

Paediatric pharmacy —drug therapy

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This month's special feature focuses on paediatric pharmacy. The four articles consider drug therapy, parenteral nutrition, the use of automation to prepare artificial feeds, and the role of the pharmacist in neonatal and paediatric intensive care



Delivering a child's dose: sometimes liquids have to be prepared extemporaneously with little information to support the bioavailability of the medicine, and the physical, chemical and microbial stability of the preparation

Safe and effective drug treatment for children requires an understanding of the wide variability and constant changes in pharmacokinetic handling and pharmacodynamic response to drugs that occur during the time from birth to adulthood.

An awareness of, and empathy with, the problems and challenges of drug administration throughout childhood is essential if the pharmacist is to be competent and confident in becoming part of the multidisciplinary team caring for paediatric patients and their families.

Children are not just "small adults", particularly when drug handling is considered;

children are not "just children" either. Patients range from premature babies, born as early as 24 weeks gestation, to 18-year-old adolescents. They suffer from cardiac, respiratory, renal, and other system diseases, in the same way as adults. The "specialist" paediatric pharmacist usually also has to be a "generalist".

Recently, there has been international agreement on age groups to be used when considering medicines for children¹ (see Panel 1, p50). These age groups are aimed at the pharmaceutical industry to help rationalise the licensing of medicines for children. They will avoid product licences having recommendations based on age bands, which have sometimes appeared to be arbitrarily chosen rather than being based on relevant physiological and pharmacokinetic principles.

ALTERED PHARMACOKINETICS

The altered pharmacokinetic handling of medicines seen at the different stages of childhood development gives rise to practical problems in drug absorption and distribution.

Absorption — oral At birth, gastric pH is between 6 and 8. Other than a small lowering, it remains relatively high until gradually falling to adult levels by the age of two or three years.

A relatively high gastric pH occurs in the premature neonate, whose immature gastric mucosa leads to reduced acid secretion. This can lead to increased absorption of acid-labile medicines, such as penicillin, because of reduced drug breakdown. Increased or decreased absorption of weakly acidic or basic medicines can occur

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Panel 1: Age ranges and definitions

- **Preterm newborn infants**
Born at less than 37 weeks gestation
- **Term newborn infants**
0-27 days
- **Infants and toddlers**
28 days to 23 months
- **Children**
Two to 11 years
- **Adolescents**
12 to 16–18 years (dependent on region — consensus not obtained)

Panel 2: Criteria for TDM

- Clinically interpretable correlation between serum drug concentration and pharmacological effect
- Narrow margin between serum concentrations causing toxic effects and those producing therapeutic effects
- Serum concentration produced by a given dose cannot be predicted because of inter- and intra-patient pharmacokinetic differences
- Pharmacological effects of the drug cannot be measured easily
- A rapid and reliable method for drug serum concentration analysis must be available

because of changes in ionisation state, eg, slowed and reduced absorption of acidic medicines, such as phenytoin and phenobarbital.^{2,3}

During the first six months of life, peristalsis is reduced and gastric emptying is relatively slow,² and are dependent on gestational and postnatal age, feeding patterns, and the nature of the feed. Reduced production of bile results in reduced solubilisation of fat-soluble medicines. Variable rates of colonisation by gut microflora, high levels of beta-glucuronidase activity in the gut, vomiting, and the spitting out of medicines, all add to variability and unreliability in the absorption of oral medicines. Despite this, some drugs can be given orally with success to babies tolerating milk feeds, eg, caffeine for the treatment of apnoeas.

Absorption — intramuscular (IM) Muscle mass is low in premature neonates, and blood flow is reduced and variable throughout muscle tissue. Muscle contractions are also inefficient and vasomotor instability can produce an exaggerated vasoconstrictor reflex.³ This makes drug absorption from IM sites unpredictable. The IM route is also painful and should be avoided if possible.

Absorption — percutaneous Increased systemic absorption of topical substances is possible in neonates and infants because of their large surface area relative to body weight and skin that is well hydrated. However, drug toxicity has occurred through increased systemic drug absorption. For example, there are well documented cases of neurotoxicity and death following hexachlorophene absorption.³

The immature skin of preterm newborns presents little barrier to systemic drug absorption. It therefore offers a possible route of administration that may avoid the problems presented by other methods of neonatal drug delivery, eg, difficult venous access and unreliable oral administration. Research is needed to develop medicines to be delivered by the percutaneous route.⁴

Absorption — rectal Giving medicines rectally can be a useful adminis-

tration route if oral or intravenous administration is impossible. However, in the neonate, rectal absorption may be incomplete and relatively slow. Suppositories containing appropriate doses are often not available. Common practice is to administer fractions of suppositories, but it must be remembered that the drug content is not necessarily distributed evenly and, therefore, the actual dose administered may differ from that intended.

Distribution Compared with adults, total body water is relatively high in the foetus (94 per cent), premature neonate (92 per cent), newborn baby (75 per cent) and small children (60 per cent).⁵ Extracellular water follows a similar pattern. Fat content is much lower in preterm babies (3 per cent) compared with full term babies (12 per cent), one-year-olds (30 per cent) and adults (18 per cent).

For medicines distributed extensively into extracellular water, significantly increased volumes of distribution in neonates and young infants result. For example, the volume of distribution of gentamicin is 0.35–0.78L/kg in the neonate, compared with 0.2L/kg in adults.⁶ Similar loading doses/kg, given to a neonate or older child, will provide lower serum concentrations in the neonate, making the use of larger doses/kg necessary for therapeutic serum concentrations to be achieved.

Plasma protein concentration, binding affinity and capacity are reduced in the neonate. Competition for binding sites by endogenous compounds, such as bilirubin, can occur. Highly protein-bound drugs, such as phenytoin, furosemide and indometacin, are significantly less protein-bound in the neonate than adults. This results in increased volumes of distribution and levels of free drug. Larger loading doses of highly protein-bound drugs may be needed in neonates to produce the desired serum concentrations.

Metabolism Many hepatic microsomal enzyme processes are immature in infants. Some pathways mature more quickly than others. For example, in older children and adults, paracetamol is metabolised mainly by glucuronidation. In the neonate, paracetamol is metabolised by sulphation because this pathway is an alternative metabolic route and is more advanced at birth than the glucuronidation process. The latter route takes several months to become fully mature.

Phenytoin is slowly metabolised in the first few days of life of a term baby, and has a half-life of 24–48 hours. By two weeks of age, this has fallen to around eight hours. In a premature baby, phenytoin metabolism is less predictable, but is likely to be of the order of 72 hours.

Impaired phenobarbital metabolism develops similarly to result in half-lives of 70–200 hours in the first few days of life, to 20–50 hours by two or three weeks of age.

Once daily dosing is, therefore, adequate in a newborn baby. However, twice daily dosing soon becomes necessary because of the reduction in half-life in the first few weeks, and because of liver enzyme induction resulting from phenobarbital use.

Theophylline is also metabolised by a different pathway in newborn babies, resulting in the production of caffeine rather than methyluric acids, as in older children and adults. Caffeine is also active and, therefore, a lower dose is needed in newborns. Theophylline clearance in children aged between one and nine years exceeds values of either young infants or adults, and hence much larger doses/kg, and shorter dosing intervals, are required because of shorter half-lives. This is thought to be associated with the relatively larger size of the liver in children aged between one and nine years. At puberty, theophylline clearance reduces to reflect that of adults. Cyclosporin is similarly affected.

For other hepatically metabolised drugs, there is a steady increase in the clearance rate throughout childhood as enzyme systems mature.

Excretion Renal excretion depends on glomerular filtration and tubular secretion. These are highly dependent on gestational age. Both are much reduced in babies compared with adults, and the difference persists until about one year of age. Consequently, clearance of renally excreted medicines is prolonged in infants and, particularly, in preterm babies in the first week of life. Extended dose intervals are required. Antenatal steroids may reduce the gestational age-dependent differences in renal excretion.^{6,7}

DOSE CALCULATION

Most doses are calculated on an individual patient basis.

Using body surface area to calculate drug doses is the most accurate method because surface area reflects cardiac output, fluid requirements and renal function better than weight-based dosing. In practice, however, using surface area for dose calculations tends to be used only for a limited number of drugs, eg, cytotoxic agents. This is because surface area can increase by 1–2 per cent per day in a young child and, therefore, doses require frequent adjustments. Surface area estimations from height/weight nomograms can be problematic because height is difficult to measure accurately, especially in small children. Weight-based nomograms are now available and are used in children's cancer study group protocols within the United Kingdom. Only a few published dose recommendations are surface area-based, making this method impractical for many drugs. Weight-based doses are mainly used. Doses based on age bands may be used for some drugs with a wide therapeutic index.

A reputable paediatric dose reference source should be used. A number of hospitals have developed and published their own.^{8–10} In 1999, "Medicines for children" was published,¹¹ through collaboration between paediatric pharmacists and medical staff. This reference is published jointly by the Neonatal and Paediatric Pharmacists Group (NPPG) and the Royal College of Paediatrics and Child Health. It contains guidelines for the management of common paediatric diseases and monographs of drug doses, administration details and licence information. The document is peer reviewed and is accepted as the UK national paediatric drug reference source. A pocket-sized edition was published in 2001 and updated editions are expected this year.

LICENSING OF MEDICINES

Many manufacturers write disclaimers stating that their products should not be used in children. Recommendations may be limited to specific age groups, indications or routes of administration for which medicines are licensed. This has led to unlicensed medicines being used and medicines being used outside these licence restrictions (off-label).

Around 90 per cent of babies in neonatal intensive care,¹² 70 per cent of patients in paediatric intensive care,¹³ and almost 70 per cent of children in hospital in Europe,¹⁴ receive at least one unlicensed or off-label medicine during a hospital stay. These medicines have not been subjected to the licensing process, either at all (unlicensed medicines), or in the situations where they are used (off-label medicines), and safety, efficacy and quality cannot be assured. This does not reflect inappropriate prescribing but, instead, shows that there is a lack of suitable, licensed medicines for children.

With certain medicines, there are real and proven problems associated with their use in children and, therefore, they are only recommended for administration to adults. More commonly, however, there is a lack of clinical trials providing evidence to support licensing applications for paediatric drug use. The ethical, practical and technical problems involved in conducting clinical trials in children make such research more difficult and time consuming than in adults.^{15,16} Conducting paediatric clinical trials is also an additional expense for the manufacture, that may not be balanced by the commercial benefit of licensing a medicine for the relatively small paediatric market.

Increasing pressure on the pharmaceutical industry might change this. A European Commission consultation document, "Better medicines for children", makes suggestions for improving the availability of suitable licensed products for children.¹⁷ The document proposes legislative changes to require pharmaceutical companies to study appro-

appropriate medicines in children. It also suggests an incentive to extend patents to compensate for the additional expense. In the United States, the Food and Drug Administration Modernisation Act was introduced in 1997.¹⁸ It provided economic incentives in the form of six-month extensions of existing patent protection on drugs for which the FDA requested paediatric studies. (The studies had to be conducted in accordance with the act's requirements.)

The FDA also introduced the Paediatric Rule in 1999, legally requiring that manufacturers of medicines likely to be used in a substantial number of children, or those offering a "meaningful therapeutic benefit" to children over existing treatments, conduct studies to provide adequate labelling for use in paediatrics.¹⁸ This legislation has generated paediatric clinical studies and useful prescribing information. Medicines that are used to treat a variety of conditions, eg, gastro-oesophageal reflux, diabetes, pain, and asthma, have, or soon will have, paediatric use information in their licences.

There are still gaps in the information being provided. For example, older medicines that are not eligible for the financial incentive of enhanced patent protection, drugs with low sales and drugs for neonates are being neglected. Amendments to the FDA act are planned to address these deficiencies.¹⁹ It is hoped that European legislation will soon be passed and lessons will be learnt from the US experience.

DAY-TO-DAY PROBLEMS

The following are the day-to-day problems that are encountered within paediatric pharmacy.

Lack of information sources Problems arise from the difficulty in finding information on doses, etc, for unlicensed medicines in children. However, the reference source, "Medicines for children", has helped alleviate this problem.

The Drug Information Advisory Line (DIAL, www.dial.org.uk) is another useful information resource, offering advice on the use of medicines in children to health care professionals. It is based at the Royal Liverpool Children's Hospital (Alder Hey). DIAL staff handle all paediatric enquiries with the exception of those concerning poisoning. DIAL also offers an active e-mail query sharing group, which is a useful support system.

Lack of suitable formulations Medicines are often only commercially available as a tablet or capsule in strengths appropriate for adult doses. To deliver a child's dose, suitable products, such as oral liquids, powders or capsules, have to be prepared extemporaneously. This must often be carried out with little information to support the bioavailability of the medicine, and the physical, chemical and

microbial stability of the preparation.²⁰ The resulting preparation is often unpleasant to take and has a short shelf-life, obliging the family to obtain a prescription frequently and to find a community pharmacist to organise further supplies. Communication between hospital and community pharmacists to share information on formulations and ingredient sources, or to arrange preparation by a specials manufacturer, is essential to ensure seamless care for the patient.

Importing licensed formulations from other countries may be a preferable alternative.²⁰ However, difficulties surrounding importation and free movement of medicines between countries can make this a complicated process. Also, gaining access to information on product availability can be difficult and time consuming.

Other means must sometimes be used to overcome the lack of suitable products for children. It may be necessary to use orally solutions intended for injection. This must be done carefully because different formulations may include different salts and, therefore, have different bioavailability and stability. A paediatric formulation may be available from a specials manufacturer.

Tablet cutters can be used to halve or quarter tablets, although this is inaccurate and dose equivalence is unlikely to be achieved. Soluble tablets are used if available. Doses less than a full tablet may be made up by dissolving in a specified volume and administering an aliquot of the resulting liquid using an oral syringe. Some tablets are soluble even if not marketed as such, and a list of such tablets can be helpful. There is a lack of research, however, to confirm the drug content of aliquots of liquids when doses are measured in this way.

Having an awareness of inappropriate excipients in some drug formulations (even those licensed for children) is important. Examples are a commercial formulation of phenobarbital elixir containing 38 per cent alcohol. Phenobarbital injection contains between 80 and 90 per cent propylene glycol, which can cause hyperosmolality if the injection is not diluted appropriately.

MEDICATION ERRORS

The lack of suitable, licensed formulations for children can potentially lead to medication errors. Dilution of adult strength injections, or administration of fractions of an ampoule, is often needed, and fatal errors have been reported.²¹ Displacement values must be taken into account, and careful use of syringes is essential to avoid administration of the contents of the "dead space", and to avoid overdosing with high strength adult preparations.

THERAPEUTIC MONITORING

For therapeutic drug level monitoring (TDM) to aid in drug therapy, the criteria in Panel 2 (page 50) must be satisfied.²²

As in adults, the timing of blood sampling for serum analysis is important. Steady state should be reached before levels are meaningful, unless toxicity is suspected. In neonates, drugs such as digoxin have a half-life of around 20–180 hours, depending on gestational and postnatal age.² Steady state will not be achieved until after one to four weeks of treatment. This is reduced by giving a loading dose.

Neonates have a rapidly changing pharmacokinetic response, with significant improvements in renal and hepatic elimination mechanisms occurring almost constantly, with the effect that steady state may actually never be achieved. Neonates have a circulating blood volume of 80ml/kg.²³ For a small preterm baby, blood sampling is a common cause of anaemia. The use of microassay techniques, which will analyse drug levels in microlitre rather than millilitre volumes of blood, are desirable. Recommended therapeutic ranges for drugs are mainly based on adult data. Little is known about whether the same ranges should be applied to children and neonates. Hospital laboratories tend to quote the same reference ranges irrespective of the patient's age, leading to the tendency to assume that all patients will respond in the same way to similar blood levels.²⁴ This is unlikely, because receptor numbers and sensitivities may be different, and the actual drug concentration reaching the receptor site is also likely to vary because of altered pharmacokinetics.

Differences in plasma proteins cause drugs that are normally highly protein-bound to be less so in the neonate, resulting in higher free, and therefore active, fractions of drug. Levels are usually reported in terms of total serum concentration and, therefore, the same level in a neonate and an adult may produce different effects in terms of efficacy and toxicity.

Further complications are the presence of interfering endogenous compounds that may not be present in adult patients,⁵ eg, the presence of digoxin-like immuno-reactive substances in the infant and neonate. These compounds cross-react with many digoxin assay methods, falsely elevating total serum drug concentrations.

DECISION-SUPPORT SYSTEMS

The future for prescribing, already a reality in some areas, is for medical staff to write their prescriptions on computer, with information made immediately available on screen to help them choose the best treatment for an individual patient. This will be based on real time clinical information, such as gestational and postnatal age, weight, renal and hepatic function, disease

NPPG

The Neonatal and Paediatric Pharmacists Group (NPPG) exists for pharmacists involved in the care of children, whether as a chosen specialty or as part of a job, or with an interest in paediatrics. It aims to improve the care of neonates, infants and children by advancing the personal development of pharmacists and the provision of quality pharmacy services in relation to practice, research and audit, education and training, communication and advice. The NPPG offers network and advice support systems with active e-mail discussion and an informative website (www.nppg.demon.co.uk). The group also organises regular study days and annual conferences.

The Faculty of Neonatal and Paediatric Pharmacy is the result of collaboration between the NPPG and the College of Pharmacy Practice. It aims to offer members access to education, training and accreditation in neonatal and paediatric pharmacy, and to provide a structured route for continuing professional development (details can be found at www.collpharm.org.uk).

state, allergies and laboratory values, etc. It will be supported by evidence-based clinical practice guidelines appearing as prompts on the computer screen as patient information is entered.²⁵ The system will ensure that prescribers select the correct drug and dose, avoiding interactions and the potential for adverse drug reactions. Computerised decision support systems have already been shown to reduce medication errors considerably.²⁶ These support systems are often linked to computerised prescribing.

Designing and implementing decision support systems for paediatric patients is more difficult than for adults.²⁷ For example, systems for paediatrics need to be capable of allowing frequent patient weight updates (daily in neonatal patients) and incorporation of normal ranges for laboratory values at different ages.

A computerised anti-infective decision support tool used in a paediatric intensive care unit in the US has been associated with a reduction by 59 per cent in pharmacy interventions for incorrect drug doses; sub-therapeutic patient days decreased by 36 per cent and excessive dose days by 28 per cent.²⁸ The number of antibiotic doses and costs were also substantially reduced.

Before use of decision support systems becomes a reality in many children's hospitals, there are many barriers and difficulties to be overcome, including organisational, technical and cultural issues. However, deci-

sion support systems provide exciting opportunities for the future. It is hoped that information databases, such as the "Medicines for children" guidelines, can be incorporated into such decision support systems to maximise accessibility and use of this important reference source.

CONCLUSION

The paediatric patient suffers many of the diseases that adults suffer, as well as diseases specific to children. The altered and ever changing pharmacokinetics from birth to adolescence, the need for individualised dose calculation, the lack of suitable formulations and the increased potential for medication errors in paediatric drug therapy mean that life as a paediatric pharmacist offers many challenges.

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