Practical pharmacokinetics: what do you really need to know?

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ABSTRACT

Having some understanding of pharmacokinetics is important for all clinicians when prescribing medications. Key elements to effective and safe prescribing include making sure that we don't underdose a medication making it ineffective, but also do not overprescribe a treatment known to cause toxic effects. In paediatrics, there are significant physiological and developmental differences that add to the challenges of safe prescribing. This article aims to provide the clinician with some basic paediatric pharmacokinetic principles with clinical examples to aid their prescribing skills.

INTRODUCTION

Having some understanding of pharmacokinetics is important for clinicians when prescribing. Key elements to effective and safe prescribing include ensuring that we don't underdose drugs making them ineffective, while not overprescribing and causing toxicity. In paediatrics, significant physiological and developmental differences add to these challenges. This article aims to provide clinicians with basic paediatric pharmacokinetic principles and examples to aid their understanding.

IMPORTANT PHARMACOKINETIC PARAMETERS AND THEIR CLINICAL RELEVANCE

Pharmacokinetics (PK) describes the course of a drug when it enters the body, including absorption, distribution, metabolism and excretion. Pharmacodynamics (PD) refers to the effect the drug has on the body.

PK allows us to understand the profile of drug concentration over time and the links to clinical practice. It allows us to recommend drug-dosing regimens or for novel paediatric drug therapies, provides us with knowledge to prescribe safely and effectively. The important parameters involved are discussed below.

Volume of distribution

Volume of distribution (Vd) represents the hypothetical volume that the total dose administered would need to occupy (if uniformly distributed), to provide the same concentration as it currently is in blood plasma. It is calculated by dividing the amount of drug by the plasma concentration.

A small Vd indicates that the drug mainly stays within the systemic circulation, whereas a large Vd means a drug is well distributed into other peripheral compartments. Knowledge of Vd can be used to determine loading doses of drugs required to reach target concentrations and to predict expected drug concentrations produced by loading doses. Loading doses can be calculated from the product of target concentration and Vd, for example, the gentamicin dose in a 1 kg neonate to achieve a peak concentration of 10 mg/L where the known Vd is 0.5 L/kg would be 10 mg/L×0.5 L/kg×1 Kg=5 mg[1]. However, in practice, we often do not know the Vd of given drugs in given patients, particularly in neonates when the Vd changes rapidly over the first few weeks of life as extracellular fluid volume decreases.

Clearance

Total body clearance is the intrinsic ability of the body to remove a drug from the plasma/blood, and is the sum of drug clearance by each organ. For many drugs this is equal to hepatic plus renal clearance. Renal clearance is the clearance of an unchanged drug in the urine, whereas liver clearance can occur via biotransformation to a metabolite/metabolites with subsequent excretion in urine and/or excretion of the unchanged drug into the biliary tract.

When drugs are administered on a regular basis, concentrations will increase until the absorption or infusion rate is balanced by the elimination rate. This is

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the steady-state concentration (C_{ss}) (figure 1). Clearance is the pharmacokinetic parameter that determines the maintenance dose (MD) required to reach a certain steady-state concentration, where MD=Css×Cl, for example, the maintenance dose of an intravenous aminophylline infusion to achieve a theophylline level of 10 mg/L in a 20 kg child where clearance is 0.087 mg/kg/h[2] is 10 mg/L×(0.087×20) =17.4 mg/h. This formula can be applied to any route of administration. If a drug is given as regular boluses, the 'average' target C_{ss} is used as steady-state fluctuates between the peak and trough, and the dosing interval (π) is also added into the equation. For oral medications, bioavailability also needs to be taken into consideration so MD=($_{av}C_{ss}$×Cl×π)/bioavailability.

Half-life

Half-life is another pharmacokinetic parameter, and is the time taken for the serum drug concentration to decrease by half. It can be calculated from the Vd and clearance (where half-life ($t_{1/2}$)=(0.693×Vd)/ Clearance). It can be used to determine the time it takes to achieve steady-state, and the time to be completely eliminated. It takes around 3–5 times the drugs' half-life to reach steady-state, and the same for it to be completely eliminated. For instance, the $t_{1/2}$ of intravenous midazolam is approximately 1.1 h in 3–10 year olds,[3] therefore, it takes around 3.3 to 5.5 h to reach steady-state.

Half-life can also help clinicians to establish appropriate drug dosing intervals. When medications are given every half-life, the plasma concentration will fluctuate twofold over the dosing interval (figure 1). If a drug is given more frequently than the half-life, fluctuations in peaks and troughs will be smaller. By contrast, when dosed at less than the half-life, lower drug accumulation occurs with greater fluctuation in the peak and trough. The effective concentration and the safety profile of the drug needs to be considered to assess if large fluctuations are acceptable, for example, a higher once-daily gentamicin dose is acceptable despite its short half-life of approximately 3 h.[4] It produces higher peak levels than the standard regime and this in turn increases the rate and extent of bacterial cell death, as well as lengthening the post-antibiotic effect (suppression of bacterial regrowth) without increasing the risk of any drug toxicity.[5]

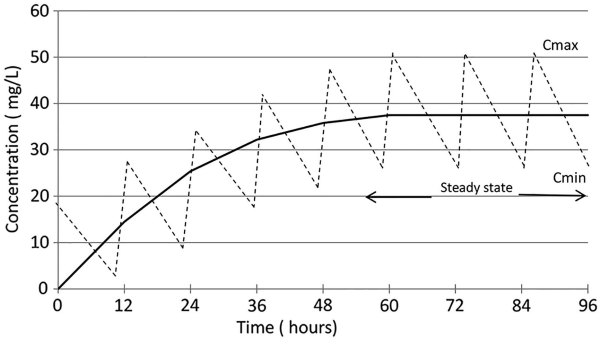

Figure 1 This graph shows a time concentration profile of a drug with a half-life of 11.5 h given by continuous infusion (solid line) and intermittent dosing every 12 h (dotted line). The steady-state is reached by 57.5 h (5 times the 11.5 h half-life). With the intermittent dosing, serum drug concentrations increase, after each dose, to a peak amount and then decline to a trough concentration before the next dose. Repeated dosing increases the peak and trough concentrations due to drug accumulation until steady-state is achieved. At steady-state, all the peak and trough concentrations become equal and steady-state is achieved to the same 57.5 h as the continuous infusion. Note, as the half-life is similar to the dosing frequency, there is twofold difference between the peak and trough concentrations. Adpated from Kraus.[31]

For drugs with a half-life <6 h, it is sometimes not practical to give frequent doses, so sustained release formulations are given if a steady serum concentration is necessary (eg, theophylline).

For drugs with a very long half-life (eg, phenobarbital), once-daily treatment may be appropriate, however, a loading dose may be required to reach steady-state quickly. In neonates, the $t_{1/2}$ of phenobarbital is 67–99 h,[4] so without a loading dose it could take 8–20 days to reach steady-state. Although drug half-lives are quoted in the literature, these represent average values mainly in adults, and should be used cautiously.

The PK principles outlined above assume that the drug follows first-order or linear PK characteristics. This means that the steady-state concentration changes in direct proportion to a dose alteration. However, for some drugs, the relationship is more complex. For example, phenytoin saturates metabolising enzymes at clinical doses. Subsequent increases in dosing cause a disproportionate elevation of the steady-state concentration. This is known as zero order or saturated kinetics.

Bioavailability

When a drug is given intravenously, the entire dose administered enters the systemic circulation and is subsequently distributed. For any other route, the drug must overcome chemical, physical, mechanical and biological barriers, and the percentage that enters the systemic circulation is the drug's bioavailability.

Drugs taken orally are absorbed from the gastrointestinal tract into the liver via the portal circulation, before reaching the systemic circulation. Most drugs undergo some degree of metabolism in the liver before reaching the central compartment. This is known as first-pass metabolism. Those drugs undergoing a large first-pass effect, for example, propranolol, have lower bioavailability.

Bioavailability is important because it allows us to understand how drug (eg, formulation, drug solubility) or human factors (eg, comorbidities, diet) can alter the dose-exposure relationship. For example, the

bioavailability of digoxin given as tablets is 63% but 75% in the paediatric elixir form.[6] Bioavailability can also affect apparent Vd and clearance by reducing the amount of drug that enters the bloodstream.

ABSORPTION

Absorption is the process of drug movement from the site of administration/application into the systemic circulation. There are a number of differences between children and adults attributable to normal growth and development.

At birth, gastric pH is around neutral but drops to pH 1–3 within a few hours. It returns to neutral by 24 h where it remains for 1–2 weeks. Adult values for gastric acidity are reached only after age 2 years.[7] This higher gastric pH results in decreased absorption of acidic drugs, such as phenobarbital and phenytoin, but increases absorption of weak base or acid-labile drugs, such as penicillins.[8 9] Proportionally higher and lower oral doses, respectively, may be needed to achieve therapeutic plasma concentrations in neonates and infants.

Gastric emptying and intestinal motility are slower in neonates and improve with increasing gestational age.[10 11] This may delay absorption in neonates and small infants[12 13] Neonates also have an immature biliary system, producing less bile acids and pancreatic fluid. This reduces fat absorption and can affect the absorption of lipophilic drugs,[14] for example, diazepam and fat-soluble vitamins.

Intramuscular absorption depends on skeletal muscle blood flow which improves during childhood. Neonates have poor muscle contractions and muscle density reducing bioavailability.[15] Percutaneous absorption is enhanced in childhood due to a larger surface area relative to body weight, increased skin hydration and perfusion. In neonates and young infants absorption is further increased due to an immature epidermal barrier. This makes children, especially neonates, more prone to increased systemic absorption and potential side effects of topical medications. Past use of the topical disinfectant hexachlorophene in neonates caused neurotoxicity and death.[16] Developmental changes in pulmonary structure and capacity in young patients may also alter patterns of inhaled drug absorption. In the rectum, a richer blood supply potentially allows increased drug absorption, but this can vary.[17]

DISTRIBUTION

Drug distribution is dependent upon the physicochemical properties of the drug and also on patient specific physiological factors. Understanding variables affecting distribution explains some of the variation in dosing requirements required in different paediatric populations. Drug distribution is affected by changes in body composition. Neonates have a high total body water which decreases in adulthood (table 1).

Table 1 Changes in body water with age. Adapted from Friis-Hansen[30]

	Total body water (%)	Extracellular fluid (%)	Intracellular fluid (%)
Preterm neonate	85	60	25
Neonate	80	45	35
Infant 1 year	60	25	35
Adult	60	20	40

Neonates also have less fat compared with adults resulting in them having a higher water to fat ratio. This means that water-soluble drugs have a higher Vd in the neonate resulting in lower peak concentration levels when using the same drug dose/weight compared with adults. A greater loading dose per kilogram may be required compared with older children/adults to have a similar therapeutic effect. For example, the Vd of gentamicin in neonates is higher compared with older children/adults due to the increased extracellular water. They, therefore, require higher doses per kilogram to produce adequate serum concentrations.[18] The lower fat content in neonates results in a decreased Vd for fat-soluble drugs though the effect of this is not well understood.

Changes in the composition and amount of circulating plasma proteins, such as albumin and α1-acid glycoprotein can also influence the distribution of highly protein-bound drugs, such as phenytoin and furosemide. Neonates and infants have less total plasma proteins which increases the free (active) fraction of drug.[17] Additionally, endogenous compounds, like bilirubin, compete for protein binding contributing to a higher free fraction of highly protein-bound drugs. Conversely, sulfonamides are an example of highly protein-bound drugs which can displace bilirubin in neonates leading to a risk of kernicterus.[18]

Other factors that may affect drugs distribution include changes in haemodynamic status, changes in acid–base balance, and permeability of cell membranes. These are particularly important when dealing with severely ill patients, for example, those on extracorporeal membrane oxygenation.[19]

METABOLISM

In general, most drugs are converted into more water-soluble compounds in order to be excreted from the body. This can take place in several sites (eg, gastrointestinal tract, skin, plasma, kidney, lungs), but most are metabolised in the liver via hepatic enzymes in phase 1 and phase 2 reactions. Phase 1 involves altering the structure of the drug, for example, by oxidation or hydrolysis. The major pathway is oxidation involving the cytochrome P450-dependent (CYP) enzymes. Phase 2 reactions conjugate the drug to another

molecule (eg, glucuronidation). Total cytochrome P450 content in the foetal liver is between 30% and 60% of adult values, and approaches adult values by 10 years of age.[20] Different developmental patterns have been identified for CYP enzymes (figure 2). Some are active in the foetal liver (CYP3A7), others increase rapidly hours after birth (CYP2D6 and CYP2E1), while others develop more slowly in infancy (CYP1A2).[16] Clinically, this means that drugs metabolised by the liver in newborns and small infants, tend to stay in the body longer. This, therefore, requires lower doses, longer dose intervals, or to give adequate therapeutic concentrations and prevent toxicity. Phenytoin,[21] chloramphenicol[13] and caffeine[22] are examples of drugs showing slower neonatal metabolism. Historically, chloramphenicol was used to treat neonatal infections using adult doses of 12.5–25 mg/kg four times a day. Large numbers developed cardiovascular collapse, irregular respiration and death—features known as grey baby syndrome. Neonates have immature levels of the enzyme converting chloramphenicol to the excreted water-soluble chloramphenicol glucuronide which, therefore, accumulates and causes toxicity. Consequently, dosing in neonates has been reduced to 12.5 mg/kg twice daily.[23]

In some circumstances, alternative metabolic pathways are used in younger children. Paracetamol undergoes metabolism by glucuronidation and sulfation. In neonates, glucuronidation is reduced, but there is, however, compensatory sulfation.[24] With large amounts of paracetamol, glucuronidation and sulfation pathways become saturated, so paracetamol is metabolised by CYP2E1. This produces toxic products and subsequently liver damage. In neonates, immaturity of this pathway may produce less toxins sparing them from liver damage.[25]

EXCRETION

For many drugs and metabolites, the kidney is the most important route of excretion. The kidney has three physiologic functions: glomerular filtration, tubular secretion and tubular reabsorption. Renal elimination of drugs is dependent on a balance of these. Some drugs are eliminated by glomerular filtration (eg, aminoglycosides) and clearance correlates well with glomerular filtration rate. Others are eliminated by proximal tubular secretion (eg, penicillins, furosemide). Tubular reabsorption of drugs also affects total body clearance.

Maturation of renal function is a dynamic process beginning during fetal organogenesis. All three physiologic functions of the kidney are decreased in newborns. The development of kidney structure and function is associated with prolongation and maturation of the tubules, increase in renal blood flow and improvement of filtration efficiency. By around 12 months of age, these functions reach adult levels.[19] Having some knowledge of renal development and anatomy is essential in providing rational dose schedules for drugs exclusively eliminated via the kidneys. In general, the neonate will need longer dose intervals than the infant/older child to maintain target concentrations. For example, the dose of benzylpenicillin changes from 25–50 mg/kg 12 hourly in a neonate <7 days, 8 hourly in a 7–28 day neonate and then 4–6 hourly in children over a month old, reflecting the improving renal function and excretion.[23]

INTERINDIVIDUAL VARIABILITY

It is known that different patients respond differently to the same medication. This is known as interindividual variability. In children, it is complicated further by the impact of physiological development and maturation. A large amount of interindividual variability is caused by genetic variations in activity of drug metabolism enzymes and transporters. CYP2D6 polymorphism is used as an example. This enzyme metabolises a number of drugs including β blockers, antidepressants and codeine. Homozygous individuals characteristically have negligible or no metabolism

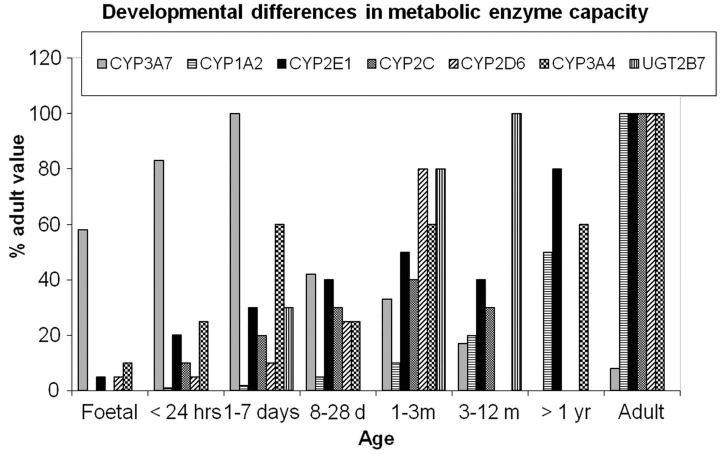

Figure 2 Developmental differences in enzyme capacity. Adapted from: Kearns[17] and Johnson.[32]

Box 1 Criteria for therapeutic drug monitoring

- Good correlation between serum concentrations and pharmacological effect.
- A narrow margin between serum concentrations that cause toxic effects and those that produce therapeutic effects.
- Marked pharmacokinetic intra and interindividual variability.
- The pharmacological effects of drugs are not readily measurable.
- A rapid and reliable method for the analysis of the drug.

Learning points

- Pharmacokinetics is the study of how a drug is affected as it passes through the body by absorption, distribution, metabolism and elimination.
- Growth and development of children impacts in multiple ways on pharmacokinetics.
- A therapeutic agent administered other than intravenously must overcome chemical, physical, mechanical and biological barriers in order to be absorbed.
- Knowledge about the impact of developmental differences is important in providing adequate drug dosing and frequency.

and are 'poor metabolisers'. If the drug is a 'prodrug', such as codeine (whose main analgesic effect is produced by its major metabolite morphine), then little benefit will be produced, and increased side effects may be experienced due to delayed excretion. Those with gene duplications or multiplications are described as 'ultrarapid metabolisers', they are at risk of reduced effects or toxicity from quick metabolism depending on the drug. Case reports in children post-adenotonsillectomy highlight fatalities from respiratory depression secondary to codeine use in CYP2D6 'ultrametabolisers', due to increased morphine production.[26] There have also been similar reports in breastfeeding neonates whose mothers were taking codeine and were CYP2D6 'ultrametabolisers'.[27]

Underlying disease may affect the disposition of drugs and impact drug variability. For example, clearance of most drugs is thought to be higher in children with cystic fibrosis (CF), resulting in higher dosages being required for therapeutic benefit, and to achieve similar serum drug concentrations to children without CF.[28] Tobramycin dosing increases from 2–2.5 mg/kg three times a day to 8–10 mg/kg three times a day to provide optimal bacterial penetration within CF bronchial secretions.[23] Many other factors can influence interindividual variability in drug response including ethnicity, organ function, concomitant medications and drug interactions.

THERAPEUTIC DRUG MONITORING (TDM)

TDM measures drug concentrations and uses PK principles to allow individualised drug dosing with minimal toxicity and maximal efficacy. A number of criteria are required for TDM, as shown in the box 1. In clinical practice, to interpret drug concentrations, basic information about the sample and patient are required, as well as some understanding of the drugs disposition and pharmacology. Timing of samples plays a large part in interpretation. Levels should only be taken once the drug has reached its steady-state unless there are concerns regarding toxicity. In general, trough levels measured just prior to drug administration provide accurate interpretation of drug concentrations. Peak levels are less accurate due to individual variability and are reserved for treatments with short half-lives where peak levels are associated with efficacy or toxicity, for example, gentamicin.

IMPORTANCE OF PHARMACOKINETICS IN PAEDIATRIC CLINICAL STUDIES

Since the paediatric EuropeanUnion regulations came into force in 2007, it is mandatory for pharmaceutical companies to submit a Paediatric Investigation Plan outlining how they will study their new drug in children. This has increased the number of paediatric trials, including more PK studies allowing more defined paediatric dosing regimens for new drugs.[29] Different techniques, such as population PK (using large numbers of children with a condition but less blood samples) and PK/PD modelling (using statistical validated models for predicting the effect and efficacy of a drug) are now well established. This avoids children being exposed to the unethical practice of excessive numbers and large volumes of blood sampling seen in adult PK studies. Despite this, there are still significant gaps in our knowledge, especially in the older medications in current practice. The paediatric regulation introduced a paediatric-use marketing authorisation (PUMA) which gives drug companies incentives to develop new paediatric indications or formulations appropriate for children of all ages. Since 2007, there has been only one PUMA granted for buccal midazolam in seizures.[29] The ultimate goal of providing infants and children with safe and effective drug therapy can only be made possible by specifically evaluating PK as well as drug efficacy and safety in this population.

CONCLUSIONS

Having some knowledge of PK is important for any clinician, however, in children, there is the added complexity of developmental influence on drug

Test your knowledge

One or more of the answers can be correct

1. Which factors cause neonates to have increased drug absorption through the skin compared with adults?
   - A. a thinner epidermis
   - B. a larger surface area
   - C. reduced skin blood flow
   - D. improved skin perfusion
   - E. less subcutaneous tissue
2. Half-life determines:
   - A. the loading dose
   - B. the time to reach steady-state
   - C. the drug concentration at steady-state during constant dosing
   - D. duration of action of a single dose
   - E. the fluctuation in plasma drug concentration during a dosing interval
3. Which of the following is true with regards to volume of distribution:
   - A. Equals the total amount of drug in the body divided by the concentration found in the plasma
   - B. A large volume of distribution (Vd) implies a drug primarily resides in the systemic circulation
   - C. Neonates have a larger Vd for hydrophilic drugs
   - D. A larger Vd requires a lower loading dose of a drug
   - E. Neonates have a lower Vd with fat-soluble drugs
4. Which is true about renal elimination in children?
   - A. Affected by immature glomerular filtration
   - B. GFR is similar to adults by 12 months of age
   - C. Drug dosing intervals are usually increased compared with neonates
   - D. Penicillin is eliminated by proximal tubule secretion
   - E. Glomerular filtration rate affects elimination of furosemide.

Answers are at the end of the references.

disposition. Understanding these differences will hopefully allow clinicians to be better equipped to optimise the care of their patients and ultimately provide safer and more effective prescribing.

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REFERENCES

1 Thomson A. Clinical Pharmacokinetics. *Paediatr Perinat Drug Ther* 2000;4:3–11.
2 Ellis EF, Koysooko R, Levy G. Pharmacokinetics of Theophylline in Children With Asthma. *Pediatrics* 1976;58:542–7.
3 Payne K, Mattheyse FJ, Liebenberg D, *et al*. The pharmacokinetics of midazolam in paediatric patients. *Eur J Clin Pharmacol* 1989;37:267–72.
4 Soldin OP, Soldin SJ. Therapeutic Drug Monitoring in Pediatrics. *Ther Drug Monit* 2002;241–8.
5 Miron D. Once daily dosing of gentamicin in infants and children. *Pediatr Infect Dis J* 2001;20:1169–73.
6 SPC for Lanoxin PG Elixir in electronic medicines compendium. http://www.medicines.org.uk/emc/medicine/2176/SPC/Lanoxin+PG+Elixir/ (accessed2 May 2014).
7 Morselli PL. Clinical pharmacokinetics in neonates. *Clin Pharmacokinet* 1976;1:81–98.
8 Morselli PL. Clinical pharmacology of the perinatal period and early infancy. *Clin Pharmacokinet* 1989;17:13–28.
9 Huang NN, High RH. Comparison of serum levels following the administration of oral and parenteral preparations of penicillin to infants and children of various age groups. *J Pediatr* 1953;42:657–68.
10 Ittmann PI, Amarnath RA, Berseth CL. Maturation of antroduodenal motor activity in preterm and term infants. *Dig Dis Sci* 1992;37:14–9.
11 Berseth CL. Gestational evolution of small intestine motility in preterm and term infants. *J Pediatr* 1989;115:646–51.
12 McCracken GH, Ginsburg CM, Clahsen JC, *et al*. Pharmacokinetic evaluation of orally administered antibiotics in infants and children: effect of feeding on bioavailability. *Pediatrics* 1978;68:738–43.
13 Meissner HC, Smith AL. The current status of chloramphenicol. *Pediatrics* 1979;64:348–56.
14 Poley JR, Dower JC, Owen CA Jr, *et al*. Bile acids in infants and children. *J Lab Clin Med* 1964;63:838–4.
15 Morselli PO, Franco-Morselli R, Bossi L. Clinical pharmacokinetics in newborns and infants; age-related differences and therapeutic implications. *Clin Pharmacokinet* 1980;5:485–527.
16 Tryala EE, Hillman LS, Hillman RE, *et al*. Clinical pharmacology of hexachlorophene in newborn infants. *J Pediatr* 1977;91:481–6.
17 Kearns GL, Abdel-Rahman SM, Alander SW, *et al*. Developmental Pharmacology—Drug Disposition, Action, and Therapy in Infants and Children. *N Engl J Med* 2003;349:1157–67.
18 Hussain M, Lawson G, Firmin RK, *et al*. Drug Disposition During Extracorporeal Membrane Oxygenation (ECMO). *Paediatr Perinat Drug Ther* 2001;4:109–20.
19 Koren G. Therapeutic drug monitoring principles in the neonate. *Clin Chem* 1997;43:222–7.
20 Shimada T, Yamazaki H, Mimura M, *et al*. Characterization of microsomal cytochrome P450 enzymes involved in the oxidation of xenobiotic chemicals in human fetal liver and adult lungs. *Drug Metab Dispos* 1996;24:515–22.
21 Loughnan PM, Greenwald A, Purton WW, *et al*. Pharmacokinetic observations of phenytoin disposition in the newborn and young infant. *Arch Dis Child* 1977;52:302–9.
22 Aranda JV, Collinge JM, Zinman R, *et al*. Maturation of caffeine elimination in infancy. *Arch Dis Child* 1979;54:946–9.
23 Paediatric Formulary Committee. *BNF for Children* (online). London: BMJ Group, Pharmaceutical Press, and RCPCH publications. http://www.medicinescomplete.com [Accessed on 3rd November 2013].

24 Miller RP, Roberts RJ, Fischer LJ. Acetaminophen elimination kinetics in neonates, children and adults. *Clin Pharmacol Ther* 1976;19:284–94.
25 Ogilvie JD, Rieder MJ, Lim R. Acetaminophen overdose in children. *CMAJ* 2012;184:1492–623. Paracetamol
26 Kelly LE, Rieder M, van den Anker J, *et al*. More codeine fatalities after tonsillectomy in North American children. *Pediatrics* 2012;129:e1343–7.
27 Koren G, Cairns J, Chitayat D, *et al*. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet* 2006;368:704.
28 Rey E, Tréluyer JM, Pons G. Drug disposition in cystic fibrosis. *Clin Pharmacokinet* 1998;35:313–29.
29 The European Medicines agency. http://www.ema.europa.eu/ema. [accessed 23 Oct 2013].
30 Friis-Hansen B. Body water compartments in children: changes during growth and related changes in body composition. *Pediatrics* 1961;28:169–81.
31 Kraus D. Clinical Pharmacology. In: Curley MAQ, Moloney-Harmon PA. eds. *Critical Care nursing of infants and children*. Philadelphia: Saunders, 2001:425–42.
32 Johnson TN. The development of drug metabolising enzymes and their influence on the susceptibility to adverse drug reactions in children. *Toxicol* 2003;192:37–48.

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Notes