Pediatric Anesthesia 2009 **19**: 289–295 doi:10.1111/j.1460-9592.2008.02680.x

Editorial
Intravenous neonatal paracetamol dosing: the magic of 10 days

BRIAN J. ANDERSON PhD FANZCA* AND
KAREL ALLEGAERT MD†

**Department of Anaesthesiology, University of Auckland, Auckland, New Zealand and †Neonatal Intensive Care Unit, University Hospital Gasthuisberg, Leuven, Belgium*

Introduction

Intravenous (i.v.) paracetamol (acetaminophen) is gaining increasing use in neonates (1–3), despite an off-label status in some countries. Product information for i.v. paracetamol does not consider the clearance maturation with age in neonates in its dosing recommendations. In Australasia the same dose of 15 $mg \cdot kg^{-1}$ 6 h is suggested for neonates over 10 days of age and for infants and children up to 33 kg. A reduced dose of 7.5 $mg \cdot kg^{-1}$ 6 h is proposed in term neonates <10 days of age. In Europe there is no labeled use for neonates <10 days of age. The registered dose is 7.5 $mg \cdot kg^{-1}$ 6 h for neonates after 10 days of age through to infants of 10 kg. A dose of 15 $mg \cdot kg^{-1}$ 6 h (max daily dose 60 $mg \cdot kg^{-1}$) is recommended between 10 and 40 kg. These dosing regimens suggest something magic about 10 days.

There are data concerning the pharmacokinetics of this formulation in neonates. Population pharmacokinetics of the i.v. prodrug (propacetamol) have been studied in neonates following single (4,5) and repeat dose administration (6). Parameter estimates from neonates given repeat doses of i.v. paracetamol over a median of 4 days duration are consistent with those estimated using propacetamol (7). Dosing regimens used in some institutions for neonates have been published in *Pediatric Anesthesia* (2,8), but there are few data validating the safety or effectiveness of these regimens.

The idea that a target effect and associated target concentration can be used to make rational individual dose decisions has acceptance (9). A knowledge of neonatal pharmacokinetics assists with dose prediction to achieve the target concentration. There are, however, flaws and constraints of current knowledge that limit implementation of this approach to dosing.

Correspondence to: Assoc. Professor Brian Anderson, C/- PICU, Auckland Children's Hospital, Park Road, Auckland, New Zealand (email: briana@adhb.govt.nz).

Current practice

Neonates suffer a wide range of pain insults that vary from congenital abnormalities, trauma during the birth process, surgical interventions and pain associated with routine nursing or medical cares. The benefit of paracetamol in some of these situations remains indeterminate; the target effect desired in others is undefined. A target effect for pain reduction of 2.6 pain units (VAS 0-10) has been proposed in children after tonsillectomy (10). This target effect was achieved with an effect compartment concentration of 10 $mg \cdot l^{-1}$ (10), but the applicability of this target concentration to neonates is uncertain.

Intravenous paracetamol has been successfully used for neonatal analgesia (3) and two European Centres have published dosing guidelines in neonates (2,8). These regimens are based on documented pharmacokinetics and attempt to achieve a steady-state target concentration of 10 $mg \cdot l^{-1}$. The effect compartment concentration is assumed the same as plasma concentration at steady-state. Dose increases from 20 $mg \cdot kg^{-1} \cdot day^{-1}$ in premature neonates <31 weeks postmenstrual age (PMA) through to 40 $mg \cdot kg^{-1} \cdot day^{-1}$ for term neonates (>37 weeks PMA). Palmer *et al.* have reported higher doses (7). Neonates were given 6-hourly i.v. paracetamol according to PMA: 28–32 weeks 10 $mg \cdot kg^{-1}$; 32–

36 weeks 12.5 mg·kg^{-1}; ≥36 weeks 15 mg·kg^{-1}. The dose used by Palmer *et al.* (7) in term neonates is similar to the dose registered for use in 10–40 kg cohort. Despite product information suggesting a postnatal age dose change at 10 days, this cut off does not feature in any of the three current dosing regimens reported.

Safety of current regimens

Hepatotoxicity, generated through the production of highly reactive electrophilic arylating metabolites [e.g. *N*-acetyl-*p*-benzoquinone-imine (NAPQI)] by the hepatic cytochrome P-450-dependent (CYP) mixed function oxidase enzyme system, is possible in neonates. However, paracetamol concentrations associated with increased NAPQI are not reported in neonates and the activity of CYP2E1, the major enzyme producing NAPQI, is not quantified, but thought to be reduced (11). Hepatotoxicity is dependent on the balance between the rate of NAPQI formation, the capacity of the safe elimination pathways of sulfate and glucuronide production, and the initial content and maximal rate of synthesis of hepatic glutathione. The balance of these factors in term and preterm neonates remains unknown. Neonates with high serum paracetamol concentrations following intentional maternal overdose prepartum are reported (12,13). They were managed with exchange transfusion postpartum and suffered no clinical hepatotoxicity. Neonatal hepatotoxicity has been reported in a term neonate who presented encephalopathic at postnatal age (PNA) 5 days following 3 days of oral paracetamol dosing (initially 156 mg·kg^{-1}·day^{-1} and then 78 mg·kg^{-1}·day^{-1}).

The question about safety of neonatal dosing regimens is still open, but preliminary results are encouraging. There is no simple test to assess for potential hepatotoxicity. Hepatic enzyme profiles have been used as a surrogate assessment in two neonatal studies (7,14). Neither group of authors noted hepatic changes during the treatment periods that extended over a median of 4 days, but the value of hepatic changes is debated. Kozer *et al.* (15) have demonstrated that ill children receiving repeated large doses of paracetamol (>90 mg·kg^{-1}·day^{-1}) may show abnormalities in liver function. Previously adult studies have shown alanine amniotransferase changes during long-term (1–12 months) chronic dosing for osteoarthritis are mild and resolve (16), while recently alanine amniotransferase elevations (over three times normal) were documented more commonly in volunteers after 1 week's treatment with acetaminophen with or without opioids, while all placebo receivers had alanine amniotransferase concentrations below three times normal (17). Gross hepatic enzyme changes are a late manifestation of toxicity and it would be nice to have a sensitive early marker of adverse event.

Difficulties estimating pharmacokinetic parameters

Growth and development, the two specific characteristics of childhood, are most prominent in neonates. These aspects can be investigated using readily observable demographic factors such as weight and age. How these factors interact is not necessarily easy to determine from observations because they exhibit co-linearity. Drug elimination clearance, for example, may increase with weight, height, age, body surface area, and creatinine clearance. All of these covariates may show a high degree of correlation and they are not mutually exclusive (18). Any one factor may or may not predict between subject differences in clearance.

Size

Size is the commonest covariate used for clearance and subsequent dosing. Linear predictions of dose based on weight (per kg model) are used universally, although it is now more widely recognized that there is a non-linear relationship between weight and drug elimination (19). Adjustment of drug dose using a body weight exponent of <1 is justified and the allometric 3/4 power model has been found useful in normalizing a large number of physiological (20) and pharmacokinetic variables (21). The surface area model can also be calculated from weight, but uses an exponent of 2/3 rather than 3/4. The 2/3 exponent is satisfactory for human weight above 10 kg but is unsuitable for neonatal or interspecies scaling (21).

The allometric model allows comparison of neonatal parameter estimates with adult estimates. The use of the common linear model (the per kg model) can be misleading. At the first glance a clearance of

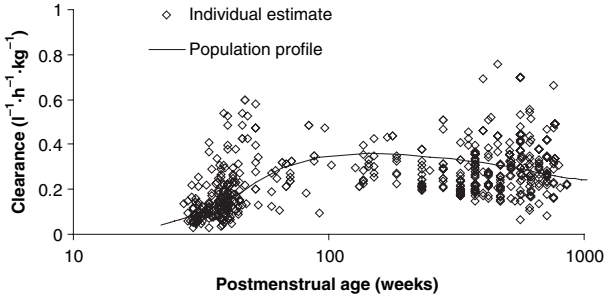

Figure 1
Paracetamol clearance, expressed using the linear per kilogram ($l \cdot h^{-1} \cdot kg^{-1}$) model, changes with age. Clearance is maximal at 1 year of age.

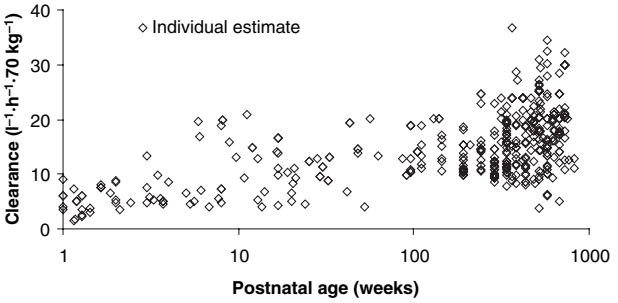

Figure 2
There is no clear maturation trend when postnatal age is used to map paracetamol clearance maturation, expressed using an allometric 3/4 power model.

$0.2\ l^{-1} \cdot h^{-1} \cdot kg^{-1}$ in a 1.5 kg intrauterine growth retarded term neonate or a 4 kg term neonate or an adult may appear equal. Clearances are quite different when standardized using allometric 3/4 power scaling. Clearance in a 70 kg person ($14\ l^{-1} \cdot h^{-1} \cdot 70\ kg^{-1}$) is greater than that in a 4 kg term neonate ($6.9\ l^{-1} \cdot h^{-1} \cdot 70\ kg^{-1}$) or in a 1.5 kg intrauterine growth retarded term neonate ($5.4\ l^{-1} \cdot h^{-1} \cdot 70\ kg^{-1}$). Clearance is the same in the adult and two neonates when expressed as per kilogram ($0.2\ l^{-1} \cdot h^{-1} \cdot kg^{-1}$), but is quite different in all three individuals when size scaling is introduced. Paracetamol clearance, when expressed using the linear per kilogram model, increases in the first year of life as clearance pathways mature. There is a subsequent decrease from late infancy (2 years) until adulthood (Figure 1). This increased clearance in infancy, greater than that of adults, is a consequence of the per kilogram size model and is a common observation in pediatric pharmacology.

Age

Maturation of pharmacokinetic parameters is usually expressed using age as the secondary covariate. Maturation of clearance begins before birth, suggesting that PMA would be a better predictor of drug elimination than PNA. The use of postnatal age does not account for the degree of immaturity at birth. Clearance on day 1 for neonates born at 24 weeks cannot be realistically compared with those neonates born at term. There is no clear maturation trend when postnatal age is used to map paracetamol clearance maturation (Figure 2). Paracetamol is mostly metabolized by sulfate and glucuronide conjugation (uridine 5′-diphosphate glucuronosyl transferase-1A6, UGT1A6). The foetus is capable of metabolizing morphine that also uses a member of the UGT family (UGT2B7), from 15 weeks gestation (22,23). The foetus and neonate can use sulfate conjugation as an alternative route for substrates such as morphine or paracetamol before glucuronidation matures. In addition, elimination routes of limited relevance in adults play a more important role in neonates. Approximately 5% of unmetabolized paracetamol is excreted unchanged in the urine of adults, but this percentage is higher in the premature neonate (24). Figure 3 demonstrates maturation of clearance using PMA, with clearance expressed using an allometric 3/4 power model.

There may be an additional, independent impact of PNA over PMA. Phenotypic glucuronidation activity was significantly lower in the first week of postnatal life after correction for PMA in an investigation of tramadol (25) and paracetamol (24)

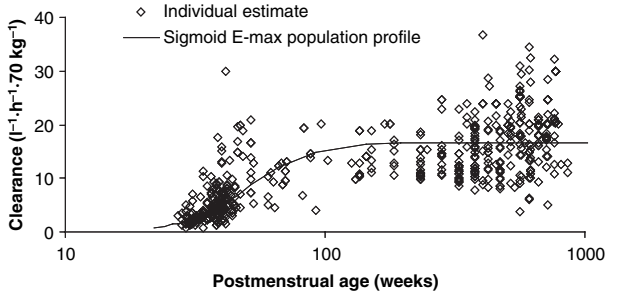

Figure 3
The maturation of clearance in children. Clearance matures over the first year of life described using a sigmoid Emax function. Premature neonates who are born before 37 weeks have a clearance that is <25% that of the 'mature' value.

determined from urinary elimination in neonates. The nature of the impact of PNA above PMA is uncertain. Other factors such as enzyme induction by substrate after repeat dosing may play a role (24). A temporal switch has been proposed to explain rapid increases in clearance after birth. Some CYPs, for example, appear to be switched on by birth, while in others birth is necessary but not sufficient for the onset of expression (26–28). There are no direct demonstrations that clearance changes as a consequence of being born.

Maturation of clearance in neonates may be described by both PMA and PNA, but PMA is a more physiologically appropriate covariate to explain the time course of changes in clearance. A model describing clearance changes with age should allow gradual maturation of clearance in early life and a 'mature' clearance to be achieved at a later age. A linear model may not allow maturation of clearance before birth. An exponential function allows for a gradual increase in clearance at earlier PMAs, but extrapolates badly by predicting continuously increasing clearance with age (Figure 4).

Sigmoidal curves are well recognized by anesthetists (oxygen dissociation curve, ligand–receptor binding, Michaelis–Menten pharmacokinetics) and present an attractive alternative for describing clearance maturation. A sigmoid Emax model allows gradual maturation of clearance in early life and a 'mature' clearance to be achieved at a later age (Figure 3).

$$F_{\mathrm{PMA}} = \frac{\mathrm{PMA}^{\mathrm{HillCL}}}{\mathrm{PMA}^{\mathrm{HillCL}} + \mathrm{MATCL}_{50}^{\mathrm{HillCL}}}$$

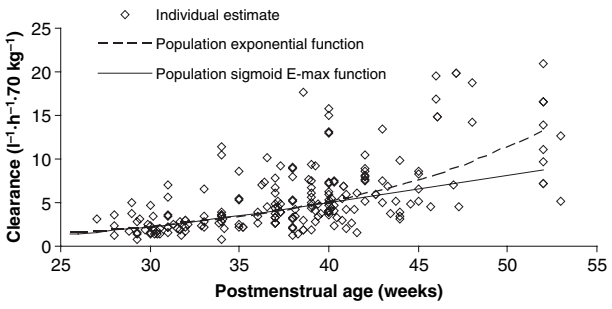

Figure 4
Paracetamol maturation in neonates. The sigmoid Emax model for paracetamol closely approximates a linear model in this age group. An exponential function also fits these individual estimates reasonably well.

where MATCL_{50} is the PMA at which clearance is 50% that of the mature value; HillCL is the Hill coefficient for clearance. A sigmoid Emax model has been used to investigate vancomycin clearance and covariate effects in premature neonates (29). The use of a sigmoid Emax model to describe the relationship between clearance and PMA predicted a reasonable adult clearance of 3.79 (95% CI 2.76–4.98) $l^{-1}{\cdot}h^{-1}{\cdot}70\ kg^{-1}$ from premature neonatal data (29). This model has also been used to describe acyclovir clearance maturation (30). Variants on this model have been proposed to quantify any apparent asymmetry (31). Maturation profiles are similar to those determined from data on ontogeny of individual clearance pathways, derived from measurements of enzyme expression and activity in postmortem livers (32).

Maturation of paracetamol clearance happens over the first year of life. Maturation of some cytochrome P-450-dependent mixed function oxidase enzyme systems are, in contrast rapid. Tramadol clearance (CYP2D6) increased from 25 weeks PMA ($5.5\ l^{-1}{\cdot}h^{-1}{\cdot}70\ kg^{-1}$) to reach 84% of the mature value by 44 weeks PMA (33). The rapid maturation of this clearance pathway around 40 weeks PMA contributes to the debate about temporal switches.

Variability

There is considerable paracetamol clearance variability within the neonatal age range (Figure 4). Most of the overall variability in pediatric clearance is predictable from covariate information such as size and age (5), but other unexplained covariates also make a contribution. For example, pharmacogenomics acting through CYP2D6 expression, has an impact on tramadol clearance by 45 weeks PMA (34). Drug interactions, disease, circadian rhythms and pharmacokinetic analysis techniques also add variability.

Pharmacokinetic studies in neonates commonly involve drug administration and subsequent analysis of the resulting plasma time–concentration profiles. Dose impression may be reflected in parameter variability. The neonatal dose is usually extracted from an adult orientated ampoule and may require serial dilution to achieve the required dose. Intravenous paracetamol is available as $1000\ mg{\cdot}100\ ml^{-1}$ and $500\ mg{\cdot}50\ ml^{-1}$. It is anticipated that a dose of 20 mg (equal to 2 ml) required for a 2 kg neonate will

have some, but limited inaccuracy. In general, when smaller volumes are used to prepare solutions from concentrated solutions or to prepare small doses (e.g. for neonates), then the magnitude of error increases (35). The introduction of an amikacin pediatric vial (50 $mg \cdot ml^{-1}$) instead of the adult vial (250 $mg \cdot ml^{-1}$) reduced clearance variability by 53% (36).

Other covariates such as severity of illness also contribute variability. Morphine clearance maturation occurs more quickly in infants undergoing non-cardiac surgery than those undergoing cardiac surgery (37) and reduced clearance is reported in critically ill neonates (38,39). Pharmacokinetic parameters reported in one population may not be applicable to another with different population demographics.

Use of markers to identify reduced clearance

Unconjugated bilirubin has been suggested as a covariate for the clearance of both morphine (40) and paracetamol (7). Dose should be reduced in the presence of a high unconjugated bilirubin concentration because measurement of unconjugated bilirubin concentration is a crude measure of hepatic conjugating ability. Paracetamol clearance will be reduced. Bilirubin, morphine and paracetamol are all cleared by glucuronosyltransferases: bilirubin by UGT1A1, morphine by UGTB27 and paracetamol by UGT1A6. Paracetamol is metabolized in neonates by both sulfate and glucuronide conjugation. Glucuronide conjugation increases with age and this is reflected in urinary glucuronide/sulfate ratios. Glucuronide/sulfate ratios range from 0.12 in premature neonates of 28–32 weeks PMA (41), 0.28 in those at 32–36 weeks PMA (41) and 0.34 in term neonates 0–2 days old (42).

Increased unconjugated bilirubin may reflect increased bilirubin production. Increased unconjugated bilirubin concentration is a late sign of reduced clearance; clearance will be reduced before this marker is elevated, in the first few days of life. While it seems sensible that paracetamol dose should be reduced in the presence of unconjugated hyperbilirubinemia, dosing before the onset of unconjugated hyperbilirubinemia is in doubt.

The use of serum creatinine concentration as a marker of glomerular filtration rate (GFR) suffers a similar lack of discriminating ability in the first few days of life. Creatinine in the first few days of life reflects maternal concentrations more than neonatal renal function and subsequent concentrations are influenced by tubular reabsorption (43). Neonatal nursery candidates (a commonly investigated population) may also suffer sepsis. Septic patients are often catabolic with increased muscle breakdown and creatinine production. A more accurate measure of GFR other than serum creatinine concentration is required to assess renal function in neonates immediately after birth.

Practical clinical solutions

Paracetamol is a valuable analgesic that should not be denied to neonates. There are reasonable data describing maturation pharmacokinetics that have been used to determine dosing. The use of a 10-day cut off for dose is not justified by the available evidence. Although physiological neonatal jaundice often resolves around this time, unconjugated hyperbilirubinemia is a crude marker of hepatic conjugation. PNA may be an additional covariate for clearance maturation over and above PMA, but there are few data available supporting this contention. It does not seem reasonable to suddenly increase dose on postnatal day 10, irrespective of PMA. Clearance dose not suddenly increase on day 10 (Figure 2). The idea that one dose fits all (7.5 $mg \cdot kg^{-1}$ 6 h for neonates after 10 days of age through to infants of 10 kg) is similarly flawed. Neonates will be receiving comparatively large doses in relation to clearance, which is low in neonates and highest in a 10 kg 1-year-old (when expressed as per kilogram). Similar considerations apply to oral dosing where 30–60 mg 8 h may be prescribed for ages 1–3 months (44).

Although the applicability of a pediatric target effect and concentration to neonates can be questioned, use of these targets has had value with concomitant reduction of morphine (3) or sedative use (45). Reduced morphine use may decrease morbidity from gastrointestinal motility reduction (constipation, gastric stasis, reduced feed tolerance) and urinary retention problems. Reduced morphine and sedative use has potential to speed weaning from artificial ventilation.

There are alternative analgesics that can be used in neonates. Oral glucose, sucrose or breast milk

have gained acceptance for procedures associated with mild pain (46). Ibuprofen and indomethacin are widely used for patent ductus arteriosus closure and can be used for analgesia, although their use is associated with reduced GFR (47). Tramadol is gaining acceptance in the neonatal age range as its pharmacokinetics are clarified (33), but analgesic activity is in part due to an active metabolite. Immaturity of CYP2D6 in premature neonates denies this population that active metabolite. Consequently, paracetamol retains its popularity.

The main concern with paracetamol is that of hepatotoxicity. Preliminary data (7,14) from neonates suggests that current evaluated dosing regimens are safe. It must be stressed that these are preliminary data only. The combined subject numbers were only 239 neonates. These numbers are too few to exclude the possibility of future hepatotoxicity; caution and continued monitoring of neonates given paracetamol is vital. The two studies had daily doses that varied by a factor of 2. Both authors report satisfactory analgesia and so it is probably safer to implement the lower rather than the upper dose regimen. Clearance variability and the lack of a suitable marker of reduced clearance in the first few days of life dictate the lower dose.

Paracetamol retains its position as the most popular analgesic in children. It is encouraging to observe its increasing use among neonates. This use must be accompanied by continued monitoring. That monitoring is currently crude and comprises measurement of hepatic aminotransferase activity. There is a desperate need for better markers of hepatic compromise.

Financial support and acknowledgments

BJ Anderson has consulted for Bristol–Myers Squibb and received assistance with airfares to conferences from this company. The clinical research of K Allegaert is supported by the Clinical Research Fund of the University Hospitals Leuven, Belgium.

References

1 Palmer GM, Chen SP, Smith KR *et al.* Introduction and audit of intravenous paracetamol at a tertiary paediatric teaching hospital. *Anaesth Intensive Care* 2007; **35:** 702–706.

2 Allegaert K, Murat I, Anderson BJ. Not all intravenous paracetamol formulations are created equal. *Pediatr Anesth* 2007; **17:** 811–812.

3 Agrawal S, Fitzsimons JJ, Horn V *et al.* Intravenous paracetamol for postoperative analgesia in a 4-day-old term neonate. *Pediatr Anesth* 2007; **17:** 70–71.

4 Allegaert K, Van der Marel CD, Debeer A *et al.* Pharmacokinetics of single dose intravenous propacetamol in neonates: effect of gestational age. *Arch Dis Child Fetal Neonatal Ed* 2004; **89:** F25–F28.

5 Anderson BJ, Pons G, Autret-Leca E *et al.* Pediatric intravenous paracetamol (propacetamol) pharmacokinetics: a population analysis. *Pediatr Anesth* 2005; **15:** 282–292.

6 Allegaert K, Anderson BJ, Naulaers G *et al.* Intravenous paracetamol (propacetamol) pharmacokinetics in term and preterm neonates. *Eur J Clin Pharmacol* 2004; **60:** 191–197.

7 Palmer GM, Atkins M, Anderson BJ *et al.* I.V. acetaminophen pharmacokinetics in neonates after multiple doses. *Br J Anaesth* 2008 (doi:10.1093/bja/aen208).

8 Bartocci M, Lundeberg S. Intravenous paracetamol: the 'Stockholm protocol' for postoperative analgesia of term and preterm neonates. *Pediatr Anesth* 2007; **17:** 1120–1121.

9 Holford NH. The target concentration approach to clinical drug development. *Clin Pharmacokinet* 1995; **29:** 287–291.

10 Anderson BJ, Woollard GA, Holford NH. Acetaminophen analgesia in children: placebo effect and pain resolution after tonsillectomy. *Eur J Clin Pharmacol* 2001; **57:** 559–569.

11 Krumbiegel P, Domke S, Morseburg B *et al.* Maturation of hepatosomal mono-oxygenation and glucuronidation activities in pre- and full-term infants as studied using the [15N] methacetin urine test. *Acta Paediatr* 1997; **86:** 1236–1240.

12 Roberts I, Robinson MJ, Mughal MZ *et al.* Paracetamol metabolites in the neonate following maternal overdose. *Br J Clin Pharmacol* 1984; **18:** 201–206.

13 Lederman S, Fysh WJ, Tredger M *et al.* Neonatal paracetamol poisoning: treatment by exchange transfusion. *Arch Dis Child* 1983; **58:** 631–633.

14 Allegaert K, Rayyan M, De Rijdt T *et al.* Hepatic tolerance of repeated intravenous paracetamol administration in neonates. *Pediatr Anesth* 2008; **18:** 388–392.

15 Kozer E, Barr J, Bulkowstein M *et al.* A prospective study of multiple supratherapeutic acetaminophen doses in febrile children. *Vet Hum Toxicol* 2002; **44:** 106–109.

16 Kuffner EK, Temple AR, Cooper KM *et al.* Retrospective analysis of transient elevations in alanine aminotransferase during long-term treatment with acetaminophen in osteoarthritis clinical trials. *Curr Med Res Opin* 2006; **22:** 2137–2148.

17 Watkins PB, Kaplowitz N, Slattery JT *et al.* Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily: a randomized controlled trial. *JAMA* 2006; **296:** 87–93.

18 Bonate PL. The effect of collinearity on parameter estimates in nonlinear mixed effect models. *Pharm Res* 1999; **16:** 709–717.

19 Dawson WT. Relations between age and weight and dosages of drugs. *Ann Intern Med* 1940; **13:** 1594–1613.

20 Peters HP. Physiological correlates of size. In: Beck E, Birks HJB, Conner EF, eds. *The Ecological Implications of Body Size*. Cambridge: Cambridge University Press, 1983:48–53.

21 Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. *Annu Rev Pharmacol Toxicol* 2008; **48:** 303–332.

22 Pacifici GM, Sawe J, Kager L *et al.* Morphine glucuronidation in human fetal and adult liver. *Eur J Clin Pharmacol* 1982; **22:** 553–558.
23 Pacifici GM, Franchi M, Giuliani L *et al.* Development of the glucuronyltransferase and sulphotransferase towards 2-naphthol in human fetus. *Dev Pharmacol Ther* 1989; **14:** 108–114.
24 Allegaert K, de Hoon J, Verbesselt R *et al.* Intra- and interindividual variability of glucuronidation of paracetamol during repeated administration of propacetamol in neonates. *Acta Paediatr* 2005; **94:** 1273–1279.
25 Allegaert K, Vanhole C, Vermeersch S *et al.* Both postnatal and postmenstrual age contribute to the interindividual variability in tramadol glucuronidation in neonates. *Early Hum Dev* 2008; **84:** 325–330.
26 Hines RN, McCarver DG. The ontogeny of human drug-metabolizing enzymes: phase I oxidative enzymes. *J Pharmacol Exp Ther* 2002; **300:** 355–360.
27 Koukouritaki SB, Manro JR, Marsh SA *et al.* Developmental expression of human hepatic CYP2C9 and CYP2C19. *J Pharmacol Exp Ther* 2004; **308:** 965–974.
28 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:** 1157–1167.
29 Anderson BJ, Allegaert K, Van den Anker JN *et al.* Vancomycin pharmacokinetics in preterm neonates and the prediction of adult clearance. *Br J Clin Pharmacol* 2007; **63:** 75–84.
30 Tod M, Lokiec F, Bidault R *et al.* Pharmacokinetics of oral acyclovir in neonates and in infants: a population analysis. *Antimicrob Agents Chemother* 2001; **45:** 150–157.
31 Van der Graaf PH, Schoemaker RC. Analysis of asymmetry of agonist concentration-effect curves. *J Pharmacol Toxicol Methods* 1999; **41:** 107–115.
32 Edginton AN, Schmitt W, Willmann S. Development and evaluation of a generic physiologically based pharmacokinetic model for children. *Clin Pharmacokinet* 2006; **45:** 1013–1034.
33 Allegaert K, Anderson BJ, Verbesselt R *et al.* Tramadol disposition in the very young: an attempt to assess in vivo cytochrome P450 2D6 activity. *Br J Anaesth* 2005; **95:** 231–239.
34 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:** 525–532.
35 Parshuram CS, To T, Seto W *et al.* Systematic evaluation of errors occurring during the preparation of intravenous medication. *CMAJ* 2008; **178:** 42–48.
36 Allegaert K, Anderson BJ, Vrancken M *et al.* Impact of a paediatric vial on the magnitude of systematic medication errors in preterm neonates: amikacin as an example. *Paediatr Perinat Drug Ther* 2006; **7:** 59–63.
37 Lynn A, Nespeca MK, Bratton SL *et al.* Clearance of morphine in postoperative infants during intravenous infusion: the influence of age and surgery. *Anesth Analg* 1998; **86:** 958–963.
38 Pokela ML, Olkkola KT, Seppala T *et al.* Age-related morphine kinetics in infants. *Dev Pharmacol Ther* 1993; **20:** 26–34.
39 Peters JW, Anderson BJ, Simons SH *et al.* Morphine metabolite pharmacokinetics during venoarterial extra corporeal membrane oxygenation in neonates. *Clin Pharmacokinet* 2006; **45:** 705–714.
40 Bouwmeester NJ, Anderson BJ, Tibboel D *et al.* Developmental pharmacokinetics of morphine and its metabolites in neonates, infants and young children. *Br J Anaesth* 2004; **92:** 208–217.
41 van Lingen RA, Deinum JT, Quak JM *et al.* Pharmacokinetics and metabolism of rectally administered paracetamol in preterm neonates. *Arch Dis Child Fetal Neonatal Ed* 1999; **80:** F59–F63.
42 Miller RP, Roberts RJ, Fischer LT. Acetaminophen elimination kinetics in neonates, children and adults. *Clin Pharmacol Ther* 1976; **19:** 284–294.
43 Guignard JP, Drukker A. Why do newborn infants have a high plasma creatinine? *Pediatrics* 1999; **103:** e49.
44 Bua J, L'Erario I, Barbi E *et al.* When off-label is a good practice: the example of paracetamol and salbutamol. *Arch Dis Child* 2008; **93:** 546–547.
45 Prins SA, van Dijk M, van Leeuwen P *et al.* Pharmacokinetics and analgesic effects of intravenous propacetamol vs rectal paracetamol in children after major craniofacial surgery. *Pediatr Anesth* 2008; **18:** 582–592.
46 Stevens B, Yamada J, Ohlsson A. Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database Syst Rev* 2004: CD001069.
47 Allegaert K, Anderson BJ, Cossey V *et al.* Limited predictability of amikacin clearance in extreme premature neonates at birth. *Br J Clin Pharmacol* 2006; **61:** 39–48.

