use in children less than 3 months old.

Proguanil (as mentioned in the section on “Maternal medication and the baby”) provides a better studied alternative for preventing and treating malaria during pregnancy and lactation. The usual prophylactic dose for a baby would be 5 mg/kg once a day by mouth, but no liquid formulation is available.

Areas of chloroquine resistance

World Health Organisation (WHO) advice on travel, and on the prevalence of drug resistant organisms, can be found on www.who.int/ith/chapter07_0-1.html. Much detailed advice is also available on www.cdc.gov/travel/diseases.html#malaria from the Center for Disease Control (CDC) in the USA. A useful summary of this advice is available in the *British National Formulary (BNF)*. Specialist advice should be sought regarding the problems of multiple drug resistance being encountered in Southeast Asia.

Prophylactic strategies

Nets impregnated with permethrin offer substantial night-time protection. Diethyltoluamide (DEET) sprays and lotions are effective for 5–10 hours. Use a formulation with <30% DEET to minimise the risk of toxicity. Long sleeves and trousers lessen the risk after dusk. Start chemoprophylaxis with chloroquine 1 week before entering any endemic area, and continue for 4 weeks after leaving.

Treatment

Prevention: Give 5 mg/kg of mefloquine by mouth once a week. Start treatment 3 weeks before entering any endemic area (since most adverse effects will manifest themselves within 3 weeks of starting treatment), and continue treatment for 4 weeks after leaving. There is little experience with sustained use for more than 1 year, and use is not advised in children with a history of seizures.

Cure: Give 15 mg/kg by mouth, followed, after 12 hours, by one further 10 mg/kg dose.

Supply

Scored 250 mg tablets of mefloquine cost £1.80 each. They have a bitter taste, making administration difficult in small children (although the crushed tablet can be mixed with jam or other food). In addition, no low dose tablet or liquid formulation exists, making accurate administration to a small baby extremely problematic. Protect from sunlight and humidity once removed from the foil wrapping.

Proguanil is cheaper (scored 100 mg tablets cost only 8p); a suspension could be prepared but its “shelf life” remains uncertain. The tablets can generally be quartered, crushed, and administered on a spoon or down a nasogastric tube. Malarone® provides an alternative approach to prophylaxis and treatment, although the manufacturers have not yet recommended its use in babies weighing less than 11 kg; tablets containing 25 mg of proguanil and 62.5 mg of atovaquone cost 75p each. No suspension exists.

References

- Edstein MD, Veenendaal JR, Hyslop R. Excretion of mefloquine in human breast milk. *Chemotherapy* 1988;**34**:165–9.
- Anonymous. Are insect repellents safe? [Editorial] *Lancet* 1988;**ii**:610–11.
- Palmer KJ, Holliday SM, Brogden RN. Mefloquine. A review of its antimalarial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1993;**45**:430–75.
- Nosten F, ter Kuile F, Maellankiri L, et al. Mefloquine prophylaxis prevents malaria during pregnancy: a double-blind placebo-controlled study. *J Infect Dis* 1994;**169**:595–603. [RCT]
- Radloff PD, Phillips J, Nkeyi M, et al. Atovaquone and proguanil for *Plasmodium falciparum* malaria. *Lancet* 1996;**347**:1511–14. [RCT]
- Smoak BL, Writer JV, Keep LW, et al. The effects of inadvertent exposure of mefloquine chemoprophylaxis on pregnancy outcomes and infants of US army servicewomen. *J Infect Dis* 1997;**176**:831–3.
- Vamhauwere B, Maradit H, Kerr L. Post-marketing surveillance of prophylactic mefloquine (Lariam®) use in pregnancy. *Am J Trop Med Hyg* 1999;**58**:17–21.
- Croft A. Malaria: prevention in travellers. *Clin Evid* 2002;**8**:744–61 (and updates). [SR]

Use

Vaccines offer protection from some, but not all, forms of meningococcal meningitis and septicaemia.

Meningococcal disease

Meningococcal infection is a notifiable illness caused by the Gram negative diplococcus *Neisseria meningitidis*. At least 13 antigenically different serogroups are known. The group C strain currently accounts for 40% of all meningococcal infection in the UK, but a much higher proportion of meningococcal deaths. Group B strains account for most other UK isolates, with a much lower case fatality rate. Group A strains are common in sub-Saharan Africa and the Indian subcontinent. Meningococci are spread by droplet and by direct contact. The incubation period is 2–7 days. Babies usually present with pyrexia, irritability, vomiting, and a full fontanelle, older children with headache, photophobia, and drowsiness. The petechial or purpuric rash, which fails to blanch on pressure (best tested using a glass slide or tumbler), is not always an early feature. Infection is commonest in children under 5 years old, and in young people aged 15–20. Preventive measures are important, because 1 in 10 will die despite prompt treatment with benzylpenicillin. Contacts should be given rifampicin (q.v.). Vaccines are, as yet, able to provide protection only from serogroups A, C, W135, and Y infection.

Indications

Group C conjugate vaccine (MenC): This vaccine, first introduced in 1999, using the same technology as was used to produce the very safe and effective haemophilus (Hib) vaccine (q.v.), should be used to offer babies early and lasting protection from group C disease.

Groups A&C polysaccharide vaccine: This plain vaccine, first introduced in 1979, offers protection from group A and group C disease, but generates little response to the group C polysaccharide in infants less than 18 months old, or to the group A polysaccharide in babies less than 3 months old. It provides 3–5 years of immunity in older children, but should be offered only to those planning to travel abroad.

Contraindications

Immunisation should not be offered to a child who is acutely unwell, or to a child who has had a severe proven reaction to a previous injection. Minor infections unassociated with fever are not a reason to delay immunisation, however, and the contraindications associated with the use of a live vaccine (cf. polio vaccine) do not apply.

Administration

MenC for children under 1 year old: Give three 0.5 ml doses by deep IM injection into the anterolateral aspect of the thigh, using a 25 mm, 23 gauge, needle, at monthly intervals starting at 2 months. If this is started when the baby is more than 4 months old, two doses will suffice. Use a different limb from that used for any simultaneous diphtheria/tetanus/pertussis, Hib, or inactivated polio vaccination.

MenC for older children: Offer previously unimmunised children just one 0.5 ml IM, or deep subcutaneous, injection when opportunity arises. There is no contraindication to simultaneous immunisation with other routine vaccines, but it is best to use a different injection site.

A&C vaccine: Give a single 0.5 ml deep subcutaneous injection.

Anaphylaxis

The management of anaphylaxis (which is very rare) is outlined in the monograph on immunisation.

Documentation

Inform the district immunisation coordinator (see monograph on immunisation) when any child is immunised in hospital, and complete the relevant section of the child's own personal health booklet.

Supply

Free supplies of the conjugate group C (MenC) vaccine in 0.5 ml vials are available from three firms through Farrillon in the UK, as part of the National Childhood Immunisation Programme. The products are interchangeable. Vials must be stored at 2–8°C, but stability is probably unaffected if they are allowed to reach a temperature not exceeding 25°C on the day of use. Vaccine remaining unused should be re-refrigerated only once. Vials must not be exposed to a temperature of less than 2°C.

Single dose 0.5 ml vials of the lyophilised A&C vaccine, with diluent for reconstitution, cost approximately £7 each. Do not let the diluent become frozen. Use within 1 hour of reconstitution.

References

UK Health Departments. *Immunisation against infectious disease*. Chapter 23. London: HMSO, 1996. (Revised version as issued in 1999 with a letter from the Chief Medical Officer for England and Wales (PL/CMO/99/4).)

MacLennan J. Meningococcal group C conjugate vaccines. *Arch Dis Child* 2001;**84**:383–46.

Lakshman R, Jones I, Walker D, et al. Safety of a new conjugate meningococcal C vaccine in infants. *Arch Dis Child* 2001;**85**:391–7.

MEROPENEM

Use

Meropenem is a very valuable, recently introduced, broad spectrum antibiotic. There is general agreement that it should be held in reserve and used only in consultation with a microbiologist or in a research context, when no other satisfactory alternative exists.

Pharmacology

Meropenem is a carbapenem β lactam antibiotic active against a very wide range of Gram positive and Gram negative aerobic and anaerobic bacteria that first came into general clinical use in 1985. Methicillin resistant staphylococci and *Enterococcus faecium* are resistant to meropenem, as are some strains of *Pseudomonas aeruginosa*. Meropenem is excreted in the urine, mostly unchanged, but partly as an inert metabolite. The elimination half life in adults is only 1 hour, but longer in children less than 2 years old. There is, as yet, only limited information on neonatal drug elimination. The initial half life in the term baby is 2 hours, and in the preterm baby 3 hours; the speed with which the half life declines in infancy is not yet known.

Meropenem has many of the same properties, and most of the same adverse effects, as imipenem (q.v.), but it seems to cause less nausea. It is also stable to the renal enzyme that inactivates imipenem and does not need, therefore, to be given with cilastatin. It has not been in use as long as imipenem, and has not been so extensively studied, but the evidence to date suggests that meropenem is less likely to induce seizures than imipenem/cilastatin (which is not licensed for the treatment of central nervous system infection). Meropenem can also, unlike imipenem/cilastatin, be given as a standard slow IV bolus injection. It readily penetrates the cerebrospinal fluid of patients with bacterial meningitis, and also most other body fluids. It crosses the placenta, but there is (as yet) no evidence of teratogenicity. Only a small amount of meropenem appears in animal milk, and its use during lactation is unlikely to be hazardous. There is too little published experience for the manufacturers to have yet recommended the use of meropenem in children less than 3 months old.

Treatment

There is very little published information on the clinical use of meropenem in the neonatal period. Try 20 mg/kg IV once every 12 hours in the first 4 weeks of life, and once every 8 hours in babies more than 4 weeks old. Higher doses (40 mg/kg) have been used in older children with meningitis. IM use is not recommended. Dosage frequency should be halved if there is evidence of renal failure, and treatment stopped altogether if there is anuria, unless dialysis is instituted.

Supply

Vials suitable for IV use containing 250 mg of meropenem as a powder cost £10 each. Vials should be reconstituted with 4-8 ml of water for injection to give a solution containing 50 mg/ml. The manufacturers recommend prompt use after reconstitution, and say that vials are for "single use only", but they also say that the preparation can be kept for up to 24 hours after reconstitution if kept at 4°C.

References

- Schuler D, and the Meropenem Paediatric Study Group. Safety and efficacy of meropenem in hospitalised children: randomised comparison with cefotaxime, alone and combined with metronidazole or amikacin. *J Antimicrob Chemother* 1995;**36**(Suppl A):99-108. [RCT]
- Klugman KP, Dagan R and the Meropenem Meningitis Study Group. Randomised comparison of meropenem with cefotaxime for treatment of bacterial meningitis. *Antimicrob Agents Chemother* 1995;**39**:1140-6. [RCT]
- Blumer JL. Pharmacokinetic determinants of carbapenem therapy in neonates and children. *Pediatr Infect Dis J* 1996;**15**:733-7.
- Bradley JS. Meropenem: a new, extremely broad spectrum beta-lactam antibiotic for serious infections in pediatrics. *Pediatr Infect Dis J* 1997;**16**:263-8.
- Odio CM, Puig JR, Ferris JM, et al. Prospective randomised investigator-blinded study of the efficacy and safety of meropenem vs. cefotaxime in bacterial meningitis in children. *Pediatr Infect Dis J* 1999;**18**:581-90. [RCT]
- van Enk JG, Touw DJ, Lafeber HN. Pharmacokinetics of meropenem in preterm neonates. *Ther Drug Monit* 2001;**23**:198-201.

Use

Methadone is used in the management of opioid addiction, and to control the more severe withdrawal ("abstinence") symptoms seen in some babies born to mothers with such an addiction.

Pharmacology

Methadone hydrochloride is a useful synthetic opioid analgesic developed in Germany during the second world war that is capable of providing sustained pain relief. It is usually taken by mouth, and is less sedating than morphine. Opiate addiction may be associated with reduced fetal growth (as outlined in the monograph on diamorphine [heroin]), but there is no evidence of teratogenicity. Methadone is well absorbed when taken by mouth (90% bioavailability) and is largely metabolised by the liver, the neonatal half life being about 20 hours. Tissue levels exceed plasma levels ($V_D \sim 6$ l/kg). Excessive doses can cause ileus and respiratory depression. Use during lactation will result in the baby receiving only about 3% of the weight adjusted maternal dose, so there is no reason why a mother should not breastfeed if she is on *only* methadone once HIV infection has been excluded. The drug's potential as a neonatal analgesic has not yet been studied.

Opiate addiction

In the UK, many mothers with an opiate addiction will have been placed on methadone before delivery, in an attempt to reduce illicit opioid usage. Methadone is useful because it can be taken orally, needs to be taken only once or twice a day, and has a long lasting effect. Maternal blood levels are therefore more stable, reducing some of the intoxicating (and potentially damaging) "swings" to which the fetus of an addicted mother is otherwise exposed. Despite this, many babies still start to show signs of an abstinence syndrome 1–2 days after birth, with restlessness, irritability, rapid breathing, vomiting, and intestinal hurry, especially when the mother was on a dose of more than 20 mg per day. Feeding problems may exacerbate weight loss. Swaddling and the use of a dummy or pacifier should be enough to control the symptoms in up to half the babies of drug dependent mothers, but a rapidly reducing dose of methadone can be given to babies with severe symptoms. Fits are uncommon, seldom seen in the first few days, and more suggestive of a non-opiate drug dependency. Symptoms coming on after 2½ days are usually mild and more typically seen when the mother is dependent on a hypnotic or sedative (barbiturates, diazepam (q.v.), etc.). A mixed picture due to the abuse of several drugs is not uncommon, and may justify giving phenobarbital (q.v.) as well as methadone (or morphine). Chlorpromazine (q.v.) is an understudied alternative where the problem is not opiate addiction. The web commentary reviews the care of the drug dependent mother and her baby.

Managing neonatal opiate withdrawal

Achieving control: Give one dose every 6 hours by mouth. Start with 100 micrograms/kg, and increase this by 50 micrograms/kg each time a further dose is due until symptoms are controlled.

Maintaining control: Calculate the total dose given in the 24 hours before control was achieved, and give half this amount by mouth once every 12 hours.

Weaning: Once control has been sustained for 48 hours, try to reduce the dose given by 10–20% once each day. Treatment can usually be stopped after 7–10 days, although mild symptoms may persist for several weeks.

Seizures: Give 250 micrograms/kg IM, and monitor for possible apnoea.

Antidote

Naloxone (q.v.) is effective, but may unmask withdrawal symptoms in an opiate dependent patient.

Supply and administration

A clear yellow-green non-proprietary oral mixture of this controlled drug, containing 1 mg/ml of methadone hydrochloride, can be provided on request (100 ml costs £1.50). A more dilute solution (100 micrograms/ml) with a 1 month shelf life could be provided by the pharmacy for neonatal use on request. An IM preparation containing 10 mg/ml is also available; to obtain a 1 mg/ml solution for accurate neonatal administration, take 1 ml of this and dilute to 10 ml with sterile water for injection.

Storage and administration of methadone is controlled under Schedule 2 of the UK Misuse of Drugs Regulations, 1985 (Misuse of Drugs Act, 1971).

References

- American Academy of Pediatrics. Committee on Drugs. Neonatal drug withdrawal. *Pediatrics* 1998;**101**:1079–88.
- Kandall SR, Doberczak TM, Jantunen M, et al. The methadone-maintained pregnancy. *Clin Perinatol* 1999;**26**:173–83.
- Begg EJ, Malpas TJ, Hackett JH, et al. Distribution of R- and S-methadone into human milk during multiple, median to high oral dosing. *Br J Clin Pharmacol* 2001;**52**:681–5.
- Johnson K, Gerada C, Greenough A. Treatment of neonatal abstinence syndrome. *Arch Dis Child* 2003;**88**:F2–5. [SR]
- Philipp BL, Merewood A, O'Brien. Methadone and breast feeding: new horizons. *Pediatrics* 2003;**111**:1429–30.

See also the Cochrane reviews on opiate withdrawal 

METHYLDOPA

Use

Methyldopa is the best studied of all the antihypertensive drugs used in pregnancy. It used to be used quite widely with hydralazine (q.v.) for resistant neonatal hypertension, but nifedipine (q.v.) is now the drug normally used to manage sustained hypertension in infancy.

Pharmacology

Methyldopa interferes with the normal production of the neurotransmitter noradrenaline (norepinephrine), but also seems to have direct effects on arterioles and on the central vasomotor centre. Methyldopa was first shown to be of use in the management of hypertension in 1960. It causes a fall in blood pressure and a reduction in total peripheral vascular resistance, without any change in cardiac output or renal blood flow. It has been widely used in the management of maternal hypertension and in patients with pre-eclamptic toxemia. It readily crosses the placenta, but fetal side effects have not been identified. There is no known contraindication to use during lactation because the baby receives less than 5% of the maternal dose when this is compared on a weight for weight basis.

Oral absorption is variable and incomplete, and much of the drug is eliminated by the kidney. There is some evidence that treatment should be modified in the presence of serious renal failure. The way in which the half life varies with age is not well defined, but it is probably only about 2–4 hours. The drug's therapeutic action does not, however, seem to be related to this half life. Long term medication induces salt and water retention unless a diuretic is prescribed. Side effects include haemolytic anaemia, thrombocytopenia, and gastrointestinal disturbances. Large doses have a sedative effect. If treatment is stopped suddenly there may be a hypertensive rebound "crisis".

Treatment

Start with 2.5 mg/kg of methyldopa by mouth once every 8 hours, together with a diuretic, and increase the dose as required once every 3–5 days to a maximum of no more than 15 mg/kg once every 8 hours. The same dose of methyldopate can be given as a slow infusion over 30–60 minutes when oral treatment is not possible.

Supply

5 ml ampoules of methyldopate containing 250 mg cost £2.30. In order to ensure accuracy, dilute 1 ml (50 mg) from the ampoule with 9 ml of 5% dextrose to provide a solution containing 5 mg/ml prior to oral or IV administration. An oral suspension with a 7 day shelf life could be prepared on request.

References

- Sinaiko AR, Mirkin BL. Clinical pharmacology of antihypertensive drugs in children. *Pediatr Clin North Am* 1978;**25**:137–57.
- Jones HMR, Cummings AJ. A study of the transfer of alpha-methyldopa to human foetus and newborn infant. *Br J Clin Pharmacol* 1978;**6**:432–4.
- Anon. Managing high blood pressure in pregnancy. *Drug Ther Bull* 1993;**31**:53–6.

See also relevant Cochrane reviews 

Use

Methylene blue is used to treat methaemoglobinaemia. It has also been used experimentally to treat the refractory hypotension sometimes associated with septic shock.

Methaemoglobinaemia

Methaemoglobin is the oxidised (ferric) form of the haemoglobin molecule; it lacks the normal molecule's ability to carry oxygen to the tissues. The condition can be inherited (as a recessive reductase enzyme deficiency, or as a dominant haemoglobinopathy), or occur briefly as a result of drug exposure. Babies are at particular risk because reductase enzyme levels are initially low. Nitric oxide (q.v.) is rapidly inactivated by the haemoglobin molecule, forming nitrosohaemoglobin, which is then converted to methaemoglobin. It is for this reason that excess inhaled nitric oxide can cause methaemoglobinaemia. Aniline dyes (even when absorbed through the skin) can have the same effect, as can the local anaesthetic prilocaine (see the monograph on lidocaine). Excess nitrates in drinking water were once a common cause. If a drop of suspect blood turns chocolate brown, rather than red, over 30 seconds as it dries on a filter paper when compared with a control sample, the suspect specimen almost certainly contains more than 10% of methaemoglobin.

Pharmacology

Methylene blue is a basic dye that was first synthesised in 1876. Histologists have used it for more than a century to dye living nerve tissue. It is reduced in the red cell to leucomethylene blue, where it then acts to convert methaemoglobin back to haemoglobin. It is therefore used in the treatment of both congenital and acquired methaemoglobinaemia. It has also been used as a dye to monitor reflux, trace fistulae, position tubes, identify premature rupture of membranes, and to "mark" the different amniotic sacs in multiple pregnancy, although this last use can cause serious haemolytic anaemia and neonatal jaundice, and is claimed to be associated with a high risk of jejunal atresia. Recently there has been experimental interest in the use of the same drug to control the severe hypotension seen in septic shock when this fails to respond to inotropes and hydrocortisone (q.v.) because this condition seems to be mediated, at least in part, by excess tissue nitric oxide synthesis. Nitric oxide causes vasodilatation by activating soluble guanylate cyclase in smooth muscle cells to produce cyclic guanosine monophosphate; methylene blue inhibits this activation.

Methylene blue is moderately well absorbed when given by mouth and slowly excreted in the urine, after partial conversion to leucomethylene blue. Repeated use may be hazardous if renal function is poor. IV administration can cause a number of adverse reactions, including pain, nausea, vomiting, confusion, dizziness, sweating, and hypotension. Repeated treatment, or an overdose, can actually *cause* methaemoglobinaemia, haemolysis, and hyperbilirubinaemia, and there is no effective treatment for this other than exchange transfusion. Infants with glucose-6-phosphate dehydrogenase (G6PD) deficiency are at particular risk in this regard. Long term treatment has been known to cause haemolytic anaemia. Heinz body formation has also been reported. Methylene blue turns the urine, stools, and body secretions blue. The skin also becomes discoloured. Nothing is known about the safety of giving IV treatment to a mother during pregnancy or lactation.

Treatment

Give 1 mg/kg IV (1 ml of a solution made up as described below) over 1 hour. A repeat dose can be given if necessary after a few hours. Oral treatment has occasionally been used to manage serious congenital methaemoglobinaemia, even though this tends to make the cyanosed patient blue for a different reason. Doses of up to 2 mg/kg once a day by mouth have been used. Oral ascorbic acid (500 mg once a day) may also be effective.

Supply

Methylene blue trihydrate is available as a 1% solution in 5 ml ampoules costing £4.20 each. To give 1 mg/kg IV take 1 ml from the 1% ampoule for each kilogram the baby weighs, dilute to 10 ml with 5% dextrose immediately before use and infuse 1 ml of the resultant solution over 1 hour. More rapid infusions have, on occasion, been given with apparent safety. Take care to avoid tissue extravasation as this can cause necrotic ulceration.

Reference

Driscoll W, Thurin S, Carrion V, *et al.* Effect of methylene blue on refractory neonatal hypotension. *J Pediatr* 1996;**129**:904–8. (See also pp. 790–3.)

METOCLOPRAMIDE

Use

Metoclopramide is an effective and safe medicine to use to control severe nausea and vomiting in pregnancy. A number of studies have shown that its use can enhance breast milk production after delivery.

Pharmacology

Metoclopramide hydrochloride is a substituted benzamide related to procainamide, which stimulates motility in the upper gastrointestinal tract without affecting gastric, biliary, or pancreatic secretion. It was being evaluated as a possible antiarrhythmic agent when its antiemetic properties came to light in 1964. It is rapidly absorbed from the intestinal tract, but plasma levels are rendered unpredictable by variable first pass hepatic metabolism. Metoclopramide possesses parasympathomimetic activity. It has been used to control some forms of nausea and vomiting (particularly in cancer patients undergoing cytotoxic treatment or radiotherapy), and in the management of gastric stasis and gastro-oesophageal reflux. It is also a dopamine receptor antagonist, and idiosyncratic dystonic and dyskinetic extrapyramidal signs are not infrequently seen in children, even at the normally recommended dose. For these reasons, it is now generally used only in patients less than 20 years old without malignant disease as a preanaesthetic medication, or as an aid to gastrointestinal intubation. Domperidone (q.v.) is a related drug that causes fewer dystonic problems. Erythromycin (q.v.) is sometimes used in the neonatal period to stimulate gastrointestinal motility. Cisapride (q.v.) was also, at one time, widely used for the same purpose.

Metoclopramide has also been used to treat the severe nausea and vomiting that occasionally occurs during pregnancy (hyperemesis gravidarum) and a study of the outcomes of these pregnancies found no evidence of teratogenicity. It has also been given to speed gastric emptying during labour, or as a preanaesthetic medication to reduce the risk of vomiting. Metoclopramide stimulates prolactin secretion from the anterior pituitary and there have been at least five papers attesting to its successful use to enhance lactation. It does not work in all women (possibly because they already have raised prolactin levels) and side effects, such as cramp and diarrhoea, sometimes limit compliance. The drug accumulates in breast milk, but ingestion by the baby would be unlikely to exceed 50 micrograms/kg per day, one tenth of the maximum dose sometimes used for medicinal purposes. Domperidone may prove a better alternative, although it has received only limited study as yet.

Treatment

Mother: Give 10 mg (or even 15 mg) to the mother by mouth three times a day to stimulate milk production. Taper off treatment over 5–10 days to limit the risk of milk production declining again after 7–10 days.

Baby: 100 micrograms/kg every 6–8 hours by mouth (or IV) may speed gastric emptying but seems to have little effect on reflux, while higher doses may be associated with more reflux and increased general irritability.

Toxicity

The therapeutic dose in children is only slightly less than the toxic dose. Tachycardia, agitation, hypertonia, feeding problems, and diarrhoea have all been reported after a neonatal overdose, together with methaemoglobinaemia, which responded to treatment with methylene blue (q.v.).

Supply

10 mg tablets cost less than 4p each, if a generic formulation is used. 2 ml ampoules containing 10 mg of metoclopramide (costing 27p) are also available for IV or IM use. For IV use take 1 ml of the liquid formulation in the ampoule, dilute to 50 ml with 0.9% sodium chloride to provide a solution containing 100 micrograms/ml, and give the prescribed dose as a slow bolus.

Metoclopramide is also available from the pharmacy as a sugar-free liquid containing 1 mg/ml (100 ml costs £1.90); it can be further diluted with an equal quantity of pure water, but should be used within 2 weeks of being dispensed. The liquid preparation *must* be protected from light. Discoloured ampoules should be discarded.

References

- Ehrenkranz RA, Ackerman BA. Metoclopramide effect on faltering milk production by mothers of premature infants. *Pediatrics* 1986;**78**:614–20.
- Machida HM, Forbes DA, Gall DG, et al. Metoclopramide in gastroesophageal reflux in infancy. *J Pediatr* 1988;**112**:483–7.
- Tolia V, Calhoun J, Kuhns L, et al. Randomised, prospective double blind trial of metoclopramide and placebo for gastroesophageal reflux in infants. *J Pediatr* 1989;**115**:141–5. [RCT]
- Toppare MF, Laleli Y, Senses DA, et al. Metoclopramide for breast milk production. *Nutr Res* 1994;**14**:1019–23.
- Berkovitch M, Elbirt D, Addis A, et al. Fetal effects of metoclopramide therapy for nausea and vomiting in pregnancy. *N Engl J Med* 2000;**343**:445–6.
- Sørensen HT, Nielsen GL, Christensen K, et al. Birth outcome following maternal use of metoclopramide. *Br J Clin Pharmacol* 2000;**49**:264–8.

Use

Metronidazole is used in the management of anaerobic bacterial infection (including meningitis), and in the treatment of a range of protozoal infections such as amoebiasis, giardiasis, and trichomoniasis. It is also widely used in the UK after intestinal surgery and in the management of necrotising enterocolitis.

Pharmacology

Metronidazole, a unique bactericidal antibiotic that first came into clinical use in 1960, is a 5-nitroimidazole derivative. It is particularly useful in the treatment of dental, surgical, and gynaecological sepsis because of its activity against obligate anaerobes such as *Bacteroides* and *Clostridium* species, and facultative anaerobes such as *Gardneriella* and *Helicobacter*. It seems rare for bacterial resistance to develop. Both partners should be treated when trichomonal infection is suspected. Short prophylactic courses, with or without ampicillin, are frequently given during abdominal and pelvic surgery in Europe, but cefoxitin (q.v.) is more often used for this purpose in North America (where metronidazole is not recommended for use in children). A reversible sensory neuropathy has been reported in adults after prolonged high dose treatment. Mild gastrointestinal symptoms can occur.

Metronidazole can be given IV, but it is very well absorbed by mouth. Rectal bioavailability is about 60%. The drug has a large volume of distribution ($V_D \sim 0.8$ l/kg), penetrates most body fluids well (including cerebrospinal fluid and ascitic fluid), and is excreted in the urine after partial breakdown to a product that also has some antimicrobial activity. The plasma half life is long and inversely related to gestational age at birth, but soon approaches that seen in adults (7–10 hours). The dosage interval may need to be increased when there is hepatic failure, but it does not usually require modification in renal failure, although metabolites may accumulate with prolonged usage. See the website commentary for the reasoning behind the dose regimen recommended in this monograph.

Use in pregnancy was long considered controversial because the drug crosses the placenta with ease, is mutagenic to bacteria, and seems to produce tumours in rodents. However, there is no evidence that the drug is a carcinogen in humans, nor is there any evidence to suggest it is a teratogen, although it can increase the fetotoxic and teratogenic effect of alcohol in mice. More recently it has been widely used with apparent safety to treat trichomonal and bacterial vaginitis during both pregnancy and lactation. Even in the absence of inflammation, the replacement of lactobacilli by anaerobic bacteria (vaginosis), with increased vaginal discharge and a characteristic odour, certainly merits treatment. Oral clindamycin (q.v.) is an alternative drug that may be better at reducing the risk of preterm birth. Other strategies that can sometimes be of benefit are summarised in the monograph on erythromycin.

Levels in breast milk are the same as in blood, but those seen in babies being breastfed by mothers on the dose usually used to treat urogenital trichomoniasis (400 mg twice a day for 7 days) never rise above a quarter of the normal therapeutic blood level. No immediate adverse effects have ever been recognised as a result of treatment during lactation; women with trichomonal infection who are concerned for the theoretical long term risks may, however, choose to suspend lactation for 24 hours and request the well recognised alternative of treatment with one single high (2 g) oral dose of metronidazole. The drug is said to affect the taste of milk, but this seems to have been noticed more often by mothers (who read what the books have to say) than by babies (who do not).

Drug interactions

Concurrent barbiturate use can decrease the half life in children, making a higher daily dose necessary. Steroids and rifampicin may have a similar but less marked effect.

Treatment

Give a 15 mg/kg IV loading dose. Then give 7.5 mg/kg, orally or IV, once every 12 hours in babies less than 4 weeks old, and every 8 hours in older babies. Higher doses have been used in meningitis. Slow IV administration is necessary only in older children and adults because of the volume of fluid involved.

Supply

20 ml ampoules containing 100 mg of metronidazole (5 mg/ml) for IV use cost £1.50 each. A 7.5 mg/kg dose contains 0.2 mmol/kg of sodium. Limited solubility precludes IM use; the volume involved would be too large. An oral suspension containing 40 mg/ml in sucrose is available (100 ml costs £7.70). A more dilute (10 mg/ml) oral suspension can be prepared with a 2 week shelf life.

References

- Burtin P, Taddio A, Ariburnu O, et al. Safety of metronidazole in pregnancy: a meta-analysis. *Am J Obstet Gynecol* 1995;172:525–9. [SR]
Klebanoff MA, Carey JC, Hauth JC, et al. Failure of metronidazole to prevent preterm delivery among pregnant women with asymptomatic trichomonas vaginalis infection. *N Engl J Med* 2001;345:487–93. [RCT]
Joesoef M, Schmid G. Bacterial vaginosis. *Clin Evid* 2003;9:1712–19 (and updates). [SR]

See also relevant Cochrane reviews

MICONAZOLE

Use

Miconazole and nystatin (q.v.) are both widely used in the treatment of topical infection with *Candida*. There is good controlled trial evidence that miconazole is better than nystatin at eliminating oral thrush.

Pharmacology

Miconazole is an artificial imidazole agent first developed in 1969, which is active against a wide range of pathogenic yeasts and dermatophytes, as well as a range of Gram positive bacteria (staphylococci and streptococci). These properties make it particularly useful in the treatment of oral and vaginal thrush, candidal nappy rash, intertrigo, paronychia, ringworm, and athlete's foot. It seems to work by interfering with ergosterol synthesis, damaging fungal cell wall permeability. It is moderately well absorbed when given by mouth (unlike nystatin) and then inactivated by the liver before excretion in the urine, but much of any oral dose is excreted unchanged in the stool. It was, for some years, given IV or by mouth in the treatment of a range of systemic fungal infections, but it is now used only topically to treat infection of the skin, gut, or mucous membranes. Miconazole seems to eliminate vaginal candidiasis in pregnancy better than nystatin, and there is no evidence that topical use by the mother during pregnancy or lactation poses any hazard to the baby.

Candidal dermatitis

Candida can be found in the vagina of one in four pregnant women; a fifth of their babies become colonised at birth, and more over the next month. *Candida* proliferates in moist skin, but overt infection is seldom seen except in babies with excessive intestinal colonisation. It is not surprising, therefore, that overt skin damage (dermatitis) usually starts in the perianal region, especially if the skin is already damaged. Prior prolonged and broad spectrum antibiotic use makes overt infection more likely.

Use of gentian violet

Gentian violet (otherwise known as crystal violet), a triphenylmethane antiseptic dye, is an old fashioned treatment for candidal infection of the skin that is also active against a range of Gram positive organisms, including staphylococci. Although it is at least as effective as its colour is alarming, it is no longer used in the UK (especially on broken skin or mucous membranes) because of theoretical concern about carcinogenicity in mice. However, a 0.5% aqueous solution is still sometimes used to treat infection of the skin by *Candida* elsewhere in the world, and is often thought to be the most effective topical product currently available because of its deep penetration. It is probably not wise to apply the solution to mucosal surfaces more than twice a day for 3–4 days. It stains everything it touches, including clothing and skin. It is worth treating the gut with miconazole or nystatin at the same time.

Drug interaction

Never give oral miconazole to a patient who is taking cisapride because of the risk of arrhythmia.

Treatment

Oral thrush: Smear 1 ml of miconazole oral gel round the mouth and gums with a finger after feeds four times a day, and take steps to prevent reinfection as outlined in the monograph on nystatin. Continue treatment for at least 2 days after all the signs of infection have gone (usually 7–10 days in all).

***Candida* (Monilia) dermatitis:** Use miconazole nitrate as a cream twice a day for at least 10 days, even if the rash improves quickly. There is a real risk of the problem recurring if treatment is stopped too soon. It may be advisable to treat the gastrointestinal tract as well as the skin if there is evidence of stubborn infection (nystatin may be better at eradicating *Candida* from the lower bowel).

Supply

One 30 g tube of miconazole skin cream (2% w/w) costs £2. One 80 g tube of the sugar free oral gel (24 mg/ml) costs £5. The gel has not been licensed for use in the USA, but small (15 g) quantities are available in the UK without prescription. The cream, and a dusting powder, are also available "over the counter" without prescription.

Inexpensive crystal violet paint (as a 0.5% aqueous preparation) is dispensable on request. Avoid the use of alcoholic solutions and solutions that are more concentrated than this, especially when treating the mouth and tongue.

References

- Rosa FW, Baum C, Shaw M. Pregnancy outcomes after first-trimester vaginitis drug therapy. *Obstet Gynecol* 1987;**69**:751–5.
Drinkwater P. Gentian violet: is it safe? *Aust N Z J Obstet Gynaecol* 1990;**30**:65–6.
Piatt JP, Bergeson PS. Gentian violet toxicity. *Clin Pediatr* 1992;**31**:756–7.
Hoppe JE. Treatment of oropharyngeal candidiasis and candidal diaper dermatitis in neonates and infants: review and reappraisal. *Pediatr Infect Dis J* 1997;**16**:885–94. [SR]

See also relevant Cochrane reviews



Use

Midazolam is an effective sedative and anticonvulsant, but it does not relieve pain.

Pharmacology

Midazolam hydrochloride is a short acting benzodiazepine with hypnotic, anxiolytic, muscle relaxant, and anticonvulsant activity that is mostly used to induce sleep and generate anterograde amnesia. It was first patented in 1976. Use during pregnancy and lactation should be approached with the same caution as with diazepam (q.v.). It is cleared from the body 20 times more quickly than diazepam, the half life being 2 hours in adults (but 12 hours in the neonate). Because of this, midazolam is now increasingly used to stop epileptic and febrile seizures in children (the rapidity of nasal and buccal mucosal absorption making IV administration less important).

Unfortunately, the first IV dose in a preterm baby not infrequently causes respiratory depression, with hypotension and a fall in cerebral blood flow. Myoclonus unassociated with any EEG abnormality is sometimes seen, and paradoxical agitation has been reported. Prolonged use can also cause drug accumulation, with tissue levels that variably exceed plasma levels. Severe encephalopathic symptoms have sometimes been reported 1–2 days after sustained treatment has been stopped, with drowsiness and dystonic posturing, and choreoathetosis persisting for a week or more. The manufacturer does not recommend use as a sedative or anticonvulsant in any child less than 7 years old, and the Cochrane overview found inadequate evidence to support neonatal use (see website commentary). Chloral hydrate (q.v.) can be used to provide short term sedation for babies during investigative procedures.

Treatment

Short term sedation: A 150 micrograms/kg dose by mouth, or IM, is used to premedicate children prior to anaesthesia, while 200 micrograms/kg can be used to provide sedation during an investigational procedure (if use is monitored with an oximeter). Rapid IV administration (< 2 minutes) seems safe in children, but sometimes causes seizure-like myoclonus in the preterm baby.

Continuous sedation: Some units give 60 micrograms/kg per hour to sedate the ventilated newborn baby for 2–4 days after birth, but this strategy has been questioned. The rate of infusion *must* be halved after 24 hours in babies of less than 33 weeks postconceptional age to prevent drug accumulation.

Controlling seizures: A 200 micrograms/kg dose rapidly stops most fits in infancy, and an injection can be avoided by dropping the IV preparation into the back of the nose or mouth. It seldom stops seizures that have not been controlled by phenobarbital.

Antidote

All benzodiazepines cause hypotonia, hypotension, and coma in excess, but these effects can be reversed by flumazenil, a competitive antagonist with a relatively short (50 minute) half life, first synthesised in 1979. While the manufacturers are not yet ready to recommend such use, there are reports of flumazenil being used in children. Give one (or even two) 10 micrograms/kg IV doses and assess the effect. If there is a definite but unsustained response, start a continuous IV infusion with 10 (or more) micrograms/kg per hour. Such use may unmask fits suppressed by benzodiazepines.

Compatibility

Midazolam can be added (terminally) to an IV line containing morphine, fentanyl, milrinone, or TPN.

Supply and administration

5 ml ampoules containing 10 mg of midazolam cost £1. To give 60 micrograms/kg of midazolam per hour as a continuous IV infusion, place in a syringe 1.5 ml (3 mg) of this solution for each kg the infant weighs, dilute to 50 ml with 10% dextrose saline, and infuse at a rate of 1 ml/hour. (A less concentrated solution of dextrose or dextrose saline can be used where necessary.) Note that a 2 ml ampoule containing a more concentrated preparation of midazolam (10 mg) is also available. The drug is stable in solution so it is not necessary to change the infusate daily. The product used in North America contains 1% benzyl alcohol.

5 ml ampoules containing 500 micrograms of flumazenil cost £15-60.

References

- Bergman I, Steeves M, Buckart G, *et al.* Reversible neurologic abnormalities associated with prolonged intravenous midazolam and fentanyl administration. *J Pediatr* 1991;**119**:644–9.
- Blumer JL. Clinical pharmacology of midazolam in infants and children. *Clin Pharmacokinet* 1998;**35**:37–47.
- Anand KJS, McIntosh N, Lagercranz H, *et al.* Analgesia and sedation in neonates who require ventilatory support – results from the NOPAIN trial. *Arch Pediatr Adolesc Med* 1999;**153**:331–8. [RCT]
- Lahat E, Goldman M, Barr J, *et al.* Comparison of intranasal midazolam with intravenous diazepam for treating febrile seizures in children: prospective randomised study. *BMJ* 2000;**321**:83–6. (See also pp. 64–5.) [RCT]
- de Wildt SN, Kearns GL, Hop WCJ, *et al.* Pharmacokinetics and metabolism of intravenous midazolam in preterm infants. *Clin Pharmacol* 2001;**70**:525–31.

See also relevant Cochrane reviews

MILK FORMULAS

Use

Artificial milks designed to mimic human breast milk have been commercially available for 30 years. Modified formulas designed for use in preterm babies have been developed more recently, while formulas with a higher casein: whey ratio have now been designed for children over 6 months old. Fortifying powders are also available for use when breast milk (q.v.) is used to feed the very preterm baby.

Nutritional factors

Most milk formulas are made from protein enriched whey, skimmed milk, vegetable oils and milk fat, glucose, lactose and/or maltodextrin, with mineral and vitamin supplements.

Composition per 100 ml of various neonatal milks available in the UK

	Protein (g)	Fat (g)	Carbo- hydrate (g)	Energy (kcal)	Na (mmol)	Ca (mmol)	P (mmol)	Fe (mg)	Vit D (μ g)
Infant milks									
Farleys <i>First milk</i> [®]	1.5	3.6	7.0	68	0.8	0.9	0.9	0.6	1.0
Cow & Gate <i>Premium</i> [®]	1.4	3.5	7.5	67	0.8	1.4	0.9	0.5	1.4
SMA <i>Gold</i> [®]	1.5	3.6	7.2	67	0.7	1.2	1.1	0.8	1.1
Milupa <i>Aptamil First</i> [®]	1.5	3.6	7.2	67	0.8	1.5	1.1	0.7	1.0
Preterm milks									
Farleys <i>Osterprem</i> [®]	2.0	4.6	7.6	80	1.8	2.8	2.0	< 0.1	2.4
Cow & Gate <i>Nutriprem</i> [®]	2.4	4.4	7.9	80	1.8	2.5	1.6	0.9	5.0
SMA <i>LBW Formula</i> [®]	2.0	4.4	8.6	82	1.5	2.0	1.4	0.8	1.5
Milupa <i>Pre-Apamil</i> [®]	2.4	3.5	7.8	80	1.2	1.2	1.3	0.9	2.4
Hydrolysed protein milks with MCT									
Mead Johnson <i>Pregestimil</i> [®]	1.9	3.8	6.9	68	1.4	1.6	1.4	1.2	1.1
Cow & Gate <i>Peptijunior</i> [®]	1.8	3.6	6.6	66	0.9	1.4	0.9	0.5	1.3
Mature human breast milk									
Widdowson (1977)	1.3	4.2	7.4	70	0.7	0.9	0.5	0.1	< 0.1

A low lactose product will minimise intolerance in the very preterm baby. Specialised formulas where the protein is provided as "predigested" hydrolysed peptides and amino acids derived from casein (Pregestimil) or whey (Peptijunior) are also available. In these two products half the fat is provided as medium chain triglyceride (MCT). Advice on special products is available from hospital dietitians.

Although breast milk is the food of choice for almost every baby, most grow very well on 130–150 kcal/kg per day of any one of these formulas in the neonatal period, and can accept an oral intake of 200 ml/kg per day once feeding is fully established. In some babies of less than 2 kg, growth can be enhanced by using a nutrient enriched preterm formula. Details of four different low birth weight (LBW) formulas widely used in the UK are shown in the above table. All have a potassium content of between 1.4 mmol/100 ml and 2.0 mmol/100 ml. With the exceptions noted below, artificial milk formulas contain adequate quantities of all the nutrients, trace elements, and vitamins known to be necessary for growth in the neonatal period. In particular, there is no evidence that babies ever need further supplemental vitamin K (q.v.) once established on an artificial milk formula. Nor do babies need more folic acid (q.v.) than is provided by every one of the artificial infant milk products currently on sale in the UK, even when born preterm.

Further supplements

Sodium: Most babies of less than 30 weeks gestation require further routine sodium with their milk to bring their total intake up to between 4.5 mmol/kg and 6.0 mmol/kg per day (the equivalent to the intake provided by 150–200 ml/kg of 10% dextrose in 0.18% sodium chloride). This high need is caused by the immature kidney's limited ability to conserve sodium. The necessary extra sodium is best provided by adding a further 2 mmol of sodium chloride to every 100 ml of preterm milk formula or breast milk fed to all babies of less than 30 weeks gestation (for details see the monograph on sodium chloride). Sodium loss should also be monitored intermittently, because some very preterm babies require more supplemental sodium than most, especially in the first 2 weeks of life. If the sodium content of a "spot" urine sample is high, something is limiting renal tubular reabsorption, unless intake has been abnormally high.

continued ...

Vitamin D: Babies are known to require 5 micrograms of vitamin D a day, irrespective of their weight. The content of most artificial milk averages only 1 microgram/100 ml (with an agreed maximum of 5 micrograms/100 ml because of the risk associated with excessive intake). All preterm babies should therefore have supplemental vitamin D drops once a day until they weigh at least 3 kg. For further details see the monograph on vitamin D.

Iron: All babies have reasonable iron stores at birth, even if born prematurely, but dietary iron becomes necessary within 2–3 months to provide the additional iron needed by the child's growing red cell mass. Repeated blood sampling in babies who are ill may further reduce available body iron if the blood taken is not replaced by transfusion. All standard artificial UK milk formulas contain enough iron to provide for the needs of babies born at term, being formulated to contain much more iron than breast milk in order to compensate for poor iron absorption. The same is not true in all countries.

Most of the preterm formulas available in the UK (other than Osterpremm) contain similar supplements of iron, but there is no evidence that babies absorb this iron in the first month of life, even when they are offered it, and there are theoretical reasons for limiting early supplementation because this interferes with the antimicrobial activity of lactoferrin in the gut. However, all babies who are not breastfed should certainly be on a milk containing at least 500 micrograms/100 ml of iron by the time they are 2 months old. While it has long been traditional to provide preterm babies with further supplementation, it is now clear that this routine is quite unnecessary. For further details see the monograph on iron.

Phosphate: Human milk is capable of sustaining excellent bone growth in the full term baby, but bone growth and increased bone mineralisation is so rapid in the preterm baby that babies weighing < 1.3 kg at birth are at serious risk of rickets, and of spontaneous pathological fractures in the second and third month of life if not offered further supplementation. Both calcium and phosphorus are usually given, and all artificial preterm milk formulas provide some supplementation. Calcium and phosphorus absorption are linked and a calcium:phosphorus ratio of between 1.4:1 and 2:1 seems to optimise absorption and minimise the risk of late neonatal hypocalcaemia. Phosphorus is well absorbed and its availability appears to limit calcium absorption. It is now thought that optimum phosphorus intake in the growing preterm baby is probably provided by a milk containing between 1.3 mmol and 2.3 mmol of phosphorus per 100 ml. Human milk contains only a third of this and requires regular supplementation (see the monograph on phosphate). Additional calcium is probably not necessary if adequate phosphorus is provided. Most commercial preterm milks contain at least the minimum amount of phosphorus now recommended (see table).

Bicarbonate: Some preterm babies develop a late metabolic acidosis when on formula feeds owing to the neonatal kidney's limited ability to excrete acid. Oral bicarbonate will relieve this, improving weight gain and nitrogen retention, as described in the monograph on sodium bicarbonate.

Supply

Hospital catering departments are responsible for the supply and distribution of artificial milks. Manufacturers are now banned from subsidising the cost of prepacked milk supplied to hospitals or from providing free samples in an attempt to increase their share of the market with newly delivered mothers (this practice has been shown in nine controlled trials to reduce the number of mothers achieving a sustained lactation). Most prepacked neonatal milks cost about 25p per bottle. Equivalent volumes of Pregestimil and Poptijunior can be made up for 30p per feed. Individually packed sterile disposable teats cost about 14p each.

References

- Radde IC, Chance GW, Bailey K, et al. Growth and mineral metabolism 1. Comparison of the effects of two modes of NaHCO₃ treatment of late metabolic acidoses. *Pediatr Res* 1975;9:564–8. [RCT]
- European Society of Paediatric Gastroenterology and Nutrition (ESPGAN) Committee on Nutrition of the Preterm Baby. Nutrition and feeding of preterm infants. *Acta Paediatr Scand Suppl* 1987;(suppl 336).
- Wharton BA, ed. *Nutrition and feeding of preterm infants*. Oxford: Blackwell Scientific, 1987.
- Steer PA, Lucas A, Sinclair JC. Feeding the low birthweight infant. In: Sinclair JC, Bracken MB, eds. *Effective care of the newborn infant*. Chapter 7. Oxford: Oxford University Press, 1992:94–140. (See also pp. 161–77.) [SR]
- Tsang RC, Lucas A, Uauy R, et al, eds. *Nutritional needs of the preterm baby*. Baltimore, MA: Williams and Wilkins, 1993.
- American Academy of Pediatrics. Committee on Nutrition. Iron fortification of infant formulas. *Pediatrics* 1999;104:119–23.
- Donnelly A, Snowden HM, Renfrew MJ, Woolridge MW. Commercial hospital discharge packs for breastfeeding women. *The Cochrane Library*. Oxford: Update Software, 2000. [SR]
- Klein CJ. Nutrient requirements for preterm infant formulas. *J Nutr* 2002;132:1395S–577S.
- McGuire W, Anthony MY. Donor human milk versus formula for preventing necrotising enterocolitis in preterm infants: systematic review. *Arch Dis Child* 2003;88:F11–F14. [SR]

See also other relevant Cochrane reviews



MILIRINONE

Use

Milrinone lactate is used, together with a catecholamine such as dobutamine (q.v.), to support cardiac output in babies with septic shock. It is also increasingly used to provide short term support to babies after cardiac surgery, and is more effective, and easier to administer, than enoximone (q.v.).

Pharmacology

Milrinone is a selective phosphodiesterase inhibitor with the same properties as enoximone, first developed in 1981. There is good evidence that short term use, in conjunction with dobutamine, can reduce systemic vascular resistance and increase cardiac output. The mode of action has not been fully determined, but it seems to involve an increase in cyclic adenosine monophosphate concentration secondary to inhibition of phosphodiesterase, leading to an increase in the contractile force of cardiac muscle. A trial of long term oral use in patients with heart failure in 1991 found an unexpected, and unexplained, increased mortality in those taking milrinone. Sustained use has been avoided ever since, although recent studies have reported safe IV use for up to 8 weeks in both children and adults with endstage heart failure who are awaiting a heart transplant.

Milrinone appears to be actively excreted by the kidney, the half life being something in excess of 1 hour in healthy adults, but three times as much as this in the first year of life. Drug accumulation could occur, therefore, when there is renal failure. The volume of distribution in young children is also substantially more than in adult life, making it important to administer an initial loading dose if an early response to treatment is required (V_D in infancy ~ 0.9 l/kg). An optimal response seems to be achieved when the blood level is approximately 200 ng/ml. Mild thrombocytopenia is common when milrinone is infused for more than 24 hours. Other complications, such as arrhythmia, are rare in children. Treatment should only be contemplated after ultrasound assessment. Those ill enough to require treatment with milrinone also merit central venous pressure monitoring. Milrinone crosses the placenta. There is no evidence of teratogenicity in animals, but no published reports relating to use during human pregnancy or lactation. The manufacturers have not yet endorsed the use of milrinone in children.

Treatment

Initial treatment: Give 60 micrograms/kg IV over 15 minutes, followed by a maintenance infusion of 0.5 micrograms/kg per minute (1.0 ml of a solution made up as described below over 15 minutes, and then 0.5 ml/hour). Hypotension occurring while the loading dose is given should be corrected with extra volume. Treatment is usually necessary for only 36–48 hours. Reduce the dose if there is severe renal failure.

High dose treatment: Higher doses are sometimes necessary when first getting acute septic shock under control. Some babies have responded only after one or even two further 30 micrograms/kg loading doses followed by a continuing infusion of 0.75 or even 1 microgram/kg per minute

Compatibility

Milrinone can be added (terminally) to a line containing adrenaline, atracurium, dobutamine, dopamine, fentanyl, glyceryl trinitrate, heparin, insulin, isoprenaline, midazolam, morphine, nitroprusside, noradrenaline, propofol, ranitidine, or standard TPN. Compatibility with IV lipid has not been assessed.

Supply and administration

10 ml ampoules containing 10 mg of milrinone (as lactate) cost £17.40. Take 1.2 ml (1.2 mg) of milrinone for each kilogram the baby weighs, and dilute this to 20 ml with 10% dextrose or dextrose saline. To give an infusion of 0.5 micrograms/kg per minute, infuse this dilute solution at a rate of 0.5 ml/hour. Less concentrated solutions of dextrose or dextrose saline can be used. The drug is stable in solution, so a fresh infusion does not need to be prepared every 24 hours. Injecting furosemide into a line containing milrinone will cause precipitation.

References

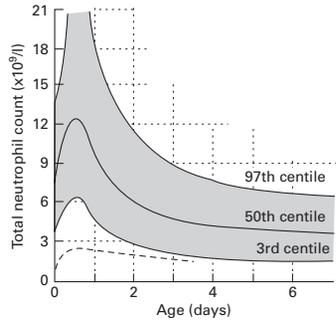
- Pridjian AK, Frohlich ED, VanMeter CH, *et al.* Pharmacologic support with high-energy phosphate preservation in the posts ischemic neonatal heart. *Ann Thorac Surg* 1995;**59**:1435–40.
- Barton P, Garcia J, Kouatli A, *et al.* Hemodynamic effects of IV milrinone lactate in pediatric patients with septic shock. A prospective, double-blinded, randomized, placebo-controlled, interventional study. *Chest* 1996;**109**:1302–12. [RCT]
- Lindsay CA, Barton P, Lawless S, *et al.* Pharmacokinetics and pharmacodynamics of milrinone lactate in pediatric patients with septic shock. *J Pediatr* 1998;**132**:329–34.
- Ramamoorthy C, Anderson GD, Williams GD, *et al.* Pharmacokinetics and side effects of milrinone in infants and children after open heart surgery. *Anesth Analg* 1998;**86**:283–9.
- Akkerman SR, Zhang H, Mullins RE, *et al.* Stability of milrinone lactate in the presence of 29 critical care drugs and 4 i.v. solutions. *Am J Health Syst Pharm* 1999;**56**:63–8.
- Bailey JM, Miller BE, Lu W, *et al.* The pharmacokinetics of milrinone in pediatric patients. *Anesthesiology* 1999;**90**:1012–18.
- Hoffman TM, Wernovsky G, Atz A, *et al.* Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. *Circulation* 2003;**107**:996–1002. [RCT]
- Paradis M, Evans N, Osborn D, *et al.* Pilot study for prevention of low blood flow to brain and upper body in very preterm infants [Abstract]. *Pediatr Res* 2003;**53**:418A.

Use

Molgramostim, a granulocyte-macrophage colony-stimulating factor (GM-CSF), and filgrastim (q.v.), a granulocyte colony-stimulating factor (G-CSF), both stimulate the production and release of white blood cells from bone marrow. Whether either can be effective, prophylactically or therapeutically, in combating neonatal bacterial or fungal infection, remains to be established.

Pathophysiology

Neutrophil white cells (so called because they form a thin white line above the red cells when blood is spun, and turn neither red nor blue when stained) engulf and kill bacteria. They usually remain in circulation for only ~6 hours after leaving the bone marrow pool before entering other body tissues. Birth causes a transient increase in the number in circulation (see figure), especially when this is stressful. Neonatal sepsis can rapidly decrease the number in circulation, because production is already close to its peak at birth. This, and functional immaturity, make babies more vulnerable to infection. Babies of < 1.5 kg often have very low counts when 2–4 weeks old, when the marrow mounts a first response to the growing postdelivery anaemia, as well as during the first 3–4 days (dotted line on figure). Whether they are at more risk of infection is not known.



Pharmacology

Marrow colony-stimulating factors are naturally occurring glycoprotein growth promoters (cytokines) that stimulate the proliferation and differentiation of red and white blood cell precursors in the bone marrow. A number of these factors – including erythropoietin (q.v.) – have been produced by recombinant DNA technology and brought into clinical use in the last 10 years. G-CSF is now used routinely to prevent chemotherapy induced neutropenia, and to accelerate neutrophil recovery after bone marrow transplantation. Subcutaneous rather than IV use doubles the elimination half life to about 3 hours, increases therapeutic efficacy, and minimises the risk of toxicity associated with high peak blood levels. Adverse effects, including fever, dyspnoea, nausea, and vomiting, seem to have been uncommon with neonatal use. Administration during pregnancy is associated with increased fetal death in primates. Its use during lactation has not been studied but it seems unlikely, on theoretical grounds, to pose any serious risk.

Both G-CSF and GM-CSF have been shown to abolish the postnatal neutropenia, and the sepsis induced neutropenia, seen in preterm neonates, and to augment neutrophil function. GM-CSF enhances both neutrophil and monocyte production and function, but may have proinflammatory side effects. Prophylactic use did not reduce the incidence of later infection in the only neonatal trials completed to date, but it did improve survival in one recent small trial in babies with overt infection. Long term safety is not yet established, and the manufacturers have not yet endorsed its use in children, but a UK trial of prophylactic GM-CSF (PROGRAMS) in babies who are light for dates (< 10th centile), less than 32 weeks gestation, and less than 72 hours old continues to recruit. For details contact Dr Modi (email: n.modi@imperial.ac.uk). G-CSF provokes a more rapid rise in the neutrophil count, and a trial of this product in babies with suspected sepsis could serve to test an alternative, focused, treatment strategy (as outlined in the monograph on filgrastim).

Treatment

10 micrograms/kg is usually given subcutaneously once a day for 5 (or 7) days. Inject the cytokine subcutaneously into alternate thighs using a 1 ml syringe and a 26 or 27 French gauge needle.

Supply and administration

Reconstitute 150 microgram (1.67 million unit) vials of molgramostim (costing £42 each) with 1.5 ml of water to obtain a preparation containing 100 micrograms/ml. Store vials at 4°C and use within 24 hours of reconstitution, even if refrigerated. The product contains human albumin. The related product sargramostim is in use in North America.

References

- Schibler KR, Osborne KA, Leung LY, *et al.* A randomised placebo-controlled trial of granulocyte colony-stimulating factor administration to newborn infants with neutropenia and clinical signs of early-onset sepsis. *Pediatrics* 1998;**102**:6–13. [RCT]
- Cairo MS, Agosti J, Ellis R, *et al.* A randomised double-blind placebo-controlled trial of prophylactic recombinant human granulocyte-macrophage colony-stimulating factor to reduce nosocomial infection in very low birth weight neonates. *J Pediatr* 1999;**134**:64–70. [RCT]
- Carr R, Modi N, Doré CJ, *et al.* A randomised, controlled trial of prophylactic granulocyte-macrophage colony-stimulating factor in human newborns less than 32 weeks gestation. *Pediatrics* 1999;**103**:796–802. [RCT]
- Modi N, Carr R. Promising stratagems for reducing the burden of neonatal sepsis. *Arch Dis Child* 2000;**83**:F150–3.
- Bilgin K, Yaramis A, Haspolat K, *et al.* A randomised trial of granulocyte-macrophage colony-stimulating factor in neonates with sepsis and neutropenia. *Pediatrics* 2001;**107**:36–41. [RCT]

Use

Morphine is the best studied neonatal analgesic. Use a loading dose and continuous infusion.

Pharmacology

Morphine, the principle alkaloid of opium, has been used medicinally for well over 2000 years. A pure extract was obtained from poppy heads in 1805. It is well absorbed when taken by mouth but undergoes rapid first pass metabolism in the liver (bioavailability about 30%). The half life in the preterm baby is 6–12 hours and *very* variable, but inversely related to gestational age at birth. Some tissue accumulation occurs after multiple dose administration ($V_D \sim 2$ l/kg). Elimination becomes much more rapid in babies more than 2 months old, the half life in 1–6 year old children (about 1 hour) being less than in adults. Ordinary doses cause constipation, urinary retention, and respiratory depression, while an overdose can cause hypotension, bradycardia, and even (rarely) fits. One study suggests that full pain relief in the neonatal period may require a blood level of about 120 ng/ml, while adverse effects start to appear at levels exceeding 300 ng/ml. Lower levels (20–40 ng/ml) seem adequate in older children. The high levels required in the newborn may reflect drug receptor differences, and low glucuronide (M6G) metabolite levels. Tolerance may develop with prolonged treatment and withdrawal symptoms can also occur. Addiction has not been seen with neonatal use for pain relief. Morphine crosses the placenta readily, causing some neonatal depression (as discussed in the monograph on pethidine), but use during lactation probably exposes the baby to only a tenth of the maternal dose on a weight for weight basis. Maternal addiction is discussed in the monograph on diamorphine.

Treatment

Opioid withdrawal: Give 40 micrograms/kg by mouth once every 4 hours. Double the dose interval as soon as symptoms are controlled and then reduce the dose. Aim to stop treatment after 6–10 days.

Severe or sustained pain: Provide ventilatory support, give a loading dose of 240 micrograms/kg, and then a maintenance infusion of 20 micrograms/kg per hour (12 ml/hr of a solution prepared as described below **for 1 hour**, followed by a maintenance infusion of 1 ml/hour). While this will usually control even severe pain in the first 2 months of life, providing a plasma morphine level of 120–160 ng/ml, treatment *has* to be individualised (as discussed in the web commentary). Staff need discretion to give a further 20 micrograms/kg bolus up to once every 4 hours to control any "breakthrough" pain.

Sedation while ventilated: Babies given a loading dose and a maintenance dose **half** as large as that recommended for managing severe pain seldom breathe out of phase with the ventilator.

Short term pain relief: Give 100 micrograms/kg IM or IV (or twice this by mouth). Rapid IV administration does *not* cause hypotension but may cause respiratory depression. A further 50 micrograms/kg dose can usually be given after 6 hours without making ventilator support necessary.

Older children: While the dose needed by any baby more than 2 months old might be expected to rise, because drug clearance becomes more rapid, the plasma level needed to provide pain relief seems to fall. The interplay between these factors has not yet been studied. Use the above guidance as a starting point and then individualise treatment.

Compatibility

Compatibility with other continuously infused drugs is noted, where known, in the monographs for the products concerned. Morphine can also be added (terminally) to an IV line containing standard TPN.

Antidote

Naloxone (q.v.) is a specific opioid antagonist.

Supply and administration

Ampoules of morphine sulphate containing 10 mg in 1 ml are available at a cost of 72p each. The use of a preservative free ampoule will reduce the risk of phlebitis. **Always** start by diluting the contents 10-fold for accurate neonatal administration. For single bolus doses, 0.1 ml of morphine can be made up to 1 ml with 0.9% sodium chloride, giving a solution of 1 mg/ml. To set up a continuous infusion, dilute the 1 ml of fluid from the ampoule to 10 ml with 0.9% sodium chloride (as above), place 1 ml of this diluted preparation for each kilogram the baby weighs in a syringe, dilute to 50 ml with 10% dextrose or dextrose saline, and infuse at 1 ml/hour to provide an infusion of 20 micrograms/kg per hour. The drug is chemically stable in solution so the infusate does not need to be changed daily.

The storage and administration of morphine is controlled under Schedule 2 of the UK Misuse of Drugs Regulations 1985 (Misuse of Drugs Act, 1971).

References

- Olkkola KT, Hamunen K, Maunuksela E-L. Clinical pharmacokinetics and pharmacodynamics of opioid analgesics in infants and children. *Clin Pharmacokinet* 1995;28:385–403.
van Lingen RA, Simons SHP, Anderson BJ, *et al*. The effects of analgesia in the vulnerable infant during the perinatal period. *Clin Perinatol* 2002;29:511–34.

Use

This antibiotic ointment has been used to treat staphylococcal skin infections and to control surface colonisation by methicillin resistant staphylococci.

Pharmacology

This unusual antibiotic, a fermentation product of the bacterium *Pseudomonas fluorescens*, was formerly called pseudomonic acid. It is structurally unlike any other antibiotic, containing a unique hydroxy-nonanoic acid linked to monic acid. It is bacteriostatic in low concentrations and slowly bactericidal at high concentrations against *Mycoplasma* and most Gram positive aerobes in an acid environment such as that provided by the skin (pH 5-5). It is non-toxic but rapidly de-esterified and rendered inert by the tissues after parenteral injection, making the drug suitable only for topical use. The drug first came into clinical use in 1988. Microbiological advice should be taken before using mupirocin, and the product should be used for only a limited period to minimise the risk of drug resistance developing. There has been one report suggesting that mupirocin may be more effective in treating candidal skin infection than in vitro assessments of its sensitivity would suggest; further controlled studies seem called for. The drug may be of value in eliminating the chronic nasal carriage of pathogenic staphylococci by staff. Localised skin reactions have occasionally been reported. Transient stinging can occur. There is no evidence of teratogenicity, and nothing to suggest that mupirocin needs to be avoided during pregnancy or lactation in situations where its use seems otherwise justified on clinical grounds.

Treatment

Use on the skin (avoiding the eyes) three times a day for not more than 10 days.

Supply

Mupirocin ointment (2% w/w) is available in 15 g tubes costing £4.70 each. This formulation uses a macrogol (polyethylene glycol) base, and it is possible that renal toxicity could result from macrogol absorption through mucous membranes, or through extensive application to thin or damaged neonatal skin. In that situation the equivalent paraffin based formulation of calcium mupirocin may be preferable; this is currently marketed as an ointment officially designed for nasal use in 3 g tubes costing £6.20. A cream is also available but this contains benzyl alcohol.

References

Davies EA, Emmerson AM, Hogg GM, *et al.* An outbreak of infection with a methicillin resistant *Staphylococcus aureus* in a special care baby unit: value of topical mupirocin and traditional methods of infection control. *J Hosp Infect* 1978;**10**:120-8.
 Rode H, de Wet PM, Millar AJW, *et al.* Bactericidal efficacy of mupirocin in multi-antibiotic resistant *Staphylococcus aureus* burn wound infection. *Antimicrob Agents Chemother* 1988;**21**:589-95. (See also 1989;**24**:78-9.)
 Britton JW, Fajardo JE, Krafte-Jacobs B. Comparison of mupirocin and erythromycin in the treatment of impetigo. *J Pediatr* 1990;**117**:827-9.
 Rode H, de Wet PM, Millar AJW, *et al.* Efficacy of mupirocin in cutaneous candidiasis. *Lancet* 1991;**338**:578.
 Tan KW, Tay L, Lim SH. An outbreak of methicillin-resistant *Staphylococcus aureus* in a neonatal intensive care unit in Singapore: a 20 month study of clinical characteristics and control. *Singapore Med J* 1994;**35**:277-82.

Use

Naloxone reverses the respiratory depression sometimes caused by the use of opioids such as codeine, dextropropoxyphene, diamorphine (heroin), fentanyl, meptazinol (Meptid[®]), methadone, morphine, nalbuphine (Nubain[®]), papaveretum (Omnopon[®]), pentazocine (Fortral[®]), and pethidine (q.v.). Inevitably, however, naloxone interferes with the ability of these drugs to reduce pain.

Pharmacology

Naloxone is a potent pure opioid antagonist, first discovered in 1961. It crosses the placenta rapidly but is not known to be teratogenic. Large doses can be given without apparent toxicity (except in patients dependent on opioids) and repeated use does not cause dependence or tolerance. The drug is largely metabolised by glucuronide conjugation. The plasma half life is 1–3 hours immediately after birth but approaches that seen in adults (65 minutes) within a few days ($V_D \sim 2.5$ l/kg). The drug is widely used, but even more widely abused, in the "resuscitation" of babies at birth. Since it is a specific opioid antagonist, it can have no place whatsoever in the resuscitation of a baby who has not been rendered drowsy by maternal analgesia. Even in these babies the drug is of no use during primary cardiorespiratory resuscitation; its only role is to check that opioid depression is not causing continued respiratory depression *after* breathing has been established (artificially if necessary) and *after* a reliable sustained cardiac output has been secured. Intratracheal administration is safe but almost never called for if the steps involved in resuscitation are conducted in a logical order.

However, lesser degrees of opioid depression can last quite a long time. A large maternal dose of pethidine during labour can sometimes make a baby drowsy and reluctant to feed for 2 days. While a single IV dose of naloxone will immediately reverse this depression, the benefit will be only transient because pethidine has such a long half life and naloxone such a short half life. Luckily, a single 100 micrograms/kg IM dose of naloxone seems to produce a drug "depot" at the site of the injection that generates an effective plasma level of naloxone for at least 24 hours. Only rarely is a further IM dose necessary on the second day of life. Continuous infusions of naloxone have been used to counteract accidental opiate poisoning in infancy. Such babies present with drowsiness, respiratory depression, and pinpoint pupils. Hypotension is not uncommon and fits may occur. Infusions have also been used, anecdotally, to counteract the effect of the body's own endogenous opioids (β endorphins) when their excessive release in severe septic shock lowers blood pressure and reduces cardiac output. Try the effect of a bolus dose first. Methylene blue (q.v.) has also been used experimentally for the same purpose.

Treatment

Opioid sedation at birth: 100 micrograms/kg (0.25 ml/kg of "adult" naloxone) IM has a gradual effect as an opioid antagonist, but an effect that is sustained for 24 hours. Treatment may be repeated if necessary. It is not necessary to calculate a precise weight related dose; an initial 200 microgram dose, irrespective of weight, provides a pragmatic delivery room approach suitable for most babies.

IV use: A 100 micrograms/kg dose is of diagnostic help in opioid poisoning. A continuous infusion of 100 micrograms/kg per hour in dextrose or dextrose saline has occasionally been used.

Contraindications

Administration of naloxone to the baby of an opiate dependent mother could precipitate withdrawal symptoms. Nevertheless there is, at the moment, only one published report of this precipitating seizures during resuscitation (see web commentary). The mother had taken a very high dose of methadone (60 mg) 8 hours earlier and documented fetal distress complicates the interpretation of this isolated case report.

Supply

1 ml (400 microgram) ampoules of naloxone marketed for "adult" use are available costing £4.50 each. 40 microgram "neonatal" ampoules are also available but not so useful. Midwives can give 100 micrograms/kg IM on their own authority to counteract the depressive effect of maternal opioid medication if the baby remains sleepy after neonatal resuscitation is complete.

References

- Werner PC, Hogg MI, Rosen M. Effects of naloxone on pethidine-induced neonatal depression. Part II – intramuscular naloxone. *BMJ* 1977;ii:229–31.
- Morland TA, Brice JEH, Walker CHM, *et al.* Naloxone pharmacokinetics in the newborn. *Br J Clin Pharmacol* 1979;9:609–12.
- Tenenbein M. Continuous naloxone infusion for opiate poisoning in infancy. *J Pediatr* 1984;105:645–8.
- Furman WL, Menke JA, Barson WJ, *et al.* Continuous naloxone infusion in two neonates with septic shock. *J Pediatr* 1984;105:649–51.
- American Academy of Pediatrics. Committee on drugs. Naloxone dosage and route of administration for infants and children: addendum to emergency doses for infants and children. *Pediatrics* 1990;86:484–5. (See also 101:1085.)

See also relevant Cochrane review



Use

Neostigmine and edrophonium are used in the diagnosis and treatment of myasthenia.

Myasthenia

Myasthenia gravis is an acquired autoimmune disorder causing progressive muscle fatigue and weakness. About 10–15% of the babies born to mothers with myasthenia are affected by transient neonatal myasthenia due to transfer from the maternal circulation of antibodies directed against the acetylcholine receptors of the muscle–nerve junction. Symptoms present within 1–3 days and usually persist for 3–6 weeks. There is no way of knowing before birth whether a baby is going to be affected or not, but most affected babies have mothers with high antibody titres and a history of affected siblings. The presence of hydramnios predicts severe involvement. In contrast, maternal disease is sometimes recognised only when the baby presents with symptoms at birth. Symptoms persist for months in the other congenital, recessively inherited, forms of myasthenia, although they usually become less severe with time. Respiratory and feeding difficulties may cause prolonged apnoea, aspiration, and even death. Hypotonia is common and stridor can be a problem. Some babies have multiple joint contractures (arthrogryposis) at birth. Ptosis (a drooping of the upper eye lid) is usually seen only in babies with maternally acquired autoimmune disease. Aminoglycoside antibiotics are hazardous in patients with any of the myasthenic disorders because they interfere with neuromuscular transmission, causing respiratory depression. Some congenital myasthenic syndromes do not respond to neostigmine.

Pharmacology

Neostigmine (first developed in 1931) inhibits cholinesterase activity. It prolongs and intensifies the muscarinic and nicotinic effects of acetylcholine, causing vasodilatation, increased smooth muscle activity, lacrimation, salivation, and improved voluntary muscle tone. It is therefore the drug of choice in the management of both maternal and neonatal myasthenia gravis. IV edrophonium has a similar and much more rapid effect, but the response frequently lasts only 5–10 minutes. For this reason, most clinicians now prefer to use IM neostigmine methylsulphate (with or without atropine to control any side effects) for both diagnostic and maintenance purposes since this produces a response lasting 2–4 hours after a latent period of 20–30 minutes. Other rarer disorders require more complex diagnostic techniques (see paper by Matthes *et al.*).

Diagnostic use

Always have 15 micrograms/kg of IV atropine on hand to control any undue salivation, and equipment to control unexpected respiratory arrest.

Edrophonium: Give 20 micrograms/kg IV followed, after 30 seconds, by a further 80 micrograms/kg IV if there is no adverse effect. Watch for bradycardia or arrhythmia. Double this dose has been used.

Neostigmine methylsulphate: Use a 150 micrograms/kg IM test dose.

Treatment

Short term management: 150 micrograms/kg of neostigmine methylsulphate subcutaneously, or IM, once every 6–8 hours is usually used for maintenance, but twice this dose may be necessary once every 4 hours. Oral treatment with neostigmine bromide can be used once control is achieved. An oral dose that is 10–20 times the IM maintenance dose will need to be given every 3 hours.

Long term management: Oral pyridostigmine (another anticholinesterase) is probably preferable in the long term management of myasthenia because it has a slightly longer duration of action. The usual starting dose is 1 mg/kg by mouth every 4 hours (unless the child is asleep). Adjust later as necessary.

Reversing drug induced muscle paralysis: The effects of non-depolarising muscle relaxants such as pancuronium (q.v.) can be largely reversed by giving 20 micrograms/kg of IV atropine followed by one, or occasionally two, 40 micrograms/kg doses of neostigmine.

Supply

1 ml (2.5 mg) ampoules of neostigmine methylsulphate for IM use cost 58p each. For accurate administration take the contents of the ampoule and dilute to 16.5 ml with dextrose or dextrose saline immediately before use, to give a solution containing approximately 150 micrograms/ml. 1 ml (10 mg) ampoules of edrophonium (costing £4.80) are also available on request. Inexpensive oral suspensions of neostigmine bromide or pyridostigmine in syrup are available on request.

References

- Morel E, Eymard B, Vernet de Gatabedian B, *et al.* Neonatal myasthenia gravis: a new clinical and immunological appraisal of 30 cases. *Neurology* 1988;**38**:138–42.
- Matthes JWA, Kenna AP, Fawcett PRW. Familial infantile myasthenia: a diagnostic problem. *Dev Med Child Neurol* 1991;**33**:924–9.
- Dubowitz V. *Muscle disorders in childhood*, 2nd ed. London: Saunders, 1995:298–421.
- Volpe J. *Neurology of the newborn*, 4th ed. Philadelphia, PA: Saunders, 2001:657–70.

NETILMICIN

Use

Netilmicin is an alternative to gentamicin (q.v.) in the treatment of Gram negative bacterial infection.

Pharmacology

Netilmicin, first developed in 1976, is an aminoglycoside antibiotic with properties very similar to gentamicin. Although it is sometimes effective against organisms (such as coagulase negative staphylococci) that are resistant to gentamicin, it is rather less active against *Pseudomonas*. Netilmicin is less ototoxic but currently costs more than gentamicin.

All aminoglycosides cross the placenta (producing fetal levels that are about half the maternal level), but streptomycin and kanamycin are the only products known to have caused ototoxicity in utero. All have to be given IM or IV. Too little is absorbed from the gut for there to be any contraindication to maternal use during lactation (although the baby's gut flora could be altered). Aminoglycosides undergo no change in the body, but are passively filtered by the glomerulus and concentrated in the urine. The resultant half life is inversely related to postmenstrual age, but also falls significantly during the first week after delivery. It averages 12 hours in babies of less than 28 weeks gestation at birth, but falls to 6 hours in term babies more than 1 week old. All aminoglycosides are potentially toxic to the ear and kidney. Damage to the renal tubules builds up with time (and can even produce a Bartter-like syndrome), but this is reversible when treatment is stopped and is seldom severe. Simultaneous treatment with vancomycin (q.v.) can increase these difficulties. Ear problems are uncommon in young children, but netilmicin can cause balance problems as well as high tone deafness, which may be permanent if early symptoms go unrecognised (as they will in the neonatal period). While many units measure blood levels routinely in order to minimise this risk, it is *at least* as important to avoid simultaneous treatment with furosemide (q.v.), and to try to stop treatment after 7–10 days. Products marketed in North America come with routine guidance about the need to give an IV dose slowly over 30 minutes, but no such advice is issued with any of the products on sale in Europe. There are theoretical reasons for not giving a β lactam penicillin or cephalosporin at precisely the same time as an aminoglycoside (as outlined in the monograph on tobramycin), but the clinical relevance of this finding has not yet been clarified.

Treatment

Intermittent high dose treatment: Start by giving 5 mg/kg IV or IM once every 24 hours. If the trough serum level when the third dose was given exceeded 2 mg/l, increase the dosage interval to 36 hours and check the level again after two more doses have been given. The rationale for this regimen is outlined in the monograph on gentamicin. IV doses do *not* need to be given slowly over 30 minutes.

Conventional twice daily treatment: Some clinicians still give term babies 4 mg/kg IV or IM once every 12 hours (once every 8 hours in babies over 6 months). Always give a 6 mg/kg loading dose first.

Blood levels

Measure the trough blood level just before the third dose is given (unless treatment is about to be stopped), especially if the baby is unwell or less than 10 days old, and recheck this level every few days if renal function is poor. Peak levels need to be measured only when a non-standard treatment policy is used. Collect a minimum of 0.2 ml of serum immediately before and (if necessary) 60 minutes after IV administration (remembering to calculate the time taken for the drug to pass down the giving set) and give the laboratory details of every antibiotic being used. Aim for a peak concentration in the serum of 9–12 mg/l, and a trough level of about 1 mg/l (1 mg/l = 2.1 μ mol/l). Extend the dosage interval if the trough level exceeds 2 mg/l. A high trough level can be a very helpful early sign of poor renal function, but a low level does not mean ototoxicity will not develop. Samples should be spun and frozen if not analysed promptly.

Supply

1.5 ml ampoules containing 10 mg/ml are available (costing £1.50 each).

References

- Coulthard MG. Maturation of glomerular filtration in preterm and mature babies. *Early Hum Dev* 1985;11:281–92.
- Koren G, James A, Perlman M. A simple method for estimation of glomerular filtration rate by gentamicin pharmacokinetics during the routine monitoring of the newborn. *Clin Pharmacol Ther* 1985;38:680–5.
- Ettlinger JJ, Bedford KA, Lovering AM, *et al*. Pharmacokinetics of once-a-day netilmicin (6 mg/kg) in neonates. *J Antimicrob Chemother* 1996;38:499–505.
- Borradori C, Fawer C-L, Bucin T, *et al*. Risk factors of sensorineural hearing loss in preterm infants. *Biol Neonat* 1997;17:1–10.

Use

Nevirapine is an oral antiviral drug that is active against the human immunodeficiency virus (HIV-1). Resistance develops rapidly if it is used on its own, but short term use is a powerful way of preventing babies of HIV infected women becoming infected themselves during delivery, even when more complex treatment regimens are unaffordable. Twice weekly use may also reduce the risk of infection during lactation.

Pharmacology

Nevirapine is a *non*-nucleoside reverse transcriptase inhibitor that binds to the membrane of the HIV virus, inhibiting viral replication. It also probably inactivates cell-free virions present in the genital tract and in human milk. It is best used synergistically (see below) with at least one nucleoside reverse transcriptase inhibitor drug, the most widely studied of which is zidovudine (q.v.). Nevirapine is well absorbed by mouth, widely distributed ($V_D \sim 1.2$ l/kg), penetrates the cerebrospinal fluid well and, because it is lipophilic, rapidly transferred across the placenta. A substantial quantity appears in breast milk. There is no evidence of teratogenicity. It is extensively metabolised by the P450 cytochrome isoenzyme system in the liver, with a half life of 40–60 hours when treatment is first started, a half life that is almost halved by enzyme autoinduction after 1–2 weeks. It is also reduced in patients on rifampicin (q.v.), but extended in patients taking a range of other drugs including cimetidine, erythromycin, and fluconazole (q.v.). The most important adverse effects occasionally seen with sustained use are a skin rash (which is sometimes severe) and liver dysfunction (which is reversible if treatment is stopped).

Postdelivery care of babies born to HIV infected mothers

Without treatment, at least a fifth of babies born to infected mothers will themselves become infected. A third of these will die, or become ill with AIDS by the time they are 6 years old. Most will become symptomatic within 5–11 months. The higher the mother's viral load the greater the risk of transmission. Vertical infection can be taken to have occurred if virus or antigen is detected (using a viral DNA polymerase chain reaction probe) in blood samples taken on two separate occasions (excluding any sample taken at birth because of the risk of contamination with maternal blood). One of these samples should be collected at least 4 months after birth. Conversely, freedom from infection can be presumed once two separate blood samples from the baby are antibody negative and no virus or antigen has ever been detected (remembering that transplacentally acquired maternal antigen can persist in the baby for up to 18 months). With appropriate treatment it has recently become possible to reduce the risk of vertical transmission to 1%. However, expert advice **must** be sought because the most appropriate strategy for the mother often involves the use of more than one drug, and is currently subject to frequent revision. For up to date information see the website: www.AIDSinfo.nih.gov

Intrapartum prophylaxis

Mothers already taking zidovudine: Give zidovudine to the mother and baby as outlined in the monograph on this drug. Whether it is also worth giving nevirapine (as below) is difficult to prove.

Other mothers: Give a single 200 mg oral dose of nevirapine to the mother in labour, and a 2 mg/kg dose of oral nevirapine to the baby at 2 days. Give zidovudine as well if possible.

Postdelivery treatment

Start with 120 mg/m² (~8 mg/kg for a term baby at birth). Give this once a day for 2 weeks, and then twice a day for 2 weeks. Then give 200 mg/m² twice a day indefinitely, unless a rash or other serious side effect develops. Such treatment should be contemplated only when there is at least some provisional evidence that the baby has become infected, as discussed in the monograph on lamivudine.

Supply

200 mg nevirapine tablets cost £2.80 each; a 10 mg/ml suspension is also available (100 ml costs £21).

References

- Mirochnick M, Clarke DF, Dorenbaum A. Nevirapine. Pharmacokinetic considerations in children and pregnant women. *Clin Pharmacokinetics* 2000;**39**:281–93.
- Thorne C, Newell ML. Epidemiology of HIV infection in the newborn. *Early Hum Dev* 2000;**58**:1–16.
- Lyall EGH, Blot M, de Ruiter A, *et al*. Guidelines for the management of HIV infection in pregnant women and the prevention of mother-to-child transmission. British HIV Association. *HIV Medicine* 2001;**2**:314–34. [SR] (available on: www.bhiva.org).
- Bardsley-Elliott A, Perry CM. Nevirapine. A review of its use in the prevention and treatment of paediatric HIV infection. *Paediatr Drugs* 2000;**2**:373–407.
- US Public Health Service Task Force. Recommendations for the use of antiretroviral drugs in pregnant women infected with HIV-1 for maternal health and for reducing perinatal transmission in the United States. Available from: URL: www.AIDSinfo.nih.gov
- Dabis F, Ekpini ER. HIV-1/AIDS and maternal and child health in Africa. *Lancet* 2002;**359**:2097–104. [SR]
- Volmink J. Mother to child transmission of HIV. *Clin Evid* 2003;**9**:785–94 (and updates). [SR]
- Moodley D, Moodley J, Coovadia H, *et al*. A multicenter randomised controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *J Infect Dis* 2003;**187**:725–35. [RCT]

See also relevant Cochrane review



NIFEDIPINE

Use

Nifedipine is a smooth muscle relaxant used to manage hypertension, cardiomyopathy, angina, and Raynaud's phenomenon. It seems to inhibit preterm labour better than ritodrine or salbutamol (q.v.).

Pharmacology

Nifedipine, first introduced in 1968, is one of a range of oral drugs to cause a reduction in vascular tone (including coronary artery tone) by reducing slow-channel cell membrane calcium uptake. All calcium channel blocking drugs also reduce cardiac contractility, but the vasodilator effect of nifedipine is more influential than the myocardial effect. Nifedipine also reduces uterine muscle tone. It is rapidly absorbed when taken by mouth (having some effect within 5 minutes if the liquid capsule is bitten open before being swallowed) and then metabolised by the liver (adult half life 2–3 hours) before being excreted in the urine. Experience is limited, and the manufacturers are not prepared to recommend the use of this antihypertensive drug in childhood, or in pregnancy (and there are two reports of brief, but profound, muscle weakness associated with simultaneous magnesium sulphate use (q.v.)), but there is no evidence of teratogenicity in humans. Breastfeeding is not contraindicated because the baby will receive only about 3% of the maternal dose when intake is calculated on a weight for weight basis.

Controlling preterm labour

Unexplained spontaneous preterm labour accounts for more than half of all births before 32 weeks gestation. Obstetric intervention has yet to make any impact on this cause of preterm birth. Indometacin (q.v.), ethanol (alcohol), nifedipine, and the betamimetics terbutaline and salbutamol (q.v.), are all capable of delaying delivery for 2–3 days, but nifedipine is the only tocolytic that has yet been shown to inhibit labour for long enough to reduce the number of babies requiring intensive care. It also halved the number delivering within 7 days in one small trial. Atosiban, an oxytocin receptor antagonist introduced in 1998, may be equally effective and, like nifedipine, does not cause any of the side effects seen with betamimetic use. Atosiban has to be given IV (6.75 mg over 1 minute followed by 18 mg/hour for 3 hours and then 6 mg/hour for not more than another 45 hours), while nifedipine is given by mouth. Antibiotic treatment does nothing to delay delivery in uncomplicated preterm labour as the large ORACLE trial showed, but treatment with erythromycin (q.v.) *did* delay delivery and improve neonatal outcome in women with preterm, prelabour rupture of the membranes in this trial.

Treatment

Controlling preterm labour: Crush one 10 mg capsule between the teeth to achieve sublingual absorption. Up to three further doses may be given at 15 minute intervals if uterine contractions persist. If this stops labour, give between 20 mg and 50 mg of modified release nifedipine three times a day for 3 days. Some then recommend maintenance with 20 mg 3 times a day until pregnancy reaches 34 weeks.

Hyperinsulinaemic hypoglycaemia: 100–200 micrograms/kg by mouth once every 6 hours seem to improve glucose control in some patients also taking diazoxide (q.v.). When there is no response, doubling or tripling the dose may occasionally be helpful. Watch for hypotension.

Hypertension in children: 200–500 micrograms/kg by mouth every 6–8 hours is now increasingly used to control hypertension, and to treat angina in Kawasaki disease. Start with the lowest dose and increase as necessary. Consider managing the initial reduction in pressure in a controlled way using IV labetalol (q.v.), especially if hypertension has existed for a sustained, or unknown, time.

Supply

10 mg nifedipine capsules cost 5p each. A range of modified release tablets and capsules are available; a sustained release tablet that needs to be taken only once a day is now also available for use in adults. A 20 mg/ml (1 mg per drop) dropper bottle formulation is importable on a "named patient" basis for babies. A suspension containing 1 mg/ml could be prepared on request but stability is uncertain, especially with exposure to light. No IV or IM formulation is available.

5 ml vials containing 37.5 mg of atosiban acetate cost £55.

References

- Bas F, Darendeliler F, Demirkol D, *et al.* Successful therapy with calcium blocker (nifedipine) in persistent neonatal hyperinsulinaemic hypoglycaemia of infancy. *J Pediatr Endocrinol Metab* 1999;**12**:673–8.
- Papatsonis DNM, Kok JH, van Geijn HP, *et al.* Neonatal effects of nifedipine and ritodrine for preterm labour. *Obstet Gynecol* 2000;**95**:477–81. [RCT]
- Romero R, Sibai BM, Sanchez-Ramos L, *et al.* An oxytocin receptor antagonist (atosiban) in the treatment of preterm labour: a randomised double-blind, placebo-controlled trial with tocolytic rescue. *Am J Obstet Gynecol* 2000;**182**:1173–83. (See also pp. 1191–9.) [RCT]
- Blaszsek RT, Savage JA, Ellis EN. The use of short-acting nifedipine in pediatric patients with hypertension. *J Pediatr* 2001;**139**:34–7.
- Adcock KM, Wilson JT. Nifedipine labelling illustrates the pediatric dilemma for off-patent drugs. *Pediatrics* 2002;**109**:319–21.
- Byrne B, Morrison J. Preterm birth. *Clin Evid* 2003;**9**:1601–15 (and updates). [SR]

See also relevant Cochrane reviews



Use

Nitric oxide (NO) use can reduce the need for extracorporeal membrane oxygenation (ECMO) in babies of ≥ 34 weeks gestation with persisting high pulmonary vascular resistance, but survival is not increased. No trial has yet shown treatment to be of any lasting benefit in babies less mature than this. Prior ECG is essential to confirm pulmonary hypertension and exclude structural heart disease.

Pharmacology

It has long been realised that one influence on the muscles that surround all blood vessels is a "relaxing factor" produced in the vessel's endothelial lining cells. That "factor" was finally shown, in 1987, to be NO. This small, elusive molecule influences blood flow by affecting vessel tone and inhibits labour by reducing uterine muscle tone. It also influences macrophage function and acts as a neurotransmitter. Breathing this highly diffusible colourless gas can reduce the tone of blood vessels in the lung and, because the gas has only a very short half life in the body (2–4 seconds), it can lower pulmonary vascular resistance without lowering systemic blood pressure. Whether an equally effective response can be achieved with an endotracheal bolus of tolazoline (q.v.) or nebulised epoprostenol or nitroprusside (q.v.) remains to be more formally evaluated. "Rescue" treatment is of only transient benefit in babies of < 34 weeks gestation, but a further large trial in the USA is currently assessing whether earlier intervention may be more effective.

Excess NO enters the blood stream, where it is quickly inactivated, combining with haemoglobin to produce methaemoglobin. Although this molecule is inert, its existence reduces the oxygen carrying capacity of the blood. The level should therefore be checked 1 hour after treatment is started and then once every 12 hours, aiming to keep the level below 2.5%. Try to reduce the dose of NO if the level exceeds 4%, and give methylene blue (q.v.) if it exceeds 7%. Many trials have limited recruitment to babies with a platelet count of $>50 \times 10^9/l$, international normalised ratio (INR) < 2 and/or a partial thromboplastin time of < 72 seconds because NO increases the risk of haemorrhage by inhibiting platelet aggregation, but its use does not usually seem to cause a bleeding problem. NO reacts with oxygen to form nitrogen dioxide; the level of this needs to be monitored because some byproducts are toxic. Leakage could put staff at risk unless environmental alarms are in place and poorly ventilated working areas need a gas scavenging system, but modern delivery systems address both these issues.

Neonatal use

Starting treatment: Start by adding 20 parts per million (ppm) of NO to the ventilator gas circuit. If this produces a response (a rise of at least 3 kPa in postductal arterial pO_2 within 15 minutes while ventilator settings are held constant) the amount given should be reduced, after 1 hour, to the lowest dose compatible with a sustained response. Babies of less than 34 weeks gestation should normally be started on a dose of 5 ppm, although occasionally a response may be seen only with a dose four or eight times as high as this. Stop treatment promptly if there is no response.

Weaning: Failure to use the lowest effective dose causes dependency; so does prolonged use. Try to reduce the dose needed in "responders" once every 12 hours. Lower the concentration by 10% once every 3 minutes, but reverse any reduction that causes arterial saturation to drop by more than 2–3%. Babies sometimes require a low dose (< 0.5 ppm) for several days during "weaning", even if no response was seen initially. Increasing the inspired oxygen concentration by 20% may facilitate final weaning.

Use in other children

The use of NO is occasionally very helpful in controlling postoperative pulmonary hypertension after cardiac surgery. The drug's role in other children with severe respiratory failure has yet to be clarified. Trials suggest that treatment is not usually helpful in patients with adult respiratory distress syndrome.

Supply and administration

NO was, until recently, an ill defined therapeutic product, but its use in term infants with pulmonary hypertension has now been approved by the regulatory authorities in Europe and in North America. Now the gas has received formal recognition as a medicinal product, a single company (INO Therapeutics Inc.) has acquired sole marketing rights. New uniform delivery and monitoring systems are available to hospitals for an hourly fee. Since this arrangement seems likely to increase the cost of treatment more than 20-fold, it is going to be important to mount further studies into the cost effectiveness of this and other strategies for controlling pulmonary vascular tone.

References

- Miller OI, Tank SF, Keech A, *et al.* Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: a randomised double-blind study. *Lancet* 2000;**356**:1464–9. [RCT]
- Hoehn T, Krause MC. Response to inhaled nitric oxide in premature and term neonates. *Drugs* 2001;**61**:27–39.
- Finer NN, Sun JW, Rich W, *et al.* Randomized, prospective study of low-dose versus high-dose inhaled nitric oxide in the neonate with hypoxic respiratory failure. *Pediatrics* 2001;**108**:949–55. [RCT]

See also relevant Cochrane reviews



NITROPRUSSIDE

Use

Sodium nitroprusside is a direct, very rapidly acting, peripheral vasodilator that is used to reduce afterload when left ventricular function is impaired. It is useful in controlling hypertension, and is often used to control the paradoxical hypertension seen after surgery for coarctation of the aorta.

Pharmacology

Sodium nitroprusside was first developed in 1951. It is a vasodilator that acts directly on the vascular smooth muscle of the arteries and veins. The drug activates guanylate cyclase, triggering a cascade of reactions that lead to smooth muscle relaxation. At **low** doses nitroprusside reduces systemic vascular resistance and increases cardiac output. This may be associated with a slight increase in heart rate, but significant tachycardia is unusual. It decreases right atrial pressure, pulmonary capillary wedge pressure, and pulmonary vascular resistance. At **high** doses nitroprusside can produce systemic hypotension, which can be profound. It can also exacerbate myocardial ischaemia. This tendency is aggravated by volume depletion and can occur idiosyncratically at low doses. Continuous blood pressure monitoring is, therefore, essential when using nitroprusside.

Nitroprusside has been used to treat pregnancy induced hypertension without any apparent adverse effects on the fetus, although it has been shown to cause a 30% reduction in uterine blood flow. Nitroprusside is broken down to cyanide in the body. This is then quickly metabolised in the liver to thiocyanate, which is slowly excreted by the kidneys (half life 4 days). Tissue levels exceed plasma levels ($V_D \sim 3$ l/kg). Prolonged or high dose infusions of nitroprusside, or the presence of hepatic or renal impairment, can cause a dangerous accumulation of these toxic products. Prolonged use can also lead to hypothyroidism as thiocyanate inhibits the uptake of iodine into the thyroid gland. Little is known about the long term use or safety of nitroprusside when prescribed during pregnancy or lactation.

The manufacturers have not yet issued any advice about the use of nitroprusside in children, but toxic side effects have never been described at infusion rates of 2 micrograms/kg per minute, and infusion rates of up to 8 micrograms/kg per minute are generally regarded as safe. The cerebral vasodilatation caused by nitroprusside may be undesirable in some neonates, but many cardiothoracic centres routinely use this drug in the initial control of the paradoxical hypertension sometimes seen after coarctectomy. The rapidity with which the drug works, and the speed with which it is degraded, make nitroprusside a relatively safe drug to use with due monitoring in an intensive care setting. Continuous blood pressure monitoring is advisable and invasive monitoring may be necessary. One preliminary report suggests that the nebulised administration of a 25 mg dose can be as effective as treatment with nitric oxide (q.v.) in ventilated term babies with hypoxic respiratory failure.

Treatment

Nitroprusside is usually started as a continuous infusion at a rate of 500 nanograms/kg per minute. Monitor the systemic blood pressure and cautiously increase the dose infused, as necessary, to a maximum rate of no more than 8 micrograms/kg per minute.

Compatibility

Nitroprusside can be added (terminally) to an IV line containing atracurium, dobutamine and/or dopamine, glyceryl trinitrate, midazolam or milrinone.

Antidote

Tachycardia, arrhythmia, sweating, and an acidosis suggest cyanide toxicity, especially after sustained treatment despite poor renal function. Correct the acidosis and give 0.3 ml/kg of 3% sodium nitrite IV (unless there is overt cyanosis) followed by 0.8 ml/kg of a 50% solution of IV sodium thiosulphate.

Supply and administration

Sodium nitroprusside is supplied in 50 mg vials costing £6.60. Reconstitute with 2 ml of 5% dextrose. Take 0.2 ml (5 mg) of this solution and dilute up to 10 ml with 5% dextrose (500 micrograms/ml). Then take 3 ml of this solution for each kilogram the baby weighs and dilute to 25 ml with 5% dextrose (60 micrograms/kg per ml). Infuse this solution at 1 ml/hour to give 1 microgram/kg per minute. Nitroprusside breaks down into cyanide and ferrocyanide on exposure to light. Ampoules of the drug must therefore be stored in the dark, and any ampoules developing a brownish discolouration discarded. Special amber giving sets should be used where possible. If these are not available the infusate must be covered with foil during administration. Prepare a fresh infusion every 24 hours.

References

- Benitz WE, Malachowski N, Cohen RS, *et al.* Use of sodium nitroprusside in neonates: efficacy and safety. *J Pediatr* 1985;**106**:102–10.
- Artman M, Graham TP. Guidelines for vasodilator therapy of congestive heart failure in infants and children. *Am Heart J* 1987;**113**:994–1004.
- Gin-Mestan KK, Carlson AD, White M, *et al.* Comparison of the oxygenation effect of nebulized nitroprusside to inhaled nitric oxide in term infants with hypoxic respiratory failure [Abstract]. *Pediatr Res* 2002;**51**:50A.

Use

A mixture of 50% nitrous oxide in oxygen has long been used to provide conscious analgesia. Higher, anaesthetic, concentrations should be given only by a trained intensivist.

History

Humphry Davy, who first described this gas in 1800, was shrewd enough to see that it could be used "with great advantage in surgical operations where no great effusion of blood takes place". Despite this it was the intoxicating and amnesic effect of "laughing gas" that was exploited for 44 years before Wells first used the drug during dentistry. Although Queen Victoria used chloroform, it was many years before inhalation analgesia became common in childbirth, partly because the early Minnitt machine could leave a woman breathing as little as 10% oxygen. The "Lucy Baldwin" machine (named after the UK Prime Minister's wife who did much to champion its use by midwives) made safe pain relief available during home birth, but this was later replaced with cylinders containing a 50:50 oxygen mixture.

Pharmacology

The use of a 50% mixture causes conscious analgesia after 3 minutes, and this persists for about 3 minutes after inhalation ceases. Swallowing is depressed but laryngeal reflexes are retained. Use in any patient with an air-containing closed space (such as a pneumothorax or loculated air within a damaged lung) is potentially dangerous because nitrous oxide diffuses into the space causing a significant increase in pressure. Diffusion hypoxia, due to nitrous oxide returning to the alveoli from the blood stream more rapidly than it is replaced by nitrogen at the end of the procedure, can be minimised by giving oxygen.

A recent large French study has shown that, in children, nitrous oxide use supervised by nurses to provide short term analgesia for a range of investigative and treatment procedures can be extremely safe. The only significant problems encountered during procedures lasting up to 30 minutes were mild hypoxaemia, brief apnoea, bradycardia, and oversedation (loss of verbal contact lasting more than 5 minutes); such problems were encountered in only 0.3% of all procedures. These were, however, slightly commoner in children who had also been given both an opioid and a benzodiazepine sedative, and in children less than 1 year old (2% of whom experienced some mild adverse effect). Only 1% of procedures had to be cancelled because of inadequate sedation or a side effect. Nausea and dizziness were the only occasional disadvantages of such a strategy.

Safe use in young children

Use must be supervised by someone who has undergone appropriate training; it should be supervised by a qualified anaesthetist in any child who is drowsy or who has also had another sedative (especially any benzodiazepine or opioid). Do nothing for 4 hours after the child last had milk or solid food (2 hours after clear liquids). Do nothing painful for 3 minutes after starting to give the gas, and stop the procedure if pain relief is inadequate, as may happen inexplicably in 5% of all procedures. Always use a pulse oximeter, and have oxygen at hand in case brief diffusion hypoxia occurs during recovery. Appropriate use requires the presence of at least two people. The person undertaking the procedure for which analgesia is being offered must **never** be the person who is supervising the administration of nitrous oxide. Frequent use could dangerously lower body cobalamin (B₁₂) stores.

Pain relief

Maternal pain relief in labour: An MRC trial found a 50% mixture in oxygen to be uniformly safe and helpful. A 70% mixture probably brought added benefit, but rendered a few women briefly unconscious.

Pain relief in infancy: Use must be supervised by appropriately trained staff (see above).

Supply and administration

Premixed supplies of 50% nitrous oxide in oxygen (Entonox[®] and Equanox[®]) come in blue cylinders with a blue and white shoulder. Refills cost about £10. Storage at temperatures below -6°C can cause the gases to separate; should this happen, the cylinder *must* be laid horizontally in a warm room for 24 hours before use. Use in adults and school age children is usually by self administration using a face mask and demand valve, ensuring that use ceases if the patient becomes drowsy. A constant flow system with a blender like the Quantiflex[®], which shuts down if the oxygen supply fails, makes safe administration of a variable dose possible. Adequate room ventilation, or a waste gas scavenging system, must be provided, especially where frequent use occurs, to stop the ambient level exceeding 100 ppm, since chronic exposure can cause megaloblastic anaemia by interfering with the action of vitamin B₁₂. There is one report that chronic exposure (once common during dental surgery) may lower female fertility.

References

- Medical Research Council. Committee on Nitrous Oxide and Oxygen Analgesia in Midwifery. Clinical trials of different concentrations of oxygen and nitrous oxide for obstetric analgesia. *BMJ* 1970;**i**:709–13.
- Gall O, Annequin D, Benoit G, et al. Adverse events of premixed nitrous oxide and oxygen for procedural sedation in children. *Lancet* 2001;**358**:1514–15.
- Rosen MA. Nitrous oxide relief of labour pain; a systematic review. *Am J Obstet Gynecol* 2002;**186**:S110–26. [SR]

NORADRENALINE = Norepinephrine (rINN)

Use

Noradrenaline is a potent vasoconstrictor that has been used to treat severe refractory hypotension (as in patients with septic shock). Milrinone (q.v.) should be used to correct the drop in cardiac output that is the commonest preterminal event in infancy once the hypovolaemia associated with the leakage of fluid from damaged capillaries into the extravascular tissue space has been corrected.

Pharmacology

Sympathomimetic agents mimic the actions produced by stimulation of the postganglionic sympathetic nerves, preparing the body for "fight or flight". Three natural catecholamine agents have been identified: dopamine (q.v.) (primarily a central neurotransmitter), noradrenaline (a sympathetic neurotransmitter), and adrenaline (q.v.) (which has metabolic and hormonal functions). Metabolism is rapid, if variable, so stable concentrations are reached within 10–15 minutes of starting an infusion and clearance is not influenced by renal function. The agents, and their synthetic counterparts, differ in their actions according to the receptors on which they mainly act (although many stimulate most receptors to a varying degree): α_1 smooth muscle receptors, which cause vasoconstriction; α_2 presynaptic nerve receptors, which are thought to inhibit gastrointestinal activity; β_1 receptors, which stimulate cardiac activity; β_2 smooth muscle receptors, which cause vascular and bronchial dilatation; and two central nervous system dopamine receptors (D_1 and D_2).

Noradrenaline is the main postganglionic neurotransmitter in the sympathetic nervous system. Some is also produced along with adrenaline by the adrenal glands in response to stress. It is inactivated when given by mouth and cannot be given by subcutaneous or IM injection because it is such a powerful vasoconstrictor. The main effects are to increase cardiac contractility, heart rate, and myocardial oxygen consumption (via β_1 stimulation), but high dose infusions also cause intense peripheral vasoconstriction (an α_1 agonist effect) unless vasopressin insufficiency (q.v.) has developed. Such peripheral vasoconstriction can sometimes, by increasing the afterload on the heart, counteract the drug's inotropic effect and cause a decrease in cardiac output. Similarly, the increase in myocardial oxygen consumption can exacerbate any existing cardiac failure and compromise ventricular function. Noradrenaline may have advantages over adrenaline in this situation because the balance between α_1 and β_1 stimulation causes a vasoconstrictor-generated rise in blood pressure without causing ventricular hypercontractility. Infants with sepsis who are hypotensive but have good cardiac function and adequate vascular volume are the most likely to benefit, although even here the optimum dose calls for careful judgement. Noradrenaline can cause the pregnant uterus to contract.

Drug equivalence

1 mg of noradrenaline acid tartrate contains 500 micrograms of noradrenaline base. The drug is always best prescribed in terms of the amount of **base** to be given, to prevent ambiguity.

Treatment

Start with an infusion of 100 nanograms/kg per minute of noradrenaline base (0.1 ml/hour of a solution made up as described below) and infuse into a *central* vein. Severe complications can be associated with peripheral infusion as outlined in the monograph on dopamine. The rate of infusion can be increased slowly to a maximum of 1.5 micrograms/kg per minute (1.5 ml per hour), as long as limb perfusion and urine output are watched carefully. Monitor central vascular pressures where possible.

Compatibility

Noradrenaline can be added (terminally) into a line containing dobutamine, dopamine, heparin (q.v.), milrinone or standard TPN (with or without lipid).

Supply and administration

Noradrenaline is available in 2 ml and 4 ml ampoules containing 2 mg/ml of noradrenaline acid tartrate (the equivalent of 1 mg/ml of noradrenaline base) costing £1 and £1.70 each. To give an infusion of 100 nanograms/kg per minute of noradrenaline base, take 1.5 mg (1.5 ml) of noradrenaline base for each kilogram the baby weighs, dilute to 25 ml with 10% dextrose or dextrose saline, and infuse at a rate of 0.1 ml/hour. The drug is stable in solutions with a low pH, such as dextrose, but is best prepared afresh every 24 hours unless protected from light. Ampoules should also be protected from light during storage, and discarded if discoloured.

References

- Barnard MJ, Linter SPK. Acute circulatory support. *BMJ* 1993;**307**:35–41.
- Ceneviva G, Paschall JA, Maffei F, *et al*. Hemodynamic support in fluid refractory septic shock. *Pediatrics* 1998;**102**:e19.
- von Rosensteil N, von Rosensteil I, Adam D. Management of sepsis and septic shock in infants and children. *Paediatr Drugs* 2001;**3**:9–27.
- Carcillo JA, Fields AI. Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock. *Crit Care Med* 2002;**30**:1365–78. [SR]
- Germanakis I, Bender C, Hentschel R, *et al*. Hypercontractile heart failure caused by catecholamine therapy in premature neonates. *Acta Paediatr* 2003;**92**:836–8.

Use

NTBC is used to prevent the accumulation of toxic metabolites in patients with type I tyrosinaemia.

Biochemistry

Tyrosinaemia type I is a rare, recessively inherited, disorder that is caused by a deficiency of fumarylacetoacetase, the enzyme involved in the fifth step of tyrosine breakdown. It is seen in about 1:100,000 births. Symptoms result from the accumulation of fumarylacetoacetate and succinylacetone, which are toxic. The condition is of variable severity but can present within weeks of birth with signs of liver failure, including jaundice (which is often misleadingly mild), diarrhoea, vomiting, oedema, ascites, hypoglycaemia, and a severe bleeding tendency. Cirrhosis usually develops over time and there is a significant long term risk of hepatocellular carcinoma. Milder cases present later in childhood or in early adult life with isolated hepatomegaly, liver failure, or hypophosphataemic rickets due to renal tubular dysfunction. Plasma tyrosine levels are usually elevated, but diagnosis depends on demonstrating raised urinary levels of succinylacetone. In a few patients succinylacetone levels are only slightly raised, and enzyme assay may be needed to confirm the diagnosis. Acute neurological crises can occur, with abdominal pain, muscle weakness, and hypertension, when toxic metabolites trigger other problems similar to those seen in acute intermittent porphyria.

For some years patients with tyrosinaemia type I have been treated with a diet that is low in tyrosine and phenylalanine, but this has had only a limited impact on disease progression. Management was, however, transformed in 1992 by the development of NTBC (2-(2-nitro-4-trifluoro-methylbenzoyl)-1,3-cyclohexanedione). This inhibits the second enzyme in the pathway of tyrosine metabolism (4-hydroxyphenylpyruvate dioxygenase). However, while this prevents the formation of fumarylacetoacetate and succinylacetone, it causes a marked rise in the tyrosine level, and high levels can lead to the deposition of crystals in the cornea, causing photophobia and corneal erosions. Because of this, treatment with NTBC still needs to be combined with a diet low in tyrosine and phenylalanine. Other adverse effects include transient thrombocytopenia and neutropenia. Treatment should be started as soon as the diagnosis is made and continued indefinitely. Whether management with NTBC can completely eliminate the need for liver transplantation will only be known once it is shown that such treatment removes the latent risk of liver cancer. Use during pregnancy or lactation is, as yet, unevaluated.

Treatment

Initial care: Infants presenting with liver failure when first diagnosed require intensive support, including urgent electrolyte and acid–base correction. Infection also needs to be treated aggressively. Such patients are best transferred to a liver unit because a few do not respond to NTBC and require urgent transplantation. Fresh frozen plasma (q.v.) may be required for coagulation failure.

Continuing care: Minimise the intake of tyrosine and phenylalanine while the patient is acutely unwell and start regular maintenance with a 1 mg/kg daily dose of NTBC by mouth. The intake of natural protein can then be increased cautiously, but much of the child's protein will still have to be provided using an amino acid mixture free of tyrosine and phenylalanine. Supplemental oral vitamin K (q.v.) is sometimes required, and rickets may benefit from treatment with additional vitamin D (q.v.).

Monitoring

Patients should be managed in collaboration with a specialist in metabolic disease. Diet needs to allow normal growth while aiming to keep the plasma tyrosine level below 500 $\mu\text{mol/l}$. The dose of NTBC is adjusted by assessing the biochemical response. Some centres also monitor the plasma concentration (the therapeutic NTBC level usually being between 25 $\mu\text{mol/l}$ and 50 $\mu\text{mol/l}$). Serum α fetoprotein levels should be measured serially, and regular liver scans undertaken to watch for early signs of liver cancer.

Supply and administration

2 mg, 5 mg, and 10 mg capsules of NTBC (costing £7.50, £14.60, and £26 each) are available on a "named patient" basis from Orphan Europe. Divide the daily dose, where possible, into two (not necessarily equal) parts, given morning and evening. An application for a licence to market this product is said to be pending with the European regulatory authorities.

References

- Holme E, Lindstedt S. Tyrosinaemia type 1 and NTBC (2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione). *J Inherit Metab Dis* 1998;21:507–17.
- Kvittingen EA, Holme E. Disorders of tyrosine metabolism. In: Fernandes J, Saudubray J-M, van den Berghe G, eds. *Inborn metabolic diseases. Diagnosis and treatment*, 3rd ed. Chapter 16. Berlin: Springer-Verlag, 2000:186–94.
- Mitchell GA, Grompe M, Lambert M, et al. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular bases of inherited disease*, 8th ed. New York: McGraw-Hill, 2001:1777–806.

Use

Nystatin is used to treat gastrointestinal and topical infection with *Candida albicans*. Miconazole gel (q.v.) seems better at eliminating oral infection. There is a need for further simple comparative nursing trials.

Pharmacology

Nystatin was the first naturally occurring antifungal polyene antibiotic to be developed (in 1951) and is still the most widely used. It is very insoluble and is usually prescribed as a suspension. Nystatin is particularly active against yeast-like fungi and has long been used in the treatment of topical infection with *Candida albicans*. Full purification is impracticable and the drug dosage is therefore usually quoted in "units". The drug works by combining with the sterol elements of fungal cell membranes, causing cell death by producing increased cell wall permeability. Oral absorption is poor. There is no contraindication to maternal use during pregnancy or lactation, although treatment with miconazole seems a more effective way of eliminating vaginal candidiasis.

The dose usually recommended for oral infection ("thrush") is 1 ml of the suspension four times a day, but this is not as effective as treatment with oral miconazole gel. A 4 ml dose of nystatin may be more effective, but this still needs controlled trial confirmation. Oral drops can be used to clear *Candida* from the gastrointestinal tract, and ointment to treat skin infection. Fluconazole (q.v.) costs more, but is probably more effective, and it should certainly be used if there is tracheal colonisation or systemic infection. Such colonisation and overt infection can become a serious problem in babies on broad spectrum antibiotic treatment (because of the resultant change in the normal bacterial flora).

Maternal breast and nipple pain

A tender, lumpy, inflamed breast is best treated for incipient bacterial mastitis with flucloxacillin (q.v.). Local *nipple* pain is usually due to poor positioning (an art that has to be learnt), and this can be rapidly relieved by improved technique. Topical treatments usually do more harm than good and some mothers are even sensitive to lanolin cream. Keep the skin dry (while allowing any expressed milk to dry on the nipple). Candidal infection ("thrush") can occasionally be part of the problem and should be suspected if difficulties are encountered after lactation has been established, especially if the baby has signs of this infection or the mother has vaginitis. Recent antibiotic treatment makes this problem more likely. Miconazole cream and oral gel, sold "over the counter" under the trade name Daktarin®, may help, but a maternal course of fluconazole may be the treatment of choice when there is severe burning, stinging, or radiating pain, presumably due to duct infection. Give 100 mg of fluconazole once a day for 2 weeks after a 200 mg loading dose, and treat the baby with nystatin as well to minimise the risk of reinfection. Sudden severe pain with marked blanching may be a vasomotor reaction. Anxiety can be one trigger. Local warmth may help; keeping warm may forestall trouble. Some cases may be a form of Raynaud's phenomenon, but whether this ever merits pharmacological intervention (with 10 mg of nifedipine (q.v.) for the mother, usually as a slow release preparation, 2–3 times a day) remains unclear.

Neonatal treatment

Prophylaxis: 1 ml (100,000 units) of the oral suspension every 8 hours can lower the risk of systemic infection in the very low birth weight baby.

Oral candidiasis (thrush): It is standard practice to give 1 ml (100,000 units) by mouth 4 times a day after feeds, but a larger dose may be more effective.

Candida (Monilia) dermatitis: Dry the skin thoroughly and apply nystatin ointment at least twice a day for 1 week. Leave the skin exposed if possible. A cream is better if the skin is broken and wet.

General considerations: Continue treatment for at least 3 days after a response is achieved to minimise the risk of a recurrence. Consider the possibility of undiagnosed genital infection, especially in the mother of an infected but otherwise healthy full term baby. Check that the child is not reinfected by a contaminated bottle or teat. It is often advisable to treat the gastrointestinal tract as well as the skin in any baby with a stubborn monilial nappy (diaper) rash.

Supply

30 g tubes of nystatin ointment and cream cost £1.80 and £2.20 respectively. One 30 ml bottle of the sugar-free oral suspension (100,000 units/ml) costs £2. The 500,000 unit tablets cost 8p each.

References

- Sims ME, Too Y, You H, *et al.* Prophylactic oral nystatin and fungal infections in very-low-birthweight infants. *Am J Perinatol* 1988;5:33–6.
- Tanquay KE, McBean MR, Jain E. Nipple candidiasis among breastfeeding mothers. *Can Fam Phys* 1994;40:1407–13.
- Sachs M, Jones W. Breastfeeding and thrush. *MIDIRS Midwifery Digest* 1998;8:486–9.
- Goins RA, Ascher D, Waecker N, *et al.* Comparison of fluconazole and nystatin oral suspensions for treatment of oral candidiasis in infants. *Pediatr Infect Dis J* 2002;21:1165–7. [RCT]

See also relevant Cochrane reviews



Use

Omeprazole is used to suppress gastric acid secretion when reflux oesophagitis or peptic ulceration fails to respond to other non-surgical interventions. Controlled trial evidence of efficacy is, as yet, limited.

Pharmacology

Omeprazole, a substituted benzimidazole, was the first of a series of gastric acid pump inhibitors (proton pump inhibitors) to come into clinical use in 1983. The drug works by inhibiting the last step in the chain of reactions that lead to the secretion of hydrochloric acid by the parietal cells of the stomach. The resultant reduction in gastric acidity, even in the fed state, allows even severe oesophageal erosions to heal. Treatment is necessary only once a day, although the plasma half life in adults is only about 1.5 hours, since a single dose more than halves the secretion of gastric acid for over a day. The plasma half life is even shorter in young children, but this does not seem, on its own, to explain the higher treatment dose sometimes found to be necessary in children. Side effects are uncommon. Pharmacokinetic studies have not been done in children under 1 year old; nor have the manufacturers carried out the studies necessary to recommend the drug's use either during pregnancy or lactation, or in children younger than 2 years old. The drug is not generally teratogenic in animals, but a number of unusual defects have been reported to the US Food and Drug Administration among the women who have taken this drug in the first half of pregnancy, and more information is clearly needed. Neither is anything known about the safety of use during lactation but, since the drug is rapidly destroyed by acid (the reason why the drug is formulated in enteric coated granules), ingestion by the baby of a mother taking omeprazole is likely to be limited. Oral bioavailability, even with coating, is only about 65%. Prophylactic IV use has been recommended to minimise the risk of aspiration pneumonitis (Mendelson's syndrome) in advance of urgent caesarean delivery under general anaesthesia. Ranitidine (q.v.) seems to be an equally effective alternative.

Treatment

Start by giving approximately 0.7 mg/kg by mouth once a day in the morning, half an hour before breakfast, and double this dose after 7–14 days if severe acid reflux persists. A few patients may need as much as 2.8 mg/kg a day. No published information exists on IV or IM use in infancy.

Monitoring

Treatment with omeprazole should be initiated only if endoscopically proven oesophagitis fails to respond to high dose ranitidine. Stop treatment within 3 months unless there continues to be evidence of active oesophagitis. The risks of long term, and high dose, treatment are, as yet, unclear (and the dose necessary in young children is sometimes much higher than the dose used in adult life). Patients not responding to a dose of 1.4 mg/kg a day should probably be offered 24 hour oesophageal pH monitoring, and a higher dose used only when the gastric pH is less than 4 for more than 1–2 hours a day.

Supply and administration

10 mg and 20 mg dispersible, film coated, tablets cost 68p and £1 each. Capsules containing enteric coated granules are also available at the same cost. Small doses can be administered by giving a quarter or a half of a 10 mg tablet dissolved in water, or by sprinkling some of the contents of a capsule in a small quantity of yoghurt or fruit juice. Powders that can be reconstituted and administered IV are available in 40 mg vials costing £5.20. Because granules can block any nasogastric tube down which they are forced, some hospitals have tried adding the granules to a bicarbonate solution (see DiGiacinto *et al*, 2000), but it is not known how well such a preparation resists inactivation by stomach acid.

References

Kato S, Shibuya H, Hayashi Y, *et al*. Effectiveness and pharmacokinetics of omeprazole in children with refractory duodenal ulcer. *J Pediatr Gastroenterol Nutr* 1992;**15**:184–8.
 Gunasekaran TS, Hassall EG. Efficacy and safety of omeprazole for severe gastroesophageal reflux in children. *J Pediatr* 1993;**123**:148–54. (See also **124**:332–4.)
 Jacqz-Aigrain E, Bellaich M, Faure C, *et al*. Pharmacokinetics of omeprazole in children. *Eur J Clin Pharmacol* 1994;**47**:181–5.
 Stuart JC, Kan AF, Rowbottom SJ, *et al*. Acid aspiration prophylaxis for emergency caesarean section. *Anaesthesia* 1996;**51**:415–21. [RCT]
 Alliet P, Raes M, Bruneel E, *et al*. Omeprazole in infants with cimetidine-resistant peptic esophagitis. *J Pediatr* 1998;**132**:352–4.
 DiGiacinto JL, Olsen KM, Bergman KL, *et al*. Stability of suspension formulation of lansoprazole and omeprazole stored in amber-coloured plastic oral syringes. *Ann Pharmacother* 2000;**34**:600–4.
 Hassall E, Israel D, Shepherd R, *et al*. Omeprazole for treatment of chronic erosive esophagitis in children: a multicenter study of efficacy, safety, tolerability and dose requirements. International omeprazole study group. *J Pediatr* 2000;**137**:800–7.
 Andersson T, Hassall E, Lundborg P, *et al*. Pharmacokinetics of orally administered omeprazole in children. *Am J Gastroenterol* 2000;**95**:3101–6.
 Varughese LA, Mazur LJ. Is omeprazole helpful in the management of children with reflux oesophagitis? *Arch Dis Child* 2002;**87**:78–80.
 Gold BD, Freston JW. Gastroesophageal reflux in children. Pathogenesis, prevalence, diagnosis, and role of proton pump inhibitors in treatment. *Pediatr Drugs* 2002;**4**:673–85.

OXYGEN

Use

Supplemental oxygen is used to correct hypoxia in babies with pulmonary problems, especially where this is causing a mismatch between the ventilation and the perfusion of the lung.

Pathophysiology

Oxygen deserves its place in any pharmacopoeia because – like almost any other drug – it can do a lot of harm as well as a lot of good. It should therefore be used with care and understanding; its use must always be documented and the “dose” recorded. Lack of oxygen can be damaging, although the body can manage with blood that is only about 50–60% saturated as long as the *quantity* of oxygen delivered to the tissues is adequate. Were this not true, the fetus would be in substantial trouble before birth, as would the brain of the baby with cyanotic congenital heart disease. Cardiac output and tissue perfusion matter more than blood pressure, and anaemia can undermine oxygen delivery as much as overt cyanosis. While tissue hypoxia can be damaging, it is the combined effect of CO₂ accumulation and oxygen lack (asphyxia) that is most damaging, causing a respiratory (carbonic acid) as well as a metabolic (lactic acid) acidosis.

Too much oxygen can also be damaging, however. Prolonged high concentrations of oxygen can be toxic to the pulmonary epithelium and hyperbaric oxygen can cause convulsions. There is also evidence that a relatively high partial pressure of oxygen in the blood is one of a range of factors that can interfere with the normal growth of blood vessels into the retina at the back of the eye in the last 10 weeks of what should have been intrauterine life. In most cases the retinal changes resolve spontaneously, leaving no damage, but severe change can lead to permanent (“cicatrical”) scarring if it involves more than the outer rim of the retina; this scarring can sometimes progress to retinal detachment and complete blindness. Controlled trial evidence of this first appeared in 1952.

The more immature the baby the greater the risk, but changes never develop until the baby is at least 6 weeks old, and most severe disease develops at a postmenstrual age of 33–40 weeks. Damage can be reduced by cryotherapy to limit the capillary proliferation that precedes permanent scarring, but the disease can progress quite rapidly. It is essential, therefore, for every baby born before 30 weeks gestation to be seen by an experienced ophthalmologist when 6 weeks old, and then serially every 10–14 days until any acute proliferative change has started to regress (many units screen all babies of less than 32 weeks). Review can be discontinued after 36 weeks if there is still no retinal abnormality because disease appearing for the first time after this is extremely unlikely to progress to permanent scarring. Diode laser treatment is currently offered if disease involves five or more contiguous, or eight or more cumulative, clock hours of the retinal surface, because these babies have at least a 50% chance of developing permanent retinal scarring if left untreated. A trial of earlier intervention (ET-ROP) is currently recruiting in the USA.

Administration

Oxygen is usually given in an incubator, especially in small babies, but cot nursing using a nasal cannula is a valuable alternative that simplifies parental involvement when the concentration of oxygen called for does not exceed 50%. A humidified head box (see below) is the only satisfactory way of providing more than 60% oxygen; oxygen tents are seldom very satisfactory at any age. It is not generally recognised that substantial (but not very precisely controlled) amounts of oxygen can also be given directly into any high sided carry cot or basinette since oxygen, because of its temperature and density, “layers” immediately above the surface of the mattress; it is not necessary to put a plastic sheet over the top of the basinette.

Measurement in air

The amount of oxygen (as a percentage) each baby is breathing should be recorded regularly, and babies given oxygen via a nasal catheter should also have the ambient concentration needed to provide an equivalent arterial saturation documented periodically, because the relationship between catheter flow and inspiratory concentration varies. Equipment requires daily calibration against room air (20.9% oxygen).

Measuring blood levels

What constitutes a safe range for arterial oxygen pressure is not known. It is said that there must be 50 g/l of desaturated haemoglobin for cyanosis to be visible. Cyanosis is certainly difficult to detect by eye until 25% of the blood is desaturated. In the neonate this often occurs only when the arterial partial pressure (PaO₂) is down to 35 mmHg or 4.7 kPa (Fig. 1). There is no good controlled trial evidence that the use of arterial catheters improves outcome, although their use can reduce trauma to the heels from repeated capillary sampling. Transcutaneous pressure and saturation monitors are valuable but not free from error.

continued ...

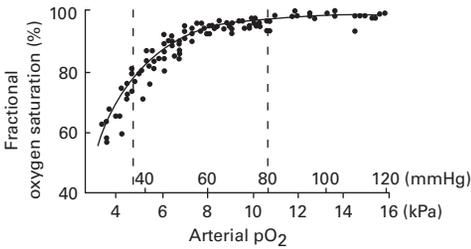


Figure 1

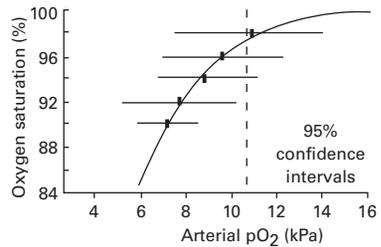


Figure 2

Measuring blood levels (continued)

The largest cohort study ever mounted showed an association between the prevalence of acute retinopathy and the duration of exposure to a transcutaneous oxygen pressure (TcPO₂) of more than 80 mmHg (~10.7 kPa). As a result it has long been considered good practice to monitor all babies with a postmenstrual age of less than 37 weeks who require supplemental oxygen to prevent unnecessary hyperoxia, aiming for TcPO₂ levels of 5–11 kPa. Pulse oximeters are now widely used to supplement, or replace, the monitoring of TcPO₂ even though the relationship between PaO₂ and arterial saturation is quite variable (Fig. 1). In particular, blood that is cool and contains relatively few hydrogen ions, little carbon dioxide, and a minimum of adult haemoglobin, remains well saturated at relatively low pressures. To be 98% certain of keeping PaO₂ below 80 mmHg, the *fractional* saturation in babies has to be kept from exceeding 92% (Fig. 2), equivalent to a *functional* saturation of 94%. Given the variable performance of some monitors even this probably leaves preterm babies at some small risk of hyperoxia.

No such restriction needs to limit management in babies in whom retinal vascular development is complete (or in whom retinopathy has already developed). Here, monitoring is necessary only to identify hypoxia, and significant central cyanosis is not difficult to detect (although badly chosen fluorescent lighting can affect assessment). Babies with chronic lung disease are often given oxygen in the belief that this will improve weight gain and reduce emergency hospital readmission, but there was no evidence of this in the recent Australian BOOST trial. Babies given enough supplemental oxygen to maintain a *fractional* saturation of 96–99% in the American STOP-ROP trial actually had *more* pulmonary problems than those given only enough oxygen to maintain a saturation of 89–94%.

Supply

Piped hospital supplies result in our taking the provision of oxygen for granted; the same is not true in many developing countries. Size F cylinders containing 1360 litres of oxygen with a bullnose pressure regulator can be prescribed by GPs and provided for domiciliary use by community pharmacists. Hospital cylinders and regulators can be loaned for portable use, while GPs can prescribe a concentrator for patients requiring *continuous* supplemental home oxygen.

Humidification

Piped supplies and cylinders are devoid of water vapour, so humidification is essential to avoid excessive drying of the respiratory tract when giving > 50% oxygen. Bubbling through water at room temperature (25°C) adds 20 g of water to each cubic metre of gas (equivalent to 50% saturation at body temperature); this is generally adequate unless the baby has been intubated and the nose's humidification system bypassed. Better humidification requires the water itself to be fairly close to body temperature. For babies breathing high concentrations of head box oxygen in an incubator this can be achieved without a heated humidifier by placing a humidification bottle in the incubator itself.

References

- Duc C, Sinclair JC. Oxygen administration. In: Sinclair JC, Bracken MB, eds. *Effective care of the newborn infant*. Chapter 10. Oxford: Oxford University Press, 1992:178–99. (See also pp. 617–39.) [SR]
- Flynn JT, Bancalari E, Snyder ES, et al. A cohort study of transcutaneous oxygen tension and the incidence and severity of retinopathy of prematurity. *N Engl J Med* 1992;**326**:1050–4. (See also pp. 1078–80.)
- Brockway L, Hay WW. Prediction of arterial partial pressure of oxygen with pulse oximeter oxygen saturation measurements. *J Pediatr* 1998;**133**:63–6.
- Tin W, Wariyar U. Giving small babies oxygen: 50 years of uncertainty. *Semin Neonatal* 2002;**7**:361–7.
- Askie LM, Henderson-Smart DJ, Irwig L, et al. Oxygen saturation targets and outcomes of extremely preterm infants. *N Engl J Med* 2003;**349**:(in press). [RCT]
- Chow LC, Wright KW, Sola A. Can changes in clinical practice decrease the incidence of severe retinopathy in very low birth weight infants? *Pediatrics* 2003;**111**:339–45.
- Frey B, Shann F. Oxygen administration in infants. [Review] *Arch Dis Child* 2003;**88**:F84–88.

See also relevant Cochrane reviews

OXYTOCIN

Use

Oxytocin is used to induce or augment labour, and to reduce postpartum haemorrhage.

Pharmacology

Oxytocin is a synthetic octapeptide identical to the naturally occurring hypothalamic hormone. Crude pituitary extracts were first used clinically in 1909 and became commercially available in 1928. Its structure was confirmed by synthesis in 1953. The drug is widely used to initiate and augment labour, given as a continuous IV infusion because uptake is erratic from mucous membranes and the natural half life is only 3–4 minutes. A sudden bolus can cause transient vasodilatation and tachycardia; secondary hypotension can be dangerous in patients with underlying heart disease. Uterine hyperstimulation can also cause fetal hypoxia, but this can be reversed by stopping the infusion and/or giving a betamimetic drug. There is some risk of uterine rupture, especially in patients with a uterine scar, even in the absence of cephalopelvic disproportion. Effectiveness is enhanced by exogenous prostaglandins, and by amniotomy (which seems to stimulate local prostaglandin synthesis). Doses of more than 0.015 units/min have an antidiuretic effect, and the risk of symptomatic fetal and maternal hyponatraemia is compounded if the mother is given a lot of 5% dextrose while in labour. Such problems can be minimised by always using a motor driven syringe pump when administering IV oxytocin. Its use marginally increases subsequent peak neonatal jaundice levels.

While oxytocin use in mothers delivering under epidural anaesthesia can speed up the second stage of labour, there is no controlled trial evidence that use (with or without early amniotomy) to "augment" spontaneous labour is of any significant clinical benefit. On the other hand, such augmentation can certainly cause increased pain and there is a significant risk of uterine hyperstimulation. Oxytocin (10 units IV or IM) can also reduce the risk of postpartum haemorrhage, and a continuous infusion can be used if bleeding continues after the placenta is delivered. A combined IM injection of oxytocin and ergometrine maleate (Syntometrine®) is marginally more effective in reducing blood loss, but can sometimes cause nausea, vomiting, and other unpleasant symptoms, together with a transient rise in blood pressure. Misoprostol by mouth (600 micrograms) or rectally (1 mg) is marginally less effective, but very useful in any setting where it may not be possible to keep drug supplies refrigerated. The inadvertent administration of Syntometrine to a baby (in mistake for an injection of vitamin K) causes respiratory depression, seizures, and severe hyponatraemia. Ventilation and anticonvulsant treatment may well be needed for 1–3 days. Paralysis and a tolazoline infusion have sometimes been required. Luckily, such errors of administration are compatible with complete recovery.

Treatment

Inducing and augmenting labour: Start with 0.001 units/min and increase this by 0.001 units/min every 30 minutes as necessary, using a motor driven syringe. If more than 0.004 unit/min proves necessary, increase the dose by 0.002 units/min increments once every 30 minutes to a maximum of 0.012 units/min.

Postpartum use: Give 10 units of oxytocin (or 1 ml of Syntometrine) IM once the anterior shoulder of the baby is safely delivered. Continuous IV oxytocin will usually limit residual postpartum bleeding.

Supply and administration

Oxytocin comes in 1 ml ampoules containing 5 or 10 units/ml. 1 ml ampoules of Syntometrine contain 5 units of oxytocin and 500 micrograms of ergometrine. Midwives can use these products on their own authority. Both cost £1.40. Store them in the dark at 4°C. For accurate, continuous, dose adjusted IV administration, dilute 3 units of oxytocin to 50 ml with 0.9% sodium chloride (or with Hartmann's solution). This gives a solution containing 0.060 units/ml. Such a solution, when infused at a rate of 1 ml/hour, gives the patient 0.001 unit/min of oxytocin. (1 international unit = 2.2 micrograms of oxytocin).

200 microgram tablets of misoprostol cost 17p. They are not licensed for the control of postpartum bleeding, but, unlike other products, do not have to be kept at 4°C to maintain their potency.

References

See also relevant Cochrane reviews 

- Irons DW, Thornton S, Davison JM, *et al.* Oxytocin infusion regimens: time for standardisation. *Br J Obstet Gynaecol* 1993;**100**:786–7.
- Soriano D, Dulitzki M, Schiff E, *et al.* A prospective cohort study of oxytocin plus ergometrine compared with oxytocin alone for prevention of postpartum haemorrhage. *Br J Obstet Gynaecol* 1996;**103**:1068–73. (See also **104**:643–4.)
- Daraville PA, Campbell NT. Overdose of ergometrine in the newborn infant: acute symptomatology and long-term outcome. *J Paediatr Child Health* 1998;**34**:83–9.
- Hofmeier GJ, Alfirevic Z, Matanhodze B, *et al.* Titrated oral misoprostol solution for induction of labour: a multi-centre, randomised trial. *Br J Obstet Gynaecol* 2001;**108**:952–9. [RCT]
- Gülmezoglu AM, Villar J, Ngoc NTN, *et al.* WHO multicentre randomised trial of misoprostol in the management of the third stage of labour. *Lancet* 2001;**358**:689–95. (See also pp. 682–3 and pp. 707–10.) [RCT]

Use

Prophylactic use of this monoclonal antibody can reduce the risk of a baby requiring hospital admission with bronchiolitis as result of respiratory syncytial virus (RSV) infection. Treatment is of no use in babies with established infection; neither is treatment with RSV immune globulin (RSV-IVIG). The safety of using either of these products in babies with congenital heart disease has not yet been established.

RSV infection

This infection occurs in epidemic form every winter. Adults usually get only a mild cold, but babies can develop chest infection severe enough to need hospital admission, and a few need ventilation. Infection is rapidly diagnosed from a nasopharyngeal wash specimen using immunofluorescence or an ELISA test (although the latter is not always positive early on). Coryza and/or apnoea may be the only symptoms in a preterm baby, but infants 2–9 months old can become seriously ill, particularly if they have congenital heart disease or chronic lung disease. Much can be done to reduce these risks by making parents more aware of the extent to which cross infection can be reduced by really careful hand washing and by limiting “social” family exposure. Barrier nursing reduces the risk of infection spreading to other vulnerable inpatients. Ribavirin and salbutamol (q.v.) are of limited benefit, but nebulised adrenaline (q.v.) has produced enough short term benefit to reduce the number needing hospital admission. Corticosteroids may also be of some marginal benefit in those starting to reveal early signs of asthma. Most babies just need help with fluid intake and a little oxygen until the dyspnoea recedes.

Pharmacology

Palivizumab is a combined human and murine monoclonal antibody produced by recombinant DNA technology that inhibits RSV replication. It has a 20 day half life. The first large placebo controlled trials were reported in 1998. A monthly injection during the seasonal winter epidemic reduces the need for hospitalisation owing to RSV infection in babies of less than 36 weeks gestation. However, a net reduction in total health service costs is probably achieved only when treatment is limited to babies who are oxygen dependent because of chronic lung disease. The risk of such babies becoming ill is further increased where there are other young school age children in the house. Side effects, other than pain and swelling at the injection site, are rare. Use does not interfere with the administration of other vaccines. Monthly RSV-IVIG treatment (750 mg/kg IV) may be more appropriate in babies needing immunoglobulin for other reasons, and offers some protection from other viral illnesses. However, it seems to do more harm than good in babies with cyanotic heart disease. Whether palivizumab should be given to such babies currently remains under study; early reports suggest that babies with heart defects can be treated safely, and that some probably do merit prophylaxis.

Prophylaxis

Give babies who are, or were until recently, oxygen dependent because of postventilator lung scarring 15 mg/kg IM once a month for 3–5 months from the start of the winter RSV epidemic. Use the anterolateral aspect of the thigh (and employ two sites when the injection volume exceeds 1 ml).

Supply and administration

The 50 mg and 100 mg vials of palivizumab (costing £424 and £706) should be stored at 4°C. Do not freeze. The small 50 mg vial actually contains more than 50 mg of palivizumab, but it is not possible to draw all the drug back out of the vial after reconstitution. This is why the manufacturers recommend that the powder should be dissolved by running 0.6 ml (50 mg vials) or 1 ml (100 mg vials) of water for injection slowly down the side of the vial. Rotate gently for 30 seconds without shaking and then leave at room temperature for at least 20 minutes until the solution clarifies (it will remain opalescent). The resultant 100 mg/ml solution must be used within 6 hours. Cost can be reduced by using the larger vial and scheduling several babies for treatment on the same day. RSV-IVIG is licensed only in the USA.

References

- Madge P, Paton JY, McColl JH, *et al.* Prospective controlled trial of four infection-control procedures to prevent nosocomial infection with respiratory syncytial virus. *Lancet* 1992;**340**:1079–83. [RCT]
- van Woensel J, Kimpen J. Therapy for respiratory tract infections caused by respiratory syncytial virus [Review]. *Eur J Pediatr* 2000;**159**:391–8.
- Garrison MM, Christakis DA, Harvey E, *et al.* Systemic corticosteroids in infant bronchiolitis: a meta-analysis. *Pediatrics* 2000;**105**:e44. [SR]
- Kumal-Bahl S, Doshi J, Campbell J. Economic analysis of respiratory syncytial virus immunoprophylaxis in high-risk infants. *Arch Pediatr Adolesc Med* 2002;**156**:1034–41. (See also pp. 1180–1.) [SR]
- Shireman TI, Brame KS. Impact and cost-effectiveness of respiratory syncytial virus prophylaxis for Kansas Medicaid's high-risk children. *Arch Pediatr Adolesc Med* 2002;**156**:1251–5.
- Vogel AM, Lennon DR, Broadbent R, *et al.* Palivizumab prophylaxis of respiratory syncytial virus infection in high-risk infants. *J Paediatr Child Health* 2002;**38**:550–4.
- Vogel AM, McKinlay MJ, Ashton T, *et al.* Cost-effectiveness of palivizumab in New Zealand. *J Paediatr Child Health* 2002;**38**:352–9.

See also relevant Cochrane reviews



PANCREATIN

Use

Pancreatic supplements are given to aid digestion in patients with cystic fibrosis.

Cystic fibrosis

Cystic fibrosis is a relatively common, recessively inherited, genetic disorder associated with abnormal mucus production. It seems to be caused by a primary defect of chloride ion secretion. Pancreatic damage causes malabsorption, while the production of viscid sputum renders patients vulnerable to recurrent bacterial infection. Thick meconium may cause intestinal obstruction (meconium ileus) at birth. Other complications include liver disease (due to biliary tract obstruction) and male infertility. The high chloride content of sweat is diagnostic, and a sample of sweat for laboratory analysis can be obtained by pilocarpine iontophoresis in most term babies more than a few weeks old. Most defective mutant genes are identifiable in the laboratory and prenatal diagnosis is now possible. Lung damage, including bronchiectasis, used to limit the number of patients reaching adult life, but survival has now improved significantly. Diagnosis and treatment should start as soon after birth as possible to minimise lung scarring, and management should be supervised from a specialist clinic. Nutritional support to counteract malabsorption has played an important part in improving survival. Lung transplantation has been offered to a few patients, but progressive liver disease remains an unsolved problem. Gene replacement therapy offers hope for the future. Neonatal screening has its advocates but screening couples in early pregnancy may be a more appropriate approach.

The condition, which affects about 1:2500 of all children born in Europe and North America, was rapidly fatal when first recognised 50 years ago, but the median age of survival is now into the late 20s and still rising. Lower respiratory tract infection needs prompt and vigorous treatment, and there is one small controlled trial to suggest that continuous prophylaxis with 250 mg/day of oral flucloxacillin (q.v.) during the first 2 years of life may reduce the need for frequent hospital admission. Only a few babies need pancreatic supplements at birth, but almost all need supplementation before they are 6 months old.

Pharmacology

Pancreatin is an extract prepared from pancreatic tissue that is given by mouth to aid digestion in patients with cystic fibrosis and pancreatic insufficiency. It contains protease enzymes that break down protein to peptides and proteases, lipases that hydrolyse fats to glycerol and fatty acids, and amylases that convert starch into dextrins and sugars. It is available as a powder, in capsules containing powder, in capsules containing enteric coated granules, as free granules, and as a tablet. Pancreatin should be taken with food, or immediately before food, in order to speed transit into the small intestine, because the constituent enzymes are progressively inactivated by stomach acid. The extent to which the enteric coated formulations actually improve intact passage into the duodenum is open to some doubt. Buccal soreness can occur if the powdered product is not swallowed promptly. Perianal soreness can be helped by a zinc oxide barrier ointment, but it may be a sign of excessive supplementation. High dose enteric coated formulations have occasionally caused colonic stricture in children 2–12 years old.

Treatment

Sprinkle the powder from one capsule of Pancrex V® '125' into each feed and increase this dose cautiously as necessary, as judged by the amount of undigested fat in the stool.

Vitamin supplements

The risk of subclinical vitamin A and D (q.v.) deficiencies (the main fat soluble vitamins) can be eliminated by giving Abidec® or Dalivit® drops (as outlined in the monograph on multiple vitamins). Marginally low serum α tocopherol levels occasionally persist, however, even in children taking pancreatin, a well balanced diet, and a 25 mg supplement of vitamin E (q.v.) by mouth each day. Whether this matters is far from clear.

Supply

Pancrex V '125' capsules are a convenient first preparation to use in the neonatal period. They contain a minimum of 160 protease units, 2950 lipase units, and 3300 amylase units per capsule, and cost 3p each. Enteric coated microspheres, which deliver a higher proportion of the constituent enzymes intact into the small intestine, have completely replaced powders for older children. Store all products in a cool place.

References

- Davis PB, Drumm M, Konstan MW. Cystic fibrosis. *Am J Respir Crit Care Med* 1996;**154**:1229–56.
- Feranckak AP, Sontag MK, Wagener JS, et al. Prospective, long-term study of fat-soluble vitamin status in children with cystic fibrosis identified by newborn screen. *J Pediatr* 1999;**135**:601–10.
- Littlewood JM, Wolfe SDP. Control of malabsorption in cystic fibrosis. *Paediatr Drugs* 2000;**2**:205–22.
- Anonymous. Neonatal screening for cystic fibrosis. *J Med Screen* 2001;**8**:404–5.
- Ratjen F, Döring G. Cystic fibrosis [Seminar]. *Lancet* 2003;**361**:681–9.

See relevant Cochrane reviews of cystic fibrosis care



Use

Pancuronium causes sustained muscle paralysis. Ventilated babies should not be paralysed unless they are sedated, and most sedated babies do not need paralysis. Sustained paralysis is usually offered only to babies needing major respiratory support who continue to "fight" the ventilator despite sedation.

Pharmacology

Pancuronium is a competitive non-depolarising muscle relaxant developed in 1966 as an analogue of curare (tubocurarine), the arrowtip poison used by South American Indians. Pancuronium competes (like tubocurarine) with acetylcholine for the neuromuscular receptor sites of the motor end plates of voluntary muscles. It is partly metabolised by the liver and then excreted in the urine with a half life that is variably prolonged in the neonatal period. Simultaneous treatment with magnesium sulphate (q.v.) or an aminoglycoside will further prolong the period of blockade. Pharmacokinetic information does not seem to have influenced the empirical dose regimens generally used in neonatal practice. Very little crosses the placenta but doses of 100 micrograms/kg have been given into the fetal circulation to induce fetal paralysis prior to intrauterine fetal transfusion. Larger doses cause paralysis for 2–4 hours.

Sedation or paralysis can reduce lung barotrauma in small babies requiring artificial ventilation, reducing the risk of pneumothorax and prolonged oxygen dependency due to early bronchopulmonary dysplasia, but there are no grounds for sedating or paralysing babies as a *routine*. Paralysis makes it much more difficult to judge whether a baby is in pain, and sedation or paralysis each make it harder to watch for seizures or assess a baby's neurological status. Vecuronium (q.v.) is a related drug that is largely cleared from the body through the biliary tract rather than the renal tract; it may be a better drug to use where there is renal failure. Atracurium (q.v.) may be the best drug to use in this situation; it is usually given as a continuous infusion because it has a much shorter duration of action. Suxamethonium (q.v.) is the drug to use when paralysis is required for only a few minutes.

Never paralyse a non-ventilated baby without first checking that you can achieve facemask ventilation, and never paralyse a ventilated baby without first checking whether pain, correctable hypoxia, respiratory acidosis, inadequate respiratory support, or an inappropriate respiratory rate is the cause of the baby's continued non-compliance. The prophylactic use of pancuronium may theoretically reduce the risk of fluctuations in cerebral blood flow velocity, but only two very small trials have, as yet, looked at this issue. Pancuronium sometimes produces a modest but sustained increase in heart rate and blood pressure, but does not usually have any noticeable effect on gastrointestinal activity or bladder function, and its use does not preclude continued gavage feeding. Joint contractures responsive to gentle physiotherapy have been reported in a few chronically paralysed babies but such problems seem to resolve spontaneously once the infant is no longer paralysed.

Treatment

First dose: Give 100 micrograms/kg to obtain prompt paralysis. Take a blood gas sample 20–30 minutes later (or use transcutaneous monitoring) to check for CO₂ accumulation. Restless babies who appear to be "fighting the ventilator" may have been contributing to their own ventilation because of inadequate artificial ventilatory support, in which case paralysis will only exacerbate the problem.

Further doses: Most babies continue to comply with the imposed ventilatory rate as they "wake" from the first paralysing dose (especially if a moderately fast rate and a relatively short (< 0.7 second) inspiratory time is used) but a few require prolonged paralysis. The standard repeat dose is half the initial dose IV (or IM) every 4–6 hours as need arises, but some larger and older babies seem to require a higher maintenance dose.

Antidote

Give a combination of 10 micrograms/kg of glycopyrronium (or 20 micrograms/kg of atropine) and 50 micrograms/kg of neostigmine IV, as outlined in the monograph on glycopyrronium.

Supply

2 ml ampoules containing 2 mg/ml cost 65p each. Dilute 0.5 ml from the ampoule with 0.5 ml of 0.9% sodium chloride in a 1 ml syringe before use to obtain a preparation containing 100 micrograms in 0.1 ml. Pancuronium is stable for up to 6 weeks at 25°C, but is best stored, wherever possible, at 4°C. Open ampoules should not be kept. The US product contains 1% benzyl alcohol.

References

- Costarino AT, Polin RA. Neuromuscular relaxants in the neonate. *Clin Perinatol* 1987;**14**:965–99.
 Besunder JB, Reed MD, Blumer JL. Principles of drug biodisposition in the neonate. A critical evaluation of the pharmacokinetic–pharmacodynamic interface (part II). *Clin Pharmacokinet* 1988;**14**:261–86.
 Fanconi S, Ensner S, Knecht B. Effects of paralysis with pancuronium bromide on joint mobility in premature infants. *J Pediatr* 1995;**127**:134–6.

See also relevant Cochrane reviews



PAPAVERINE

Use

Papaverine has been used experimentally in a few centres to reduce vasospasm and prolong the life of peripheral arterial catheters.

Pharmacology

Papaverine is an alkaloid present in opium, although it is not related, either chemically or pharmacologically, to the other opium alkaloids. It was first isolated in 1848 and was briefly in vogue as a vasodilator and antispasmodic in the 1920s prior to the development of synthetic analogues of atropine. It has a direct relaxant effect on smooth muscle, probably because it inhibits phosphodiesterase, and is now most frequently used by intercavernosal injection in the treatment of male impotence. It can, however, cause general vasodilatation, and has been shown, in a randomised controlled trial involving over 200 children, to extend the functional life of peripheral arterial cannulas. A similar trial will be needed to show that this form of prophylaxis is not only effective but also safe when used in the preterm baby, because vasodilatation could have adverse cerebrovascular consequences. A sustained low dose intra-arterial infusion of tolazoline (q.v.) has been used for the same purpose, and has also been used to abolish the acute "white leg" occasionally caused by femoral artery spasm following umbilical artery catheterisation (the usual dose being 100 micrograms/kg per hour). Low dose heparin (q.v.) can also be used to extend catheter patency.

Adverse effects of papaverine are uncommon, but they include flushing, hypotension, and gastrointestinal disturbances. High doses can cause cardiac arrhythmia. The drug is rapidly metabolised by the liver and excreted in the urine, the adult half life being variable, but usually only a little more than 1 hour. Nothing is known about the time course of drug elimination in the neonatal period, or the effect of maternal use during pregnancy or lactation.

Take care not to confuse papaveretum for papaverine. Papaverine can be confused with papaveretum, a preparation containing a mixture of opium alkaloids (including morphine and codeine as well as papaverine hydrochloride) with potentially fatal consequences.

Treatment

A slow syringe-controlled infusion should be used to maintain catheter patency. 100 micrograms/ml of papaverine made up as described below, and infused at a rate of 1 ml/hour (with or without additional heparin), can prolong the functional life of a peripheral arterial line. This fluid must **not** be used to flush the catheter through after sampling; any such bolus of papaverine could cause marked vasodilatation.

Compatibility

Papaverine was co-infused with heparin in the controlled trial referred to above.

Supply

Papaverine is an unlicensed product obtainable by the pharmacy to special order. Ampoules containing 30 mg in 2 ml cost £2.20 each. To obtain a solution containing approximately 100 micrograms/ml take 5 mg (0.3 ml) of papaverine, dilute to 50 ml with dextrose, dextrose saline, or saline, and infuse at a rate of not more than 1 ml/hour using a syringe pump. 0.9% sodium chloride is the most frequently used infusion fluid, but the sodium thus infused needs to be carefully considered when calculating the preterm baby's total daily sodium requirements. Dextrose or dextrose saline may be a better option.

References

- Heulitt MJ, Farrington EA, O'Shea TM, *et al*. Double blind, randomised, controlled trial of papaverine-containing infusions to prevent failure of arterial catheters in pediatric patients. *Crit Care Med* 1993;**21**:825-9. [RCT]
Griffin MP, Kendrick AS. Does papaverine prevent failure of arterial catheters in neonates? [Abstract] *Pediatr Res* 1995;**37**:207A.

Use

Paracetamol is a useful oral analgesic also sometimes used to control fever.

Pharmacology

Paracetamol is an analgesic and antipyretic with no anti-inflammatory properties, first marketed as an alternative to phenacetin in 1953. With the implication of aspirin (q.v.) as a trigger factor in some cases of Reye's syndrome, this is now no longer recommended for children under 16 years (except as an antithrombotic and in Kawasaki disease), and paracetamol has become the most widely used analgesic for children with headache, earache, or musculoskeletal pain. Although it can help to control postoperative pain if started 1–2 hours before surgery, visceral pain needs opiate analgesia. It has not been shown to reduce the response seen to the pain caused by neonatal circumcision or blood sampling, but the dose used in some of these studies was not very high. Its value in babies with cerebral irritability has never been properly evaluated. Intermittent (p.r.n.) administration provides suboptimal pain relief. Tolerance does not develop with repeated use (as it does with opioid drugs), and respiratory depression is not a problem, but there is an analgesic ceiling that cannot be overcome by using a higher dose.

Paracetamol is rapidly absorbed by mouth, widely distributed in the body ($V_D \sim 1$ l/kg), and mostly conjugated in the liver before being excreted in the urine. An IV formulation (propacetamol) exists, but it is available only in mainland Europe. The principal metabolite changes during childhood, but elimination in babies over 3 months old (half life ~ 3 hours) is as rapid as in adults. Elimination is a little slower in term babies at birth (4 hours), and initially 8 hours in babies born more than 8 weeks early. Rectal absorption is slow, incomplete, and influenced by the volume given. Toxicity is uncommon in infancy, possibly because reduced cytochrome P450 activity limits toxic arene metabolite production, but an overdose could still cause late lethal liver failure if not treated promptly. Use is safe during pregnancy and lactation (the baby receives only 5% of the weight related maternal dose from breast milk).

Management of fever

While paracetamol, like ibuprofen (q.v.), can undoubtedly give symptomatic relief to a child with a severe flu-like illness (just as an adult will sometimes take two aspirins and retire to bed), its use to control fever *per se* is usually uncalled for, and animal evidence suggests that its use in infection can actually do harm. A single 30 mg/kg oral dose often suffices. Prophylactic use in children prone to febrile convulsions is of no proven value, because most seizures actually occur while the body temperature is still rising, and the seizures themselves (which are hazardous only if prolonged) can be stopped with rectal diazepam (q.v.). Most feverish children merely need to be unwrapped. Forced cooling does not work.

Treatment

Oral pain relief: Give a loading dose of 24 mg/kg (1 ml/kg of the oral elixir) followed by a maintenance dose of 12 mg/kg every 4 hours (every 8 hours in babies of less than 32 weeks gestation). The maintenance dose can be 18 mg/kg every 4 hours in children over 3 months old. While this is more than is usually recommended, much current treatment is subtherapeutic. Check the blood level before giving sustained high dose treatment for more than 24 hours to a baby under 3 months old.

Rectal administration: Give a 36 mg/kg loading dose. Term babies can have further 24 mg/kg doses every 8 hours, and children over 2 months old can have such a dose once every 6 hours.

Toxicity

Lethal liver damage can occur if the plasma level exceeds 150 mg/l 4 or more hours after ingestion (1 mg/l = 6.62 mmol/l). The maximum safe level after repeated use is less certain. Give 150 mg/kg of IV acetylcysteine *promptly* over 30 minutes, in a little 5% dextrose, if there is concern. Then give 12 mg/kg per hour for 4 hours, followed by 4 mg/kg per hour for 48 hours. Later doses can be given orally.

Blood levels

Levels can be measured in 50 μ l of plasma. Pain relief probably requires a plasma level of 12–24 mg/l, as does the optimal control of fever. Patients can be asymptomatic despite toxic blood levels.

Supply

A sugar-free elixir containing 24 mg/ml is available (100 ml costs 30p). Dosing can be more precise, and uptake is quicker, when this elixir is used instead of a suppository for rectal administration. 10 ml ampoules of acetylcysteine (200 mg/ml) cost £2-60.

References

- Anderson BJ. What we do not know about paracetamol in children. *Paediatr Anaesth* 1998;**8**:451–60.
Hahn TW, Henneberg SW, Hol-Knudsen RJ, et al. Pharmacokinetics of rectal paracetamol after repeated dosing in children. *Br J Anaesth* 2000;**85**:512–19.
Arana A, Morton NS, Hansen TG. Treatment with paracetamol in infants. *Acta Anaesthesiol Scand* 2002;**45**:20–9.

See also relevant Cochrane reviews



PARALDEHYDE

Use

Paraldehyde can be used to achieve the rapid short term control of persistent non-hypoglycaemic convulsions that are resistant to full loading doses of IV phenobarbital (q.v.).

Pharmacology

Paraldehyde, a polymer of acetaldehyde, has been used for a century as a sedative hypnotic and for seizure control. It is a potent anticonvulsant capable of controlling seizures refractory to phenobarbital and phenytoin (q.v.) without causing respiratory depression. It exerts its action rapidly and is then eliminated from the body with a half life that is rather variable, but only a little shorter than that of most other anticonvulsants used in the neonatal period. It crosses the placenta, but there is nothing to suggest that its use is hazardous in pregnancy.

Drug elimination is by oxidation to acetaldehyde and CO₂ in the liver and also by direct excretion through the lungs. Dispersal into body tissues is very variable ($V_D \sim 4$ l/kg). The half life in babies is also very variable (8–27 hours) but generally rather longer than in children (7–5 hours) and adults (6 hours). The dose given does not need to be modified in babies with kidney failure because renal clearance is negligible. Further doses should not be given for 2 days because of the drug's variable and prolonged neonatal half life. It has been suggested that high barbiturate levels can retard drug clearance by the liver, probably because of competition for the liver's oxidative pathways, but this remains to be confirmed. It is equally possible that the prolonged half life often seen in the first week of life could be a consequence of the impact of intrapartum asphyxia on liver metabolism. The management of babies in whom EEG evidence of seizure activity persists despite treatment with both phenobarbital and phenytoin is in urgent need of further study. Paraldehyde has fallen out of favour, but may well turn out to be quite effective if a blood level of 100 mg/l can be achieved. Lidocaine and valproate (q.v.) are alternatives currently under study.

The IM route has been widely used in babies. Although standard texts now generally consider the rectal route to be safer, absorption is then slower and rather less reliable. Large injections are painful and can cause an unpleasant sterile abscess with subsequent muscle and/or nerve damage, but such problems are uncommon following the deep IM injection of volumes not exceeding 1 ml. Diazepam (q.v.) is more widely used to control seizures in a home setting. It was, until recently, usually given rectally, but is now known to be more rapidly and reliably absorbed from the nasal or buccal mucosa.

Treatment

Intramuscular: Give 0.2 ml/kg *deep* IM. A second identical dose should be given if seizures persist or recur. Undiluted paraldehyde can be given from a plastic syringe as long as it is injected as soon as it is drawn up, but it should not be left in the syringe for more than 10 minutes because it reacts chemically with most plastics other than polythene or polypropylene.

Intravenous: Paraldehyde *can* be given as an IV infusion, but the use of this route is now generally discouraged, and there is no need to use a continuous infusion in order to sustain satisfactory anticonvulsant levels for at least 24 hours, given the drug's long neonatal half life. To give 0.4 ml/kg of paraldehyde (the maximum safe dose) as an IV infusion, dilute 2.5 ml of paraldehyde to 50 ml with 5% dextrose and then give 4 ml/kg per hour of this solution as a continuous infusion for *just 2 hours*. Such an infusion has to be given through a polypropylene (not a polyvinyl chloride (PVC)) syringe and infusion line.

Rectal: Give 0.4 ml/kg once only, mixed in a syringe with an equal volume of olive oil (or mineral oil).

Supply

Stock 5 ml ampoules of paraldehyde (containing 1 g/ml) cost £9.50 each. Do not use the ampoule if there is evidence of brown discolouration.

Most syringes and infusion sets are made with PVC. The Plastipak® syringes made by Becton Dickinson are made of polypropylene, as are some of the extension sets marketed by Vygon.

References

- Giacioia GP, Gessner IK, Zaleska MM, *et al*. Pharmacokinetics of paraldehyde disposition in the neonate. *J Pediatr* 1984;**104**:291–6.
Koren G, Butt W, Tajchgot P, *et al*. Intravenous paraldehyde for seizure control in newborn infants. *Neurology* 1986;**36**:108–11.

Use

Amino acid solutions, together with glucose and other trace nutrients, are used with or without Intralipid® (q.v.), to supplement or replace enteral feeding when milk feeds are contraindicated or poorly tolerated.

Nutritional factors

Intravenous solutions are capable of providing every nutrient necessary for growth, although enteral feeding is always to be preferred where it is possible. Serious progressive cholestatic jaundice can occur in the preterm baby who is not offered at least a little milk by mouth, and sepsis can exacerbate this problem. Preterm babies not given at least 1 g/kg of protein a day develop a progressive negative nitrogen balance, and an intake of at least 2–3 g/kg a day is necessary to support growth.

The standard neonatal preparation that is most widely used in the north of England contains glucose and a mixture of synthetic L-amino acids (Vaminolact®) with trace minerals (7.5 ml/l of Peditrace®) water soluble vitamins (0.7 of a vial of Solivito N®) and an extra 30 mg ascorbic acid per litre, and a basic quantity of sodium (27 mmol/l), potassium (20 mmol/l), calcium (12.5 mmol/l), magnesium (1.3 mmol/l) and phosphate (12.3 mmol/l). This provides either 2.7 or 3.5 g/l of nitrogen (17 or 22 g/l of protein), and is available formulated so that the final glucose concentration is 10%, 12.5%, or 15% (providing 400, 500, or 600 kcal/l of energy). It contains no iron. Solutions containing more than 10% glucose rapidly cause thrombophlebitis unless infused into a large vessel. Intralipid with Vitlipid N® infant should be added to augment the calorie intake and provide the baby's other nutritional needs. Amino acid solutions with a profile derived from placental uptake, or similar to that seen in breast milk, are now generally used; these contain taurine, and do not produce the high plasma tyrosine and phenylalanine levels seen when a product based on egg protein is used. The acidosis that develops when the intake of non-metabolisable chloride exceeds 6 mmol/kg per day can be reduced by substituting up to 6 mmol/kg of acetate. Aluminium (present as a contaminant in some ingredients – notably calcium gluconate) can cause permanent neurological damage.

Intake

Babies taking nothing by mouth can usually be started on 6 ml/kg per hour of the standard 10% solution with 2.7 g/l of nitrogen. It is usually possible to further increase the energy intake, once the baby is stable, by using formulations containing 12.5% or 15% glucose (if a central 'long line' is available), or by increasing the infusion rate to 7 or 8 ml/kg per hour. Such a policy provides 2.4 g/kg of protein a day from the outset. A higher protein intake may be needed to optimise growth if all nutritional needs need to be met IV for many weeks. Additional phosphate (q.v.) may also be needed. Babies of <30 weeks gestation may also need another 2–3 mmol/kg of sodium a day to replace loss due to renal immaturity.

Administration

Individually prepared infusions can be supplied, but this doubles the total cost, and outcomes using a standardised preparation are generally just as good. Whether it is appropriate to add heparin (q.v.) remains inadequately studied. A few other drugs (as noted in the relevant monographs in this compendium) can be co-infused with the formulation specified here if lack of vascular access so demands, but this may increase the risk of sepsis. These should be infused using a Y connector sited as close to the patient as possible. Add *nothing* to any amino acid solution after it leaves the pharmacy.

Monitoring

Clinically stable children require only marginally more biochemical monitoring than bottle fed babies when on the formulation described here: it is the problem that made parenteral nutrition necessary that usually makes monitoring necessary. Ignore urinary glucose loss unless it exceeds 1%. Liver function should be monitored. Sepsis is the main hazard associated with any reliance on IV nutrition.

Tissue extravasation

'Tissue burns' are much more serious than those caused by a comparable solution of glucose. A strategy for the early treatment is described in the monograph on hyaluronidase (q.v.).

Supply

Standard nominal half-litre bags cost about £20 each. Specially formulated bags are also available. Bags should be changed aseptically after 48 hours; change bag, filter **and** giving set every 96 hours.

References

- Heird WC. Parenteral feeding. In: *Effective care of the newborn infant*. Sinclair JC, Bracken MB, eds. Chapter 8, pp. 141–60. Oxford: Oxford University Press, 1992. [SR]
- Bishop NJ, Morley R, Day JP, et al. Aluminium neurotoxicity in preterm infants receiving intravenous-feeding solutions. *N Engl J Med* 1997;**336**:1557–61. [RCT]
- Kelly DA. Liver complications of pediatric parenteral nutrition – epidemiology. *Nutrition* 1998;**14**:153–7.
- Beecroft C, Martin H, Puntis JW. How often do parenteral nutrition prescriptions for the newborn need to be individualized? *Clinical Nutrition* 1999;**18**:83–5.

See also relevant Cochrane reviews



PENICILLAMINE

Use

Penicillamine is used to treat heavy metal poisoning and in the long term management of severe rheumatoid arthritis and Wilson's disease. Two small studies of prophylaxis have suggested that it has the potential to reduce the risk of retinopathy of prematurity.

Pharmacology

Penicillamine is obtained by controlled hydrolysis of penicillin. It was discovered in 1943 and first came into clinical use in 1956 because of its ability to bind with (chelate) lead, copper, mercury, iron, and other heavy metals to form a stable complex that is then excreted in the urine. It is well absorbed when taken by mouth and mostly metabolised by the liver prior to slow biphasic excretion in the urine (the plasma half life being 1–6 hours). No complications have been seen with short term oral treatment, but sustained use has been associated with skin problems and marrow dysfunction, and with nephrotic syndrome caused by a membranous nephropathy.

The drug is sometimes used in children with cystinuria (a recessively inherited defect of dibasic amino acid transport in the proximal tubule) if simpler measures, such as a high fluid intake and the use of sodium bicarbonate (q.v.) to keep the urine alkaline (pH predominantly ≥ 6), do not suffice to prevent stone formation. Use the minimum dose needed to keep the urinary cystine concentration reliably below its solubility limit (300 mg/l). Treatment with 20 mg/kg per day is routinely used in Wilson's disease (a recessively inherited metabolic disorder associated with excessive copper accumulation) where lifelong treatment has revolutionised the management of a previously fatal condition. A similar dose may counteract the copper poisoning that seems to be responsible for Indian childhood cirrhosis, if started early enough. Variable amounts may be needed in the management of rheumatoid factor positive juvenile chronic arthritis. Adverse effects are not uncommon, and can be severe, but they usually resolve when the drug is discontinued. Reports exist of the use of penicillamine in more than 100 pregnancies. Most babies have been unaffected at birth, although a minority have shown signs of cutis laxa. Treatment should certainly not be stopped in a woman with Wilson's disease, although it may be wise to keep the daily dose below 500 mg. There is no information on drug use during lactation.

Two small Hungarian trials, involving 281 preterm babies, have suggested that early, prophylactic, high dose administration in the very preterm baby may significantly reduce the risk of retinopathy of prematurity, either by impeding new vessel growth by reducing the bioavailability of vascular growth factors, or by acting as a free-radical oxygen scavenger (a property it shares with vitamin E (q.v.), which has also been used in much the same way). Such treatment should at present be contemplated only within the context of a properly conducted, randomised controlled trial, because safety needs to be established as systematically as efficacy before any drug as potent as penicillamine is used on the many in order to benefit the few.

Prophylaxis for retinopathy

The only trials undertaken to date have used 100 mg/kg of penicillamine IV once every 8 hours for 3 days, and then 50 mg/kg once a day for 2 weeks.

Monitoring long term treatment

The care of patients requiring sustained treatment with penicillamine should be supervised by a clinician experienced in the management of metabolic disease. It is generally considered important to check the blood count initially once a week and then monthly, and to suspend treatment if the white cell count falls below $2.5 \times 10^9/l$, or the platelet count falls below $120 \times 10^9/l$. Nephrotoxicity with proteinuria is an occasional problem. Prednisolone has sometimes been given briefly if toxic symptoms develop.

Supply

Penicillamine is usually supplied as 125 mg tablets costing 9p each, but the pharmacy can prepare a sugar-free 10 mg/ml suspension for oral use, which is stable for 4 weeks if stored at 4°C. No commercial IV preparation is available at present, and the pharmacy would require substantial prior notice of any request for an IV product.

References

- Oga M, Matsue N, Anai T, *et al.* Copper disposition of the fetus and placenta in a patient with untreated Wilson's disease. *Am J Obstet Gynecol* 1993;**169**:196–8.
- Bavdekar AR, Bhawe SA, Pradhan AM, *et al.* Long term survival in Indian childhood cirrhosis treated with D-penicillamine. *Arch Dis Child* 1996;**74**:32–5.
- Chow GK, Strem SB. Medical treatment of cystinuria: results of contemporary clinical practice. *J Urol* 1996;**156**:1579–80.
- Sanchez-Albisua I, Gartde T, Hierro L, *et al.* A high index of suspicion: the key to the early diagnosis of Wilson's disease in childhood. *J Pediatr Gastroenterol Nutr* 1999;**28**:186–90.
- Cox DW, Tümer Z, Roberts EA. Copper transport disorders: Wilson disease and Menkes disease. In: Fernandes J, Saudubray J-M, van den Berghe G, eds. *Inborn metabolic diseases. Diagnosis and treatment*, 3rd ed. Chapter 33. Berlin: Springer-Verlag, 2000:384–91.

See also Cochrane review of use to prevent retinopathy of prematurity



Use

Benzylpenicillin is the treatment of choice for pneumococcal, meningococcal, aerobic and anaerobic streptococcal, and gonococcal infections. It is also very adequate for infection with *Listeria*, although ampicillin or amoxicillin (q.v.) is even better. Flucloxacillin (q.v.) is more appropriate for staphylococcal infection because most staphylococci produce penicillinase. Procaine penicillin (q.v.) is traditionally used to treat syphilis. Poor umbilical care can cause death from tetanus (clostridial infection) when the mother is unimmunised unless the baby is given high dose penicillin and 150 units/kg of IM tetanus immune globulin.

Pharmacology

Benzylpenicillin is a naturally occurring, bactericidal substance, first used clinically in 1941, which acts by interfering with bacterial cell wall synthesis. Fetal concentrations approach those in maternal serum, but extremely little is ingested in breast milk. Since it is also destroyed by gastric acid and poorly absorbed by the gut, there is no contraindication to its use during lactation. Phenoxymethylpenicillin (penicillin V), which is acid stable, should be used when penicillin is given by mouth; give 25 mg/kg doses at the same time intervals as for the IV or IM drug. Active excretion by the renal tubules is the most important factor affecting the serum half life, which falls from 4–5 hours at birth to 1.5 hours by 1 month (gestation at birth having only a modest influence on this). Exposure may further stimulate tubular secretion. Very high levels are neurotoxic, making it important to reduce the dose or choose a different drug when there is renal failure. Transient thrombocytopenia can also occur. Allergic reactions are the main hazard in those with a history of prior exposure. Penetration into the cerebrospinal fluid is limited, even when the meninges are inflamed, and the recommended dose regimen takes this into account. Intrathecal injections are seldom necessary.

Intrapartum group B streptococcal prophylaxis

Neonatal death from intrapartum acquired group B streptococcal infection is now more common than death from surfactant deficiency in babies weighing ≥ 1.5 kg, but North American screening policies have still not been widely adopted in the UK. Intermittent bowel carriage is common in adults. This seldom causes symptoms but can cause urinary infection during pregnancy. However, half the babies born to carriers also become carriers for a time, and 1–2% develop life threatening infection within hours of birth. Carriage cannot be eliminated by antenatal treatment and early neonatal infection often spreads too rapidly for postdelivery treatment to be effective, but prophylaxis started at least 4 hours before delivery greatly reduces the risk of neonatal illness. Current US guidelines recommend that "at risk" mothers should have 3 g of benzylpenicillin every 6 hours as a slow IV injection in labour. Women who are allergic to penicillin should receive IV erythromycin or clindamycin (q.v.). Offer prophylaxis to known carriers, to mothers in active preterm labour, mothers whose membranes have been ruptured ≥ 18 hours, and mothers with intrapartum pyrexia ($\geq 38^\circ\text{C}$). These babies require further investigation or treatment after delivery only if they are symptomatic or born before 35 weeks gestation. An alternative strategy for protecting babies from *all* early onset bacterial sepsis is outlined in the monograph on ampicillin.

Treatment

Dose: Give 60 mg/kg per dose IM or (slowly) IV when there is evidence of meningitis (especially group B streptococcal meningitis); 30 mg/kg is more than adequate in all other circumstances. Consider giving gentamicin (q.v.) synergistically for 48 hours for infection with group B streptococci or *Listeria*.

Timing: Give one dose every 12 hours in the first week of life, one dose every 8 hours in babies 1–3 weeks old, and one dose every 6 hours in babies 4 or more weeks old. The dose should be halved and the dosage interval doubled when there is renal failure. Give treatment for at least 10 days in proven pneumonia and septicæmia, and in the management of congenital syphilis. Treat meningitis for 3 weeks and osteitis for 4 weeks. Oral medication is sometimes used to complete a course of treatment.

Supply and administration

A 600 mg (one million units or one "mega unit") vial costs 44p. Add 5.6 ml of sterile water for injection to get a solution containing 10 mg in 0.1 ml. Slow IV administration has been advocated, but there is no published evidence to support this advice (see website commentary). A 60 mg/kg dose of the UK product contains 0.17 mmol/kg of sodium (most US products contain the potassium salt). Staff handling penicillin regularly should avoid getting the antibiotic on their hands as this can cause skin sensitisation. Oral penicillin V (25 mg/ml) is available as a syrup (£1.70 per 100 ml) which is stable for 2 weeks after reconstitution if stored at 4°C .

References

- See the relevant Cochrane reviews of group B streptococcal prophylaxis American Academy of Pediatrics. Committee on Infectious Disease and Committee on Fetus and Newborn. Revised guidelines for prevention of early onset group B streptococcal (GBS) infection. *Pediatrics* 1997;**99**:489–96.
- Mercer BM, Carr TL, Beazley DD, et al. Antibiotic use and drug-resistant infant sepsis. *Am J Obstet Gynecol* 1999;**181**:816–21.
- Schrag SJ, Zywicki S, Farkey MM, et al. Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis. *N Engl J Med* 2000;**342**:15–20.
- Oddie S, Embleton ND. Risk factors for early onset neonatal group B streptococcal sepsis: case control study. *BMJ* 2002;**325**:308–11.



Use

Pethidine remains widely used to relieve pain during labour, although evidence of efficacy is limited. Use in infancy has received little study, and toxic quantities of the active metabolite, norpethidine, can accumulate with repeated administration. Morphine (q.v.) remains by far the best studied neonatal analgesic.

Pharmacology

Pethidine is a synthetic opioid developed in Germany during a review of the many analogues of atropine in 1939. The dose required to provide analgesia is variable. It is only a tenth as potent as morphine and its analgesic effect is not as well sustained. It was originally hoped that, because it bears no chemical similarity to morphine, it would not be addictive, but this is not so. Oral bioavailability is limited (about 50%) because of rapid first pass clearance by the liver, where the drug undergoes hydrolysis or demethylation and conjugation before excretion. Tissue levels markedly exceed plasma levels ($V_D \sim 7 \text{ l/kg}$), and clearance in the first 3 months is much slower than later in infancy. The average half life in young babies is about 11 hours and also very variable (range 3–60 hours), but in babies 3–18 months old it may be even lower than it is in adults (half life about 3.5 hours). Similar half life changes have been documented for morphine. This variation between patients and over time, and the lack of any clear evidence as to what constitutes an effective analgesic dose, makes it difficult to recommend the use of pethidine in young children. The active metabolite, norpethidine, is renally excreted. It has an extended half life, and neurotoxic quantities can accumulate with repeated usage, particularly if there is renal failure.

Increased scepticism is being voiced about the drug's central place in the management of pain relief in labour but, at the moment, it remains the only parenteral analgesic that midwives in the UK can give on their own authority. It often causes more drowsiness, disorientation, and nausea than genuine relief from pain. Morphine is no better. Sclerotic legislation denies midwives and their patients straight access to any other parenteral analgesic, while the scope for nitrous oxide analgesia (q.v.) remains undervalued.

Pethidine crosses the placenta rapidly, and cord levels in babies delivered 1–5 hours after the mother has had an IM injection during labour are higher than the corresponding maternal levels. Neonatal respiratory depression is most often seen 2–3 hours after such an injection. Feeding may be slow, and some babies show impaired behavioural responses and EEG abnormalities for 2–3 days after birth. The drug appears in breast milk, but no adverse effects have been recorded after maternal use during lactation. There is no evidence of teratogenicity.

Pain relief

Maternal pain relief in labour: A single dose of 100 mg or 150 mg is usually administered IM. This may be repeated once during labour but rarely, if ever, more often than this. Try to avoid using a total of more than 1.5 mg/kg.

Pain relief in infancy: A dose of 1 mg/kg IM or IV has been used, but usually only in babies receiving ventilatory support. No repeat dose should be given for 10–12 hours in babies less than 2 months old (or for 4–6 hours in infants more than 3 months old) if drug accumulation is to be avoided.

Antidote

Opiate depression is readily reversed by naloxone (q.v.), although this antidote still costs eight times as much as the earlier dose of pethidine. It does not seem to reverse the signs of neurotoxicity.

Supply and administration

1 ml and 2 ml ampoules containing 50 mg/ml are available. They cost approximately 50p each. Take 0.2 ml (10 mg) from the ampoule and dilute to 1 ml with dextrose, saline, or dextrose saline to obtain a preparation containing 10 mg/ml for accurate IM or IV administration.

The storage and administration of pethidine is controlled under Schedule 2 of the UK Misuse of Drugs Regulations 1988 (Misuse of Drugs Act 1971). Midwives in the UK have the legal right to prescribe pethidine or pentazocine with or without promazine, oxytocin or Syntometrine® and naloxone, and to give lidocaine during labour, on their own authority, (as outlined in the website commentary). Other analgesics can be given if use is covered by a patient group direction.

References

- Armstrong PJ, Bersten A. Normeperidine toxicity. *Anesth Analg* 1986;**65**:536–8.
- Pokela M-L, Olkkola KT, Koivisto M, et al. Pharmacokinetics and pharmacodynamics of intravenous meperidine in neonates and infants. *Clin Pharmacol Ther* 1992;**52**:342–9.
- Pokela M-L. Pain relief can reduce hypoxia in distressed neonates during routine treatment procedures. *Pediatrics* 1994;**93**:379–83. [RCT]
- Saneto RP, Fitch JA, Cohen BH. Acute neurotoxicity of meperidine in an infant. *Pediatr Neurol* 1996;**14**:339–41.
- Hunt S. Pethidine: love it or hate it. *MIDIRS Midwifery Digest* 2002;**12**:363–5.
- Bricker L, Laender T. Parenteral opioids for labor pain relief: a systematic review. *Am J Obstet Gynecol* 2002;**186**:S94–109. [SR]

See also relevant Cochrane reviews

Use

Phenobarbital is widely used in the initial management of neonatal fits. It is seldom the most appropriate drug to use in the longer term management of epilepsy.

Pharmacology

Phenobarbital, first marketed as a hypnotic in 1904, was widely used as an anticonvulsant for many years but, because of its adverse effect on cognition and behaviour, its popularity has now declined sharply. There are, however, many adults still on long term medication. Oral phenobarbital is only slowly absorbed, and IM absorption can take 2–4 hours, so the drug must be given IV if a rapid response is required. An overdose can cause drowsiness, vasodilatation, hypotension, and dangerous respiratory depression. Hypothermia and hypoglycaemia have been reported. The drug is largely metabolised in the liver, but a quarter is excreted unchanged in the urine in the neonatal period. The plasma half life is so long in the neonatal period (**2–4 days**) that treatment once a day is perfectly adequate, but the half life decreases with age, and is halved after 1–2 weeks of medication because the drug acts to induce liver enzymes. This enzyme inducing property has been used to speed the liver's conjugation and excretion of bilirubin. It also influences the metabolism and half life of a number of other drugs. Phenobarbital, phenytoin, and carbamazepine (q.v.) all induce hepatic microsomal enzymes, speeding the metabolism of oestrogens and progestogens, making it unwise for women to rely on a low dose oral contraceptive when taking any of these anticonvulsants.

Maternal use

Fetal consequences: Barbiturates rapidly cross the placenta, the fetal blood level being two thirds the maternal level. There is little clear evidence of teratogenicity, but minor cardiac anomalies, skeletal defects, and palatal clefts are more common in the babies of mothers taking anticonvulsants for epilepsy. Phenytoin has been implicated more than phenobarbital in this regard and some of the reported defects may have more to do with the epilepsy than its treatment. Fetal exposure to phenobarbital may, however, have some impact on later cognitive development. The hazards associated with uncontrolled epilepsy are, however, almost certainly greater than the hazards associated with continued medication.

Neonatal consequences: The babies of mothers who are taking phenobarbital are occasionally hypoproteinaemic at birth, but this bleeding tendency can be easily corrected by giving the baby 100 micrograms/kg of vitamin K (q.v.) IM at birth. (A standard 1 mg dose is widely used.) Giving phenobarbital during labour can cause the baby to be rather sleepy and to feed poorly for 2–3 days. Some authorities (including the *BNF*) feel that breastfeeding may be unwise in mothers who are taking phenobarbital on a regular basis, and calculations suggest that neonatal blood levels could approach or exceed those seen in the mother. More information is needed because few problems have been reported in practice. Drowsiness has occasionally been alluded to, however, and there is one report of a baby who appeared to develop severe withdrawal symptoms when breastfeeding was stopped abruptly at 7 months.

Use to prevent intraventricular haemorrhage: While early reports that giving phenobarbital immediately after birth could reduce the incidence of intraventricular haemorrhage were not supported by later larger trials, there remained a belief that *antenatal* prophylaxis (typically 10 mg/kg slowly IV to the mother, followed by an oral maintenance dose of 100 mg once or twice a day) could be beneficial. Six trials involving over 1600 women have now been reported and it would seem that, yet again, the benefits suggested by a number of small trials of variable quality have not been confirmed by subsequent larger studies.

Use to prevent neonatal jaundice: Maternal treatment (typically 100 mg/day) reduces the chance that neonatal jaundice will need treatment. Neonatal treatment (typically 5–8 mg/kg per day for 2–7 days) also has a measurable effect, but is not widely used. Phototherapy (q.v.) usually suffices.

See the valproate website for a general discussion of anticonvulsant use during pregnancy and lactation.

Neonatal use

Intrapartum asphyxia: Animal evidence suggests that phenobarbital reduces the amount of damage caused by cerebral anoxia (independent of its anticonvulsant effect) and the evidence from one small trial using a prompt 40 mg/kg loading dose suggests it may also be of clinical value, although another small study, and a small trial of the barbiturate thiopental (q.v.), failed to find evidence of clinical benefit. Other possible strategies are discussed in the monograph on mannitol.

Cholestatic jaundice: Phenobarbital (5 mg/kg per day) will improve bile flow and can sometimes alleviate pruritis, although ursodeoxycholic acid (q.v.) is usually more effective. Additional vitamin K will be required. Vitamins A, D, and E (q.v.) may be needed if jaundice is prolonged.

Maternal drug dependency: Babies of mothers who are dependent on other drugs as well as opiates and who are suffering *serious* withdrawal symptoms sometimes benefit from a short 4–6 day course of phenobarbital. Start with the same loading as for seizure control (see below)

continued ...

Neonatal use (continued)

Seizures: There is no evidence that failure to control *all* seizure activity puts the baby at increased risk of long term cerebral damage. However, it is now also becoming clear that electroencephalographic (EEG) seizure activity often occurs in the absence of visible motor activity in the newborn baby, and that, when such activity is semicontinuous, it is potentially damaging. Animal evidence certainly points in that direction. Much remains to be learnt from conventional or amplitude-integrated EEG examination. Although some babies who fail to respond to a standard loading dose of phenobarbital seem to respond clinically to a higher loading dose, EEG seizure activity often continues unabated. High dose treatment (up to 40 mg/kg) also makes most babies drowsy enough to render neurological assessment difficult, and a few babies become ventilator dependent. When a high loading dose *has* been used, no daily maintenance dose should be started for at least 3–4 days (especially if there has been intrapartum asphyxia). Seizures that fail to respond to phenobarbital may respond to phenytoin (q.v.) or high dose lidocaine (q.v.), although some believe paraldehyde (q.v.) is a more appropriate first option. Clonazepam and midazolam (q.v.) seldom arrest EEG evidence of seizure activity if phenobarbital has not been successful. See the website for a longer discussion of what is currently known about the available options. Pyridoxine dependency (q.v.) and biotin deficiency (q.v.) **must** be considered if unexplained seizures do not respond to phenobarbital.

The tonic posturing and motor automatisms, the repetitive stereotypic mouthing movements, rotatory arm movements, pedalling, and stepping activity that is seen in most encephalopathic babies is clearly abnormal. The background (inter-ictal) EEG activity in these babies is also usually very abnormal.

Isolated seizures in a baby who appears alert, awake, and normal when not actually fitting, are usually well controlled by phenobarbital. These babies generally have a normal inter-ictal EEG, and their long term prognosis is usually good. If phenobarbital and phenytoin fail, carbamazepine (q.v.), valproate (q.v.), or vigabatrin (q.v.) may work. It is seldom necessary to use more than one drug. Most babies given an anticonvulsant in the neonatal period can be weaned from all treatment within 7–10 days, and few need medication at discharge from hospital.

Treatment

Give 20 mg/kg as a slow IV loading dose over 20 minutes to control seizures (once any biochemical disturbance, such as hypoglycaemia, has been excluded or treated), followed by 4 mg/kg once a day IV, IM, or by mouth. Increase this to 5 mg/kg once a day if treatment is needed for more than 2 weeks. Higher loading doses have been used (see above), but can cause significant respiratory depression.

Blood levels

The therapeutic level in the neonatal period is 20–40 mg/l (1 mg/l = 4.42 µmol/l). This is higher than the range generally quoted for use in later childhood. Drowsiness is common, especially if levels exceed 50 mg/l, and respiratory depression becomes progressively more likely, particularly in the preterm baby. Levels can be measured in 50 µl of plasma. Because of the long half life, timing is not critical.

Supply and administration

IV ampoules contain viscous propylene glycol (80–90% w/v). 1 ml (30 mg) ampoules, costing £2, are convenient for neonatal use; dilution with an equal quantity of water (giving a 15 mg/ml solution) makes injection through a fine (24 gauge) cannula easier. Greater dilution, although widely recommended, is not necessary with slow administration when this strength ampoule is used, but slow administration is important to minimise the risk of shock, hypotension, or laryngospasm. Extravasation is also damaging because the solution has a high osmolality and a high pH (10–11). An oral BNF elixir containing 3 mg/ml is available, but the alcohol content of this is potentially toxic. An aqueous, sugar-free preparation with a 2 week shelf life can be made in various strengths on request (100 ml for about 70p). Use is controlled under Section 3 of the UK Misuse of Drugs Regulations 1985 (Misuse of Drugs Act 1971).

References

See also the relevant Cochrane reviews

- Gilman JT, Gal P, Duchowny MS, *et al*. Rapid sequential phenobarbital treatment of neonatal seizures. *Pediatrics* 1989;**83**:674–8.
- Hellstrom-Westas L, Blennow G, Lindroth M, *et al*. Low risk of seizure recurrence after withdrawal of antiepileptic treatment in the neonatal period. *Arch Dis Child* 1995;**72**:F97–101.
- Hall RT, Hall FK, Daily DK. High-dose phenobarbital therapy in term newborn infants with severe perinatal asphyxia: a randomised, prospective study with three-year follow-up. *J Pediatr* 1998;**132**:345–8. [RCT]
- Painter MJ, Scher MS, Stein AD, *et al*. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. *N Engl J Med* 1999;**341**:485–9.
- Boylan GB, Rennie JM, Pressler RM, *et al*. Phenobarbitone, neonatal seizures, and video-EEG. *Arch Dis Child* 2002;**86**:F165–70.
- Toet MC, van der Meij W, de Vries LS, *et al*. Comparison between simultaneously recorded amplitude integrated electro-encephalogram (cerebral function monitor) and standard electroencephalogram in neonates. *Pediatrics* 2002;**109**:772–9.
- Coyle MG, Ferguson A, Lagasse L, *et al*. Diluted tincture of opium (DTO) and phenobarbital versus DTO alone for neonatal opiate withdrawal in term infants. *J Pediatr* 2002;**140**:561–4. [RCT]

Use

Phenytoin controls acute neonatal seizures as effectively as phenobarbital (q.v.), but phenytoin is seldom the first anticonvulsant used because it has a rather unpredictable half life. Giving one or other of these drugs controls about 45% of all neonatal seizures; giving both controls about 60%.

Pharmacology

Phenytoin was first developed and used as an antiepileptic drug in 1936. Cosmetic changes, such as gum hypertrophy, acne, hirsutism, and facial coarsening have now reduced the popularity of phenytoin as a drug of first choice in the long term management of epilepsy. Unwanted psychological changes, such as aggression, sedation, depression, and impaired memory, are also common, making carbamazepine (q.v.) and sodium valproate (q.v.) preferable first choice drugs. Phenytoin may control the arrhythmia seen with digoxin (q.v.) toxicity. An overdose can cause restlessness or drowsiness, vomiting, nystagmus, and pupillary dilatation, but symptoms resolve without specific intervention when treatment is stopped. The related prodrug, fosphenytoin (1.5 mg of fosphenytoin = 1 mg of phenytoin), is less irritant, but neonatal experience is limited and prescribing this drug in "phenytoin equivalent" units risks causing confusion.

Pharmacology in pregnancy

Phenytoin crosses the placenta freely and there is a slightly increased risk of congenital malformation (especially cleft palate and congenital heart disease) in the babies of mothers with epilepsy, which is thought to be at least partially due to anticonvulsant medication. Fetal exposure can also occasionally affect the child's appearance and measurably retard growth and intelligence. The issues are more fully discussed in a website entry linked to the monograph on valproate. While uncontrolled epilepsy is more of a hazard to the fetus than well controlled medication, many adult patients continue to take medication unnecessarily for many years without review. Mothers who need to remain on medication during pregnancy may need to take more phenytoin in the third trimester because of pharmacodynamic changes. In utero exposure can depress fetal vitamin K dependent clotting factor levels, but the risk of haemorrhage can be controlled by giving IM vitamin K (q.v.) at birth. Treatment during lactation will result in the baby receiving about a tenth of the mother's dose on a weight related basis.

Pharmacology in the neonate

Oral treatment in babies is more reliable than most texts currently maintain. Phenytoin is excreted by the liver as a glucuronide, but elimination varies unpredictably with age, is influenced by many other drugs, and changes rapidly during the neonatal period. The V_D is 1.2 l/kg. The elimination process is also rapidly saturated at plasma levels near the upper end of the therapeutic range. Small changes in the amount prescribed can have a disproportionate effect on the plasma level once clearance exceeds half the maximum rate possible (the Michaelis constant), prolonging the half life ("zero-order" kinetics).

Treatment

A loading dose of 20 mg/kg given IV over at least 20 minutes (to avoid cardiac dysrhythmia) will usually control acute status epilepticus at any age. The optimum maintenance dose is variable, but 2 mg/kg IV every 8 hours will usually maintain a therapeutic level in the first week of life, and the same maintenance dose normally works when given by mouth (at least in babies over 2 weeks old). Older babies may require two or three times as much as this. Crystallisation makes the IM route unsatisfactory.

Blood levels

The optimum plasma concentration is usually 10–20 mg/l (1 mg/l = 3.96 μ mol/l), but 20% less than this in the first 3 months of life because of reduced protein binding. Levels must be measured if phenytoin is given for more than 2–3 days. Collect 50 μ l of plasma just before the drug is due to be given.

Supply and administration

5 ml (250 mg) ampoules of phenytoin cost £3.60. Give IV through a filter, **always** preceded and followed by a bolus of 0.9% sodium chloride because crystals form when phenytoin comes into contact with any solution containing dextrose. To give IV maintenance treatment accurately, first draw 1 ml of fluid from the ampoule into a syringe and dilute to 10 ml with 0.9% sodium chloride to get a solution containing 5 mg/ml. The fluid is very alkaline (pH 12). UK ampoules contain 2 g propylene glycol; the US product also contains 10% benzyl alcohol. An oral suspension in sucrose contains 6 mg/ml (100 ml costs 71p). 750 mg (10 ml) vials of fosphenytoin (which can be given IV or IM) cost £40.

References

- Bourgeois BFD, Dodson WE. Phenytoin elimination in newborns. *Neurology* 1983;**33**:173–8.
 Takeoka M, Krishnamoorthy KS, Soman TB, et al. Fosphenytoin in infants. *J Child Neurol* 1998;**13**:537–40.
 Frey OR, von Brendorff AI, Probst W. Comparison of phenytoin serum concentrations in premature neonates following intravenous and oral administration. *Ann Pharmacother* 1998;**32**:300–3.
 Painter MJ, Scher MS, Stein AD, et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. *N Engl J Med* 1999;**341**:485–9. [RCT]

See also relevant Cochrane reviews



PHOSPHATE

Use

Supplemental phosphate (as oral sodium phosphate) can be used prophylactically to prevent neonatal rickets due to phosphate deficiency in the very low birth weight baby.

Nutritional factors

The transplacental fetal uptake of calcium and phosphate is high, especially in the second trimester of pregnancy, and comparable intakes are hard to achieve after birth in the preterm baby. The mineral content of breast milk is particularly inadequate and ordinary neonatal milk formulas (q.v.) are also deficient. Most special preterm formulas contain additional calcium and phosphate, and breast milk fortifiers (q.v.) contain calcium and phosphate for the same reason.

Deficient mineral intake after birth compromises subsequent bone growth. Poor bone mineralisation leads to osteopenia, and pathological fractures can develop once bone growth starts to accelerate after 6–8 weeks; severe deficiency can also cause rickets, with fraying and cupping of the bony metaphyses on x-ray examination. When breast milk is used, phosphate deficiency is normally the limiting factor. Low plasma phosphate levels are associated with increased hydroxylation of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol (the metabolically active form of vitamin D), increased phosphate absorption from the gut, maximum renal retention of phosphate, and hypercalciuria (which is corrected by phosphate supplementation). Parenterally fed babies develop similar problems. Formula fed babies can, on the other hand, sometimes develop a calcipenic type of rickets, with marginal hypocalcaemia and no renal calcium spill, but with secondary hyperparathyroidism with hyperphosphaturia.

There is some evidence of a prenatal deficiency of phosphate in some very low birth weight babies, possibly as a result of pre-eclampsia and/or placental insufficiency. A controlled trial of oral phosphate supplementation in those babies with a low plasma phosphate level and a high initial urinary calcium loss shortly after birth has shown that early supplementation can prevent the development of osteopenia of prematurity.

Treatment

Oral administration: Very low birth weight babies developing a plasma phosphate level of < 1.5 mmol/l in the first few weeks of life should be offered 250 micromol of extra phosphate twice a day by mouth. A few babies benefit from supplementation three times a day.

IV administration: The low solubility of inorganic calcium and phosphorus can compromise bone growth in low birth weight babies needing prolonged parenteral nutrition (q.v.). Intake can be increased to 1.5 mmol/kg per day by using the soluble organic salt, sodium glycerophosphate.

Monitoring

Treatment can be reduced or stopped when the plasma phosphate level exceeds 1.8 mmol/l and/or the tubular reabsorption of phosphate in the urine falls below 95% (in the absence of acute tubular necrosis). The renal tubular reabsorption of phosphate (%TPR) can be calculated from the formula:

$$\%TPR = 1 - \frac{\text{Urine phosphate}}{\text{Urine creatinine}} \times \frac{\text{Plasma creatinine}}{\text{Plasma phosphate}} \times 100$$

Supply

An oral solution containing 500 micromol/ml (50 mg/ml) of phosphate (similar to that used in the study published in *The Lancet* in 1990) can be prepared by adding 94.5 g of disodium hydrogen phosphate dodecahydrate and 41 g of sodium dihydrogen phosphate dihydrate to 1 litre of chloroform water.

10 ml ampoules containing 2.16 g of anhydrous sodium glycerophosphate suitable for continuous IV infusion are available in the UK through the pharmacy at The Queen's Medical Centre, Nottingham. These "special order" ampoules contain 1 mmol/ml of phosphate and 2 mmol/ml of sodium. They cost £1.10.

References

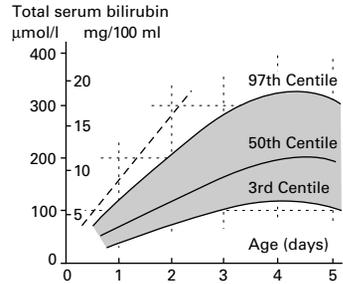
- Holland PC, Wilkinson AR, Diaz J, *et al*. Prenatal deficiency of phosphate, phosphate supplementation, and rickets in very-low-birthweight babies. *Lancet* 1990;**335**:697–701. [RCT]
- Pohlant F. Prevention of postnatal bone demineralisation in very low-birth-weight infants by individually monitored supplementation with calcium and phosphorus. *Pediatr Res* 1994;**35**:125–9.
- Costello I, Powell C, Williams AF. Sodium glycerophosphate in the treatment of neonatal hypophosphataemia. *Arch Dis Child* 1995;**73**:F44–5.
- Ryan S. Nutritional aspects of metabolic bone disease in the newborn. *Arch Dis Child* 1996;**74**:F145–8.
- Catache M, Leone CR. Role of plasma and urinary calcium and phosphorus measurements in early detection of phosphorus deficiency in very low birthweight infants. *Acta Paediatr* 2003;**92**:76–80.

Use

Effective phototherapy will immediately stop jaundice increasing unless there is abnormal haemolysis.

Physiology

Bilirubin is formed during the breakdown of the iron-containing haem component of the haemoglobin molecule. Biliverdin, the first product formed, is then converted to bilirubin in the reticuloendothelial system. One gram of haemoglobin yields 35 mg of bilirubin, and the newborn baby normally produces 8–10 mg/kg of bilirubin per day. Before birth this then crosses the placenta to be conjugated in the mother's liver and excreted in the bile, a task that the neonatal liver has to take on after birth. Conjugated (direct acting) bilirubin is water soluble and harmless, but excess unconjugated bilirubin is toxic to the brain, causing deafness, athetoid cerebral palsy, and death from kernicterus, so babies go through a vulnerable period until their liver enzymes "switch on" after birth. Normal bilirubin levels in the healthy breastfed term baby are shown in the graph. Levels above the 97th centile at 24–36 hours do not always predict high levels at 4–5 days, but levels above the dotted line suggest abnormal red cell breakdown (haemolysis) requiring additional diagnostic assessment.



Photochemistry

Phototherapy causes photo-oxidation or bleaching (as recognised by a neonatal nursing sister in 1958), a reversible configurational isomerisation (a change in molecular shape without any change in composition), and a non-reversible structural isomerisation of bilirubin, to a product called lumirubin, which is rapidly excreted in the bile and the urine without prior conjugation in the liver. The natural isomer is toxic and fat soluble, but not very water soluble. The products resulting from phototherapy are non-toxic and water soluble. As a result, phototherapy starts to detoxify the bilirubin in the blood stream even before any lumirubin is excreted into the gut or any decline in the plasma bilirubin is detectable. The bilirubin level will also fall within 2 hours, unless there is excess haemolysis, making early "just in case" treatment of moderate jaundice quite unnecessary. Skin bronzing can occur if biliary stasis causes a high conjugated bilirubin level, from an effect of light on accumulating copper porphyrin.

Treatment

Use phototherapy to prevent the total plasma bilirubin (µmol/l) from rising above a value equal to 10 times the gestational age (in weeks). Lower this ceiling by 50 µmol/l if there is haemolysis, or if the baby is ill. Remember that duplicate measurements, even from the same laboratory, may differ by 10% (95% confidence limits). Some allowance can be made for conjugated bilirubin in babies over 1 week old, but such measurements have only limited accuracy. Exchange transfusion is seldom needed. However, this does have a role where antibodies have developed in response to fetomaternal red cell incompatibility, not so much to correct anaemia or jaundice as to remove antibody coated cells, especially when anaemia (Hb < 130 g/l) has developed before birth and no intrauterine transfusion has been undertaken.

Administration

Phototherapy works only when jaundice already exists, so there is little point in starting treatment until the level approaches 170 µmol/l. The speed of decline is directly related to the amount of light used, until a plateau intensity is reached similar to that achieved outdoors in the shade on a sunny day. Unfortunately, much standard treatment is "homeopathic": a standard light cradle, with 4–8 white strip lights placed 50 cm above the baby, or a fiberoptic BiliBlanket®, provides only about one fifth as much light as this. Halogen lights are even less effective. Halving the distance between the cradle and the baby, or using both a blanket and a cradle (to give light from above and below), will double the speed with which the bilirubin level falls. Doing both speeds the fall fourfold. "Special blue" (F20T12/BB) lights are more effective than white lights. Skin exposure should be maximised and the eyes covered to prevent retinal damage. Treatment can be stopped while feeding. Extra fluid is not necessary. Skin colour cannot be used to judge jaundice in babies once they have been started on phototherapy.

References

- Maisels MJ. Why use homeopathic doses of phototherapy? *Pediatrics* 1996;98:283–7.
 Hansen TWR. Acute management of extreme neonatal jaundice – the potential benefits of intensified phototherapy and interruption of enterohepatic bilirubin circulation. *Acta Paediatr* 1997;86:843–6.

Use

There are few established indications for using plasma albumin. Pentastarch or gelatin (q.v.) serve to expand plasma volume at lower cost. Fresh frozen plasma (q.v.) is more appropriate when there is a bleeding tendency. Hypotension should be managed with an inotrope such as dobutamine (q.v.).

Blood levels

Ninety-five per cent of normal babies have a plasma albumin of between 20 g/l and 40 g/l at term, but values of between 10 g/l and 30 g/l are normal at 28 weeks gestation.

Products

Pooled plasma prepared from donated whole blood contains soluble proteins and a caprylate stabiliser, but no bactericide or clotting factors. It is prepared by cold ethanol fractionation, sterilised by filtration, and heated to 60°C for 10 hours to inactivate any contaminating viruses. An isotonic solution with a similar colloid osmotic pressure to plasma contains 4.5% albumin. A hyperoncotic, isotonic 20% solution is also available. Some products contain significant amounts of aluminium. Albumin cost five times as much as pentastarch, and 10 times as much as dextran and gelatin. A large trial in adults in Australia and New Zealand is currently addressing the doubt over safety raised by a systematic review in 1998.

Indications

Hypovolaemia: The value of plasma infusions in the neonatal period is very imperfectly established. Persisting hypotension immediately after birth, once acidosis has been corrected, can, rarely, be due to acute hypovolaemia, which is best treated by blood transfusion. Most affected babies are more appropriately treated with an inotrope such as dopamine (q.v.) and/or dobutamine. Trials in adults with burns or trauma found that crystalloids (like Ringer lactate) reduce mortality more than an albumin infusion. Some artificial colloids, such as pentastarch, may nevertheless be of value in selected patients with anaphylaxis, peritonitis, or septic shock when there are features suggesting increased capillary permeability (a capillary "leak" syndrome), although trials to support such a view have not yet been done.

Hypoproteinaemia: Underproduction due to liver failure, or to excess gut or renal loss, can cause oedema and hypovolaemia, triggering a compensatory retention of salt and water. Where this does not respond to a diuretic, 20% albumin may produce a diuresis, although the effect will be relatively shortlived because most of the body's albumin is in the extravascular space, intercompartmental exchange is rapid (even when vascular permeability is normal), and plasma protein turnover is high (25% per day). The use of albumin to treat hypoproteinaemia was actually found to increase the risk of death in one recent systematic review.

Polycythaemia: Consider a partial (dilutional) exchange transfusion if there are symptoms and a venous haematocrit of 75% or more, even though this has not yet been shown to have any impact on long term outcome, and has occasionally caused necrotising enterocolitis. While a colloid (20–30 ml/kg of gelatin or 4.5% albumin) is often used for this purpose, 0.9% sodium chloride is just as effective.

Treatment and administration

20 ml/kg of 4.5% albumin or 5 ml/kg of 20% albumin may be pickabacked terminally into an existing glucose infusion; stopping the glucose will merely precipitate reactive hypoglycaemia. Infusion (distal to any filter) into a line containing an amino acid solution (total parenteral nutrition) increases the risk of bacterial proliferation, but may have to be accepted. Any 20% albumin **must** be given slowly to prevent vascular overload.

Supply

50 ml bottles of 4.5% human albumin solution cost £5.20, and 50 ml bottles of 20% human albumin solution cost £21.90. Blood grouping is not necessary. Preparations contain 120–150 mmol/l of sodium and small amounts of potassium and are stable for 3 years at room temperature. Do not use if turbid.

References

See also relevant Cochrane reviews 

- Reading RF, Ellis R, Fleetwood A. Plasma albumin and total protein in preterm babies from birth to eight weeks. *Early Hum Dev* 1990;**22**:81–7
- Werner EJ. Neonatal polycythemia and hyperviscosity. *Clin Perinatol* 1996;**22**:693–710.
- Wong W, Fok TF, Lee CH, et al. Randomised controlled trial: comparison of colloid or crystalloid for partial exchange transfusion for treatment of neonatal polycythemia. *Arch Dis Child* 1997;**77**:F115–18. [RCT]
- Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ* 1998;**317**:235–40. [SR]
- Nicholson JP, Wolmarans MR, Park GR. The role of albumin in critical illness. *Br J Anaesth* 2000;**85**:599–610.
- Wilkes M, Navickis R. Patient survival after human albumin administration: a meta-analysis of randomised controlled trials. *Ann Intern Med* 2001;**135**:149–64. [SR]
- Horsley P. Albumin and hypovolaemia: is the Cochrane evidence to be trusted? *Lancet* 2002;**359**:70–2. (See also pp. 72–3 and 2278.)
- Finfer S, Bellomo R, Myburgh J. Efficacy of albumin in critically ill patients [Editorial]. *BMJ* 2003;**326**:559–60.

Use

Platelet concentrates are used in the management of severe thrombocytopenia with bleeding.

Pathophysiology

The risk of serious internal haemorrhage increases significantly when the platelet count falls below $20 \times 10^9/l$, and the risk of intracranial haemorrhage may be particularly high in the preterm baby shortly after birth. Always check first that the "thrombocytopenia" is not due to clots in the sample.

A number of inherited conditions, and syndromes (such as thrombocytopenia absent radius (TAR) syndrome) are associated with thrombocytopenia. These seldom call for active treatment. Ill babies can have sepsis or a consumption coagulopathy (disseminated intravascular coagulation (DIC)); the main need here is usually to treat the underlying condition. Platelets can pool in the spleen in conditions causing hypersplenism (such as rhesus isoimmunisation) and exchange transfusion can further exacerbate thrombocytopenia. A low count may point to thrombus formation in a long line. Marrow disorders will reduce platelet production, but the results of a full blood count and examination of a blood film will usually provide a diagnostic clue in these situations.

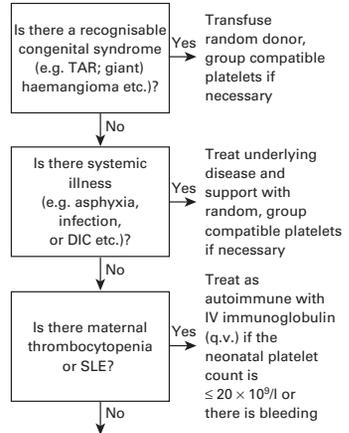
Platelet antibodies cause most cases of *isolated* neonatal thrombocytopenia. Platelet transfusions are of little value in **auto**immune thrombocytopenia because the maternal antiplatelet antibodies also attack any transfused platelets. Most of these mothers will have idiopathic thrombocytopenia (ITP) or systemic lupus erythematosus (SLE). **Allo**immune thrombocytopenia is more hazardous. Here, maternal antibodies, produced as a result of transplacental sensitisation, attack fetal platelets (in a process analogous to the red cell destruction that occurs in rhesus haemolytic disease), antenatal immunoglobulin treatment (q.v.) may be appropriate, and fully compatible platelets are required (i.e. they must lack the antigen against which the antibodies are directed). Platelet function in alloimmune thrombocytopenia is usually substantially poorer than in autoimmune thrombocytopenia.

Administration

10 ml/kg of platelets from a single ABO and rhesus compatible cytomegalovirus negative donor will usually suffice unless there is alloimmune thrombocytopenia. Here, maternal blood could be used to provide washed platelets in consultation with the haematologists if it proves impossible to obtain compatible platelets. To minimise loss, draw the contents of the pack into a 50 ml syringe through a special platelet or fresh blood transfusion set with a 170–200 μm filter and then infuse, using a narrow bore extension set linked (near the patient) to an IV line primed with 0.9% sodium chloride. **Always confirm compatibility by checking that the patient's name is on the pack.**

Supply

Platelets are obtainable from the hospital blood bank in leucodepleted single-unit packs containing 60×10^9 platelets. These 50 ml packs cost about £40 to prepare and dispense. Packs for intrauterine use are irradiated and further concentrated before issue. Other packs can also be concentrated to 50% of their original volume by the blood centre immediately before issue on request (although this results in the loss of potentially beneficial "fresh" plasma). The National Blood Service (NBS) normally uses donor apheresis to produce four such packs simultaneously. Larger (4–6 unit) packs from a single donor are available but seldom needed when treating a baby. Packs need to be stored under special conditions, kept at room temperature, and used *promptly* on receipt. Send 2 ml of blood for grouping.



Get the red cells and the platelets of the mother and baby "typed" by the NBS without delay. Give IV immunoglobulin and treat as alloimmune with washed or compatible platelets if the neonatal platelet count is $< 50 \times 10^9/l$.

References

- Menell JS, Bussell JB. Antenatal management of the thrombocytopenias. *Clin Perinatol* 1994;**21**:591–614.
 Cohen DL, Baghi TP. Assessment and management of immune thrombocytopenia in pregnancy and in neonates. *Arch Dis Child* 1995;**72**:F71–6.
 British Society for Haematology. Guidelines on the investigation and management of thrombocytopenia in pregnancy and neonatal alloimmune thrombocytopenia. *Br J Haematol* 1996;**95**:21–6.

PNEUMOCOCCAL VACCINES

Use

Two vaccines are now available that offer protection from some, but not all, forms of pneumococcal otitis media, pneumonia, septicaemia, and meningitis.

Pneumococcal infection

A range of potentially serious bacterial infections are caused by the encapsulated Gram positive coccus *Streptococcus pneumoniae*; 84 capsular forms have been identified, but 8–10 of these are responsible for 85% of the cases seen in childhood. The organism, which is becoming increasingly resistant to penicillin and erythromycin (q.v.), often causes community acquired pneumonia, and is now the commonest cause of bacterial meningitis. Patients with impaired immunity are at particular risk.

Infants at **high risk** include those with homozygous sickle cell disease, with no spleen (or a poorly functioning spleen), or with congenital or acquired immunodeficiency (including HIV infection). All such patients should be vaccinated and offered prophylactic antibiotics (see the monograph on immunisation), because the current vaccines offer protection from only *some* of the capsular types of pneumococcal infection. Immunisation should also be offered 2 weeks ahead of any planned splenectomy or chemotherapy. Also vaccinate children with diabetes, or chronic heart, lung, liver, or kidney disease.

Products

Plain polysaccharide vaccine: An unconjugated vaccine, active against 23 of the more commonly encountered capsular types of pneumococcal infection, has been available for some years. Because this vaccine offers relatively little protection when given to children under 2 years, it has generally been offered only to adults, and to older children considered to be at particularly high risk of infection.

New conjugate vaccine: All children under 2 years old in North America are now being immunised with a new seven-valent conjugate vaccine. No such strategy has yet been agreed in the UK, partly because it was decided to give priority to offering universal protection from meningococcal infection (q.v.) in late 1999, using a vaccine that has not yet been released for general use in North America.

Contraindications

Avoid immunisation during an acute infection, and while pregnant. Patients already immunised with the plain 23-valent vaccine (or the earlier 12- or 14-valent vaccines) do not need to be reimunised with the present 23-valent vaccine for 3–5 years.

Interactions

The conjugate vaccine can be given (into a different limb) at the same time as any of the normal childhood vaccines. Parents who are unhappy at the thought of their child facing three separate needles at a single clinic visit can be offered a different, staged, plan. The plain vaccine should not be given until at least 8 weeks after the new conjugate vaccine has been given. Anaphylaxis is extremely unlikely; its management is discussed in the monograph on immunisation.

Administration

Plain vaccine: High risk children (see above) who are 2 or more years old should still be offered a single 0.5 ml deep IM injection of the plain 23-valent vaccine because this provides broader protection from pneumococcal infection.

Conjugate vaccine: Young high risk children who have not yet started their primary course of immunisations should be offered three 0.5 ml doses of the new conjugate 7-valent vaccine by deep IM injection at the same time as they receive their other early vaccines. Those who are 7–11 months old need only two doses given at least 1 month apart. All these children then need a further booster dose in the second year of life and then a dose of the plain vaccine after their second birthday.

Documentation

Inform the district immunisation coordinator whenever any immunisation procedure is undertaken in hospital, and also record what has been given in the child's own personal health booklet.

Supply

0.5 ml vials of the plain polysaccharide vaccine (Pneumovax® or Pnu-Imune®) cost £10; 0.5 ml vials of the conjugate vaccine (Prevenar®) cost £39 (but are available on the NHS). Vials must be stored at 4°C.

References

- UK Health Departments. *Immunisation against infectious disease*. Chapter 25. London: HMSO, 1996:167–72.
- Giebink GS. The prevention of pneumococcal disease in children. *N Engl J Med* 2001;**345**:1177–83. (See also pp. 1206–9.)
- Finn A, Booy R, Moxon R, et al. Should the new pneumococcal vaccine be used in high-risk children? *Arch Dis Child* 2002;**87**:18–21.
- Shinefield H, Black S, Ray P, et al. Efficacy, immunogenicity and safety of heptavalent pneumococcal conjugate vaccine in low birth weight and preterm infants. *Pediatr Infect Dis J* 2002;**21**:182–6. [RCT]
- Lin PL, Michaels MG, Janosky J, et al. Incidence of invasive pneumococcal disease in children 3 to 36 months of age at a tertiary care pediatric center 2 years after licensure of the pneumococcal conjugate vaccine. *Pediatrics* 2003;**111**:896–9.
- Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *N Engl J Med* 2003;**348**:1737–46.

See also relevant Cochrane reviews



Use

Polio vaccine gives lasting immunity to the three polio viruses.

Poliomyelitis

Poliomyelitis is a notifiable infectious illness. The disease still occurs in some parts of South Asia and in West and Central Africa, but it has now been eradicated from most other parts of the world. Infection may be clinically unapparent, but may also produce aseptic meningitis and severe lasting paralysis. An injectable formaldehyde inactivated triple strain (Salk) vaccine first became available in 1958, and a live, attenuated, triple strain oral (Sabin) vaccine, was introduced in 1962. The Salk vaccine is now being used again with increasing frequency in some parts of Europe, and is the only product now used in the USA, but the Sabin vaccine is still the product normally used in the UK to provide lasting immunity to paralytic poliomyelitis. These two products have, between them, made the eventual global eradication of polio a realistic aim. Polio (and measles) could, with commitment and good management, soon go the same way as smallpox did in 1980. Sabin vaccine use reduces the number of injections required, but there is a one in a million chance that it will itself cause paralytic disease.

Indications

Live oral vaccine: Offer three doses at monthly intervals, starting 2 months after birth at the same time as the diphtheria/tetanus/pertussis (DTP), meningococcal (MenC), and haemophilus (Hib) vaccines (q.v.) are given, unless there is a specific contraindication. Further doses should be given before starting and leaving school. Remember, however, that children excrete the virus in their stools for up to 6 weeks after immunisation, putting other unimmunised or immunocompromised patients at risk.

Inactivated parenteral vaccine: This should always be used in preference to the live vaccine when a baby is immunised in a hospital setting where there are other ill or unimmunised babies. It is also the safer product to use when someone in the immediate family is immunodeficient. The live and inactivated vaccines can be used interchangeably and there is, therefore, nothing to stop the live vaccine being used to complete a course of treatment started using the inactivated product. Indeed, such a combination may enhance the serological response.

Contraindications

Early pregnancy, immunodeficiency, immunosuppression, reticuloendothelial malignancy, and high dose corticosteroid treatment (the equivalent of more than 1 mg/kg prednisolone a day, or 2 mg/kg for more than 1 week in the last 6 weeks) are contraindications to the use of any live vaccine (but not the Salk vaccine). Children should not be immunised while febrile, or given the oral vaccine while suffering from diarrhoea or vomiting. For anaphylaxis (rare even with the IM product) see under immunisation.

Interactions

Polio vaccine can be given at the same time as other live and inactivated vaccines. The oral vaccine should not, ideally, be given less than 3 weeks before or 3 months after any planned injection of normal immunoglobulin.

Administration

Oral live vaccine: The normal dose is three drops by mouth. Repeat if regurgitated. Older children can be offered the drops on a sugar cube.

Inactivated vaccine: Give 0.5 ml by deep IM injection into any limb not simultaneously used for DTP, MenC, or Hib vaccination, using a fresh syringe and a 25 mm, 23 gauge, needle.

Documentation

Inform the district immunisation coordinator (see monograph on immunisation) when any child is immunised in hospital, and complete the relevant section of the child's own personal health booklet.

Supply

Oral live polio vaccine is available in 10 × 1 dose packs, and in packs containing 10 doses. Supplies of single doses of the inactivated vaccine are also available for *named patients* on request from Farillon. All products should be stored in the dark at 4°C. Discard once open.

References

- Modlin JF, Onorato IM, McBean M, *et al.* The humoral immune response to Type 1 oral poliovirus vaccine in children immunised with enhanced potency inactivated poliovirus vaccine or live oral poliovirus vaccine. *Am J Dis Child* 1990;**144**:480–4.
- UK Health Departments. *Immunisation against infectious disease*. Chapter 26. London: HMSO, 1996:173–82.
- American Academy of Pediatrics. Committee on Infectious Diseases. Poliomyelitis prevention: revised recommendations for use of only inactivated poliovirus vaccine for routine immunisation. *Pediatrics* 1999;**104**:1404–6.
- Sutter RW, Prevots R, Cochi SL. Poliovirus vaccines. *Pediatr Clin North Am* 2000;**47**:287–308.

POLYSTYRENE SULPHONATE RESINS

Use

Sodium and calcium polystyrene sulphonates are cation exchange resins administered orally or rectally in the treatment of severe hyperkalaemia (a plasma potassium level of ≥ 7.5 mmol/l). IV salbutamol (q.v.) seems to provide a more immediate, and an IV glucose infusion with added insulin (q.v.) a more reliable, way of achieving a sustained lowering of the plasma potassium level in the neonatal period.

Pharmacology

Sodium and calcium polystyrene sulphonates are cation exchange resins used to draw potassium out of the body and into the gut in exchange for sodium or calcium, thus effecting the elimination of potassium from the body in the faeces. Faecal impaction has been reported after rectal administration in children, as have gastrointestinal concretions when the drug is given by mouth in early infancy, especially if there is already some degree of intestinal ileus for any reason.

Because none of the exchange resins are entirely selective for potassium it is best to choose a calcium resin if the plasma calcium level is already low, since a sodium resin will inevitably draw further calcium out of the body. The calcium resin is also to be preferred if the plasma sodium level is already high, because this will cause a further rise in the plasma sodium level, and severe hypernatraemia (a plasma sodium level of ≥ 160 mmol/l) can cause serious neurological damage. Each gram of sodium resin is capable, in practice, of extracting about 1 mmol of potassium from the body (as much as 3 mmol in theory). An equivalent weight of the calcium resin is marginally less effective.

Do not attempt **any** treatment for hyperkalaemia without first checking that the apparently high plasma potassium level is not merely due to potassium leaking from damaged red cells (as a result of haemolysis) into the plasma sample sent for laboratory analysis. Neonates seem to tolerate high plasma potassium levels much better than older patients, but treatment should be considered, as a matter of urgency, if there are severe electrocardiographic changes. Treatment with 2 ml/kg of 10% calcium gluconate IV (q.v.) can control cardiac excitability, at least briefly. IV or nebulised salbutamol, and IV glucose and insulin, are both capable of lowering plasma potassium levels more rapidly than any cation exchange resin, while an exchange transfusion with *fresh* blood (or washed red cells), although it may take a little time to set up, is probably better at achieving a *sustained* fall in the plasma potassium level. Peritoneal dialysis, or haemodialysis, may be a better option in centres with the necessary expertise to do this, although this should be necessary only if there is renal failure and/or fluid overload. Consider adrenal failure (usually due to congenital adrenal hyperplasia) if there is hyponatraemia, hypoglycaemia, and/or hypotension, and treat as outlined in the monograph on hydrocortisone.

Treatment

Give 500 mg/kg as a retention enema. Ensure evacuation by colonic irrigation after 8–12 hours (preferably with the aid of x-ray image intensification) in order to ensure complete recovery of the resin. Treatment may be repeated after 12 hours if necessary. Double this dose can be employed at least once in severe hyperkalaemia. Do **not** give polystyrene sulphonate resins by the oral route in the neonatal period. Monitor the plasma electrolytes to minimise the risk of overtreatment.

Supply and administration

Sodium polystyrene sulphonate (Resonium A[®]) can be provided as a powder by the pharmacy on request. Calcium polystyrene sulphonate (Calcium Resonium[®]) can also be provided where the use of a sodium containing resin has to be avoided because of latent hypocalcaemia or hypernatraemia. Both resins cost 14p per gram. The sodium resin contains approximately 4.5 mmol of sodium per gram. It is best to get the pharmacy to prepare the enema in advance using a mixture of water and methylcellulose (which acts as a faecal softener), but the resin can be prepared on the ward immediately prior to use if necessary, using 6 ml/kg of water. In the USA, polystyrene sulphonate resins are usually made up in a solution of 25% sorbitol rather than in a mixture of water and methylcellulose.

References

- Malone TA. Glucose and insulin versus cation-exchange resin for the treatment of hyperkalaemia in very low birth weight infants. *J Pediatr* 1991;**118**:121–3.
- Hu P-S, Su B-H, Peng C-T, *et al.* Glucose and insulin infusion versus kayexalate for the early treatment of non-oliguric hyperkalaemia in very-low-birth-weight infants. *Acta Paediatr Taiwan* 1999;**40**:314–18.

Use

Potassium is an essential nutrient and potassium chloride is often used to correct bodily depletion.

Pathophysiology

An intake of 2 mmol/kg of potassium per day is more than enough to meet all the body's normal needs. Breast milk, artificial milk formulas (q.v.) and the standard neonatal parenteral nutrition solution (q.v.) all contain more than enough potassium to meet basic needs, and a low plasma potassium level in the neonatal period (hypokalaemia) is more often the result of potassium redistribution than any true body deficit.

While urinary sodium loss (as summarised in the monograph on sodium chloride) can vary widely in the neonatal period, potassium loss seldom varies very much. Most healthy preterm babies remain in positive potassium balance throughout the neonatal period. Stressed, ventilator dependent preterm babies sometimes show a raised renal potassium loss during the first 2 days of life, although this almost always resolves spontaneously within 3–4 days and seldom causes a serious fall in the plasma level. Indeed, urinary loss is almost always sufficiently small as to make supplementation unnecessary in an unfed baby, even if fluid support is limited to the provision of dextrose saline for up to 1 week after birth. There are, however, a few conditions associated with excessive renal potassium loss that can produce severe hypokalaemia. Some diuretics, if used for a sustained period, can cause significant urinary potassium loss (cf. the monographs on chlorothiazide and furosemide), while chronic diarrhoea can also induce a significant body potassium deficit.

Potassium is the most important intracellular cation in the body, and a cellular deficit causes ileus, retention of urine, neuromuscular weakness, and electrocardiographic (ECG) changes (including ST segment depression, a low-voltage T wave, and U wave changes). Alkalosis drives extracellular potassium into the cells, making the plasma level a poor marker of whole body depletion. Insulin can have a similar effect. Compartmental shifts are the commonest cause of apparent neonatal hypokalaemia; true depletion requiring replacement is really quite rare. Overtreatment, on the other hand, can easily cause hyperkalaemia (a serious management problem discussed in the monograph on salbutamol). A dose of 3 mmol/kg has been used to cause immediate cardiac asystole in those rare situations where deliberate fetocide is deemed necessary.

Treatment

Oral treatment: This is the preferred route for correcting any potassium deficit. Start with a total of 2 mmol/kg per day, given in a series of small divided doses with feeds to minimise gastric irritation.

IV treatment: Correct any true body deficit slowly over 1–2 days, using a solution that does not contain more than 40 mmol of potassium per litre, given at a rate of no more than 0.2 mmol/kg per hour (a higher rate of up to 0.5 mmol/kg per hour may rarely be justified if there is severe potassium depletion). ECG monitoring is recommended during infusion in some centres. Concentrated solutions can cause thrombophlebitis and pain at the injection site, while extravasation can cause tissue necrosis. **Always check the dose carefully; an overdose can be rapidly fatal.**

Supply and administration

A sugar free oral 7.5% solution of potassium chloride containing 1 mmol (75 mg) per ml is available from the pharmacy on request (100 ml costs 60p).

10 ml ampoules of strong 15% potassium chloride (containing 1.5 g, or approximately 20 mmol, of potassium) for IV use are available as stock costing 44p each. Note that ampoules are also available in a range of **other** strengths. Strong potassium chloride must normally be diluted **at least 50-fold** with 0.9% sodium chloride (or a mixture of 0.9% sodium chloride in dextrose) prior to administration, and the resultant solution mixed with some care in order to make quite sure that the potassium does not separate or "layer" out prior to administration.

The inadvertent use of potassium chloride instead of sodium chloride during the reconstitution of other IV drugs has caused several deaths. There are strong grounds for insisting that all potassium chloride ampoules should be stored well away from all other routinely used ampoules. Many hospitals keep all such ampoules with the controlled drugs.

References

- Engle WD, Arant BS Jr. Urinary potassium excretion in the critically ill neonate. *Pediatrics* 1984;**74**:259–64.
John E, Klavdianou M, Vidyasagar D. Electrolyte problems in neonatal surgical patients. *Clin Perinatol* 1989;**16**:219–32.
Brem AS. Electrolyte disorders associated with respiratory distress syndrome and bronchopulmonary dysplasia. *Clin Perinatol* 1992;**19**:223–32.

POTASSIUM IODATE

Use

Iodine is an essential trace element. Larger doses of potassium iodate can be used, in an emergency, to block the uptake of radioactive iodine by the thyroid and thus reduce the later risk of thyroid cancer.

Nutritional factors

Iodine is necessary for thyroid hormone formation, and is an essential trace element. Maternal goitre is common in areas of the world where the diet is deficient; perinatal mortality is also increased and cretinism (a syndrome characterised by spasticity, deaf mutism, intellectual deficit, and variable hypothyroidism) is common. Problems can be prevented by the routine addition of 10–80 parts per million of potassium iodate (or potassium iodide) to all cooking salt. A single prophylactic 500 mg injection of iodised poppy seed oil (containing ~38% w/w iodine) can be used in pregnancy in areas where cretinism is endemic. Subclinical deficiency can also occur in babies on parenteral nutrition who are on standard doses of Peditrace®.

Pharmacology

The UK Departments of Health issued guidance on the use of iodine prophylaxis in the unlikely event of a nuclear accident causing radiation “fallout” 5 years after the Chernobyl nuclear disaster in 1991. Similar, updated and more detailed advice was issued by the Food and Drug Administration in the USA in late 2001 (see www.fda.gov/cder/guidance/index.htm). The use of a stable iodine preparation can block further inhaled radioactive iodine uptake by the thyroid, reducing the subsequent risk of thyroid cancer (oral intake being minimised by appropriate restrictions on the use of contaminated food). Fresh meat and dairy products pose a particular problem if pasture is affected. Young children are at particular risk. Treatment cannot, of course, reduce the radiation dose from external radiation or from other radionuclides. Two 85 mg tablets of potassium iodate (containing the equivalent of 100 mg of stable iodine) will reduce exposure by half, even if this is taken only 5 hours after exposure to radioiodine.

Iodine inhibits the extrathyroidal conversion of thyroxine (T_4) to triiodothyronine (T_3), and inhibits the thyroidal excretion of these two hormones. It is used for this purpose (as Lugol’s iodine) in the management of neonatal thyrotoxicosis (as outlined in the monograph on propranolol).

Radiation hazard prophylaxis

Adults in the vicinity of any incident (including pregnant and lactating women) in the UK are advised to take two 85 mg tablets of potassium iodate *immediately* any nuclear emergency is notified. This dose may need to be repeated daily if the hazard persists, but repeated dosing should be avoided in those who are pregnant or breastfeeding where possible.

Babies can, most conveniently, be given 0.1 ml of Lugol’s iodine (see below) where this is available. Otherwise, in an emergency, they may be given half an adult tablet of potassium iodate crushed in a teaspoon of jam or dissolved in a small quantity of milk or juice. Repeated doses should not, in general, be given in very young babies because there is some risk that this will cause hypothyroidism.

Contraindications

The only contraindications to such prophylaxis are a known allergy to iodine and patients with hypocomplementaemic vasculitis or dermatitis herpetiformis.

Subsequent management

Neonates given iodine will need to have their TSH (thyroid stimulating hormone) levels monitored and, if these are raised, their T_4 levels checked, with replacement T_4 offered as appropriate. Babies of mothers who have been given iodine in the last trimester of pregnancy should have a cord blood sample taken at birth so that the TSH and T_4 levels can be measured.

Supply

Potassium iodate tablets are held in a range of specifically approved locations in the UK (such as schools and police stations) in all areas close to a nuclear installation. Hospital pharmacies have been advised to maintain a stock of potassium iodate crystals. These can be freshly dissolved when required to give the necessary 12.5 mg dose (since no pre-prepared liquid preparation of the iodate is indefinitely stable). Lugol’s iodine (a solution of 5% iodine and 10% potassium iodide), which contains 130 mg/ml of iodine is a more readily available liquid formulation of very comparable efficacy (100 ml costs £1.80).

References

- Connolly KJ, Pharoah POD, Hetzel BS. Fetal iodine deficiency and motor performance. *Lancet* 1979;**ii**:1149–51. [RCT]
- Department of Health. *Nuclear accident countermeasures: iodine prophylaxis*. Report on Health and Social Subjects No 39. London: HMSO, 1991.
- Delange F. Administration of iodized oil during pregnancy: a summary of the published evidence. *Bull WHO* 1996;**74**:101–8.
- Ibrahim M, Morreale de Escobar G, Visser TJ, *et al*. Iodine deficiency associated with parenteral nutrition in extreme preterm infants. *Arch Dis Child* 2003;**88**:F56–7.
- American Academy of Pediatrics. Committee on environmental health. Radiation disasters and children. *Pediatrics* 2003;**111**:1455–66.

See also Cochrane reviews of nutritional issues



Use

Procaine G penicillin was, for many years, the antibiotic normally used to treat congenital syphilis. Benzylpenicillin (q.v.), if given diligently, should, in theory, be just as effective.

Pharmacology

The microbiological properties of procaine penicillin are the same as those of benzylpenicillin. It is a sustained release drug given by deep IM injection that is slowly hydrolysed to benzylpenicillin. Benzathine penicillin (which is even more slowly hydrolysed to benzylpenicillin over 2–3 weeks) has been widely used to treat syphilis in the USA, but it does not always seem to produce therapeutic serum levels in pregnancy. The organism *Treponema pallidum* still remains totally sensitive to benzylpenicillin, despite the universal use of this antibiotic to treat syphilis for more than 50 years.

Congenital syphilis

Latent untreated maternal syphilis is associated with a 20% risk of fetal loss and a 20% risk of premature delivery, even if maternal infection has been present for only 1–2 years. Intrauterine growth retardation is common. The placenta is often large, and fetal hydrops may develop. Half the liveborn babies will have congenital syphilis at birth. The longer the maternal disease has been left untreated, the greater the risk to the fetus. Florid neonatal disease is now rare, but babies can present with hepatosplenomegaly, anaemia, thrombocytopenia, jaundice, and generalised lymphadenopathy. Skin desquamation is a characteristic feature, together with a characteristic pink maculopapular rash that later turns brown. Osteitis is usually asymptomatic at birth, and rhinitis ("snuffles") develops after a few weeks.

Syphilis in pregnancy is uncommon in the UK (about 1:10,000 pregnancies). Because of screening, most women will have been diagnosed and treated before delivery. The usual treatment of the mother used to be 900 mg of deep IM procaine benzylpenicillin once daily for 2 weeks, but many specialists in genitourinary medicine now prefer to use benzylpenicillin. Treatment may need to be more exacting than this if there is longstanding maternal infection because of poor transplacental passage. Check for other venereal disease, including HIV infection, and review all sexual contacts.

If the mother was fully treated at least 1 month before delivery, as demonstrated by at least a fourfold fall in a non-treponemal serological test for syphilis (the Venereal Disease Research Laboratory (VDRL) and rapid plasma regain tests being the most widely used), and the baby seems asymptomatic at birth, neonatal treatment is not called for, although follow up is essential at 3, 6, and 12 months to ensure that all the serological tests eventually become negative. If there is any doubt about the adequacy of treatment, or treatment was started only in the second half of pregnancy, it is probably wise to x-ray the long bones for osteitis and carry out a VDRL test on the cerebrospinal fluid (also looking at the cell count and protein level). Treat possible infection after birth like proven infection.

Treatment

Babies thought to be infected at birth have traditionally been given 50 mg/kg of procaine benzylpenicillin IM once a day for 10 days, but this can easily cause a sterile abscess with subsequent fibrosis and muscle atrophy; 30 mg/kg of benzylpenicillin IV or IM once every 12 hours for 10 days is equally effective. If congenital syphilis is suspected for the first time only when the baby is already more than 2 weeks old, then treatment needs to be given once every 6 hours for 10 days.

Supply

Procaine benzylpenicillin is designed to provide sustained slow release of benzylpenicillin from an IM depot. It should *never* be given IV. Vials containing 1.8 g of procaine penicillin and 360 mg of benzylpenicillin sodium are still commercially available in many countries, but they are no longer marketed in the UK. Reconstitute the powder with 4.6 ml of water for injections to give 6 ml of solution containing 300 mg/ml of procaine penicillin. Use this solution within 24 hours of reconstitution (even if it is stored at 4°C), and discard the remainder promptly after use. (Note that 300 mg of procaine benzylpenicillin is equivalent to 180 mg [300,000 units] of benzylpenicillin.)

References

- See also Cochrane review of treatment for syphilis
- Nathan L, Bowdon RE, Siawi JE, *et al.* Penicillin levels following the administration of benzathine penicillin G in pregnancy. *Obstet Gynecol* 1993;**82**:338–42.
- Paryani SG, Vaughn AJ, Crosby M, *et al.* Treatment of asymptomatic congenital syphilis: benzathine versus procaine penicillin G therapy. *J Pediatr* 1994;**125**:471–5. [RCT]
- Centers for Disease Control. Guidelines for the prevention and control of congenital syphilis. *MMWR* 1988;**37**(suppl S-1):1–13.
- Sánchez PJ, Wendel GD. Syphilis in pregnancy. *Clin Perinatol* 1997;**24**:71–90.
- Hurtig A-K, Nicoll A, Carne C, *et al.* Syphilis in pregnant women and their children in the United Kingdom: results from national clinician reporting surveys 1994–7. *BMJ* 1998;**317**:1617–19.
- Delport SD, Pattinson RC. Syphilis: prevention, diagnosis and management during pregnancy and infancy. In: Newell M-L, McIntyre J, eds. *Congenital and perinatal infections*. Cambridge: Cambridge University Press, 2000:258–75.

PROPOFOL

Use

Propofol is a rapid acting IV anaesthetic. It does not relieve pain. A sustained infusion is often used to sedate adults requiring intensive care, but severe (potentially lethal) metabolic complications were encountered when a similar strategy was adopted in children.

Pharmacology

Propofol is a clear colourless insoluble phenolic compound supplied in an isotonic, oil-in-water Intralipid emulsion that came into use as a useful, short acting, IV anaesthetic in 1984. It is unrelated, chemically, to any other anaesthetic agent, but behaves rather like ketamine (q.v.). Recovery from propofol is, however, rather more rapid, and "hangovers" are less common. The drug is widely redistributed into fat and other body tissues, with a half life of about 40 minutes after IV administration ($V_D \sim 10$ l/kg). It is then slowly conjugated and metabolised in the liver, with an elimination half life of 5–10 hours (but closer to 2–3 days after sustained use). Propofol is not teratogenic or fetotoxic in animals but crosses the placenta readily, and the manufacturers do not recommend use during pregnancy or delivery, although problems have not been encountered with use during caesarean delivery. Neither has the main manufacturer recommended the use of propofol to induce anaesthesia in patients under 3 years old, or to provide continuous sedation in patients under 17 years. Substantial quantities appear in breast milk, but a baby taking milk from the breast 12 hours after the mother's delivery under propofol anaesthesia would ingest less than 1% of the maternal dose on a weight related basis.

The drug was used as a sedative in paediatric intensive care for 15 years before any controlled trials were undertaken, and it was several years before occasional cases of unexpected metabolic acidosis and sudden cardiac failure started to appear. However, in an as yet unpublished controlled trial reported to the US Food and Drug Administration, in which 222 children received a sustained 1% or 2% propofol infusion and 105 some other sedative, all but four of the 25 deaths occurred in children given propofol. A further trial has now been set up. See: www.FDA.gov/medwatch/safety/2001/diprivan_deardoc.pdf for details. It looks as though prolonged infusion can cause a myopathy due to impaired fatty acid oxidation in patients of any age, which is reversible only by stopping treatment and offering prompt haemoperfusion. Maintaining a generous dextrose infusion may make this hazard less likely, by limiting the tendency of the body to mobilise energy stores from fat.

Indications

Neonatal use has received very little study as yet but, since the response to an IV dose is both rapid and short lived, it may be a way of providing brief anaesthesia prior to elective tracheal intubation (a manoeuvre too often conducted without providing any sedation or analgesia). However, given the alternatives available, such use should be contemplated for the moment only under trial conditions.

Anaesthesia

Give 3 mg/kg IV over 10 seconds. A further 1 mg/kg or 2 mg/kg can be given if this dose does not induce adequate anaesthesia in half a minute. Anaesthesia will usually last about 10 minutes after a 3 mg/kg dose. Sustained sedation should **never** be considered at present in any child less than 1 year old.

Precautions

Propofol should be used only by an experienced intensivist ready and equipped to take immediate control of the airway should this be necessary. The child must be monitored until recovery is complete.

Supply and administration

20 ml ampoules of an IV emulsion containing 10 mg/ml cost £3-90. Store ampoules at room temperature, shake before use, and do not freeze. The lipid content makes it important to protect any line used for sustained infusion from microbial contamination. Do not infuse through a < 5 µm filter.

References

- Dailland P, Cockshott ID, Lirzin JD, *et al.* Intravenous propofol during cesarean section: placental transfer, concentrations in milk, and neonatal effects. A preliminary study. *Anesthesiology* 1989;**71**:827–34.
- Parke TI, Stevens JE, Rice ASC, *et al.* Metabolic acidosis and fatal myocardial failure after propofol infusion in children: five case reports. *BMJ* 1992;**305**:613–16.
- Schrum SF, Hannallah RS, Verghese PM, *et al.* Comparison of propofol and thiopental for rapid anaesthesia induction in infants. *Anesth Analg* 1994;**78**:482–5.
- Levati A, Colombo N, Arosio EM, *et al.* Propofol anaesthesia in spontaneously breathing paediatric patients during magnetic resonance imaging. *Acta Anaesthesiol Scand* 1996;**40**:561–5.
- Bray RJ. Propofol infusion syndrome in children. *Paediatr Anaesth* 1998;**8**:491–9.
- Duncan HP, Zurick NJ, Wolf AR. Should we reconsider awake neonatal intubation? A review of the evidence and treatment strategies. *Paediatr Anaesth* 2001;**11**:135–45. (See also pp. 630–1.)
- Wolf A, Weir P, Segar P, *et al.* Impaired fatty acid oxidation in propofol infusion syndrome. *Lancet* 2001;**357**:606–9.

Use

Oral propranolol is used in neonatal thyrotoxicosis, in the management of hypercyanotic spells in Fallot's tetralogy, and (in combination with hydralazine (q.v.)) in the control of dangerous hypertension. It is occasionally used to control arrhythmia and to manage the long QT syndrome.

Pharmacology

Propranolol hydrochloride became the first non-selective β adrenoreceptor blocking agent when it was developed in 1964. It works by reducing the rate and force of contraction of the heart and slowing cardiac conduction. The hypotension and bradycardia seen with an overdose is best treated with glucagon (q.v.). Respiratory depression and fits can also occur. Propranolol, together with a vasodilator such as hydralazine, is of value in the management of severe hypertension, although its mode of action is not clearly understood. The drug should be used with great caution in the presence of heart failure. The half life in children and adults is 3–6 hours; the neonatal half life is not known. Propranolol and the related β blockers have no known teratogenicity. The drug crosses the placenta, however, and there is some anecdotal evidence that it may cause a degree of fetal growth retardation. Continuous maternal medication may also cause some transient neonatal bradycardia and hypoglycaemia. Treatment during lactation only exposes the baby to 1% of the maternal dose on a weight for weight basis. Propranolol is sometimes given IV in the initial management of arrhythmia and cyanotic "spells", but a 600 micrograms/kg bolus of IV esmolol over 1–2 minutes (followed, if necessary, by a continuous infusion of 300–900 micrograms/kg per minute) may be a safer alternative, because this β blocker has a very short half life. If propranolol is initially given IV a substantially higher dose will be required once oral treatment is started because of high first pass liver metabolism.

Neonatal thyrotoxicosis

This rare but potentially fatal disorder, seen in 1–2% of the offspring of mothers with Graves disease, results from the transplacental passage of thyrotropin receptor antibody. Neonatal problems are most frequently seen in babies of mothers with a high antibody titre. Such problems can occur even after the mother has been rendered medically or surgically euthyroid. Propylthiouracil (5 mg/kg every 12 hours) should be given to symptomatic babies. Propranolol is a further mainstay of treatment in severe cases. It may need to be continued for 3–12 weeks after delivery. Lugol's iodine provides the most easily obtained source of iodine for inhibiting thyroid function (cf. the monograph on potassium iodate). Digoxin (q.v.) and a diuretic may be required if there is heart failure. Sedation is occasionally called for. Always seek the advice of an experienced paediatric endocrinologist if symptoms are severe.

Treatment

Neonatal hypertension: Start with 250 micrograms/kg every 8 hours by mouth, together with hydralazine, and increase as necessary to a maximum of 2 mg/kg per dose.

Neonatal thyrotoxicosis: Give 250–750 micrograms/kg every 8 hours by mouth to control symptoms, with one drop of Lugol's iodine every 8 hours to control the transient neonatal thyrotoxicosis.

Arrhythmia: Try 20 micrograms/kg IV over 10 minutes with electrocardiographic monitoring and increase this, in steps, to a cumulative total of 100 micrograms/kg if necessary. Give the effective dose IV once every 8 hours for maintenance. The same strategy may also work for the "spells" sometimes seen in severe Fallot's tetralogy (with oxygen, morphine, and, if necessary, sodium bicarbonate, to correct serious acidosis). For sustained oral maintenance try 1 mg/kg (never more than 2 mg/kg) once every 8 hours.

Blood levels

The therapeutic blood level for propranolol in adults is said to be 20–100 $\mu\text{g/l}$ (1 $\mu\text{g/l}$ = 3.86 $\mu\text{mol/l}$). It is, however, usually best to adjust the amount of drug prescribed by reference to the patient's blood pressure and response to treatment.

Supply

1 mg (1 ml) ampoules of propranolol cost 21p. Dilute, for accurate IV use, to 10 ml with 10% dextrose to get a solution containing 100 micrograms/ml. A commercial syrup with a long "shelf life" containing 10 mg in 5 ml is available (100 ml costs £11.70). 100 mg (10 ml) vials of esmolol cost £6. A suspension of propylthiouracil (usually available only in tablet form) could be prepared by the pharmacy on request.

References

Gardner LI. Is propranolol alone really effective in neonatal thyrotoxicosis? *Am J Dis Child* 1980;134:707–8. (See also pp. 819–20.)
 Skusa KA, Stene M, Rapaport R. Prediction of neonatal hyperthyroidism in infants of mothers with Graves disease. *J Pediatr* 1996;128:264–7.
 Ogilvy-Stuart AL. Neonatal thyroid disorders [Review]. *Arch Dis Child* 2002;87:F165–71.

PROSTAGLANDIN E₂ = Dinoprostone (rINN)

Use

Prostaglandin E₁ and E₂ can both be used to maintain patency of the ductus arteriosus pending surgery in babies with duct dependent congenital heart malformations.

Pharmacology

Prostaglandins E₁ and E₂ are potent vasodilators, originally isolated from prostate gland secretions, which inhibit platelet coagulation and stimulate uterine contractility. Prostaglandin E₂ was first synthesised in 1970 and is now widely used to terminate pregnancy by extra-amniotic administration, while tablets, gels, pessaries, and IV infusions are also used to ripen the cervix and/or initiate labour at term. Infusions of 0.25–1 microgram/minute are usually used to initiate labour but higher rates have, on occasion, been employed when it is necessary to induce labour after fetal death. A 2 mg vaginal gel or 3 mg vaginal tablet repeated once, if necessary, after 6–8 hours, is now the most widely used method of inducing labour. Caution should be employed in using prostaglandins and oxytocin simultaneously because each drug potentiates the effect of the other.

Prostaglandins were first used experimentally to sustain ductal patency in 1975, and continuous IV infusions are now frequently employed in the early preoperative management of babies with duct dependent congenital heart disease. Prostaglandin E₁ (alprostadil) is the licensed preparation, but a similar dose of prostaglandin E₂ is equally effective and eight times as cheap. Because of rapid inactivation during passage through the lung, the half life during IV infusion is less than 1 minute, and no loading dose is necessary. Respiratory depression and apnoea are common with high dose treatment (many texts still recommend a dose that is 5–10 times higher than necessary) and may occur, even with the dose recommended here, especially in the cyanosed or preterm baby. Other occasional effects of high dose treatment include diarrhoea, irritability, seizures, tachycardia, hypotension, pyrexia, and metabolic acidosis. Continued IV use for more than 5 days has occasionally been associated with gastric outlet obstruction due to reversible antral hyperplasia, and very long term use with cortical hyperostosis.

Sustained oral administration is still widely used in some centres, but now rarely employed in the UK because delay is not thought to render surgery any less technically difficult. Start with 25 micrograms/kg by mouth once an hour and double this if necessary. Some babies manage with treatment every 3–4 hours, but many need a dose every 2 hours to remain stable.

Treatment

Start with a slow continuous IV infusion of 10 nanograms/kg per minute (0.6 ml/kg per hour of a solution made up as described below) and monitor arterial oxygenation to determine the adequacy of the response. Increase the dose as necessary. A dose of more than 40 nanograms/kg per minute is very seldom necessary, but doses of 100 nanograms/kg per minute have occasionally been tried. Use the lowest effective dose to minimise side effects, and prepare a fresh solution every 24 hours.

Compatibility

Prostaglandin E₂ (dinoprostone) is very unstable in solution, and should never be infused with any other drug. In contrast, it *may* be acceptable to add prostaglandin E₁ (alprostadil) (terminally) when absolutely necessary, into a line containing dobutamine and/or dopamine, heparin, midazolam, morphine, or ranitidine, although the manufacturers remain reluctant to endorse this advice.

Supply and administration

IV prostaglandin E₂ should be stored at 4°C. One 0.75 ml ampoule (containing 1 mg/ml) costs £7.10. Note that more concentrated 10 mg/ml ampoules are sometimes stocked for use in termination of pregnancy. A sugar free oral solution with a 1 week shelf life could be prepared by the pharmacy on request.

To give an infusion of 10 nanograms/kg per minute, add 0.5 ml of dinoprostone from an ampoule containing 1 mg/ml to 500 ml of 10% dextrose saline, to produce a solution containing 1 microgram of dinoprostone per ml and then infuse this at a rate of 0.6 ml/kg per hour. A less concentrated solution of dextrose or dextrose saline can be used where necessary.

References

- Heymann MA. Prostaglandins and leukotrienes in the perinatal period. *Clin Perinatol* 1987;14:857–80.
Peled N, Dagan O, Babyn P, et al. Gastric-outlet obstruction induced by prostaglandin therapy in neonates. *N Engl J Med* 1992;327:505–10.
Madar RJ, Donaldson T, Hunter S. Prostaglandins in congenital heart disease. *Cardiol Young* 1995;5:202–3.
Kaufman MB, El-Charaf GM. Bone and tissue changes following prostaglandin therapy in neonates. *Ann Pharmacother* 1996;30:269–77.

See also Cochrane reviews of obstetric use 

Use

Pyridoxine is used to diagnose and treat neonatal convulsions due to pyridoxine dependency (a rare, genetically inherited disorder). It is also used in the treatment of homocystinuria.

Pharmacology

Pyridoxine is widely available in most foodstuffs and nutritional deficiency is extremely rare. Pyridoxine dependency is an autosomal recessive condition. Although it was first described in 1954, the nature of the underlying biochemical defect still remains uncertain. Pyridoxine given in pharmacological doses controls the seizures but subsequent development often remains delayed. The diagnosis should always be considered in a baby with neonatal fits, especially if they are resistant to conventional anticonvulsant medication whether or not there is an identified cause for the seizures (some children may have structural cerebral dysgenesis). Many are restless and hyperalert. Seizures may even be noticed in utero. In older children, status epilepticus is a common presentation. The electroencephalogram (EEG) is said to show a characteristic pattern. The diagnosis can, at present, be only empirically based and requires a trial of withdrawal because some babies have transient pyridoxine responsiveness rather than a familial condition.

Homocystinuria most commonly results from cystathionine β synthase deficiency. Pyridoxal phosphate is a cofactor for this enzyme, and many patients improve biochemically and clinically with pharmacological doses of pyridoxine. Babies with homocystinuria detected by neonatal screening programmes, however, tend not to be pyridoxine responsive. Other patients present with developmental delay, or subsequently with dislocated lenses, skeletal abnormalities, or thromboembolic disease.

Diagnostic use

Neonatal fits: A single dose of 100 mg IV will stop most neonatal fits due to pyridoxine dependency within minutes. Watch for apnoea. The test is best conducted while the EEG is being monitored (although visible seizure activity may cease some hours or even days before the EEG trace returns to normal), but pyridoxine administration should not be delayed overlong if fits are severe merely because such monitoring is hard to organise. If fits subside only to reappear after a latent interval and then respond to IV pyridoxine a second time, the case for continued maintenance treatment has been made.

Fits later in infancy: Infants with intractable seizures or infantile spasms should have a trial of pyridoxine. Consider 30 mg/kg by mouth once a day for 10 days if a 100 mg IV dose has no effect.

Homocystinuria: Pyridoxine responsiveness should be assessed by measuring plasma methionine and homocysteine levels under basal conditions, and during a 2–3 week trial of pyridoxine, while maintaining a constant protein intake. The dose depends on the patient's age: 150 mg/day in infants; up to 750 mg/day in older children. Give 5 mg folic acid a day to ensure that the response to pyridoxine is not impaired by folate deficiency.

Treatment

Pyridoxine dependency: Infants with fits that respond to pyridoxine and recur when this is withdrawn benefit from having 50–100 mg once a day indefinitely. The prognosis for siblings may be improved if mothers with a pyridoxine dependent child take 100 mg of pyridoxine daily in any subsequent pregnancy.

Homocystinuria: Pyridoxine responsive infants are usually given 50 mg twice a day; older patients are usually given 50–250 mg twice a day and 5 mg of folic acid once a day. If this does not completely correct the abnormality, treatment can be combined with a low methionine diet, betaine, and/or vitamin B₁₂ (q.v.). These forms of treatment can also be used in patients who are unresponsive to pyridoxine.

Adverse effects

The first dose occasionally causes severe transient hypotonia requiring respiratory support. High doses can cause a sensory neuropathy in adults (and may be neurotoxic in children), so long term management should be supervised by a paediatric neurologist or expert in metabolic disease.

Supply

Units should maintain a stock of 2 ml IV ampoules containing 50 mg/ml. These ampoules cost £1 each. Tablets containing 10, 20, and 50 mg of pyridoxine costing 2p each are available, and a sugar-free oral suspension (with a 2 week shelf life) can be prepared on request.

References

- Gibson KM, Jakobs C. Disorders of β - and γ -amino acids in free and peptide-linked forms. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular bases of inherited disease*, 8th ed. New York: McGraw-Hill, 2001:2079–105.
- Mudd SH, Levy HL, Kraus JP. Disorders of transsulfuration. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular bases of inherited disease*, 8th ed. New York: McGraw-Hill, 2001:2007–56.
- Baxter P. Pyridoxine-dependent and pyridoxine-responsive seizures. *Dev Med Child Neurol* 2001;**43**:416–20.
- Hellström-Westas L, Blennow, Rosén I. Amplitude-integrated encephalography in pyridoxine-dependent seizures and pyridoxine-responsive seizures. *Acta Paediatr* 2002;**91**:977–80.

See also relevant Cochrane reviews 

PYRIMETHAMINE

Use

Pyrimethamine is used, with sulfadoxine, to treat malaria and, with sulfadiazine (q.v.), in the treatment of toxoplasmosis. The only controlled trial evidence relating to use in toxoplasmosis comes from patients with disseminated toxoplasmosis complicating HIV infection.

Pharmacology

Pyrimethamine is a di-aminopyrimidine that blocks nucleic acid synthesis in the malaria parasite. It also interferes with folate metabolism. It was developed in 1951 and is still the drug of choice in the treatment of toxoplasmosis (the natural history of which is briefly summarised in the monograph on spiramycin). Prolonged administration can depress haemopoiesis. Other side effects are rare, but skin rashes may occur and high doses can cause atrophic glossitis and megaloblastic anaemia. Folinic acid (the 5-formyl derivative of folic acid) is used to prevent this during pregnancy because folic acid does not interfere with the impact of pyrimethamine on malaria and toxoplasma parasites. Pyrimethamine is well absorbed by mouth and slowly excreted by the kidney, the average plasma half life being about 4 days. Tissue levels exceed plasma levels ($V_D \sim 3$ l/kg). The efficacy of pyrimethamine in treating toxoplasmosis is increased eightfold by sulfadiazine. Other sulphonamides are not as effective. Efficacy in treating malaria is also improved by giving sulfadoxine. For this reason a sulphonamide should *always* be prescribed when pyrimethamine is used to treat a baby for malaria or toxoplasmosis unless there is significant neonatal jaundice, even though the manufacturer endorses its use only in children over 5 years old. Long term administration can sometimes cause problems (as outlined in the monograph on sulfadiazine). Lactation should not be discouraged during treatment, although the baby probably receives approximately a third of the maternal dose on a weight for weight basis.

Treatment of malaria

During pregnancy: Follow a 1 week course of quinine with a single three tablet dose of Fansidar® (a total of 75 mg of pyrimethamine and 1.5 g of sulfadoxine) to eliminate tissue parasites. Some think this unwise in the first trimester, but the teratogenicity seen in animals has not been seen in humans.

In infancy: A synergistic mixture of 1.25 mg/kg of pyrimethamine and 25 mg/kg of sulfadoxine (as Fansidar) given by mouth once a day for 3 days is an effective treatment for uncomplicated malaria in most countries. Giving two 10 mg/kg doses, and then also one 5 mg/kg dose of amodiaquine at daily intervals, makes an early recurrence less likely. Treat severe infection with quinine (q.v.).

Treatment of toxoplasma infection

During pregnancy: Spiramycin (q.v.) is often used to try to prevent transplacental spread. If fetal infection is thought to have occurred, sustained maternal treatment with 50 mg of pyrimethamine once a day and 1 g of sulfadiazine 3 times a day by mouth may possibly lessen disease severity.

In infancy: Give an oral loading dose of 1 mg/kg of pyrimethamine twice a day for 2 days, followed by maintenance treatment with 1 mg/kg once a day for 8 weeks if there is evidence of congenital infection. Treatment with 50 mg/kg of oral sulfadiazine once every 12 hours should be started at the same time. Check weekly for possible thrombocytopenia, leucopenia, and megaloblastic anaemia.

Older children: It is not known whether a year's sustained treatment improves the outcome. Dormant cysts, which often give rise to ocular disease in later life, cannot be eradicated by such an approach. Some centres intersperse continued treatment as outlined above with 4–6 week courses of spiramycin.

Ocular disease: Clindamycin (q.v.) is sometimes given to babies with ocular disease. Consider photocoagulation for choroidal scars. Prednisolone (2 mg/kg once a day) is of uncertain value.

Prophylaxis with calcium folinate = Leucovorin (USAN)

Give 15 mg by mouth twice a week during pregnancy to prevent pyrimethamine causing bone marrow depression. Exactly the same dose is often given to infants on long term pyrimethamine treatment.

Supply

25 mg pyrimethamine tablets cost 7p, and 25 mg tablets compounded with sulfadoxine as Fansidar (see above) cost 27p each. Suspensions can be provided on request. Amodiaquine is not currently marketed in the UK or the US, but it is available as a suspension from Parke Davis.

Calcium folinate is available in 15 mg tablets and as 15 mg ampoules for injection costing £3.80 and £4.50 respectively.

References

- Roizen N, Swisher CN, Stein MM, *et al.* Neurologic and developmental outcome in treated congenital toxoplasmosis. *Pediatrics* 1995;**95**:11–20.
- Remington JS, McLeod R, Thulliez P, *et al.* Toxoplasmosis. In: Remington JS, Klein JO, eds. *Infectious diseases of the fetus and newborn infant*, 5th ed. Philadelphia, PA: Saunders, 2001:205–346.
- Dorsey G, Njama D, Kamya MR, *et al.* Sulfadoxine/pyrimethamine alone or with amodiaquine or artesunate for treatment of uncomplicated malaria: a longitudinal randomised trial. *Lancet* 2002;**360**:2031–8. (See also p. 1998.) [RCT]

See also relevant Cochrane reviews



Use

Quinine is still used to treat acute malarial infection when there can be no certainty that the parasite is sensitive to chloroquine (q.v.). Mefloquine (q.v.), or a combination of pyrimethamine (q.v.) with sulfadoxine, available as Fansidar[®], can be used instead if oral treatment is possible.

Pharmacology

An extract from the bark of the cinchona tree has long been valued as a specific cure for marsh or "four day" (quaternary) fever. Jesuit priests brought such knowledge back from Peru four centuries ago, and we now know that the active ingredient, the alkaloid quinine, kills the malarial schizonts when they transiently enter the blood stream. Because it is ineffective against tissue parasites, it is not curative. Nor is it a good prophylactic. Treatment with quinine *always* has to be followed by further treatment to eradicate tissue parasites, either with a combination of pyrimethamine and sulfadoxine, or an antibiotic such as tetracycline or clindamycin (q.v.).

Although high dose quinine is a recognised abortifacient, its use to treat maternal malaria during pregnancy does not seem hazardous, there is no clear evidence of teratogenicity, and use during lactation would expose the baby to only about 5% of the weight adjusted maternal dose.

Managing severe malaria

Malaria can be rapidly fatal, especially in children under 1 year old, and symptoms may be non-specific. There may be vomiting, diarrhoea, and weakness or drowsiness, as well as fever. Monitor, prevent, and treat hypoglycaemia with dextrose (q.v.), correct severe anaemia (haematocrit < 15%) with blood (q.v.), and consider exchange transfusion if anaemia is gross or more than 10% of the red cells are parasitised. Give phenobarbital (q.v.) if there are signs suggestive of cerebral malaria. Shock may indicate that there is both malaria and septicaemia (with or without meningitis); start treatment for both if the situation is unclear and review later. Transplacentally acquired infection may not manifest itself until 2–8 weeks later, with fever, jaundice, anaemia, respiratory symptoms, and a large spleen.

Treatment with quinine

By mouth: Give 10 mg/kg of quinine sulphate (or quinine dihydrochloride) by mouth once every 8 hours for between 3 and 7 days.

As an IV infusion: Give a loading dose of 20 mg/kg of quinine dihydrochloride (2 ml/kg of a solution made up as specified below) over 4 hours. Then give a continuing infusion of 1 mg/kg per hour (0.1 ml/kg per hour of the same solution). Rapid administration must be avoided (using a pump or inline infusion chamber) because of potential cardiotoxicity. Change to oral treatment as soon as possible.

By injection: A first 20 mg/kg IM dose and then 10 mg/kg once every 8 hours for 3 days can be used if IV administration is impractical, although injections can be painful and cause a sterile abscess.

Other drug treatment

Pyrimethamine and sulfadoxine: Give a quarter tablet of Fansidar[®] once on the final day of treatment; babies 3 or more months old can probably have half a tablet. For more information on these two synergistic drugs see the monograph on pyrimethamine.

Tetracycline: Alternatively, give 7.5 mg/kg of tetracycline (q.v.) once every 8 hours for 7 days. Treatment with clindamycin for 5 days is an alternative that avoids the risk of the dental staining caused by tetracycline use. Neither drug normally needs to be started before oral treatment is possible.

Supply and administration

Quinine dihydrochloride is available from Martindale Pharmaceuticals, Romford, UK, in 1 ml and 2 ml ampoules containing 300 mg/ml, costing £2.60 and £3.50 respectively. Accurate administration is best achieved by taking 1 ml of this preparation and diluting it to 30 ml with 5% or 10% dextrose saline to give a solution containing 10 mg/ml. Quinine sulphate is available as a 200 mg tablet that costs 7p.

References

- Phillips RE, Looareesuwan S, White NJ, *et al.* Quinine pharmacokinetics and toxicity in pregnant and lactating women with falciparum malaria. *Br J Clin Pharmacol* 1986;**21**:677–83.
- Panisko DM, Keystone JS. Treatment of malaria – 1990. *Drugs* 1990;**39**:160–89.
- Gilles HM. *Management of severe and complicated malaria*. Geneva: World Health Organization, 1991.
- Phillips-Howard PA, Wood D. The safety of antimalarial drugs in pregnancy. *Drug Safety* 1996;**14**:131–45.
- Schapira A, Solomon T, Julien M, *et al.* Comparison of intramuscular and intravenous quinine for the treatment of severe and complicated malaria in children. *Trans R Soc Trop Med Hyg* 1993;**87**:299–302.
- Brabin BJ, Ganley Y. Imported malaria in children in the UK. *Arch Dis Child* 1997;**77**:76–81.
- van der Torr M, Thuma PE, Mabeza GF, *et al.* Loading dose of quinine in African children with cerebral malaria. *Trans R Soc Trop Med Hyg* 1998;**92**:325–31.
- Omari A, Garner P. Malaria in endemic areas. *Clin Evid* 2002;**8**:734–43 (and updates). [SR]

See also relevant Cochrane reviews



RANITIDINE

Use

Ranitidine inhibits gastric acid secretion, and is used to treat symptomatic oesophagitis, gastritis, and peptic ulceration. Omeprazole (q.v.) may be effective if ranitidine is not. Trials have not yet shown prophylactic use to be of measurable benefit in adults or children requiring intensive care.

Pharmacology

Ranitidine (first developed in 1979) works by blocking the H₂ histamine receptors in the stomach, which control the release of gastric acid, thereby triggering pepsin production. A low dose 75 mg tablet is now available without prescription for the short term treatment of heartburn and indigestion in adults. Higher doses are used to treat peptic ulceration. It does little for stress related upper gastrointestinal bleeding.

The pharmacology of ranitidine is very similar to that of cimetidine (q.v.), but ranitidine does not interact with the metabolism of other drugs in the same way as cimetidine, and it has no antiandrogenic properties. Higher doses have to be used when the drug is given by mouth because of rapid first pass metabolism in the liver (oral bioavailability being about 50%; the comparable figure for cimetidine being 60–70%). Tissue levels exceed plasma levels (V_D ~ 1.8 l/kg). Excretion is largely in the urine. Because ranitidine has a slightly longer half life than cimetidine in adults it is often given only once every 12 hours, instead of once every 6–8 hours. Most reports of the use of ranitidine in the neonatal period relate to IV administration and there are suggestions that oral absorption could be unreliable. The manufacturers are not, however, yet ready to recommend its IV use in children.

Ranitidine crosses the placenta, and should be used with caution in early pregnancy, although teratogenicity has not been reported. No adverse effects have ever been noted in the baby after birth, although it is widely used, with or without an antacid, to minimise the potentially life threatening pneumonitis that results from the maternal aspiration of gastric fluid into the lung during birth (Mendelson's syndrome). The standard maternal dose for this is 150 mg by mouth, repeatable after 6 hours. (A liquid non-particulate antacid, such as 30 ml of 0.3M sodium citrate, is often given as well if a general anaesthetic becomes necessary. Such a strategy has been shown to reduce gastric acidity but, because the complication is so uncommon, it is difficult to prove that this reduces the threat of serious pneumonitis, and problems have been documented despite prophylaxis.) Ranitidine appears in breast milk in concentrations significantly in excess of those present in the maternal plasma, but there have been no adverse reports following its use by mothers during lactation.

Treatment

By mouth: Experience is limited. Try 2 mg/kg every 8 hours.

IV administration: Giving 500 micrograms/kg slowly IV twice a day will usually keep the gastric pH above 4 in the first week of life in babies of less than 32 weeks gestation. Term babies may need this dose every 6 hours. Rapid administration can (rarely) cause an arrhythmia.

Continuous IV infusion: A loading dose of 250 micrograms/kg, followed by a maintenance infusion of 50 micrograms/kg per hour has been used (or 5 ml of a solution prepared as described below given over 1 hour, followed by a continuing infusion of 1 ml/hour).

Renal failure: Double the dosage interval if there is renal failure.

Compatibility

Ranitidine can be added (terminally), when necessary, into a line containing adrenaline, atracurium, dobutamine, dopamine, fentanyl, glyceryl trinitrate, heparin, insulin, isoprenaline, midazolam, milrinone, morphine, nitroprusside, noradrenaline, or vancomycin, or with standard total parenteral nutrition (with or without lipid).

Supply and administration

2 ml ampoules containing 25 mg/ml of ranitidine hydrochloride for IV or IM use are available costing 65p. For accurate IV administration take 1 ml (25 mg) from this ampoule and dilute to 50 ml with 5% dextrose to get a preparation containing 500 micrograms/ml. To give a continuous infusion of 50 micrograms/kg per hour, take 1 ml (25 mg) of drug from the ampoule and dilute to 10 ml with 5% dextrose. Then take 1 ml of this diluted solution for each kilogram the baby weighs, make this up to 50 ml with 5% dextrose, and infuse at a rate of 1 ml/hour. The drug is stable in solution, so a fresh infusion does not need to be prepared every 24 hours. A sugar-free syrup containing 15 mg/ml (which should not be diluted further) is also available (100 ml costs £7.40).

References

- Fontana M, Massironi E, Rossi A, *et al.* Ranitidine pharmacokinetics in newborn infants. *Arch Dis Child* 1993;**68**:602–3.
- Kelly DA. Do H₂ receptor antagonists have a therapeutic role in childhood? *J Pediatr Gastroenterol Ther* 1994;**19**:270–6.
- Kuusela A-L. Long term gastric pH monitoring for determining optimal dose of ranitidine for critically ill preterm and term neonates. *Arch Dis Child* 1998;**78**:F151–3.
- Messori A, Tripoli S, Vaiani M, *et al.* Bleeding and pneumonia in intensive care patients given ranitidine and sucralfate for prevention of stress ulcer: meta-analysis of randomised controlled trials. *BMJ* 2000;**321**:1103–6. [SR]

Use

Rhesus (D) immunoglobulin is used to prevent rhesus isoimmunisation.

Product

A human immune globulin (currently collected by apheresis from the plasma of donors with high levels of anti-D antibody in the USA) has been used since 1970 to prevent rhesus negative mothers developing antibodies to transplacentally acquired Rh D positive fetal red cells during childbirth. It is also used after miscarriage, threatened miscarriage, and abortion after 12 weeks gestation, or any other obstetric manoeuvre such as chorion villus biopsy, amniocentesis, fetal blood sampling, and external cephalic version that could be associated with fetomaternal bleeding. Other events such as ectopic pregnancy, antepartum haemorrhage, and blunt abdominal trauma (from, for example, seat belt injury) should also be covered. The product works by eliminating fetal red cells from the circulation before they can stimulate active maternal antibody production. While it should be given within 72 hours, if possible, with a view to preventing rhesus isoimmunisation compromising any future pregnancy, it still offers some protection if given within 12 days. A monoclonal IgG₃ antibody is still under development.

Approximately 1% of rhesus negative mothers develop rhesus antibodies late in their first pregnancy but before delivery in the absence of any recognisable sensitising event. Furthermore, these "hypersensitive" mothers seem to be at risk of having a baby with disease of atypical severity in any subsequent pregnancy. Antenatal treatment at 28 and 34 weeks more than halves this risk, but there may be better ways to use the money this would cost in communities where such problems are rare.

Indications

The amount of anti-D (Rh₀) immunoglobulin actually required is proportional to the size of the fetomaternal bleed. For events occurring before 20 weeks gestation it has been traditional to give 250 units (50 micrograms) of anti-D immunoglobulin. Later in pregnancy and after delivery the usual dose is 500 units (100 micrograms), but this should be increased if a Kleihauer test on the mother's blood shows more than one fetal cell per 500 adult red cells (equivalent to 4–5 ml of packed fetal red cells). Such bleeds should be quantified by flow cytometry and an additional 150 units of anti-D immunoglobulin given for each ml by which the transplacental bleed exceeds 4 ml of packed fetal red cells.

Contraindications

There are no known contraindications. Use of the UK product has never caused the acquisition of any infection transmitted by blood products, such as hepatitis B or HIV, and current supplies come from the USA, where there is minimal risk of the donor having latent variant Creutzfeldt–Jakob disease. Simultaneous rubella (but not MMR: measles, mumps, rubella) vaccination is acceptable as long as separate syringes are used and the products injected into different limbs. Treat any reaction as outlined in the monograph on immunisation.

Administration

During pregnancy: Every rhesus (D) negative woman should be offered an injection at 28 and 34 weeks gestation to prevent the baby becoming immunised before birth (500 units seems adequate, but a 1250 unit dose is widely used), unless she is sure this is going to be her last pregnancy or she is confident that the child's father is rhesus negative. Injections are usually given into the deltoid muscle.

After delivery: It is worth treating only rhesus negative mothers whose babies are rhesus positive (or whose blood group is unknown). It is pointless to treat mothers who have already started to produce antibodies to the D antigen, but important to remember that mothers with *other* antibodies (anti-c, anti-Kell, etc.) may still require protection from the D antigen if they are rhesus (D) negative.

Supply and administration

A range of commercial and volunteer donor products are now available in vials and prefilled syringes containing from 250 units to 1500 units of anti-D immunoglobulin. Most products cost less than £24 per dose. Most should be stored at 4°C, but lyophilised powders (which should be reconstituted with 0.9% sodium chloride) are safe for 1 month at room temperature. The products need prescribing; maternity units in the UK are now starting to develop patient group directions, since these give midwives a more direct and proactive role in ensuring that all rhesus negative mothers have easy access to prophylaxis.

References

- Lee D (convenor), for a joint working group of the British Blood Transfusion Society and the Royal College of Obstetricians and Gynaecologists. Recommendations for the use of anti-D immunoglobulin for Rh prophylaxis. *Transfus Med* 1999;9:93–9.
- National Institute for Clinical Excellence. Guidance on the use of routine anti-D prophylaxis for RhD negative women. Technology Appraisal Guidance No 41. London: NICE, 2002. (See: www.nice.org.uk)
- Mason G, Glanville T. Guidelines for antenatal anti-D prophylaxis [Letter]. *Lancet* 2002;360:880.

See also relevant Cochrane reviews



RIBAVIRIN = Tribavirin (former BAN)

Use

Treatment with ribavirin may reduce the severity of bronchiolitis due to the respiratory syncytial virus (RSV) if started within 3 days of the onset of lower respiratory tract symptoms. A nebulised bronchodilator such as salbutamol (q.v.) can produce short term symptomatic improvement, but does not increase oxygen saturation, or reduce the need for hospital admission.

Pharmacology

Ribavirin (first synthesised in 1972) is a stable, white, synthetic nucleoside with in vitro antiviral properties against RSV and the adenoviruses, as well as the influenza, parainfluenza, and measles viruses. A significant amount of drug is absorbed systemically after aerosol administration and the concentration in respiratory secretions is particularly high. Ribavirin is teratogenic and embryolethal, and should never be given to pregnant patients; the manufacturers even advise against it being administered by staff who are pregnant. There is some evidence that it can be mutagenic in cell culture, and may (with chronic exposure) induce benign glandular tumours. Its clinical use is therefore currently limited to high risk children (those with congenital heart disease, existing bronchopulmonary dysplasia, or immunodeficiency) with proven lower respiratory tract RSV infection. It needs to be remembered that the drug is efficacious only if given early in the course of the disease. There is only one study suggesting that its use speeds recovery in ventilator dependent infants and there is little evidence that it reduces the time it takes for the patient to stop shedding live virus particles. Unsubstantiated reports suggest that it may be of value in parainfluenza lung infection and in measles in infancy. The only common adverse effect in children on standard treatment is conjunctivitis, but little is known about possible long term morbidity or toxicity. While widespread US experience suggests that ribavirin is safe, most clinicians in Europe believe that further evidence of efficacy is needed. Nine small controlled studies have now been done, but the total number of children studied (291 in all) remains inadequate to establish the utility of this form of treatment.

Diagnosing RSV

RSV infection is easily and rapidly diagnosed from a nasopharyngeal wash specimen using immunofluorescence or an enzyme linked immunoabsorbent assay (ELISA) test, as outlined in the monograph on palivizumab. Infected babies should be nursed in isolation and nosocomial spread limited by careful attention to hand washing.

RSV prophylaxis

Palivizumab (q.v.) is sometimes used to reduce the risk that RSV infection will precipitate hospital readmission in babies with bronchopulmonary dysplasia severe enough to need home oxygen. An immune globulin with a high titre of RSV neutralising antibody has also been used in North America, as outlined in the same monograph.

Treatment

Administer nebulised ribavirin (20 mg/ml) for between 12 and 20 hours per day using a small particle aerosol generator (SPAG) for 3–7 days, preferably a modified Easy Vent[®] constant positive airway pressure (CPAP) device. A more concentrated solution (60 mg/ml) given for just 2 hours three times a day may be equally effective. Early treatment *may* be appropriate in high risk children with proven infection to try to reduce the chance of their needing ventilator support. There is no good evidence that it shortens the duration of treatment in children already ill enough to be receiving respiratory support; such use can easily cause the ventilator to become clogged.

Supply and administration

Ribavirin is supplied in 100 ml vials containing 6 g of lyophilised drug at a cost of £116 per vial. Many units in the UK require its use to carry a consultant's endorsement. Dissolve the powder with 100 ml of sterile water for injection free of all preservatives and then further diluted with a further 200 ml of water to give a solution containing 20 mg/ml. A SPAG for drug administration can be borrowed from the pharmacy on request. Any of the reconstituted solution not used within 24 hours of preparation should be discarded.

References

- Englund JA, Piedra PA, Ahn Y-M, *et al*. High-dose, short-duration ribavirin aerosol therapy compared with standard ribavirin therapy in children with suspected respiratory syncytial virus infection. *J Pediatr* 1994;**125**:635–41. [RCT]
- American Academy of Pediatrics. Committee on Infectious Disease. Reassessment of the indications for ribavirin therapy in respiratory syncytial virus infections. *Pediatrics* 1996;**97**:137–40.
- Smedsaas-Löfvenberg A, Nilsson K, Moa G, *et al*. Nebulisation of drugs in a CPAP system. *Acta Paediatr* 1999;**88**:89–92.
- Guerguerian AM, Gauthier M, Lebel MH, *et al*. Ribavirin in ventilated respiratory syncytial virus bronchiolitis. *Am J Respir Crit Care Med* 1999;**160**:829–31. [RCT]
- Lozano JM. Bronchiolitis. *Clin Evid* 2003;**9**:328–40 (and updates). [SR]

See also relevant Cochrane reviews on bronchiolitis 

Use

Rifampicin is used with isoniazid (q.v.) to treat tuberculosis, and with vancomycin or teicoplanin (q.v.) to treat severe staphylococcal infection. It is also given prophylactically to the contacts of patients with meningococcal or haemophilus infection, and has a role in the treatment of cholestatic pruritis.

Pharmacology

This bactericidal antibiotic, first developed in 1966, interferes with DNA dependent RNA polymerase. It has activity against many mycobacteria, *Neisseria meningitidis*, and *N gonorrhoeae* and is the most active antistaphylococcal agent known. However, since resistant strains of *Mycobacterium* and *Staphylococcus* emerge quickly if rifampicin is used alone, it is recommended that it should always be used in combination with a second antibiotic, except when the drug is used prophylactically to eliminate bacterial carriage and reduce the risk of meningitis. Rifampicin is readily absorbed when given by mouth. It is highly protein bound and undergoes enterohepatic recirculation. Up to 30% may be excreted unchanged, but the metabolites are excreted in urine and bile. Dose intervals do not need to be modified in the presence of renal failure. Rifampicin colours urine and other secretions red. The half life is 3–4 hours, but twice this in the first month of life. Transient jaundice can be ignored, but treatment must be stopped at once if thrombocytopenia, nausea, and vomiting, or other signs of more serious liver toxicity, develop. Such adverse effects are rare in children unless there is prior liver disease. Rifampicin crosses the placenta, but its use is not contraindicated in pregnancy, although use in the third trimester is said to be associated with an increased risk of neonatal bleeding meriting routine IM vitamin K prophylaxis (q.v.). Only small quantities of the drug appear in breast milk.

Drug interactions

Rifampicin induces microsomal liver enzymes and therefore affects the metabolism of a wide range of other drugs. Chloramphenicol, corticosteroids, most benzodiazepines, digoxin, fluconazole, nifedipine, phenobarbital, phenytoin, theophylline, and warfarin (q.v.) are all metabolised more rapidly, and dosage levels may need adjustment. Rifampicin also induces its own metabolism and, as a result, clearance increases markedly during the first 2 weeks of use. Treatment of HIV infection with the protease inhibitors nelfinavir or ritonavir (q.v.) greatly increases the clearance of rifampicin, making cotreatment with this drug unwise.

Treatment

Synergistic use with teicoplanin or vancomycin: Experience remains limited. Give 10 mg/kg (1 ml/kg of dilute solution made up as described below) slowly IV once every 12 hours for 10 days, pickabacked onto an existing IV infusion of dextrose or dextrose saline, or 20 mg/kg once a day by mouth.

Treatment of tuberculosis: Seek expert advice. Give 10 mg/kg once a day by mouth (20 mg/kg if meningitis is suspected), together with isoniazid (q.v.). Warn parents that the urine may turn red.

Prophylaxis against meningococcal and haemophilus infection: Give a 5 mg/kg dose to children under 1 month old, and a 10 mg/kg dose to older children. Meningococcal carriage can be eliminated by giving four doses at 12 hour intervals, but this dose should be given once a day for 4 days to any unvaccinated child less than 4 years old exposed to known infection with *Haemophilus influenzae*.

Pruritis due to cholestasis: Try 5 mg/kg twice a day. Monitor liver function for the first month.

Supply

Rifampicin is available as a powder for IV use in 300 mg or 600 mg vials (costing about £7 and £8 each) normally dispensed with 5 ml or 10 ml of solvent. Reconstitute the 600 mg vial with 9.6 ml of the solvent and shake well. Take 60 mg of rifampicin (1 ml of the fluid from a 600 mg vial), dilute to 10 ml with 5% or 10% dextrose to obtain a solution containing 6 mg/ml of rifampicin, and use within 6 hours. Slow infusion over 30–60 minutes is recommended in adults because of the volume involved, and because there is some slight risk of hypotension and phlebitis. Do not co-infuse with any alkaline solution. Rifampicin should not be given IM. A 20 mg/ml syrup is also available with an undiluted shelf life of 3 years (100 ml costs £3.10).

References

- Acocella G. Clinical pharmacokinetics of rifampicin. *Clin Pharmacokinet* 1978;**3**:108–27.
- American Academy of Pediatrics. Committee on Infectious Diseases. Chemotherapy for tuberculosis in infants and children. *Pediatrics* 1992;**69**:161–5.
- Rosenfeld EA, Hageman JR, Yogev R. Tuberculosis in infancy in the 1990s. *Pediatr Clin North Am* 1993;**40**:1087–103.
- Tan TQ, Mason EO, Ou C-N, et al. Use of intravenous rifampicin in neonates with persistent staphylococcal bacteremia. *Antimicrob Agents Chemother* 1993;**37**:2401–6.
- Cynamon HA, Andres JM, Iafraite RP, et al. Rifampicin relieves pruritis in children with cholestatic liver disease. *Gastroenterology* 1990;**98**:1013–16.
- Shama A, Patole SK, Whitehall JS. Intravenous rifampicin in neonates with persistent staphylococcal bacteraemia. *Acta Paediatr* 2002;**91**:670–3.

RITONAVIR

Use

Ritonavir is used to control HIV infection. Several drugs are best used in combination to optimise the suppression of viral replication and prevent the development of drug resistance.

Pharmacology

Ritonavir is a protease inhibitor that binds to HIV-protease causing the formation of immature viral particles that are incapable of infecting other cells. It first came into general clinical use in 1996. It is well absorbed by mouth (especially when given with food), metabolised by the liver, and excreted in the faeces. The half life in adults is about 4 hours. Diabetes can develop or be exacerbated in patients taking a protease inhibitor. Placental transfer is very limited and there is no evidence of teratogenicity but, to increase information on safety, all use in pregnancy should be reported (anonymously) to the Antiretroviral Pregnancy Register, as outlined in the monograph on zidovudine. How much of the drug is excreted into breast milk is not yet known. Because its use is still under controlled trial evaluation, the manufacturers are not yet ready to recommend the use of ritonavir in children under 2 years old.

Nelfinavir is a related protease inhibitor that shares many of the same pharmacological properties as ritonavir. Infants seem to need as much as 50 mg/kg three times a day by mouth, but it is probably better to start with 40 mg/kg twice a day in the first 4 weeks of life until drug handling is better understood.

Principles of overt HIV management

Combined treatment with several drugs, or "highly active antiretroviral therapy", is now widely used to control overt HIV infection. The commonest strategy (where it can be afforded) is a combination of two nucleoside reverse transcriptase inhibitor drugs (the best known of which is zidovudine (q.v.)) with either a protease inhibitor such as ritonavir or nelfinavir, or a *non*-nucleoside reverse transcriptase inhibitor such as nevirapine (q.v.). Such treatment should not be modified during pregnancy; to do so risks jeopardising the mother's health. Opinion is more divided as to the best management of infection in early infancy. Vigorous treatment is clearly indicated where there is a high HIV RNA viral load because there is a high risk of rapid disease progression. The best strategy where there is only a low viral load is less clear. No strategy seems capable of eliminating all virus from the body, so some clinicians would prefer to use as little potentially toxic drug treatment as is compatible with inhibiting all detectable virus replication. A major collaborative trial (PenPact 1) comparing various drug combinations started recruiting in late 2001. For further information contact the MRC Clinical Trials Unit in the UK (+ 44 (0)207 670 4700 or PENTA@ctu.mrc.ac.uk). A wealth of authoritative, up to date, information on *all* aspects of HIV care is available on the website www.AIDSinfo.nih.gov

Drug interactions

Ritonavir and nelfinavir are best taken with food, but didanosine (mentioned in the monograph on lamivudine) is best given on an empty stomach, so simultaneous administration should be avoided. Since ritonavir and nelfinavir are partly metabolised by the liver's cytochrome P450 enzyme system, their clearance is increased by cotreatment with a wide range of other drugs; these protease inhibitors can, in turn, increase the clearance of other drugs. This is certainly true of carbamazepine, dexamethasone, phenobarbital, phenytoin, and theophylline (q.v.). Cotreatment with antihistamines, benzodiazepines, cisapride, rifampicin (q.v.) and a range of cardiac drugs (including amiodarone and flecainide (q.v.)), is also discouraged because clearance is unpredictably decreased. Digoxin (q.v.) levels are variably affected. Always consult the manufacturer's summary of product characteristics. See also: www.hivdruginteractions.org

Treatment

Little information is available on the best dose of ritonavir to use in the first month of life. Older children are usually given 400 mg/m² by mouth twice a day but, to minimise the nausea caused by the poor taste, treatment is usually started with half this dose and increased gradually over a few days.

Supply

Ritonavir is available as a sugar-free, but alcohol containing, 80 mg/ml solution (100 ml costs £90). The bitter taste can be disguised by giving the drug with chocolate flavoured milk; the product must *not* be mixed with water. It is best kept at 4°C, but is stable at room temperature for 1 month. Nelfinavir is available as a 50 mg/g powder that can be mixed, just before use, with water, milk, ice cream, or puddings, but crushed 250 mg tablets (costing £1 each) are more palatable. These products cannot be given IV or IM. Give with a little food to minimise gastric irritation.

References

- de Martino M, Tovo P-A, Balducci M, *et al.* Reduction in mortality with availability of antiretroviral therapy for children with perinatal HIV-1 infection. *JAMA* 2000;**284**:190-7.
- Litalien C, Faye A, Compagnucci A, *et al.* Pharmacokinetics of nelfinavir and its active metabolite hydroxy-*tert*-butylamide, in infants perinatally infected with human immunodeficiency virus type 1. *Pediatr Infect Dis J* 2003;**22**:48-55.

Use

A live attenuated rubella virus vaccine is used to provide active immunity in children, and in seronegative women of childbearing age. A trivalent vaccine offering protection against measles, mumps, and rubella (MMR) is the product usually offered to 1 year old children.

Rubella

Rubella (or German measles) is a mild infectious illness with an incubation period of 14–21 days. Patients are infectious from 1 week before the rash appears for a period of about 10 days. Symptoms may be mild and the rash is often not diagnostic (see: www.phls.org.uk/topics_az/rashes/rash/pdf). Diagnosis currently depends on testing paired sera samples taken 2–3 and 8–9 days after the first appearance of the rash for rubella antibody; or a single sample taken 1–6 weeks after the rash first appears may be tested for the presence of rubella specific immunoglobulin M (IgM) antibody. A new, more rapid and sensitive test that can identify the presence of specific IgM in saliva is available from the Public Health Laboratory Service. Natural infection causes lasting immunity. Maternal infection in early pregnancy can cause serious fetal damage (as first recognised by Gregg during the Australian epidemic in 1941), but the multifaceted nature of this damage became clear only 25 years later. Infection at 8–10 weeks gestation damages up to 90% of babies. The risk of damage is about 10–20% by 16 weeks. It is negligible after this. Immunoglobulin (750 mg of human normal immunoglobulin IM) is sometimes given to reduce the chance of clinical infection in pregnant seronegative mothers, but there is no good evidence that it does much good.

Problems associated with congenital infection include cataract, glaucoma, pneumonia, meningoencephalitis, hepatitis, purpuric skin lesions, and fetal growth retardation. Cardiac lesions include patent ductus, septal defects, and pulmonary artery stenosis. Progressive deafness may develop, even in babies who seem normal at birth. The policy of vaccinating all teenage girls, which ran from 1970 to 1996, caused a progressive fall in the incidence of congenital rubella, while the policy of universal vaccination in infancy introduced in 1988 further reduced the risk of community exposure. Infection in pregnancy is now rare, but unvaccinated and susceptible women of childbearing age still exist. Many immigrants currently remain at risk. Even in France, Germany, and Italy, 10% still remain susceptible.

Product

A vaccine made from an attenuated live virus has been used in the UK since 1970. A single dose promotes an antibody response in more than 95% of recipients. The antibody response seems to be well maintained for at least 20 years and protection against clinical rubella seems to persist even in the presence of a declining antibody level. Nevertheless, natural infection does occasionally occur after immunisation (due, presumably, to primary vaccination failure or subsequent loss of immunity), and such infection can cause fetal damage if it occurs in early pregnancy.

Indications in adult life

All women of childbearing age should be made aware of their rubella status and told the outcome of any serological test. Any found to be seronegative during pregnancy should also be offered vaccination before discharge from the maternity unit after delivery. It is perfectly acceptable to give the monovalent rubella vaccine and anti-D (Rh₀) immunoglobulin at the same time, as long as different syringes and different sites are employed. Blood transfusions during delivery blunt the response to vaccination, however. In such cases a test for seroconversion should be undertaken 8 weeks later and revaccination offered if necessary. Short term contraceptive cover can, if necessary, be offered in the interim with medroxyprogesterone acetate (Depo-Provera®), as long as the mother is counselled appropriately and shown the manufacturer's leaflet first; give 150 mg in 1 ml once by deep IM injection.

Vaccination should be avoided in early pregnancy (and patients told not to become pregnant within 1 month of vaccination), but there has been no recorded case of fetal damage in the USA, Canada, Sweden, Germany, or the UK among the significant number of mothers inadvertently immunised with the attenuated virus in early pregnancy. Seronegative male and female health service staff in maternity units should also be vaccinated to prevent their transmitting rubella to pregnant patients. A mild reaction, with fever, rash, and arthralgia, may occur 1–3 weeks after vaccination.

Indications in childhood

All children should be offered one dose of the MMR vaccine when 12–15 months old, unless there is a specific contraindication (see overleaf), and a second dose as part of the preschool programme. Children not immunised at this time should be immunised before they start school (or nursery school) and again 3 months later. Measles, mumps, and rubella are all notifiable illnesses. The incidence of all three infections has declined dramatically in the UK since the MMR vaccine was introduced in 1988, and uptake was consistently above 90% until mid 1997. However, uptake had dipped below 85% both in the UK and in some other countries by 2002 because of an unfounded fear that the MMR vaccine could be causing autism or a non-specific colitis; epidemics of measles and congenital rubella could easily reappear if this decline is not reversed.

continued ...

RUBELLA VACCINE (continued)

Interactions

More than one live vaccine can be given at different sites on the same day, but an interval of 3 weeks should be allowed if vaccination is not simultaneous. If a booster injection of the diphtheria and tetanus vaccine is to be given at the same time as primary MMR immunisation, the two products should be given into opposite arms. Do not give within 3 weeks of BCG administration.

Contraindications

Pregnancy, immunodeficiency, immunosuppression, reticuloendothelial malignancy, and high dose corticosteroid treatment (the equivalent of more than 1 mg/kg of prednisolone per day, or 2 mg/kg for more than 1 week in the last 6 weeks) are contraindications to vaccination, as is known hypersensitivity to gelatin or neomycin. Egg allergy does not seem to be a problem, as was at one time feared. A history of fits is not a contraindication to either the monovalent or the trivalent vaccine, but advice should be given on how to handle any febrile response to immunisation as outlined in the monograph on paracetamol (q.v.). Vaccination should be delayed if there is any febrile illness and postponed after immunoglobulin injection (other than rhesus anti-D) for 3 months. For the latest advice on the safety of the combined MMR vaccine see the UK Government's website: www.doh.gov.uk/mmr/index.html

Administration

98% of patients probably achieve immunity to rubella with a single 0.5 ml deep IM injection of the monovalent or trivalent vaccine using a 25 mm, 23 gauge, needle.

Anaphylaxis

The management of anaphylaxis (which is very rare) is outlined in the monograph on immunisation.

Documentation

Inform the district immunisation coordinator (see monograph on immunisation) when any child is immunised in hospital, and complete the relevant section of the child's own personal health booklet.

Case notification

All cases of suspected congenital rubella (in people with or without symptoms) in the UK should be notified to the National Congenital Rubella Surveillance Programme. This can be done directly (telephone Pat Tookey on 020 7242 9789 or e-mail ptookey@ich.ucl.ac.uk) or via the British Paediatric Surveillance Unit (telephone 020 7307 5671, fax 020 7307 5694). Women who are inadvertently vaccinated during pregnancy, or less than 1 month before becoming pregnant, should also be notified direct to this register.

Supply

Single dose vials of the freeze dried live monovalent and trivalent vaccines are available from health authorities in the UK and also distributed, in England, by Farillon. The vaccines must be stored at 2–8°C and used within 1 hour of reconstitution with the diluent provided. They must not be frozen.

References

- Miller E, Cradock-Watson JE, Pollock TM. Consequences of confirmed maternal rubella at different stages of pregnancy. *Lancet* 1982;**ii**:781–4.
- UK Health Departments. *Immunisation against infectious disease*. Chapter 28. London: HMSO, 1996: 193–202.
- Tookey PA, Peckham CS. Surveillance of congenital rubella in Great Britain, 1971–96. *BMJ* 1999;**318**:769–70.
- Lakshman R, Finn A. MMR vaccine and allergy. *Arch Dis Child* 2000;**82**:93–7.
- Bedford H, Elliman D. Concerns about immunisation. *BMJ* 2000;**320**:240–3.
- Cooper LZ, Alford CA. Rubella. In: Remington JS, Klein JO, eds. *Infectious diseases of the fetus and newborn infant*, 5th ed. Chapter 6. Philadelphia, PA: Saunders, 2001:347–88.
- Tookey P. Pregnancy is contraindication for rubella vaccination still. *BMJ* 2001;**322**:1489.
- Mehta NM, Thomas RM. Antenatal screening for rubella – infection or immunity? *BMJ* 2002;**325**:90–1 (See also pp. 596–7.)
- Best JM, O'Shea S, Tipples G, et al. Interpretations of rubella serology in pregnancy – pitfalls and problems. *BMJ* 2002;**325**:147–8.
- Sheridan E, Aitken C, Jeffries D, et al. Congenital rubella syndrome: a risk in immigrant populations. *Lancet* 2002;**359**:674–5 (See also **360**:803–4).
- Tookey PA, Cortina-Borja M, Peckham CS. Rubella susceptibility among pregnant women in North London 1996–1999. *J Public Health Med* 2002;**24**:211–16.

Use

Salbutamol and terbutaline are β adrenergic stimulants (betamimetics) widely used by asthmatics for their bronchodilator activity. Given IV, they can at least briefly inhibit preterm labour. Both can also, in the short term, control a sudden life threatening rise in plasma potassium.

Pharmacology

Salbutamol is a synthetic sympathomimetic related to noradrenaline and isoprenaline (q.v.) that has its main effect on the β_2 receptors in bronchial muscle. It was first developed in 1967. An excessive dose can cause tachycardia, tremor, and agitation; headache and nausea have also been reported. Inhaled salbutamol from a nebuliser seems to be of short term benefit in a minority of babies with chronic lung damage, but no trial has yet been done to show whether sustained use is helpful. Use seems to be of very little benefit in the majority of "wheezy" babies in the first 2 years of life. Drug binding to liver and muscle adrenergic receptors stimulates cyclic adenosine monophosphate (AMP) production, causing a rise in intracellular potassium uptake and a fall in plasma potassium.

Use in pregnancy

None of the steroid or β adrenergic drugs commonly used in asthma pose a threat to the baby, either during pregnancy or during lactation. Undertreatment is the commonest problem.

Use in early labour

IV betamimetics can be used to delay delivery for 2–3 days and "buy time" to effect transfer and/or offer antenatal steroid prophylaxis (cf. the monograph on betamethasone), as long as the risk of pulmonary oedema from concurrent IV fluid overload is recognised. The risk of such a potentially disastrous complication does, nevertheless, make such treatment unwise in mothers with cardiac disease, hyperthyroidism, or diabetes. Mothers with impaired renal function or a multiple pregnancy may also be at increased risk. Betamimetics cross the placenta but alter the fetal heart rate less than the maternal heart rate. Transient neonatal hypoglycaemia and hyperinsulinaemia have been noted after birth. Such use has not been shown to have any impact on perinatal morbidity or mortality. One small trial suggests that oral nifedipine (q.v.) may be better in this regard.

Neonatal hyperkalaemia

Potassium toxicity (hyperkalaemia) is relatively common in low birth weight babies in the first 3 days of life, and seems to correlate with low systemic blood flow soon after delivery. Plasma potassium levels >6.5 mmol/l are very common. Most babies are asymptomatic, but cardiac arrhythmia can occur when potassium levels exceed 7.5 mmol/l. Dialysis, exchange transfusion, polystyrene sulphonate resins (q.v.), and infusions of dextrose and insulin (q.v.) have all been used to reduce plasma potassium levels and the consequential risk of arrhythmia. IV salbutamol offers a simpler and more rapid way of controlling *anic* hyperkalaemia, lowering the plasma potassium by at least 1 mmol/l, and time may show it to be equally effective in idiopathic neonatal hyperkalaemia. Nebulised salbutamol can be used if the IV drug is unavailable; in children it produces a slightly more sustained response.

Treatment

Hyperkalaemia: Give an infusion of 4 micrograms/kg IV over 5–10 minutes. Sustained benefit may sometimes require one repeat infusion after a minimum of 2 hours.

Chronic lung disease: A minority of babies show an unequivocal short term response to nebulised salbutamol. A 1 mg dose is more than enough, but a standard 2.5 mg Nebule[®] can be used once every 6–8 hours, irrespective of age or body weight, because little of the drug enters the blood stream.

Supply and administration

Salbutamol is available in 5 ml IV ampoules containing 50 micrograms/ml (costing £2.80 each). To give a 4 micrograms/kg infusion, take 1.6 ml of this product for each kilogram the baby weighs, dilute to 20 ml with 10% dextrose saline, and infuse at a rate of 6 ml/hour for just 10 minutes. A less concentrated solution of dextrose or dextrose saline can be used if necessary. 2.5 mg (2.5 ml) Ventolin[®] nebulisers (costing 17p) are available for nebuliser use, and ipratropium can be added to this fluid (as outlined in the monograph on atropine).

References

- Barrington KJ, Finer NN. Treatment of bronchopulmonary dysplasia. *Clin Perinatol* 1998;**25**:177–202.
 Chavasse RJ, Bastian-Lee Y, Richter H, et al. Inhaled salbutamol for wheezy infants: a randomised controlled trial. *Arch Dis Child* 2000;**82**:370–5. [RCT]
 Helfrich E, de Vries TW, van Roon EN. Salbutamol for hyperkalaemia in children. *Acta Paediatr* 2001;**90**:1213–16.
 Kluckow M, Evans N. Low systemic blood flow and hyperkalaemia in preterm infants. *J Pediatr* 2001;**139**:227–32.
 Singh BS, Sadiq HF, Noguchi A, et al. Efficacy of albuterol inhalation in treatment of hyperkalaemia in premature neonates. *J Pediatr* 2002;**141**:16–20.

See also relevant Cochrane reviews



Use

Emollient creams and ointments improve the appearance and the integrity of the skin, but regular use in the very preterm baby does not reduce the risk of sepsis as was once thought.

Physiology

The skin of the very preterm baby is extremely delicate and very easily damaged. That of a baby born more than about 8 weeks early is not even waterproof and, in a baby born more than 12 weeks early, a *lot* of water leaks “insensibly” out of the body in this way in the first few days of life. (Extra incubator humidity can halve insensible water loss during this time.) However, maturation occurs quite rapidly over a period of 10–14 days after birth as long as the skin is protected from damage during that time. As a result, the skin of a 2 week old baby born at 24 weeks gestation is much more waterproof than that of a 2 day old baby of 27 weeks gestation. Prevention is the key ingredient of good nursing care. Even minor trauma (such as the brisk removal of adhesive tape) can easily strip the skin of all its surface sheet of keratinised cells, leaving the baby with the equivalent of a third degree “skin burn”. Infection can also seriously damage the outer “waterproofing” layer of the preterm baby’s skin.

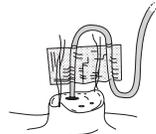
Pharmacology

Skin thin enough to let water out is also thin enough to let drugs in; the widely used skin disinfectant, hexachlorophene, had to be withdrawn in 1972 when its use was found to have caused brain damage. Alcoholic lotions not only penetrate the skin of the preterm baby but also damage the outer layer, causing haemorrhagic surface necrosis. The risk is highest when the skin is left lying in liquid alcohol for several minutes. Absorption of iodine, or povidone iodine, can make the preterm baby hypothyroid (as can the IV use of x-ray contrast media containing iodine). Aniline dyes can cause methaemoglobinaemia by penetrating the skin even in the full term baby. Hydrocortisone, oestrogens, propylene glycol, urea, and lindane have all caused toxicity after absorption through the skin. Neomycin, if absorbed through damaged skin, can cause severe, lifelong deafness.

Routine skin care

The term baby: Babies should be towelled dry after birth to prevent dangerous hypothermia, but not bathed until the body temperature has stabilised (12–24 hours after birth). Soap and water suffices. Antiseptics are not necessary. Babies usually need to be only “topped and tailed” most days after that. Small areas of vernix can be removed with acetone when monitoring leads need to be applied. Pretreatment with “tinc benz” (compound benzoin tincture BPC) can limit the damage caused by adhesive tape, etc. A pledget of collodion hardened cotton wool will stabilise a scalp drip better than tape or plaster. A pectin based barrier (Hollister® skin barrier, or something similar) limits the skin damage caused by the tapes used to secure oral and nasal tubing. Zinc ointment BP is a useful barrier agent.

The preterm baby: A transparent plastic wrap will do more than a blanket to prevent the stressful evaporative heat loss that occurs immediately after birth. A waterproof, but water vapour permeable, transparent polyurethane dressing or spray (OpSite® or Tegaderm®) can also provide a useful protective barrier over the skin during the first week of life, but it does not reduce water loss. Electrodes and transcutaneous blood gas monitoring devices can still be used on areas of skin covered by one such layer (and this dressing can be safely left in place for a full week). The use of a stay suture to fix every drain and catheter removes the need to stick *any* tape on the skin (see figure). The use of an emollient cream (aqueous cream BP) can reduce dermatitis and other signs of minor skin trauma, as can an emulsifying ointment, but excessive use can actually increase the risk of staphylococcal infection in the very preterm baby.



Supply

100 g of aqueous cream costs 21p, 100 g of zinc ointment 56p, and 100 g of the emulsifying ointment Epaderm® £3. A 10 × 14 cm OpSite or Tegaderm dressing costs £1.20, and 10 cm² of Hollister skin barrier £2.

References

- Anonymous. Hexachlorophene today [Editorial]. *Lancet* 1982;*i*:87–8.
- Rutter N. Percutaneous drug absorption in the newborn: hazards and uses. *Clin Perinatol* 1987;**14**:911–30.
- Smedley P, Lim A, Boyages SC, *et al*. Topical iodine-containing antiseptics and neonatal hypothyroidism in very-low-birthweight infants. *Lancet* 1989;*ii*:661–4.
- Dollison EJ, Beckstrand J. Adhesive tape vs pectin-based barrier use in preterm infants. *Neonatal Network* 1995;**14**:35–9. [RCT]
- Donahue ML, Phelps DL, Richter SE, *et al*. A semipermeable skin dressing for extremely low birthweight infants. *J Perinatol* 1996;**16**:20–4. [RCT]
- Edwards WH, Conner JM, Soll RF. The effect of Aquaphor® original emollient ointment on nosocomial sepsis rates and skin integrity in infants of birth weight 500 to 1000 grams [Abstract]. *Pediatr Res* 2001;**49**:388A. [RCT]

See also relevant Cochrane reviews



Use

Skin preparation is very important before any invasive procedure. Clean hands are just as important, and supplementing a 30 second hand wash with an alcoholic hand rinse further reduces contamination.

Pharmacology

Chlorhexidine is a biguanide antiseptic used to cleanse skin and wounds, and to disinfect working surfaces and instruments. It is sometimes combined with cetrimide (a quaternary ammonium antiseptic). Both can cause skin hypersensitivity. Hexachlorophene (a chlorinated biphenol) is used on skin. All are rapidly bactericidal and particularly effective against Gram positive bacteria. Avoid contact with the eyes. Alcohol is a bactericidal antiseptic and disinfectant. Povidone–iodine (a loose complex of iodine and carrier polymers) also has a slowly lethal effect on bacteria, fungi, viruses, and spores.

Neonatal management routines

IV access: Preparation with 0.5% aqueous chlorhexidine reduced the risk of catheter related sepsis more than alcohol or povidone–iodine in a recent trial in adults. The latter two products also pose hazards when used on immature skin (see previous page). Employ two different swabs, applying each for 10 seconds, and then leave the skin to dry for 30 seconds. A surgical “keyhole” drape and a no-touch technique will reduce the risk of recontamination. A transparent polyurethane dressing can help to secure the line, reduce gross soiling, and minimise skin damage while allowing regular site inspection. Concern that moisture build up under the dressing could cause catheter colonisation by skin bacteria can be further addressed by placing a chlorhexidine impregnated disc under the dressing.

IM injections: While it is sensible to make the skin socially clean, the “swabolics” who insist on trying to achieve sterility with spirit or a “mediswab” are indulging in a pointless ritual. Indeed, when a live vaccine is to be given it is said that alcohol should *not* be used.

Umbilical cord care: Bathing with the antiseptic hexachlorophene was first introduced to deal with the outbreaks of superficial staphylococcal infection seen in hospital born babies in the 1950s, at a time when the cord was routinely left long, secured with two linen ties, and covered with a sterile gauze dressing. The policy was eventually discontinued when the use of hexachlorophene was shown to be causing brain damage. Excessive systemic absorption of the neomycin in a triple antibiotic (Polybactrin[®]) spray has, more recently, been incriminated as a possible cause of profound deafness in the very preterm baby. The routine toilet still performed in many units is probably no longer dangerous, but it is almost certainly a waste of time. There is clearly no controlled trial evidence of benefit. With a plastic clamp in place for 24 hours the umbilical stump heals rapidly and naturally if cut short and kept dry. Colonisation can be reduced in various ways, but a policy of treating only those stumps that look inflamed reduces overt sepsis just as effectively as routine prophylaxis for every baby in the unit. Hexachlorophene powder (Ster-Zac[®]) is widely used, and limited use does not cause the damaging systemic absorption that was seen when babies were bathed in hexachlorophene. Treatment with spirit merely delays separation.

Hand washing

The importance of hand washing was brought home to all the staff in one nursery when five babies in different rooms developed a salmonella infection on a single day, from an unwell baby born to an unrecognised maternal carrier. The busy medical resident collected serum bilirubin specimens from all five one Christmas morning without washing his hands each time. Hand washing, to be effective, *must*, however, be sustained for at least 30 seconds. Rings and watches need to be removed, but active scrubbing is counterproductive, because of the skin damage that eventually builds up. The use of a medicated soap such as Hibiscrub[®] reduces the number of viable bacteria left, but studies show that staff usually comply with unit policy better when allowed to use an alcoholic hand rinse instead.

Supply

The ingredients for 100 ml of 0.5% chlorhexidine gluconate in water (or alcohol) cost only 25p, and 30 g of hexachlorophene dusting powder (Ster-Zac) costs 83p. 100 ml of 4% chlorhexidine gluconate hand lotion (Hibiscrub) costs 42p. A range of commercial alcoholic hand rinses are available.

References

- Doebbleing BN, Stanley GL, Sheetz CT, *et al.* Comparative efficacy of alternative hand-washing agents in reducing nosocomial infections in intensive care units. *N Engl J Med* 1992;**327**:88–93. [RCT]
- Malathi I, Millar MR, Leming JP, *et al.* Skin disinfection in preterm infants. *Arch Dis Child* 1993;**69**:312–16.
- Larson EL. APIC guideline for handwashing and hand antiseptics in health care settings. *Am J Infect Control* 1996;**23**:251–69. [SR]
- Garland JS, Alex CP, Mueller CD, *et al.* A randomized trial comparing povidone–iodine to a chlorhexidine gluconate-impregnated dressing for prevention of central venous catheter infections in neonates. *Pediatrics* 2001;**107**:1431–6. [RCT]
- Kramer A, Rudolph P, Kampf G, *et al.* Limited efficacy of alcohol-based hand gels. *Lancet* 2002;**359**:1489–90. (See also **360**:1509–11.)
- Girou E, Loyalé S, Legrand P, *et al.* Efficacy of handrubbing with alcohol based solution versus standard handwashing with antiseptic soap: randomised clinical trial. *BMJ* 2002;**325**:362–5. [RCT]
- Naomi NP, Alexander M, Dellinger EP, *et al.* Guidelines for the prevention of intravascular catheter-related infections. *Pediatrics* 2002;**110**:e51. [SR]

See also the Cochrane review of umbilical cord care 

SODIUM BENZOATE AND SODIUM PHENYLBUTYRATE

Use

Sodium benzoate and sodium phenylbutyrate are used to control the hyperammonaemia seen in children with urea cycle defects.

Pharmacology

Sodium benzoate is excreted in the urine as hippurate after conjugation with glycine. As each glycine molecule contains a nitrogen atom, if there is complete conjugation, 1 mole of nitrogen is cleared for each mole of benzoate given. Phenylbutyrate is oxidised to phenylacetate and excreted in the urine after conjugation with glutamine. Since phenylacetylglutamine contains two nitrogen atoms, 2 moles of nitrogen are cleared, if there is complete conjugation, for each mole of phenylbutyrate given. Both drugs can lower plasma ammonia levels in patients with urea cycle disorders. Sodium phenylbutyrate is more effective than sodium benzoate but is less palatable.

Indications

Measurement of ammonia should be considered in any patient with unexplained encephalopathy (vomiting, irritability, or drowsiness, etc.), particularly in term neonates who deteriorate after an initial period of good health. Inform the laboratory in advance and send the specimen urgently, on ice. Levels of up to 180 $\mu\text{mol/l}$ sometimes occur in the absence of metabolic disease.

Severe hyperammonaemia ($> 500 \mu\text{mol/l}$) causes serious neurological damage, and urea cycle defects presenting in the neonatal period have a very poor prognosis. Circulating ammonia levels should be lowered as quickly as possible, if treatment is considered appropriate, using haemodialysis (peritoneal dialysis is too slow). Sodium benzoate and sodium phenylbutyrate can also be given, if available, while organising dialysis. These drugs are mainly used for the long term management of urea cycle disorders, including in patients with milder defects presenting after the neonatal period. They need to be combined with a low protein diet and other treatment, such as arginine (q.v.), appropriate to each disorder.

Treatment

Acute hyperammonaemia: Brusilow and Horwich recommend an IV loading dose of 250 mg/kg of each drug, given over 90 minutes, followed by a continuing maintenance infusion of each drug at 10 mg/kg per hour. Co-infusion is safe. Note that an overdose can cause metabolic acidosis and a potentially fatal encephalopathy. There is a theoretical risk that this could displace bound bilirubin, so consider treating any severe jaundice. Arginine should generally be given as well.

Maintenance treatment: Up to 250 mg/kg per day of sodium benzoate can be given orally in 3–4 divided doses. The usual oral dose of sodium phenylbutyrate is also 250 mg/kg per day, but doses of up to 600 mg/kg per day can be given, again in 3–4 divided doses. The nausea and vomiting caused by the unpleasant taste of the raw products can be minimised by the use of a fruit flavoured solution.

Sodium overload

Note that 500 mg of sodium benzoate contains 3.5 mmol of sodium, and 500 mg of sodium phenylbutyrate contains 2.7 mmol of sodium. Take care to avoid sodium overload.

Monitoring

Drug dosages and diet should be adjusted to keep the plasma ammonia concentration below 60 $\mu\text{mol/l}$, and the plasma glutamine level below 800 $\mu\text{mol/l}$, while maintaining a normal essential amino acid profile. In arginase deficiency, aim to keep plasma arginine concentrations below 300 $\mu\text{mol/l}$. The optimum dose of sodium benzoate remains uncertain. Monitoring of plasma levels is possible (contact the Clinical Biochemists at Birmingham Children's Hospital, tel. 0121 333 9910).

Supply

Sodium benzoate is available for "named" patients as a 100 mg/ml sugar free, blackcurrant flavoured oral liquid from Special Products Ltd (100 ml costs £5). 500 mg tablets are also available. 10 ml (200 mg/ml) ampoules for IV use cost £4.10; dilute the contents with 90 ml of 5% or 10% dextrose to obtain a solution containing 20 mg/ml, and give as a continuous infusion.

Sodium phenylbutyrate is available from Orphan Europe; 100 g of the EU licensed granules cost £380. They need to be given with milk, fruit juice, or food to disguise the taste. Sodium phenylbutyrate is also available for "named patients" as a 250 mg/ml strawberry flavoured liquid from Special Products (100 ml costs £50). Reconstitute the powder with 80 ml of purified water and use within 28 days. 10 ml (200 mg/ml) ampoules for IV use costing £7, and 500 mg film coated tablets are also available. The use of these unlicensed products can be supported only when clinical grounds for such a preference exist.

References

Leonard JV. Disorders of the urea cycle. In: Fernandes J, Saudubray J-M, van den Berghe G, eds. *Inborn metabolic diseases. Diagnosis and treatment, 3rd ed.* Chapter 17. Berlin: Springer-Verlag, 2000:214–22.

Brusilow SW, Horwich AL. Urea cycle enzymes. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. *The metabolic and molecular bases of inherited disease, 8th ed.* McGraw-Hill: New York, 2001:1909–64.

Use

Sodium bicarbonate is valuable for correcting severe metabolic acidosis. Significant respiratory acidosis is almost always more appropriately managed by providing adequate respiratory support.

Pharmacology

Sodium bicarbonate is one of the most important natural buffers of the hydrogen ion (acid) content of the blood, and the body responds to a build up of metabolic acids by increasing the amount of buffering bicarbonate. The process is controlled by the kidney and is very slow to operate. The neonatal kidney also has a limited ability to excrete acid. The infusion of small doses of sodium bicarbonate is a way of maintaining the acid–base balance of the blood by speeding up these processes.

Controversy rages about the role of sodium bicarbonate therapy in neonatal medicine. It was used very liberally for a number of years but it is now used less extensively with the recognition that it can cause sudden osmolar shifts that could be damaging to the brain, and that its excessive use can also cause hypernatraemia. There is also some limited evidence to suggest that it may possibly cause intraventricular haemorrhage, especially if administered rapidly. The drug still has a valuable role, however, because there is no doubt that serious acidosis (pH < 7.2) compromises cardiac output and surfactant production as well as causing gastrointestinal ileus. THAM (q.v.) is a useful alternative where there is CO₂ retention or a risk of hypernatraemia (as for example, when a continuous alkaline infusion is employed in the management of persistent pulmonary hypertension) and is probably the drug of choice (combined, if possible, with dextrose) in the management of cardiac arrest.

Treatment

Severe asphyxia: In a real emergency it is probably safe to give 2 mmol/kg IV “blind” in a severely asphyxiated infant, diluted, where possible, with an equal quantity of 10% dextrose, remembering that this will be largely ineffective if there is circulatory standstill until the drug reaches the heart and coronary circulation. Half this dose should be enough to revive cardiac output if it becomes necessary to give the drug directly into a cardiac cavity. Remember, however, that extravasation causes severe tissue necrosis, as can injection into an artery where there is circulatory standstill.

Exchange transfusion: Add 4 mmol of sodium bicarbonate to the first unit and 2 mmol to any second unit of CPD (citrate-phosphate-dextrose) blood used in an exchange transfusion undertaken in the first day of life to buffer the citrate load. This advice constitutes the one exception to the rule that no drug should be added to blood or any blood product.

IV treatment: Give 0.5 mmol/kg for each unit (mmol) by which it is hoped to reduce the measured blood gas base deficit. Do not inject it at a rate of more than 0.5 mmol/kg per minute or allow it to mix with any other IV drug. Partial correction is normally quite adequate.

Oral treatment: Preterm babies often develop a late metabolic acidosis because of the kidney’s limited ability to excrete acid and this can inhibit weight gain. Give 2 mmol/kg of sodium bicarbonate once a day with feeds for 7 days to babies with a consistent urine pH of less than 5.4.

Tissue extravasation

Tissue extravasation due to IV administration can be managed with hyaluronidase (q.v.). The use of a dilute preparation reduces the risk of serious tissue damage.

Supply

Stock ampoules of 8.4% sodium bicarbonate contain 1 mmol of sodium and 1 mmol of bicarbonate per millilitre. Each 10 ml ampoule costs £1.50. Some units prefer to stock a less concentrated ampoule containing 4.2% sodium bicarbonate (costing £4.80 each). Prior dilution is not necessary as long as any infusion is given slowly (as indicated above). Polyfusor bags containing 200 ml of 8.4% sodium bicarbonate are also available costing £3.50 each. Sachets of powder for oral use that can be used for 24 hours after reconstitution (with instructions on their use) are available on request.

References

Howell JH. Sodium bicarbonate in the perinatal setting – revisited. *Clin Perinatol* 1987;**14**:807–17.

Kalhoff H, Diekmann L, Stick GJ, *et al.* Alkali therapy versus sodium chloride supplement in low birth weight infants with incipient late metabolic acidosis. *Acta Paediatr* 1997;**86**:96–101. [RCT]

See also relevant Cochrane reviews



SODIUM CHLORIDE

Use

Sodium chloride is an essential nutrient and, because renal tubular sodium loss is high, it is important to supplement the normal oral sodium intake of very preterm babies in the first few weeks of life.

Pathophysiology

The kidney of the term newborn infant rapidly develops an ability to conserve salt, and the fractional excretion of sodium falls 10-fold in the first few days of life, but the preterm infant has a high persisting obligatory salt loss. As a result, the sodium requirement of most healthy infants of less than 34 weeks gestation is at least 3 mmol/kg per day, while many babies of less than 30 weeks gestation benefit from receiving 6 mmol/kg per day during the first 2 weeks of life. This is more than the sodium intake provided by any of the standard preterm milk formulas (q.v.). Losses may be even higher after renal tubular damage owing to severe hypoxia or hypotension. Optimising intake and sodium balance involves more than just eliminating any fall in the plasma sodium level below 130 mmol/l.

While **hyponatraemia** is often caused by excessive renal sodium loss, it can also be dilutional, and limitation of water intake is then appropriate. However, if the serum sodium is less than 120 mmol/l, water deprivation alone is unlikely to correct the hyponatraemia, and supplementation to increase the serum sodium to above 120 mmol/l may be necessary. Calculation assumes that sodium is distributed through almost all the extracellular space (i.e. through 60% of the body in the very preterm baby, and 40% of the term baby). Regular weighing and calculation of fractional sodium excretion (as outlined in the introductory section on "Renal failure") will help to define the disordered electrolyte and fluid balance.

Hyponatraemia is also a risk, however, because the neonatal kidney's ability to excrete excess sodium is also limited, and its maximum ability is as yet undefined. While the apathy and hypotonia caused by severe hyponatraemia (< 120 mmol/l) is always regrettable because it may on occasion render a small baby ventilator dependent, the permanent brain damage that can be caused by severe hyponatraemia (> 160 mmol/l) is a disaster of an entirely different magnitude. "Normal" (0.9%) saline and Hepsal® (see monograph on heparin) both contain 0.15 mmol of sodium (9 mg of sodium chloride) per ml. When used during the reconstitution, dilution, or continuous infusion of drugs, or to maintain the patency of an intravascular line, these fluids can result in the infusion of a significant amount of sodium: a baby given a constant infusion of 1 ml/hour of 0.9% sodium chloride gets 3.6 mmol of sodium per day. The aim must be a serum sodium of 130–145 mmol/l. If severe hyponatraemia does occur, the level should be lowered slowly. Peritoneal dialysis or haemodialysis may occasionally be necessary.

Management

IV intake: A daily IV intake of 150–200 ml/kg of "fifth normal" (0.18%) sodium chloride provides between 4.5 mmol and 6 mmol/kg of sodium per day (a safe basic minimum intake for the very preterm baby without being a dangerously high intake for the full term baby). Babies of ≤ 30 weeks gestation, especially if they are on a lower total fluid intake than this in the first 2 weeks, may require further oral or IV sodium, particularly if renal function is compromised. It is better not to start supplementation if the baby requires ventilation, until the physiological adjustment of extracellular fluid volume (and weight loss) that normally occurs in the first few days of life has occurred. Giving large bolus volumes during neonatal resuscitation to correct perceived hypovolaemia may not be risk free.

Oral intake: Preterm milk formulas (q.v.) contain enough sodium for most babies of more than 30 weeks gestation. Babies more immature than this seem to need a further 2 mmol of sodium once a day by mouth for each 100 ml of milk they are given for at least the first 2 weeks of life, to optimise both their early growth and their later motor and neuropsychological development. Those fed breast milk should receive a supplement of 3–4 mmol per 100 ml of milk. Such supplements are probably best given, to prevent confusion, once a day at a fixed time. Although dietary supplements must be documented on the feed chart, they do not need a medical prescription. It is a matter of local unit policy whether or not to record such dietary supplementation on the drug prescription sheet.

Supply

Sterile 5 ml ampoules of 18% sodium chloride (3 mmol/ml) cost 12p. An inexpensive oral solution containing 1 mmol/ml is also available. The ampoules of 0.9% sodium chloride frequently used to flush IV lines cost 16p each. Extreme care must be taken not to confuse the 0.9% and 18% ampoules.

References

- Hartnoll G, Bêtrémieux P, Modi N. Randomised controlled trial of postnatal sodium supplementation on oxygen dependency and body weight in 25–30 week gestation infants. *Arch Dis Child* 2000;**82**:F19–23. (See also 2001;**85**:F29–32.) [RCT]
- Al-Dahhan J, Jannoun L, Haycock GB. Effect of sodium salt supplementation of newborn premature infants on neurodevelopmental outcome at 10–13 years of age. *Arch Dis Child* 2002;**86**:F120–3.
- Ewer AK, Tyler W, Francis A, et al. Excessive volume expansion and neonatal death in preterm infants born at 27–28 weeks gestation. *Paediatr Perinat Epidemiol* 2003;**17**:180–6.

See also relevant Cochrane reviews 

Use

Sodium fusidate is a powerful antistaphylococcal antibiotic primarily of value in the treatment of penicillin resistant osteomyelitis. Only limited information is available on its use in the neonatal period.

Pharmacology

Sodium fusidate is a powerful narrow spectrum antistaphylococcal antibiotic, first isolated in 1960. Virtually all staphylococci are sensitive, including methicillin resistant and coagulase negative strains. The antibiotic is also active against *Neisseria* and *Clostridium* species. However, concurrent treatment with a second antistaphylococcal antibiotic (such as flucloxacillin or vancomycin (q.v.)) is advisable, especially if treatment is prolonged, despite a few reports of antagonism in vitro because, if this is not done, there is a serious risk of drug resistance developing. Treatment with two antibiotics is generally considered particularly important when treating methicillin resistant staphylococci.

Sodium fusidate is relatively well absorbed from the gastrointestinal tract and widely distributed in most body tissues, but it does not penetrate the cerebrospinal fluid well. Some crosses the placenta and appears in breast milk, but there is no evidence of teratogenicity or to suggest that breastfeeding is contraindicated. Caution is advised, however, in the use of sodium fusidate in any baby with jaundice because the drug is highly bound to plasma proteins, and there may be competitive binding with bilirubin. Reported toxic effects have included skin rashes and jaundice (which can be reversed by stopping treatment). The half life in adults is 10–15 hours; the half life in neonates is less certain. The drug is largely excreted in the bile (making combined treatment with rifampicin (q.v.) unwise). Very little is excreted by the kidney.

IV treatment can cause vasospasm or thrombophlebitis unless the drug is given slowly after suitable dilution into a large vein. Rapid infusion can also cause a high concentration of sodium fusidate to develop locally, causing red cell haemolysis and jaundice.

Treatment

Oral administration: The only available liquid formulation (fusidic acid) is not as well absorbed as sodium fusidate. Offer 15 mg/kg of fusidic acid once every 8 hours.

IV administration: Infuse 10 mg/kg of sodium fusidate, after reconstitution as described below, once every 12 hours. It should be given slowly over 6 hours (2 hours may be adequate when a central venous line is employed). Doses twice as high as this have been given with apparent safety on occasion.

Long term administration: High blood levels are often encountered when adult patients are given a standard dose (1.5 g/day) for more than 4–5 days. In the absence of any reliable pharmacokinetic information it may be advisable to monitor liver function to watch for any rapid rise in liver enzyme levels and/or to reduce the dose used in the neonatal period if treatment is continued for more than 5 days.

Supply and administration

Note that there are different formulations for oral and IV use. A sugar-free oral suspension containing 50 mg/ml of fusidic acid (equivalent to 35 mg/ml of sodium fusidate) is available, which should not be diluted prior to administration (50 ml bottles cost £7.20). Vials with 500 mg of sodium fusidate that can be reconstituted with 10 ml of specially provided phosphate/citrate buffer are available for £7.80 each. Take 0.4 ml of the freshly reconstituted 50 mg/ml concentrate for each kg the baby weighs, dilute to 24 ml with 0.9% sodium chloride, prime the giving set, and infuse at a rate of 2 ml/hour for 6 hours. (Note that this should leave about 10 ml of fluid still in the syringe when the infusion is complete.) The drug is not compatible with acidic solutions, but can be terminally co-infused with 5% or 10% dextrose or dextrose saline when necessary. While the drug can be kept for up to 24 hours after reconstitution, the vial should not be kept after it has been opened. There is no suitable IM formulation.

References

- Bergdahl S, Elinder G, Eriksson M. Treatment of neonatal osteomyelitis with doxycycline in combination with fusidic acid. *Scand J Infect Dis* 1981;**13**:281–2.
- Reeves DS. The pharmacokinetics of fusidic acid. *J Antimicrob Chemother* 1987;**20**:467–76.
- Turnidge J, Collignon P. Resistance to fusidic acid. *Int J Antimicrob Agents* 1999;**12**:S35–44.

SOTALOL

Use

Sotalol can control atrial flutter. It has also been used, under expert supervision, in the control of ventricular and supraventricular arrhythmia, although flecainide or amiodarone (q.v.) may be better.

Pharmacology

Many β adrenoreceptor blocking drugs now exist. Such drugs have been widely used, over many years, to control hypertension, manage angina, and treat myocardial infarction, arrhythmia, heart failure, and thyrotoxicosis; it is now clear that some are better at some things than others. Some, like propranolol (q.v.), the first β blocker to be developed, are essentially non-selective, and act indiscriminately on receptors in the heart, peripheral blood vessels, liver, pancreas, and bronchi (making their use in asthmatics hazardous). Others, like labetalol (q.v.), which affect receptors more selectively, are used to control hypertension because of their effect on arteriolar tone. Non-cardioselective β blockers like sotalol, which are water rather than lipid soluble, are less likely to enter the brain and disturb sleep, and are excreted largely unchanged in the urine. All β blockers slow the heart and can depress the myocardium. Sotalol, in particular, can prolong the QT interval and cause a life threatening ventricular arrhythmia, especially if there is hypokalaemia. Because of this, sotalol is now used *only* to manage pre-existing arrhythmia. In this, sotalol functions both as a class II antiarrhythmic by decreasing the heart rate and AV nodal conduction as a result of non-selective β blockade, and as a class III antiarrhythmic by prolonging the atrial and the ventricular action potentials and the heart muscle's subsequent refractory period. Esmolol is an alternative short acting cardioselective β blocker.

Sotalol, which was first synthesised in 1964, is well and rapidly absorbed when given by mouth (although food, including milk, decreases absorption). The terminal half life (7–9 hours) remains much the same throughout childhood, but is seriously prolonged in renal failure. The manufacturers have not done the studies needed to be able to recommend its use in children. Furthermore, because the drug can provoke as well as control cardiac arrhythmia, patients should be subject to continuous electrocardiographic (ECG) monitoring when treatment is started; treatment should be initiated only by a consultant who is well versed in the management of cardiac rhythm disorders. Sotalol may be the drug of choice for fetal atrial flutter. Lack of controlled trial evidence makes it impossible to say what drug regimen is best for other fetal arrhythmias.

There is no evidence that β blockers are teratogenic, but they can cause intermittent mild fetal bradycardia (90–110 bpm). Sustained high dose use in the second and third trimester can also be associated with reduced fetal growth. Although there is no evidence that this is harmful, the long term effect of sustained maternal use has not been studied; this warrants evaluation. The use of β blockers in pregnancy can also cause transient bradycardia and hypoglycaemia in the baby at delivery. Sotalol appears in breast milk in high concentrations (milk:plasma ratio 2.8–5.5). Babies so fed have, to date, been asymptomatic, but it has been shown that they are ingesting 20–40% of the weight adjusted maternal dose. Propranolol is the β blocker associated with the lowest drug exposure during lactation.

Treatment

Mothers: The dose given when trying to control a fetal arrhythmia has usually been between 60 mg and 160 mg by mouth twice or three times a day. Watch the mother's ECG carefully for QT changes.

Children: Start cautiously with 1 mg/kg by mouth once every 12 hours and increase the dose as necessary once every 3–4 days to no more than 4 mg/kg. Withdraw treatment gradually.

Toxicity

Extend the dosage interval if renal function is poor, and discontinue treatment if the corrected QT interval (QT_c) exceeds 550 ms. Any β blocker can, in overdose, cause serious bradycardia and/or hypotension. Give 40 micrograms/kg of IV atropine (q.v.), and treat unresponsive cardiogenic shock with IV glucagon (q.v.) and glucose. Monitor the blood glucose level and control ventilation. Isoprenaline (q.v.) may help. Cardiac pacing is occasionally needed. Some β blockers, such as propranolol, can cause central nervous system signs.

Supply and administration

80 mg tablets of sotalol cost 6p each, and a 5 mg/ml oral suspension, stable for up to 3 months at room temperature, can be prepared on request. 4 ml (10 mg/ml) IV ampoules cost £1.70.

References

- Wagner X, Jouglard J, Moulin M, *et al*. Coadministration of flecainide acetate and sotalol during pregnancy: lack of teratogenic effects, passage across the placenta, and excretion in human breast milk. *Am Heart J* 1990;**119**:700–2.
- Baufort-Krop GCM, Bink-Boelkens MTE. Effectiveness of sotalol for atrial flutter in children after surgery for congenital heart disease. *Am J Cardiol* 1997;**79**:92–4.
- Sauk JP, Ross B, Schaffer MS, *et al*. Pharmacokinetics and pharmacodynamics of sotalol in a pediatric population with supraventricular and ventricular tachyarrhythmia. *Clin Pharmacol Ther* 2001;**69**:145–57.
- Lisowski LA, Verheijen PM, Benatar AA, *et al*. Atrial flutter in the perinatal age group: diagnosis, management and outcome. *Am J Coll Cardiol* 2002;**35**:771–7.

Use

Spiramycin is now widely used to protect the fetus from infection when a woman develops toxoplasma infection during pregnancy, although, since parasitic transmission becomes increasingly unlikely as the mother's immune response builds up, most infection probably occurs before diagnosis is possible.

Pharmacology

Spiramycin is a macrolide antibiotic related to erythromycin, first isolated in 1954. It is well absorbed when taken by mouth, and mostly metabolised in the liver, although biliary excretion is also high. The serum half life in adults is about 8 hours. Spiramycin crosses the placenta, where it is also concentrated, and there is a belief that early treatment can prevent the transplacental passage of the toxoplasma parasite. Treatment with pyrimethamine and sulfadiazine (q.v.) may be a more effective way of limiting damage once fetal infection has occurred, but termination is often offered if there is ultrasound evidence of cerebral damage, even though many children with antenatally detected cerebral calcification or ventriculomegaly seem to develop normally. Spiramycin appears in therapeutic quantities in breast milk but is not the treatment of choice after delivery. It can also prolong the QT interval and has occasionally caused a dangerous neonatal arrhythmia. Cerebrospinal fluid penetration is poor.

Toxoplasmosis

Toxoplasma gondii is a common worldwide protozoan parasite that infects many warm blooded animals. Cats are the main host, replication occurring in the small intestine, but sheep, pigs, and cattle become infected if they ingest faecally contaminated material; infected cysts within the muscles and brain then remain viable almost indefinitely. Humans usually become infected by ingesting cysts from contaminated soil or by eating undercooked or poorly cured meat (although transplant recipients are at risk of cross infection). Infection normally goes unrecognised, but fever, muscle pain, sore throat, and a lymphadenopathy may manifest themselves after 4–21 days. Hepatosplenomegaly and a maculopapular rash are sometimes seen. Although the illness is usually benign and self limiting, chronically infected immunodeficient patients can (like the fetus) experience reactivated central nervous system disease. Screening cannot be advocated until the benefit of treatment becomes less uncertain.

The risk of a susceptible woman becoming infected during pregnancy is quite low (~0.5%), and congenital infection is uncommon (1:1000 to 1:10,000 births). The fetus is more likely to become infected if the mother is infected late in pregnancy, but more likely to show signs of that infection within 3 years of birth if infected early. Overt signs of infection develop in less than 5% of babies born to mothers infected in the first 16 weeks of pregnancy. Reliable early recognition requires serial testing of all antibody negative women, since IgM and IgG tests cannot be used to time infection accurately and often result in mothers receiving unnecessary antenatal treatment, even when the baby is not at risk. Fetal infection can be diagnosed by polymerase chain reaction detection of *T gondii* DNA in amniotic fluid or by mouse inoculation. Persistence of circulating IgG antibody for 1 year confirms that the baby was congenitally infected. Most, but not all, have IgM antibodies at birth. Many show no overt sign of illness at birth, but a quarter develop retinochoroiditis, intracranial calcification, and/or ventriculomegaly within 3 years. Only a few (< 5%) develop severe neurological impairment, but how many develop minor disabilities is not known. Some unilateral vision loss eventually occurs in up to half of those with retinal lesions.

Treatment

Mother: It is common practice to give 1 g of spiramycin prophylactically once every 8 hours as soon as maternal infection is first suspected, to minimise the risk of placental transmission; this is often continued for the duration of the pregnancy. Pyrimethamine and sulfadiazine are often given as well, if there is evidence of fetal infection. No controlled trial evidence exists to support this strategy.

Baby: Use pyrimethamine and sulfadiazine to initiate treatment (as outlined in the pyrimethamine monograph). Some clinicians alternate this with 3–4 week courses of spiramycin (50 mg/kg twice a day).

Supply

Spiramycin has a licence for use in Europe (where it has been used for nearly 20 years), but it has not yet been licensed for general use in the USA or the UK. It can, however, be obtained by the pharmacy from Rhône-Poulenc Rorer Ltd, for use on a "named-patient" basis on request. The 250 mg (750,000 unit) tablets cost 69p each; 100 ml of the sugar-free suspension (25 mg/ml) costs £10.40.

References

- Matsui D. Prevention, diagnosis and treatment of fetal toxoplasmosis. *Clin Perinatol* 1994;**21**:675–89.
 Dunn D, Wallon M, Peyron F, et al. Mother-to-child transmission of toxoplasmosis: risk estimates for clinical counselling. *Lancet* 1999;**353**:1829–33.
 Wallon M, Liou C, Garner P, et al. Congenital toxoplasmosis: systematic review of evidence of efficacy of treatment in pregnancy. *BMJ* 1999;**318**:1511–14. [SR]
 Gilbert RE, Peckham CS. Congenital toxoplasmosis in the United Kingdom: to screen or not to screen. *J Med Screen* 2002;**9**:135–41.
 Olliare P. Congenital toxoplasmosis. *Clin Evid* 2003;**9**:763–6. [SR]

See also relevant Cochrane reviews



SPIRONOLACTONE

Use

Sustained treatment with spironolactone is of value in patients with congestive heart failure, in the diagnosis and management of primary hyperaldosteronism, and in the management of ascites due to liver disease. Whether the use of spironolactone, as well as a thiazide diuretic such as chlorothiazide (q.v.), is of value in babies with bronchopulmonary dysplasia is much less clearly established.

Pharmacology

Spironolactone is a potassium-sparing diuretic that was developed in 1959, which acts by competitively inhibiting the action of aldosterone (a natural adrenocortical hormone) on the distal part of the renal tubule. It is well absorbed by mouth and mainly excreted (partly metabolised) in the urine. The half life in adults is 1–2 hours, but several of the metabolic products (including canrenone) that also have diuretic properties have a 12–24 hour half life. It is not known whether metabolism and excretion differ in early infancy. Benefits may not become apparent for up to 48 hours after treatment is started and may continue for a similar period after the treatment has stopped. Its use declined after sustained high doses were shown to cause tumours in rats. However, a large multinational trial in 1999 (the RALES trial) showed that sustained low dose use in adults with severe heart failure relieves symptoms and reduces the risk of death by as much as 30%. These findings will certainly encourage wider use in infancy, even though no comparable evaluation has yet been attempted in children. Fluid retention develops in heart failure when the kidney responds inappropriately to underperfusion, in the same way as it does to volume depletion, by conserving sodium and retaining water. While ACE (angiotensin-converting enzyme) inhibitors such as captopril (q.v.) work by countering this response, at least temporarily, it is now clear that spironolactone use confers additional benefit.

A loop diuretic such as furosemide (q.v.) can improve pulmonary compliance in babies with ventilator induced chronic lung disease. A thiazide, such as chlorothiazide, is better for long term treatment, and it is common practice to give both a thiazide and spironolactone, although the value of this practice has, as yet, been assessed in only one small trial (which found no evidence of benefit). Spironolactone can be of use in the long term management of Bartter's syndrome, while high dose treatment can also help to control ascites in babies with chronic neonatal hepatitis. Treatment should always be stopped if there is renal failure because of the risk of hyperkalaemia. Spironolactone crosses the placenta and its use during pregnancy has produced feminisation in male rat fetuses, but there is no other evidence to suggest that use during pregnancy is dangerous. Some of the metabolites appear in breast milk, but use during lactation has not caused problems and results in the baby ingesting only 1–2% of the maternal dose (when this is calculated on a weight for weight basis).

Treatment

Use as a diuretic: Give 1 mg/kg of spironolactone together with 10 mg/kg of chlorothiazide twice a day by mouth for the management of chronic congestive cardiac failure. Congestive failure that fails to respond to this standard dose may sometimes do so if the dose of both drugs is doubled.

Use in hepatic ascites: A dose of up to 3.5 mg/kg by mouth twice a day is sometimes used in ascites secondary to liver disease, although patients need monitoring for possible hyperkalaemia.

Supply

Spironolactone is available as a sugar-free oral suspension containing 2 mg/ml (costing £29 per 100 ml), although this is a special formulation for which there is currently no formal product licence. Other strength suspensions also exist. It is also widely available in tablet form from a number of pharmaceutical companies.

References

- Hobbs SM, Fower RC, Row RD, *et al.* Spironolactone therapy in infants with congestive heart failure secondary to congenital heart disease. *Arch Dis Child* 1981;**56**:934–8. [RCT]
- Pérez-Ayuso RM, Arroyo V, Planas R, *et al.* Randomized comparative study of efficacy of furosemide versus spironolactone in nonazotemic cirrhosis with ascites. *Gastroenterology* 1983;**84**:961–8. [RCT]
- Pitt B, Zannad F, Remme WJ, *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;**341**:709–17. (See also pp. 753–5.) [RCT]
- Hoffman DJ, Gerdes JS, Abbasi S. Pulmonary function and electrolyte balance following spironolactone treatment in preterm infants with chronic lung disease: a double-blind, placebo-controlled, randomized trial. *J Perinatal* 2000;**1**:41–5. [RCT]

Use

Streptokinase can be used to lyse arterial thrombi when there is symptomatic vascular occlusion. Take the advice of a vascular surgeon where this is available. For a detailed discussion see p. 26.

Pharmacology

Streptokinase is a protein obtained from certain strains of the group C haemolytic streptococcus. It was first purified in 1962; its amino acid sequence was established in 1982. The half life on infusion is about 25 minutes. It activates human plasminogen to form plasmin, a proteolytic enzyme with fibrinolytic effects used to dissolve intravascular blood clots. The plasminogen activator alteplase (q.v.) is a more expensive alternative. Start treatment as soon as there is evidence of an obstructive intravascular thrombus and seek confirmation either by ultrasound or, preferably, by angiography. The relative merits of embolectomy, anticoagulation with heparin (q.v.), and treatment with streptokinase remain undetermined, but embolectomy is often impracticable, and treatment with heparin is of more use as a prophylactic measure than as a therapeutic strategy. Documentary evidence of the value of lytic therapy does not exist; treatment is not risk free, but is probably merited for arterial lesions that look set to cause tissue necrosis (gangrene). There is no good evidence that thrombosed renal veins benefit from active treatment and even less information on the wisdom of treating other venous thrombi. A collaborative controlled trial could shed some light on these issues. Streptokinase antibodies develop and persist for 6–12 months after treatment, making repeat treatment less effective and adverse reactions more likely. Use during pregnancy to treat maternal thromboembolism does not seem to have caused any direct or indirect threat to the fetus to date, and the teratogenic risk must be minimal because the drug does not cross the placenta. Its use in the intrapartum period may be more problematic, but during lactation it would seem unlikely, on theoretical grounds, to pose a serious problem.

Treatment

Arterial thrombi: Give a loading dose of 3000 units/kg of streptokinase slowly IV as soon as the diagnosis is made, followed by a continuous infusion of 1000 units/kg per hour (1 ml/hour of a solution made up as described below). Higher doses have been used with apparent impunity, but there is no evidence, as yet, that they are more effective. Treatment should continue until vascular flow returns, which may take only 4 hours, but can be delayed for 24–36 hours. Avoid IM injections during treatment and treat any bleeding from puncture sites with local pressure.

Blocked shunts and catheters: Dilute 10,000 units with enough 0.9% sodium chloride to fill the catheter dead space. Instill and leave for 1 hour before aspirating. Flush with heparinised saline.

Dose monitoring

Monitor the fibrinogen level if treatment is necessary for more than 6 hours, aiming for a level of between 1 g/l and 1.4 g/l. Slow or stop the infusion temporarily if the level falls below 1 g/l.

Antidote

Tranexamic acid can control bleeding by inhibiting the activation of plasminogen to plasmin. Try an IV infusion of 10 mg/kg over 10 minutes and repeat if necessary after 8–12 hours.

Supply and administration

Vials of streptokinase as a powder for reconstitution in 5 ml of water for injection are available from the pharmacy (250,000 unit vials cost £15). Take care to prevent the production of foam. Vials kept at 4°C can be used for 12 hours after reconstitution. For IV use, take 0.4 ml of reconstituted solution for each kilogram the baby weighs, dilute to 20 ml with 10% dextrose saline, and infuse at a rate of 1 ml/hour. This provides 1000 units/kg of streptokinase per hour. (A less concentrated solution of dextrose or dextrose saline can be used if necessary.) Prepare a fresh solution every 12 hours. 5 ml (500 mg) ampoules of tranexamic acid cost £1.30.

References

- Kothari SS, Varma S, Wasir HS. Thrombolytic therapy in infants and children. *Am Heart J* 1994;**127**:651–9.
- Schmidt B, Andrew M. Neonatal thrombosis: report of a prospective Canadian and international registry. *Pediatrics* 1995;**96**:939–43.
- Turrentine MA, Braems G, Ramirez MM. Use of thrombolytics for the treatment of thromboembolic disease during pregnancy. *Obstet Gynecol Surv* 1995;**50**:534–41.
- Nowak-Göttl U, von Kries R, Göbel U. Neonatal symptomatic thromboembolism in Germany: two year survey. *Arch Dis Child* 1997;**76**:F163–7.
- Cheah F-C, Boo N-Y, Rohana J, et al. Successful clot lysis using low dose of streptokinase in 22 neonates with aortic thromboses. *J Paediatr Child Health* 2001;**37**:479–82.

See also relevant Cochrane reviews



SUCROSE

Use

Giving the newborn baby something sweet to suck reduces the physical response to blood letting. Nevertheless, while such distraction significantly reduces the physical response to pain, it has yet to be shown that sucrose works because it has some pharmaceutical property.

Pharmacology

The potential analgesic effect of sucrose has been only poorly studied, but there is some evidence that a concentrated sugar solution may affect the endogenous opioid system in young rats if given shortly before a painful stimulus is experienced. There is also one experiment suggesting that the effect can be reversed by concurrent exposure to the opiate antagonist naltrexone.

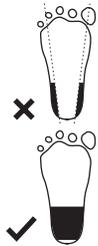
Managing brief pain

Fourteen randomised controlled trials included in a recent Cochrane Review provide unequivocal evidence that babies cry less when given sucrose to suck 2 minutes before being subjected to a painful procedure. Blood letting was the cause of pain investigated in all these studies. A wide range of doses have been used (0.01–1 g), and higher doses seem to produce a greater effect. Only one study has yet looked at the efficacy of this strategy in babies more than 1 month old. Efficacy is enhanced if sucrose is combined with the use of a pacifier, and if the baby is held throughout the procedure. Two recent studies suggest that breastfeeding on its own can be just as effective. The artificial sweetener aspartame seems as effective as sucrose; so is glucose, but milk is not. Sucrose works only when given orally; it is ineffective when given direct into the stomach. Preterm babies, who often experience multiple painful procedures, show less of a reduction in their composite “pain score” than term babies.

Sucrose seems as effective in babies as lidocaine–prilocaine (Emla®) cream. However, other studies have shown that, although the latter significantly reduces the pain associated with venepuncture in older children, it has relatively little impact on the way babies respond to this procedure (as discussed in the monograph on lidocaine). No comparison with tetracaine (q.v.) has yet been published. Sweets possess a magical ability to keep a child of any age quiet, but this does not mean that other strategies do not need to be pursued in parallel. The best way to avoid both heel prick pain and iatrogenic anaemia is, of course, not to take the sample at all. When sampling is necessary, much can be done to ensure that all required specimens are collected at the same time.

Minimising heel prick pain

People with diabetes know that the pain associated with collecting blood is minimised by using a spring loaded lance. A 2.4 mm Autolet® is ideal for collecting up to 1 ml of blood and seems to cause no more pain than venepuncture. The Tenderfoot®, which has a blade rather than a lance, is more expensive but more effective when a larger sample is required. A wide range of manual devices also exist. Some that are very easy to use (such as the Becton Dickson Microtainer Safety Flow®) look as though they are automated but are not. Prior warming is of negligible value, and ultrasound studies have shown that there is no risk of hitting bone with a 2.4 mm lance, irrespective of where you take blood. It is not, therefore, necessary to restrict sampling to the sides of the heel as once recommended; this just leaves the heel of any baby who has had much blood taken hypersensitive and very scarred. The whole dark shaded area in the figure is safe. Just avoid the area at the back (where you get a blister if your shoes are too tight).



Care strategy

The optimum approach is probably to drop 2 ml of a 25% solution of sucrose onto the swaddled baby's tongue 2 minutes before starting to take blood, and then give the baby a dummy or comforter to suck.

Supply

Any pharmacy can easily make up a safe, stable 25% solution of sucrose at negligible cost. The Autolet is manufactured by Owen Mumford Ltd, Woodstock, Oxford, UK, and the Tenderfoot by International Technidyne Corporation, Edison, NJ, USA.

References

- Barker DP, Latty BW, Rutter N. Heel blood sampling in preterm infants: which technique? *Arch Dis Child* 1994;**71**:F206–8.
- Barr RG, Pantel MS, Young SN, *et al*. The response of crying newborns to sucrose: is it a sweetness effect? *Physiol Behav* 1999;**66**:409–17. [RCT]
- Jain A, Rutter N. Ultrasound study of heel to calcaneum depth in neonates. *Arch Dis Child* 1999;**80**:F243–5.
- Anand KJS and the International Evidence-Based Group for Neonatal Pain. Consensus statement for the prevention and management of pain in the newborn. *Arch Pediatr Adolesc Med* 2001;**155**:173–80.
- Carbajal R, Veerapen S, Couderc S, *et al*. Analgesic effect of breast feeding in term neonates: randomised controlled trial. *BMJ* 2003;**326**:13–15. [RCT]
- Gilbert R, Frank L. Reducing pain during blood sampling in infants. *Clin Evid* 2003;**9**:419–35 (and updates). [SR]

See also Cochrane reviews of pain relief

Use

Sulfadiazine is used with pyrimethamine (q.v.) in the treatment of toxoplasmosis.

History

The story of how penicillin was discovered has often eclipsed any memory of how the study by Bayer of a simple chemical dye (prontosil) led to the discovery of the first effective antibacterial drug in 1932. The German discovery soon led the French to show that the smaller molecule, *p*-aminobenzenesulphonamide (or sulphanilamide), was as effective as prontosil itself, and that prontosil dye worked only after it was broken down to sulphanilamide in the body. Within 4 years, clinical trials backed by the Medical Research Council at Queen Charlotte's Hospital in London had established that both drugs could save women from almost certain death from streptococcal infection in childbirth (puerperal sepsis).

Other sulphonamides followed, including sulphapyridine from May and Baker (M&B 693), which was effective in pneumococcal pneumonia. Soon all the sulphonamides were shown to work by blocking bacterial folic acid synthesis. The drug was lethal to bacteria and not to humans because they acquired folic acid in their diet instead of metabolising it in the body. Recognition of this underlying principle was later to help to shape the discovery of a wide range of other antimicrobial drugs. While the importance of the sulphonamides has dwindled as many previously susceptible organisms have developed resistance, sulphadimidine is still occasionally used to treat urinary infection, silver sulfadiazine cream was used in several neonatal trials of skin care and is still used in the management of burns, sulfasalazine is used in ulcerative colitis, and sulfamethoxazole is used as a component of co-trimoxazole (q.v.).

Evidence that the prophylactic use of sulfafurazole to prevent infection in preterm babies actually caused an increase in deaths and kernicterus eventually led to a recognition that sulphonamides could displace bilirubin from albumin and cause free bilirubin to enter the brain, resulting in toxic brain damage. The trial by Silverman that brought this problem to light in 1956 did much to convince neonatologists that a trial with random allocation is the only way of establishing both the possible benefits and the possible hazards associated with every new form of treatment.

Pharmacology

Most sulphonamides are well absorbed when given by mouth, widely distributed in the body, and excreted after partial conjugation by a combination of renal filtration and tubular secretion. Hypersensitivity reactions usually present with a rash and a fever after about 9 days; treatment should be stopped before more serious symptoms develop. Blood dyscrasias have been reported. Exfoliative dermatitis, epidermal necrolysis (Lyell's syndrome), and a severe, potentially lethal, form of erythema multiforme (Stevens-Johnson syndrome) have occurred in children and adults. Haemolysis is a hazard in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. There is no evidence that any of the sulphonamides are teratogenic, but maternal treatment should be avoided, if possible, in the period immediately before delivery. Small quantities appear in breast milk, but breastfeeding is probably contraindicated only in babies who are ill, premature, or jaundiced. The adult half life of sulfadiazine is 10 hours, but double this in the first week of life. Sulfadiazine is not very soluble in urine, so damaging crystal formation in the renal tract (with haematuria) is possible if fluid intake is low. Because of the risk of kernicteric brain damage, manufacturers do not endorse the use of any sulphonamide in a child younger than 6–8 weeks, although the evidence is that sulfadiazine does not displace bilirubin nearly as strongly as sulfafurazole.

Treatment

Maternal disease: Give 1 g of sulfadiazine every 8 hours by mouth, together with 50 mg of pyrimethamine once a day, if infection seems to have spread to the fetus. Spiramycin (q.v.) is a more appropriate alternative if transplacental spread is not thought to have occurred.

Neonatal disease: Treatment of toxoplasma infection with pyrimethamine should be augmented by giving 50 mg/kg of sulfadiazine by mouth once every 12 hours.

Supply

500 mg tablets of sulfadiazine cost 31p each. A sugar-free suspension can be prepared from these, with a 1 week shelf life if stored at 4°C.

References

- Fichter EG, Curtis JA. Sulfonamide administration in newborn and premature infants. *Pediatrics* 1956;**18**:50–8.
Silverman WA, Anderson TH, Blanc WA, et al. A difference in mortality rate and incidence of kernicterus among premature infants allotted to two prophylactic antibacterial regimens. *Pediatrics* 1956;**18**:614–25. [RCT]
Odell GB. Studies in kernicterus. I. The protein binding of bilirubin. *J Clin Invest* 1959;**38**:823–33.

Use

Both "natural" and synthetic surfactants (q.v.) reduce the respiratory problems faced by preterm babies in the first 3 days of life, especially if given *early*. High dose treatment with a natural surfactant also reduces the severity of the illness in babies ventilated for meconium aspiration or pulmonary infection.

Pharmacology

Surfactant deficiency was first recognised in 1959 to be the cause of the respiratory distress seen in preterm babies in the first 2–3 days of life, but replacement products of animal origin became widely available for the first time only in 1990. Poractant alfa (Curosurf®) is an extract of porcine lung, with polar phospholipids and some hydrophobic, low molecular weight, surfactant associated proteins, while beractant (marketed as Survanta®) is a bovine extract containing phospholipids, neutral lipids, fatty acids, and surfactant associated proteins with added phosphatidylcholine, palmitic acid, and tripalmitin. Another product of bovine origin (BLES® or Bovine Lung Extract Surfactant) is available in Canada. Two commercial products obtained by bovine lung lavage are also in use: calfactant (Infasurf®) is marketed only in the USA, and SF-R11 (Alveofact®) is available only in Europe.

Natural surfactants have a more rapid onset of action. Head-to-head trials of a natural surfactant (beractant or calfactant) and an artificial surfactant (colfosceril) in 2500 preterm babies with established respiratory distress have shown that survival is marginally better with beractant. Although beractant did not seem to reduce the risk of chronic lung damage, and was associated with a marginal increase in the incidence of all (but not of severe) intraventricular haemorrhage, pneumothorax was less common and there was slightly less retinopathy. Using beractant instead of colfosceril produced two more survivors for every 100 babies studied. The different natural surfactants may not have identical properties but few direct comparisons have yet been done. New synthetic products containing surfactant proteins and peptides, currently under development, may eventually replace the present natural products. For a review of the potential role of these surfactants in other respiratory conditions see the web commentary.

In one recent trial, early use of constant lung distending pressure (nasal continuous positive airway pressure (CPAP)) and a single endotracheal dose of poractant alfa decreased the number of babies with early respiratory distress subsequently needing sustained intubation and artificial ventilation. Two other UK trials published so far only in abstract form point to the same conclusion. Another large trial is currently assessing whether immediate nasal CPAP in babies of 25–28 weeks gestation who are vigorous enough not to need intubation at birth can reduce the number ever needing intubation or surfactant. Outcome will be death or the need for supplemental oxygen at 36 weeks postmenstrual age, and respiratory and developmental outcome at 1 year. For details of the COIN trial contact Professor Colin Morley in Melbourne (+613 39344 2610).

Treatment

Poractant alfa: Give 100 mg/kg (1.25 ml/kg) into the trachea as soon after birth as possible if surfactant deficiency seems likely. Give a second dose after 12 hours if the base deficit was > 10 mmol/l at birth or there are possible signs of infection. Other babies probably merit a second dose only if they need ventilation with a mean airway pressure of > 7 cmH₂O in ≥ 40% oxygen. It may be appropriate to give double the normal dose if there is pneumonia or severe meconium aspiration.

Beractant: Give 100 mg/kg (4 ml/kg) in the same way as for poractant alfa. (The manufacturers say that up to three further doses can be given, at intervals of not less than 6 hours, within the next 48 hours.)

Administration

Guidance on administration is given in the monograph on synthetic surfactant.

Supply

Poractant alfa comes in 1.5-ml and 3 ml ready-to-use vials containing 120 mg and 240 mg of phospholipid, costing £380 and £760 each. Beractant comes in 4 ml and 8 ml vials containing 100 mg and 200 mg of phospholipid, costing £310 each; 100 mg vials are also available in some countries. Store vials at 4°C, but warm to room temperature before use and invert gently without shaking to resuspend the material. Do not use, or return vials to the refrigerator, more than 8 hours after they reach room temperature.

References

- Lotze A, Mitchell BR, Bulas DI, *et al.* Multicenter study of surfactant (beractant) use in the treatment of term infants with severe respiratory failure. *J Pediatr* 1998;**132**:40–7.
- Verder H, Albertsen P, Ebbesen F, *et al.* Nasal continuous positive airway pressure and early surfactant therapy for respiratory distress syndrome in newborns of less than 30 weeks' gestation. *Pediatrics* 1999;**101**:e24. [RCT]
- Herting E, Gefeller O, Land M, *et al.* Surfactant treatment with respiratory failure and group B streptococcal infection. *Pediatrics* 2000;**106**:957–64.
- Kattwinkel J, Bloom BT, Delmore P, *et al.* High- versus low-threshold surfactant retreatment for neonatal respiratory distress syndrome. *Pediatrics* 2000;**106**:282–8. [RCT]
- Suresh GK, Soll R. Lung surfactants for neonatal respiratory distress syndrome. Animal-derived or synthetic agents? *Pediatr Drugs* 2002;**4**:485–92.

See also relevant Cochrane reviews 

Use

Lack of surfactant is the commonest cause of death in the preterm baby. Synthetic and "natural" products have the same ability to reduce mortality by 40% in babies of less than 30 weeks gestation. Antenatal treatment with betamethasone (q.v.) can be an even more cost effective strategy.

Physiology

The lung of the very preterm baby may contain as little as 10 mg/kg of surfactant at birth (a tenth of the amount found at term) and, while labour and/or birth triggers a surge of production, this takes 48 hours to become effective. Acidosis and hypothermia are particularly damaging at this time because they interfere with this process. The development of artificial, and then natural, products to bridge this time gap, and their rigorous controlled trial evaluation, has been one of the major achievements of neonatal medicine in the last 20 years. Natural surfactant has a half life of about 12 hours, after which time some is recycled and some is degraded. The baby who is deficient at birth, therefore, needs to be given 100 mg/kg as soon as possible to prevent atelectasis (alveolar collapse) developing and, if destruction initially exceeds production, one (and occasionally two) further doses 12 and 24 hours later. Inactivation seems to occur more rapidly when there is infection or meconium aspiration, rendering a rather larger dose appropriate. There is a naïve belief that, because paediatricians decided, back in 1970, to call all births at 37–41 weeks gestation "term" births, there is no risk of these babies being surfactant deficient at birth. Unfortunately, this is not true for babies of 37 weeks gestation who have been subject to elective delivery. Only one synthetic surfactant, colfosceril (Exosurf Neonatal®), containing 108 mg of phosphatidylcholine, 12 mg of hexadecanol, and 8 mg of tyloxapol per vial, is currently licensed for sale, but a new product, lucinactant (Surfaxin®), which contains an analogue of surfactant protein C, is under development.

Indications

Many units now give all babies of less than 30 weeks gestation a first dose at birth, soon after the lung is first aerated, if they merit intubation at that time. When the cost of treatment is a major consideration, it may be harder to justify treating babies who are more mature than this until it is clear that they have established respiratory distress and require more than 40% oxygen to achieve a sustained arterial pO_2 of >7 kPa.

Treatment

Colfosceril: Give 67.5 mg/kg (5 ml/kg) into the trachea (babies weighing >1.6 kg need more than one vial), and one further dose after 12 hours if the baby is still ventilated.

Lucinactant: Give 175 mg/kg (5.8 ml/kg) of trial material. Up to two more doses can be given 6 hours apart.

Administration

Clear the trachea of any mucus and preoxygenate the lungs to minimise cyanosis during administration. Instil the prescribed dose down the tracheal tube with the baby supine. Use the minimum pressure needed to aerate the lung at birth, especially in the preterm baby. Administration over 4 minutes, as the manufacturers often recommend, does not reduce bradycardia or cyanosis, and it is doubtful whether changing the position of the baby during or after instillation improves distribution either. It has been held that colfosceril should be given through a special adapter, but instillation using a fine catheter passed down the tracheal tube, and positioned just beyond the tip of the tracheal tube, is just as effective. It is also widely thought that, if the appropriate dose of surfactant is contained in a small volume of fluid, administration will cause less disturbance, but studies show that a larger volume improves even dispersal within the lung. Ignore any surfactant that subsequently reappears in the tracheal tube. Hand ventilate, or reintubate, if you think the tube has become blocked. Be ready to adjust the ventilator pressure or oxygen settings after giving natural surfactant because of its more immediate effect.

Supply

Vials containing 108 mg of colfosceril cost £290 each. Reconstitute with 8 ml of water (as supplied), and use within 8 hours. Active marketing has recently ceased. Lucinactant is available for trial use only.

References

- Broadbent R, Fok T-F, Dolovich M, *et al*. Chest position and pulmonary disposition of surfactant in surfactant depleted rabbits. *Arch Dis Child* 1995;72:F84–9.
- Sweet DG, Halliday HL. Current perspectives on the drug treatment of neonatal respiratory distress syndrome. *Paediatr Drugs* 1999;1:19–30.
- Madar J, Richmond S, Hey E. Surfactant-deficient respiratory distress after elective delivery at "term". *Acta Paediatr* 1999;88:1244–8.
- Stenson B. Resuscitation of extremely preterm infants: the influence of positive pressure, surfactant replacement and supplemental oxygen on outcome. In: Hansen TN, McIntosh N, eds. *Current topics in neonatology* (no. 4). London: Saunders, 2000:125–48.
- Sinn JKH, Ward MC, Henderson-Smart DJ. Developmental outcome of preterm infants after surfactant therapy: systematic review of randomized controlled trials. *J Paediatr Child Health* 2002;28:597–600. [SR]
- Ainsworth SB, Milligan DWA. Surfactant therapy for respiratory distress syndrome in premature neonates. A comparative review. *Am J Respir Med* 2002;1:417–33.

See also relevant Cochrane reviews



SUXAMETHONIUM = Succinylcholine

Use

Suxamethonium speeds endotracheal intubation by producing short term muscle paralysis.

Pharmacology

Suxamethonium was first developed in 1906, but came into clinical use only in 1951. It acts by mimicking acetylcholine, the chemical that normally transmits all nerve impulses to voluntary muscle. However, because suxamethonium is more slowly hydrolysed by plasma and liver cholinesterases (the adult half life being 2–3 minutes), the nerve terminal becomes blocked for a time to all further stimuli. As a result, suxamethonium produces rapid and complete muscle paralysis. An effect (phase I block) is seen within 30 seconds after IV injection, but usually lasts for only 3–6 minutes. Recovery is spontaneous, but somewhat delayed in patients taking magnesium sulphate (q.v.). Unlike the *non*-depolarising muscle relaxants, such as pancuronium (q.v.), the action of suxamethonium cannot be reversed.

Large doses cause excessive quantities of suxamethonium to accumulate at the nerve–muscle junction, producing prolonged, competitive (phase II) block. Suxamethonium causes a 0.5 mmol/l rise in plasma potassium, making its use unwise in babies with existing hyperkalaemia. It also causes prolonged paralysis in patients who have inherited one of the abnormal genes associated with deficient cholinesterase production (about 0.04% of the population). While this seldom complicates neonatal care to a serious degree, it has occasionally caused prolonged respiratory depression after caesarean delivery when both mother and baby have such a defect. Breastfeeding is not contraindicated. Children with a parental history of cholinesterase deficiency should probably have their genetic status determined when they are 6 or more months old. The pseudocholinesterase level and type can easily be determined from a 2 ml serum sample.

Use to facilitate tracheal intubation

Trials have shown that prior paralysis can prevent the rise in intracranial pressure and reduce the fall in arterial pO₂ usually seen during neonatal intubation, even though it does not prevent a rise in blood pressure. However, paralysis does nothing to reduce the pain and distress associated with intubation, while suxamethonium, because it mimics acetylcholine, often causes an initial transient period of painful muscle fasciculation. Indeed, the rise in blood pressure seen in these studies suggests that the babies were still under stress. Atracurium (q.v.) has advantages over suxamethonium, even though it causes paralysis for about 20 minutes, because it does not cause transient muscle spasm. One recent review article has put forward a theoretical case for using ketamine (q.v.). Anaesthetists nearly always administer an IV or volatile anaesthetic before inducing neuromuscular blockade. One alternative strategy is to give a preparatory IV injection of morphine (q.v.) since this produces significant analgesia within 1 minute, which deepens progressively for the next 5–10 minutes. Thiopental (q.v.) or methohexital can also be used in a similar manner. Midazolam (q.v.) only sedates.

Premedication

A 15 micrograms/kg dose of atropine (q.v.) is traditionally given prior to suxamethonium administration, to reduce any reactive bradycardia and increased salivation. However, problems are so uncommon with neonatal *single* dose use that this step can be omitted as long as the drug is readily “to hand”.

Treatment

A 2 mg/kg dose of suxamethonium IV provides 5–10 minutes of muscle paralysis. A 3 mg/kg IV dose provides maximum neuromuscular blockade. A 4 mg/kg dose IM can be used to provide 10–30 minutes of paralysis after a latent period of 2–3 minutes. **Never** paralyse a baby unless you are confident the airway can be maintained and that hand ventilation can be provided.

Supply

2 ml ampoules containing 50 mg/ml of suxamethonium chloride cost 70p. Take 0.2 ml and dilute to 1 ml with 5% dextrose or dextrose saline in a 1 ml syringe to obtain a preparation containing 10 mg/ml for accurate neonatal administration.

References

- Cook DR, Windhard LB, Taylor FH. Pharmacokinetics of succinylcholine in infants, children and adults. *Clin Pharmacol Ther* 1976;**20**:493–8.
- Meakin G, McKiernan EP, Baker RD. Dose-response curves for suxamethonium in neonates, infants and children. *Br J Anaesth* 1989;**62**:655–8.
- Whyte S, Birrell G, Wyllie J. Premedication before intubation in UK neonatal units. *Arch Dis Child* 2000;**82**:F38–F41.
- Duncan HP, Zurick NJ, Wolf AR. Should we reconsider awake neonatal intubation? A review of the evidence and treatment strategies. *Paediatr Anaesth* 2001;**11**:135–45.
- Shah V, Ohlsson A. The effectiveness of premedication for endotracheal intubation in mechanically ventilated neonates. A systematic review. *Clin Perinatal* 2002;**29**:535–54. [SR]
- Oei J, Butha T, Lui K. Facilitation of neonatal nasotracheal intubation with premedication: a randomised controlled trial. *J Paediatr Child Health* 2002;**38**:146–50. [RCT]

Use

Teicoplanin is a useful antibiotic that is probably best held in reserve for use in treating vancomycin resistant, coagulase negative staphylococcal infection. The drug is currently more expensive vial for vial than vancomycin (q.v.), but it needs to be given only once a day, does not need to be given as slowly as vancomycin, and may have other advantages.

Pharmacology

Teicoplanin is a complex of five closely related glycopeptide antibiotics with similar antibacterial properties to vancomycin that were first isolated in 1976. Teicoplanin is active against many Gram positive anaerobes and is particularly potent against *Clostridium* species. It is also active against most *Listeria* species, enterococci, and staphylococci (including methicillin resistant strains), although it may work more as a bacteriostatic than a bactericidal drug. Rifampicin (q.v.) may sometimes be synergistic in the management of staphylococcal infection. Some coagulase negative staphylococci are now resistant, but acquired vancomycin cross resistance is also starting to be reported.

Teicoplanin cannot be given by mouth, but it can be given IM (unlike vancomycin), and does not usually need to be infused slowly to avoid thrombophlebitis when given IV (as vancomycin does). Few adverse effects have been detected as yet, and the risk of ototoxicity and nephrotoxicity may be rather less than that associated with vancomycin. Watch for possible leucopenia, thrombocytopenia, and disturbances of liver function. Teicoplanin has been used prophylactically in vulnerable babies with a long line in place, but this, like the prophylactic use of vancomycin, remains controversial. Teicoplanin crosses the placenta, and some appears in the milk when given to lactating animals. Little is known about the safety of using teicoplanin during pregnancy or lactation. The drug penetrates most tissue fluids well, but penetration into the cerebrospinal fluid is unsatisfactory and often unpredictable. Nearly all of the drug is excreted unchanged in the urine, the half life in adults being between 3 and 4 days (many times longer than the half life of vancomycin).

Prophylaxis

To prevent bacterial endocarditis in babies with congenital heart disease, give 6 mg/kg of teicoplanin and 2 mg/kg of gentamicin IV or IM 30–60 minutes before any invasive operation (particularly any genitourinary procedure). Use oral amoxicillin or clindamycin (q.v.) for oral or ENT procedures.

Treatment

Give a slowly administered loading dose of 16 mg/kg IV followed by 8 mg/kg IV or IM once every 24 hours for proven systemic infection. Treatment should be continued for at least 7 days. Double the dosage interval in renal failure.

Blood levels

While there is, as yet, no evidence that excessive levels are toxic, it may be wise to aim for a trough level of 10–15 mg/l.

Supply

Stock 200 mg vials come supplied with an ampoule of sterile water. They cost £19 each. Reconstitute by adding the whole of the ampoule of water (3.2 ml) slowly to the vial, and roll the vial gently between the hands until all the powder has dissolved without foaming. If foam does develop let the vial stand for 15 minutes until it subsides. Then remove some air and add a further 2 ml of 0.9% sodium chloride. The solution so prepared contains 40 mg/ml of teicoplanin. Administer using a 1 ml syringe. The solution can, if economic pressures so dictate, be kept for up to 24 hours if stored at 4°C, but it contains no preservative. Slow infusion over 30 minutes when giving the drug to any baby less than 1 month old, as recommended by the manufacturer, is not necessary if the administrative procedures outlined in the introduction to this compendium are followed.

References

- Kacet N, Dubos JP, Russel-Delvallee M, *et al.* Teicoplanin and amikacin in neonates with staphylococcal infection. *Pediatr Infect Dis J* 1993;**12**:510–513.
- Neumeister B, Kastner S, Conrad S, *et al.* Characterisation of coagulase-negative staphylococci causing nosocomial infections in preterm infants. *Eur J Clin Microb Infect Dis* 1995;**14**:856–63.
- Möller JC, Nelskamp I, Jensen R, *et al.* Teicoplanin pharmacology in prophylaxis for coagulase-negative staphylococcal sepsis in very low birthweight infants. *Acta Paediatr* 1996;**85**:638–40.
- Fanos V, Kacet N, Mosconi G. A review of teicoplanin in the treatment of serious neonatal infections. *Eur J Pediatr* 1997;**156**:423–7.
- Degraeuwe PJ, Beuman GH, van Tiel FH, *et al.* Use of teicoplanin in preterm neonates with staphylococcal late-onset sepsis. *Biol Neonate* 1998;**73**:287–94.

TETRACAINE = Amethocaine (former BAN)

Use

Tetracaine is a useful, well absorbed, topical anaesthetic.

Pharmacology

Tetracaine is an ester-type local anaesthetic related to para-aminobenzoic acid that first came into clinical use in 1932. It acts to block nerve conduction by inhibiting nerve depolarisation, and is destroyed by hydrolysis once it enters the blood stream. Some hydrolysis also occurs in the liver. Systemic absorption can lead to myocardial depression complicated by arrhythmia, while restlessness, tremor, and convulsions can be followed by drowsiness, respiratory depression, and coma. However, absorption is minimal when the product is applied only to unbroken skin as described here. The elimination half life in adults is about 70 minutes; the neonatal rate of elimination is not known. Methaemoglobinaemia has been reported, but such a problem is much more common with the topical anaesthetic prilocaine. Surface application may cause slight oedema and mild itching, possibly due to local histamine release. Some mild erythema is often seen, enough on occasion to delineate the treated area. The manufacturers have not yet endorsed the use of tetracaine gel in preterm babies, or in babies less than 1 month old. The product is, however, available "over the counter" without a doctor's prescription. There is no evidence that its use in pregnancy is hazardous.

Strategies for surface anaesthesia

Several local anaesthetics have been utilised to anaesthetise the skin of the newborn baby. Lidocaine and bupivacaine (q.v.) work best if injected into the skin, but can also be used to infiltrate deep tissues. Lidocaine is more rapidly effective, but bupivacaine provides more sustained pain relief. Lidocaine is less cardiotoxic than bupivacaine if accidentally injected into a blood vessel. Lidocaine gel can be used to anaesthetise the urethra, and has also been used during nasal intubation. A eutectic mixture of 2.5% lidocaine and 2.5% prilocaine (Emla®) can be used to anaesthetise the skin if applied under an occlusive dressing for at least 1 hour before venepuncture (as outlined in the monograph on lidocaine), but tetracaine gel may be rather more effective. It certainly works more quickly, probably because it is more lipophilic and therefore better at penetrating the stratum corneum of the skin. Tetracaine causes some mild vasodilatation, whereas lidocaine causes mild blanching and vasoconstriction. Further comparative study may well show topical tetracaine to be the better product to use before neonatal venepuncture or lumbar puncture, although the greater toxicity of systemic tetracaine needs to be noted. Some treatment failures seem to occur whichever product is used. Unfortunately, Emla cream does not seem to reduce the behavioural response to neonatal heel lancing, and tetracaine gel is also of little value.

Pain relief

To achieve anaesthesia for 1–2 hours, apply the whole of a 1.5 g tube of the 4% gel to the skin and cover with an occlusive dressing such as OpSite® (or one of a range of other, rather cheaper, products). Remove the dressing after 30 minutes (1 hour at most) and *wipe away all the remaining gel* before attempting venepuncture. Never apply the gel to mucous membranes, or to damaged or broken skin. Tetracaine gel cannot be recommended as a way to reduce significantly the pain caused by heel prick blood sampling.

Toxicity

Wipe the cream off promptly if signs of blistering develop. The effects of systemic toxicity are reviewed in the monograph on bupivacaine.

Supply and administration

Tetracaine is available as a 4% (40 mg/g) gel in 1.5 g tubes costing £1.20 each, designed to deliver about 1 g of gel when squeezed. Although this is enough to anaesthetise a 5 × 5 cm area of skin, the gel should never be applied to a larger area of skin than is actually necessary. Use does not require a doctor's prescription, but hospital use does have to be covered by a patient group direction.

References

- Lawson RA, Smart NG, Gudgeon AC, *et al.* Evaluation of an amethocaine gel preparation for percutaneous analgesia before venous cannulation in children. *Br J Anaesth* 1995;**75**:282–5
- Bishai R, Taddio A, Bar-Oz B, *et al.* Relative efficacy of amethocaine gel and lidocaine–prilocaine cream for Port-a-cath puncture in children. *Pediatrics* 1999;**104**:e31. [RCT]
- Jain A, Rutter N. Local anaesthetic effect of topical amethocaine gel in neonates: randomised controlled trial. *Arch Dis Child* 2000;**92**:F42–5. [RCT]
- Arrowsmith J, Campbell C. A comparison of local anaesthetics for venepuncture. *Arch Dis Child* 2000;**82**:309–10. [RCT]
- Jain A, Rutter N, Ratnayaka M. Topical amethocaine gel for pain relief of heel prick blood sampling: a randomised double blind controlled trial. *Arch Dis Child* 2001;**84**:F56–9. [RCT]

Use

Tetracosactide is used diagnostically in the evaluation of adrenal cortex hormone deficiency.

Pharmacology

Serum cortisol levels may be low in the newborn, particularly in babies born before term, and show no detectable diurnal variation for 8–12 weeks, but stimulation tests can be used to test the functional integrity of the adrenal gland. Treatment with dexamethasone (q.v.) and other steroid drugs can suppress cortisol secretion, and the normal reactivity of the adrenal gland can remain depressed for several weeks after treatment stops. Preterm babies with a low cortisol level despite stress in the first few days of life who require ventilation seem to be at greater risk of developing chronic lung damage.

Tetracosactide (Synacthen®) is a polypeptide with properties similar to corticotrophin (or ACTH), the hormone produced by the anterior lobe of the pituitary gland, which stimulates the secretion of several adrenal gland hormones, including cortisol (hydrocortisone) and corticosterone. It was first synthesised in 1961. Corticotrophin secretion is, itself, controlled by corticorelin (CRH) release from the hypothalamus in the brain, and influenced by circulating glucocorticoid hormone levels. Stress can stimulate corticotrophin release. Tetracosactide can be used to test the adequacy of the adrenocortical response to stress (colloquially known as a "Synacthen test" because that is the trade name of the product). A 1 microgram/kg IV test dose of corticorelin provides a better test of pituitary function. Both hormones are rapidly metabolised to a range of inactive oligopeptides within an hour or two of administration. While it is difficult to see how administration could cause any harm, these hormones should only be given to a pregnant or lactating mother for good reason.

Tetracosactide (as Synacthen depot) is one of three treatment strategies for the initial management of infantile spasms currently under controlled trial evaluation as outlined in the monograph on vigabatrin.

Adverse reactions

Anaphylactic and hypersensitivity reactions can occur, so tetracosactide should only be administered under the direct supervision of an experienced and senior hospital specialist. Most severe reactions occur within 30 minutes. See the monograph on immunisation for the management of anaphylaxis. Intramuscular adrenaline always needs to be followed by a prompt infusion of hydrocortisone.

Test procedure

Standard test: It has been traditional to measure the plasma cortisol level immediately before and exactly 30 minutes after giving a 36 microgram/kg test injection of tetracosactide IV. Some advise the collection of a second specimen 60 minutes after the test injection. Tetracosactide administration normally causes a 70 microgram/l (200 nmol/l) rise in the plasma cortisol concentration unless there is primary adrenal failure, but equivocal results are sometimes obtained, especially in the first month of life. The help and advice of a paediatric endocrinologist should always be sought before undertaking any such test in the neonatal period.

Low dose tests: The procedure described above involves a supramaximal test dose. Very much smaller doses have been used to assess the response of the adrenal gland to a more physiological stimulus (doses as low as 500 nanograms have sometimes been used in adults). What constitutes a "normal" response to such a low stimulus in the preterm baby is not yet clear. A 1 microgram/kg dose causes a 2–3 fold rise in the base line cortisol level within 60 minutes in most, but not all, healthy babies of less than 30 weeks gestation in the second week of life (mean peak value 500–700 nmol/l).

Supply

1 ml ampoules containing 250 micrograms of tetracosactide (as acetate) for IV or IM use (made by CIBA and marketed under the trade name Synacthen) cost £3 each. Note that a 1 mg depot preparation (using a zinc phosphate complex) for intramuscular use is also available in 1 ml ampoules costing £4.30 each. The depot preparation should **not** be used when conducting the standard diagnostic test described above. All ampoules should be protected from light and stored at 4° C.

References

- Hingre RV, Gross SJ, Hingre KS, *et al.* Adrenal steroidogenesis in very low birth weight preterm babies. *J Clin Endocrinol Metab* 1994;**78**:266–70.
- Korte C, Styne D, Merritt TA, *et al.* Link between early adrenal function and respiratory outcome in preterm infants: airway inflammation and patent ductus arteriosus. *Pediatrics* 2000;**105**:320–24.
- Karlsson R, Kallio J, Irljala K, *et al.* Adrenocorticotropin and corticotropin-releasing hormone tests in preterm infants. *J Clin Endocrinol Metab* 2000;**85**:4592–5.
- Bolt RJ, van Weissenbruch MM, Popp-Snijders C, *et al.* Maturity of the adrenal cortex in very preterm infants is related to gestational age. *Pediatr Res* 2002;**52**:405–10.

TETRACYCLINE

Use

Although there are few reasons for using this antibiotic during childhood, it remains the treatment of choice for rickettsial infection, and the most effective treatment for certain uncommon erythromycin resistant mycoplasmal infections. Malaria is also sometimes treated with quinine (q.v.) followed by tetracycline.

Mycoplasma infection

The mycoplasmas are the smallest free-living microorganisms. They seem to have evolved from Gram positive bacterial ancestors but lack a cell wall, making them resistant to most antibiotics (which work by attacking these walls). Special techniques are necessary for laboratory isolation. *Mycoplasma hominis* and *Ureaplasma urealyticum* are potential perinatal pathogens that colonise the female genital tract. *M. pneumoniae* seems to cause infection only in older children. Ureaplasma infection seems to be an important cause of ascending chorioamnionitis, preterm labour, and prelabour rupture of membranes. Overt maternal infection has been documented. Such organisms can cause congenital pneumonia, are suspected of being a cause of postnatal pneumonia, and may be a factor in the pathogenesis of chronic lung disease. A 2 week course of erythromycin (q.v.) usually suffices. Tetracycline or chloramphenicol (q.v.) may be necessary to eliminate central nervous system infection, but isolation of the organism from the trachea, urine, or cerebrospinal fluid (CSF), in the absence of any evidence of inflammation (radiological evidence of pneumonia or a raised white cell count), is not in itself evidence of systemic infection. Infections with *M. hominis* are resistant to erythromycin and require treatment with tetracycline.

Pharmacology

Tetracycline is a naturally occurring antibiotic produced by a streptomycete fungus. It was first isolated in 1952. Tetracycline is bacteriostatic, inhibiting bacterial protein synthesis and cell growth. It is only partially absorbed from the gastrointestinal tract, absorption being further affected by the formation of insoluble complexes in milk. Oral administration can also cause adverse gastrointestinal symptoms, probably as a result of mucosal irritation. CSF penetration is very poor. Most of the drug is excreted in the urine, but substantial amounts appear in bile and faeces. The half life (8 hours) does not seem to vary with age. Tetracycline can exacerbate any existing renal impairment, and IV treatment should also be avoided where there is hepatic impairment. Tetracycline was once widely used in the management of many Gram positive and Gram negative infections but the emergence of drug resistant strains, and the development of alternative agents, have led to a decline in the use of this once popular antibiotic. Doxycycline (a semisynthetic derivative) is sometimes used in adults because of its longer half life.

Systemic tetracycline should normally be avoided during childhood because sustained use causes an unsightly green discolouration of the permanent teeth. It remains of value, however, in the treatment of malaria, and of chlamydial, rickettsial, mycoplasma, and protozoal infections, and there are situations where efficacy, availability, and low cost still make short term administration a logical treatment option. Tetracycline is also active against most spirochetes. While there is no evidence of teratogenicity, tetracycline should not normally be used during late pregnancy because the drug is avidly taken up by developing fetal teeth and bone. More seriously, its use in pregnancy has occasionally been associated with fatal maternal hepatotoxicity. Treatment during lactation probably carries little risk; the amount ingested by the baby in breast milk represents less than 5% of the usual therapeutic dose, and absorption seems to be limited by chelation to calcium. Tetracycline has been shown to retard bone growth in the preterm baby, probably because of its absorption by the epiphyseal plate. Treatment can occasionally provoke a dangerous rise in CSF pressure (so-called benign intracranial hypertension).

Treatment

Systemic treatment: Treat malaria and erythromycin resistant mycoplasma infection with 5 mg/kg IV once every 12 hours (or 7.5 mg/kg by mouth once every 8 hours) for at least 7 days.

Eye ointment: Topical chlortetracycline ointment is used (with oral erythromycin) to treat chlamydial conjunctivitis, as discussed in the monograph on eye drops.

Supply

500 mg vials are available on a "named patient" basis costing £5 each. Reconstitute the powder with 25 ml of water for injection to obtain a solution containing 20 mg/ml. Take 2.5 ml of this solution, dilute immediately before use to 10 ml with 10% dextrose to give a solution containing 5 mg/ml for accurate administration, and give through an IV line that contains a terminal 0.22 µm filter. The IV preparation can also be given by mouth (a fresh vial should be opened daily). A 25 mg/ml suspension is available in the USA. IM injection is painful and absorption can be erratic. 250 mg tablets cost 4p each. There is currently no commercial source of tetracycline eye ointment in many countries. Erythromycin ointment should be used if tetracycline ointment is unobtainable.

References

- Gidion R, Marget W. Zur frage der dosierung injizierbarer Tetracycline im säuglingsalter. *Munch Med Wochenschr* 1961;103:967-71.
Wang EEL, Matlow AG, Ohlsson A, et al. *Ureaplasma urealyticum* infections in the perinatal period. *Clin Perinatol* 1997;24:91-105.
Digre KB. Not so benign intracranial hypertension [Commentary]. *BMJ* 2003;326:613-14. (See also pp. 641-2.)

Use

THAM is an organic buffer of occasional value in the management of metabolic acidosis where poor renal function and/or the risk of hypernatraemia make it unwise to use sodium bicarbonate (q.v.).

Pharmacology

THAM (or tris-hydroxymethyl-amino-methane) is an organic buffer that was used widely at one time in the management of severe *metabolic* acidosis (the appropriate management of *respiratory* acidosis being, almost without exception, ventilatory support). It is sometimes known as TRIS (from the first four letters of the drug's full chemical name). The drug has to be given IV and is normally fairly rapidly excreted by the kidney; some caution needs to be exercised when the drug is used in a baby with impaired renal function. Infusion has also occasionally been reported to cause apnoea, respiratory depression, and hypoglycaemia. Extravasation can cause tissue necrosis after IV infusion (see below).

THAM (or sodium bicarbonate) is of considerable value in the management of neonatal circulatory arrest (so called "cardiac arrest"), and in this context administration by direct cardiac puncture through the fourth left intercostal space is much safer than is generally recognised, at least in infancy, and is much more effective than blind peripheral administration in the presence of circulatory arrest. THAM should be used instead of sodium bicarbonate in patients in whom CO₂ retention is a problem. Bicarbonate is largely ineffective in such a "closed" system because the additional CO₂ produced by bicarbonate administration causes respiratory acidosis if it is not eliminated promptly through the lungs. Because THAM is only 80% ionised when pH is in the physiological range, it is not as therapeutically effective as an equivalent molar volume of sodium bicarbonate.

Treatment

Cardiac arrest: THAM, or a mixture of glucose and THAM, appears to be the most effective way of re-establishing cardiac output experimentally when neonatal circulatory standstill does not immediately respond to intubation, ventilation, and cardiac massage. Try injecting 1.5 ml/kg of 0.6M THAM directly into one of the cavities of the heart. This can be mixed with a small amount of 10% dextrose if time allows, or followed by some 10% dextrose if there is no immediate circulatory response to the injection of base.

Metabolic acidosis: Give 0.6 mmol/kg for each unit (mmol/l) by which it is hoped to lower the base deficit, giving the infusion slowly at a rate never exceeding 0.5 mmol/kg per minute. Partial correction is usually adequate and it is not generally necessary to give more than 5 mmol/kg, but twice as much as this can be given on demand in a real emergency. Because of the risk of respiratory depression, the drug is usually given only to babies already receiving respiratory support.

Tissue extravasation

Extravasation after IV infusion can cause tissue necrosis; a strategy for the early management of this complication is described in the monograph on hyaluronidase (q.v.). Accidental intra-arterial injection of THAM is reported to have produced severe haemorrhagic necrosis in some newborn infants (probably because there was circulatory stasis at the time the drug was injected). Localised liver necrosis has also been reported when THAM has been given blind and undiluted into the umbilical vein, but most published reports relate to the use of concentrated solutions containing more than 0.6 mmol/ml.

Supply

No commercial preparation of THAM is available at present, but sterile 5 ml and 10 ml ampoules containing 3.6% (0.3M) or 7.2% (0.6M) THAM costing about £6 each are prepared by a number of NHS manufacturing units using the Addenbrooke's Hospital formula. The 3.6% solution, containing 0.3 mmol/ml is iso-osmotic, while the 7.2% solution, containing 0.6 mmol/ml, is hyperosmolar. Conversion factor: 1 mmol = 120 mg.

References

- Adamsons K, Behrman R, Dawes GS, *et al.* Resuscitation by positive pressure ventilation and TRIS-hydroxymethyl-aminomethane of rhesus monkeys asphyxiated at birth. *J Pediatr* 1964;65:807–18.
- Blench HL, Schwartz WB. TRIS buffer (THAM): an appraisal of its physiological effect and clinical usefulness. *N Engl J Med* 1966;274:782–6.
- Robertson NRC. Apnoea after THAM administration in the newborn. *Arch Dis Child* 1970;45:206–13.

See also relevant Cochrane reviews



THEOPHYLLINE

Use

Theophylline (given IV as aminophylline) is a useful respiratory stimulant in babies with neonatal apnoea, but caffeine (q.v.) is the drug of choice because it has a wider safe therapeutic range.

Pharmacology

Theophylline, a naturally occurring alkaloid present in tea and coffee, was widely used in the treatment of asthma for more than 50 years. The optimum bronchodilator effect is seen only with a plasma level of 10–20 mg/l, but toxic symptoms are sometimes seen in the newborn when the level exceeds 14 mg/l, and gastro-oesophageal reflux may be made worse. Sustained use increases urinary calcium loss. Very high blood levels cause hyperactivity, tachycardia, and fits that seem to respond to the oral administration of activated charcoal even when the drug has been given IV. Correct any hypokalaemia or metabolic acidosis. Arrhythmias that fail to respond to adenosine (q.v.) may respond to propranolol (q.v.). A single prophylactic 8 mg/kg IV dose seems to reduce some of the adverse renal consequences of perinatal asphyxia. Theophylline is moderately well absorbed in the neonate when given by mouth, but slowly metabolised by a series of parallel liver pathways, some of which are saturable. The neonatal half life (15–50 hours) is five times as long as in adults. There is no evidence that moderate maternal use during pregnancy or lactation is hazardous to the baby, although calculations suggest that a breastfed baby could receive (on a weight for weight basis) about an eighth of the maternal dose.

Caffeine has many advantages over theophylline in the management of neonatal apnoea. The gap between the optimum therapeutic blood level and the blood level at which toxic symptoms first appear is much wider with caffeine than it is with theophylline, and caffeine usually needs to be given only once a day. Theophylline is, in any case, partly metabolised to caffeine in the liver in the neonatal period.

Drug interactions

Toxicity can occur in patients who are also taking cimetidine, ciprofloxacin, erythromycin, or isoniazid unless a lower dose of theophylline is used. Conversely, a higher dose may be needed in patients on carbamazepine, phenobarbital, phenytoin, or rifampicin because of enhanced drug clearance. Treatment with theophylline, in turn, may make it necessary to increase the dose of phenytoin.

Drug equivalence

Aminophylline (which includes ethylenediamine in order to improve solubility) is only 85% theophylline, but there is a suggestion that neonatal bioavailability is reduced by first pass liver metabolism, and that the dose of theophylline used for oral treatment can be the same as the dose of aminophylline given IV.

Treatment

IV treatment for the preterm baby: Try 8 mg/kg of aminophylline as a loading dose over not less than 10 minutes, followed by 2.5 mg/kg (or, if necessary, 3.5 mg/kg) once every 12 hours. Because of the long half life, a continuous infusion is not necessary. A rapid IV bolus can cause arrhythmia.

Oral treatment for the preterm baby: Try an initial loading dose of 6 mg/kg of theophylline (if the patient is not already on IV treatment) followed by 2.5 mg/kg every 12 hours.

Older children: A reasonable rule of thumb when starting oral treatment in babies aged 1–11 months is to calculate the **total** daily dose of theophylline required per kilogram body weight as 5 mg plus 0.2 times the child's postnatal age in weeks.

Blood levels

The optimum plasma level in neonates is probably 9–14 mg/l (1 mg/l = 5.55 μ mol/l). Significant side effects can appear when the level exceeds 15 mg/l in the newborn baby (see p. 9), and when the level exceeds 20 mg/l (100 μ mol/l) in older children, the difference probably being due to variation in protein binding. Theophylline can be measured in 0.1 ml of plasma. Timing is not crucial because of the long neonatal half life, but specimens are best collected 1 hour after the drug has been given.

Supply

One 10 ml ampoule containing 250 mg of aminophylline costs 69p, and 100 ml of an oral syrup containing 12 mg/ml of theophylline hydrate (as sodium glycinate) costs £1.

References

- Aranda JV, Lopes JM, Blanchard P, *et al.* Treatment of neonatal apnoea. In: Rylance G, Harvey D, Aranda JV, eds. *Neonatal clinical pharmacology and therapeutics*. Chapter 8. Oxford: Butterworths, 1991:95–115.
- Hogue SL, Phelps SJ. Evaluation of three theophylline dosing equations for use in infants up to one year of age. *J Pediatr* 1993;**123**:651–6.
- Jenik AG, Cernadas JMC, Gorenstein A, *et al.* A randomised, double-blind, placebo-controlled trial of the effects of prophylactic theophylline on renal function in term neonates with perinatal asphyxia. *Pediatrics* 2000;**105**:e45. [RCT]

See also relevant Cochrane reviews



Use

Thiopental is most widely used during induction of anaesthesia. A continuous infusion will nearly always control seizures that do not respond to any other standard therapy, if ventilation is supported artificially.

Pharmacology

Thiopental sodium is a hypnotic and anticonvulsant barbiturate, but it does not relieve pain. It was first used in 1934. It causes marked respiratory depression and should be used only in situations where immediate respiratory support can be provided. Large doses cause a fall in peripheral vascular resistance and cardiac output, making it imperative to monitor blood pressure. The drug reaches the central nervous system very rapidly and is then progressively redistributed away from the brain into body fat stores. Elimination by the liver is slow, and the half life at birth (20–30 hours) can be double that found in adults. Accumulation is almost inevitable if an infusion is continued for more than a few hours (neonatal $V_D \sim 4$ l/kg). Thiopental crosses the placenta rapidly, but the amount transferred following a single maternal injection is small because the maternal blood level remains high for only a short time. Continuous infusions may, however, cause fetal accumulation. Very little appears in breast milk after use during routine operative anaesthesia.

Thiopental can be used to provide sedation and analgesia during brief but painful neonatal procedures such as endotracheal intubation. It is also very effective in controlling seizures that are resistant to more conventional treatment, but, because the drug acts as a general anaesthetic, its ability to abolish continuing and potentially damaging cerebral discharges can be confirmed only by monitoring the EEG. These properties also interfere with other aspects of routine neurological surveillance, and experience shows that most babies whose seizures are controlled only by thiopental anaesthesia die later in the neonatal period or survive with a severe handicap. Thiopental does not therefore, as yet, have any proven role in the treatment of hypoxic ischaemic encephalopathy.

Methohexital sodium is a related barbiturate with similar anaesthetic but no anticonvulsant properties. A 2 mg/kg bolus dose IV produces anaesthesia after less than 1 minute. Induction may not be as smooth as with thiopental, but recovery starts sooner (usually after 3–5 minutes).

Treatment

Short term IV use: 5 mg/kg IV produces sleep after about 45 seconds if flushed in with saline. Recovery begins 5–10 minutes later. Twice this dose will often produce anaesthesia for 15–30 minutes, but causes a significant fall in blood pressure.

Long term infusion: A 5 mg/kg loading dose and a maintenance infusion of 2.5 mg/kg per hour is usually enough to control seizure activity. Check the infusate for haze or precipitation, and prepare a fresh solution after 24 hours. Recovery will be slow if the infusion is continued for more than 24–48 hours because of substantial tissue drug accumulation.

Tissue extravasation

Extravasation can cause tissue necrosis and intra-arterial injections are extremely damaging, but this should not be a problem if the product is diluted before use. A strategy for the early treatment of tissue extravasation is described in the monograph on hyaluronidase.

Blood levels

The therapeutic blood level of thiopental base for anticonvulsant purposes is probably 60–100 mg/l (1 mg/l = 4–13 μ mol/l). Much lower levels suffice to produce anaesthesia. Send 0.2 ml of plasma.

Supply and administration

500 mg vials of thiopental cost £3. Reconstitute the vial with 20 ml of preservative free water for injection; take 125 mg (5 ml) of this solution and dilute to 50 ml with 5% dextrose to give a solution containing 2.5 mg/ml for safe, accurate administration. Thrombophlebitis can be a problem when a more concentrated solution than this is employed. Methohexital (originally known in the UK as methohexitone) is commercially available in the USA but not, at present, in the UK.

References

- Goldberg PN, Moscoso P, Bauer CR, *et al.* Use of barbiturate therapy in severe perinatal asphyxia: a randomised controlled trial. *J Pediatr* 1986;**109**:851–6. [RCT]
- Garg DC, Goldberg RN, Woo-Ming RB, *et al.* Pharmacokinetics of thiopental in the asphyxiated neonate. *Dev Pharmacol Ther* 1988;**11**:213–18.
- Tasker RC, Boyd SG, Harden A, *et al.* EEG monitoring of prolonged thiopentone administration for intractable seizures and status epilepticus in infants and children. *Neuropediatrics* 1989;**20**:147–53.
- Bonati M, Marraro G, Celardo A, *et al.* Thiopental efficacy in phenobarbital-resistant neonatal seizures. *Dev Pharmacol Ther* 1990;**15**:16–20.
- Naulaers G, Deloof E, Vanhole C, *et al.* Use of methohexital for elective intubation in neonates. *Arch Dis Child* 1997;**77**:F61–4.
- Bhutada A, Sahni R, Rastogi E, *et al.* Randomised controlled trial of thiopental for intubation in neonates. *Arch Dis Child* 2000;**82**:F34–7. [RCT]

TIN-MESOPORPHYRIN

Use

Tin-protoporphyrin and tin-mesoporphyrin have been used in the management of porphyria, and used experimentally since 1989 to inhibit bilirubin production in the neonatal period.

Pharmacology

Phenobarbital (q.v.) was the first drug used both antenatally and after birth to prevent potentially dangerous levels of jaundice developing in the neonatal period. Phenobarbital works by inducing liver enzyme activity and enhancing bilirubin excretion. The use of a specific enzyme inhibitor to decrease the rate at which haem is degraded to bilirubin as a result of red cell destruction provides an alternative strategy in the management of neonatal jaundice. A range of tin-porphyrins have been shown to inhibit the activity of haem oxygenase, the rate limiting enzyme in this process. Tin-protoporphyrin was used in most early studies, but tin-mesoporphyrin has been shown to be a particularly potent inhibitor of bilirubin production, and this is the product that has been used in all the most recent studies into the management of jaundice. Following experience of short term use (1 micromol/kg IV every other day) in older children with uncontrolled jaundice due to type 1 Crigler–Najjar syndrome, it has now been used experimentally to reduce peak bilirubin levels in babies at serious risk of significant neonatal jaundice.

Evidence that tin-mesoporphyrin can **prevent** jaundice when given early does not, however, mean that it will necessarily prove to be of much value in the management of babies who have already become seriously jaundiced, unless the jaundice is likely to be prolonged. Neither should the use of this still experimental drug be encouraged in most clinical settings merely in order to reduce the need for phototherapy (q.v.) until as much is known about the safety of this drug as is known about the safety of phototherapy. Exchange transfusion will certainly remain central to the initial management of haemolytic disease in babies born to mothers with anti- \bar{c} , anti-D and anti-Kell antibodies (including the correction of severe anaemia at birth). The drug may eventually come to have a place however, if given early, in the management of several of the conditions capable of causing dangerous neonatal jaundice.

When treatment is sustained, the drug seems to have an effect on intestinal haem oxidase, reducing iron absorption and causing a mild iron deficiency anaemia after about 2 months unless further supplemental oral iron is given. Inhibiting bilirubin production does not cause haem to accumulate, because of a compensatory increase in haem excretion through the biliary tract.

Treatment

Treatment is still experimental. A single dose of 6 micromol/kg of tin-mesoporphyrin IM shortly after birth seems to be enough to reduce neonatal jaundice in the preterm baby by at least 40%.

Phototherapy

Phototherapy causes troublesome erythema in babies given tin-protoporphyrin. This is less of a problem with tin-mesoporphyrin, especially if special blue (F20T12/BB) phototherapy strip lights are used.

Supply

Vials containing 24 micromol/ml of tin-mesoporphyrin were used in the recently reported neonatal studies. Vials kept in the dark and stored at 4°C are stable for up to 1 year. The product is given IM (or IV where the volume involved makes this necessary). Supplies could be imported from the USA on an investigational basis if a request was lodged with Dr Kappas at the Rockefeller University, 1230 York Avenue, New York, NY 10021 that satisfied the Federal Drug Agency's "technology transfer" guidelines. Details of the formulation are also held in the Royal Victoria Infirmary pharmacy in Newcastle upon Tyne. Tin-**protoporphyrin** has, in the past, been provided as a "special" at the Western Infirmary, Glasgow.

References

- Valaes TN, Harvey-Wilkes K. Pharmacologic approaches to the prevention and treatment of neonatal hyperbilirubinaemia. *Clin Perinatol* 1990;**17**:245–73.
- Dover SB, Graham A, Fitzsimons E, et al. Haem arginate plus tin-protoporphyrin for acute hepatic porphyria. *Lancet* 1991;**338**:263.
- Galbraith RA, Drummond GS, Kappas A. Suppression of bilirubin production in the Crigler Najjar type 1 syndrome: studies with the heme oxygenase inhibitor tin-mesoporphyrin. *Pediatrics* 1992;**89**:175–82.
- Martinez JC, Garcia HO, Otheguy LE, et al. Control of severe hyperbilirubinemia in full-term newborns with the inhibitor of bilirubin production Sn-mesoporphyrin. *Pediatrics* 1999;**103**:1–5. [RCT]
- Kappas A, Drummond GS, Valaes T. A single dose of Sn-mesoporphyrin prevents development of severe hyperbilirubinemia in glucose-6-phosphate dehydrogenase-deficient newborns. *Pediatrics* 2001;**108**:25–30.

Use

Tobramycin is an alternative to gentamicin (q.v.) in the management of Gram negative bacterial infections.

Pharmacology

Tobramycin is a bactericidal antibiotic related to kanamycin, which is handled by the body in much the same way as netilmicin (q.v.). It was first discovered in 1968. All the aminoglycoside antibiotics have a relatively low therapeutic:toxic ratio; there is little to choose between amikacin (q.v.), gentamicin, netilmicin and tobramycin in this regard. Tobramycin crosses the placenta moderately well but has not been found to cause as much ototoxic damage to the fetus as is sometimes seen with streptomycin. It penetrates the cerebrospinal fluid and the bronchial lumen rather poorly. Some is also excreted in breast milk but this is of little consequence as oral absorption is negligible.

Tobramycin has certain theoretical advantages over gentamicin in the management of infection with *Pseudomonas* because of greater in vitro sensitivity, and twice daily inhalation (80 mg in 2 ml of 0.9% sodium chloride) seems capable of eliminating both lung infection and carriage of *Pseudomonas* in children with cystic fibrosis, if sustained for a full year. Gentamicin is more normally used when treating an undiagnosed Gram negative infection, while a combination of gentamicin and ceftazidime (q.v.) is often thought to be the optimum treatment for neonatal *Pseudomonas* infection. It is not always as easy to get blood tobramycin as blood gentamicin levels estimated. This should be checked with the local laboratory before the drug is prescribed. The dose regimen recommended in this compendium mirrors the one outlined in the monograph on gentamicin, although very few of the studies of once versus thrice daily aminoglycoside treatment have actually involved the use of tobramycin.

Interaction with other antibiotics

Aminoglycosides are capable of combining chemically with equimolar amounts of most penicillins. Such inactivation has been well documented in vitro, and is the basis for the advice that these antibiotics should never be mixed together before administration. Clinical problems have been encountered, however, only after simultaneous administration in patients with severe renal failure and sustained high plasma antibiotic levels. Leaving a 2–4 hour gap between aminoglycoside and β lactam antibiotic administration has been shown to enhance bactericidal potency in vitro by an unrelated mechanism, but the clinical relevance of this observation is not yet clear.

Treatment

Intermittent high dose treatment: Start by giving 5 mg/kg IV or IM once every 24 hours. If the trough serum level when the third dose was given exceeded 2 mg/l, increase the dosage interval to 36 hours and check the level again after two more doses have been given.

Conventional twice daily regimen: Some clinicians still give term babies 3.5 mg/kg IV or IM once every 12 hours (once every 8 hours in babies over 6 months old). Give a 5 mg/kg loading dose first.

Blood levels

The trough level is all that usually needs to be monitored in babies on intermittent high dose treatment, and this is probably necessary as a routine only in babies in possible renal failure or less than 10 days old. Aim for a trough level of about 1 mg/l (1 mg/l = 2.14 μ mol/l). Extend the dosage interval if the trough level exceeds 2 mg/l. The 1 hour peak level, when measured, should be 8–12 mg/l. Collect and handle specimens in the same way as for netilmicin.

Supply and administration

Some hospitals no longer routinely stock this antibiotic. Vials containing 80 mg in 2 ml can be supplied by the pharmacy on request. They currently cost £3-80 each. Smaller vials (costing £2-50) are stocked in some hospitals. IV doses do *not* need to be given slowly over 30 minutes.

References

- Nahata MC, Powell DA, Durrell DE, *et al.* Effects of gestational age and birth weight on tobramycin kinetics in newborn infants. *J Antimicrob Ther* 1984;**14**:59–65.
- Barclay ML, Begg EJ, Chambers ST, *et al.* Improved efficacy with nonsimultaneous administration of first doses of gentamicin and ceftazidime *in vitro*. *Antimicrob Agents Chemother* 1995;**39**:132–6.
- Daly JS, Dodge RA, Glew RH, *et al.* Effect of time and temperature on inactivation of aminoglycosides by ampicillin at neonatal dosages. *J Perinatol* 1997;**17**:42–5.
- Skopnick H, Heimann G. Once daily aminoglycoside dosing in full term neonates. *Pediatr Infect Dis J* 1995;**14**:71–2.
- de Hoog M, Schoemaker RC, Mouton JW, *et al.* Tobramycin population pharmacokinetics in neonates. *Clin Pharmacol Ther* 1997;**62**:392–9.
- Ratjen F, Dring G, Nikolaizik WH. Effect of inhaled tobramycin on early *Pseudomonas aeruginosa* colonisation in patients with cystic fibrosis. *Lancet* 2001;**358**:983–4.
- de Hoog M, van Zanten BA, Hop WC, *et al.* Newborn hearing screening: tobramycin and vancomycin are not risk factors for hearing loss. *J Pediatr* 2003;**142**:41–6.

TOLAZOLINE

Use

A single dose of tolazoline will often correct pulmonary artery vasospasm when this causes severe right-to-left shunting soon after birth. The dose recommended here seldom causes systemic hypotension.

Pharmacology

Tolazoline is an α adrenergic antagonist that produces both pulmonary and systemic vasodilatation. The first paper to describe neonatal use appeared in 1979. Several papers now attest to the drug's ability to improve systemic arterial oxygen tension in some critically ill babies with a transitional circulation, especially where there is clear evidence of pulmonary hypertension. Anecdotal evidence suggests that the drug works best once serious acidosis ($\text{pH} < 7.2$) is corrected. Continuous infusion is not nearly as necessary as was once thought, because the half life exceeds 6 hours. Babies given a continuous tolazoline infusion must have their blood pressure measured periodically, but systemic hypotension should be rare with the dose recommended here. Many texts have recommended higher doses and sustained treatment, but this can be cardiotoxic, and, since tolazoline is actively excreted by the kidney but not otherwise metabolised by the baby, such problems will be exacerbated by renal failure. Other side effects of tolazoline include sympathomimetic cardiac stimulation, parasympathomimetic gastrointestinal symptoms, and increased gastric secretion due to a histamine-like action. The skin may take on an alarmingly blotchy appearance. Transient oliguria and gastric bleeding have been reported.

Management of pulmonary artery vasospasm

A single bolus dose of tolazoline is quite often all that is required to stop a "vicious circle" developing, with hypoxia and acidosis fuelling a further increase in pulmonary vascular tone, especially in the period immediately after birth, although the first priority must always be to optimise ventilator management. Raising the pH above 7.5 by a combination of mild hyperventilation (pCO_2 3.5–4.5 kPa) and IV sodium bicarbonate or THAM (q.v.) is often the most potent and physiological way of influencing pulmonary vascular tone. Nitric oxide (q.v.) is frequently effective in babies of ≥ 34 weeks gestation, but it is a complex treatment strategy to deliver and many use it if tolazoline fails. Epoprostenol (q.v.) may be tried when tolazoline proves ineffective, but it is seldom of lasting benefit. Systemic hypotension and/or a high right atrial pressure causing right-to-left ductal, or interatrial, shunting, may be a more important factor than a high pulmonary vascular tone in some babies with a "transitional" circulation. In such circumstances dobutamine (q.v.) with or without adrenaline (q.v.) may be more effective. Magnesium sulphate (q.v.) is still used by some, but seldom has any rapid impact.

Drug interactions

The use of an H_2 blocker such as cimetidine or ranitidine prophylactically, to minimise the risk of gastric bleeding, renders tolazoline ineffective as a vasodilator.

Treatment

IV correction of pulmonary vasospasm: Give 1 mg/kg IV over 2–4 minutes while watching for systemic hypotension. It is just occasionally necessary to sustain this by giving 200 micrograms/kg per hour IV diluted in a little saline or 10% dextrose. Prepare a fresh solution daily.

Endotracheal administration: While administration by this route is still under evaluation, there are now several reports that this strategy can be successful. It certainly makes systemic side effects less likely. Try 200 micrograms/kg diluted in 0.5–1 ml of 0.9% sodium chloride.

Use to correct peripheral vasospasm: Low dose infusion (even as little as 20 micrograms/kg per hour) may serve to correct local systemic arterial vasospasm caused by an indwelling arterial line.

Compatibility

Tolazoline can be added (terminally) into a line containing standard TPN when necessary, and into a line containing dobutamine and/or dopamine or vancomycin (q.v.). Do not add to a line containing lipid.

Supply

Ampoules containing 25 mg in 1 ml are available from the manufacturers, on special order, for £1-40.

References

- Ward RM. Pharmacology of tolazoline. *Clin Perinatol* 1984;**11**:703–13.
- Ward RM, Daniel CH, Kendig JW. Oliguria and tolazoline pharmacokinetics in the newborn. *Pediatrics* 1986;**77**:307–15.
- Bush A, Busst CM, Knight WB, et al. Cardiovascular effects of tolazoline and ranitidine. *Arch Dis Child* 1987;**62**:241–6.
- Lemke RP, al Saedi SA, Belik J, et al. Use of tolazoline to counteract vasospasm in peripheral arterial catheters in neonates. *Acta Paediatr* 1996;**85**:1497–8.
- Parida SK, Baker S, Kuhn R, et al. Endotracheal tolazoline administration in neonates with persistent pulmonary hypertension. *J Perinatol* 1997;**17**:461–4.
- Nuntnarumit P, Korones SB, Yang W, et al. Efficacy and safety of tolazoline for treatment of severe hypoxemia in extremely preterm infants. *Pediatrics* 2002;**109**:852–6.

Use

Trimethoprim is widely used to limit the risk of urinary infection in babies with ureteric reflux or a structural renal tract abnormality. It is also a useful oral antibiotic in the management of many aerobic Gram positive and Gram negative infections.

Pharmacology

While trimethoprim is licensed for neonatal use only "under careful medical supervision", the drug is now very widely used both to prevent and to treat urinary tract infection in infancy and throughout childhood (although there is little controlled trial evidence to support prophylaxis). Trimethoprim works by inhibiting steps in the synthesis of tetrahydrofolic acid, an essential metabolic cofactor in the synthesis of DNA by bacteria. Adverse effects are rare. Prolonged treatment in adults can rarely cause bone marrow changes, but extensive experience confirms that there is no need to subject young children on sustained low dose prophylaxis to routine blood testing. A combined preparation with sulphamethoxazole (called co-trimoxazole (q.v.)) has occasionally proved of value in the management of pneumonia and meningitis. Both drugs are known to penetrate the lung, kidney, and cerebrospinal fluid extremely well. There is, however, no evidence that co-trimoxazole is better than trimethoprim in the prevention, or treatment, of renal tract infection, and trimethoprim has been marketed for use on its own since 1979.

Trimethoprim is well absorbed by mouth, widely distributed ($V_d > 1$ l/kg), and excreted, largely unmetabolised, in the urine, especially in the neonatal period. Dosage should be halved after 2 days of treatment, therefore, in the presence of severe renal failure. The half life in the neonate is very variable but averages 18 hours at birth, falling rapidly to only 4 hours within 2 months, before increasing once more to about 11 hours in adults. Trimethoprim crosses the placenta, so it should be avoided where possible in the first trimester of pregnancy, because of its teratogenic potential as a folate antagonist. When taken during lactation the baby receives about a tenth of the weight related maternal dose.

Urinary tract infection

Neonatal infection is uncommon but easily missed. Bag specimens are very misleading, but urine obtained from a collection pad can make bladder tap unnecessary. Immediate direct examination under a phase contrast microscope, looking for bacteria rather than cells, can provide a prompt working diagnosis, and eliminate many of the "false positive" diagnoses generated by routine laboratory culture. Infants with a proven infection need investigation with renal ultrasound, a micturating cystogram, and a delayed succimer (dimercaptosuccinic acid or DMSA) radioisotope scan to look for reflux or structural urinary tract abnormality. Consider prophylaxis until structural abnormality is confirmed or disproved.

Guthrie test screening

Trimethoprim interferes with the Guthrie test for phenylketonuria. It may be best to delay prophylaxis, therefore, until the Guthrie test has been taken; when this is not appropriate, a venous blood sample should be sent to the biochemistry laboratory so that the phenylalanine level can be measured and the screening laboratory then notified of the outcome.

Prophylaxis

Give 2 mg/kg once a day. Evening administration in older children will generate a peak drug level at the time when infrequent nocturnal bladder emptying makes infection more likely.

Treatment

A loading dose of 3 mg/kg, either IV or by mouth, followed by 1 mg/kg twice a day, is widely used to treat urinary infection in the neonatal period. One week's treatment is usually enough. By 6 weeks of age babies require 3 mg/kg twice a day (three times a day for non-renal infection).

Supply

A sugar-free oral preparation (Monotrim[®]) containing 10 mg/ml that can be stored at room temperature (5–25°C) is available costing £1.80 for 100 ml. It remains stable for 2 weeks if further diluted with water or sorbitol. The only commercial IV preparation has recently been withdrawn, but a formulation also containing sulphamethoxazole is still available, as outlined in the co-trimoxazole monograph.

References

- Hoppe K. Age differences in trimethoprim pharmacokinetics: need for revised dosing in children? *Clin Pharmacol Ther* 1987;**41**:336–43.
- Hoppu K. Changes in trimethoprim pharmacokinetics after the newborn period. *Arch Dis Child* 1989;**64**:343–5.
- Smellie JM, Gruneberg RN, Bantock HM, *et al*. Prophylactic co-trimoxazole and trimethoprim in the management of urinary tract infection in children. *Pediatr Nephrol* 1988;**2**:12–7.
- Vickers D, Ahmad T, Coulthard MG. Diagnosis of urinary tract infection in children; fresh urine microscopy or culture? *Lancet* 1991;**338**:767–70. (See also 1994;**344**:612.)
- Anon. The management of urinary tract infection in children. *Drug Ther Bull* 1997;**35**:65–9.
- Larcome J. Urinary tract infection. *Clin Evid* 2002;**8**:406–20 (and updates). [SR]

See also relevant Cochrane reviews



UROKINASE

Use

Urokinase can clear clotted catheters and shunts, and speed the drainage of a pleural empyema. Streptokinase or alteplase (q.v.) are more frequently used to lyse intravascular thrombi.

Pharmacology

Urokinase is an enzyme derived from human urine that directly converts plasminogen to the proteolytic enzyme plasmin. This then, in turn, converts the fibrin within any clot of blood or plasma into a range of soluble breakdown products. It was first isolated in 1947 and crystallised in 1965. Urokinase is rapidly metabolised by the liver (the circulating half life being about 15 minutes). It is often used to clear occluded intravascular catheters, and to lyse intraocular thrombi. Streptokinase has been more commonly used to treat intravascular thrombi, even though there is some suggestion that the risk of a hypersensitivity reaction may be higher. Continuous urokinase infusions are relatively expensive and, because plasminogen levels are relatively low in the neonatal period, high dose treatment may be necessary. A fresh frozen plasma (q.v.) infusion may help by providing additional plasminogen. The manufacturers do not recommend the use of urokinase during pregnancy or in the puerperium because of the possible risk of haemorrhage, but no problems have actually been reported in clinical practice.

A prompt infusion of urokinase-activated plasmin, or a concentrate of plasminogen obtained by fractionating human plasma, both seem to reduce morbidity and mortality from respiratory distress (hyaline membrane disease) in babies of less than 32 weeks gestation. However, despite evidence in its favour from a trial involving 500 babies in 1977, the strategy was never adopted in clinical practice or further evaluated. Concern for a possible increase in the risk of intracerebral haemorrhage may be one reason. How the specially prepared product works remains unclear. It has been suggested that the provision of additional plasminogen may speed the resorption of fibrin from the lungs of babies with surfactant deficiency (the "hyaline membranes" found in the alveoli at postmortem).

Other strategies for blocked catheters

Instilling enough sterile 0.1 molar hydrochloric acid to fill the catheter dead space will usually clear any block caused by calcium or phosphate deposition. A similar quantity of 70% ethanol will often clear a block due to lipid. Alteplase can be used to unblock thrombosed central venous catheters.

Treatment

Blocked catheters: 5000 or 10,000 units of urokinase made up in 2 ml of 0.9% sodium chloride can be used to try to unblock a thrombosed intravascular catheter or shunt. The usual procedure is to instil and leave the urokinase in the catheter for 2 hours. Aspirate the urokinase before then attempting to flush the catheter with heparinised saline with a view to resuming the original infusion.

Vascular thrombi: Try a dose of 5000 units/kg per hour, and consider increasing the dose two- or even fourfold if blood flow does not improve within 8 hours.

Pleural empyema: Inject 10,000 units in 10 ml saline; drain after 4 hours. Repeat twice daily for 3 days.

Antidote

Tranexamic acid can control bleeding by inhibiting the activation of plasminogen to plasmin. Try an IV infusion of 10 mg/kg over 10 minutes and repeat if necessary after 8–12 hours.

Supply and administration

Although production has recently ceased in North America, it continues in Germany, and vials containing 25,000 units of urokinase (costing £29) could be made available from the pharmacy. Reconstitute with 1 ml of water for injection and then dilute to 5 ml with 0.9% sodium chloride to obtain a solution containing 5000 units/ml. The solution is fully stable for only 12 hours after reconstitution. 100,000 unit vials are also available; they should be reconstituted with 2 ml of water for injection. To give 5000 units/kg per hour place in a syringe 1 ml of the reconstituted solution from a 100,000 unit vial for each kilogram the baby weighs, dilute to 10 ml with 0.9% sodium chloride, and infuse at a rate of 1 ml/hour.

500 mg (5 ml) ampoules of tranexamic acid are available for £1.30.

References

- Ambrus CM, Choi TS, Cunnanan E, *et al.* Prevention of hyaline membrane disease with plasminogen. *JAMA* 1977;**237**:1837–41. [RCT]
Wever M, Liem K, Geven W, *et al.* Urokinase therapy in neonates with catheter related central venous thrombosis. *Thromb Haemost* 1995;**73**:180–5.
Werlin SL, Lausten T, Jessen S, *et al.* Treatment of central venous catheter occlusions with ethanol and hydrochloric acid. *J Parenter Enteral Nutr* 1995;**19**:416–18.
Rimensberger PC, Humbert JR, Beghetti M. Management of preterm infants with intracardiac thrombi. *Paediatr Drugs* 2001;**3**:883–98.
Thomson AH, Hull J, Kumar MR, *et al.* Randomised trial of intrapleural urokinase in the treatment of childhood empyema. *Thorax* 2002;**57**:343–7. [RCT]

Use

Ursodeoxycholic acid is used to improve bile acid dependent bile flow in babies with cholestasis due to biliary atresia and cystic fibrosis, and as a complication of parenteral nutrition. Treatment often relieves the severe itching (pruritus) this can cause, even when it does not retard disease progression.

Pharmacology

Ursodeoxycholic acid is a naturally occurring bile acid first isolated by Shoda in Japan in 1927. Small quantities are excreted in human bile and then reabsorbed from the gastrointestinal tract (enterohepatic recirculation). It suppresses the synthesis and secretion of cholesterol by the liver and the intestinal absorption of cholesterol. A trial in 1980 showed that it could be used to effect the slow dissolution of symptomatic cholesterol rich gallstones in patients reluctant to undergo surgery or lithotripsy.

Ursodeoxycholic acid has also been employed in the management of a number of other conditions, although such use has not been endorsed by the manufacturer, who does not, for example, recommend its use during pregnancy, although treatment with 1 g/day is increasingly being used in patients with intrahepatic cholestasis. Several reports now attest to the drug's ability to reduce the intense itching and to reverse the laboratory signs of liver damage, although controlled trial evidence that it improves perinatal outcome is still limited. Safe use has also been reported in a patient with primary biliary cirrhosis who took the drug throughout pregnancy. Nothing is known about its use during lactation, but it seems unlikely to cause a problem. Reports suggest that the drug is of benefit in some babies with cholestasis due to biliary atresia, cystic fibrosis, and Alagille syndrome, although it is less clear whether it delays the development of cirrhotic liver damage. Unfortunately, while it may reduce the serum bilirubin level in babies who are developing cholestasis as a complication of prolonged parenteral nutrition, liver enzyme levels usually remain high. Side effects are uncommon, although intestinal discomfort may occur when the drug is first introduced, and diarrhoea has occasionally been reported.

Neonatal hepatitis

A wide range of individually uncommon conditions cause inflammatory liver disease in infancy and can interfere with bile flow ("cholestatic" liver disease). Although the word "hepatitis" is often used when describing all these conditions, few are infectious in origin. Breastfed babies often have prolonged mild jaundice (10% are still clinically jaundiced at 1 month), but even mild jaundice merits review if the stools become grey or putty coloured rather than yellow or green. This is even more true of the bottle fed baby, especially if the jaundice has a significant conjugated component (over 20 µmol/l). Biliary atresia (a rare, poorly understood, condition causing perinatal bile duct obliteration in one baby for every 15,000 born) is surgically treatable if diagnosed within 8 weeks of birth. No specific treatment is available for most other conditions but it is important to prevent fat soluble vitamin deficiency. Vitamin K deficiency, in particular, can cause potentially lethal intracranial bleeding. Phenobarbital, and rifampicin (q.v.) are useful, widely employed, alternatives to ursodeoxycholic acid for controlling pruritus.

Treatment

Give 15 mg/kg by mouth once a day. Doses twice as large as this have occasionally been employed.

Supply and administration

Ursodeoxycholic acid is available as a sugar-free suspension containing 50 mg/ml; 100 ml costs £12.10. 150 mg tablets (costing 30p) and 250 mg capsules (costing 50p) are also available.

References

- Rudi J, Schonig T, Stremmel W. Therapie mit Ursodeoxycholsäure bei primär biliärer Zirrhose während der Schwangerschaft. *Z Gastroenterol* 1996;**34**:188–91.
- Palma J, Reyes H, Ribalta J, et al. Ursodeoxycholic acid in the treatment of cholestasis of pregnancy: a randomised double-blind study controlled with placebo. *J Hepatol* 1997;**27**:1022–8. [RCT]
- Balisteri WF. Bile acid therapy in pediatric hepatobiliary disease: the role of ursodeoxycholic acid. *J Pediatr Gastroenterol Nutr* 1997;**24**:573–89.
- Scher H, Bishop WP, McCray PB Jr. Ursodeoxycholic acid improves cholestasis in infants with cystic fibrosis. *Ann Pharmacother* 1997;**31**:1003–5.
- Crofts DJ, Michel VJ-M, Rigby AS, et al. Assessment of stool colour in community management of prolonged jaundice in infancy. *Acta Paediatr* 1999;**88**:869–74.
- McKiernan PJ, Baker AJ, Kelly DA. The frequency and outcome of biliary atresia in the UK and Ireland. *Lancet* 2000;**355**:25–9.
- Milkiewicz P, Elias ER, Williamson C, et al. Obstetric cholestasis [Editorial]. *BMJ* 2002;**324**:123–4.
- Jenkins JK, Boothby LA. Treatment of itching associated with intrahepatic cholestasis of pregnancy. *Ann Pharmacother* 2002;**36**:1462–5. [SR]
- Heubi JE, Wiechmann DA, Creutzinger V, et al. Tauroursodeoxycholic acid (TUDCA) in the prevention of total parenteral nutrition-associated liver disease. *J Pediatr* 2002;**141**:237–42.
- McKiernan PJ. Neonatal cholestasis. *Semin Neonatal* 2002;**7**:153–65.

See also relevant Cochrane reviews



Use

Sodium valproate has been widely used in the treatment of several types of epilepsy since 1974, but it has only rarely been used in the neonatal period, as yet, because of its potential liver toxicity.

Pharmacology

Sodium valproate has a unique chemical structure. Its mode of action is not fully understood, although it may involve the modification of gamma-aminobutyric acid behaviour in the brain. It is slowly but completely absorbed by mouth, although peak levels are not reached for 3–8 hours in the newborn. It is highly protein bound and undergoes hepatic metabolism. Sodium valproate has a long half life (10–67 hours) at birth, which falls to 7–13 hours by 2 months.

Severe liver toxicity has been reported in infants and young children, and valproate should be used only with great caution in children less than 2 years old. Nausea, vomiting, lethargy, and coma can occur, as can reversible neutropenia and thrombocytopenia. Such problems usually develop soon after treatment is started, but they sometimes appear after 3–6 months. Hyperglycaemia may occur; this has been reported in an infant whose mother was treated during pregnancy. Treatment with 100 mg/kg per day of L-carnitine IV improves survival. Respiratory support may be needed in severe cases.

Sodium valproate crosses the placenta and is known to be teratogenic. A constellation of dysmorphic features has been ascribed to valproate exposure in pregnancy. Feeding problems and irritability seem to be common immediately after birth, and hypoglycaemia has been reported. Some of these difficulties may be dose related. Longer term developmental problems have also been described and, where this has been documented, subsequent siblings may be at increased risk. The risk involved in taking anticonvulsants during pregnancy and lactation is further discussed in the website commentary. Cardiac problems may occur, and 1–2% of these babies have a neural tube defect. In consequence, when valproate has been used during early pregnancy, it is important to undertake serum α fetoprotein screening for spina bifida and also arrange for expert ultrasound screening of the fetal spine at 18 weeks gestation. Amniocentesis may be necessary in addition if obesity or fetal posture makes detailed examination difficult. High dose folate prophylaxis may be appropriate (4 mg per day), but this needs to be started before conception. Maternal use does not seem to cause hypoprotrombinaemia requiring neonatal vitamin K (q.v.) prophylaxis at birth in the same way as most other "first line" anticonvulsant drugs, but afibrinogenaemia has been described. Breastfeeding is not contraindicated because the baby will receive only 5% of the maternal dose when intake is calculated on a weight for weight basis.

Drug interactions

Treatment with valproate substantially increases the half life of phenobarbital.

Treatment

Experience with the neonatal use of sodium valproate remains *extremely* limited. A loading dose of 20 mg/kg followed by 10 mg/kg every 12 hours has been suggested. It can be given orally or IV. Watch for hyperammonaemia during the first week of administration and suspend treatment at least temporarily if the serum ammonia level exceeds 350 $\mu\text{mol/l}$. The dose used needs to be guided by blood levels in early infancy because of the way drug clearance changes over time.

Blood levels

The immediate predose serum concentration will usually be between 40 mg/l and 100 mg/l (1 mg/l = 6.93 $\mu\text{mol/l}$). However, while monitoring may help to identify non-compliance, it seldom helps to optimise treatment. Levels can be measured in 50 μl of plasma (c. 150 μl of heparinised whole blood).

Supply

Sodium valproate is available as a red, sugar-free liquid (£2 for 100 ml) containing 40 mg/ml. The pharmacy could provide a diluted syrup but the shelf life is only 2 weeks. An IV preparation in powder form (a 400 mg vial with 4 ml of diluent costing £9.60) is also available. The reconstituted solution (containing 100 mg/ml) is compatible with IV dextrose and dextrose saline but the resultant solution should not be mixed with any other drug.

References

- Koch S, Jäger-Roman E, Lösche G, *et al.* Antiepileptic drug treatment during pregnancy: drug side effects in the neonate and neurological outcome. *Acta Paediatr* 1996;**85**:739–46.
- Bohan TP, Helton E, König S, *et al.* Effect of L-carnitine treatment for valproate-induced hepatotoxicity. *Neurology* 2001;**56**:1405–9.
- Williams G, King J, Cunningham M, *et al.* Fetal valproate syndrome and autism: additional evidence of an association. *Devel Med Child Neurol* 2001;**43**:202–6. (See also p. 847.)
- Adab N, Jacoby A, Smith D, *et al.* Additional educational needs in children born to mothers with epilepsy. *J Neurol Neurosurg Psychiatry* 2001;**70**:15–21.

See also relevant Cochrane reviews



Use

Vancomycin and teicoplanin (q.v.) are widely used to treat systemic staphylococcal infection with organisms resistant to flucloxacillin and/or gentamicin (q.v.). Consider giving rifampicin (q.v.) as well.

Pharmacology

The glycopeptide antibiotic vancomycin, first isolated in 1956, is bactericidal to most Gram positive organisms, but inactive against Gram negative organisms. The drug is very poorly absorbed by mouth and causes pain and tissue necrosis when given IM. It crosses the placenta and penetrates most body fluids reasonably well, but enters the cerebrospinal fluid (CSF) to any extent only when the meninges are inflamed. Rapid IV infusions cause erythema and intense pruritis due to histamine release (the so called "red man syndrome"), and may cause dangerous arrhythmia, while concentrated solutions cause thrombophlebitis. There is no evidence of renal or auditory toxicity in animals, and most clinical case reports of problems have involved patients who are also taking aminoglycosides (suggesting that damage was wrongly attributed, or that combined use increases the risk). Vancomycin is excreted virtually unchanged in the urine, and has to be given with caution in patients with poor renal function. The serum half life is 4–10 hours at birth, later falling to 2–4 hours (6–8 hours in adults). There is no evidence that its use during pregnancy or lactation is hazardous to the baby.

Initially sensitive organisms only occasionally develop drug resistance, but the synergistic combination of vancomycin and rifampicin minimises this risk. Similar combined treatment is also particularly useful in managing catheter and shunt related coagulase negative staphylococcal infection. Oral prophylaxis (15 mg/kg every 8 hours for 7 days) can decrease the risk of necrotising enterocolitis, as can an oral aminoglycoside. Adding 25 micrograms of vancomycin to each ml of TPN can, similarly, reduce the risk of catheter related staphylococcal infection, but all such policies risk encouraging the proliferation of multiresistant bacteria. Teicoplanin has been used IV in the same way.

Treatment

IV treatment: Give 15 mg/kg (3 ml/kg of the dilute solution made up as described below) IV over 60 minutes pickbacked onto an existing IV infusion of dextrose or dextrose saline. Give one dose every 24 hours in babies of 28 weeks or less, one dose every 12 hours in babies of 29–35 weeks, and one dose every 8 hours in babies of 36 or more weeks postmenstrual (gestational plus postnatal) age. Monitor the trough level if there is renal failure or treatment does not seem to be working, and adjust the dosage interval as necessary.

Intrathecal use: Intraventricular injections (and the additional use of rifampicin) should be considered if CSF cultures remain positive 48 hours after starting treatment. The normal neonatal dose is 1 ml of the normal IV preparation containing 5 mg of vancomycin once every day, or every other day (2–3 doses should suffice). Check the CSF drug level before sustained use and aim for a level of 30–50 mg/l.

Blood levels

The need for routine monitoring is being increasingly questioned. Efficacy is assured by maintaining a trough level of 5–10 mg/l (1 mg/l = 0.67 μ mol/l). Collect at least 0.5 ml of blood when the next dose falls due.

Compatibility

Vancomycin may be added (terminally) to TPN when absolutely necessary, and mixed (terminally) with insulin, midazolam, or morphine. Do not mix vancomycin with IV gelatin.

Supply

Stock 500 mg vials cost £6-70 each. Add 9.7 ml of sterile water for injections to the dry powder to get a solution containing 50 mg/ml. Individual doses are prepared by drawing 1 ml of this reconstituted (50 mg/ml) solution into a syringe and diluting to 10 ml with 10% dextrose or dextrose saline to provide a solution containing 5 mg/ml. The fluid has a pH of 2.8–4.5.

References

- Cantú TG, Yamanaka-Yuen NA, Lietman PS. Serum vancomycin concentrations: reappraisal of their clinical value. *Clin Infect Dis* 1994;**18**:533–43. (See also pp. 544–6.)
- Shay DK, Goldmann DA, Jarvis WR. Reducing the spread of antimicrobial-resistant microorganisms. Control of vancomycin-resistant enterococci. *Pediatr Clin North Am* 1995;**42**:703–16.
- Siu YK, Ng PC, Fung SCK, et al. Double blind, randomised, placebo controlled study of oral vancomycin in prevention of necrotising enterocolitis in preterm, very low birthweight infants. *Arch Dis Child* 1998;**79**:F105–9. [RCT]
- Capparelli EV, Lane JR, Romanowski GL, et al. The influences of renal function and maturation on vancomycin elimination in newborns and infants. *J Clin Pharmacol* 2001;**41**:927–34.
- Tan W-H, Brown N, Kelsall AW, et al. Dose regimen for vancomycin not needing serum peak levels? *Arch Dis Child* 2002;**87**:F214–16.
- de Hoog M, van Zanren BA, Hop WC, et al. Newborn hearing screen: tobramycin and vancomycin are not risk factors for hearing loss. *J Pediatr* 2003;**142**:41–6.

See also relevant Cochrane reviews



VARICELLA-ZOSTER IMMUNOGLOBULIN

Use

Varicella-zoster immunoglobulin (VZIG or ZIG) is used to provide passive immunity to chickenpox.

Pharmacology

This product is prepared from the pooled plasma of HIV, hepatitis B, and hepatitis C negative blood donors in the UK with a recent history of chickenpox or shingles. The product has a minimum potency of 100 units/ml of varicella-zoster antibody. Supplies are limited. Normal immunoglobulin offers some protection. No comparable product is available for treating herpes simplex virus (HSV) infection.

Chickenpox

Primary infection with the varicella-zoster virus (or human herpes virus 3) causes chickenpox. Reactivation of the latent virus causes herpes zoster (shingles); vesicles then appear in the skin area served by the spinal nerve ganglia where the virus has lain dormant. Spread is by droplet or contact causing infection after an incubation period of 10–21 (usually 14–17) days, people with chickenpox being infectious for about 1 week (from 1–2 days before the rash appears until all the vesicles have encrusted). The illness in children is usually less severe than in adults. Of women of childbearing age in the UK, 95% have lasting immunity as a result of natural infection during childhood. Chickenpox during pregnancy can cause severe pulmonary disease (although selective reporting may have led to the magnitude of the risk being exaggerated). Illness late in the first half of pregnancy also exposes the fetus to a 1–2% risk of embryopathy. Lesions include cicatricial skin scarring and limb hypoplasia; central nervous system and eye lesions also occur. No technique has yet been developed for identifying whether the fetus has been affected or not. Infection shortly before birth exposes the baby to the risk of severe neonatal infection. The babies at greatest risk are those delivered 2–4 days before or after the onset of maternal symptoms; such babies have been exposed to a massive viraemia but have not had time to benefit from placentally transferred maternal antibody. These babies are at risk of multiorgan involvement and death from necrotising pneumonia. They need *urgent* treatment with VZIG and careful monitoring for the next 2 weeks. Try to delay labour for at least 3 days if the mother develops a typical rash shortly before delivery is due. Shingles during pregnancy presents little hazard to the baby.

An attenuated live varicella vaccine (costing £95) is now available in the UK on a “named patient” basis. Vaccination should certainly be considered in non-immune children with leukaemia or a transplant because the use of immunosuppressant drugs puts these children at risk of life threatening infection. Even postexposure vaccination seems to work if carried out within 2–3 days of the exposure. There are suggestions that vaccination should also be offered to women who are contemplating pregnancy but have no natural immunity to chickenpox (the cost effectiveness of such an approach being influenced by the likelihood of the woman being exposed to the virus during pregnancy). Universal vaccination is now being recommended in many countries, including North America.

Prophylaxis

Give an immediate dose of VZIG IM to:

- women with no serological immunity to chickenpox who are exposed to the virus while pregnant
- babies born within 7 days of the onset of maternal chickenpox
- babies of mothers developing chickenpox within 7 days of delivery
- babies exposed to chickenpox or shingles within 28 days of birth who were < 30 weeks gestation at birth, or whose mothers have no history of having had chickenpox, and no serological immunity.

The neonatal dose is 250 mg; the maternal dose is 1 g.

It may also be appropriate to give IV aciclovir (q.v.) to mothers developing chickenpox around the time of birth, to limit the viraemia, although only limited evidence yet exists to suggest that this is effective. The baby certainly merits similar early treatment if symptomatic, to limit the severity of the infection.

Supply and administration

VZIG is available from the local public health laboratory. Ampoules containing 250 mg in 1.7 ml for IM use should be stored at 4°C, but they are sufficiently heat stable to withstand dispatch by post. Ampoules have a nominal shelf life of 3 years; they must not be frozen.

References

- UK Health Departments. *Immunisation against infectious disease*. Chapter 34. London: HMSO, 1996:251–61.
- Gershon A. Varicella: to vaccinate or not to vaccinate. *Arch Dis Child* 1998;**79**:470–1. (See also pp. 473–7.)
- Royal College of Obstetricians and Gynaecologists. *Clinical Green Top Guideline. Chickenpox in pregnancy*. (See the Good Practice guideline issued in 2001 on the College website: www.rcog.org.uk)
- Forrest JM, Mego S, Burgess MA. Congenital and neonatal varicella in Australia. *J Paediatr Child Health* 2000;**36**:108–13.
- American Academy of Pediatrics. Committee on Infectious Diseases. Varicella vaccine update. *Pediatrics* 2000;**105**:136–41.
- Chartrand SA. Varicella vaccine. *Pediatr Clin North Am* 2000;**47**:373–94.

Use

Vasopressin (AVP), and its long acting analogue desmopressin (DDAVP), act to limit water loss in the urine. Artificially high levels of vasopressin given IV can cause arteriolar vasoconstriction.

Pharmacology

Vasopressin and oxytocin (q.v.) are natural hormones produced by the posterior lobe of the pituitary gland. Arginine-vasopressin is a nine peptide molecule first synthesised in 1958, with a structure very similar to that of oxytocin that acts to increase the reabsorption of solute free water from the distal tubules of the kidney. It is also sometimes known as the antidiuretic hormone (ADH). High (supraphysiological) blood levels cause a rise in blood pressure due to arteriolar vasoconstriction, hence the name vasopressin. Evidence is accumulating that, in septic or postoperative shock with hypotension and vasodilation resistant to treatment with catecholamines such as adrenaline (q.v.), natural AVP levels sometimes become depleted. In this situation even a modest dose of AVP can resensitise the vessels to catecholamine, raising blood pressure without threatening tissue perfusion.

DDAVP is a synthetic analogue of AVP with a longer functional half life and enhanced diuretic potency, but little vasoconstrictor potency. DDAVP (unlike AVP) is only partially inactivated when given by mouth, making oral treatment possible (although the dose required varies greatly). Treatment is usually necessary only once or twice a day. DDAVP stimulates factor VIII production, and a 0.4 micrograms/kg IV dose is enough to produce a fourfold rise in patients with only moderately severe haemophilia (factor VIII levels $\geq 7\%$) within 30 minutes. Maternal treatment with AVP, which is inactivated by placental vasopressinase and destroyed by trypsin in the gut, is very unlikely to affect the baby, and reports show that DDAVP can also be used during pregnancy and lactation with confidence when clinically indicated.

Diabetes insipidus

The polyuria seen in diabetes mellitus is caused by loss of sugar in the urine (the word mellitus indicating that the urine is sweet or honey-like). Any failure of AVP production causes the kidney to pass large quantities of *unsweet* (insipid) urine, hence the term diabetes insipidus. Similar symptoms can be caused by hormone insensitivity (nephrogenic diabetes insipidus). Inappropriately dilute urine (a urine osmolality of <300 mosmol/kg when plasma osmolality exceeds this value) makes diabetes insipidus likely, and the response to a dose of DDAVP clinches the diagnosis. Midline cranial anomalies, infection, and haemorrhage account for most cases of neonatal intracranial diabetes insipidus. Most mild cases are best managed by merely altering fluid intake. Insufficiency is sometimes only transient.

Treatment

Vasopressin: Treat severe vasodilatory shock (i.e. hypotension resistant to 200 nanograms/kg per minute of adrenaline with adequate vascular filling and peripheral perfusion, and a good cardiac output) with 0.02 units/kg per hour of vasopressin (0.2 ml/hour of a solution made up as described below). Increase this, if hypotension persists, by stages, to no more than 0.1 units/kg per hour (1 ml/hour). One tenth of this dose is enough to control the diabetes insipidus sometimes triggered by brain injury.

Desmopressin: The impact of treatment is difficult to predict, and it is very important to give a low starting dose. In babies with cranial diabetes insipidus this should be 1–4 micrograms orally, 0.1–0.5 micrograms into the nose, or 0.1 micrograms IM, irrespective of body weight. A second dose should be given only when the impact of the first has been assessed. Monitor fluid balance with great care and adjust the size (and timing) of further doses as necessary. Avoid changing the route of administration unnecessarily. Obtain expert endocrine advice, especially if there is co-existent hypoadrenalism.

Supply and administration

Vasopressin: A 1 ml 20 unit (49 microgram) ampoule of synthetic vasopressin (argipressin [rINN]) for IV use costs £17. Store at 4°C. To give 0.01 units/kg per hour take 0.1 ml of this fluid for each kilogram the baby weighs, dilute to 20 ml with dextrose or dextrose saline, and infuse at a rate of 0.1 ml/hour.

Desmopressin: 1 ml (4 microgram) ampoules of desmopressin suitable for subcutaneous, IM, or oral use cost £1.20. Store ampoules at 4°C. To obtain a 1 microgram/ml solution for more accurate low dose administration take the contents of this ampoule and dilute to 4 ml with 0.9% sodium chloride. If this dilute solution is to be given into the nose or mouth it can be stored for up to 1 week at 4°C. 2.5 ml dropper bottles of a 100 micrograms/ml multidose intranasal solution cost £10.40. These can be kept for 2 weeks at room temperature. Do *not* dilute further. 100 microgram dispersible tablets cost 52p each.

References

- Ray JG. DDAVP use during pregnancy: an analysis of its safety for mother and child. *Obstet Gynaecol Survey* 1998;**53**:450–5.
 Rossenzweig EB, Starc TJ, Chen JM, *et al.* Intravenous arginine-vasopressin in children with vasodilatory shock after cardiac surgery. *Circulation* 1999;**100**(suppl II):182–6.
 Stapleton G, DiGeronimo RJ. Persistent central diabetes insipidus presenting in a very low birth weight infant successfully managed with intranasal dDAVP. *J Perinatol* 2000;**2**:132–4.
 Landry DW, Oliver JA. The pathogenesis of vasodilatory shock [Review]. *N Engl J Med* 2001;**345**:588–95.
 Cheetham TD, Baylis P. Diabetes insipidus in children. Pathophysiology, diagnosis and management. *Pediatr Drugs* 2002;**4**:785–96.

VECURONIUM

Use

Vecuronium is occasionally used instead of pancuronium (q.v.), to provide sustained muscle paralysis. Atracurium (q.v.) is a better alternative when only short term paralysis is required.

Pharmacology

Vecuronium bromide is a competitive non-depolarising muscle relaxant that came onto the market in 1980, as an alternative to pancuronium. The duration of action is not as long as that provided by a comparable dose of pancuronium. Vecuronium is slightly more expensive than pancuronium, but generates even less histamine release, and produces few or no adverse cardiovascular effects. It is rapidly taken up by the liver and partially metabolised prior to excretion, largely in the bile. Some of the metabolites, such as 3-desacetyl-vecuronium, which retain considerable neuromuscular blocking activity, are mostly excreted in the urine. The normal plasma elimination half life in adults is 30–60 minutes, but considerably (and sometimes unpredictably) longer than this in infancy, especially when high dose treatment is used. Renal failure seems to have relatively little clinical effect on the duration of neuromuscular blockade, but 25% of the drug is renally excreted and atracurium may be the best drug to use in a baby with severe renal failure and requiring paralysis. Concurrent treatment with an aminoglycoside may double the length of time this blockade lasts, making atracurium a better drug to use for short term paralysis. Treatment with magnesium sulphate (q.v.) may have a similar effect. The manufacturers recommend an initial test dose of 10–20 micrograms/kg. Placental transfer is limited, and doses of up to 100 micrograms/kg given to mothers requiring caesarean delivery seem to have no significant clinical effect on the baby.

Rocuronium, a more recently introduced analogue, has similar properties. A dose of 60 micrograms/kg IV is commonly employed. Paralysis is achieved as quickly as with suxamethonium (30 seconds), and much quicker than with vecuronium (120 seconds), but the duration of action of rocuronium and vecuronium is similar. The manufacturers have not yet endorsed neonatal use. Atracurium has an even slower onset of action (180 seconds).

Treatment

First dose: 100 micrograms/kg IV will cause prompt respiratory paralysis. Take a blood gas sample 20–30 minutes later to check for CO₂ accumulation. Restless babies who appear to be “fighting the ventilator” may have been contributing to their own ventilation because of inadequate artificial ventilatory support, in which case paralysis will only exacerbate the problem.

Further doses: Most babies continue to comply with the imposed ventilator rate as they wake from the first paralysing dose (especially if a moderately fast rate and a relatively short inspiratory time (< 0.7 seconds) is used) but a few require prolonged paralysis. The standard repeat dose is half the initial dose IV (or IM) every 2–4 hours as necessary, but some larger and older babies seem to require a higher maintenance dose. Babies who are paralysed should always also be sedated.

Antidote

Give a combination of 10 micrograms/kg of glycopyrronium (or 20 micrograms/kg of atropine) and 50 micrograms/kg of neostigmine IV, as outlined in the monograph on glycopyrronium.

Supply and administration

Vecuronium comes as a powder in 10 mg vials, with water for reconstitution. They cost £4.20 each. Dissolve the powder with 5 ml of sterile water (as supplied) to give a solution containing 2 mg/ml. Further dilute 0.5 ml of this solution with 0.5 ml of 0.9% sodium chloride or 5% dextrose in a 1 ml syringe to obtain a preparation containing 100 micrograms in 0.1 ml for accurate neonatal administration. Vials can, if necessary, be kept for up to 24 hours after reconstitution but, because the vials contain no preservative, material not used promptly is best discarded.

Rocuronium comes in 5 ml vials containing 10 mg/ml of rocuronium bromide. They cost £3.20 each. Take 0.1 ml and dilute to 1 ml with 0.9% sodium chloride or 5% dextrose to obtain a solution containing 100 micrograms in 0.1 ml for accurate neonatal administration.

References

- Meretoja OA, Wirtavouri K, Neuvonen PJ. Age-dependence of the dose-response curve of vecuronium in pediatric patients during balanced anesthesia. *Anesth Analg* 1988;67:21–6.
- Gravlee GP, Ramsey FM, Roy RC, et al. Rapid administration of a narcotic and neuromuscular blocker: a hemodynamic comparison of fentanyl, sufentanil, pancuronium and vecuronium. *Anesth Analg* 1988;67:39–47.
- Scheiber G, Ribeiro FC, Marichal A, et al. Intubating conditions and onset of action after rocuronium, vecuronium, and atracurium in young children. *Anesth Analg* 1996;83:320–4.
- Martin LD, Bratton SL, O'Rourke P. Clinical uses and controversies of neuromuscular blocking agents in infants and children. *Crit Care Med* 1999;27:1358–68.
- Playfor S. Neuromuscular blocking agents in critically ill children. *Paediatr Perinat Drug Ther* 2002;5:35–46.

Use

Vigabatrin has been used to manage epilepsy since 1989, and increasingly used, on its own, to treat infantile spasms since 1994. Young children given this drug must be monitored for retinal problems.

Pharmacology

Vigabatrin is a recently developed anticonvulsant currently licensed only for use as a secondary *additional* drug in the management of seizures resistant to other antiepileptic drugs. It is also being used on its own ("monotherapy") in the management of infantile spasms (West's syndrome), especially in children with tuberous sclerosis. It may also be of value in the management of partial seizures with, or without, secondary generalisation, and in infantile epileptic encephalopathy (Ohtahara syndrome). There does not appear to be any very clear dose–response relationship, and the plasma level seems to bear no relationship to the concentration in the central nervous system (CNS). It is not, therefore, either necessary or helpful to monitor drug levels. In West's syndrome responders usually show total spasm suppression (clinically and on electroencephalography (EEG)) within 4–7 days; if there has been no response within 7–10 days the drug can be withdrawn.

Vigabatrin is an amino acid with a structure similar to gamma-aminobutyric acid (GABA), a potent inhibitory neurotransmitter. It acts as an irreversible inhibitor of GABA transaminase, the enzyme responsible for degrading GABA. It is rapidly absorbed when given by mouth, achieving good bioavailability because of limited first pass metabolism in the liver. It is excreted mostly in the urine, with a plasma elimination half life of 5–10 hours in both infancy and adult life. Vigabatrin is given as a racemic mixture, but only the S(+) enantiomer is pharmacologically active. The drug penetrates the CNS, where levels seem to stabilise after about 2 weeks. Because the drug is neither plasma protein bound nor metabolised by the liver, it does not interact with, or influence, the metabolism of other anticonvulsants.

Adverse effects in infancy (usually drowsiness, irritability, and hypo- or hypertonia) are few and usually transient and mild, but those recommending usage of this drug should be aware that a significant number of children, as well as adults, develop retinal changes and visual field defects. These can easily go undetected in children too young to be able to report such problems for themselves. Little is known about the drug's potential teratogenicity in humans; high dose treatment in rabbits was associated with a slight increase in the incidence of cleft palate, but similar effects were not seen in rats. The baby will ingest only about 2% of the weight-adjusted maternal dose when breastfed.

A randomised controlled trial of the short term (14 month) outcome of treatment of infantile spasms with vigabatrin, prednisolone, or tetracosactide (q.v.) is recruiting in the UK, but some clinicians consider some of the treatment options controversial. For details contact the UKISS Office in Bath (Tel 01225 824 206).

Treatment

Start with a dose of 50 mg/kg twice a day by mouth. Increase this, if necessary, with EEG monitoring, to no more than 75 mg/kg twice a day after 3–6 days. Double the dosage interval if there is renal failure.

Supply

Vigabatrin is available as a white sugar-free powder in 500 mg sachets costing 50p each. The powder dissolves immediately in water, juice, or milk, giving a colourless, odourless, and virtually tasteless solution that is stable for at least 24 hours after reconstitution if kept refrigerated at 4°C. Dissolve the sachet in 20 ml of water to obtain a solution containing 25 mg/ml.

References

- Vauzelle-Kervroëdan FR, Rey E, Pons G, *et al.* Pharmacokinetics of the individual enantiomers of vigabatrin in neonates with uncontrolled seizures. *Br J Clin Pharmacol* 1996;**42**:779–81.
- Chiron C, Dumas C, Jambaqué I, *et al.* Randomized trial comparing vigabatrin and hydrocortisone in infantile spasms due to tuberous sclerosis. *Epilepsy Res* 1997;**26**:389–95. [RCT]
- Villeneuve N, Soufflet C, Plouin P, *et al.* Traitement des spasmes infantiles par vigabatrin en première intention et en monothérapie: à propos de 70 nourrissons. *Arch Pediatr* 1998;**5**:731–8.
- Tran A, O'Mahoney T, Rey E, *et al.* Vigabatrin: placental transfer *in vivo* and excretion into breast milk of the enantiomers. *Br J Clin Pharmacol* 1998;**45**:409–11.
- Appleton RE, Peters ACB, Mumford JP, *et al.* Randomised, placebo-controlled study of vigabatrin as first-line treatment of infantile spasms. *Epilepsia* 1999;**40**:1627–33. [RCT]
- Koo B. Vigabatrin in the treatment of infantile spasms. *Pediatr Neurol* 1999;**20**:106–10.
- Vigabatrin Paediatric Advisory Group. Guideline for prescribing vigabatrin in children has been revised [Letter]. *BMJ* 2000;**320**:1404–5. (See also 2001;**322**:236–7.)
- Koul R, Chacko A, Ganesh A, *et al.* Vigabatrin associated retinal dysfunction in children with epilepsy. *Arch Dis Child* 2001;**85**:469–73.
- Spence SJ, Sankar R. Visual field defects and other ophthalmological disturbances associated with vigabatrin. *Drug Safety* 2001;**24**:385–404.
- Lewis H, Wallace SJ. Vigabatrin. *Dev Med Child Neurol* 2001;**43**:833–5.

VITAMIN A (Retinol)

Use

Very preterm babies are relatively deficient of vitamin A at birth, and IM supplementation can marginally reduce the risk of chronic oxygen dependency in those who require sustained ventilation.

Nutritional factors

Vitamin A is the generic name given to a group of fat soluble compounds exhibiting the same biological activity as the primary alcohol, retinol. The compounds have many cellular functions, and deficiency can affect immunocompetence, reproductive function, growth, and vision (the vitamin being responsible for the formation of the retina's photosensitive visual pigment). Deficiency, first recognised in 1912, can also damage the epithelial cells lining the respiratory tract.

Green vegetables, carrots, tomatoes, fruit, eggs and dairy produce all provide vitamin A. Deficiency is rare in the UK but is still a common cause of blindness due to xerophthalmia ('dry eye') in the developing world, increasing the mortality associated with pregnancy and with measles in the first two years of life. A single 50,000 unit oral dose at birth lowered infant mortality in one recent trial in Indonesia, while weekly supplements reduced maternal mortality in one trial in Nepal. Supplements also eliminated anaemia on one trial in Indonesia in mothers also taking iron, but this finding could not be replicated during trials in Malawi. Regular supplements can reduce the amount of ill health caused by malaria.

However, vitamin A is toxic in excess and also teratogenic, and women planning to become pregnant should avoid an intake in excess of 8000 units per day. Inappropriate and excessive multivitamin supplementation can be unwittingly hazardous, and women are advised not to eat liver during pregnancy because of its high vitamin A content (650 units per gram). The anti-acne drugs tretinoin and isotretinoin are also teratogenic when taken by mouth around the time of conception. Topical use may be safe, but many will not wish to take any such risk. Toxicity might also (in theory) develop in a breast fed baby whose mother was taking an excess of any of these retinoids. The dietary anti-oxidant precursors of vitamin A, including β -carotene, are not teratogenic.

Human milk contains 100 to 250 units of vitamin A per 100 ml, and the term baby requires no further supplementation whether artificially or breast fed. However, the fetal liver only accumulates vitamin A in the last third of pregnancy, and plasma levels are low in the preterm baby at birth. While overt clinical deficiency has not been detected, additional supplementation has been widely recommended for the very preterm baby. Those fed IV are often given a 900 unit/kg daily supplement with their Intralipid[®] (q.v.). Many orally fed preterm babies are also supplemented – often with a product that also contains vitamin D (q.v.). A trial involving 807 babies weighing 1 kg or less has recently shown that an even larger dose IM (5000 units three times a week from birth) slightly reduces the number of babies still oxygen dependent at a postmenstrual age of 36 weeks (odds ratio 0.85). Earlier small trials had pointed to a similar conclusion. Mortality was not reduced. Some will consider the benefit marginal, given the number of injections required. A trial of oral prophylaxis in 157 babies of under 1 kg failed to detect any benefit from a 5000 unit daily dose. IV prophylaxis remains unexplored.

Prophylaxis

Prematurity: Ventilator dependent babies of less than 28 weeks gestation (< 1kg babies actually entered the trial) may benefit from 5000 units (0.1 ml) of IM vitamin A three times a week for 4 weeks.

Liver disease: Counteract malabsorption due to prolonged cholestasis by giving 4000 or 5000 units once a day by mouth. Give babies with complete biliary obstruction 50,000 units once a month IM.

Supply

2 ml ampoules containing 50,000 units of vitamin A palmitate per ml cost £4.10. (1 unit is equivalent to 0.3 microgram of preformed retinol.) Store ampoules at less than 15°C, and protect from light. Do not dilute, or use if the yellowish opalescent solution shows signs of flocculation. An unlicensed oral preparation containing 5000 units per drop can be imported on request. For information on Dalivit[®] (which contains 5000 units of vitamin A in 0.6 ml) see the monograph on multiple vitamins.

References

- Mitchell AA. Oral retinoids: what should the prescriber know about the teratogenic hazards among women of child-bearing age? *Drug Safety* 1992;2:79–85.
- Shenai JP. Vitamin A. In: Tsang RC, Lucas A, Uauy R, et al, eds. *Nutritional needs of the preterm infant*. Baltimore, MA: Williams and Wilkins, 1993:87–100.
- Rothman KJ, Moore LL, Singer MR, et al. Teratogenicity of high dose vitamin A intake. *N Engl J Med* 1995;333:1369–73.
- Tyson JE, Wright LL, Oh W, et al. Vitamin A supplementation for extremely-low-birth-weight infants. *N Engl J Med* 1999;340:1962–8. (See also 341:1697–8.) [RCT]
- Wardle SP, Hughes A, Chen S, et al. Randomised controlled trial of oral vitamin A supplementation in preterm infants to prevent chronic lung disease. *Arch Dis Child* 2001;84:F9–F13. [RCT]
- Grotto, I Mimouni M, Gdalevich M, et al. Vitamin A supplementation and childhood morbidity from diarrhea and respiratory infections: a meta-analysis. *J Pediatr* 2003;142:297–304. [SR]

See also relevant Cochrane reviews



Use

Breastfed babies of vitamin B₁₂ deficient vegetarian mothers occasionally also become B₁₂ deficient, and older children occasionally become deficient from malabsorption. Pharmacological doses are beneficial in several rare (autosomally recessive) disorders of cobalamin (vitamin B₁₂) transport and metabolism.

Nutritional factors

Vitamin B₁₂ is a water soluble vitamin that is actively transported across the placenta. Babies have high serum levels and significant liver stores at birth. Meat and milk are the main dietary sources. Toxicity has not been described. Absorption requires binding to intrinsic factor (a protein secreted by the stomach), recognition of the complex by receptors in the terminal ileum, and release into the portal circulation bound to transcobalamin II. Ileal absorption can be affected by surgery for necrotising enterocolitis, while congenital transcobalamin II deficiency can also affect tissue delivery. The first sign of deficiency is neutrophil hypersegmentation. Megaloblastic anaemia develops, and severe deficiency causes neurological damage that can be irreversible. A high folic acid intake can mask the haematological signs of vitamin B₁₂ deficiency. Intrinsic factor failure causes pernicious anaemia, which Whipple was first able to cure in 1926 with a liver diet. The active ingredient (cyanocobalamin) was finally isolated in 1948, and a bacterial source of production developed the following year.

Pharmacology

Cobalamin is released from transcobalamin II within target cells and converted to adenosylcobalamin or methylcobalamin, cofactors respectively for methylmalonyl mutase and methionine synthase. Rare genetic defects can impair cobalamin metabolism at various stages. Patients can present at any age from 2 days to 5 years with symptoms ranging from vomiting and encephalopathy to developmental delay and failure to thrive. Investigations may show a megaloblastic anaemia, methylmalonic aciduria, and/or homocystinuria, depending on the precise defect. A trial of vitamin B₁₂ should be undertaken in all patients with methylmalonic aciduria, whether or not this is accompanied by homocystinuria. It needs to be conducted when the patient is well and on a constant protein intake. Hydroxocobalamin (1 mg IM) is given daily for 5 consecutive days and methylmalonate excretion measured before, during, and after the intervention. Patients with isolated homocystinuria who do not respond completely to pyridoxine (q.v.) should have a similar trial of vitamin B₁₂. Those with these conditions who are acutely unwell should be started on vitamin B₁₂ at once and a formal trial deferred until later. Patients who respond should be started on a 1 mg dose daily IM. Treatment should be accompanied by other measures appropriate to the specific defect, such as protein restriction, metronidazole, carnitine, pyridoxine, folic acid, and/or betaine (q.v.) under the guidance of a consultant experienced in the management of metabolic disease.

Treatment

Dietary deficiency: Give a single IM injection of between 250 micrograms and 1 mg, and then ensure that the diet remains adequate (1 microgram/kg per day is sufficient).

Absorptive defects: Malabsorption is treated with 1 mg of hydroxocobalamin IM at monthly intervals, but 1 mg IM three times a week is usually given in transcobalamin II deficiency during the first year of life, later reducing to 1 mg once a week with haematological monitoring.

Metabolic disease: The initial maintenance dose is 1 mg daily IM irrespective of weight, but this can often be reduced later to 1–3 injections a week, with biochemical monitoring to ensure that there is no deterioration. Oral hydroxocobalamin (1–20 mg/day) is sometimes substituted, but is usually less effective because the intestine's absorptive capacity becomes saturated.

Supply

1 ml ampoules containing 1 mg of hydroxocobalamin for IM use cost £2.50.

References

- Kuhne, Bubl R, Baumgartner R. Maternal vegan diet causing a serious infantile neurological disorder due to vitamin B₁₂ deficiency. *Eur J Pediatr* 1991;**150**:205–8.
- Monagle PT, Tauro GP. Long term follow up of patients with transcobalamin II deficiency. *Arch Dis Child* 1995;**72**:237–8.
- Andersson HC, Shapira E. Biochemical and clinical response to hydroxocobalamin versus cyanocobalamin treatment in patients with methylmalonic acidemia and homocystinuria (*cbIC*). *J Pediatr* 1998;**132**:121–4.
- Rosenblatt DS. Disorders of cobalamin and folate metabolism. In: Fernandes J, Saudubray J-M, van den Berghe G, eds. *Inborn metabolic diseases. Diagnosis and treatment*, 3rd ed. Chapter 25. Berlin: Springer-Verlag, 2000:284–98.
- Rosenblatt DS, Fenton WA. Inherited disorders of folate and cobalamin transport and metabolism. In: Scriver CR, Beaudet AL, Sly WS, et al., eds. *The metabolic and molecular bases of inherited disease*, 8th ed. New York: McGraw-Hill, 2001:3897–934.

Use

Irrespective of weight, all babies need 5 micrograms (200 units) of vitamin D a day for bone growth.

Pharmacology

Vitamin D controls calcium and phosphate absorption from the intestine, their mobilisation from bone, and also possibly their retention by the kidneys. Ingested vitamin D₂ (ergocalciferol) and vitamin D₃ (cholecalciferol) have to be hydroxylated to 25-hydroxyvitamin D by the liver, however, and further hydroxylated to 1,25-dihydroxyvitamin D by the kidney and placenta before becoming metabolically active. The vitamin's existence was first unequivocally established in 1925.

Nutritional factors

Eggs, breakfast cereals, and margarine provide dietary vitamin D. So do oily fish (cod liver oil was once a popular source). Exposure to ultraviolet summer sunlight is, however, the main reason why most people in the UK avoid becoming vitamin D deficient. Veiled clothing can block this. So can the excessive use of sunblock cream. Severe maternal deficiency can cause congenital rickets and craniotabes. Less severe deficiency leaves the baby with a limited body store at birth and, because milk contains little vitamin D, deficiency disease starts to appear after a few months unless the child is fed an artificially supplemented formula milk (q.v.). Giving such mothers 25 micrograms daily during the last trimester of pregnancy appears to eliminate this risk. A single 2.5 mg oral or IM dose at 7 months gestation is equally effective, as outlined in the website commentary.

The amount of vitamin D required in infancy is influenced by the adequacy of the stores built up during fetal life and by subsequent exposure to sunlight. If neither can be guaranteed, a dietary intake of at least 5 micrograms a day is needed. Formula milk is sufficiently supplemented to provide this for the term baby but, because the amount in breast milk varies with the mother's own nutritional status, some breastfed babies become deficient if they are not given supplements, especially during the winter. It used to be thought that very small babies needed more vitamin D than this, but it is now known that the poor bone mineralisation, and the spontaneous fractures seen in these babies, are caused by an inadequate intake of phosphate (or occasionally calcium) and not by vitamin D deficiency. One strategy for giving additional phosphate is outlined in the monograph on phosphate.

Many weaning foods are fortified with vitamin D and all formula milks contain at least 1 microgram/100 ml. It is important to remember that, although vitamin D deficiency causes rickets, a total daily intake of more than 100 micrograms can cause hazardous hypercalcaemia. Excessive maternal supplementation during lactation is, therefore, a theoretical hazard. Babies who are unable to make the active metabolite for themselves because of serious renal or liver failure are the only children needing, respectively, either alfacalcidol (1 α -hydroxycholecalciferol) or calcitriol (1,25-dihydroxycholecalciferol).

Maternal prophylaxis

Give 5 mg IM in the third trimester to Muslim and other women likely to have limited vitamin D stores.

Prophylaxis with D₂ after birth

Breastfed babies: Give 5 micrograms once a day until mixed feeding is established. The most convenient UK source is four drops (0.12 ml) of the welfare product listed in the multivitamin monograph.

Preterm babies: Give all preterm babies 5 micrograms once a day until they weigh about 3 kg.

Malabsorption: Give babies with complete biliary obstruction 750 micrograms IM once a month.

Renal disease: Start babies who are unable to hydroxylate vitamin D₂ (ergocalciferol) on 20 nanograms/kg of oral or IV *alfacalcidol* once a day, and monitor need with care as indicated in the website commentary.

Supply

Ergocalciferol (D₂): 1 ml (7.5 mg, 300,000 unit) ampoules for IM use cost £5.90. 10 microgram (400 unit) tablets, containing redundant calcium, cost 3p each. A 3000 unit/ml oral liquid is available from Martindale; 100 ml costs £37. See the multivitamin monograph for other low dose alternatives.

Alfacalcidol: 10 ml bottles of a sugar-free oral liquid (100 nanograms/drop) cost £24. 1 microgram 0.5 ml ampoules for IV or IM use cost £2.30. They contain 207 mg of propylene glycol.

References

- See also relevant Cochrane reviews 
- Brooke DG, Brown IR, Bone CD, *et al.* Vitamin D in pregnant Asian women: effect of calcium status on fetal growth. *BMJ* 1980;**280**:751-4. [RCT]
- Koo WWK, Tsang RC. Calcium, magnesium, phosphorus and vitamin D. In: Tsang RC, Lucas A, Uauy R, *et al.*, eds. *Nutritional needs of the preterm infant*. Baltimore, MD: Williams & Wilkins, 1993:135-55.
- Mughal MZ, Salama H, Greenaway T, *et al.* Florid rickets associated with prolonged breast feeding without vitamin D supplementation. *BMJ* 1999;**318**:39-40. (See also pp. 2-3.)
- Backström MC, Mäki R, Kuusela A-L, *et al.* Randomised controlled trial of vitamin D supplementation on bone density and biochemical indices in preterm infants. *Arch Dis Child* 1999;**80**:F161-6. [RCT]
- American Academy of Pediatrics. Clinical report. Prevention of rickets and vitamin D deficiency: new guidelines for vitamin D intake. *Pediatrics* 2003;**111**:908-10.

Use

Vitamin E is used to prevent haemolytic anaemia in vitamin E deficient babies, and in babies with malabsorption due to cholestasis. Pharmacological doses are used in abetalipoproteinaemia.

Pharmacology

Vitamin E is the name given to a group of fat soluble antioxidant tocopherols of which alpha tocopherol shows the greatest activity. The natural vitamin, first isolated in 1936, is concentrated from soya bean oil. Excessive intake (100 mg/kg daily) is toxic to the newborn kitten. Plasma levels in excess of 100 mg/l caused hepatomegaly and levels over 180 mg/l were sometimes lethal. The effect of excessive medication in humans is unknown. Vitamin deficiency was first identified as causing fetal death and resorption in the laboratory rat. It is now known to cause enhanced platelet aggregation and also thought to cause a haemolytic anaemia, probably as a result of peroxidation of the lipid component of the red cell membrane (a problem that seems to be exacerbated by giving artificial milk containing extra iron).

Pharmacological doses administered IM or IV shortly after birth were used in a range of studies between 1980 and 1990 designed to reduce the risk of intraventricular haemorrhage, bronchopulmonary dysplasia, and retinopathy of prematurity, but all these parenteral preparations have now been withdrawn from general sale because of concern about one of the stabilisation agents used, and oral administration has been associated with an increased incidence of necrotising enterocolitis that may (or may not) have been related to the product's high osmolarity. Early parenteral prophylaxis may reduce the incidence of haemorrhage; it is less clear whether it reduces the amount of parenchymal damage. Mortality was not reduced. No trials of long term outcome have yet been conducted. Other preventive strategies are discussed in the monograph on etamsylate. A systematic review in 1997 concluded that a further trial of its prophylactic use to reduce the severity of retinopathy of prematurity was justified.

High doses of vitamin E can prevent neuromuscular problems in abetalipoproteinaemia, an autosomal recessive disorder associated with fat malabsorption and acanthocytosis. Such babies should also be treated with a low fat diet and supplements of vitamin A (7 mg) and vitamin K (5–10 mg) once a day by mouth, irrespective of weight.

Nutritional factors

Human milk contains an average of 0.35 mg of alpha tocopherol per 100 ml (some four times as much as cows' milk) and commercial feeds contain between 0.5 mg/100 ml and 4.0 mg/100 ml. Babies are relatively deficient in vitamin E at birth, and plasma levels (2.5 mg/l) are less than a quarter of those in the mother. Plasma levels rise rapidly after birth in the breastfed term baby but remain low for several weeks in artificially fed preterm babies (especially those weighing less than 1.5 kg at birth). No significant anaemia develops, however, with artificial feeds that provide a daily intake of 2 mg/kg of d-alpha tocopherol (approximately 3 units/kg vitamin E) as long as the ratio of vitamin E to polyunsaturated fat in the diet is well above 0.4 mg/g, even if the milk contains supplemental iron. Haemolytic anaemia, when it does occur, generally becomes apparent 4–6 weeks after birth and is usually associated with a reticulocytosis (> 8%), an unusually high platelet count, and an abnormal peroxide induced haemolysis test (> 30%).

Treatment

Neonatal prophylaxis: A single 20 mg/kg IM injection is given at birth to babies weighing less than 1 kg, or 1.5 kg in some UK neonatal units. This is less than the dose used in most trials.

Nutritional deficiency: 10 mg/kg by mouth once a day will quickly correct any nutritional deficiency.

Malabsorption: Babies with cholestasis may benefit from a 50 mg supplement once a day by mouth. Give babies with complete biliary obstruction 10 mg/kg twice a month IM.

Abetalipoproteinaemia: Give 100 mg/kg by mouth once a day.

Supply

An oral suspension of alpha tocopherol acetate (£16.60 per 100 ml) containing 100 mg/ml of vitamin E can be obtained by the pharmacy on request; some say it should be diluted before use with syrup BP because of its hyperosmolarity (see above). 2 ml vials of Ephyнал®, costing £1.30 and containing 50 mg/ml suitable for IM use, are obtainable from Roche in the UK on a "named patient" basis but no licensed parenteral preparation is commercially available either in the UK or North America.

References

- Muller DPR, Lloyd JK, Wolff OH. Vitamin E and neurological function. *Lancet* 1983;i:225–8.
 Phelps DL. The role of vitamin E therapy in high-risk neonates. *Clin Perinatol* 1988;15:955–63.
 Low MR, Wijewardene K, Wald NK. Is routine vitamin E administration justified in very low-birthweight infants? *Dev Med Child Neurol* 1990;32:442–50.
 Raju TNK, Lagenberg P, Bhutani V, et al. Vitamin E prophylaxis to reduce retinopathy of prematurity: a reappraisal of published trials. *J Pediatr* 1997;131:844–50. [SR]

Use

Vitamin K is required for the hepatic production of coagulation factors II, VII, IX, and X.

Nutritional factors

The term vitamin K refers to a variety of fat soluble methyl naphthoquinone derivatives. Vitamin K₁ (first isolated in 1939) occurs in green plants, while vitamin K₂ is synthesised by microbial flora in the gut. Human milk contains about 1.5 µg of vitamin K per litre, while cows' milk contains about four times as much as this. Most artificial milks contain over 50 µg/l. Vitamin K crosses the placenta poorly and babies are relatively deficient at birth. Any resultant vitamin-responsive bleeding used to be called "haemorrhagic disease of the newborn" but is now, more informatively, called "vitamin K deficiency bleeding" (VKDB), since it can occur at any time in the first 3 months of life. Any unexplained bruise or bleed requires *immediate* attention as outlined below if catastrophic cerebral bleeding is to be avoided.

Pharmacology

Bleeding in the first week of life is usually mild, except in the babies of mothers who are on some anticonvulsants. Later VKDB can, however, cause potentially lethal intracranial bleeding, and there is a 1:6000 risk of this in any breastfed baby not offered a supplement. Malabsorption, especially as a result of hepatic disease, puts babies at even greater risk. A single 1 mg IM dose gives almost complete protection, and seems to provide an IM "depot" of slowly released drug. Safe prophylaxis presents a challenge, however, because the six published studies in which patients were matched with controls for both time and place of birth all found an increase in the incidence of childhood leukaemia after IM prophylaxis. While such studies do not prove a link, and were too small for any of the individual estimates of increased risk to reach statistical significance, they are hard to ignore. Oral prophylaxis is an appropriate option for all babies well enough to be fed at birth, but, because liver stores have a short turnover time, those who are breastfed are fully protected only if given further doses after discharge from hospital. A 50 microgram daily supplement may be best, since this is, in effect, what all bottle fed babies get (other than those on some soy based milks). Where no low dose daily formulation is available, a weekly 1 mg oral dose is equally effective.

Prophylaxis

Traditional IM prophylaxis: Give 1 mg IM (with parental consent) to every baby at birth. Note that IV administration does *not* provide the sustained protection provided by a "depot" IM injection.

The oral option: Babies who are born to mothers on carbamazepine, phenobarbital, phenytoin, rifampicin, or warfarin (q.v.), and babies who are too ill for early feeding, should receive 100 micrograms/kg at birth IM. All other babies should, with parental consent, be given 1 mg or 2 mg at birth by mouth. Every breastfed baby should then be offered at least four further 1 mg, or two further 2 mg, oral doses over the next 6–8 weeks. A 1 mg oral dose once a week seems to be necessary to protect the occasional baby with unrecognised liver disease. Babies with severe biliary obstruction are often given 1 mg by mouth once a day.

Treatment

Give 100 micrograms/kg IV (or IM) to any baby with active bleeding that could be due to vitamin K deficiency, after taking blood for clotting studies. A prolonged prothrombin time (international normalised ratio ≥ 3.5) that falls within 1 hour of IV treatment, with a normal platelet count and fibrinogen level, confirms the diagnosis.

Administration

Midwives can, under the 1968 Medicines Act, give licensed vitamin K products on their own authority.

Supply and administration

Soft 1 ml capsules containing 1 mg of vitamin K (Orakay[®]) are about to be licensed for oral use. They cost 33p. Cut across the narrow tubular tip and squeeze the contents (~40 drops) into the child's mouth. A further dose should be given if this is spat out, or if the child vomits within 3 hours.

0.5 ml ampoules containing 1 mg (Konaktion[®]) are intended for IM use only. They cost 23p and contain 20 mg of propylene glycol. A concentrated colloidal (mixed micelle) preparation (Konaktion MM[®]) designed to make IV use safe, and containing 2 mg in 0.2 ml, came onto the UK market in 1996. Ampoules cost £1.55. This can be given IV, IM, or by mouth, although the manufacturer originally designed the product for administration by a health professional, and cautions against oral use in babies weighing under 2.5 kg. Prior dilution is not recommended, making the accurate administration of small doses difficult. The studies needed to optimise oral prophylaxis when using this product in the breastfed baby have not yet been done.

References

- Greer FR. Vitamin K deficiency and hemorrhage in infancy. *Clin Perinatol* 1995;**22**:759–77.
 Sutor AH, von Kries R, Cornelissen EAM, *et al.* Vitamin K deficiency bleeding (VKDB) in infancy. *Thromb Haemost* 1999;**81**:456–61.
 Wariyar U, Hilton S, Pagan J, *et al.* Six years' experience of prophylactic oral vitamin K. *Arch Dis Child* 2000;**82**:F64–8.
 von Kries R, Hachmeister A, Göbel U. Oral mixed micellar vitamin K for prevention of late vitamin K deficiency bleeding. *Arch Dis Child* 2003;**88**:F109–12. (See also pp. F80–3.)
 Hansen KN, Minousis M, Ebbesen F. Weekly oral vitamin K prophylaxis in Denmark. *Acta Paediatr* 2003;**92**:802–5.

See also relevant Cochrane reviews 

Use

Multivitamin preparations are a convenient and cost effective approach to dietary supplementation for babies with severe malabsorption, and for babies requiring sustained IV nutrition.

Nutritional factors

Most healthy children do not need vitamin supplements, but those with malabsorption often develop subclinically fat soluble vitamin deficiency. Vitamin D deficiency can be a problem, however, even in the otherwise healthy breastfed child, as was well recognised when a Welfare Food Scheme was introduced in the UK in 1940 as part of the war effort. While vitamin D deficiency rickets is now rare in artificially fed babies because all formula milks are supplemented, it still occurs in many parts of the world in breastfed babies because many mothers are, themselves, subclinically deficient. Late vitamin K deficiency also occurs rarely. This is a problem that has never received the attention it deserves, largely because it had not been recognised as a clinical condition when national schemes for giving vitamin supplements during pregnancy and early infancy first evolved. Unfortunately, the continued advocacy of a multivitamin drop that contains two unnecessary constituents but lacks vitamin K serves only to confuse the general public. It panders to the belief that multiple vitamin supplements are a "good thing" even for normal children on a healthy diet, while failing to drive home the message that even a healthy breastfed baby can, very rarely, become dangerously deficient in vitamin D and vitamin K.

The UK scheme, as originally introduced in 1940, included liquid milk, National Dried Milk, concentrated orange juice, and cod liver oil; few disputed Winston Churchill's claim that there could be "no finer investment for any country than putting milk into babies". Dried eggs were included, briefly, in the 1940s for all children less than 5 years old. Mothers also received special supplements. Because the scheme was generally credited with actually improving the health of children during the war years, the relevant regulations were never repealed, although infant vitamin drops (and maternal tablets) replaced cod liver oil and orange juice in 1975, and commercial formula milks replaced National Dried Milk in 1977.

Oral vitamins

UK child welfare vitamin drops: These are an excellent and cheap source of vitamin D. The usually recommended dose is five drops (0.15 ml) once a day. This dose provides approximately 250 micrograms (830 units) of vitamin A, 20 mg of vitamin C, and 7 micrograms (280 units) of vitamin D.

Abidec® drops: The usual dose is 0.3 ml once a day by mouth throughout the first year of life. Children with cystic fibrosis and other forms of malabsorption are often given 0.6 ml once a day. The latter dose provides 400 micrograms (1333 units) of vitamin A, 10 micrograms (400 units) of vitamin D, supplemental vitamin B₁, B₂, B₆, C, and nicotinamide (but no vitamin E, or vitamin K).

Dalivit® drops: These are given in the same way, and in the same dose, as Abidec. The vitamin content is very similar, but there is 1.5 mg (5000 units) of vitamin A in a 0.6 ml dose. High dose use in conjunction with other dietary supplements may, therefore, provide 2 mg/kg per day of this vitamin, which could be toxic.

IV vitamins

Water soluble vitamins: Amino acid solutions used to provide parenteral nutrition (q.v.) will usually have had all the more important vitamins added (as Solivito N®) prior to issue by the pharmacy.

Fat soluble vitamins: The manufacturers say that babies weighing under 2.5 kg should have 4 ml/kg of Vitlipid N® infant added to their Intralipid® (q.v.) each day so they get the vitamin D₂ and K₁ that they need, but this strategy reduces calorie intake (since Vitlipid is formulated in 10% Intralipid) – a quarter of this dose normally suffices. A dose of 10 ml/day is recommended for all children weighing more than 2.5 kg, but such supplements are only important when sustained IV feeding becomes necessary.

Supply

Oral preparations: Mothers' and Childrens' Vitamin Drops are available under the UK Welfare Food Scheme. A 10 ml bottle costs 80p. A 25 ml bottle of Abidec costs £1.80, and a 25 ml bottle of Dalivit costs £1.60. These preparations do not require a doctor's prescription.

IV preparations: 10 ml ampoules of Vitlipid N (infant) designed for adding to Intralipid, contain 690 micrograms (2300 units) of vitamin A, 10 micrograms (400 units) of vitamin D, 7 mg of vitamin E, and 200 micrograms of vitamin K. They cost £1.70. Any amino acid solution designed for IV use will normally have had a vial of Solivito N (containing small amounts of vitamins B₁, B₂, B₆, B₁₂, nicotinamide, sodium pantothenate, vitamin C, and folic acid) added prior to issue. Such vials cost £1.70 each. Supplements of Solivito N can, alternatively, be added to Intralipid, or to a plain infusion of IV dextrose.

References

- Ferenchak AP, Sontag MK, Wagener JS, *et al.* Prospective long-term study of fat-soluble vitamin status in children with cystic fibrosis identified by newborn screen. *J Pediatr* 1999;**135**:601–10.
- Greer FR. Do breastfed infants need supplemental vitamins? *Pediatr Clin North Am* 2001;**48**:415–23.
- Department of Health. *Scientific review of the welfare food scheme.* (Report on Health and Social Services no. 51.) London: The Stationery Office, 2002.

WARFARIN

Use

Warfarin is used in the long term control of thromboembolic disease. Heparin (q.v.) is better for short term treatment. There is limited experience of use in the neonatal period.

Pharmacology

Warfarin is an oral coumarin anticoagulant that works, after a latent period of 1–2 days, by depressing the vitamin K dependent synthesis of a range of plasma coagulation factors, including prothrombin, by the liver. It was developed as a rat poison in 1948 before later coming into clinical use. Because the half life is about 36 hours, blood levels stabilise only after 1 week of treatment. Babies need a higher weight related dose than adults. Those with chronic atrial fibrillation, dilated cardiomyopathy, or certain forms of reconstructive heart surgery, benefit from prophylactic warfarin, and it has occasionally been used to manage intravascular or intracardiac thrombi. Treatment can initially precipitate purpura fulminans (a form of tissue infarction) in patients with thromboses due to homozygous protein C or S deficiency.

Warfarin crosses the placenta, but is not excreted in breast milk. Exposure at 6–9 weeks gestation can cause a syndrome simulating chondrodysplasia punctata, and drug use may not be entirely safe even in later pregnancy because of the risk of fetal and neonatal haemorrhage. Problems are minimised by not allowing the dose to exceed 5 mg/day. The small risk of congenital optic atrophy, microcephaly, and mental retardation (possibly caused by minor recurrent bleeding) may be of more concern than the commoner, but less serious, defects associated with exposure in early pregnancy. Unfortunately, while heparin provides reasonable prophylaxis for most women at risk of thromboembolism during pregnancy, it does not provide adequate protection for mothers with pulmonary vascular disease, atrial fibrillation, or an artificial heart valve. Here, the balance of risk is such that warfarin should be given until delivery threatens or the pregnancy reaches 37 weeks, and then restarted 2 days after delivery (the intervening period being covered with heparin). Babies of mothers taking warfarin at the time of delivery need to be offered immediate prophylaxis with at least 100 micrograms/kg of IM vitamin K (q.v.).

Drug interactions

Many drugs increase the anticoagulant effect of warfarin, including amiodarone, some cephalosporins, cimetidine, erythromycin, fluconazole, glucagon, metronidazole, miconazole, phenytoin, ritonavir and the sulphonamide drugs. L-carnitine, ciprofloxacin and some penicillins can sometimes have a similar effect. So can high dose paracetamol. Other drugs, including barbiturates, carbamazepine, rifampicin, spironolactone, and vitamin K, decrease warfarin's anticoagulant effect.

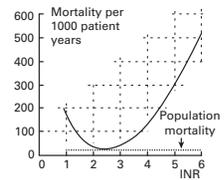
Treatment

Initial anticoagulation: Give 200 micrograms/kg by mouth on day 1, and half this dose on the next 2 days (unless the international normalised ratio (INR) is still < 1.5). Always seek expert advice before starting anticoagulation.

Maintenance: Laboratory monitoring is essential to determine long term needs. Most children need 100–300 micrograms/kg once a day, but babies under 1 year old often need 150–400 micrograms/kg per day, especially if bottle fed (possibly because of the high vitamin K intake that this provides).

Dose monitoring

Collect 1 ml of blood into 0.1 ml of citrate, avoiding any line that has **ever** contained heparin. Testing is needed only every few weeks once treatment has stabilised but, because many drugs affect the half life of warfarin, additional checks are needed each time other treatment is changed. Aim for an INR of between 2 and 3 (see figure). Slightly higher values used to be recommended for adults after heart valve replacement. Parents must be told about the need for monitoring, given an anticoagulant book with a note of all treatment, and have the book's importance explained.



Antidote

Stop treatment if the INR exceeds 4.5. Give fresh frozen plasma (q.v.) if it exceeds 7, plus 1 mg of IV vitamin K (q.v.) if there is overt bleeding.

Supply

Warfarin can be provided as a 1 mg/ml sugar-free suspension. This is stable for 2 weeks. 500 microgram (white), 1 mg (brown) and 3 mg (blue) tablets are available, costing a few pence each.

References

- Streif W, Andrew M, Marzinotto V, *et al.* Analysis of warfarin therapy in pediatric patients: a prospective cohort study of 319 patients. *Blood* 1999;**94**:3007–14.
- Vitali N, de Feo M, de Santo LS, *et al.* Dose dependent fetal complications of warfarin in pregnant women with mechanical heart valves. *J Am Coll Cardiol* 1999;**33**:1637–41. (See also pp. 1642–5.)
- Odén A, Fahlén M. Oral anticoagulation and risk of death: a medical record linkage study. *BMJ* 2002;**325**:1073–5.

Use

An understanding of neonatal fluid balance, and of the limits of neonatal homeostasis, are essential to the management of any baby on IV fluids. See also the monograph on sodium chloride.

Physiology

Term babies lose about 30 ml/kg of water through the skin and nose each day ("insensible" water loss). Babies born more than 10 weeks early may lose twice as much water as this during the first few days of life through their semipermeable skin, and very immature babies may lose three times as much in the first week of life, especially if the skin is damaged (cf. monograph on skin care). These losses can be reduced and made much more predictable by the use of a humidified incubator; there is no evidence that this need increases the risk of infection. Compressed oxygen contains no water vapour, so babies nursed in > 40% oxygen also need supplemental humidity to stop their nasal and tracheal secretions becoming excessively dry. Some water is lost in the stool and mature babies also sweat intermittently. As a useful rule of thumb, therefore, babies should be allowed 60 ml/kg of water a day to balance these insensible losses, even when anuric.

Babies require a further 60 ml/kg of water a day to provide the kidney with an appropriate "vehicle" for the excretion of waste products. The *minimum* basic requirement of a baby with normal renal function is, therefore, 100–120 ml/kg of water a day, and it is traditional to give 120 ml/kg because this gives the necessary 8 mg/kg per minute of glucose required to prevent any risk of hypoglycaemia if infused as 10% dextrose (in the absence of marked hyperinsulinism). Infusing drugs that need continuous administration in 10% dextrose limits unnecessary water intake. The *maximum* safe intake in most stable babies more than 48 hours old who are not undergoing surgery is probably almost double the minimum requirement, even if the baby is both immature and ventilator dependent. With total intake in the range 120–200 ml/kg of water a day, most clinically stable babies more than 2 days old can autoregulate their own fluid balance, making it unnecessary to adjust for clinical factors such as gestation, postnatal age, insensible loss, phototherapy (q.v.), etc. The only limitation that needs to be placed on this guideline relates to the controlled trial evidence that ventilator dependent babies of < 1.5 kg who are offered liberal fluids in the first week of life are more likely to develop patent ductus arteriosus.

Hydration decreases after delivery. Intravascular volume can fall by 15% within a few hours as plasma leaves the circulation, while extracellular volume falls ~10% irrespective of fluid intake over the first 3–5 days of life, once no longer under placental control. Restricting early water intake has often been advocated in the belief that this aids these postnatal changes (at a time when oral intake is usually low anyway), but there is no evidence that restricting early fluid intake below 90 ml/kg a day is beneficial unless renal function is compromised, and a low intake can cause much unnecessary hypoglycaemia.

Management

Shocked, ill babies: Postasphyxial, posthypotensive, septicaemic, and hydropic babies should be started on 60 ml/kg of 10% dextrose with 0.18% sodium chloride a day once any initial fluid deficit has been corrected, and blood glucose levels monitored until renal function can be assessed.

Babies in renal failure: If output does not respond to 10 ml/kg of gelatin, pentastarch, or 5% plasma albumin and 5 mg/kg of IV furosemide, insert a central long line and give 2 ml/kg per hour of 20% dextrose to avert hypoglycaemia without giving more water than is being lost insensibly, adding an inotrope to this infusate as necessary. Replace all other loss (and its electrolyte content) with further 20% dextrose containing added sodium chloride, or bicarbonate, from a second line as appropriate.

Other babies < 30 weeks gestation: Hold total intake from milk and 10% dextrose to 100 ml/kg a day for the first 5 days if the baby is ventilated unless there is clinical fluid depletion (urine osmolality > 300 mosmol/l and/or there has been a >10% weight loss). Fluid (and calorie) intake can usually be increased rapidly after this, using IV 10% dextrose with 0.18% sodium chloride to supplement oral intake

Other babies in special care: A total oral and/or IV intake of 200 ml/kg a day is perfectly safe after the first 48 hours, and continued IV supplementation can sometimes help to optimise early calorie intake.

Supply

Half litre bags of 10% anhydrous dextrose with 0.18% sodium chloride cost 70p, 60 ml syringes cost 25p, and simple IV giving sets with an extension set and T tap cost £1.90.

References

- Sedin G. Fluid management in the extremely preterm infant. In: Hansen TN, McIntosh N, eds. *Current topics in neonatology, no. 1*. London: Saunders, 1996:50–66.
- Bell EF, Acarregui MJ. Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants. *The Cochrane Library*. Oxford: Update Software, 2001. [SR]
- Kavvadia V, Greenough A, Dimitriou G, et al. Randomised trial of two levels of fluid input in the perinatal period – effect on fluid balance, electrolyte and metabolic disturbances in ventilated VLBW infants. *Acta Paediatr* 2000;**89**:237–41. [RCT]

See also relevant Cochrane reviews



WHOOPING COUGH VACCINE

Use

Whooping cough (pertussis) vaccine, made from a suspension of killed *Bordetella pertussis* organisms, is still used to provide substantial immunity against infection in the UK. Children are particularly vulnerable in the first year of life. Passive immunity at birth is relatively weak, making early immunisation important. Vaccine toxoids that also provide prolonged protection against diphtheria and tetanus are usually employed in a combined "trivalent" (DTP) vaccine. All three infections are notifiable.

Clinical factors

More than 100,000 cases of whooping cough were notified every year prior to the introduction of a vaccine in the UK in 1956. Notifications then fell 50-fold, but severe infections still occur in young unimmunised children, and children with pre-existing pulmonary problems are almost certainly at particular risk. Death is now rare, but severe non-fatal infection in early infancy is not that uncommon. It often goes unrecognised, and is also under-reported. Serology, and polymerase chain reaction (PCR) tests can often reveal evidence of infection even when direct culture fails. Several acellular whooping cough vaccines have recently been developed. They remain, for the moment, of variable potency, but are increasingly preferred in Europe and North America because they trigger fewer adverse reactions. Serious problems are, however, uncommon in babies less than 6 months old. The product still in general use in the UK (where primary immunisation is normally complete by 6 months) currently remains a whole-cell vaccine.

Diphtheria was an even more dread disease until the introduction of an effective vaccine in 1940. Only 1–2 cases are now recognised each year in the UK but there can be little doubt that a policy of universal immunisation remains appropriate, as with polio. Tetanus is an even more common and extremely dangerous condition that can strike at any time. Protection requires a personal immunisation programme with boosters (covered, where necessary, by tetanus immunoglobulin) following any injury where the wound is likely to have been contaminated with tetanus spores. Maternal immunisation also serves to protect the baby from death from neonatal tetanus (still a problem in developing countries).

Indications

Immunisation against diphtheria, tetanus and pertussis should normally be started 8 weeks after delivery, as transplacental immunity wanes. Use the "triple" DTP vaccine and give the meningococcal (MenC) and haemophilus (Hib) vaccine at the same time. A personal or family history of allergy is not a contraindication. Neither is the existence of a congenital abnormality (such as Down's syndrome or a cardiac anomaly). While immunisation should not be delayed because of prematurity, it is *never* too late to immunise someone who was not immunised at the optimum time.

Contraindications

Immunisation strategy needs review after any severe local or general reaction to a previous dose of vaccine. Anaphylaxis, stridor, bronchospasm, prolonged unresponsiveness, or uncontrollable screaming, a temperature of > 39.5°C within 48 hours, or seizures within 72 hours of immunisation, suggest a general reaction. Redness and induration involving much of the thigh or upper limb are evidence of a serious local reaction. Such severe reactions are rare. When they occur they must be reported to the Committee on Safety of Medicines. Immunisation should then be completed using a trivalent product that incorporates an *acellular*, rather than a whole cell, pertussis vaccine. A brief period of hypotonia or unresponsiveness is not a reason to withhold further doses.

The one important relative contraindication is the existence of an evolving cerebral abnormality of perinatal origin. Should any such child develop new signs or symptoms shortly after immunisation starts, diagnostic difficulties may occur and the possibility of litigation could arise. In this situation the perceived risk of immunisation needs to be balanced against the risk of whooping cough (a very real risk if there are coexisting pulmonary problems) and a decision on timing reached with the parents that allows immunisation to proceed as soon as the child's neurological condition has stabilised.

Immunisation against whooping cough should also be delayed in any child who is acutely unwell, but the specific contraindications associated with the administration of live vaccines (such as polio vaccine) do not apply, and minor infections unassociated with fever or systemic symptoms are not a reason to delay immunisation, even if the child is on an antibiotic or other medicine.

A personal history of seizures (or, more doubtfully, a history of seizures in a brother, sister, or parent) was for some years considered a "relative" contraindication to pertussis immunisation in the UK (but not in the USA). Such children may be at increased risk of a febrile seizure if immunised when more than 6 months old, but there is no evidence that such an untoward effect carries with it any long term risk. Primary care and community staff should *not* therefore advise against pertussis immunisation without first discussing the issues with a consultant paediatrician familiar with all the issues and circumstances.

continued ...

Administration

General guidance: Give 0.5 ml deep into anterolateral thigh muscle using a 25 mm, 23 gauge, needle. Stretch the skin taut, and insert the needle, up to its hilt, at right angles to the skin surface. Use deep *subcutaneous* injection for children with haemophilia. Simultaneous vaccination against type C meningococcal infection (MenC), *Haemophilus influenzae* (Hib), and polio (q.v.) is normally undertaken. Babies who are given BCG do not need to have the timing of these other procedures modified. The normal vaccine schedule is as laid out in the monograph on immunisation, where brief guidance on documentation and on parental consent is also given.

Systemic steroids: Inactivated vaccines (such as DTP), unlike live virus vaccines, are completely safe in patients on high dose steroid medication, but the immune response can be blunted by such treatment. It is usually best to delay immunisation until steroid treatment has been stopped. However, this may not be the best strategy to adopt if a baby is going to be discharged home while still steroid dependent. Primary DTP, MenC, and Hib vaccinations should not be delayed in this situation (indeed babies with bronchopulmonary dysplasia may be at particular risk of whooping cough infection), but consideration should be given to offering a fourth "booster" injection 1 year after birth if the child was on long term systemic steroid treatment when, or until shortly before, vaccination started.

Abnormal reactions: Fever is uncommon when vaccination is undertaken in the first 6 months of life, and usually responds to a single 30 mg/kg dose of paracetamol (q.v.). Such reactions are of no lasting consequence, even when associated with a febrile fit. Parents should be told to seek medical advice if fever persists for more than 12 hours. Anaphylaxis (which is extremely rare) should be managed as laid out in the monograph on immunisation. Sudden limpness, with pallor and brief loss of consciousness, can occur in young children, especially in the hours after they receive their first dose of vaccine. These babies recover without treatment, and such reactions, though alarming, should not result in further doses of the whooping cough vaccine being withheld. Parents can be told that the episode is not unlike a fainting attack, is unlikely to recur, and is of no lasting significance.

Documentation

Inform the district immunisation coordinator (see monograph on immunisation) when any child is immunised in hospital, and complete the relevant section of the child's own personal health booklet.

Supply

A range of products exist; some are of limited efficacy. The long established combined trivalent whole-cell vaccine with aluminium hydroxide adjuvant in 0.5 ml vials (the DTaP vaccine) is still normally used in the UK, but an acellular trivalent vaccine (in 0.5 ml syringes costing £11) has also now been licensed (the DTwP vaccine), and such products are widely used in Europe and North America. A multivalent vaccine is also available that provides additional immunity against *Haemophilus influenzae* type b (q.v.). This costs £10 (a product that includes the acellular whooping cough toxin costs £19). The DTP vaccine contains a small amount of thiomersal (a mercury based preservative) but, since it is the only standard UK childhood product that does, there is not the same theoretical risk of toxicity as there is in the USA.

No monovalent vaccine is currently available for use in the UK, but children less than 7 years old who have not previously been immunised against whooping cough can be protected with two doses of the new acellular vaccine, usually given 6 months apart. For the most up to date advice see: www.doh.gov.uk/pertussis.htm

Vaccines must be stored in the dark at 2–8°C, but not frozen, and the ampoules must be used as soon as possible after they are opened.

References

See also relevant Cochrane reviews

- UK Health Departments. *Immunisation against Infectious Disease*. Chapter 24. London: HMSO, 1996:155–66.
- Kingo ARM, Scheifele D, Pendary M, et al. Does treatment with dexamethasone affect the immunological response to antigenic challenge of infants born preterm? [Abstract] *Pediatr Res* 1996;**39**:289A.
- Powell PJ, Heal CA, Ashworth LEA, et al. Antibody production in preterm infants receiving dexamethasone for chronic lung disease [Abstract]. *Early Hum Dev* 1997;**47**:211–12.
- Vermeer-de Bondt PE, Labadie J, Rümke HC. Rate of recurrent collapse after vaccination with whole cell pertussis vaccine: follow up study. *BMJ* 1998;**316**:902–3. (See also p. 876.)
- Goodwin H, Nash M, Gold M, et al. Vaccination of children following a previous hypotonic-hyporesponsive episode. *J Paediatr Child Health* 1999;**35**:549–52.
- Cherry JD, Olin P. The science and fiction of pertussis vaccines. *Pediatrics* 1999;**104**:1381–4.
- Hoppe JE. Neonatal pertussis. *Pediatr Infect Dis J* 2000;**19**:244–9.
- Diggle L, Deeks J. Effect of needle length on incidence of local reactions to routine immunisation in infants aged four months: randomised controlled trial. *BMJ* 2000;**321**:931–3. (See also **322**:492–3.) [RCT]
- Ramsay M. Time to review policy on contraindications to vaccination [Commentary]. *Lancet* 2000;**356**:1459–60.
- Crowcroft NS, Britto J. Whooping cough – a continuing problem [Commentary]. *BMJ* 2002;**324**:1537–8.
- Robbins JB, Schneerson R, Trollfors B. Pertussis in developed countries [Commentary]. *Lancet* 2002;**360**:657–8.
- Grant CC, Roberts M, Scragg R, et al. Delayed immunisation and risk of pertussis in infants: unmatched case-control study. *BMJ* 2003;**326**:852–3. (See also comment p. 853).

ZIDOVUDINE (Azidothymidine)

Use

Zidovudine inhibits the replication of HIV, reducing foeto–maternal transmission and slowing the progression of the resultant AIDS.

HIV infection

AIDS is a notifiable disease caused by infection with one of two closely related human retroviruses (HIV 1 and HIV 2). The viruses target T helper (CD4) lymphocytes and other cells such as macrophages with CD4 receptors, rendering the patient immunodeficient and vulnerable to a range of chronic low grade infectious illnesses that are not normally lethal. Infection is generally by sexual contact or the use of contaminated needles. Babies of infected mothers have a one in five chance of becoming infected around the time of birth if avoidance action is not taken. Contaminated blood infected many haemophiliacs before the nature of the condition was understood. The risk of infection after needlestick exposure is < 0.5%.

Care of HIV infected women during pregnancy

Since chemoprophylaxis and caesarean delivery before the membranes rupture can almost eliminate the risk of materno–fetal transmission, there is an overwhelming case for routine screening in pregnancy, as long as this has the mother's full and informed consent. Bottle feeding is wise where this can be done hygienically, and *exclusive* breastfeeding is safer than mixed feeding. Expert advice *must* be sought because maternal care may require the use of more than one drug, and policy is subject to frequent revision (see: www.AIDSinfo.nih.gov). UK staff and patients should consult www.aidsmap.com

Pharmacology

Zidovudine or azidothymidine (known as AZT) is a thymidine analogue that acts intracellularly, after conversion to triphosphate, to halt retrovirus DNA synthesis by competitive inhibition of reverse transcriptase and incorporation into viral DNA. It inhibits the replication of HIV, but does not eradicate it from the body. It is not, therefore, a cure for the resultant AIDS, but it can delay the progression of the disease. The drug's arrival in 1987 did much to transform the management of this previously untreatable condition. The most common adverse effects are anaemia and leucopenia (which make regular haematological checks essential), but myalgia, malaise, nausea, headache, and insomnia have also been reported. Zidovudine is well absorbed by mouth but first pass liver uptake reduces bioavailability. The half life is 1 hour, but 3 hours in term babies and 6 hours in preterm babies in the first week of life. Concurrent treatment with ganciclovir (q.v.) increases the risk of haematological toxicity while fluconazole (q.v.) causes some increase in the half life. Tissue levels exceed plasma levels (neonatal $V_D \sim 2$ l/kg). Zidovudine crosses the blood–brain barrier and the placenta with ease, but there is no human evidence of teratogenicity. Excretion occurs into breast milk, but has not been studied in any detail.

Prophylaxis

Mothers: Start giving 200 mg by mouth three times a day, by (or before) 28 weeks (although the risk to the baby is still much reduced even if treatment is started at 36 weeks). Then give 2 mg/kg IV over 1 hour at the onset of labour, followed by 1 mg/kg per hour IV until delivery.

Term babies: Give 2 mg/kg by mouth (or 1.5 mg/kg as an IV infusion over 30 minutes) once every 6 hours for 6 weeks, starting, if possible, 8–12 hours after birth.

Preterm babies: Give the above dose once every 12 hours in babies of less than 34 weeks gestation. Change to 8 hours after 2 weeks in babies of ≥ 30 weeks gestation, and after 4 weeks in babies of less than 30 weeks gestation at birth.

Treatment after birth

See the monographs on lamivudine, nevirapine, and ritonavir for advice on how to treat babies with known infection. Give all babies with suspected HIV infection prophylactic co-trimoxazole (q.v.).

Case notification

To improve our understanding of these problems (and of antiretroviral drug use in pregnancy), pregnant HIV positive women in the UK should be registered anonymously with the Royal College of Obstetricians and Gynaecologists Obstetric Surveillance Programme (Tel. 020 7829 8686; email p.tooke@ich.ucl.ac.uk). Report all babies to the British Paediatric Surveillance Unit (Tel. 020 7307 5671; Fax 020 7307 5694; email bpsu@rcpch.ac.uk).

Supply and administration

Diluting the contents of a 200 mg (20 ml) ampoule (costing £12) to 50 ml with 5% dextrose produces an IV solution containing 4 mg/ml. Give this, by convention, slowly. 100 mg and 250 mg capsules cost £1.20 and £3 respectively. A sugar free oral syrup (10 mg/ml) is also available (100 ml costs £12.50).

References

Bhana N, Ormrod D, Perry CM, *et al.* Zidovudine. A review of its use in the management of vertically-acquired pediatric HIV infection. *Pediatr Drugs* 2002;4:515–53. [SR]

Volmink J. Mother to child of transmission of HIV. *Clin Evid* 2003;9:1601–15 (and updates). [SR]

See the Cochrane review of materno–fetal transmission



Use

Oral zinc sulphate is used, both diagnostically and therapeutically, to supplement the dietary intake of babies with clinical signs of zinc deficiency.

Nutritional factors

Zinc is an essential nutrient, being a constituent of many enzymes. It is also a constituent of the DNA and RNA polymerases involved in cell replication and growth. Overt deficiency causes perioral and perianal dermatitis, symmetrical blistering and pustular lesions on the hands and feet, alopecia, irritability, anorexia, diarrhoea, and growth failure. The features are the same as for acrodermatitis enteropathica (a rare, and potentially lethal, condition caused by a recessively inherited abnormality of zinc absorption, first recognised in 1973). Enterostomy loss, and renal loss due to the use of a thiazide diuretic, both make zinc deficiency more likely. While the serum zinc level is usually, but not always, below the normal range (7.6–15 µmol/l at 1–3 months), the diagnosis is clinched by the response to a direct trial of supplementation. Debilitating subclinical deficiency is still common in those parts of the developing world where cereal foods account for much of the daily diet.

An intake of at least 700 micrograms/kg of zinc per day may be necessary for healthy growth in some babies during early infancy, but all the artificial formula milks commercially available in the UK currently provide more than this minimum amount. Human milk initially contains more zinc than cows' milk (0.2 mg/100 ml) and, because much of this is present as zinc citrate rather than bound to casein, absorption may be better, but the zinc content of human milk falls 10-fold during the first 6 months of lactation. Reserves of zinc accumulate in the skeleton and liver before birth, which help to tide the baby over the unexplained period of negative zinc balance normally seen in the first month of life. Nevertheless, a small number of cases of overt zinc deficiency have been seen in exclusively breastfed babies of less than 33 weeks gestation 2–4 months after birth, who responded to zinc supplementation. Deficiency was due to the milk containing little zinc, rather than a defect of absorption or utilisation. Symptoms of acrodermatitis manifest themselves only after a latent period for similar reasons.

Subclinical dietary deficiency is less easily recognised, but the consequences can be equally devastating. Trials in young children have shown that regular low dose supplementation (10 mg of elemental zinc per day) can reduce the incidence of pneumonia and of malaria by 40% in an at risk population. Mortality fell by 60% among supplemented light for dates children in another trial in India, while immediate supplementation in those developing diarrhoea halved the risk of death for any reason other than trauma in another trial in Bangladesh. Recent trials not yet included in the Cochrane Collaboration's overview when this edition of the Formulary went to press show that supplementation during pregnancy (30 mg daily from 12–16 weeks) can increase birth weight and reduce the risk of subsequent illness among children in areas where subclinical deficiency is common.

Treatment

As little as 1 mg/kg of zinc per day will rapidly cure any symptoms due to simple dietary deficiency. A regular daily 5 mg/kg oral supplement may be necessary in babies with acrodermatitis enteropathica.

Supply and administration

125 mg effervescent tablets of zinc sulphate monohydrate contain 45 mg (0.7 mmol) of zinc, and cost 15p each. One tablet dissolved in 4.5 ml of water gives a 10 mg/ml solution for accurate low dose administration. However, accurate dosing is not generally necessary when correcting acute dietary deficiency; it suffices to give most babies and toddlers half of a 45 mg tablet once a day for 2 weeks.

The use of 1 ml/kg per day of Peditrace® will meet the elemental zinc requirement of most babies on parenteral nutrition. 10 ml vials for IV use cost £3.10.

References

- Zimmerman AW, Hambridge KM, Lepow ML, *et al.* Acrodermatitis in breast-fed premature infants: evidence for a defect of mammary zinc secretion. *Pediatrics* 1982;**69**:176–83.
- Stephens J, Lubitz L. Symptomatic zinc deficiency in breast-fed term and premature infants. *J Paediatr Child Health* 1998;**34**:97–100.
- Obladen M, Loui A, Kampmann E, *et al.* Zinc deficiency in rapidly growing preterm infants. *Acta Paediatr* 1998;**67**:685–91.
- Zinc Investigators Collaborative Group. Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomised controlled trials. *J Pediatr* 1999;**135**:689–97. [SR]
- Osendarp SJM, van Raaij JMA, Darmstadt GL, *et al.* Zinc supplementation during pregnancy and effects on growth and morbidity in low birthweight infants: a randomised placebo controlled trial. *Lancet* 2001;**357**:1080–5. [RCT]
- Sazawal S, Black RE, Menon VP, *et al.* Zinc supplementation in infants born small for gestational age reduces mortality: a prospective randomised, controlled trial. *Pediatrics* 2001;**108**:1280–6. (See also p. 1366.) [RCT]
- Baqi AH, Black RE, El Arifeen S, *et al.* Effect of zinc supplementation started during diarrhoea on morbidity and mortality in Bangladeshi children: community randomised trial. *BMJ* 2002;**325**:1059–62. (See also pp. 1062–3.) [RCT]
- Brown KH, Pearson JM, Rivera J, *et al.* Effect of supplemental zinc on the growth and serum zinc concentrations of prepubertal children: a meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2002;**75**:1062–71. [SR]

See also relevant Cochrane reviews

Maternal medication and its effect on the baby

INTRODUCTION

No attempt has been made to review the extensive literature that now exists on the impact of medication during early pregnancy on the growing fetus. However, a summary of what is known about placental transfer, teratogenicity (the propensity to cause a malformation), fetal toxicity, and use in the lactating mother, is included in the section labelled "Pharmacology" for each drug listed in the main body of this neonatal pharmacopoeia. Where the text merely says that treatment during lactation is safe it can be taken that the dose ingested by the baby is almost certain to be less than 10% of that being taken by the mother on a weight for weight basis, and that no reports have appeared suggesting that the baby could be clinically affected. The purpose of this short addendum is to summarise what is known about the impact on the baby of those drugs that do **not** receive a mention in the main body of this compendium, even though they are commonly given to mothers during pregnancy, labour, or the puerperium. Information is also given on a range of other drugs that are often taken illicitly. A small number of entries review groups of drugs (such as the antihistamines), offering a general comment rather than information on one specific drug.

Advice to parents has, in the past, often been too authoritarian. While there are a small number of drugs whose use makes breastfeeding extremely unwise, for most drugs it is more a matter of balancing the advantages and the disadvantages, and of being alert to the possibility that the baby could conceivably exhibit a side effect of maternal medication. It is not enough just to say that a particular drug will appear in the mother's milk; that is true of almost every drug ever studied. Mothers will also question why it should be thought unwise to expose their baby to a low level of a drug during lactation when no reservation was voiced over much greater exposure during pregnancy. Much of the advice offered to UK clinicians in the *BNF*, and in *Medicines for children* (see p. 22), simply reflects, of necessity, the advice offered by the manufacturer in the summary of product characteristics. Such statements are always cautious, seldom very informative, and often designed merely to meet the minimum requirement laid down by the licensing authority. The same is true of drug use in pregnancy; the arbitrary classification of drugs into one of five "risk" categories currently used by the Federal Drugs Agency in the USA is an over simple approach to a complex issue.

The task of the clinician, in most of these situations, is to provide parents with the information they need to make up their own minds on such issues. To that end each statement in this section is backed by at least one or two published references. In certain cases readers may also wish to refer to the more comprehensive overviews provided in the books by Bennett, by Briggs, Freeman and Yaffe, by Schaefer, and by Hale (see p. 290).

The dose that the breastfed baby is likely to receive has been calculated, where this is possible, as a percentage of the maternal dose (both calculated on a weight for weight (mg/kg) basis), using the approach recommended in Bennett's authoritative text. Particular caution should be observed when this fraction exceeds 10% because drug elimination will initially be much slower in the baby than in the mother. It would be very useful to have steady state milk and plasma samples collected for analysis (once any effect of in utero exposure has been excluded) for some of the many drugs for which no such published information yet exists. The human milk:plasma (M:P) ratio is also given, where known. This shows the extent to which the drug is concentrated in breast milk. It is not, on its own, an indication of how much drug the baby will receive, because some drugs achieve a therapeutic effect even when the blood level is very low.

It is often said that risks can be minimised if the mother takes any necessary medication immediately after completing a breastfeed so that the baby avoids being exposed to peak maternal plasma levels. This, however, is something of a counsel of perfection for any mother who is feeding frequently and on demand, and the sort of advice usually offered by someone with more theoretical knowledge than practical bedside experience. In many situations

"the question is not whether a medicated mother should be allowed to nurse, but whether a nursing mother needs to be medicated."

Sumner Yaffe

MATERNAL MEDICATION AND THE BABY

Acebutolol *M:P ratio 9–12 (metabolite ratio 25)*

While there is no evidence of teratogenicity, this drug (and other β blockers) can cause neonatal bradycardia, mild hypotension, and transient hypoglycaemia when prescribed to a mother immediately before delivery. No complications have been reported following its use during lactation, but the drug and its metabolite, diacetolol, accumulate in breast milk, making labetalol or propranolol (q.v.) a better drug to use during lactation, especially if the dose exceeds 400 mg/day.

Rubin: *N Engl J Med* 1981;**305**:132.

Yassen: *Arch Fr Pediatr* 1992;**49**:351.

Acenocoumarol = Nicoumalone (former BAN) *M:P ratio < 0.01*

As for the monograph on warfarin in the central section of this compendium. Breastfeeding is safe.

Pauli: *Dev Brain Dysfunc* 1993;**6**:229.

Barbour: *Obstet Gynecol Clin North Am* 1997;**24**:499.

Acitretin

Vitamin A, in excess, is a known teratogen and, although this oral vitamin A derivative is rapidly excreted from the body, some is metabolised to etretinate (q.v.) and this can still be detected in the body 50 months after treatment is stopped. Use is not generally recommended during lactation either, although the baby would receive, weight for weight, only about 2% of the maternal dose when breastfed.

Rollman: *Acta Derm Venereol Stockh* 1990;**70**:487.

Pilkington: *Drugs* 1992;**43**:597.

Alcohol *M:P ratio 0.9; infant dose 4–19%*

A high alcohol consumption in pregnancy damages both the physical and mental development of the fetus. Even occasional "binge" consumption may not be without hazard and one, as yet uncorroborated, study found regular ingestion to be associated with delayed psychomotor development. The alcohol content of breast milk is over 90% of the mother's simultaneous plasma level. Side effects in the baby are rare, but drowsiness is occasionally seen.

Little: *N Engl J Med* 1989;**321**:425. (See also **322**:338.)

Mennella: *N Engl J Med* 1991;**325**:981.

Alimemazine = Trimeprazine (former BAN)

There is no evidence that this long established antihistamine is hazardous in pregnancy. While its use (either as a sedative or to control itch and pruritis) is not now recommended in children under 2 years old, use during lactation has not been reported to cause problems. Little appears in animal milk. The content in human milk does not seem to have been studied.

O'Brien: *Am J Hosp Pharm* 1974;**31**:844.

Allergic rhinitis

See the entry on antihistamines. The use of sodium cromoglicate and of nasal corticosteroids is also entirely safe during both pregnancy and lactation.

Amantadine

This antiviral drug used in parkinsonism is teratogenic in animals and its use is not recommended in pregnancy. Mothers should probably be advised against breastfeeding, although only a little appears in breast milk.

Nora: *Lancet* 1975;**ii**:607. (See also p. 1044.)

Rosa: *Reprod Toxicol* 1994;**8**:531.

Amitriptyline *M:P ratio 1.5; infant dose about 1%*

There is no good evidence that this tricyclic antidepressant and its metabolite, nortriptyline, are teratogenic. They are excreted in breast milk, but no hazardous neonatal consequences have been documented.

Bader: *Am J Psychiatr* 1980;**137**:855.

Breyer-Pfaff: *Am J Psychiatry* 1995;**152**:812.

Antidepressants

Experience shows that most tricyclic antidepressants are safe during both pregnancy and lactation. Blood levels may need monitoring once in each trimester if treatment is to be optimised. Neonatal withdrawal symptoms are sometimes

MATERNAL MEDICATION AND THE BABY

seen after birth. Monoamine oxidase inhibitors are often avoided in pregnancy because they can increase the risk of hypertension. Several of the newer selective serotonin re-uptake inhibitors (SSRIs) have now been subject to careful study. Those for which there is the most experience are listed separately in this overview. The problems seen with fluoxetine have not yet been encountered with any other drug in this class.

Dodd: *Paediatr Drugs* 2000;**2**:183.

American Academy of Pediatrics: *Pediatrics* 2000;**105**:880.

Antiemetics

Vomiting in pregnancy causes much alarm and distress. The alarm is largely misplaced since vomiting is not a sign that the pregnancy is "in trouble", and nausea is generally treatable. The antihistamine doxylamine (q.v.) is probably the best studied and most effective product, but, because of the pressure caused by (unsuccessful) litigation, it was withdrawn from sale in most parts of the world in the early 1980s. Meclozine is a widely recommended alternative that is available without prescription. Other antihistamines (see next entry) are probably equally safe. Chlorpromazine (q.v.) or metoclopramide (q.v.) will usually control severe nausea and vomiting when simpler remedies fail.

Broussard: *Gastroenterol Clin North Am* 1998;**27**:123.

Jewell: *Clin Evid* 2003;**9**:1561–70 (and updates) [SR]

Antihistamines

A wide range of prescribed products are used to treat allergy, hay fever, travel sickness, and nausea in early pregnancy. Many "over the counter" remedies for coughs and colds contain antihistamines, and some of these also cause drowsiness. None seems to be a hazard during pregnancy but it is probably best to try to avoid the frequent use of any formulation that carries the warning "may cause drowsiness: do not drive or operate machinery" while breastfeeding. Many such products also contain a sympathomimetic such as ephedrine (q.v.). Alimemazine (q.v.), although sedating, has been used uneventfully for many years. Loratadine (q.v.) causes less sedation; excretion into breast milk is minimal, but its use in pregnancy has not yet been studied.

Moretti: *Reprod Toxicol* 1995;**9**:588A.

Mazotta: *Drugs* 2000;**59**:781.

Antipsychotics

Chlorpromazine (q.v.) seems safe to use during pregnancy and lactation. Less is known about the safety of most other antipsychotic drugs, but little clinical evidence of teratogenicity seems to have emerged. American guidelines support the use of high potency agents such as fluphenazine, haloperidol, perphenazine, or trifluoperazine (as listed elsewhere in this overview) because they minimise maternal anticholinergic, hypotensive, and antihistaminergic effects, even though they may cause troublesome, if self limiting, extrapyramidal reactions in the neonate.

McElhatton: *Reprod Toxicol* 1992;**6**:475.

American Academy of Pediatrics: *Pediatrics* 2000;**105**:880.

Atenolol *M:P ratio 1:1–6:8; infant dose 8–19%*

While many cardioselective β adrenergic blocking agents (β blockers) have been used to control hypertension in pregnancy, methyldopa (q.v.) may be a better option when treatment needs to be started early, because there seems to be less risk of fetal growth retardation. There is not enough experience with use in the first trimester for all risk of teratogenicity to be excluded. β Blockers occasionally cause a generally benign fetal bradycardia, and can give rise to transient neonatal bradycardia and hypoglycaemia. Glucagon (q.v.) can be used if the side effects are severe. Alternatives to atenolol, such as labetalol or propranolol (q.v.), may be preferable during lactation because drug uptake by the breastfed baby is much lower.

Schimmel: *J Pediatr* 1989;**114**:476. (See also **115**:336.)

Marlettini: *Curr Ther Res* 1990;**48**:684.

Auranofin

As for aurothiomalate.

Aurothiomalate *M:P ratio 0:0–0:2; infant dose about 10%*

Auranofin is said to be teratogenic in animals (although the clinical significance of these findings is uncertain) but there is no good reason, on the basis of the published evidence, to avoid the use of aurothiomalate during pregnancy or lactation if other treatments for rheumatoid arthritis have proved unsatisfactory.

Tarp: *Arthritis Rheum* 1985;**28**:235.

Bennett: *Br J Clin Pharmacol* 1990;**29**:777.

Azathioprine *Infant dose about 0-1%*

The use of this immunosuppressant drug during pregnancy in mothers with an organ transplant has occasionally been associated with transient neonatal lymphopenia and thrombocytopenia, but treatment is usually well tolerated. There is no evidence of teratogenicity (although evidence is available from only a limited number of pregnancies). Although

small amounts of azathioprine appear in breast milk, oral absorption is limited and parents can be advised that, although lactation is not generally advised, no haematological signs of immunosuppression have been seen in the small number of breastfed babies studied to date.

Abukhalil: *Clin Exp Obstet Gynecol* 1995;**22**:111.

Kallen: *Scand J Rheumatol* 1998;**27**(suppl 107):119.

Azithromycin Infant dose about 5%

Azithromycin is a macrolide antibiotic like erythromycin but with a very much longer half life. Placental transfer is limited and only modest amounts appear in breast milk. There is good evidence that erythromycin is not teratogenic, but there is little published information on the use of azithromycin during pregnancy.

Czizel: *Reprod Toxicol* 1999;**13**:531.

Kelsey: *Am J Obstet Gynecol* 1994;**B170**:1375.

Baclofen M:P ratio 0-7; infant dose about 1%

There are few reports of the use of this muscle spasm relieving drug in pregnancy. Exposure to normal doses is not teratogenic in animals. Sudden treatment cessation can precipitate seizures, and there is one report of a baby developing fits after birth who failed to respond to anticonvulsant treatment but did respond as soon as a tapered dose of baclofen was started. Although there is only one report of short term use during lactation, the dose ingested would seem to be small.

Eriksson: *Scand J Clin Lab Invest* 1981;**41**:185.

Ratnayaka: *BMJ* 2001;**323**:85.

Barbiturates

Concerns about the use of any barbiturate during pregnancy or lactation are the same as for phenobarbital, as outlined in the central section of this compendium.

Benzodiazepines

Concerns about the use of any benzodiazepine during pregnancy or lactation are the same as for diazepam, as outlined in the central section of this compendium. Products with a short half life may pose less of a problem.

McElhatton: *Reprod Toxicol* 1994;**8**:461.

Bromide salts

These were said to cause neonatal sedation and rashes when given to lactating mothers. Most drugs containing bromide have now been withdrawn, but some mothers still face exposure from photographic chemicals.

Tyson: *J Pediatr* 1938;**13**:91.

Buprenorphine

This long acting analgesic (with both opioid agonist and antagonist properties that are only partially reversible with naloxone (q.v.)) is probably safe in pregnancy, although sustained use can cause addiction. Only small amounts of the drug appear in human milk, but there is one report that sustained extradural use after delivery can depress lactation (or the vigour with which the baby feeds) in the first few days of life.

Marquet: *Clin Pharmacol Ther* 1997;**62**:569.

Hirose: *Br J Anaesth* 1997;**79**:120.

Busulfan = Busulphan (former BAN)

This alkylating antineoplastic drug is used in the treatment of chronic myeloid leukaemia. Its use in the second and third trimesters of pregnancy seems reasonably safe. Use during lactation has never been studied.

Wiebe: *Crit Rev Oncol Hematol* 1994;**16**:75.

Carbimazole M:P ratio 1-1.2; infant dose 3-12%

There is no evidence of teratogenicity, but there is a theoretical risk of neonatal goitre or hypothyroidism, especially when the dose in pregnancy exceeds 30 mg/day. Most authorities consider propylthiouracil (q.v.) preferable to carbimazole, especially during lactation, because of the risk of neonatal hypothyroidism.

Low: *Lancet* 1979;ii:1011.

Cooper: *Am J Obstet Gynecol* 1987;**157**:234.

Carisoprodol M:P ratio 2-4; infant dose about 4%

To date, there have been no reports of teratogenicity or of problems associated with use during lactation. This muscular relaxant is, however, concentrated in breast milk and could conceivably make the baby drowsy. Baclofen (q.v.) may be a rather better drug to use during lactation.

Nordeng: *Ther Drug Monit* 2001;**23**:298.

Chlorpropamide

See the comments on tolbutamide. Both drugs were once quite widely used in patients with non-insulin-dependent (type 2) diabetes.

MATERNAL MEDICATION AND THE BABY

Zucker: *Arch Dis Child* 1970;**45**:696.
Towner: *Diabetes Care* 1995;**18**:1446.

Cyclosporin = Cyclosporin (former BAN) *M:P ratio 0.3; infant dose about 2%*

There is no evidence that this immunosuppressant is teratogenic. The fetal growth retardation sometimes seen could be due to the condition under treatment. More data are needed before the reproductive risk can be assessed accurately. Authorities have advised against lactation (citing neutropenia, immunosuppression, renal toxicity, a possible effect on growth, and the carcinogenic risk associated with any form of immunosuppression), but a recent report found neonatal blood levels to be immeasurably low, in keeping with calculations based on known drug milk levels. Mothers should, therefore, be allowed to make their own informed choice.

Nyberg: *Transplantation* 1998;**65**:253.
Bar-Oz: *Teratology* 1999;**59**:440.

Cisplatin *Infant dose about 35%*

There is, as yet, little information on the use of this anticancer drug during pregnancy, although a normal outcome has been documented after treatment in the second or third trimester. Severe transient neonatal leucopenia has been reported after maternal treatment shortly before delivery. Conflicting reports regarding the drug's excretion in breast milk make it difficult to advise on the safety of lactation while on treatment.

Egan: *Cancer Treat Rep* 1985;**69**:1387.
Ben-Baruch: *J Natl Cancer Inst* 1995;**84**:451.

Citalopram *M:P ratio 1.8; infant dose about 4%*

Information on the use of this antidepressant in pregnancy is, as yet, less than for several other serotonin re-uptake inhibitor drugs. No complications have been reported as a result of use during lactation, and the amount of citalopram and demethylcitalopram ingested is small.

Rampono: *Br J Clin Pharmacol* 2001;**50**:263.

Clemastine *M:P ratio 0.25–0.5*

Authorities have advised, because of a single anecdotal report of irritability, that this drug should be used only with caution during lactation, but infant intake is low – since breast milk levels are modest – making this product as safe as most other antihistamines (q.v.).

Kok: *Lancet* 1982;**i**:914.
Moretti: *Reprod Toxicol* 1995;**9**:588.

Clomifene = Clomephine (former BAN)

The use of clomifene to induce ovulation can cause multiple pregnancy but it does not increase the risk of congenital malformation. Only a few reports of inadvertent use in the first trimester of pregnancy have appeared and concern persists that continued use after conception might be teratogenic.

Greenland: *Fertil Steril* 1995;**64**:936.

Clormethiazole = Chlormethiazole (former BAN) *M:P ratio 0.9; infant dose 0.1–1.6%*

This hypnotic drug has been widely used in the UK (as a continuous IV infusion) in the management of toxæmia. High doses can cause severe neonatal hypotonia requiring ventilatory support. Little is known about possible teratogenicity in early pregnancy. Clormethiazole crosses the placenta easily and is only slowly metabolised by the baby, but only a little is found in breast milk. The dose obtained by breastfeeding is low.

Tunstall: *Br J Obstet Gynaecol* 1979;**86**:793.
Johnson: *BMJ* 1976;**i**:943.

Clotrimazole

There is no evidence that this widely used topical "over the counter" antifungal agent is teratogenic. It is not known whether the drug appears in breast milk, but absorption is minimal and topical use by the mother to treat vaginal candidiasis during pregnancy or lactation has not been associated with either fetal or neonatal toxicity.

Siffel: *Teratology* 1997;**55**:161.

Clozapine *M:P ratio 2.8–4.3; infant dose about 1%*

Women with schizophrenia who are taking this drug because of a failure to respond to other standard forms of treatment require regular monitoring for agranulocytosis, but there is, as yet, no evidence of teratogenicity. Experience of use during lactation is very limited, but women who are keen to breastfeed can be told that there is a study of one baby showing uptake to be only about 1% of the weight adjusted maternal dose.

Walderman: *Am J Psychiatry* 1993;**150**:168.
Barnas: *Am J Psychiatry* 1994;**151**:945.

Cocaine (Crack)

The consequences of use during pregnancy are hard to establish because many addicts take a range of drugs. There may also be a bias towards the reporting of those studies where a positive association has been found. There is a belief that cocaine use can cause a variety of birth defects by disrupting blood flow but a recent study found no such evidence. There is some increased risk of fetal growth retardation, reduced head size, and preterm birth. Increased irritability 2–3 days after birth usually settles without treatment. Some cocaine persists in breast milk for 24 hours after maternal use, but the effect of use during lactation does not seem to have been studied in any detail. There seems to be an associated increase in the risk of sudden infant death (cot death).

Chuch: *Ann N Y Acad Sci* 1998;**846**:12.

Behnke: *Pediatrics* 2001;**107**:e74.

Colchicine *M:P ratio ~1; Infant dose 2–8%*

Colchicine is mostly used to treat familial Mediterranean fever and gout. Amniocentesis or chorion villus biopsy should be offered to mothers on colchicine at conception because of possible cytogenicity. The few reports of use during lactation suggest that only modest amounts of colchicine reach the baby, although there is one unconfirmed report of neonatal toxicity.

Rabinovitch: *Am J Reprod Immunol* 1992;**28**:245.

Ben-Chetrit: *Semin Arthritis Rheum* 1998;**28**:48.

Co-phenotrope

Lomotil[®] (which contains 100 parts of diphenoxylate hydrochloride to 1 part of atropine sulphate) is widely used in many parts of the world to control diarrhoea. Very little is known about use during pregnancy or lactation; loperamide (q.v.) is a much better studied alternative. Excessive Lomotil use in young children is potentially extremely hazardous, the diphenoxylate causing a delayed opiate collapse.

Corticosteroids

See under prednisolone.

Cough and cold remedies

Many compound proprietary medicines are available “over the counter”. Avoid formulations with ingredients of the type mentioned in the commentary on antihistamines (q.v.). Pseudo-ephedrine use reduces prolactin levels, and could therefore impair lactation.

Cyclophosphamide

This anticancer drug would seem to be teratogenic when given in the first trimester, but there is less risk of fetotoxicity later in pregnancy. Treatment can affect subsequent fertility, and unconfirmed reports of problems following occupational exposure have resulted in strict guidelines being issued for the way in which staff should handle this drug. Breastfeeding would seem unwise. Enough of the drug seems to appear in breast milk to cause some degree of neonatal neutropenia.

Wiernik: *Lancet* 1971;**i**:912.

Mutchinick: *Teratology* 1992;**45**:329.

Danazol

This synthetic androgen used in the management of a range of conditions including endometriosis can cause marked female virilisation if exposure to a dose of 200 mg or more per day persists beyond the eighth week of pregnancy. Male fetuses are unaffected and the risk of other non-genital anomalies does not seem to be increased. Use during lactation does not seem to have been studied but is generally discouraged.

Brunskill: *Br J Obstet Gynaecol* 1992;**99**:212.

Dapsone *M:P ratio 0.4; infant dose about 20%*

No problems emerged when the drug was used to prevent or treat malaria, often in combination with pyrimethamine (q.v.), although the baby ingests a significant amount of the drug during lactation. Dapsone is now more widely used in the management of leprosy. It can cause haemolytic anaemia, particularly in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Keuter: *BMJ* 1990;**301**:466.

Edstein: *Br J Clin Pharmacol* 1986;**2**:733.

Dexamfetamine = Dexamphetamine (former BAN) *M:P ratio 2.8–7.5; infant dose about 6%*

Amphetamines have been widely abused for their euphoric effect, but evidence of teratogenicity has not been established. Neonatal symptoms are usually mild, even with sustained maternal use, when this is the only drug taken. Tolerance can develop, but physical dependence has not been documented. An acute overdose can cause symptoms similar to those seen with methylenedioxymethamphetamine (ecstasy). Most authorities deprecate any exposure of a

MATERNAL MEDICATION AND THE BABY

baby to this central nervous system stimulant as a result of dexamfetamine's concentration in breast milk, but documentary evidence of harm is hard to find.

Steiner: *Eur J Clin Pharmacol* 1984;**27**:123.

Diethylstilbestrol = Stilboestrol (former BAN)

After this synthetic non-steroidal oestrogen had been given, between 1940 and 1971, to 6 million women during early pregnancy to prevent miscarriage, prematurity, and intrauterine death, it was found to have caused later vaginal adenocarcinoma in over 400 of the girls born to these mothers. A range of serious reproductive disorders have since been documented in male and female offspring, while controlled studies have shown that diethylstilbestrol does nothing to prevent the problems for which it was originally given. There are no recognised hazards associated with treatment during lactation.

Robboy: *JAMA* 1984;**252**:2979.

Mittendorf: *Teratology* 1995;**51**:435.

Disopyramide M:P ratio 0.5–1.0; infant dose about 15%

The teratogenic or fetotoxic potential of this antiarrhythmic drug has not been well studied. Use during lactation has not been reported to cause problems, but the baby does ingest a very significant weight adjusted quantity of the drug (and its active anticholinergic metabolite). The drug has a demonstrable oxytocic effect and could increase the risk of preterm labour.

Tadmor: *Am J Obstet Gynecol* 1990;**162**:482.

Ellsworth: *Ann Pharmacother* 1989;**23**:56.

Dothiepin = Dosulepin (rINN) M:P ratio 0.8–1.6; infant dose about 5%

There are few published data on the risks associated with exposure to this tricyclic antidepressant during pregnancy. Use during lactation has not been reported as causing a problem. Amitriptyline (q.v.) is a better studied alternative. Ilett: *Br J Clin Pharmacol* 1992;**23**:635.

Doxepin M:P ratio 0.7–1.7; infant dose 1–3%

Very little is known about the use of this tricyclic antidepressant during pregnancy, but there is no reason to suspect teratogenicity. Calculations suggest that breastfeeding should expose the baby to only a small amount of this drug and its slowly cleared active metabolite (*N*-desmethyldoxepin), but there are two reports of a breastfed baby becoming seriously hypotonic. In the first case the baby had a blood level of the metabolite that was inexplicably high if the child's only exposure to the drug was from maternal milk. The onset of symptoms also seemed very sudden. In the second the blood level was much lower and the drowsiness rather less clearly related to maternal medication. Uncertainties over use during lactation clearly remain worryingly unresolved.

Kemp: *Br J Clin Pharmacol* 1985;**20**:497.

Frey: *Ann Pharmacother* 1999;**22**:690.

Doxylamine

Doxylamine is an antihistamine that was widely used for many years to control nausea in pregnancy. It was marketed (as Debendox® in the UK and as Bendectin® in the USA) as a compound tablet with pyridoxine, but withdrawn in 1983 as a result of the adverse publicity generated by litigation, even though there was more evidence of efficacy and better evidence of safety than for any other product. It still remains on sale in Canada (as Dialectin®).

McKeigue: *Teratology* 1994;**50**:27.

Brent: *Reprod Toxicol* 1995;**59**:337.

Ephedrine

None of the sympathomimetic drugs seem to be teratogenic. There is a single anecdotal report suggesting that the maternal use of ephedrine during lactation could cause the baby to become irritable, but studies of pseudoephedrine and terbutaline (the only two sympathomimetics studied in any detail), suggest that the amount ingested is usually too small to affect the baby. Pseudoephedrine use may reduce milk production.

Mortimer: *Pediatrics* 1977;**60**:780.

Boreus: *Br J Clin Pharmacol* 1982;**13**:731.

Findlay: *Br J Clin Pharmacol* 1984;**18**:901.

Ergotamine

There is no known teratogenic effect, but the risk of ergotism should be borne in mind if this drug is used to treat migraine in pregnancy. Significant exposure in the breastfed baby could also cause ergotism, and repeated medication could inhibit lactation.

Raymond: *Teratology* 1995;**51**:344.

Hosking: *Aust N Z Obstet Gynaecol* 1996;**36**:159.

Ethambutol *M:P ratio 1; infant dose 1–2%*

This drug can be safely used to treat tuberculosis during pregnancy and lactation. There are no reports of any adverse effect from use during lactation. Calculations, however, suggest that the plasma level in a young breastfed baby may approach therapeutic levels. Ethambutol is not generally used in children under 6 years old because it could be difficult to detect the onset of optic neuritis (an occasional but important adverse effect).

Snider: *Am Rev Respir Dis* 1980;**122**:65.
Medcill: *Obstet Gynecol Surv* 1989;**44**:81.

Ethosuximide *M:P ratio 0.8–1.0; infant dose over 50%*

There is relatively little evidence that this anticonvulsant is teratogenic in humans. The drug enters breast milk freely. While there is no evidence that this is of any clinical significance, there have been anecdotal reports of disturbed neonatal behaviour, and it is known that plasma levels in the breastfed baby sometimes approach those seen in the mother.

Kuhn: *Br J Clin Pharmacol* 1984;**18**:671.
Samren: *Epilepsia* 1997;**38**:981.

Etretinate

This oral vitamin A derivative used to treat severe psoriasis and congenital ichthyosis is a serious teratogen; pregnancy should not be contemplated until at least 3 years after treatment is stopped. Lactation is also generally considered unwise.

Geiger: *Dermatology* 1994;**189**:109.
Gollnick: *Br J Dermatol* 1996;**135**(suppl 49):6.

Fluoxetine *M:P ratio 0.3–0.5; Infant dose 6–13%*

There is no evidence that this relatively well studied, new antidepressant is teratogenic and follow up studies have been reassuring. However, significant amounts are ingested in breast milk, the drug has a long half life, and irritability and somnolence have now been reported in several babies exposed to fluoxetine both before and after delivery. Sertraline (q.v.) is less studied, but it may turn out to be a better drug to use in late pregnancy when the mother wishes to breastfeed.

Mattson: *Teratology* 1999;**59**:376.
Nulman: *Am J Psychiatry* 2002;**159**:1889.

Fluphenazine

There is no evidence of teratogenicity but treatment with this antipsychotic drug during pregnancy may result in the baby showing hyperactivity for some weeks after delivery. Use during lactation has not been studied.

Auerbach: *Neurotoxicol Teratol* 1992;**14**:399.

Fluvoxamine *M:P ratio 0.3; infant about 1%*

There is no evidence, as yet, that this selective serotonin re-uptake inhibitor is teratogenic. Minimal quantities are ingested from breast milk.

Wright: *Br J Clin Pharmacol* 1991;**31**:209.
Hendrick: *Br J Psychiatry* 2001;**179**:163.

Glibenclamide = Glyburide (USAN)

This is a sulphonylurea used in the treatment of non-insulin-dependent (type 2) diabetes mellitus, which, unlike tolbutamide (q.v.), is said to cross the human placenta only in trace quantities. Use has, so far, been studied only in "gestational" diabetes, a poorly characterised condition of uncertain significance that probably calls for no active treatment. Use during lactation does not seem to have been studied.

Langer: *N Engl J Med* 2000;**343**:1134–8.

Griseofulvin

Itraconazole (q.v.) has now largely replaced griseofulvin in the treatment of fungal skin infections. Griseofulvin is known to be teratogenic and embryotoxic in some animals and has, as a result, been little used during pregnancy. No information exists on use during lactation.

Anon: *Med Lett Drugs Ther* 1976;**18**:17.

Halofantrine

Little is known about the use of this drug to treat chloroquine resistant falciparum malaria during pregnancy or lactation. The manufacturers warn against its use because extremely high doses are teratogenic in animals, but such information is of limited clinical relevance.

Phillips-Howard: *Drug Safety* 1996;**14**:131.

MATERNAL MEDICATION AND THE BABY

Haloperidol *M:P ratio 2–4; infant dose about 3%*

There is no evidence that this antipsychotic is teratogenic. Maternal treatment during lactation results in the baby ingesting only a small amount of this drug, but there are no reports of this sedating the baby or affecting developmental progress.

Whalley: *BMJ* 1981;**282**:1746.

Yoshida: *Psychol Med* 1998;**28**:81.

Headache

See under migraine.

Herbal remedies

The use of herbal remedies during pregnancy has been poorly studied. The book by Thomas Hale (see bibliography) summarises the information available on the use of some 20 herbal medicines during lactation, while eight get a mention in the latest edition of the book by Briggs. It would seem that the use of blue cohosh (blue ginseng) is definitely contraindicated, and uncertainties exist over the use of chamomile, comfrey, and kava-kava. St John's wort seems safe, but may interact with other medications.

Howard: *Clin Perinatol* 1999;**26**:447.

Hale: *Medications and Mothers' Milk*, 10th ed. Amarillo, TX: Pharmasoftware, 2002.

Imipramine *M:P ratio 0.7; infant dose <2%*

There is no evidence of teratogenicity in humans. A little of the drug appears in breast milk, but there is no evidence that its use is unwise during lactation. Plasma levels are best monitored during pregnancy to optimise treatment.

McElhatton: *Reprod Toxicol* 1996;**10**:285.

Nulman: *N Engl J Med* 1997;**336**:258.

Iodine

While iodine deficiency during pregnancy can cause cretinism and other problems (as outlined in the monograph on potassium iodate), excessive intake can cause fetal goitre and hypothyroidism. Even the use of an iodine containing expectorant, topical antiseptic, or vaginal gel in late pregnancy or after delivery may alter maternal and fetal thyroid function and increase the iodine content of the mother's breast milk. The danger to the baby during lactation can be exaggerated, however, because thyroxine and thyroid stimulating hormone levels are usually normal even when serum and urinary iodine levels are grossly elevated. Extended exposure could be more hazardous, however. Premature babies seem at greatest risk.

Linder: *J Pediatr* 1997;**131**:434.

Watanabe: *J Obstet Gynecol Res* 1998;**24**:285.

Isotretinoin

Isotretinoin is an isomer of the acid form of vitamin A. Topical and oral preparations are available. The hazards associated with maternal use are the same as for tretinoin (q.v.).

Itraconazole

There is evidence of dose related toxicity and teratogenicity in animals. Brief exposure to this antifungal during early pregnancy is certainly compatible with a normal pregnancy outcome, but other azoles are known to be capable of inducing malformations in humans. Systemic use during lactation has not been studied, but it can be predicted that sustained exposure would cause widespread tissue drug accumulation in the child. Fluconazole (q.v.) is probably the antifungal of choice when systemic treatment is necessary during lactation (or after the first trimester of pregnancy), and is virtually unabsorbed when applied topically.

Bar-Oz: *Am J Obstet Gynecol* 2000;**183**:617.

Briggs: *Drugs in pregnancy and lactation*, 6th ed. Philadelphia, PA: Williams & Wilkins, 2002:744.

Ketoconazole

Little specific information exists, but the concerns relating the related azole, itraconazole, probably apply.

Moretti: *Am J Obstet Gynecol* 1995;**173**:1625.

Laxatives

Bran, and other bulk-forming laxatives such as methylcellulose, can be taken with complete safety during pregnancy and lactation. So can lactulose and bisacodyl. Laxatives containing anthraquinones (such as cascara and dantron) could, when given to a mother, conceivably cause increased gastric motility in the breastfed baby. A single dose of senna (equivalent to 15 mg of sennoside B) can also be given with complete safety. The drug is only minimally absorbed after oral administration, and cannot be detected in breast milk.

Bonapace: *Gastroenterol Clin North Am* 1998;**27**:197.

Levonorgestrel

There is no evidence of teratogenicity if the "morning after" pill is taken in error during early pregnancy, and there is no contraindication to its use during lactation.

Lithium *M:P ratio 0.3–0.7; infant dose about 30%*

Treatment with lithium has transformed the management of manic depressive illness, but its use during pregnancy calls for careful judgement. While use in the first trimester carries enough risk to warrant a detailed cardiac anomaly scan, the risk of a major malformation is low as long as the mother's plasma level is carefully monitored; however, discontinuing treatment may cause relapse of the manic depression. Aim for a level of 0.5–0.8 mmol/l 12 hours after ingestion, remembering that renal clearance increases 50% during early pregnancy and decreases again abruptly soon after delivery. Support is also needed to help the mother make an informed decision about breastfeeding. The risk of neonatal toxicity is highest shortly after birth because of the very abrupt change in maternal clearance. Maternal treatment during lactation exposes the child to a lithium level that is about one third of what it was during fetal life. It is probably advisable to monitor thyroid function at intervals.

Llewellyn: *J Clin Psychiatry* 1998;**59**(suppl 6):57.

Viguera: *Am J Psychiatry* 2000;**157**:179.

Loperamide *M:P ratio 0.4; infant dose < 0.1%*

Imodium® (which is available "over the counter" in the UK) controls diarrhoea by inhibiting intestinal motility. Absorption is limited and use during pregnancy or lactation seems safe.

Nikodem: *Eur J Clin Pharmacol* 1992;**42**:695.

Einarson: *Can J Gastroenterol* 2000;**14**:185.

Loratadine *M:P ratio 1.2; infant dose about 1%*

This non-sedating antihistamine is often used to treat allergic rhinitis. Use in pregnancy has not yet been studied systematically, but there is no reason to suspect teratogenicity. Maternal use during lactation will result in the baby ingesting only minimal amounts of the drug.

Hilbert J: *J Clin Pharmacol* 1988;**28**:234.

Lione: *Reprod Toxicol* 1996;**10**:247.

Lysergic acid (LSD)

There are no published epidemiological studies of LSD use in pregnancy. While there is no evidence that *pure* LSD harms the fetus when taken on its own (in the absence of maternal toxicity), the long term effect of fetal exposure has not been studied. Drug transfer into breast milk has not been studied either but can be expected to occur and, since even low doses can be hallucinogenic, use during lactation seems most unwise.

Aase: *Lancet* 1970;**ii**:100.

Long: *Teratology* 1972;**6**:75.

Maprotiline *M:P ratio 1.4; infant dose < 2%*

There is no animal evidence of teratogenicity, but little experience of use during human pregnancy. The increased risk of seizures may make it more appropriate to choose some other tricyclic antidepressant during pregnancy. Little is ingested from breast milk.

Mendalis: *ADR Highlights* 1983;**83**:1.

Lloyd: *J Int Med Res* 1997;**5**(suppl 4):122.

Marijuana (Cannabis) *M:P ratio 8*

There is very little evidence that this widely used illicit drug jeopardises fetal development or affects the behaviour of the baby after birth, but case control studies have shown that maternal use is associated with an increased risk of sudden infant death (even after allowing for the stronger correlation with tobacco use during and after pregnancy). Use by the mother's partner also remains an independent risk factor. No consistent effects have been seen when marijuana is used during lactation, even though the drug and its metabolites appear to be concentrated in breast milk. Traces persist in the urine for many weeks.

Dreher: *Clin Pediatr* 1994;**93**:254.

Blair: *BMJ* 1996;**313**:195.

Mebendazole

This poorly absorbed antihelminthic is widely used to treat hookworm, roundworm, threadworm, and whipworm infection. The drug is embryotoxic in rats but there are no reports of teratogenicity in humans. Treating serious intestinal helminthic infection can improve pregnancy outcome. Intake from breast milk would be negligible.

De Silva: *Lancet* 1999;**353**:1145.

Medroxyprogesterone (Depo-provera®)

There is no evidence that inadvertent use of this long acting contraceptive is hazardous during pregnancy, and no evidence that its use after delivery will affect lactation, particularly if the administration of the first injection is delayed

MATERNAL MEDICATION AND THE BABY

until at least 3 days after delivery. Indeed, there is some evidence that it raises prolactin levels and increases milk production. See also the entry for oral contraceptives.

Kennedy: *Contraception* 1997;**55**:347.

Meprobamate *M:P ratio 2–4*

When this drug is used for a maternal anxiety state it accumulates in breast milk. Although the effect on the baby is not known, its use is best avoided during lactation. Little is known about its potential teratogenicity.

Wilson: *Clin Pharmacokinet* 1980;**5**:1.

Mercaptopurine (6-MP)

Miscarriage, stillbirth, and low birth weight have all occurred when this anticancer drug is used in pregnancy, but it is difficult to know if this is the result of drug treatment or not. A few congenital malformations have been seen, but no pattern of abnormality has emerged after monotherapy. Several babies have, however, shown transient bone marrow depression at birth. Breastfeeding while on treatment does not seem to have been reported. Azathioprine (q.v.), which is transformed into mercaptopurine in the body, has occasionally been taken during lactation without apparent ill effect. Pregnancy *after* treatment with mercaptopurine for choriocarcinoma has generally been uneventful.

Song: *Am J Obstet Gynecol* 1988;**158**:538.

Green: *Arch Pediatr Adolesc Med* 1997;**151**:379.

Mesalazine *Infant dose (of the metabolite) about 7%*

Mesalazine (5-aminosalicylic acid), the prodrug balsalazide, and the dimer olsalazine, can all be used with safety to treat women with inflammatory bowel disease during pregnancy. Use during lactation also seems safe, although diarrhoea has been reported in a few babies.

Christensen: *Acta Obstet Gynecol Scand* 1994;**74**:399.

Marteau: *Aliment Pharmacol Ther* 1998;**12**:1101.

Metformin *Infant dose < 1%*

Although there is no evidence that the use of this biguanide as an oral antihyperglycaemic is teratogenic, insulin is generally considered to provide a better strategy for minimising the fetal risks associated with diabetic pregnancy (except in a developing world setting). There is no evidence that use in late pregnancy increases the risk of neonatal hypoglycaemia, and exposure to metformin in breast milk is minimal.

Coetzee: *Diabetes Res Clin Pract* 1986;**5**:281.

Methamfetamine (Speed)

Most of the comments made about dexamfetamine probably apply. There is, however, some suggestion of an excess of babies with gastroschisis or intestinal atresia (suggesting brief fetal vascular disruption).

Oro: *J Pediatr* 1987;**111**:571.

Sherman: *Pediatr Res* 2001;**49**:364A.

Methotrexate *M:P ratio < 0.1; infant dose 0.3%*

This folic acid antagonist is used in the treatment of rheumatic disease and some cancers. There is clear evidence of teratogenicity, which is probably dose related, and an increased risk of miscarriage, but most children born to mothers on low dose treatment seem normal at birth. Most standard texts advise mothers taking methotrexate not to breastfeed, and few seem to have done so, although the amount ingested by the baby seems to be less than 1% of the lowest antineoplastic dose.

Johns: *Am J Obstet Gynecol* 1972;**112**:978.

Lloyd: *Q J Med* 1999;**92**:551.

Methylenedioxymethamfetamine (Ecstasy)

This stimulant drug, structurally related to dexamfetamine (q.v.) and mescaline, is subject to abuse, although dependence has not been reported. The response to a fixed dose varies greatly. Hyperthermia, hyponatraemia (possibly due to inappropriate ADH secretion), and convulsions are amongst the more severe complications, making experimental intake during pregnancy potentially hazardous for the fetus. It can be predicted that the drug would transfer into breast milk, so exposure should be avoided during lactation.

Henry: *Lancet* 1992;**340**:384.

McElhatton: *Lancet* 1999;**354**:1441.

Migraine and headache

The aim should be to control attacks during both pregnancy and lactation by early treatment with paracetamol in combination, if necessary, with codeine and/or caffeine (q.v.). It is said that aspirin (q.v.) should be avoided during lactation, but occasional use is harmless. The nausea associated with migraine may need treating with metoclopramide (q.v.) to enable one of the above analgesics to be given by mouth. Parenteral chlorpromazine (q.v.) may rarely be

necessary. Products containing ergotamine (q.v.) should probably be avoided. Sumatriptan (q.v.) is the only newer remedy to have received enough study as yet for use to be recommended if other strategies fail.
Spigset: *Paediatr Drugs* 2000;**2**:223.

Misoprostol

This synthetic prostaglandin analogue used in the management of peptic ulceration (and therapeutic abortion) can probably be used during lactation (as long as diarrhoea is watched for) but should not be used during pregnancy because it causes increased uterine activity. There are increasing reports of teratogenicity.

Schuler: *Teratology* 1997;**55**:36.

Gonzalez: *Lancet* 1998;**351**:1624.

Nalidixic acid *M:P ratio 0.06; infant dose < 0.1%*

This antibiotic has damaged growing cartilage in animals but its use to treat urinary infection during pregnancy does not seem to have caused detectable fetal damage. Many texts warn that this drug could cause haemolysis in a baby with glucose-6-phosphate dehydrogenase (G6PD) deficiency but, in the one published case report on which this much repeated warning is based, the baby did not have G6PD deficiency. Other strategies for treatment can usually be found. Use in the neonatal period has been reported to cause a metabolic acidosis.

Belton: *Lancet* 1965;**ii**:691.

Murray: *BMJ* 1981;**282**:224.

Nausea and vomiting in pregnancy

See under antiemetics.

Nicotine

The effects of smoking during pregnancy are well known. Nicotine, and its metabolite cotinine, also appear in breast milk. The amount present in the urine of a breastfed baby is 10 times as high as the amount present in a baby whose mother smokes but gives her baby milk in a bottle. Nicotine patch use will cause less exposure than heavy smoking, but that will not be true for gum use. Mothers can, however, be advised that the advantages of breastfeeding greatly outweigh the hazards of nicotine exposure from breast milk. Parents should avoid smoking in the presence of their baby.

Mascola: *Am J Public Health* 1998;**88**:893.

Schatz: *J Hum Lactation* 1998;**14**:161.

Nitrazepam *M:P ratio 0.3; infant dose about 2%*

As for the monograph on diazepam in the central section of this compendium.

Matheson: *Br J Clin Pharmacol* 1990;**30**:787.

Nitrofurantoin *M:P ratio 6; infant dose about 6%*

There is no known hazard to the fetus, although there is a theoretical risk that the baby could develop haemolytic anaemia when the drug is given in late pregnancy, during labour, or while the mother is breastfeeding (especially in the presence of glucose-6-phosphate dehydrogenase (G6PD) deficiency).

Ben David: *Fundam Clin Pharmacol* 1995;**9**:503.

Gerk: *Pharmacotherapy* 2001;**21**:669.

Non-steroidal anti-inflammatory drugs (NSAIDs)

See the monograph on ibuprofen in the central section of this compendium. Paracetamol (q.v.) is generally considered a safer product to recommend to anyone seeking "over the counter" pain relief during pregnancy. Diclofenac (which requires a prescription) may be a good option during lactation because the short serum half life will limit transfer into milk (although no formal studies of uptake by the baby have yet been published).

Neilsen: *BMJ* 2001;**308**:266.

Nortriptyline *M:P ratio 0.9–3.7; infant dose about 2%*

As for amitriptyline.

Wisner: *Am J Psychiatry* 1991;**148**:1234.

Octreotide

This long acting octapeptide analogue of somatostatin has been used to control symptoms in patients with acromegaly, carcinoid tumour, or gastroenteropancreatic endocrine tumour. While the manufacturers advise that pregnancy should be avoided by any mother taking octreotide, there are at least three recorded cases where the drug was specifically, and successfully, used to combat infertility. The resultant babies were normal at birth. It is not known whether the drug appears in breast milk but, since it is not active when taken by mouth, supervised use during lactation seems unlikely to pose much risk to the baby.

Caron: *J Clin Endocrinol Metab* 1996;**81**:1164.

MATERNAL MEDICATION AND THE BABY

Oral contraceptives

Most oral contraceptives contain an oestrogen and a progestogen. There is very little evidence of teratogenicity, although some synthetic oestrogens like diethylstilbestrol (q.v.) can have a profound effect on genital tract development. Oestrogens can depress lactation, so mothers wishing to breastfeed should, where possible, use a progestogen only pill (mini pill) starting 3 or more weeks after birth for the first 6 months after delivery. If there is evidence that this has proved unreliable in the past, depot medroxyprogesterone (q.v.) should be considered.

Koetsawang: *Int J Gynecol Obstet* 1987;**25**(suppl):115. (See also p. 129.)

Martinez-Frias: *Teratology* 1998;**57**:8.

Oral hypoglycaemic agents

There is no clear evidence of teratogenicity, but also no established consensus over the use of such drugs during pregnancy. Chlorpropamide, glibenclamide, and tolbutamide (q.v.) can all cause serious early neonatal hypoglycaemia, but this has not been reported with metformin (q.v.). Other oral hypoglycaemic agents have not yet received much study. The use of these drugs during lactation has not been investigated but they are probably safe.

Panic disorder

Fluoxetine (q.v.) is probably the best preventive drug to use when cognitive behavioural techniques prove inadequate. If a benzodiazepine is indicated for acute symptoms, lorazepam (q.v.) has the advantage of a relatively short half life, although the baby may show withdrawal symptoms.

American Academy of Pediatrics. Committee on Drugs. *Pediatrics* 2000;**205**:880.

Paroxetine M:P ratio 0.1; infant dose about 2%

This drug is increasingly used for panic attacks and for obsessive compulsive disorder. There is no evidence of teratogenicity, but withdrawal symptoms (possibly due to serotonin toxicity) seem more common than with other serotonin reuptake inhibitors. Up to a quarter of all babies suffer from at least some symptoms for 1–2 weeks. An increased risk of miscarriage also seems possible, making fluoxetine (q.v.) a better drug to use during pregnancy. Paroxetine appears in breast milk, but no problems have been reported with use during lactation.

Misri: *J Clin Psychiatry* 2000;**6**:828.

Coste: *Arch Pediatr Adolesc Med* 2002;**156**:1129.

Perphenazine M:P ratio 1; infant dose < 1%

This antipsychotic does not seem to be teratogenic, but the baby may show hyperactivity and extrapyramidal signs (as with fluphenazine (q.v.)). Lactation is considered safe.

Stone: *Am J Obstet Gynecol* 1977;**128**:486.

Olesen: *Am J Psychiatry* 1990;**147**:1378.

Phencyclidine (PCP or "angel dust") M:P ratio > 10

This illicit hallucinogen is a potent analgesic and anaesthetic related to ketamine. Despite placental transfer, most newborns are healthy, but some show toxic irritability alternating with lethargy. Teratogenicity is not suspected and no prolonged neurobehavioural abnormalities have been documented. Because the drug is concentrated in breast milk, exposure should be avoided during lactation.

Nicholas: *Am J Obstet Gynecol* 1982;**143**:143.

Wachsmann: *Am J Drug Alcohol Abuse* 1989;**15**:31.

Phenindione Infant dose about 15%

This drug, like warfarin (q.v.), should be avoided in pregnancy. Heparin (q.v.) is the drug of choice when anticoagulation is called for during pregnancy because it does not cross the placenta. Anticoagulation with phenindione in pregnancy carries fetal risks similar to those seen with warfarin treatment. Although there is only one report of maternal treatment causing a breastfed baby to bleed after surgery, warfarin is undoubtedly a safer drug to use during lactation.

Goguel: *Rev Fr Gynecol Obstet* 1970;**65**:409.

Phenybutvon-Kries: *Monatsschr Kinderheilkd* 1993;**141**:505.

Phenylbutazone

This drug is not now as widely prescribed as other non-steroidal anti-inflammatory drugs (q.v.) and there is only limited evidence on safety during pregnancy or lactation. Animal evidence suggests that use could decrease fertility by blocking blastocyst implantation. The drug is excreted in breast milk, producing serum levels in the baby of a fifth to a half of those found in the mother.

Dawood: *Am J Obstet Gynecol* 1993;**169**:1255.

Leuxner: *Munch Med Wochenschr* 1956;**98**:84.

Prednisolone *M:P ratio 0.16; infant dose about 3%*

While corticosteroid administration to animals can cause facial clefting, there is no evidence that this happens in humans. Prolonged and repeated use can cause some degree of fetal growth retardation, but this is not a problem with short term use. Although betamethasone and dexamethasone (q.v.) readily cross the placenta, 90% of prednisolone is inactivated. Even moderately high dose systemic treatment with prednisolone during lactation (60–80 mg/day) does not seem to depress endogenous cortisol production in the baby. Whether this also holds true for other corticosteroids is less clear. Greenberger: *Clin Pharmacol Ther* 1993;**53**:324.
Rayburn: *Am J Reprod Immunol* 1992;**28**:138.

Primaquine

There are almost no published reports on the use of this antimalarial drug during either pregnancy or lactation, and it has been suggested that use (to eliminate dormant liver organisms) should usually be delayed until after delivery. Haemolysis is a potential problem, particularly in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Plasma drug levels are low, so milk levels are also likely to be fairly low.
Anonymous: *MMWR* 1978;**27**:81.

Primidone *M:P ratio 0.5–0.8; infant dose 15–25%*

This anticonvulsant can be teratogenic in mice, but there are no convincing reports of teratogenicity in humans. Studies are difficult to interpret because epilepsy itself may increase the risk of malformation, and many epileptic patients are on more than one drug. The risk of neonatal haemorrhage (as for phenobarbital (q.v.)) is easily corrected by giving vitamin K (q.v.) at birth. Treatment during lactation has been associated with reports of transient drowsiness. Kaneko: *Jpn J Psychiatry Neurol* 1993;**47**:306.
Olafsson: *Epilepsia* 1998;**39**:887.

Procainamide *M:P ratio 4; infant dose about 7%*

Use to treat maternal arrhythmia poses no recognised risk to the baby. The drug has also been used with (some) success for fetal supraventricular tachycardia. While the amount ingested by the baby is relatively small, the long term effect of maternal use during lactation has not yet been properly documented.
Allen: *Clin Pharm* 1993;**12**:58.
Itto: *Clin Perinatol* 1994;**21**:543.

Proguanil

Malaria can be a devastating disease during pregnancy and prophylaxis with proguanil is known to be of considerable value in areas where infection is endemic. Side effects are minimal with the standard prophylactic dose (200 mg once a day) and there is no evidence of teratogenicity. Consider giving a daily folate supplement too. More needs to be learnt about maternal use during lactation but it certainly exposes the baby to much less drug than would result from standard prophylactic treatment (3 mg/kg once a day).
Anonymous: *BMJ* 1984;**289**:1296.
Mutabingwa: *Trop Geogr Med* 1993;**45**:49. (See also pp. 6 and 150.)

Promethazine

Promethazine has been widely used for nausea in pregnancy, without hazard. There is one report of use during labour causing neonatal respiratory depression. Some antihistamines (q.v.) could conceivably cause neonatal drowsiness if given to the lactating mother.
Lione: *Reprod Toxicol* 1996;**10**:247.

Propylthiouracil *M:P ratio 0.6; infant dose 0.3%*

Propylthiouracil is used to control maternal thyrotoxicosis during pregnancy. It can also be given with safety to the lactating mother (despite earlier reports to the contrary). Other thiouracil drugs seem to be less safe.
O'Doherty: *BMJ* 1999;**318**:5.
Atkins: *Drug Safety* 2000;**23**:229.

Pyrazinamide

While there is little published information, UK guidelines support the short term use of this drug to treat tuberculosis during both pregnancy and lactation. Signs of liver toxicity need to be watched for. The breastfed baby probably gets less than 1% of the maternal dose on a weight for weight basis, but this estimate is based on a single case report.
Holdiness: *Arch Intern Med* 1984;**144**:1888.
Joint Tuberculosis Committee of the British Thoracic Society: *Thorax* 1998;**53**:536.

Radiopharmaceuticals

Breastfeeding should normally be suspended, at least briefly, if the mother has to be prescribed a radioactive drug. The appropriate period of suspension varies. For some radionuclides, such as chromium 51, indium 111, and thallium 201, it is generally thought necessary to express and discard milk for only 4 hours. With iodine 123, and orthoiodohippuric

MATERNAL MEDICATION AND THE BABY

acid labelled iodine 125 and 131, an interval of 2 days is usually necessary. For other products labelled with iodine 131, and with phosphorus 32, gallium 67, and selenium 75, the period of significant radioactivity may exceed 2 weeks, making any attempt at continued lactation generally inappropriate. Technetium labelled radiopharmaceuticals (^{99m}Tc) are currently used for 75% of all radioactive imaging procedures. With many of these products it is necessary to express and discard milk for only 4 hours, but, with sodium pertechnetate, milk may need to be expressed and discarded for a day if the dose to the infant is to be kept below 1 mSv. The same is true after the technetium labelling of red and white blood cells and of human serum albumin microaggregates. See also the separate comment on x-ray contrast media. Bennett: *Drugs and Human Lactation*, 2nd ed. Chapter 8. Amsterdam: Elsevier, 1996:609–77.

US Nuclear Regulatory Commission. *Regulatory guide* 8.39. April 1997, Table 3.

Sertraline M:P ratio 1.5–2. Infant dose < 2%

There is no evidence that this selective serotonin reuptake inhibitor is teratogenic, and only minimal quantities are ingested from breast milk. Although there is one report of a baby displaying what were thought to be withdrawal symptoms after delivery, it seems a good antidepressant to offer any woman wishing to breastfeed.

Shuey: *Teratology* 1992;**46**:367.

Epperson: *Am J Psychiatry* 2001;**158**:1631.

Solvent abuse

A wide range of products, including adhesives (containing toluene and xylenes), aerosols (containing butane and halons), lighter fuel (containing *n*-butane), typewriter correction fluid (containing trichloroethane), and solvents, have been associated with abuse. Other sources include petrol, paint stripper, and nail varnish remover. Excitement and euphoria can be followed by headache, dizziness, blurred vision, ataxia, and coma. Toluene, in particular, can be toxic to the kidneys, and to the central nervous system. Solvent abuse in pregnancy seems to be associated with an increased risk of prematurity and perinatal death, and there are suggestions that toluene exposure could be teratogenic. Withdrawal symptoms have been described 1–2 days after birth in babies of such mothers. A telltale odour may sometimes be present. Pearson: *Pediatrics* 1994;**93**:211. (See also p. 216.)

Tenenbein: *Arch Dis Child* 1996;**74**:F204.

Statins

Statins reduce serum cholesterol levels and are used in the primary and secondary prevention of coronary heart disease. Licensed UK preparations include atorvastatin, fluvastatin, pravastatin, and simvastatin. A related drug, lovastatin, is teratogenic in rats and mice and may also be teratogenic in humans, making it hard to justify the prophylactic use of any statin during pregnancy. Minimal amounts of pravastatin appear in breast milk (< 1% of the weight related dose) but too little is known to recommend the use of statins during lactation.

Pan: *J Clin Pharmacol* 1988;**28**:942.

Manson: *Reprod Toxicol* 1996;**10**:439.

Streptomycin

Ototoxicity is a potential problem, as with every aminoglycoside. Deafness has been seen after fetal exposure, but seems rare. There are, nevertheless, good grounds for choosing a different, less ototoxic, antibiotic during pregnancy, except when treating severe drug resistant tuberculosis. Streptomycin is excreted into breast milk but poorly absorbed by the gut, making maternal treatment compatible with lactation.

Rubin: *Am J Dis Child* 1951;**82**:14.

Donald: *Cent Afr J Med* 1991;**37**:268.

Sulfasalazine = Sulphasalazine (former BAN) M:P ratio 0.3–0.6; infant dose 6–10%

This was the main drug used in the management of ulcerative colitis and Crohn's disease until mesalazine (q.v.) came on the market. There is no evidence that it is teratogenic, or that maternal use increases the risk of kernicterus in the baby after birth, even though one of the metabolic breakdown products is a sulphonamide (these drugs are known to interfere with the binding of bilirubin to plasma albumin). This remains, nevertheless, a theoretical possibility. While some sulfasalazine appears in breast milk, most authorities consider treatment fully consistent with continued breastfeeding, although one breastfed baby is reported to have developed chronic bloody diarrhoea, which ceased 2 days after maternal treatment was stopped. Haemolysis is a theoretical hazard in the glucose-6-phosphate dehydrogenase (G6PD) deficient infant.

Esbjorner: *Acta Paediatr Scand* 1987;**76**:137.

Connell: *Drug Safety* 1999;**21**:311.

Sulpiride Infant dose 8–18%

Some authorities caution mothers who are taking this antipsychotic drug to avoid breastfeeding because significant amounts appear in breast milk. Little is yet known about use during pregnancy.

Polatti: *Clin Exp Obstet Gynecol* 1982;**9**:144.

Sumatriptan M:P ratio 5; infant dose about 3%

Experience with the use of this new treatment for migraine is limited, but no evidence of teratogenicity has yet emerged. Breastfeeding is likely to be hazard free, since, as a result of poor oral absorption, the baby will ingest only a fifth of the weight adjusted maternal dose quoted above.

Wojnar-Horton: *Br J Clin Pharmacol* 1995;**41**:217.

O'Quinn: *Arch Gynecol Obstet* 1999;**263**:7.

Tolbutamide *M:P ratio 0.1–0.4; infant dose about 15%*

Congenital malformations are common in diabetic pregnancy, especially when early glucose control is poor, and this makes it impossible to say whether chlorpropamide (q.v.) or tolbutamide are potential teratogens. There are several reports of prolonged neonatal hypoglycaemia after the use of these drugs during pregnancy, even when the mother was changed to insulin several weeks before delivery. Glibenclamide (q.v.) is an alternative sulphonylurea that does not cross the placenta that is sometimes used in patients with non-insulin-dependent (type 2) diabetes. However, most obstetricians now believe that treatment with insulin (q.v.) is the only way to optimise control over blood glucose in all diabetic patients during conception and pregnancy. The use of tolbutamide during lactation is probably safe, but has been little studied.

Moel: *Clin Pediatr* 1967;**6**:480.

Coetzee: *S Afr Med J* 1984;**65**:635.

Topiramate *Infant dose 10–20%*

Very little is yet known about the safety of using this new anticonvulsant during pregnancy or lactation.

Öhman: *Epilepsia* 2002;**43**:1157.

Tretinoin

See the monograph on vitamin A (tretinoin is the acid form of vitamin A) for a comment on this drug's serious teratogenic potential. Topical use is probably safe during lactation, but has not been properly studied.

Trifluoperazine

As for fluphenazine.

Vaccines

While there is no evidence that any commonly used vaccine is embryotoxic or teratogenic, elective use should be avoided in the first 3 months of pregnancy. Although this is particularly true for attenuated live vaccines, protection from rabies and yellow fever should not be withheld when administration would otherwise be justified simply because the woman is pregnant. There is no contraindication to vaccination during lactation.

Schaefer: *Drugs during pregnancy and lactation*. Chapters 2.18 and 4.15. Amsterdam: Elsevier, 2001.

Briggs: *Drugs in pregnancy and lactation*. Philadelphia, PA: Lippincott, Williams & Wilkins, 2002:1409–41.

Venlafaxine *M:P ratio 2.5; infant dose about 6%*

There is no evidence that this antidepressant (a serotonin and noradrenaline reuptake inhibitor) is teratogenic. The non-significant increase in early miscarriage in the only large study to date (12% v 7%), if not a chance finding, may relate to the depression for which the women were being treated. Modest amounts are ingested by the baby when the drug is taken during lactation. No adverse consequences have been recognised.

Einarson: *Am J Psychiatry* 2001;**158**:1728.

Illett: *Br J Clin Pharmacol* 2002;**53**:17.

X-ray (and magnetic resonance imaging [MRI]) contrast media

The risk of childhood leukaemia after maternal exposure to x-rays during pregnancy is now well known. In particular, none of the commonly used non-ionic radio-opaque contrast agents should be used during pregnancy, unless for the most exceptional reasons. However, these agents appear in breast milk only to a minimal extent. The use of meglumine gadopentetate in an MRI scan exposes the breastfed baby to about 1% of the weight adjusted maternal dose. Exposure after gadoteridol is probably similar. The iodine in iohexol, iopanoic acid, metrizamide, and metrizoate is so inert that these x-ray contrast agents can also be administered without exposing the baby to more than 0.5% of the maternal dose. Barium studies can also be undertaken during lactation with complete safety.

Nielsen: *Acta Radiol* 1987;**28**:523.

Kubik-Huch: *Radiology* 2000;**216**:555.

Zolpidem tartrate *M:P ratio 0.1–0.2; infant dose < 2%*

Too little is yet known about this new hypnotic ("sleeping tablet") to recommend use during pregnancy. Its use during lactation is unlikely to be a problem, given the very small amount present in breast milk.

Pons: *Eur J Clin Pharmacol* 1989;**37**:245.

Zopiclone *M:P ratio 0.5; infant dose < 4%*

As for zolpidem. One prospective study of 40 women found no evidence of teratogenicity.

Diav-Citrin: *Am J Perinatol* 1999;**16**:157.

Matheson: *Br J Clin Pharmacol* 1990;**30**:267.

BIBLIOGRAPHY

Many excellent reviews of the issues that need to be considered when prescribing medication to a mother who is pregnant or breastfeeding have been published in the last 10 years; these should be turned to for information on drugs not included in this brief, carefully revised, overview. Much high quality epidemiological work has also been done to define the risks of drug use during pregnancy. A lot of information on use during lactation is, by contrast, still anecdotal. Isolated reports recording apparent complications of use during lactation need to be interpreted with caution (especially where these relate to drugs that have been used uneventfully by large numbers of other mothers). Reports published before 1990, in particular, frequently lacked any documentary evidence that significant quantities of the offending drug were actually present in the baby's blood.

Reference texts on drug use during pregnancy and lactation

Eight recent, comprehensively referenced, reviews are:

Bennett PM, ed. *Drugs and human lactation*, 2nd ed. Amsterdam: Elsevier, 1996.

Lee A, Inch S, Finnigan D. *Therapeutics in pregnancy and lactation*. Abingdon: Radcliffe Medical Press, 2000.

Friedman JM, Polifka JE. *Teratogenic effects of drugs. A resource for clinicians*, 2nd ed. Baltimore, MA: Johns Hopkins University Press, 2000.

Briggs GG, Freeman RK, Yaffe SJ. *Drugs in pregnancy and lactation*, 6th ed. Philadelphia, PA: Lippincott, Williams & Wilkins, 2001.

Schaefer C, ed. *Drugs during pregnancy and lactation. Handbook of prescription drugs and comparative risk assessment*. Amsterdam: Elsevier, 2001.

Koren G, ed. *Maternal-fetal toxicology. A clinician's guide*, 3rd ed. New York: Marcel Dekker, 2001.

American Academy of Pediatrics. Committee on Drugs. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**:776–89.

Hale TW. *Medications and mothers' milk*, 10th ed. Amarillo, TX: Pharmasoftware, 2002.

The publishers of the book by Briggs update this with a quarterly bulletin, and the book by Hale is updated every 1–2 years. Useful up-to-date information on drug risk during pregnancy is held electronically on the REPRORISK database, which is marketed by Micromedex, 6200 S Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, USA. The UK Breast Feeding Network has a helpline that mothers can ring if they have worries on such issues (02392 598604). They can use the answerphone to leave an evening contact telephone number.

Further information

Information on drugs in **pregnancy** can be obtained, in the UK, through any local hospital pharmacy, from the Specialist Advisory and Information Service provided by the Northern & Yorkshire Drug & Therapeutics Centre at the Wolfson Unit, 24 Claremont Place, Newcastle upon Tyne, NE2 4HH (0191 232 1525). This unit also maintains the UK's main teratology database. See: www.ncl.ac.uk/pharmsc/entis.htm

More detailed information on drugs in **breast milk** can be obtained, similarly, from the Trent Drug Information Centre, Leicester Royal Infirmary, Leicester LE1 5WW (0116 255 5779) or the West Midlands Drug Information Service, Good Hope General Hospital, Sutton Coldfield, B75 7RR (0121 311 1974). Details of how to contact other similar advice centres in Europe and North America is provided at the back of the excellent book by Christof Schaefer.

USEFUL WEBSITE ADDRESSES

American Academy of Pediatrics

The American Academy makes a wealth of well-formulated advice available on its website. Abstracts of all the papers published in *Pediatrics* since 1948 can also be accessed. In fact, since 1997, only half the papers published by this journal have appeared in print in full. Others appear in abstract form only (and have an e-number instead of a page number). The full text of the latter can be accessed and downloaded, without charge, from the journal's website –

- www.pediatrics.org

British National Formulary

This formulary, sponsored jointly by the British Medical Association and the Royal Pharmaceutical Society of Great Britain, aims to provide authoritative and practical information on the selection and use of all UK-licensed medicines in a clear, concise and accessible manner. It is semi-continuously updated and published afresh in book form every six months, but it can also be accessed on line. It has grown over the years to become one of the world's most authoritative reference texts, but it seldom gives much specific advice on use during pregnancy or in the newborn baby.

- www.bnf.org

Clinical Evidence

Clinical Evidence is a "continuously updated international source of evidence on the effects of clinical interventions", based on a thorough search and appraisal of the literature. Where little good evidence exists the text says so. Relatively few perinatal issues are covered as yet (the ones in print by the time this edition went to press are mentioned in the lists of references at the end of each monograph in this book), but the number covered is increasing steadily. The text is available on the web, on CD-ROM, and in book form, and is updated every 6 months. For those in 100 developing countries online access is completely free.

- www.clinicalevidence.com

Cochrane Library

The Cochrane Collaboration [www.cochrane.org] is an international organisation dedicated to the preparation, maintenance, and dissemination of systematic reviews of the effects of health care. It maintains a register of all controlled trials, and also publishes a wide range of regularly updated systematic reviews. Summaries of those reviews that relate to drugs mentioned in the main section of this compendium can be accessed from this Formulary's website. Those living in England, Wales, and Ireland (but not, as yet, Scotland) also have free access to the full text of every monograph. The same is already true for those living in Australia, Finland, and Norway, and negotiations are in hand for the funding needed to make free access more widely available.

- www.update-software.com/cochrane/provisions.htm

Communicable disease centres

Many countries maintain a national communicable disease centre. Two that make a particularly wide range of information publicly available are the Communicable Disease Surveillance Centre and Public Health Laboratory Service (PHLS) in the UK, and the Communicable Disease Center (CDC) in the USA.

- www.phls.co.uk
- www.cdc.gov

Contact a Family

Families who are told that their child has a rare, possibly inherited, disorder often feel bereft of good quality advice and information. Charities exist both in the UK and the USA to bridge that gap. They can also offer help to those who want to contact other families facing a similar challenge.

- www.cafamily.org.uk
- www.rarediseases.org

Controlled clinical trials

Until recently it has been difficult to get information about ongoing and unpublished clinical trials. This unsatisfactory state of affairs is changing, however, at least in respect of non-commercial trials. Information about these is now becoming available through the metaRegister of Controlled Trials [www.controlled-trials.com], and, for the USA, on a user friendly site run by the National Library of Medicine. A register of trials is also available at TrialsCentral.

- www.trialscentral.org
- www.clinicaltrials.gov
- www.controlled-trials.com

USEFUL WEB SITE ADDRESSES

Drug Abuse

Drugscope is an independent, registered, UK charity that undertakes research, and provides authoritative advice, on all aspects of drug abuse and drug addiction.

- www.drugscope.org.uk

Drug use in children

The NHS in the UK supports "DIAL", a medicines advisory service for pharmacists, which provides information and a "helpline" on all issues relating to the use of medicines in children. It is based in Liverpool.

- www.dial.org.uk

Drug use during lactation

A website maintained by Thomas Hale, the author of the valuable and frequently updated book *Medications and Mothers' Milk*, is a mine of information on drug use during lactation. Thomas Hale is based at the Texas Tech University School of Medicine.

- <http://neonatal.ama.ttuhs.c.edu/lact/>

Drug use during pregnancy

For a useful alphabetical list summarising how most drugs commonly used in pregnancy are classified by the American Federal Food and Drug Administration (FDA), see this well designed Californian Perinatology Network website. One particularly useful feature is the way you can, with one more click, undertake a full Medline literature search. There is, however, only a small amount of limited, information on drug use during lactation.

- www.perinatology.com/exposures/druglist.htm

Genetic disease

The National Institutes of Health (NIH) in the USA supports a register of every known human single gene disorder (14,184 conditions at the last count). This register, "Online Mendelian Inheritance in Man", provides a wealth of constantly updated information.

- www.ncbi.nlm.nih.gov/omim/

History of controlled trials

For an insight into the way in which objectivity was eventually brought to bear on the many claims that doctors have always made for the drugs and treatments they had on offer see:

- www.jameslindlibrary.org

HIV and AIDS

An authoritative website supported by the National Institutes of Health in the USA provides extensive and very up to date information on the treatment of HIV and AIDS in patients of all ages, together with information on clinical trials currently in progress. The British HIV Association now has an active medical website and also supports another more general (aidsmap) website. The University of Liverpool in the UK provides a site giving information on drug interactions.

- www.aidsinfo.nih.gov
- www.bhiva.org
- www.aidsmap.com
- www.hiv-druginteractions.org

Immunisation

The UK Department of Health has a well stocked website from which it is possible to download a wide range of informative leaflets suitable for parents. It also offers advice on travel issues.

- www.immunisation.nhs.uk

Immunisation facts

This is an independent website run by the writer who regularly writes on vaccine issues for *Hospital Pharmacy* (John Grabenstein). It focuses down on US products and practices, but it provides links to a wide range of factual information from government and drug company sources.

- www.immunofacts.com

Immunisation Green Book

The complete text of the 1996 edition of the UK Government's official publication *Immunisation against infectious disease* has recently been posted on the web. Users need to be aware that some of the advice it gives will soon be rendered obsolete by the issue of a new edition.

- www.doh.gov.uk/greenbook

Journal of Neonatal Nursing

JNN is the official bimonthly journal of the UK Neonatal Nurses Association. Anyone can browse through abstracts of all articles published since the Journal was first launched in 1994. It is also possible to download the full text of one

article from each issue free. The journal also sponsors the list server that manages the neonatal-talk online discussion group (see below under "Web based discussion groups").

- www.neonatal-nursing.co.uk

Malaria

The malaria parasite is becoming progressively more resistant to many of the drugs usually used for prophylaxis and treatment. For area-specific advice on management from the World Health Organization (WHO), and from the Communicable Disease Center (CDC) in the USA, see:

- www.who.int/ith/chapter07_01.html
- www.cdc.gov/travel/diseases.htm#malaria

Medicines Compendium

The information issued by the manufacturer of every product licensed for sale in the UK – the manufacturer's summary of product characteristics or SPC – can be accessed electronically on the web. This information is also available in book format from Datapharm Communications. Patient information leaflets can also be accessed from the same website. Access is free but password protected, and staff need to register before using this site.

- www.eMC.vhn.net

Midwifery Digest

MIDIRS is a UK based not-for-profit organisation. The website provides extensive regularly updated information on all issues relating to childbirth. It also supports a very active enquiry service, and publishes a quarterly digest containing original articles and overviews of recent medical and midwifery research taken from over 550 international journals.

- www.midirs.org

Motherisk Program

The Motherisk Program, backed by the expertise of the Department of Clinical Pharmacology and Toxicology at the Hospital for Sick Children in Toronto, maintains a very authoritative website dealing with the safety of drug use during pregnancy and lactation.

- www.motherisk.org

National Association of Neonatal Nurses

NANN is the main neonatal nursing organisation in the USA. Most of its benefits are open only to members, but some publications are available for purchase. One feature is a study programme that allows you to download an article and then complete a self-study examination "online".

- www.nann.org

National Electronic Library for Health

This UK based facility aims to provide NHS staff, patients and the public with a comprehensive electronic information service. Look in particular at the items available by focusing on the material in the "Virtual Branch Library" for child health, accessible direct from the home page. For those in England the site provides direct access to Clinical Evidence and the Cochrane Collaboration (see above).

- www.nelh.nhs.uk/default.asp

National Institute for Clinical Excellence

This organisation provides cost benefit advice on an, as yet relatively restricted, range of treatment strategies to those working in the NHS in England and Wales.

- www.nice.org.uk

Neonatal and Paediatric Pharmacy Group

This is a UK based website providing extensive advice for pharmacists on neonatal and paediatric pharmacy issues. It can be used to search and view abstracts of recent selected paediatric (Pharm-Line) pharmacology papers.

- www.show.scot.nhs.uk/nppg

Neonatology on the web

This site contains an absorbing selection of classic papers and historical reports. The "Hot Lit" links readers (perhaps a little uncritically) to a new, recently published paper each month, while the "New Stuff" link takes you to a roundup of recently updated features. There is a useful collection of bibliographies on a wide range of topics.

- www.neonatology.org

NICU-WEB

This site provides regularly updated, referenced, articles on a wide range of neonatal topics written, largely from a US perspective, by staff from the University of Washington. It can also be used to access the site web-based neonatal discussion groups (see below).

- www.neonatal.peds.washington.edu

USEFUL WEB SITE ADDRESSES

Royal College of Obstetricians and Gynaecologists

This London based College has published a small series of clinical practice guidelines (so called "Green Top" Guidelines) in the Good Practice section of their website that cover some of the management issues mentioned in this book.

- www.rcog.org.uk

UNICEF UK Baby-Friendly Initiative

The Baby Friendly Initiative is a global UNICEF (United Nations Children's Fund) programme that works to improve practice so that parents are helped and supported by health professionals in making an informed choice over the way they feed and care for their babies. For details see:

- www.babyfriendly.org.uk

This book

The BMJ Publishing Group maintain a website where detailed commentaries on some of the individual drug entries in this Formulary are now being posted with increasing frequency. The site does not provide direct access to the main monographs themselves (although it does provide information on where an electronic version of these can be purchased), but monographs added or updated after the latest print edition went to press can be found on this site.

- www.neonatalformulary.com

Travel advice

A number of sites provide advice for members of the public thinking of travelling abroad. The following are provided by the World Health Organisation (WHO), by the Communicable Disease Centre (CDC) in America, and by the National Health Service (NHS) in the UK respectively:

- www.who.int/ith/
- www.cdc.gov/travel
- www.fitfortravel.scot.nhs.uk

US Food and Drug Administration

The Food and Drug Administration (which is responsible for licensing all drug products in the USA) maintains a full and very informative website with good search facilities.

- www.fda.gov

Web based discussion groups

Many web based discussion groups now exist. Two of the most widely supported are NICU-net and Neonatal-talk. The first is supported by both doctors and nurses, while the second is largely used by nurses. The NICU-WEB site (see above) gives information on how to access both these discussion groups. Access to neonatal-talk is also available from the Journal of Neonatal Nursing's website.

World Health Organization

The World Health Organization has long had the provision and dissemination of reliable information on a core of essential drugs "that satisfy the priority healthcare needs of the population, selected with due regard to public health relevance, efficacy and safety, and comparative cost-effectiveness" as one of its major briefs. This website provides links to a large number of relevant documents and resources, including a model formulary (which has now also been published in book form).

- www.who.int/medicines

INDEX

Note: Drug names beginning with a capital letter are proprietary (trade) names.

Where several page references are given the most important entry is printed in **bold**.

The letter **W** after a page number indicates that there is also a website commentary addressing this issue.

- abbreviations 3
 - pharmacology 9
 - prescribing 19
- abetalipoproteinaemia 263
- Abidec vitamin drops 190, **265**
- ACE inhibitors **69**, 234
- abscesses
 - breast 112
 - cerebral 8
- acebutolol 275
- acenocoumarol 275
- acetaminophen 193
- acetazolamide vii, 41
- acetone 226
- acetylcysteine 18, **193**
- acetylsalicylic acid 52
- aciclovir 42
 - eye ointment 106
 - renal failure 38
- acitretin 275
- acquired immunodeficiency syndrome (AIDS)
 - care in pregnancy **150**, 270
 - care of the baby 177
 - didanosine 150
 - lamivudine 150
 - nelfinavir 222
 - nevirapine 177
 - ritonavir 222
 - zidovudine 270
- acrodermatitis enteropathica 271
- activated charcoal 18
- acyclovir *see* aciclovir
- addiction to drugs
 - and lactation
 - general strategy 36
 - opiates 93, 161
 - other illicit drugs 275–89
 - general strategy 161 **W**
 - maternal addiction 35–6
 - opioids 91, 151
 - other drugs 82
 - neonatal withdrawal
 - symptoms 35, 161
 - use of chlorpromazine 82
 - use of methadone 161
 - use of morphine 172
 - use of paragoric 93
 - use of phenobarbital 199
- Addisonian crisis 132
- additives to milk 20, 168, 202, 230
- addresses
 - defective medicines 17
 - drug dependence 36
 - drugs in breast milk 290
 - drugs in pregnancy 290
 - ECMO centres in UK 31
 - poisons information 18
 - safety of medicines 17
 - website addresses 291–4
- adenosine 43
- adrenal gland 243
 - insufficiency
 - dexamethasone 90
 - fludrocortisone 132
 - hydrocortisone 132
 - suppression caused by steroid use
 - treatment with hydrocortisone 91
- adrenaline 44
 - use in anaphylaxis 135
- adverse reactions 17
- AIDS *see* human immunodeficiency virus (HIV)
- air embolism 12
- albumin 204
- albuterol 225
- alcohol
 - damage to neonatal skin 226
 - during lactation 35, 275
 - during pregnancy 36, 275
 - hand rinses 227
 - to sterilise skin 227
 - to unblock catheters 252
- alfentanil 108
- alfacalcidol 262
- alimemazine 34, 275
- allergic rhinitis, maternal 275
- alpha tocopherol 263
- alprostadil 214
- alteplase (t-PA) 45
- aluminium vii, 195
- aluminium hydroxide 119
- amantadine 275
- amethocaine 242
- amikacin 38, **46**
- amino acid solutions 195
 - coinfusion with other drugs 3, 14
 - infection 11
- aminoglycoside antibiotics
 - amikacin 46
 - gentamicin 121
 - interaction with penicillins 249
 - netilmicin 176
 - streptomycin 288
 - tobramycin 249
- aminophylline 246

- cardiac arrhythmia 14
- amiodarone 47
- amitriptyline 275
- amodiaquine 216
- amoebiasis 165
- amoxicillin 38, **48**
- amoxycillin 38, **48**
- amphetamine 279
- amphotericin B 49
 - and flucytosine 114
 - in renal failure 38
- ampicillin 38, **50**
- ampoules 4
- anaemia
 - assessment 61, 143
 - blood transfusion 62
 - erythropoietin 104
 - haemolytic 219, 248, 263
 - iron deficiency 143–4
 - megaloblastic 115, 261
- anaesthesia
 - epidural 34, 66
 - general 34
 - ketamine 148
 - methohexital sodium 247
 - premedication 54
 - propofol 212
 - thiopental sodium 247
 - see also* local anaesthesia
- analgesia
 - maternal
 - aspirin 52
 - buprenorphine 277
 - ibuprofen 133
 - migraine 284
 - nitrous oxide 181
 - paracetamol 193
 - pethidine 198
 - see also non-steroidal anti-inflammatory drugs (NSAIDs)*
 - neonatal *see* pain relief, neonatal
- anaphylaxis 135
- angel dust 35, **286**
- aniline dye 163, 226
- antacids 119, 218
- antibiotics
 - eye drops 106–7
 - in vitro interactions 249
 - length of treatment 25
 - oral 5
 - policy 25
 - see also individual entries*
- anticoagulation *see* heparin; warfarin
- anticonvulsant use
 - during lactation 254 **W**
 - during pregnancy 254 **W**
 - for neonatal seizures 199 **W**
- antidepressants, maternal use 275–6
- aortic catheters, siting **11**, 13
- apnoea
 - caffeine citrate 67
 - cisapride 85
 - doxapram 100
 - management 67
 - theophylline 246
- Aptamil milk 168
- APTT (Activated partial thromboplastin time) **116**, 128
- aqueous cream BP 226
- arginine 51
- argininosuccinic aciduria 51
- argipressin 257
- arrhythmias *see* cardiac arrhythmias
- arterial vasospasm 11, 192, 250
- “artificial tears” 106
- ascites 234
- ascorbic acid 163
- aspergillosis 49
- asphyxia *see* birth asphyxia
- aspirin **52**, 133
- asplenia 136
- asthma 225
- atenolol 276
- atosiban 178
- atracurium 53
- atrial flutter 232
- atropine 54
 - eye drops 106
- auranofin 276
- aurothiomalate 276
- azathioprine 276
- azidothymidine 270
- azithromycin 76, **103**, 277
- aztreonam 38, **55**
- baclofen 277
- bacterial endocarditis, prophylaxis
 - invasive surgery 241
 - oral and ENT surgery 86
 - see also* infection
- balsalazide *see* mesalazine
- basal metabolic rate 21
- BCG 56–7
- betametasone dipropionate 65
- Bendectin *see* doxylamine
- benign familial neonatal seizures 27
- benign idiopathic neonatal seizures 27
- benzathine penicillin 211
- benzodiazepines
 - clonazepam 87
 - development of 155
 - diazepam 94
 - lorazepam 155
 - maternal addiction 35
 - maternal use 277
 - midazolam 167
 - neonatal use 167 **W**
 - nitrazepam 285
 - temazepam 78
- benzoin tincture BPC 226
- benzyl alcohol **8**, 47, 86, 87, 94, 155
- benzylpenicillin 197
- beractant 238

- betaine 58
betamethasone **59, 90**
 eye drops 106
Betnesol-N 107
bicarbonate *see* sodium bicarbonate
biliary atresia 253
BiliBlanket 203
bilirubin levels in first week 203
 see also jaundice
biotin 60
biotinidase deficiency 60
birth asphyxia
 adrenaline 44
 hypothermia 157
 magnesium sulphate 156
 management 157
 mannitol 157
 phenobarbital 199–200
 sodium bicarbonate 229
 THAM 245
 theophylline 246
birth marks 141
bisacodyl *see* laxatives, maternal
BLES (Bovine Lipid Extract Surfactant) 238
β blockers
 acebutolol 275
 atenolol 276
 esmolol 213
 labetalol 149
 pharmacology of 232
 propranolol 213
 sotalol 232
 toxicity 232
blood
 administration 62
 adverse reactions 61
 clotting *see* coagulation
 catheter samples 13
 heel prick sampling 33
 loss 12, 61
 matching 61
 packed cell volume 61–2
 products
 cryoprecipitate 116
 fresh frozen plasma 116
 plasma albumin 204
 platelets 205
 red cell concentrate 61
 see also immunoglobulin
 risk of transmitting infection 61
 transfusion 61–2
 see also exchange transfusion
blood pressure
 at birth 30
 measurement 29, **149 W**
 postnatal change 97
 systolic 97, 131, 149
body weight and surface area 21
bolus injections 6
bone mineralisation 63, **169, 202, 262**
Bordetella pertussis 103, 268–9
BPD *see* bronchopulmonary dysplasia
bradycardia
 atropine 54
 isoprenaline 146
bran *see* laxatives
Braun “Sterifix-Mini-Spike” 4
breast
 abscess 112
 candida infection 113, 184
 engorgement 64
 mastitis 112, 113, 184
 nipple pain 184
breast feeding
 stimulation
 domperidone 98
 metaclopramide 164
 oxytocin 188
 suppression
 bromocriptine 64
 cabergoline 64
breast milk
 drugs in 275–9
 fortifiers 63
 general policy 274
 help line 290
 jaundice 231
breathholding attacks 135
bromide salts 277
bromocriptine 64
bronchiolitis **189, 220**
bronchopulmonary dysplasia
 immunisation policy 136
 prophylaxis
 budesonide 65
 vitamin A 235
 treatment
 dexamethasone 90–91
 furosemide 117
 ipatropium 54
 salbutamol 225
budesonide 65
bumetanide 117
bupivacaine 66
buprenorphine 36, **277**
busulfan 277
busulphan *see* busulfan
cabergoline 64
caesarean section, antibiotic prophylaxis 74
caffeine citrate **67, 246**
calcium
 glubionate 68
 gluconate **68, 191**
 lactobionate 68
 Resonium 208
calciferol 262
calcitriol 262
calcium folinate 216
calcium polystyrene sulphonate 208
calfactant 238
candidiasis

- mouth 166, **184**
- skin
 - gentian violet 166
 - miconazole 166
 - nystatin 184
- systemic 113
 - amphotericin B 49
 - fluconazole 113
 - flucytosine 114
- cannabis 35, **283**
- capillary refill time 29
- captopril 69
- carbamazepine 70
- carbamoyl phosphate synthetase deficiency 51
- carbimazole 277
- carboxylase enzyme deficiencies 60
- cardiac arrest *see* cardiopulmonary resuscitation
- cardiac arrhythmias
 - adenosine 43
 - amiodarone 47
 - digoxin 96
 - esmolol 213
 - disopyramide 280
 - flecainide 111
 - lidocaine 153
 - natural history 111
 - procainamide 287
 - propranolol 213
 - quinidine sulphate 96
 - sotalol 232
 - see also* hyperkalaemia
- cardiac output
 - adrenaline 44
 - dobutamine 97
 - dopamine 99
 - enoximone 101
 - glyceryl trinitrate 123
 - milrinone 170
- cardiomyopathy
 - nifedipine 178
- cardiopulmonary resuscitation
 - adrenaline 44
 - bicarbonate 229
 - THAM 245
- cardioversion 43, 96
- carisoprodol 277
- carnitine **71**, 124
- casarca *see* laxatives
- catheters
 - care of 11–14
 - dangers 11–12, 26
 - insertion 33
 - patency
 - alteplase 45
 - heparin 127–8
 - hydrochloric acid 252
 - streptokinase 235
 - urokinase 252
- cation exchange resin 208
- cefalexin 72
- cefotaxime 38, **73**
- cefoxitin 38, **74**
- ceftazidime 38, **75**
- ceftriaxone 38, **76**
- cefuroxime 38, **77**
- central arterial lines 13
- central venous catheters 13, 30
- central venous oxygen level 30
- central venous pressure 30
- cerebral abscess 7
- Chamomile *see* herbal remedies
- charcoal **18**, 80
- chickenpox 256
- chlamydial infection
 - azithromycin 103
 - ciprofloxacin 84
 - erythromycin 103
 - eye care 106
 - natural history 103
- chloral hydrate 78
- chloramphenicol vii, 79
 - danger of overdose 16, 79
 - eye drops 106–7
 - in renal failure 38
- chlorhexidine 227
- chlormethiazole *see* clormethiazole
- chloroquine 80
- chlorothiazide **81**, 95
- chlorphenamine maleate 61, 80, 129
- chlorpheniramine maleate 61, 80, 129
- chlorpromazine 82
- chlorpropamide 277
- chlortetracycline eye ointment 106–7, 244
- cholera 89
- cholestasis
 - treatment of pruritis
 - phenobarbital 199–200
 - rifampicin 221
 - ursodeoxycholic acid 253
 - vitamin malabsorption
 - vitamin A 260
 - vitamin D 262
 - vitamin E 263
 - vitamin K 264
- ciclosporin 278
- cilastatin 134
- cimetidine 83
 - cardiac arrhythmias 14
- ciprofloxacin 38, **84**
- circumcision 34
- cisapride 85
- cisplatin 278
- citalopram 278
- citrullinaemia 51
- clavulanic acid 48
- clemastine 278
- clindamycin 38, **86**, 216
- clomephine *see* clomifene
- clomifene 278
- clonazepam 87
- clonidine 66
- clormethiazole 278

- clostridial infection
 benzylpenicillin 197
 metronidazole 165
 teicoplanin 241
 clotrimazole 278
 clots *see* thromboses
 cloxacillin 112
 clozapine 278
 CMV *see* cytomegalovirus infection
 coagulation
 factor deficiency 116
 factors 61
 screening tests 116
 co-amoxiclav 48
 cocaine 35, **279**
 coccidioidomycosis 49
 Cochrane Collaboration
 access to reviews 291
 contact address in UK 22
 logo 3
 codeine phosphate 34, **88**
 cohosh *see* herbal remedies
 co-infusion 3, 14
 colchicine 279
 cold remedies, maternal 279
 colfosceril palmitate 239
 comfrey *see* herbal remedies
 compatibility of IV drugs 14
 congenital adrenal hyperplasia
 fludrocortisone 132
 hydrocortisone 132
 prenatal management 90
 congestive heart failure
 chlorothiazide 81
 enoximone 101
 milrinone 170
 nitroprusside 180
 spironolactone 234
 congenital heart disease, duct dependent 214
 conjunctivitis 106–7
 constant positive airway pressure
 drug delivery using 8
 for apnoea 67
 for delivering ribavirin 220
 for respiratory distress syndrome 238
 contraceptives
 Depo-provera 283
 levonorgestrel 283
 oral 286
 contractions (symbols) **3, 9, 19**
 convulsions *see* seizures
 co-phenotrope 279
 corticosteroids
 drug equivalence 132
 effect on adrenal gland 91
 immunisation while on treatment
 BCG 56
 polio 207
 rubella 223–4
 triple vaccine 268–9
 products
 betamethasone 59
 budesonide 65
 dexamethasone 90–1
 eye drops 106–7
 fludrocortisone 132
 fluticasone 65
 hydrocortisone 132
 inhaled steroids 65
 prednisolone 287
 prophylactic antenatal use
 choice of product 59 **W**
 co-trimoxazole 89
 cough and cold remedies, maternal 279
 CPAP *see* constant positive airway pressure
 Crigler-Najjar syndrome 248
 crack 279
 croup **65, 91**
 cryoprecipitate 109, **116**
 cryptococcal infection
 amphotericin B 49
 fluconazole 113
 flucytosine 114
 crystal violet 166
 cyanosis 186–7
 cyclophosphamide 279
 cyclosporin *see* ciclosporin
 cystic fibrosis 190
 cystinuria 196
 cytokines
 erythropoietin 104
 filgrastim 110
 lenograstim 110
 molgramostim 171
 storage 4
 cytomegalovirus infection 61, **118**

 dacrycystitis 106
 Dalivit vitamin drops 260, **265**
 danazol 279
 dantron *see* laxatives
 dapsone 279
 Debendox *see* doxylamine
 D-dimer levels 116
 DEET (diethyltoluamide) 158
 deferoxamine mesilate *see* desferrioxamine mesylate
 defective medicines 17
 definitions 3, 9
 Depo-provera **223, 283**
 dermatitis
 candidal 166
 prevention 184
 desferrioxamine mesylate 18, **144**
 desmopressin 257
 dexamethasone 90–1
 dexamfetamine 35, **279**
 dexamphetamine 35, **279**
 dextran 120
 dextrose 92
 diabetes melitus
 maternal
 chlorpropamide 277

- glibenclamide 281
- glyburide 281
- insulin 140
- metformin 284
- tolbutamide 289
- neonatal 140
- diabetes insipidus 257
- dialysis 37
- diamorphine 35, **93**
- diastolic blood pressure 30
- diazepam 94
- diazoxide 95
- Diclolectin *see* doxylamine
- diclofenac *see* non-steroidal anti-inflammatory drugs (NSAIDs)
- didanosine 150
- diethylstilboestrol vii, **280**
- diethyltoluamide 158
- Digibind **18, 96**
- digoxin 96
 - antidotes 18, 54, **96**
 - danger of overdose 16
- dihydrocodeine 36
- dilution of drugs 5
- dimercaptosuccinic acid 251
- dinoprostone 214
- diphenoxylate *see* co-phenotrope
- diphtheria (DTP) vaccine 268–9
- disopyramide 280
- diuretics
 - bumetanide 117
 - chlorothiazide 81
 - furosemide 117
 - hydrochlorothiazide 81
 - mannitol 157
 - spironolactone 234
- DMSA (dimercaptosuccinic acid) 251
- dobutamine 97
- domperidone 98
- dopamine 99
- dosulepin *see* dothiepin
- dothiepin 280
- doxapram 100
- doxepin 280
- doxylamine 280
- DPT (diphtheria, pertussis, tetanus) vaccine 135–6, **268–9**
- droppers 6
- drug dependency, maternal
 - care of the mother 35–6, 161 **W**
 - care of the baby at birth
 - addiction to opioid drugs 93, 161
 - addiction to other drugs 82
 - aim of neonatal management 35, 161 **W**
 - signs of neonatal abstinence 35, 82
 - risk associated with breast feeding
 - opioid addiction 93
 - other drugs 275–89.
- drug administration 3, **5–8**
- drug prescribing 19–20
- DrugScope 36
- ECMO 31, 179
- ecstasy 35, **284**
- edrophonium 175
- eclampsia 156
- emboli
 - air 12
 - clots 11, 26, 127–8
 - see also* thromboses
- Emla cream 33, **153, 242**
- empyema, treatment of 252
- enalapril 69
- enalaprilat 69
- endotracheal drug delivery 8
- Enfamil breast milk fortifier 63
- enoxaparin 127–8
- enoximone 101
- Enterobacter spp
 - aztreonam 55
 - ciprofloxacin 84
- enterococcal infection
 - amoxicillin 48
 - ampicillin 50
 - teicoplanin 241
- Eoprotin breast milk fortifier 63
- Epaderm ointment 205
- ephedrine 280
- epidural anaesthesia 34, 66
- epiglottitis 126
- epilepsy 27–8
 - in infancy *see under* seizures
 - in pregnancy 254 **W**
- epinephrine *see* adrenaline
- epoetin 104
- epoprostenol 102
- ergocalciferol 262
- ergometrine 188
- ergotamine 280
- errors
 - minimising 15–16
 - overdosing 18
 - reporting 15
- erythromycin **38, 103**
- erythropoietin 62, **104**
- esmolol 213
- etamsylate 105
- ethambutol 281
- ethamsylate 105
- ethmoiditis 106
- ethosuximide 281
- etretinate 281
- exchange transfusion
 - choice of blood 61
 - indications
 - drug poisoning 18
 - hyperkalaemia 225
 - jaundice 203
 - malaria 217
 - polycythemia **204, 230**
 - rhesus disease 205
 - severe chronic anaemia 62
 - need to buffer donor blood 229

- extracorporeal membrane oxygenation *see* ECMO
 extravasation
 glyceryl trinitrate ointment 99
 hyaluronidase 130
 management 11
 phenolamine mesilate 99
 excipients 8
 extubation 67, 90
 eye drops/ointments 106–7
- Fallop's tetralogy, spells 213
 Fansidar **216**, 217
 fat, IV emulsion 142
 fentanyl 108
 fetal therapy
 amiodarone 47
 betamethasone 59
 digoxin 96
 fentanyl 108
 flecainide 111
 indometacin 138
 levothyroxine 152
 procaine penicillin 211
 pyrimethamine 216
 quinidine sulphate 96
 spiramycin 233
 fever, management 193
 fibrin glue 109
 fibrinogen 116
 fifth day fits 27
 filgrastim 110
 filters
 for blood products 62, 205
 for IV drugs
 mannitol 157
 parenteral nutrition 142
 phenytoin 201
 tetracycline 244
 for IV fluids 12
 for reconstituting epoprostenol 102
 First milk 168
 fits *see* epilepsy; seizures
 flecainide 111
 floxacillin 112
 flucloxacillin **38**, **112**
 fluconazole **38**, **113**
 flucytosine **38**, **114**
 fludrocortisone acetate 132
 fluid balance 37–8, **267**
 flumazenil **18**, **167**
 chloral hydrate antidote 78
 clonazepam antidote 87
 diazepam antidote 94
 lorazepam antidote 155
 midazolam antidote 167
 fluorescein eye drops 106–7
 fluoxetine 276, 281
 fluphenazine 281
 fluticasone propionate 65
 fluvoxamine 281
 folic acid 63, **115**
 folic acid 216
 foreign travel 135
 fosfarnet sodium 118
 fosphenytoin 201
 fresh frozen plasma (FFP) 116
 furosemide *see* furosemide
 fungal infection
 maternal
 fluconazole 113
 griseofulvin 281
 itraconazole 282
 ketoconazole 282
 miconazole 166
 neonatal 113
 amphotericin B **38**, **49**
 fluconazole **38**, 113
 flucytosine **38**, 114
 gentian violet 166
 miconazole 166
 nystatin 184
 furosemide 117
 fusidic acid 231
- G6PD (glucose 6-phosphate dehydrogenase) deficiency
 and chloramphenicol 79
 and ciprofloxacin 84
 and co-trimoxazole 89
 and dapsone 279
 and methylene blue 163
 and nalidixic acid 285
 and nitrofurantoin 285
 and primaquine **80**, 287
 and quinine 217
 and sulfadiazine 237
 and sulfasalazine 288
 gadopentetate *see* x-ray contrast media
 gamma-aminobutyric acid (GABA) 215, 259
 gamma globulin *see* immunoglobulin
 ganciclovir 118
 gastric acid secretion
 cimetidine 83
 omeprazole 185
 ranitidine 218
 gastric emptying
 cisapride 85
 Gaviscon 119
 metoclopramide 164
 gastric reflux *see* reflux, gastric
 gastrointestinal motility
 cisapride 85
 erythromycin 103
 metoclopramide 164
 Gaviscon 85, **119**
 G-CSF 110
 gelatin 120
 Gelofusine 120
 gentamicin 121
 eye drops 106–7
 in preterm labour 50
 in renal failure 38
 intrathecal 7

- gentian violet 166
- giardiasis 165
- ginseng *see* herbal remedies
- German measles 223
- glaucoma 41, 106
 - iatrogenic 54
- glibenclamide 281
- glucagon 122
- glucose 92
- glyburide *see* glibenclamide
- glyceryl trinitrate 123
 - ointment 99
- glycine 124
- glycopyrronium 125
- GM-CSF 171
- gonococcal infection
 - benzylpenicillin 197
 - ceftriaxone 76
 - chloramphenicol eye drops 106–7
 - in pregnancy 76
- griseofulvin 281
- group B streptococcal infection
 - ampicillin 50
 - erythromycin 103
 - penicillin 197
 - prophylaxis 197
- Guthrie screening 152, 251

- haemangiomas 141
- haematocrit, normal range 61–2
- haemoglobin, normal range 61–2
- Haemophilus influenzae*
 - amoxicillin 48
 - ampicillin 50
 - aztreonam 55
 - cefotaxime 73
 - chloramphenicol 79
 - rifampicin prophylaxis 221
 - vaccine 126
- haemorrhage
 - haemorrhage in the newborn
 - iatrogenic 12
 - intraventricular *see* intraventricular haemorrhage
 - see also* haemostasis
 - postpartum maternal haemorrhage
 - oxytocin to control 188
 - misoprostol to control 188
- haemostasis
 - cryoprecipitate 116
 - fibrin glue 109
 - fresh frozen plasma 116
 - platelets 205
 - vitamin K 264
- half life (of drugs) 9
- halofantrine 281
- haloperidol 282
- hand washing 227
- hay fever *see* allergic rhinitis
- headache, maternal 284
- heart block 146
- heart failure
 - acute
 - enoximone 101
 - milrinone 170
 - chronic
 - captopril 69
 - digoxin 96
 - enalapril 69
 - see also* diuretics
 - heel prick blood sampling 33, **236**
 - heparin 127–8
 - in renal failure 38
 - hepatitis B
 - immunoglobulin (HBIG) 129
 - vaccine 129
 - hepatitis, neonatal 253
 - Hepsal 128
 - herbal remedies, maternal use 282
 - heroin 35, **93**
 - herpes simplex infection
 - aciclovir 42
 - conjunctivitis 106
 - natural history 42
 - hetastarch 120
 - hexastarch 120
 - hexachlorophene vii, 226
 - HIV *see* human immunodeficiency virus
 - Hollister skin barrier 226
 - holocarboxylase synthetase deficiency 60
 - homocystinuria 58, 215, 261
 - human albumin solution 204
 - human immunodeficiency virus (HIV)
 - drugs for
 - didanosine 150
 - lamivudine 150
 - neftravir 222
 - nevirapine 177
 - ritonavir 222
 - zidovudine 270
 - management
 - during infancy 150
 - during pregnancy 270
 - general principles 222
 - prophylaxis
 - during delivery 177, 270
 - pneumocystis 89
 - risk from needle prick injury 270
 - vaccination policy 136
- humidity
 - incubator 226, 267
 - oxygen 187
- Humulin (insulin) 140
- hyaluronidase 130
- hydralazine 131
- hydrocephalus, posthaemorrhagic 41, 105
 - acetazolamide 41
 - alteplase 45
 - isosorbide 147
- hydrochloric acid 252
- hydrochlorothiazide 81
- hydrocortisone 132
 - absorption through skin 226

- prophylaxis in adrenal suppression 90–1
- use in anaphylaxis 135
- hydroxocobalamin 261
- 11-hydroxylase deficiency 132
- 21-hydroxylase deficiency 132
- hydroxycholecalciferol 262
- hyperaldosteronism 234
- hyperammonaemia 52, 124, **228**
- hyperbilirubinaemia *see* jaundice
- hyperekplexia 27
- hyperinsulinism
 - dextrose 92
 - diazoxide 95
 - glucagon 122
- hyperkalaemia 225
 - calcium gluconate 68, 208
 - dialysis 37–8
 - insulin 140
 - polystyrene sulphonate resins 208
 - salbutamol 225
- hypernatraemia 230
- hyperprolactinaemia 64
- hypertension 131, 149 **W**
 - captopril 69
 - enalapril 69
 - hydralazine 131
 - labetalol 149
 - methyldopa 162
 - nifedipine 178
 - nitroprusside 180
 - propranolol 213
- hyperthyroidism *see* thyrotoxicosis
- hypnotic drugs
 - maternal
 - clormethiazole 278
 - temazepam 78
 - triclofos 78
 - zolpidem tartrate 289
 - neonatal
 - chloral hydrate 78
- hypocalcaemia
 - calcium gluconate 68
 - magnesium sulphate 156
- hypoglycaemia
 - dextrose 92
 - diazoxide 95
 - glucagon 122
- hypomagnesaemia 146
- hyponatraemia 230
- hypoprolactinaemia 64
- hypoproteinaemia 204
- hypotension 29–30, 97
 - dexamethasone 90–1
 - dobutamine 97
 - dopamine 99
 - hydrocortisone 132
 - milrinone 170
 - noradrenaline 182
 - vasopressin 257
 - see also* septic shock
- hypothermia 18, **147**
- hypothyroidism
 - iatrogenic 205, 282
 - treatment 152
- hypovolaemia
 - features 30
 - gelatin 120
 - hexastarch 120
 - pentastarch 120
 - plasma albumin 204
- hypoxia 31, 186–187
- hypoxic ischaemic encephalopathy *see* birth asphyxia
- hypromellose eye drops 106–7
- ibuprofen 133
- Igulin 137
- imipenem 134
- imipramine 282
- immunisation
 - anaphylactic events 135
 - BCG 56–7, 135
 - documentation 136
 - foreign travel 135
 - Haemophilus influenzae* 126
 - hepatitis B 129
 - influenza 136
 - maternal 289
 - measles 223–4
 - meningococcal 159
 - mumps 223–4
 - pneumococcal 159
 - polio 207
 - rubella 223–224
 - schedule in UK 135
 - whooping cough 268–9
- immunocompromised patients
 - BCG administration 56–7
 - live polio vaccine use 207
 - prophylactic antibiotic use 136
- immunoglobulin 137
 - hepatitis B (HBIG) 129
 - rhesus D (Rh0) 219
 - respiratory syncytial virus (RSV) 189
 - tetanus 197
 - varicella zoster (ZIG) 256
- Imodium *see* loperamide
- Indian childhood cirrhosis 196
- indometacin 138
- indomethacin *see* indometacin
- Infant Gaviscon 119
- infantile spasms 259
- infection 25
 - immunoglobulin 137
 - intravascular lines 11–12
 - meningitis 73
 - transmission by blood transfusion 61
 - urinary 251
 - use of cytokines 110, 171
- influenza: vaccine use 136
- information services
 - drug abuse 36

- drugs in breast milk 290
- drugs in pregnancy 290
- ECMO Centres 31
- poisoning 18
- teratology, 290
- website addresses 291–4
- injections
 - intradermal 7, **56**
 - intramuscular (IM) 7
 - intraosseous 8
 - intrathecal 7
 - intravenous (IV) 6–7
- inositol 139
- inotropic drugs
 - cardiac glycosides
 - digoxin 96
 - phosphodiesterase inhibitors
 - enoximone 101
 - milrinone 170
 - sympathomimetics
 - adrenaline 44
 - dobutamine 97
 - dopamine 99
 - isoprenaline 146
 - noradrenaline 182
- INR *see* international normalised ratio
- insomnia (adult) 78
- insulin 140
 - see also* hyperinsulinism
- interferon alfa 141
- international normalised ratio (INR) 116, 179, **266**
- intestinal motility
 - cisapride 85
 - erythromycin 103
 - metoclopramide 164
- Intralipid 142
 - drug incompatibility 14
 - infection 12
- intramuscular (IM) administration 7
- intraosseous administration 8
- intrathecal drugs
 - administration 8
 - alteplase 45
 - gentamicin 8, 121
 - penicillin 8, 197
 - vancomycin 255
- intrauterine blood transfusion 61
- intravascular lines *see* catheters
- intravenous (IV) drugs/fluids
 - administration 3, 6–7
 - compatibility 13
 - continuous infusions 7
 - heparinisation 127–8
 - minimising hazards 15–16
 - slow intermittent infusions 7
 - terminal co-infusion 3, 14
- intraventricular haemorrhage
 - posthaemorrhagic ventriculomegaly 41
 - acetazolamide 41
 - alteplase 45
 - isosorbide 147
 - prophylaxis
 - antenatal steroids 59
 - etamsylate 105
 - fresh frozen plasma 116
 - indometacin 138
 - phenobarbital 199–200
 - vitamin E 263
 - treatment
 - alteplase 45
- intraventricular injections 7
- intubation *see* laryngeal intubation
- iodine
 - in pregnancy 210, 282
 - Lugol's (oral) 210
 - in radiation hazard 210
 - topical 226, 227
 - x-ray contrast media 289
- iohexol *see* x-ray contrast media
- ion exchange resins 208
- iopanoic acid *see* x-ray contrast media
- ipratropium 54
- iron 62, **143–4**, 159
- isoniazid 38, **145**
- isoprenaline 146
- isoproterenol *see* isoprenaline
- isosorbide 41, **147**
- isotretinoin 260
- isovaleric acidaemia 124
- itraconazole 282
- IVH *see* intraventricular haemorrhage
- jaundice
 - cholestatic
 - phenobarbital 199
 - rifampicin 220
 - ursodeoxycholic acid 253
 - neonatal
 - in the breast fed baby 253
 - normal levels 203
 - phototherapy 203
 - tin-mesoporphyrin 248
 - vitamin K 264
 - see also* kernicterus
 - prolonged
 - investigation 229
- jitteriness 27
- Kawasaki disease 52
- kernicterus
 - cause 203
 - danger of sulphonamides 237
 - prognosis 28
- ketamine 148
- ketoconazole 282
- kidney failure *see* renal failure
- Klean-Prep 18
- labetalol hydrochloride 149
- labial herpes 42
- labour
 - nitrous oxide 181

- oxytocin 188
 pethidine 198
 prostaglandin E₂ 214
see also preterm labour
- lactation *see* breast feeding
- lactic acid 29
- lactulose *see* laxatives
- lamivudine (3TC) 150
- lamotrigine 28, **151**
- laryngeal intubation
 general management 33–4
 pain relief for
 fentanyl 108
 ketamine 148
 lidocaine spray 153
 methohexital 247
 morphine 172
 propofol 212
 thiopental 247
 paralysis for
 atracurium 53
 suxamethonium 240
 sedation for
 midazolam 167
- laryngeal stridor
 IV dexamethasone 91
 nebulised adrenaline 135
 nebulised budesonide 65
- laxatives, maternal use 282
- LBW milk formula 168
- legal issues, UK laws 10
- lenograstim *see* filgrastim
- leucovorin 216
- levocarnitine *see* carnitine
- levonorgestrel 283
- levothyroxine 152
- licensing of drugs 10
- lidocaine 153
- lignocaine *see* lidocaine
- limb ischaemia 11
- lindane 226
- linezolid 154
- listeriosis
 amoxicillin 48
 ampicillin 50
 erythromycin 103
 teicoplanin 241
- lithium 283
- liver, ascites 234
- local anaesthesia
 bupivacaine 66
 choices 33–4
 Emla cream **153**, 242
 lidocaine 153
 tetracaine 242
 toxicity 66
- Lomotil *see* co-phenotrope
- loperamide 283
- loratadine 283
- lorazepam 155
- low birth weight milks 168–9
- low blood pressure *see* hypotension
- LSD *see* lysergic acid
- lucinactant 239
- Lugol's iodine 210, 213
- lumbar puncture
 indications 25, 73
 intrathecal drugs 7–8
 pain relief 33
- lungs, fetal maturation
 betamethasone 59
 dexamethasone 90–1
- lupus erythematosus, maternal 90
- lyme disease, maternal 77
- lysergic acid (LSD) 35, **283**
- magnesium alginate 119
- magnesium sulphate 156
- malaria 80, **158**, 217
 drugs
 amodiaquine 216
 atovaquone 158
 chloroquine 80
 chlorphenamine 80
 clindamycin 86, **217**
 drug resistance 80, 158
 Fansidar **216**, 217
 halofantrine 281
 Malarone 158
 mefloquine 158
 primaquine 80, 287
 proguanil **158**, 287
 pyrimethamine **216**, 217
 quinine 217
 sulfadoxine 216
 tetracycline **217**, 244
- Malassezia infection 142
- mannitol 157
- maprotiline 283
- marijuana (cannabis) 35, **283**
- marrow colony stimulating factors
 erythropoietin 104, 110
 filgrastim (G-CSF) 110
 lenograstim (G-CSF) 110
 molgramostim (GM-CSF) 171
- mastitis 112
- maternal drug addiction 35–6
 heroin use 93
 methadone use 161
 non-opioid drug use 82
- mean blood pressure
 normal values at 1–12 hrs 29–30
 potential measurement errors 149 **W**
 use 29
- measles, mumps and rubella (MMR) vaccine
 135, 223–4
- mebendazole 283
- meclizine *see* antiemetics
- meconium aspiration, surfactant use 238
- Medicines and Healthcare products Regulatory
 Agency 10, 17–18
- medroxyprogesterone acetate 223, **283**

- mefloquine 158
 meglumine gadopentetate *see* x-ray contrast
 media 289
 Mendelson's syndrome 185, **218**
 meningitis 25, **73**
 amoxicillin 48
 ampicillin 50
 benzylpenicillin 197
 cefotaxime 73
 ceftazidime 75
 chloramphenicol 79
 ciprofloxacin 84
 co-trimoxazole 89
 dexamethasone 90–1
 flucloxacillin 112
 intrathecal drugs 7–8
 investigation 25
 length of treatment 5
 meropenem 160
 meningococcal infection
 benzylpenicillin 197
 rifampicin prophylaxis 221
 vaccine 136, **159**
 meperidine 198
 meprobamate 284
 mercaptopurine 284
 meropenem 38, **160**
 mesalazine 284
 metabolic acidosis 29, 169, **229**
 THAM 245
 metformin 284
 methadone 35, **161**
 methaemoglobinaemia 163
 aniline dye 226
 bupivacaine 66
 Emla cream 153
 lidocaine 153
 nitric acid 179
 prilocaine 153
 tetracaine 242
 methamphetamine 284
 methicillin 112
 methohexital sodium 247
 methotrexate 284
 methylcellulose
 evacuation enema 208
 maternal laxative 282
 3-methyl-crotonyl-CoA carboxylase deficiency 60
 methyl dopa 162
 methylene blue 18, **163**, 179
 methylenedioxymethamphetamine 35, **284**
 methylmalonic aciduria 261
 methylthionium chloride 163
 metoclopramide 164
 metrizamide *see* x-ray contrast media
 metrizoate *see* x-ray contrast media
 metronidazole 38, **165**
 MHRA *see* Medicines and Healthcare products
 Regulating Agency
 miconazole 166
 midazolam 167
 midwives, UK authority to give drugs 198 **W**
 chloral hydrate 78
 lidocaine 153
 oxytocin 188
 pentazocine 198
 pethidine 198
 naloxone 174
 triclofos 78
 vitamin K 264
 migraine, maternal 284
 milk formulas 168
 additives 6
 milk: plasma (M:P) ratio 274
 milrinone 170
 mineralocorticoid replacement 132
 mineral oil 194
 misoprostol 188, 285
 MMR (measles, mumps and rubella) vaccine 135, **223–4**
 molgramostim (GM-CSF) 148
 monilia *see* candidiasis
 monoamine oxidase inhibitors *see* antidepressants
 morphine 172
 in renal failure 38
 MRI contrast media *see* x-ray contrast media
 mupirocin 173
 muscle relaxation *see* neuromuscular blockade
 myasthenia gravis 175
Mycoplasma infection 103, 224
 myo-inositol 139

 nafcillin 112
 nalidixic acid 285
 naloxone 18, **174**
 antidote for
 chlorpromazine 82
 codeine phosphate 88
 diamorphine 93
 fentanyl 108
 methadone 161
 morphine 172
 pethidine 198
 risk of use in opiate addiction 161 **W**
 nausea in pregnancy 164, **276**
 necrotising enterocolitis 121, 137, 255
 gentamicin 121
 metonidazole 165
 nebulised drugs
 adrenaline 44, **135**
 budesonide 65
 delivery 8
 epoprostenol 102
 fluticasone 65
 furosemide 117
 ipratropium 54
 nitroprusside 180
 ribavirin 220
 salbutamol 225
 NEC *see* necrotising enterocolitis
 nelfinavir 222
 neomycin toxicity 226
 neonatal hepatitis 253

- neostigmine 175
antidote for
 atracurium 53
 pancuronium 191
 vecuronium 258
"nesidioblastosis" 95
netilmicin 38, **176**
neural tube defects
 antenatal prophylaxis 115 **W**
 maternal drugs causing increased risk
 carbamazepine 70
 valproate 254
neuromuscular blockade
 drugs
 atracurium 53
 pancuronium bromide 191
 rocuronium 258
 suxamethonium 240
 vecuronium 258
 reversal
 atropine 54
 glycopyrronium 125
 neostigmine 175
neutrophil white cell count 171
nevirapine 177
nicotine 285
nicoumalone *see* acenocoumarol
nifedipine 95, **178**, 184
nitrazepam 285
nitric oxide 179
nitrofurantoin 285
nitroglycerin 123
nitroprusside 180
nitrous oxide 181
non-steroidal anti-inflammatory drugs
 (NSAIDs) 133, 285
noradrenaline 182
norepinephrine *see* noradrenaline
nortriptyline 285
notifiable infections
 statutory (in UK)
 diphtheria 268
 measles 223
 meningitis 73
 meningococcal infection 159
 mumps 223
 neonatal ophthalmia (all) 106
 polio 207
 rubella 223
 tetanus 268
 tuberculosis 145
 typhoid 79
 viral hepatitis 129
 whooping cough 268
 voluntary
 Haemophilus influenzae 126
 human immunodeficiency virus HIV 270
 maternal rubella 223
NSAIDs *see* non-steroidal anti-inflammatory
 drugs (NSAIDs)
NTBC 183
nuclear accident 210
Nutriprem breast milk fortifier 63
nystatin 184
octreotide
 maternal use 285
 neonatal use (with diazoxide) 95
oesophagitis *see* reflux, gastric
Ohtahara syndrome 259
olive oil 194
olsalazine *see* mesalazine
omeprazole 185
ophthalmia neonatorum 76, **106–7**
Opsite dressings and spray 226
opiates
 alfentanil 108
 antedote *see* naloxone
 codeine 88
 diamorphine (heroin) 93
 fentanyl 108
 maternal addiction **35–6**, 93, 161 **W**
 methadone 161
 morphine 172
 pethidine 198
oral contraceptives 286
oral medication, administration 5–6
ornithine transcarbamoylase deficiency 51
osteitis
 amoxicillin 48
 ampicillin 50
 benzylpenicillin 197
 flucloxacillin 112
 length of treatment 5
 maxillary 106
 sodium fusidate 231
osteopenia of prematurity **169**, 202, 262
Osterprem milk 168
overtreatment 18
oxacillin 112
oxygen 186–7
oxygenation index 31
oxytocin **188**, 257
packed cell volume 61–2
pain relief, neonatal 32
 bupivacaine 66
 codeine phosphate 88
 diamorphine 93
 during intubation 33–4
 Emla cream 153
 fentanyl 108
 ketamine 148
 lidocaine 153
 morphine 172
 nitrous oxide 181
 nursing strategies 32–3
 paracetamol 193
 propofol 212
 review of opiate use 161 **W**
 sucrose 236
 tetracaine 242

- palivizumab 136, **189**
 pancreatin 190
 pancuronium bromide 38, **191**
 panic disorder 286
 papaverine 192
 paracetamol 193
 paregoric 36, 93
 paralysis
 atracurium 53
 during intubation 33–4
 pancuronium 191
 rocuronium 258
 suxamethonium 240
 vecuronium 258
 paraldehyde 194
 parenteral nutrition *see* total parenteral nutrition
 paroxetine 286
 partial thromboplastin time 116
 patent ductus arteriosus (PDA) 138
 drugs used to effect closure
 ibuprofen 133
 indometacin 138
 drugs used to maintain patency
 prostaglandin E₁ and E₂ 214
 patient group directions (PDGs) **10**, 198, 219
 PCP *see* phencyclidine
 PDA *see* patent ductus arteriosus (PDA)
 Peditrace **195**, 271
 penicillamine 196
 penicillin antibiotics 197
 amoxicillin 48
 ampicillin 50
 benzathine penicillin 211
 benzylpenicillin 197
 co-amoxiclav 48
 flucloxacillin 112
 in renal failure 38
 intrathecal preparation 7–8
 penicillin G 197
 penicillin V 197
 phenoxymethylpenicillin 197
 procaine penicillin 211
 pentastarch 120
 in anaphylaxis 135
 pentazocine 198
 peptic ulceration
 cimetidine 83
 misoprostol 188, 285
 omeprazole 185
 ranitidine 218
 Peptijunior milk 168
 peritoneal dialysis **37**, 208
 permethrin *see* *under* mefloquine
 perphenazine 286
 periventricular haemorrhage *see* intraventricular haemorrhage
 persistent pulmonary hypertension 31
 adenosine 43
 dopamine 99
 epoprostenol 102
 magnesium sulphate 156
 nitric oxide 179
 nitroprusside 180
 tolazoline 250
 pertussis 103
 vaccine 268–9
 pethidine 198
 phencyclidine (PCP) 36, **286**
 phenindione 286
 phenobarbital 199–200
 phenobarbitone *see* phenobarbital
 phenolphthalein *see* laxatives
 phenoxymethylpenicillin 197
 phentolamine mesilate 99
 phenylbutazone 286
 phenylephrine eye drops 107
 phenytoin 201
 cardiac arrhythmias 14
 phosphate 6, 169, **202**
 phototherapy 203
 phytomenadione 264
 plasma albumin 204
 plasminogen 116
 platelets 116, **205**
 pneumococcal infection 136, **206**
 amoxicillin 48
 benzylpenicillin 197
Pneumocystis carinii infection 89
 pneumothorax 33, 109
 poisons information centres 18
 polio vaccine 207
 polycythaemia 61–2, 204
 polyethylene glycol electrolyte solutions 18
 polyhydramnios 138
 polystyrene sulphonate resins 208
 poractant alfa 238
 porphyria 248
 postmenstrual age, definition 3
 posthaemorrhagic hydrocephalus 41
 potassium chloride **18**, **209**
 potassium iodate 210
 povidone iodine 226, 227, 282
 PPD (tuberculin) 57
 pre-anaesthetic medication 54
 Pre-Apamil milk 168
 Preconceive 115
 prednisolone
 drug equivalence 132
 haemangiomas 141
 maternal use 287
 thrombocytopenia 137
 toxoplasmosis 216
 pre-eclampsia 156
 pregnancy, medication in 274–90
 prelabour rupture of membranes 50, 103
 Premium milk 168
 prescribing
 by midwives 198
 by nurse practitioners 10
 errors 15–16
 patient group directions (PDGs) 10

- writing prescriptions 19–20
- preterm labour
- antibiotics in
 - amoxicillin 48
 - ampicillin 50
 - erythromycin 103
 - metronidazole 165
 - penicillin 197
 - drugs to control
 - atosiban 178
 - glyceryl trinitrate 123
 - indometacin 138
 - magnesium sulphate 156
 - nifedipine 178
 - salbutamol 225
 - terbutaline 225
 - steroid prophylaxis
 - betamethasone 59
 - dexamethasone 90–1
- prilocaine 153
- primaquine **80**, 287
- primidone 287
- procainamide 287
- procaine penicillin 211
- proguanil **158**, 287
- promazine 198
- promethazine 287
- propacetamol 193
- prophylactic antibiotics
- asplenia 136
 - bacterial endocarditis 86
 - caesarean section 74
 - candida infection 184
 - catheter sepsis 255
 - gonococcal ophthalmia 76, 106
 - group B streptococci 197
 - Haemophilus influenzae* 221
 - meningococcal infection 221
 - necrotising enterocolitis **121**, 255
 - neonatal ophthalmia 106
 - parenteral nutrition 255
 - Pneumocystis carinii* 89
 - prelabour rupture of membranes **50**, 103
 - preterm labour 50, 86, 165
 - routine use of 25
 - sickle cell disease 136
 - tuberculosis 145
 - urinary infection 251
 - whooping cough 103
- propionyl-CoA carboxylase deficiency 60
- propofol 212
- propranolol 213
- propylene glycol **8**, **101**, 226
- propylthiouracil **213**, 287
- prostacyclin 102
- Prostaglandin E₁ (alprostadil) 214
- prostaglandin E₂ 214
- protamine sulphate 128
- Proteus* spp
 - amoxicillin 48
 - ampicillin 50
 - aztreonam 55
- prothrombin time **116**, 264, 266
- proton pump inhibitors *see* omeprazole
- proxymetacaine eye drops 107
- Pseudomonas* infections
 - aztreonam 55
 - ceftazidime 75
 - ciprofloxacin 84
 - gentamicin eye drops 106–7
 - tobramycin 249
- pteroylglutamic acid 115
- pulmonary hypertension *see* persistent pulmonary hypertension
- pulmonary oedema, acute congestive 117
- pyloric stenosis
 - caused by erythromycin 103
 - treatment with atropine 54
- pyrazinamide **145**, 287
- pyridostigmine 175
- pyridoxine 215
- pyrimethamine **216**, 217
- pyruvate carboxylase deficiency 60
- quinidine sulphate 96
- quinine 217
- radioactive iodine, prophylaxis 210
- radiopharmaceuticals 287
- raised intracranial pressure
 - acetazolamide 41
 - during intubation 240
 - isosorbide 147
 - mannitol 157
- ranitidine 218
 - cardiac arrhythmias 14
- RDS *see* respiratory distress syndrome
- recreational drug use, maternal 35–6
 - during lactation 274–90
- rectal drugs 6
- reflex anoxic seizures 135
- reflux, gastric 119 **W**
 - and apnoea 67
 - cimetidine 83
 - cisapride 85
 - domperidone 98
 - Gaviscon 119
 - omeprazole 185
 - ranitidine 218
- renal failure 37–8
- renal vein thrombosis 26
- Resonium A 208
- respiratory distress syndrome
 - prophylaxis
 - betamethasone 59
 - dexamethasone 90–1
 - inositol 139
 - surfactant therapy 238, 239
 - respiratory syncytial virus (RSV) 136, **189**, 220
- resuscitation 44, 68, 229, **245**
- retinol *see* vitamin A
- retinopathy of prematurity

- cryotherapy for 186
- preventive care 186
- prophylaxis
 - inositol 139
 - penicillamine 196
 - vitamin E 263
- Reye's syndrome **52**, 193
- rhesus (D) immunoglobulin 219
- rheumatoid arthritis 133
- ribavirin 220
- rickettsiae
 - chloramphenicol 79
 - ciprofloxacin 84
 - tetracycline 244
- rifampin *see* rifampicin
- rifampicin 38, **221**
- ritonavir 222
- rocuronium 258
- ropivacaine 66
- RSV *see* respiratory syncytial virus
- rubella 135, **223**

- salbutamol 225
 - use in anaphylaxis 135
- saline eye drops 106
- Salmonella*
 - amoxicillin 48
 - ceftriaxone 76
 - chloramphenicol 79
 - ciprofloxacin 84
- sedation
 - chloral hydrate 78
 - chlorpromazine 82
 - midazolam 167
 - morphine 172
- seizures, neonatal 27, 199 **W**
 - acetazolamide 41
 - calcium gluconate 68
 - clonazepam 87
 - diazepam 94
 - hypoglycaemic 92
 - lamotrigine 151
 - lidocaine 153
 - lorazepam 155
 - paraldehyde 194
 - phenobarbital 199–200
 - phenytoin 201
 - pyridoxine dependency 215
 - thiopental 247
 - valproate 254
 - vigabatrin 259
 - see also* epilepsy
- senna *see* laxatives
- septic shock
 - methylene blue 163
 - milrinone 170
 - naloxone 174
 - noradrenaline 182
 - pentastarch 120
 - vasopressin 257
- serotonin re-uptake inhibitors 276
- sertraline 288
- Shigella*
 - amoxicillin 48
 - ampicillin 50
- shingles 256
- shock *see* septic shock
- sickle cell disease 136
- silver nitrate eye drops 106
- situs ambiguus 136
- skin
 - anaesthesia 33, **242**
 - care 226
 - dressings 12, 226
 - sterility 227
 - use of emollient cream 226 **W**
- sleep *see* hypnotic drugs
- SMA milks
 - breast milk fortifier 63
 - Gold milk 168
 - LBW Formula 168
- smoking *see* nicotine
- sodium benzoate 228
- sodium bicarbonate 168, **229**
- sodium chloride 230
 - eye drops 107
 - oral supplements 6, 168
- sodium citrate 218
- sodium feredetate 104, **144**
- sodium fusidate 231
- sodium glycerophosphate 202
- sodium ironedetate 104, **144**
- sodium loss in urine 37, 168, **230**
- sodium nitrite 180
- sodium nitroprusside 180
- sodium polystyrene sulphionate 208
- sodium phenylbutyrate 228
- sodium supplements 168, **230**
- sodium thiosulphate 180
- sodium valproate 254
- Solvitro N 195, **265**
- solvent abuse 288
- somatostatin 95, 285
- sorbitol 208
- sotalol 111, **232**
- SPC *see* Summary of Product Characteristics
- speed 284
- spina bifida *see* neural tube defects
- spiramycin 233
- spironolactone 234
- spleen (absence) 136
- statins 288
- steroids
 - drug equivalence 132
 - treatment of adrenal suppression 90
 - see also* corticosteroids
- Stesolid 94
- stilboestrol *see* diethylstilbestrol
- St John's wort *see* herbal remedies
- storage of drugs 4
- streptokinase 235

- streptomycin 288
 stridor *see* laryngeal stridor
 subdural haematoma 157
 succimer 251
 succinylcholine *see* suxamethonium
 sucrose 33, **236**
 sulfadiazine 237
 sulfadoxine 216
 sulfamethoxazole 89
 sulfasalazine 288
 sulphadiazine 237
 sulphasalazine 288
 sulphonamides
 history 237
 sulfadoxine 216
 sulfamethoxazole **89**, 237
 sulfasalazine 288
 sulpiride 289
 sumatriptan 289
 Summary of Product Characteristics (SPC) v, 10
 suppositories 6
 supraventricular arrhythmias
 adenosine 43
 amiodarone 47
 digoxin 96
 flecainide 111
 surface anaesthesia, strategy 46
 surface area and body weight 21
 surfactant deficiency
 prophylaxis
 betamethasone 59
 dexamethasone 90–1
 inositol 139
 replacement treatment
 natural 238
 synthetic 239
 suxamethonium 240
 sympathomimetic drugs
 adrenaline 44
 dobutamine 97
 dopamine 99
 during resuscitation 24
 ephedrine 280
 for anaphylaxis 135
 isoprenaline 146
 noradrenaline 182
 pharmacology 182
 Synacthen 243
 Syntometrine 188
 syphilis, 197, **211**
 syringes 4, 5
- $t_{1/2}$ *see* half life (of drugs)
 3TC *see* lamivudine
 tissue plasminogen activator 45
 technetium radiopharmaceuticals 287–8
 Tegaderm dressing 226
 teicoplanin 38, 221, **241**
 temazepam 78
 temperature control 18
 teratology database 290
- terbutaline 225
 tetanus 97, 268
 tetracaine 242
 tetracosactide 243
 tetracosactrin *see* tetracosactide
 tetracycline 217, **244**
 tetrahydrofolic acid 115
 THAM 245
 theophylline 9, **246**
 thiomersal 269
 thiopental sodium 247
 thiopentone sodium *see* thiopenatal sodium 247
 thrombin, bovine 109
 thrombocytopenia
 immunoglobulin 137
 investigation 205
 platelets 205
 prednisolone 137
 TAR syndrome 205
 thromboses
 investigation 26
 prevention 11
 treatment
 alteplase 45
 heparin 127–8
 streptokinase 235
 urokinase 252
 warfarin 266
 thrush *see* candidiasis
 thyroid disorders
 hypothyroidism
 iatrogenic 226, 227, 282
 nutritional 210
 treatment 152
 thyrotoxicosis
 Lugol's iodine 210
 propranolol 213
 propylthiouracil 213, 287
 thyroxine *see* levothyroxine
 tin-mesoporphyrin 248
 tissue extravasation *see* extravasation
 tissue ischaemia 11
 tissue plasminogen activator 45
 tobramycin 249
 tocolytic drugs
 atosiban 178
 choice 178
 glyceryl trinitrate 123
 indometacin 138
 magnesium sulphate 156
 nifedipine 178
 salbutamol 225
 terbutaline 225
 tolazoline 250
 tolbutamide 289
 topiramate 289
 total parenteral nutrition 195
 coinfusion with other drugs 3, 14
 extravasation 11, 130
 infection 11–12
 insulin 140

- Intralipid 142
 Vitlipid N Infant 142
 toxæmia of pregnancy 156
 toxoplasmosis 233
 pyrimethamine 216
 sulfadiazine 237
 t-PA *see* alteplase
 TPN *see* total parenteral nutrition
 trachoma 106
 tranexamic acid 235
 tranquilliser 34, 36, **82**, 167
 transcobalamin deficiency 261
 tretinoin *see* vitamin A
 tribavirin *see* ribavirin
 tricyclic antidepressants 275
 trifluoperazine 276, 289
 trimeprazine *see* alimemazine
 trimethoprim 38, **251**
 TRIS 245
 trometamol (THAM) 245
 tromethamine (THAM) 245
 tropicamide/phenylephrine eye drops 106–7
 tuberculin PPD 57
 tuberculosis
 BCG 56–7
 during pregnancy 145
 ethambutol 145, **281**
 isoniazid 145
 pyrazinamide **145**, 287
 rifampicin 221
 streptomycin 288
 typhoid *see* *Salmonella*
 tyrosinaemia 183
- umbilical cord 227
 urea cycle disorders 227
Ureaplasma infection 103, 244
 ureteric reflux 251
 urinary tract infection 251
 ursodeoxycholic acid 253
 urokinase 252
- vaccination
 maternal 289
 UK policy 135–6
 vaccines
 chicken pox 256
 diphtheria 268
 during lactation 289
 Haemophilus influenzae 126
 hepatitis B 129
 influenza 136
 in pregnancy 289
 meningococcal 159
 MMR 223
 pneumococcal 206
 policy in UK 135–6
- polio 207
 rubella 223
 storage 4
 tetanus (DTP) 268
 tuberculosis (BCG) 56–7
 whooping cough 268–9
 valproate 254
 Vaminolact 195
 vancomycin 38, 221, **255**
 varicella 256
 vascular spasm **11**, 192, 250
 vasopressin 257
 V₀ *see* volume of distribution
 vecuronium 258
 venlafaxine 289
 ventricular fibrillation **43**, 44, 96
 ventriculitis 7
 chloramphenicol 79
 ciprofloxacin 84
 gentamicin 121
 Verres needles 130
 vials 4
 vigabatrin 259
 virilisation, fetal 90
 vitamin A **260**, 275, 285
 vitamin B₆ 215
 vitamin B₁₂ 261
 vitamin C 265
 vitamin D 63, 169, **262**
 vitamin E 190, **263**
 vitamin K₁ 264
 vitamins, multiple 265
 Vitlipid N 142
 volume of distribution 9
 vomiting
 in babies *see* reflux
 in pregnancy 276
 VZIG immunoglobulin 256
- warfarin 266
 water 267
 website addresses
 this formulary ii, vi
 useful addresses 291–4
 West's syndrome *see* infantile spasms
 whooping cough
 prophylaxis 103
 vaccine 268–9
 Wilson's disease 196
- x-ray contrast media 289
- zidovudine 270
 zinc 63, **271**
 zinc ointment 226
 ZIG immunoglobulin 256
 zolpidem tartrate 289