

Neonatal pharmacology

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Abstract

The neonatal period represents a time of rapid growth and development. As a consequence, significant pharmacokinetic changes occur. In addition, pharmacodynamic changes, physiological inter-patient variability and pathological processes are factors to consider when trying to predict the action and disposition of drugs in the neonate. The problem is compounded by a relative paucity of research and data on many aspects of neonatal pharmacology. These issues pose significant challenges to the clinician to deliver safe and effective drug therapy to these vulnerable patients. Recent developments have attempted to redress this balance; many steps have been taken to increase the number of paediatric drug research programmes and the traditional challenges to research in children and neonates are being addressed by legislative authorities, pharmaceutical companies, clinicians and the academic community. These research issues are discussed along with the basic science of neonatal pharmacology and new developments in the past few years.

Keywords Drugs; neonatal; off-label; paediatric; pharmacodynamics; pharmacology; pharmacokinetics; therapeutic orphan

Traditional barriers to research in neonates (and older children)

In 1968, Dr Harry Shirkey (Chair of the American Academy of Pediatrics Committee on Drugs) described how children were being systematically excluded from studies intending to establish safety and efficacy of new drugs. He coined the term 'therapeutic orphans' to emphasize the lack of adequate prescribing information for drugs in children.^{1,2} Despite this assertion, studies for the next 30 years showed consistently that approximately 80% of prescription medicines approved and labelled for adults contained no paediatric safety or prescribing information and a disclaimer regarding use in children. As a result, there has been routine and widespread 'off-label' use of medications in infants and children in the absence of adequate safety, efficacy, and dosing information. This goes hand in hand with the risk of adverse outcomes due to under-dosing, over-dosing, or unanticipated adverse events unique to children and not predicted from experience in adults.²

A number of reasons have been cited for this void of information in childhood therapeutics:

(1) Ethical constraints and medico-legal issues

These principles concerning research on patients unable to give consent differ from the adult population. Generally it is not considered ethical for a parent to give consent to non-therapeutic research where the risk is more than a minor 'increase over

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Learning objectives

After reading this article, you should be able to:

- précis the challenges facing the clinician in delivering appropriate dosing regimes in neonates, including appreciation of the non-linear relationship between metabolic processes and size of child
- explain how growth and development in the neonate affects drug disposition (with examples)
- provide an overview of the recent developments in neonatal pharmacology (with immediate relevance to the anaesthetist)

minimal'. However, a significant body of literature has documented that a child being treated under protocol in a well-designed, carefully conducted study with appropriate institutional review board oversight, (generally) has a better outcome than comparable patients receiving 'standard care.' One could infer from this that it is more ethical to treat a child as a participant in a clinical trial rather than with 'off-label' treatment in which the child is an experiment of $N=1$ without collection of data.²

(2) Technical and logistic difficulties

- a. Difficulty in obtaining parental consent; particularly where there is some increased discomfort or risk and no direct benefit to the child.
- b. Recruiting adequate numbers of patients with the same pathology at a similar stage of growth and development is difficult.
- c. Small neonates can only tolerate a certain volume of blood to be taken for testing; sparse sampling methods, microsampling and more sensitive analytical methods have recently helped to circumvent this problem.
- d. It is often difficult to determine clinical endpoints (e.g. efficacy of analgesia).³

(3) Economics of drug development in children

There is a small market for most drugs in the paediatric age group. Financial incentives and legislative changes have been introduced to address this.

Neonatal pharmacokinetics

Absorption

Physicochemical and patient factors influence the ability of a drug to translocate from its site of administration to the bloodstream and site of action (Table 1). Enteral absorption is variable in the neonate due to a number of factors:

Enteral absorption

Extent of drug absorption – the primary mechanism for drug absorption is passive diffusion of un-ionized molecules through lipophilic membranes. Therefore the pH at the site of absorption influences the extent of absorption. Neonates are able to produce gastric acid. At birth, the gastric pH is between 6 and 8; however, this falls rapidly within a few hours. Premature neonates born at

Some factors affecting drug absorption relating to neonates (the patient factors are particularly relevant in neonates)

Physicochemical factors

Drug formulation

- Disintegration of tablets or solid phase
- Dissolution of drug in gastric or intestinal fluid
- Release from sustained-release preparations

Molecular weight

pK/proportion of drug in ionized/un-ionized form

Lipid solubility

Patient factors

General

- Surface area available for absorption

Gastrointestinal

- Gastric content and gastric emptying
- Gastric and duodenal pH
- Size of bile-salt pool
- Bacterial colonization of lower intestine
- Disease states (e.g. short-gut syndrome, biliary atresia)

Muscle

- Increased capillary density in neonatal muscle compared with adults increases absorption from muscles
- Reduced cardiac output states reduce absorption

Skin

- Blood supply
- Peripheral vasodilation
- Thickness of skin/stratum corneum
- Surface area

Rectal

- Rectal venous drainage site
- Neonatal absorption > older children

25 weeks post-menstrual age produce H-K-ATPase, and the expression increases with gestational age.⁴ The volume and pH of gastric secretion after birth are variable; gastric and duodenal content influences the ability of a drug to dissolve and alters the ratio of ionized to un-ionized particles. A low pH environment will render acidic drugs with a low pK, more un-ionized and more able to cross lipid membranes. Changes in the bile-salt pool can alter the solubilization and absorption of lipophilic drugs or formulations.

Rate of drug absorption – the irregular and unpredictable peristaltic activity of the upper gastrointestinal tract contributes to a variable rate of drug absorption in the neonate.⁵ If gastric emptying is slowed, the drug is delayed in reaching the small intestine from where it is absorbed. The peak serum drug concentration will also be reduced.⁴ Slow gastric emptying is associated with: low gestational and postnatal age; type of feed (increased calorie density and long-chain fatty acids); and disease states (eg pyloric stenosis, congestive cardiac failure). Human milk and low-calorie feed quicken gastric emptying.

Non-enteral absorption

Transdermal absorption in neonates is variable because of an incompletely formed stratum corneum and immature vasomotor control. The increased surface area-to-weight ratio must be taken into account and can be responsible for a higher drug exposure than intended compared with a similar dose per kg in an adult.⁴ Rectal administration is associated with variable plasma concentrations; factors such as variable lower gastrointestinal motility and depth of insertion may affect bioavailability. Absorption via the upper rectal veins undergoes first-pass metabolism, whereas the inferior and middle rectal veins bypass the hepatic first-pass effect and drain directly into the inferior vena cava.

Distribution

Fluid distribution: the greatest change in body water compartments occurs in the first year of life (Figure 1). In premature and term neonates, the volume of distribution for water-soluble drugs

Table 1

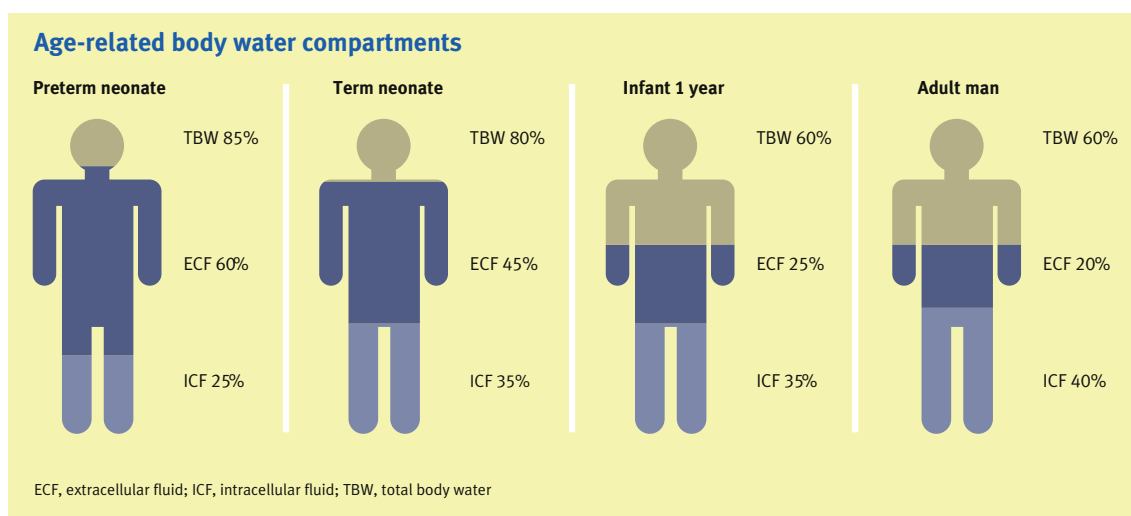


Figure 1

is increased compared to older children. To achieve the required plasma and tissue concentrations of water-soluble drugs, a higher dose per kg often needs to be administered in the neonate.

Body tissue composition: neonates have a smaller proportion of weight in the form of fat and muscle compared with adults (Figure 2). In the neonate, drugs which rely on redistribution to fat and muscle such as thiopentone or fentanyl will have prolonged and higher plasma concentrations. Opposing pharmacokinetic factors frequently need to be balanced when evaluating drug dosage in neonates. For example, water-soluble non-depolarizing neuromuscular blockers (e.g. atracurium) will have a higher extracellular volume of distribution, which may suggest that a higher dose per kg is required. However, the reduced acetylcholine released from the motor nerves reduces the concentration of non-depolarizing neuromuscular blocker required at the neuromuscular junction. Practically a similar dose per kg is therefore given to neonates as adults.⁶

Protein binding: neonates have reduced albumin and total protein concentrations. The quality of drug–protein binding also appears to be reduced. Lower protein binding in premature and term neonates compared to older children results in greater free-drug concentration and hence greater drug effect. This effect is clinically more pronounced with highly protein-bound drugs.⁵ Examples of acidic drugs binding albumin include diazepam, thiopental and phenytoin. Basic drugs tend to bind α_1 -acid glycoprotein, which will also have reduced binding in the neonate (e.g. lidocaine and alfentanil). Neonatal jaundice is common in the premature neonate; bilirubin competes with some drugs (e.g. phenytoin) for protein binding, which can result in either further increased free-drug concentration or increased free bilirubin. The latter would increase the risk of kernicterus.⁷

Blood–brain barrier: neonates have an immature barrier, which results in faster morphine uptake into the central nervous system (CNS). This may be partly responsible for the considerable neonatal sensitivity to the CNS effects of morphine.⁵ Disease states

such as sepsis, hypoxia and acidosis further reduce the integrity of the blood–brain barrier.

Metabolism

The ability of a neonate to metabolize drugs is mainly dependent on hepatic blood flow and enzyme maturation.

Hepatic blood flow: the proportion of the cardiac output delivered to the liver increases as the neonate matures. This contributes to the variability of drug clearance. Pathological processes also can reduce liver blood flow such as a low cardiac output state or raised intra-abdominal pressure (e.g. omphalocele repair). The example of fentanyl is discussed below.

Enzyme maturation: it would be inaccurate to say that neonates lack the enzymes to metabolize drugs, although most enzyme systems undergo maturation in the first few weeks or even years of life. It is more meaningful to consider the individual drug with its specific metabolic pathway. Enzyme expression and development is variable in neonates. Hepatic disease can also influence the variability between individuals.

Drugs are metabolized to render them soluble in preparation for excretion. The cytochrome P450 family is responsible for most phase I reactions. They can be classified into three gene families: *CYP1*, *CYP2* and *CYP3*. Table 2 gives examples of how different enzymes mature at different rates.

The phase II reactions involve synthetic or conjugation reactions (e.g. glucuronidation, sulfation). They mostly show limited activity during fetal life. Some enzymes, e.g. uridine diphosphoglucuronyltransferase-glucuronyl transferase (UDP-GT), include different isoforms which mature at different rates postnatally.⁵ In the 1960s, ‘standard’ paediatric doses of chloramphenicol were given to neonates without considering the immaturity of the UDP-GT. The result was fatal circulatory collapse known as the ‘gray baby syndrome’.

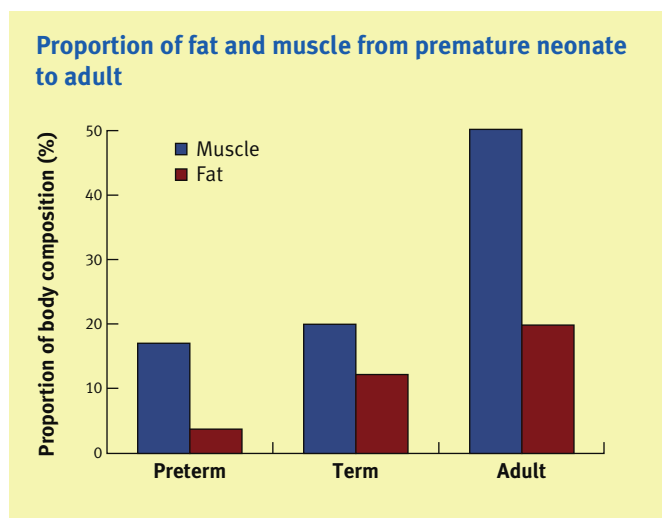


Figure 2

Examples of variable maturation and expression of different cytochrome P450 enzymes

Enzyme	Example	Enzyme comments
CYP1A2	Caffeine, theophylline	Absent in neonate, adult level 4–6 months
CYP2C9	Phenytoin	Enzyme develops rapidly in the postnatal period; phenytoin half-life is prolonged at 75 hours in preterm neonates; this decreases to 20 hours at term and 8 hours at 2 weeks
CYP2D6	Codeine, tramadol, β -blockers	Usually present at 1 week but only 20% of adult activity at 1 month. Variable because of genetic polymorphism: up to 47% of 3–12-year olds cannot convert codeine to morphine
CYP3A4	Midazolam	Activity low at birth but increases fivefold over 3 months of life

Table 2

Metabolic processes are not linearly related to body mass (the term used to describe this is 'allometry'); scaling down adult dosages using size alone, will often result in under- or overdosing. In recent years, our ability to predict a more sensible dosing regimen has improved due to a clearer picture of developmental pharmacokinetic changes. This has been due to:

- an improved knowledge of physiology
- ability to measure in-vitro enzyme activity
- development of sophisticated computer software to predict clearance and dosage regimes.⁶

Excretion

Glomerular filtration rate (GFR) is gestational age related and is reduced with increasing prematurity. At 41 weeks post-conceptual age the GFR is 1.5 ml/kg/minute (20–40 ml/minute/1.73m²), which increases rapidly to 50% of adult levels by 3 months. Incomplete glomerular development, low perfusion pressure and inadequate osmotic load (for countercurrent effects) contribute to reduced renal efficiency in the neonate. Glomerular and tubular function is fully mature by 2 years of age. Practically, healthy term babies will have relatively normal renal drug clearance by the start of infancy; however it should be remembered that drugs excreted primarily through glomerular filtration or tubular function such as aminoglycosides or cephalosporin antibiotics have a prolonged elimination half-life in neonates.⁴

Recently data have emerged on clearance of a number of drugs in the neonatal population. Figure 3 shows the clearance maturation profiles of drugs predominantly metabolized by the glucuronidation (phase II) pathway. Note how the profiles correlate with GFR. It is thought that propofol matures faster than the other drugs due to the contribution of the CYP450 enzymes to its overall metabolism.⁷

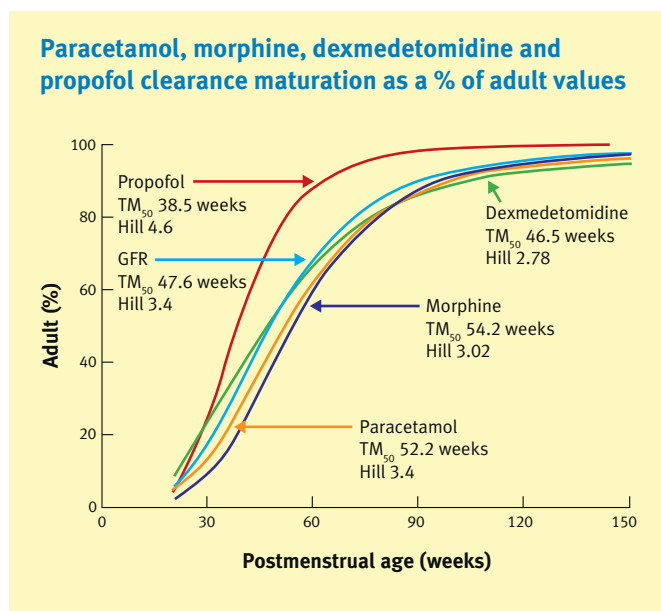


Figure 3 Notice how this correlates with glomerular filtration rate (GFR) maturation. TM₅₀ = Maturation half time. Hill = Hill coefficient, relating to the slope of the maturation profile. (Reproduced with permission from Ref.⁷)

Individual drugs and new developments

Analgesics

Morphine: the neonatal increased sensitivity to morphine is attributable to pharmacokinetic rather than pharmacodynamic differences. Morphine clearance increases rapidly in the neonatal period (2.05 litres/hour/70 kg at 24 weeks post-menstrual age (PMA) to 6.04 litres/hour/70 kg at 32 weeks PMA). Clearance reaches 80% of adult values by 6 months of age, although clearance maturation is slower in the critically ill. In a recent pharmacokinetic/pharmacodynamic study in 875 neonates, no relationship was found between morphine plasma concentrations (0–440 µg/litre) and the pain response (premature infant pain profile or heart rate) to endotracheal suctioning.⁸

Fentanyl: several factors are important in the clearance of fentanyl: hepatic blood flow, hepatic function, and age-dependent changes in the volume of distribution. It is known that fentanyl clearance is markedly reduced when there is an increase in intra-abdominal pressure (e.g. omphalocele repair). Animal data suggest that the reduction in clearance is not due to reduced hepatic blood flow but a combination of immature hepatic enzymes and a maldistribution of hepatic blood away from regions of cytochrome P450 activity.⁵

Tramadol: tramadol has multiple modes of action; in addition to mu-opioid activity of the parent compound and (stronger) mu-effects of the M1 metabolite, it also acts via 5HT and noradrenaline uptake inhibition. It is metabolized by CYP2D6, which exhibits genetic polymorphism. Therefore enzymes can be given an activity score⁹; the higher the score, the faster the clearance maturation (Figure 4).

Paracetamol: as the absorption of rectal paracetamol has been shown to be variable and slow, intravenous paracetamol is being successfully used more frequently in neonates. In many countries it is only licensed in neonates from 10 days postnatal age. It has

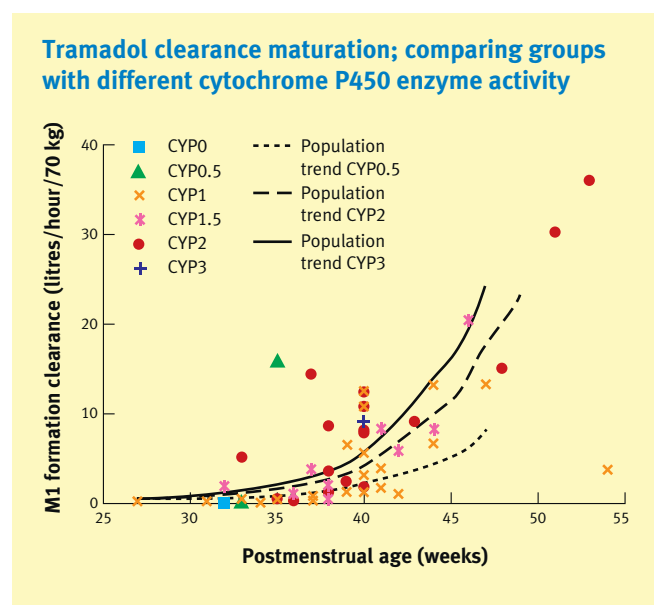


Figure 4 Differences in activity can be seen at 45 weeks post-menstrual age. (Modified with permission from Ref.⁹)

been shown that intravenous (IV) paracetamol reduces the morphine requirement in neonates.¹⁰ Dosing regimens have been suggested, however it is unclear for how many days these doses should be given.¹¹

It is thought that reduced activity of CYP2E1 (responsible for forming the toxic metabolite NAPBQI) is reduced in the neonate, so reports of hepatotoxicity are rare.

Remifentanyl: although the $T_{1/2}$ is similar in all age groups, the volume of distribution (Vd) of remifentanyl in neonates is *greater* than in older children (thought to be due to high fat content in this population with a highly lipid soluble drug). Neonatal clearance is very high and variable at 90.5 ± 36.8 ml/minute/kg compared to adolescents at 57.2 ± 21.1 ml/minute/kg. The adult estimated clearance is 40 ml/minute/kg. For neonates, the suggestion is to start with a relatively high dose (e.g. 0.4 µg/kg/minute) and carefully titrate.¹²

Intravenous anaesthetic agents

Propofol: currently, the use of propofol in neonates is off-label. Reduced clearance has been demonstrated in nine neonates (4–25 days postnatal age (PNA), 27–43 weeks PMA) following a single bolus of 3 mg/kg propofol. Although individual pharmacokinetics varied, the median clearance values (after allometric scaling to 70 kg to allow comparison), were approximately 32% of infants aged 1–3 years, and less than 50% of children 4–7 years.¹³ PMA is the most predictive covariate for clearance, although correlation is poor. The median volume of distribution at steady state was approximately 44% of the corresponding values previously reported in children aged 1–3 years, and approximately 34% of those aged 4–7 years.¹³

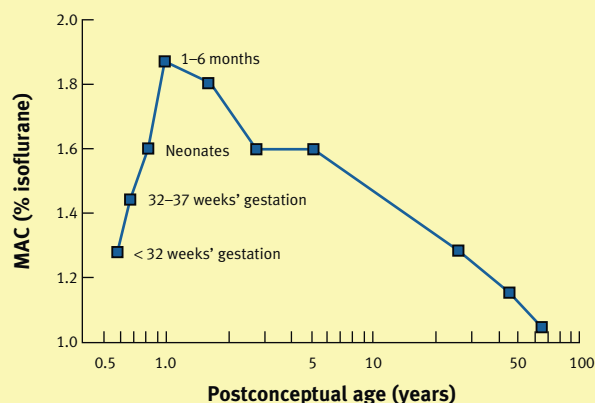
Clearance matures rapidly during the neonatal period; however PMA and PNA contribute to the inter-individual variability.¹⁴ It is currently thought that maturational clearance of propofol is complete by 3 months of age. The data above suggest that preterm neonates (and term neonates <10 days old) are at risk of propofol accumulation if given as an intermittent bolus or infusion. It would seem sensible at present to limit its use to single bolus administration.¹⁵ Work still needs to be done to fully characterize the pharmacological maturation of propofol in those less than 2 years of age.

Ketamine: concern has been raised concerning ketamine causing neuronal apoptosis in animal studies soon after birth. It is unclear if this applies to humans. Although similar observations have been made with other agents, many anaesthetists have concern over ketamine in neonates if an alternative is available. The author cannot advise on this matter until further data are available.

Inhalational anaesthetic agents

The minimum alveolar concentration (MAC) of halothane, isoflurane and desflurane is low in premature neonates, peaks at 1–6 months and then falls gradually as age increases (Figure 5). Sevoflurane differs, in that the MAC in neonates (3.3%) does not change significantly through to 3 months (3.2%). Older infants and children have an MAC of approximately 2.5% (although this is variable). The reason for this different pattern is unclear.⁵ The haemodynamic response to an age-adjusted MAC of volatile agents is no different from older children.

Minimum alveolar concentration (MAC) of isoflurane with increasing age



This pattern of the MAC throughout childhood is similar for desflurane and halothane

Reproduced with permission from LeDez KM, Lerman J. The minimum alveolar concentration of isoflurane in preterm neonates. *Anesthesiology* 1987; **67**: 301–7

Figure 5

Local anaesthetic agents

Regional techniques are used to reduce the use of systemic analgesics and may facilitate earlier extubation. The toxic plasma concentration of bupivacaine is unknown in children. However, many infusion regimens aim for a plasma concentration of less than 1 µg/ml. Pharmacokinetic data of epidural bupivacaine suggest that neonates will develop higher plasma concentrations of bupivacaine compared with older children. The immature cytochrome P450 enzyme systems are the main reason for reduced clearance of the drug, although reduced hepatic blood flow may also contribute. Pharmacokinetic studies of levobupivacaine show that neonatal clearance is approximately 25% of adult values, which increases to 80% at 6 months of age. Most of the clearance can be predicted by postnatal age and weight.¹⁶

Reduced protein binding may be less important than drug clearance in determining toxic levels. Doses per kg should be reduced in neonates compared with older children. With 1.8 mg/kg epidural bolus of bupivacaine followed by a 0.2 mg/kg/hour infusion, some neonates still have rising plasma concentrations after 48 hours, which raises concern about prolonged infusions in this age group.¹⁷ Newer local anaesthetic agents such as levobupivacaine and ropivacaine may have a safer profile. Topical local anaesthetics such as EMLA (2.5% prilocaine, 2.5% lidocaine) are frequently used in children to reduce pain of venepuncture. In the neonate it has been used for procedures such as heel-pricks and spinal injections. The risk of systemic absorption causing methaemaglobinaemia can be reduced by applying the agent to a limited surface area of skin. There are not enough data to support multiple daily applications.

Sedatives

Diazepam: reduced hepatic blood flow and immature hepatic excretory mechanisms can prolong the elimination half-life of diazepam to up to 100 hours in the neonate (18 hours in young

adults).⁵ The active metabolite N-desmethyldiazepam is similar in potency and half-life to diazepam. The prolonged action in neonates renders the drug less suitable for many applications than the shorter acting sedating agents. The intravenous solutions that contain the preservative benzyl alcohol should be avoided in neonates because of the risk of metabolic acidosis and kernicterus.

Midazolam: unlike diazepam, the active metabolite of midazolam has minimal activity; it is therefore more suited for use in neonates. The clearance is prolonged ($T_{1/2}$ B 6–12 hours) compared with older children ($T_{1/2}$ B 1.4–4.0 hours).⁵ This can be reduced by factors that reduce hepatic blood flow, vasopressors or hypovolaemic states. Intravenous bolus of midazolam in neonates has been associated with hypotension; particularly if administered with fentanyl.⁵

Inotropes

Milrinone, an inodilator, is used increasingly in children after congenital cardiac surgery. Renal clearance is the primary route of elimination, and we might anticipate that maturation of milrinone clearance closely follows that of GFR. Clearance of milrinone in adults with congestive cardiac failure has been reported as 9 litres/hour/kg. 26 week PMA infants would be expected to have a GFR 10% of adult values; accordingly, these neonates have been found to have a milrinone clearance of 0.96 litres/hour/70 kg.⁷

The future?

Pharmacogenetics

Risk of drug toxicity is not uniformly distributed across a population. An individual's clinical, genomic and environmental info can predict predisposition to toxicity. For example, maternal paracetamol exposure increases the risk of exomphalos (relative risk 1.5–1.7). By understanding fetal genetic metabolic processes, it may be possible to identify those individuals who are particularly susceptible to these maternal ingested agents.¹⁸

Pharmacodynamic studies

The difficulty in interpreting clinical endpoints in neonates makes the link between plasma concentration and clinical effect difficult to interpret. Therefore there are very little pharmacodynamic data in neonates at present. ◆

REFERENCES

- 1 Shirkey H. Therapeutic orphans. *J Pediatr* 1968; **72**: 119–20.
- 2 Ward RM, Kauffman R. Future of pediatric therapeutics: reauthorization of BPCA and PREA. *Clin Pharmacol Ther* 2007; **81**: 477–9.
- 3 Ward RM, Kern SE. Clinical trials in neonates: a therapeutic imperative. *Clin Pharmacol Ther* 2009; **86**: 585–7.
- 4 Blumer JL, Reed MD. Principles of neonatal pharmacology. In: Yaffe SJ, Aranda JV, eds. Neonatal and pediatric pharmacology: therapeutic principles in practice. 3rd edn. Philadelphia: Lippincott, Williams & Wilkins, 2005.
- 5 Cote CJ, Lerman J, Ward RM, Lugo RA, Goudsouzian N. Pharmacokinetics and pharmacology of drugs used in children. In: Cote CJ, Lerman J, Todres ID, eds. A practice of anaesthesia for infants and children. 4th edn. Elsevier, 2008.
- 6 Meakin G. Neuromuscular blocking drugs in infants and children. *Cont Educ Anaesth Crit Care Pain* 2007; **7**: 143–7.
- 7 Sumpter A, Anderson BJ. Pediatric pharmacology in the first year of life. *Curr Opin Anaesthesiol* 2009; **22**: 469–75.
- 8 Anand KJ, Anderson BJ, Holford NH, et al. Morphine pharmacokinetics and pharmacodynamics in preterm and term neonates: secondary results from the NEOPAIN trial. *Br J Anaesth* 2008; **101**: 680–9.
- 9 Allegaert K, van den Anker JN, de Hoon JN, et al. Covariates of tramadol disposition in the first months of life. *Br J Anaesth* 2008; **100**: 525–32.
- 10 Agrawal S, Fitzsimons JJ, Horn V, Petros A. Intravenous paracetamol for postoperative analgesia in a 4-day-old term neonate. *Paediatr Anaesth* 2007; **17**: 70–1.
- 11 Bartocci M, Lundberg S. Intravenous Paracetamol: the 'Stockholm Protocol' for postoperative analgesia of term and preterm neonates. *Paediatr Anaesth* 2007; **17**: 1120–1.
- 12 Rodriguez W, Selen A, Avant D, et al. Improving pediatric dosing through pediatric initiatives: what we have learned. *Pediatrics* 2008; **121**: 530–9.
- 13 Allegaert K, de Hoon J, Verbesselt R, Naulaers G, Murat I. Maturation of pharmacokinetics of single intravenous bolus of propofol. *Paediatr Anaesth* 2007; **17**: 1028–34.
- 14 Allegaert K, Peeters MY, Verbesselt R, et al. Inter-individual variability in propofol pharmacokinetics in preterm and term neonates. *Br J Anaesth* 2007; **99**: 864–70.
- 15 Allegaert K, De Hoon J, Naulaers G, Van De Velde M. Neonatal clinical pharmacology: recent observations of relevance for anaesthesiologists. *Acta Anaesthesiol Belg* 2008; **59**: 283–8.
- 16 Chalkiadis GA, Anderson BJ. Age and size are the major covariates for the prediction of levobupivacaine clearance in children. *Paediatr Anaesth* 2006; **16**: 275–82.
- 17 Larsson BA, Lonnqvist PA, Olsson GL. Plasma concentrations of bupivacaine in neonates after continuous epidural infusion. *Anesth Analg* 1997; **84**: 501–5.
- 18 Leeder JS. Developmental pharmacogenetics: a general paradigm for application to neonatal pharmacology and toxicology. *Clin Pharmacol Ther* 2009; **86**: 678–82.