INTRODUCTION
Therapeutic catastrophes in neonates such as the grey baby syndrome attributable to chloramphenicol and phocomelia due to thalidomide have shaped modern drug development. Unmonitored off-label use of medicines in neonates and infants, extrapolated from adult data, has resulted in significant morbidity that could have been avoided or minimized by investigation in this population. A surge of interest in developmental pharmacology, methods for scaling paediatric pharmacokinetic (PK) parameters from adult and individual drug studies in children of all ages is improving current drug management in the first year of life. This chapter examines pharmacokinetic and pharmacodynamic (PD) changes after birth, explores common size models and reviews the pharmacology of analgesic drugs commonly used in early infancy.

DEVELOPMENTAL PHARMACOLOGY
Absorption
The rate at which most drugs are absorbed when given by the oral route is slower in neonates and young infants than in older children. The time (T_{max}) at which maximum concentration (C_{max}) is achieved is prolonged (Fig. 9.1). Gastric emptying and intestinal motor motility mature through infancy and normal adult rates may not be reached until 6–8 months (Grand et al. 1976, Gupta and Brans 1978, Carlos et al. 1997, Liang et al. 1998). Many of the effects of the immature gastrointestinal system are either not characterized or the effect of immaturity is uncertain. Immature conjugation and transport of bile salts into the intestinal lumen may affect lipophilic drug blood concentrations (Poley et al. 1964, Suchy et al. 1981), but these effects have not been quantified. The role of altered intestinal microflora in neonates and its effect on drugs is uncertain (Linday et al. 1987).

The larger relative skin surface area, increased cutaneous perfusion and thinner stratum corneum in neonates increase absorption and exposure of topically applied drugs (e.g. local anaesthetic creams). Neonates have reduced levels of methaemoglobin reductase and fetal haemoglobin is more readily oxidized compared to adult haemoglobin. This, combined with increased
absorption through the neonatal epidermis, resulted in reluctance to use lidocaine-prilocaine cream (EMLA) in this age group. These fears are unfounded if the cream is used as a single dose but may cause harm with repeat dosing (Taddio et al. 1995, 1997).

We might expect the reduced muscle bulk, skeletal muscle blood flow and inefficient muscular contractions in neonates (Greenblatt and Koch-Weser 1976) to decrease intramuscular absorption. This is not necessarily the case (Sheng et al. 1964, Kafetzis et al. 1979), partly because of size issues (see below) and the higher density of skeletal muscle capillaries (Carry et al. 1986).

The rectal route is associated with erratic and variable absorption. Age, formulation, rectal contents, rectal contractions (with consequent expulsion) and depth of rectal insertion all affect absorption and relative bioavailability (van Hoogdalem et al. 1991a, 1991b). The rectal route has the potential to partially reduce first-pass hepatic extraction by draining into the inferior and middle haemorrhoidal veins. Age influences the relative bioavailability of some drugs, but this may not be always attributable to first-pass effects (Fig. 9.2).

The onset time of inhaled analgesic gases and vapours is generally more rapid in infants than in adults (Salanitre and Rackow 1969). Developmental changes of both the lung architecture and mechanics in these early years play a role. The greater fraction of the cardiac output distributed to the vessel-rich tissue group (i.e. a clearance factor) and the lower tissue/blood solubility (i.e. a volume factor) also affect the more rapid wash-in of inhalational anaesthetics in the younger age group (Lerman 1992). Solubility has
considerable effects on the uptake of inhalational agents in children. Solubility determines the volume of distribution. An inhalational agent with a greater volume of distribution will take longer to reach a steady-state concentration when delivered at a constant rate. The solubilities in blood of halothane, isoflurane, enflurane and methoxyflurane are 18% less in neonates than in adults. The solubilities of these same agents in the vessel-rich tissue group in neonates are approximately one half of those in adults (Lerman et al. 1986). This may be due to the greater water content and decreased protein and lipid concentration in neonatal tissues. Age has little effect on the solubility of the less-soluble agents such as nitrous oxide (Malviya and Lerman 1990). Infants, with their decreased solubility, would be expected to have a shorter time to reach a predetermined fraction exhaled/fraction inhaled (FE/FI) ratio because of a smaller volume of distribution.

**Distribution**

**Body composition**

Total body water constitutes 85% of the body weight in the preterm neonate and 75% in term neonates. This decreases to approximately 60% at 5 months and remains relatively constant from this age on (Friis-Hansen 1961). The major component contributing to this reduction in body water is the decrease in extracellular fluid (ECF). ECF constitutes 45% of the body weight at birth and 26% at 1 year. There is a further ECF reduction during childhood until adulthood where it contributes 18%. The percentage of body weight contributed by fat is 3% in a 1.5 kg premature neonate and 12% in a term neonate; this proportion doubles by 4–5 months of age. ‘Baby fat’ is lost when the infant starts walking and protein mass increases (20% term neonate, 50% adult). Relative body proportions change dramatically over the first few years of life and may affect volumes of distribution of drugs.

**Plasma proteins**

Acidic drugs (e.g. barbiturates) tend to bind mainly to albumin while basic drugs (e.g. diazepam, amide local anaesthetic agents) bind to globulins, lipoproteins and glycoproteins. Plasma protein binding of many drugs is decreased in the newborn infant relative to adults, but the clinical impact of this decrease is minor for most drugs. Reduced clearance in this age group has greater effect (Anderson et al. 1997). Protein binding changes are important for the rare case of a drug with more than 95% protein binding, a high extraction ratio and a narrow therapeutic index that is given parenterally (e.g. lidocaine IV) or a drug with a narrow therapeutic index that is given orally and has a very rapid equilibration half-time (Benet and Hoener 2002).

**Blood–brain barrier (BBB)**

The BBB is a lipid membrane interface between the endothelial cells of the brain blood vessels and the ECF of the brain. Brain uptake of drugs is dependent on lipid solubility and blood flow. It was postulated that BBB permeability to water-soluble drugs such as morphine changes with maturation. This concept originated from a study (Way et al. 1965) demonstrating that neonates less than 4 days of age developed ventilatory depression following intramuscular morphine 0.05 mg/kg. This dose should depress ventilation minimally in adults. Ventilatory depression in neonates following intramuscular pethidine (meperidine) 0.5 mg/kg was similar to that expected in adults (Way et al. 1965). This finding is consistent with pethidine, unlike morphine, being lipid soluble and therefore crossing the immature or mature BBB equally (Way et al. 1965). However, the increased neonatal respiratory depression observed after morphine could be due to pharmacokinetic age-related changes. For example, the volume of distribution of morphine is reduced in term neonates (Bouwmeester et al. 2004) and we might expect initial concentrations of morphine to be higher in neonates than in adults. Respiratory depression is the same in children from 2–570 days of age at the same morphine concentration (Lynn et al. 1993). The role of transporters across the BBB for morphine has only recently been explored (Tunblad et al. 2005) in non-human species. Direct demonstration of the developmental changes in transporter activity and their impact on drug transport across the BBB remain speculative.

**Drug metabolism**

The liver is the primary organ for clearance of most drugs. Non-polar, lipid-soluble drugs are converted to more polar and water-soluble compounds. Water-soluble drugs are excreted unchanged in the kidneys by glomerular filtration and/or renal tubular secretion. Many of these processes are immature in the neonate and mature to reach adult levels within the first year of life, although there may be exceptions to this rule (e.g. N-acetyltransferase) (Pariante-Khayat et al. 1997). These developmental changes are predictable by age and are independent of size (represented by body weight). Clearance increases with gestation, but birth may be a major stimulus for the maturation of drug metabolism (Hines and McCarver 2002, McCarver and Hines 2002). Maturation of clearance in neonates may be described by both postconception and growth.
age (PCA) and postnatal age (PNA). We believe that PCA is a more physiologically appropriate covariate to explain the time course of changes in clearance. We are not aware of any direct demonstration that clearance changes as a consequence of being born.

**Hepatic elimination**

**Phase 1 reactions** Phase 1 metabolic processes involve oxidative, reductive or hydrolytic reactions that are commonly catalyzed by the mixed function oxidase system. The cytochrome P450 (CYP) is the major enzyme system for oxidation of drugs. There are distinct patterns associated with isoform-specific developmental expression of CYPs. Some appear to be switched on by birth, while for others birth is necessary but not sufficient for the onset of expression (Hines and McCarver 2002, Koukouritaki et al. 2004). CYP2E1 activity surges after birth, CYP2D6 becomes detectable soon thereafter, the CYP3A4 and CYP2C family appear during the first week, whereas CYP1A2 is the last to appear (Kearns et al. 2003). Neonates are dependent on the immature CYP3A4 for bupivacaine clearance and CYP1A2 for ropivacaine clearance, dictating reduced epidural infusion rates in this age group (Berde 1992, Anderson and Hansen 2004).

**Phase 2 reactions** Knowledge of maturation of phase 2 enzymes remains incomplete (McCarver and Hines 2002). Some phase 2 pathways are mature at birth (sulphate conjugation), while others are not (acetylation, glycination, glucuronidation). The individual isoforms of glucuronosyltransferase (UGT) mature at different rates. Morphine is largely metabolized by uridine-5'-diphosphate UGT2B7 to morphine-3-glucuronide and morphine-6-glucuronide (de Wildt et al. 1999b). In vitro studies using liver microsomes from fetuses aged 15–27 weeks indicated that morphine glucuronidation was approximately 10–20% of that seen with adult microsomes (Pacifici et al. 1982, 1989). Morphine glucuronidation has been demonstrated in premature infants as young as 24 weeks. Clearance increases after birth with a maturation half-time of approximately 3 months (Bouwmeester et al. 2004) (Fig. 9.3). The neonate can use sulphate conjugation as an alternative route for substrates such as morphine or acetaminophen before glucuronidation develops. Clearance increases in early life as hepatic glucuronidation enzyme pathways mature. The sulphate pathway is the dominant metabolic route for acetaminophen in infancy (Alam et al. 1977).

**Renal elimination**

Drugs and their metabolites are excreted by the kidneys by two processes: glomerular filtration and tubular secretion. Glomerular filtration rate (size normalized using predicted body surface area) is at adult values at 5–6 months (West et al. 1948, Arant 1978). Proximal tubular secretion reaches adult levels by 7 months of age (West et al. 1948, Arant 1978).

**Extrahepatic elimination**

Many drugs are metabolized at extrahepatic sites. Remifentanil is rapidly broken down by non-specific esterase in tissue and erythrocytes. Clearance is increased in younger children but this may be attributable to size (see below) and maturation profiles are unknown. A rate constant representing hydrolysis by plasma esterases of propacetamol (a prodrug of acetaminophen) to acetaminophen was size related, but not age related (Anderson et al. 2005). The ester group of local anaesthetics is metabolized by plasma pseudocholinesterase, which is reduced in neonates. The in vitro plasma half-life of 2-chloroprocaine in

![Figure 9.3](Ch09-N52061.qxd 2/7/07 2:25 PM Page 118)
umbilical cord blood is twice that in maternal blood (Zsigmond and Downs 1971), but there are no in vivo studies examining the effects of age.

**Polymorphisms of metabolic enzymes**

Polymorphisms of the genes encoding for metabolic enzymes contribute to a large degree of inter-individual PK variability (de Wildt et al. 1999a). Polymorphism of CYP2D6, for example, is inherited as an autosomal recessive trait. Homozygous individuals are deficient in the metabolism of a variety of important groups of drugs – β-adrenoreceptor blocking agents, antidepressants, neuroleptic agents and opioids. Poor metabolizers have reduced morphine production from codeine (Williams et al. 2001). Tramadol is also metabolized by O-demethylation in the liver (CYP2D6) to O-demethyl tramadol (M1) and the M1 metabolite has a μ-opioid affinity approximately 200 times greater than tramadol; CYP2D6 iso-enzyme activity is important for the analgesic effect attributable to tramadol.

**PHARMACODYNAMICS**

Pharmacokinetics is what the body does to the drug, while pharmacodynamics is what the drug does to the body. The precise boundary between these two processes is ill defined and often requires a link describing movement of drug from the plasma to the biophase and its target. Drugs may exert effects at non-specific membrane sites by interference with transport mechanisms, by enzyme inhibition or induction or by activation or inhibition of receptors.

**Developmental changes**

There are few data describing age-related pharmacodynamic changes despite recognition that the number, affinity and type of receptors or the availability of natural ligands changes with age. Opioid receptors are not fully developed in the newborn rat and mature into adulthood (Freye 1996), but human neonatal increased sensitivity to morphine is attributable to PK rather than PD differences. Correlations between the opioid drug plasma concentrations and validated pain scores are weak (Suri et al. 1997, Olkkola and Hamunen 2000).

Gamma-aminobutyric acid (GABA) is the neurotransmitter at most inhibitory synapses in the human central nervous system. The GABA<sub>A</sub> receptor complex is the site of action for benzodiazepines, barbiturates and numerous anaesthetic agents (Franks and Lieb 1994). At birth the cerebellum only contains one-third the number of GABA<sub>A</sub> receptors found in an adult and these are comprised of subunits with reduced binding affinity for benzodiazepines (Brooks-Kayal and Pritchett 1993). Major changes in receptor binding and subunit expression occur during postnatal development (Chugani et al. 2001). GABA<sub>A</sub> receptor complex, identified by positron emission tomography, was more prevalent at 2 years and the values then decreased exponentially to 50% of peak values by 17 years (Chugani et al. 2001). These changes are consistent with age-related minimal alveolar concentration (MAC) changes of inhalational anaesthetics (Marshall et al. 2000). The MAC (%) of isoflurane, for example, is 1.3 in a premature neonate, 1.4 at term, 1.9 at 6–12 months and 1.6 at 17 years.

**The sigmoid Emax model**

The relation between drug concentration and effect may be described by a hyperbolic curve according to the equation:

\[
\text{Effect} = E_0 + \frac{E_{max} \times C_e}{EC_{50} + C_e}
\]

where \( E_0 \) is the baseline response, \( E_{max} \) is the maximum effect change, \( C_e \) is the concentration in the effect compartment, \( EC_{50} \) is the concentration producing 50% \( E_{max} \) and \( N \) is the Hill coefficient defining the steepness of the concentration–response curve (Holford and Sheiner 1981). At low concentrations this non-linear relationship may approach linearity (Fig. 9.4).

Efficacy is the maximum response on a dose- or concentration–response curve and is measured by \( E_{max} \). \( EC_{50} \) can be used as a measure of potency relative to another drug provided \( N \) and \( E_{max} \) for the two drugs are the same.

**The time course of drug effect**

**Immediate effects**

A simple situation in which drug effect is directly related to concentration does not mean that drug effects parallel the time course of concentration. This occurs only when the concentration is low in relation to \( EC_{50} \). In this situation the plasma half-life of the drug may correlate closely with the half-life of drug effect. Many drugs, however, have a short half-life but a long duration of effect. If the initial concentration is very high in relation to the \( EC_{50} \), then drug concentrations 5 half-lives later, when we might expect minimal concentration, may still exert considerable effect. This is because of the shape of the Emax model. Low concentrations may still be about the \( EC_{50} \) concentration, for example, and so exert effect. This is common for drugs that act on enzymes (e.g. NSAIDs).

**Delayed effects**

**Delayed effect model**

A plasma concentration–effect plot can form a counter-clockwise hysteresis loop
(Fig. 9.5) because of this delay in effect. Hull et al. (1978) and Sheiner et al. (1979) introduced the effect compartment concept for muscle relaxants. The effect compartment concentration is not the same as the blood or serum concentration and is not a real measurable concentration. A single first-order parameter \((T_{eq}, T_{1/2_{keo}})\) describes the equilibration half-time. It is assumed that the concentration in the central compartment is the same as that in the effect compartment at equilibration, but that a time delay exists before the drug reaches the effect compartment. The concentration in the effect compartment is used to describe the concentration–effect relationship.

**Physiological substance turnover model** Many drug actions are mediated through synthesis or elimination of a physiological substance (Holford 1992). The concentration at the site of drug effect either stimulates or inhibits the rate of production or elimination of the physiological substance (response variable). Warfarin, for example, inhibits the recycling of vitamin K epoxide to the active vitamin K form that is involved in the production of prothrombin complex. Turnover models provide a reasonable description of the mechanism of delayed action for many drugs (Jonkers et al. 1989).

**SIZE MODELS**

Weight is commonly used to determine dose in children. The variation of weight at any given age is considerable, being least at 1 year (+25% to −20% at 10 kg; from 3rd to 97th centile) and reaching a maximum at about 13 years (+45% to −26% at 40 kg) (Lack and Stuart Taylor 1997). Body weight is used commonly, although it is now widely recognized that there is a non-linear relationship between weight and drug elimination capacity.

Linear size models for young children have led to the idea that there is an enhanced capacity of children to metabolize drugs due to proportionally larger livers and kidneys than their adult counterparts (Tenenbein 2000). This idea arises because clearance, expressed per kg of body weight, is larger in children than adults. Developmental and physiological changes during growth such as an increased relative
liver size or increased hepatic blood flow have been invoked (Tenenbein 2000) to explain the higher clearance per kg.

Dawson, in 1940, reviewed evidence that smaller species are generally more tolerant of drug treatment than larger species and concluded that adjustment of drug dose using a body weight exponent of less than 1 was justified. Body surface area (BSA) was subsequently proposed in 1950 to be a more satisfactory index of drug requirements than body weight or age, particularly during infancy and childhood (Crawford et al. 1950). Drug dosage rules for children, based on BSA, have been described which use percentage of an adult dose to calculate an appropriate child’s dose (Catzel and Olver 1981, Lack and Stuart Taylor 1997). Another size model using an exponent of weight ($W^{3/4}$) has also been proposed (Holford 1996). The latter, which may be termed the ‘allometric $3/4$ power model’ has been found to be useful in normalizing a large number of physiological (Peters 1983) and pharmacokinetic variables (Boxenbaum 1982, Ritschel et al. 1992). The per kilogram, surface area and allometric $3/4$ power models are but three of numerous different approaches which have been described as a means of predicting physiological function from body size.

The allometric model

Most body size relations take the form:

$$y = a \cdot W^b$$

where $y$ is the biological characteristic to be predicted, $W$ is the body mass and $a$ and $b$ are empirically derived constants. In all species studied, including humans, the log of basal metabolic rate (BMR) plotted against the log of body weight produces a straight line with a slope of $3/4$ (Kleiber 1932, Brody et al. 1934, Stahl 1967, Peters 1983). This exponential function is the same for homeotherms, poikilotherms and unicellular organisms (Peters 1983). Mass- and temperature-compensated resting metabolic rates of microbes, ectotherms, endotherms (including those in hibernation), and plants in temperatures ranging from 0°C to 40°C are similar (Gillooly et al. 2001) (Fig. 9.6).

West et al. (1997) have used fractal geometric concepts to explain this phenomenon. This group analyzed organisms in terms of the geometry and physics of a network of linear tubes required to transport resources and wastes through the body. Such a system, they reasoned, must have three key attributes. The network must reach all parts of a three-dimensional body; a minimum amount of energy should be required to transport the materials in a fluid medium; and the terminal branches of the networks should all be the same size, as cells in most species are roughly similar sizes (Williams 1997). The $3/4$ power law for metabolic rates was derived from a general model that describes how essential materials are transported through space-filled fractal networks of branching tubes (West et al. 1997). These design principles are independent of detailed dynamics and explicit models.
and should apply to virtually all organisms (Banavar 1999, West et al. 1999). This allometric $3/4$ power model may be used to scale metabolic processes such as drug clearance ($CL$) as follows:

$$CL_i = CL_{std} \cdot \left( \frac{W_i}{W_{std}} \right)^{3/4}$$

where $CL_i$ is the clearance in the individual of weight $W_i$ and $CL_{std}$ is the clearance in a standardized individual with weight $W_{std}$ (Holford 1996).

When applied to physiological volumes ($V$), the power parameter is 1:

$$V_i = V_{std} \cdot \left( \frac{W_i}{W_{std}} \right)^{1}$$

This index has been demonstrated for blood volume, vital capacity and tidal volume (Guyton 1947, Adolph 1949, Stahl 1967, Prothero 1980, West et al. 1997). The volume of distribution in the central compartment ($V_c$), volume of distribution by area ($V_{beta}$) and volume of distribution at steady state ($V_{dss}$) also show direct proportionality to body weight (Mahmood 1998).

Time-related indices ($T$) such as heart rate, respiratory rate or drug half-times have a power of $1/4$ (Dedrick et al. 1970, McMahon 1980, Peters 1983, Ritschel et al. 1992, Gronert et al. 1995, West et al. 1997).

$$T_i = T_{std} \cdot \left( \frac{W_i}{W_{std}} \right)^{1/4}$$

The pharmacokinetic time scale originated from an imaginary concept of ‘physiologic time’. Most mammals have the same number of heartbeats and breaths in their life span. The difference between small and large animals is that smaller animals have faster physiologic processes and consequently a shorter life span. (Ritschel et al. 1992). A power function of $1/4$ can be derived for pharmacokinetic half-times based on basic pharmacokinetics applied to allometric predictions of clearance and volume:

$$T_{1/2} = \ln(2) \cdot \frac{V}{CL} \times \ln(2) \cdot \left( \frac{W_i}{W_{std}} \right)^{1/4} = \ln(2) \cdot W^{1/4}$$

**The surface area model**

The original surface area model proposed by Du Bois and Du Bois (1916) was predicted from nine adults of diverse body shape. These nine individuals included a tall thin adult male, a fat adult woman, and a 36-year-old cretin with the ‘physical development of a boy of 8 years’. The youngest individual from this group was 12 years old. It is now common practice to use the Du Bois and Du Bois formula to predict surface area from weight ($W$) and height ($H$):

$$BSA = W(kg)^{0.425} \cdot H(cm)^{0.725} \cdot 0.007184$$

This formula belongs to the same class of allometric models that include those using weight alone.

Nomograms determined from this formula are often used. Surface area can also be estimated from an allometric model with a power parameter of $2/3$ (Boxenbaum and DiLea 1995, Holford 1996). This ‘allometric $2/3$ power model’ assumes metabolic rate is scaled by geometric descriptors of body size (Williams 1997). The surface area formula assumes that adults and children are geometrically similar. However, infants are not morphologically similar to adults – infants have short stumpy legs, relatively big heads and large body trunks. The surface area formula is inaccurate in children with a predicted surface area of less than 1.3 m$^2$ (an average 12-year-old) by direct photometric measurement (Mitchell et al. 1971).

When a standard surface area of 1.9 m$^2$ is used with the allometric $2/3$ power surface area model, clearances agree quite well with the $3/4$ power model except at body weights below 7 kg. When the allometric surface area is used, clearance is over-predicted by more than 10% at body weights below 20 kg (Mitchell et al. 1971). The mass of empirical evidence suggests that the appropriate scaling factor is significantly different from 0.67 and is compatible with the theoretically expected value of 0.75 (Kleiber 1961, Schmidt-Nielsen 1984, West et al. 1997, 1999).

**The linear per kilogram model**

The linear per kilogram model is the poorest model when used for interspecies scaling of metabolic processes such as total body clearance, but remains the most commonly used in humans. In humans, under-prediction of clearance of more than 10% occurs at body weights less than 47 kg when compared to the allometric $3/4$ power model. This discrepancy increases as size decreases and approaches 50% for a newborn human of 3.5 kg. Because clearance is reduced in this age group for developmental reasons, use of the linear per kilogram model may get close to the right answer for the wrong reason.

Figure 9.7 shows clearance changes with weight for a hypothetical drug using the three different models. Age-related clearance increases throughout infancy and reaches adult values at approximately 1 year using an allometric $3/4$ power model. The linear per kilogram model shows an increased clearance compared to adults at approximately 1 year (10 kg). This apparent increased clearance in infants has been interpreted to mean that children have an enhanced capacity to
metabolize drugs but is more likely to be an artefact due to the use of the linear per kilogram model. The $\frac{3}{4}$ power family of allometric models forms a better basis for size scaling than either the surface area or per kilogram models. Once size is scaled then deviations from predictions based on allometry are noticeable. The cause of these deviations can then be sought. The prime example of such a deviation is the reduced clearance in neonates, attributable to immaturity of hepatic and renal clearance systems.

**COMMON ANALGESIC DRUGS**

**Acetaminophen (paracetamol)**

**Mechanism of action**

Acetaminophen is widely used in the management of pain, but is lacking in anti-inflammatory effects. Analgesia is mediated through inhibition of prostaglandin synthesis within the central nervous system (COX III, COX 2b). Analgesic effect also involves an inhibitory action on spinal nitric oxide mechanisms (Piletta et al. 1991, Bjorkman et al. 1994, Bjorkman 1995) and serotonergic pathways (Courade et al. 2001).

**Analgesic pharmacodynamics**

Acetaminophen is believed to be an effective antipyretic at serum concentrations of 10–20 mg/L (Peterson and Rumack 1978), and these concentrations have been extrapolated to those that provide analgesia. However, the paper by Rumack (Peterson and Rumack 1978), which is often cited as the source for these antipyretic serum concentrations of 10–20 mg/L, makes reference to an unpublished source. There are few data examining acetaminophen analgesia in neonates. These data suggest poor analgesic effect after painful procedures (van Lingen et al. 1999a, 2001), after circumcision (Howard et al. 1994) or during heel prick (Shah et al. 1998). This is in contrast to documented analgesic effect in infants and children (Rod et al. 1989, Korpela et al. 1999, Anderson et al. 2001). It is unclear why poor analgesic effect is reported in neonates, but it may be attributable to inadequate serum concentrations, type of pain stimulus or assessment tools for the discrimination of pain.

Korpela et al. (1999) have calculated a rectal dose after day-stay surgery at which 50% of the children did not require a rescue opioid to be 35 mg/kg. Time delays of approximately 1 hour between peak concentration and peak effect are reported (Arendt Nielsen et al. 1991, Nielsen et al. 1992). Pain fluctuations, pain type and placebo effects complicate interpretation of clinical studies. Anderson et al. (2001) obtained population parameter estimates (population parameter variability) of $E_{\text{max}}$ 5.17 (64%) and $E_{C_{50}}$ 9.98 (107%) mg/L (the greatest possible pain relief (visual analogue scale (VAS) 0–10) would equate to an $E_{\text{max}}$ of 10). The equilibration half-time ($T_{eq}$) of the analgesic effect compartment was 53 (217%) min. A target effect compartment concentration of 10 mg/L was associated with a pain reduction of 2.6/10 (using a VAS 0–10) (Anderson et al. 2001).
Pharmacokinetics

Bioavailability Acetaminophen has low first-pass metabolism and the hepatic extraction ratio is 0.11–0.37 in adults (Rawlins et al. 1977). The relative bioavailability of rectal compared with oral acetaminophen formulations (rectal/oral) has been reported as 0.52 (range 0.24–0.98) (Audenaert et al. 1995) and even as low as 0.3 (Dange et al. 1987). The relative bioavailability is higher in neonates and approaches unity. The relative bioavailability of rectal formulations appears to be age related (see Fig. 9.2) (Anderson and Meakin 2002).

Rate of absorption Acetaminophen has a pKa of 9.5 and in the alkaline medium of the duodenum acetaminophen is non-ionized. Consequently, absorption of the non-ionized form from the duodenum to the systemic circulation is rapid in children. Brown et al. (1992) have reported rapid absorption (T1/2abs 2.7, se 1.2 min; Tlag 4.2, se 0.4 min) parameters in febrile children given elixir orally. Similar absorption half-lives have been estimated in children given acetaminophen as an elixir before tonsillectomy (T1/2abs 4.5 min, CV 63%, Tlag 0) (Anderson et al. 2001). Absorption in infants under the age of 3 months was delayed 3.68 times, consistent with delayed gastric emptying in young infants (Anderson et al. 2000a). Oral absorption was considerably delayed in premature neonates in the first few days of life (see Fig. 9.2) (Anderson et al. 2002).

Rectal absorption Rectal absorption is slow and erratic with large variability (Gaudreault et al. 1988, Birmingham et al. 1997). For example, absorption parameters for the triglyceride base were T1/2abs 1.34 h (CV 90%), Tlag 0.14 h (31%). The absorption half-life for rectal formulations was prolonged in infants under 3 months (1.51 times greater) compared to those seen in older children (Anderson et al. 2000c).

Clearance Several studies confirm sulphate metabolism to be the dominant route of elimination in neonates (Levy et al. 1975b, Miller et al. 1976, van Lingen et al. 1999a). Glucuronide/sulphate ratios range from 0.12 in premature neonates of 28–32 weeks postconception, 0.28 in those at 32–36 weeks postconception (van Lingen et al. 1999b) to 0.34 in term neonates 0–2 days old (Miller et al. 1976). Ratios of 0.75 in children 3–9 years, 1.61 in those aged 12 years and 1.8 in adults are reported (Miller et al. 1976). Approximately 4% of acetaminophen is excreted in urine unmetabolized and the amount is dependent on urine flow (Miners et al. 1992).

A total body clearance in full-term neonates of 4.9 (CV 38%) L/h/70kg after enteral acetaminophen has been reported using an allometric 1/4 power model (Anderson et al. 2000c). This clearance is approximately 40% that of older children (2–15 years). Clearance over the first year of life reaches 80% of that seen in older children by 6 months. Further investigation using published data from premature neonates (Anderson et al. 2002) confirmed this trend in the very young. Clearance increased from 28 weeks postconception (0.74 L/h/70 kg) with a maturation half-life of 11.3 weeks to reach 10.9 L/h/70 kg by 60 weeks (Fig. 9.8).

Volume of distribution The population distribution volumes in children are similar to those reported in adults (56–70 L) (Prescott 1996). The volume of distribution for acetaminophen in mammals (Prescott 1996), including humans, is 49–70 L/70 kg as we would expect from the allometric size model with a power function of 1. The volume of distribution

![Figure 9.8 Individual predicted acetaminophen clearances determined after intravenous administration and standardized to a 70-kg person are plotted against postconception age. Children given multiple doses have clearance estimates from each occasion linked by a fine line. The solid line represents the non-linear relation between clearance and age. (Reproduced from Anderson BJ et al. Paediatr Anaesth 2005; 15: 282–292 with permission.)](image-url)
decreases exponentially with a maturation half-life of 11.5 weeks from 109.7 L/70 kg at 28 weeks post-conception to 72.9 L/70 kg by 60 weeks (Fig. 9.9). Fetal body composition and water distribution alter considerably during the third trimester and over the first few months of life, probably reflecting neonatal body composition and the rapid changes in body water distribution in early life.

Parenteral formulation Propacetamol (N-acetylparaaminophenoldiethyl aminoacetic ester) is a watersoluble prodrug of acetaminophen that can be administered intravenously over 15 min. It is rapidly hydroxylated into acetaminophen (1 g propacetamol = 0.5 g acetaminophen) (Granry et al. 1997, Anderson et al. 2005). An alternative intravenous acetaminophen formulation is now available that does not require hydrolysis and is associated with less pain on injection.

Toxicity

The toxic metabolite of acetaminophen, N-acetyl-p-benzoquinone imine (NAPQI) is formed by the cytochrome P450s CYP2E1, 1A2 and 3A4 (Slattery et al. 1996). This metabolite binds to intracellular hepatic macromolecules to produce cell necrosis and damage. Infants less than 90 days old have decreased expression of CYP2E1 activity in vitro compared with older infants, children and adults (Johnsrud et al. 2003). CYP3A4 appears during the first week, whereas CYP1A2 is the last to appear (Kearns et al. 2003). Neonates can produce hepatotoxic metabolites (e.g. NAPQI), but the lower activity of cytochrome P450 in neonates and higher glutathione stores may explain the low incidence of acetaminophen-induced hepatotoxicity seen in neonates (Levy et al. 1975a, Roberts et al. 1984).

Non-steroidal anti-inflammatory drugs

Mechanism of action

The non-steroidal anti-inflammatory drugs (NSAIDs) are a heterogeneous group of compounds that share common antipyretic, analgesic and anti-inflammatory effects. NSAIDs act by reducing prostaglandin biosynthesis through inhibition of cyclo-oxygenase (COX) which exists as two major isoforms (COX-1 and COX-2) (Mitchell et al. 1993). The prostanoids produced by COX-1 isoenzyme protect the gastric mucosa, regulate renal blood flow and induce platelet aggregation. NSAID-induced gastrointestinal toxicity, for example, is generally believed to occur through blockade of COX-1 activity, whereas the anti-inflammatory
By inhibiting prostaglandin synthesis, namely PGE2 (Van Overmeire et al. 2000, 2001, Shaffer et al. 2002). Smyth et al. suggested a serum concentration of 0.4 mg/L 24 h after the last dose of indometacin in 35 infants (gestational age 25–34 weeks; postnatal age 1–77 days) was associated with PDA closure (Smyth et al. 2004). Shaffer et al. (2002) examined factors affecting PDA closure after indometacin treatment in poor responders – neonates <1000 g and/or ≥10 days postnatal age. Closure appears dependent on a critical pre-dose serum concentration of 1.9 mg/L in neonates <10 days of age and 1.4 mg/L in neonates ≥10 days of age. Dose and duration of treatment were increased in the older group, which was assumed to be due to increased clearance.

Pharmacokinetics
Pharmacokinetic age-related changes and covariate effects are poorly documented for many of the NSAIDs (Litalien and Jacqz-Aigrain 2001). There is a paucity of data in infants less than 6 months of age.

NSAIDs are rapidly absorbed in the gastrointestinal tract after oral administration in children. Time to maximal concentration is generally 1–2 h, but depends on formulation and concomitant food intake (Troconiz et al. 2000). The relative bioavailability of oral preparations approaches 1 compared to intravenous. The rate and extent of absorption after rectal administration of NSAIDs such as ibuprofen, diclofenac, flurbiprofen, indometacin and nimesulide are less than oral routes (van Hoogdalem et al. 1991b).

NSAID PK is usually described using a one-compartment, first-order elimination model. Clearance is reduced in neonates and increases with age. The linear per kilogram model has been used to describe ibuprofen clearance. Clearance increases from 2.06 ml/h/kg at 22–31 weeks PCA (Aranda et al. 1997), 9.49 ml/h/kg at 28 weeks PCA (Van Overmeire et al. 2001) to 140 ml/kg/min at 5 years (Scott et al. 1999a). Similar data are reported for indometacin (Olkkola et al. 1989, Wiest et al. 1991, Smyth et al. 2004).

The apparent volume of distribution (V/F) is small in adults (<0.2 L/kg, suggesting minimal tissue binding) but is larger in children, e.g. ketorolac V/F in children 4–8 years is twice that of adults (Olkkola and Maunukseka 1991, Forrest et al. 1997). Premature neonates (22–31 weeks gestational age) given intravenous ibuprofen had a V/F of 0.62 (SD 0.04) L/kg (Aranda et al. 1997). Van Overmeire et al. (2001) report a dramatic reduction in ibuprofen central volume (Vc/F) following closure of the PDA in premature neonates (0.244 vs. 0.171 L/kg). The NSAIDs, as a group, are weakly acidic, lipophilic and highly protein bound. Compared to adults the bound fraction is high.

PDA closure
Both indometacin and ibuprofen are used to expedite PDA closure in premature neonates by inhibiting prostaglandin synthesis, namely PGE2 (Van Overmeire et al. 2000, 2001, Shaffer et al. 2002).

Pharmacodynamics
The NSAIDs are commonly used in children for antipyresis and analgesia. The anti-inflammatory properties of the NSAIDs have, in addition, been used in such diverse disorders as juvenile idiopathic arthritis, renal and biliary colic, dysmenorrhoea, Kawasaki disease and cystic fibrosis (Konstan et al. 1991, 1995, Oermann et al. 1999, Scott et al. 1999a). The NSAIDs indometacin and ibuprofen are also used to treat delayed closure of patent ductus arteriosus (PDA) in premature infants (Van Overmeire et al. 2000).

Analgesia
There are no linked PK–PD studies investigating NSAID analgesia in neonates or infants. Pain relief attributable to NSAIDs has been compared to pain relief from other analgesics or analgesic modalities, e.g. caudal blockade (Ryhanen et al. 1994, Splinter et al. 1997), acetaminophen (Watson et al. 1989, Baer et al. 1992, Watcha et al. 1992, Van Esch et al. 1995, Bertin et al. 1996, Benzie et al. 1997, Johnsson et al. 1997, Goyal et al. 1998, Davies and Skjoldt 2000, Romsing et al. 2001, Tawalbeh et al. 2001, Figueiras Nadal et al. 2002, Pickering et al. 2002, Purssell 2002) and morphine (Munro et al. 1994, Vetter and Heiner 1994, Gunter et al. 1999, Morton and O’Brien 1999, Oztekin et al. 2002) in children. These data confirm that NSAIDs in children are effective analgesic drugs, improving the quality of analgesia, but they do not quantify the effect. It is not possible to develop an understanding of the dose–effect relationship from these data, nor is it possible to determine if equipotent doses are being compared. The effectiveness of these medications in neonates, infants and children is unknown. NSAID concentration–response relationships have been described for adults (Mandema and Stanski 1996, Suri et al. 1997). Mandema and Stanski (1996) studied patients (n = 522) given a single oral or intramuscular administration of placebo or a single intramuscular dose of 10, 30, 60 or 90 mg ketorolac for postoperative pain relief after orthopaedic surgery. Pain relief was found to be a function of drug concentration (Emax model), time (waxing and waning of placebo effect), and an individual random effect. The Emax, EC50 and Teq were 8.5 (with a possible maximum of 10), 0.37 mg/L and 24 minutes respectively.

PDA closure
Both indometacin and ibuprofen are used to expedite PDA closure in premature neonates
in children (e.g. etodolac, 93.9 vs. 95.5%) (Boni et al. 1999b) and premature neonates (e.g. ibuprofen, 94.9 vs. 98.7%) (Aranda et al. 1997). The impact of this reduced protein binding is probably minimal with routine dosing because NSAIDs cleared by the liver have a low hepatic extraction ratio (Benet and Hoener 2002). In addition, they have a long equilibration time between plasma and effect compartments (Benet and Hoener 2002).

NSAIDs undergo extensive phase 1 and phase 2 enzyme biotransformation in the liver, with subsequent excretion into urine or bile. The impact of enterohepatic circulation in neonates is unknown. Hepatic NSAID elimination is dependent on the free fraction of NSAID within the plasma and the intrinsic enzyme activities of the liver. Renal elimination is not an important elimination pathway for the commonly used NSAIDs. Pharmacokinetic parameter estimate variability is large, partly attributable to covariate effects of age, size and pharmacogenomics. Ibuprofen, for example, is metabolized by the CYP2C9 and CYP2C8 subfamilies (Gal et al. 1990, Touw 1997). It is known that considerable variation exists in the expression of CYP2C activities among individuals, and functional polymorphism of the gene coding for CYP2C9 has been described (Hamman et al. 1997). CYP2C9 activity is low immediately after birth, subsequently increasing progressively to peak activity at a young age, when expressed as mg/kg/h (Tanaka 1998).

NSAID elimination is all too frequently described only in terms of half-life, which is therefore confounded by volume of distribution. The plasma half-lives of NSAIDs in adults range from 0.25 to >70 h, indicating wide differences in clearance. Elimination half-lives are longer in neonates than children. An elimination half-life of 30.5 (SD 4.2) h was reported in premature infants receiving ibuprofen within the first 12 hours of life (Aranda et al. 1997), in contrast with 1.6 (SD 0.7) h in infants and children aged 3 months to 10 years (Kelley et al. 1992). Clearance increases from birth, but reported estimates are confounded by age and weight (Wiest et al. 1991). There are no longitudinal studies describing postnatal maturation from different gestational ages. Clearance (L/h/kg) is generally increased in childhood compared to adult values both for the established NSAIDs (Korpela and Olkkola 1990, Bertin et al. 1991, Olkkola and Maunukela 1991, Brown et al. 1992, Ugazio et al. 1993, Gonzalez-Martin et al. 1997, Kauffman et al. 1999) and for the newer COX-2 inhibitors (Stempak et al. 2002), as we might expect when the per kilogram model is used.

Many NSAIDs exhibit stereoselectivity. Ketorolac, for example, is supplied and administered as a racemic mixture that contains a 1:1 ratio of the R(+) and S(−) stereoisomers. Pharmacologic activity resides almost exclusively with the S(−) stereoisomer. Clearance of the S(−) enantiomer was four times that of the R(+) enantiomer (6.2 vs. 1.4 ml/min/kg) in children 3–18 years (Kauffman et al. 1999) and the apparent volume of distribution of the S(−) enantiomer was greater than that of the R(+) form (0.82 vs. 0.50 L/kg). Because of the greater clearance and shorter half-life of S(−)-ketorolac, pharmacokinetic predictions based on racemic assays may overestimate the duration of pharmacologic effect. Selective glucuronidation of the S(−) enantiomer suggests that stereoselective metabolism may also be a contributing factor (Kauffman et al. 1999). Ibuprofen stereoselectivity is also reported in premature neonates (<28 weeks gestation). R- and S-ibuprofen half-lives were about 10 h and 25.5 h, respectively. The mean clearance of R-ibuprofen (CLR = 12.7 ml/h) was about 2.5-fold higher than for S-ibuprofen (CLS = 5.0 ml/h) (Gregoire et al. 2004).

There is relatively little transfer from maternal to fetal blood. Excretion of NSAIDs into breast milk of lactating mothers is low. Infant exposure to ketorolac via breast milk is estimated to be 0.4% of the maternal exposure (Brocks and Jamali 1992).

**Drug interactions**

NSAIDs undergo drug interactions through altered clearance and competition for active renal tubular secretion with other organic acids. High protein binding among the NSAIDs has been used to explain drug interactions with oral anticoagulant agents, oral hypoglycaemics, sulfonamides, bilirubin and other protein-bound drugs. An influential paper by Aggeler et al. (1967) showed that warfarin administered with phenylbutazone increased plasma warfarin concentrations and prothrombin time in normal volunteers. Phenylbutazone displaces warfarin from its albumin-binding sites in vitro but this observation should not be extrapolated to explain changes in prothrombin time. The observed effect is due to changes in drug metabolic clearance and not from changes in protein binding (Benet and Hoener 2002).

Ibuprofen reduced the glomerular filtration rate by 20% in premature neonates, affecting aminoglycoside clearance, and this effect appears independent of gestational age (Allegaert et al. 2004, 2005b). No significant difference in the change in cerebral blood volume, change in cerebral blood flow, or tissue oxygenation index was found between administration of ibuprofen or placebo in neonates (Naulaers et al. 2005).

**Safety issues**

The most common adverse events in NSAID recipients are nausea, dizziness and headache. NSAIDs have
potential to cause gastrointestinal irritation, blood clotting disorders, renal impairment, neutrophil dysfunction and bronchoconstriction (Kam and See 2000, Simon et al. 2002) – effects postulated to be related to COX-1/COX-2 ratios, although this concept may be an oversimplification (Lipsky et al. 2000, Brater et al. 2001, McCrory and Lindahl 2002).


**Gastrointestinal effects** Adverse gastrointestinal (GI) effects are significant in adults, particularly in those with peptic ulcer disease, *H. pylori* or advanced age (Bombardier et al. 2000, Feldman and McMahon 2000, Silverstein et al. 2000). The risk of acute GI bleeding in children given short-term ibuprofen was estimated to be 7.2/100 000 (CI 2–18/100 000) (Lesko and Mitchell 1995, 1999) and was not different from those children given acetaminophen. The incidence of clinically significant gastropathy is comparable to adults in children given NSAIDs for juvenile idiopathic arthritis (JIA) (Dowd et al. 1995, Keenan et al. 1995), but gastro-duodenal injury may be very much higher (75%) depending on assessment criteria (e.g. abdominal pain, anaemia, endoscopy) (Mulberg et al. 1993). Similar data for neonates are not available.

**Bleeding propensity** The commonly used NSAIDs such as ketorolac, diclofenac, ibuprofen and ketoprofen have reversible antiplatelet effects, which are attributable to the inhibition of thromboxane synthesis. This side effect is of concern during the perioperative period (Souter et al. 1994, Rury et al. 1995). Bleeding time is usually slightly increased, but it remains within normal limits in children with normal coagulation systems (Bean-Lijewski and Hunt 1996, Niemi et al. 1997, 2000). Neonates given prophylactic idometacin to induce PDA closure did not have an increased frequency of intraventricular haemorrhage (Ment et al. 1994).

**Opioid analgesic drugs**

**Morphine** Morphine is obtained from the poppy, *Papaver somniferum*, and is the most commonly used opioid in neonates, infants and children. Morphine’s main analgesic effect is by µ-receptor activation (Matthes et al. 1996, Sora et al. 1997, Loh et al. 1998). Morphine (named after the Greek God of dreams, Morpheus) is soluble in water, but lipid solubility is poor compared with other opioids. Morphine’s low oil/water partition coefficient of 1.4 and its pKa of 8 (10–20% unionized drug at physiologic pH) contribute to delayed onset of peak action with slow penetration into the brain. Morphine is available as elixir, immediate-release tablets, slow-release tablets or granules and parenteral formulations, as the sulphate or hydrochloride salt.

**Pharmacodynamics** Target analgesic plasma concentrations are believed to be 10–20 ng/ml after major surgery in neonates and infants (Kart et al. 1997b, Lynn et al. 1998, Bouwmeester et al. 2001, 2004). The concentration required for sedation during mechanical ventilation may be higher. Mean morphine concentrations of 125 ng/ml were required to produce adequate sedation in 50% of neonates (Chay et al. 1992). The large pharmacokinetic and pharmacodynamic variability means that morphine is often titrated to effect using small incremental doses (0.02 mg/kg) in neonates and infants suffering post-operative pain (Anderson et al. 1999). The effect compartment equilibration half-time (*Teq*) for morphine is ~17 min in adults (Inturrisi and Colburn 1986) and can be predicted for younger age groups, based on allometric modelling (Table 9.1) (Anderson et al. 2002).

The principal metabolites of morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), have pharmacologic activity. M6G has greater analgesic potency than morphine (Osborne et al. 2000, Murthy et al. 2002) and also respiratory depressive effects (Osborne et al. 1992, Thompson et al. 1995). It has been suggested that M3G antagonizes morphine and M6G has antinociceptive and respiratory depressive effects (Smith et al. 1990, Gong et al. 1992) and contributes to the development of tolerance.

**Pharmacokinetics** Morphine is mainly metabolized by the hepatic enzyme uridine-5’-diphosphoglucuronosyl transferase-2B7 (UGT2B7) into M3G and M6G (Coffman et al. 1997, Faura et al. 1998). M6G/morphine ratios increase with age from 0.8 in neonates to 4.2 in children (Smith et al. 1990, Barrett et al. 1996). These ratio changes are attributed to the maturation of hepatic and renal clearance with age, but the clinical effect of these ratio changes is probably minimal in the neonate. Reduced morphine clearance and receptor numbers (opioid, GABA, acetylcholine) in the neonate are postulated to have greater impact on pain perception (Coyle and Campochiaro 1976).

Morphine sulphation is a minor metabolic pathway (Choonara et al. 1990, McRorie et al. 1992). Clearance
is perfusion limited with a high hepatic extraction ratio. Oral bioavailability is ~35% due to this first pass effect. The metabolites are cleared renally and partly by biliary excretion (McRorie et al. 1992). Some recirculation of morphine occurs due to gastrointestinal β-glucuronidase activity (Koren and Maurice 1989). Impaired renal function leads to M3G and M6G accumulation (Choonara et al. 1989).

Fetuses are capable of metabolizing morphine from 15 weeks’ gestation (Pacifici et al. 1982, 1989). Morphine clearance matures with postconceptual age (Kart et al. 1997a, Faura et al. 1998) reaching adult values at 6–12 months (Anderson et al. 1997, van Lingen et al. 2002). The increased clearance observed in children, when expressed per kilogram, is a size artifact and not attributable to this age group’s increased liver size (Table 9.1 and Figure 9.3). Morphine pharmacokinetic parameters show large inter-individual variability contributing to the range of morphine serum concentrations observed during constant infusion. Clinical circumstances, such as type of surgery and concurrent illness (McRorie et al. 1992, Pokela et al. 1993, Lynn et al. 1998) also influence morphine pharmacokinetics. Protein binding of morphine is low (from 20% in premature neonates (Bhat et al. 1992, McRorie et al. 1992) to 35% in adults) (Olsen 1975) but has minimal impact on disposition changes with age.

### Table 9.1 Morphine clearance changes with age

<table>
<thead>
<tr>
<th>Age</th>
<th>Vd (L/70 kg)</th>
<th>CL (L/h/kg)</th>
<th>CL std (L/h/70 kg)</th>
<th>Teq (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24–27 weeks</td>
<td>0.136</td>
<td>3.378 (47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28–31 weeks</td>
<td>0.193</td>
<td>5.07 (49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Term neonate</td>
<td>84</td>
<td>0.44</td>
<td>14.5</td>
<td>8</td>
</tr>
<tr>
<td>3 months</td>
<td>131</td>
<td>1.14</td>
<td>43.1</td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>136</td>
<td>1.43</td>
<td>57.3</td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>136</td>
<td>1.57</td>
<td>67.8</td>
<td>10</td>
</tr>
<tr>
<td>3 year</td>
<td>136</td>
<td>1.51</td>
<td>71.1</td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td>136</td>
<td>1.01</td>
<td>71.1</td>
<td>17</td>
</tr>
</tbody>
</table>

Note: The increased clearance (L/h/kg) observed during infancy is a size artifact. Clearance reaches adult levels (equivalent to hepatic blood flow) using an allometric size model (L/h/70 kg) by the end of infancy. Data from Bouwmeester et al. (2003). Premature neonatal data from Scott et al. (1999b). Predictions using the allometric model are similar to those observed by Lynn et al. (1998) and McRorie et al. (1992). The effect compartment equilibration half-time (Teq) adult data are from Inturrisi and Colburn (1986) and the predictions based on allometric modelling (Anderson and Meakin 2002). Vd = volume of distribution at steady state.

### Side effects and tolerance
Respiratory depression may occur at concentrations of 20 ng/ml and is similar in children aged from 2 to 570 days at the same morphine concentration (Lynn et al. 1993). Intrathecal dosing causes similar respiratory depression at similar cerebrospinal fluid (CSF) concentrations in children 4 months to 15 years (Nichols et al. 1993). Hypotension, bradycardia and flushing reflect morphine’s histamine-releasing property and are associated with rapid intravenous bolus administration (Anand et al. 2000). The incidence of vomiting in postoperative children is related to morphine dose. Doses above 0.1 mg/kg were associated with a greater than 50% incidence of vomiting (Weinstein et al. 1994, Anderson et al. 2000b).

Withdrawal symptoms are observed in neonates after cessation of continuous morphine infusion for greater than 2 weeks and possibly shorter periods if doses >40 μg/kg/h are administered. Prevention strategies include the use of neuraxial analgesia,
Fentanyl offers greater haemodynamic stability than morphine (Hickey et al. 1985, Yaster et al. 1987), rapid onset (Teq = 6.6 min) and short duration of effect. Its relative increased lipid solubility and small molecular conformation enables efficient penetration of the BBB and redistribution.

**Pharmacodynamics** Fentanyl is a potent μ-receptor agonist with a potency 70–125 times that of morphine. A plasma concentration of 15–30 ng/ml is required to provide total intravenous anaesthesia in adults, while the IC\textsubscript{50}, based on EEG evidence, is 10 ng/ml (Wynands et al. 1983, Scott and Stanski 1987). The intra-operative use of fentanyl 3 μg/kg in infants did not result in respiratory depression or hypoxaemia in a placebo controlled trial (Barrier et al. 1989). Only three out of 2000 non-intubated infants and children experienced short apnoeic episodes after fentanyl 2–3 μg/kg for the repair of facial lacerations (Billmire et al. 1997, Tanaka 1998).

Fentanyl has similar respiratory depression in infants and adults when the plasma concentrations are similar (Hertzka et al. 1989).

**Pharmacokinetics** Fentanyl is metabolized by oxidative N-dealkylation (CYP3A4) into nor-fentanyl and hydroxylized (Tateishi et al. 1996, Labroo et al. 1997). All metabolites are inactive and a small amount of fentanyl is renally eliminated unmetabolized (Jacqz-Aigrain and Burtin 1996). Fentanyl clearance is 70–80% of adult values in term neonates and, standardized to a 70-kg person, reaches adult values (approx. 50 L/h/70 kg) within the first 2 weeks of life (Koehntop et al. 1986, Gauntlett et al. 1988, Anderson et al. 1997). The increased clearance observed in infancy, when expressed per kilogram, is most likely an artifact of the linear per kg model rather than a postulated increase in hepatic blood flow in this age group. Volume of distribution at steady state (Vss) for fentanyl is ~5.9 L/kg in term neonates and decreases with age to 4.5 L/kg during infancy, 3.1 L/kg during childhood, and 1.6 L/kg in adults (Johnson et al. 1984). Fentanyl clearance may be impaired with decreased hepatic blood flow, e.g. from increased intra-abdominal pressure in neonatal omphalocele repair (Gauntlett et al. 1988).

Fentanyl is widely distributed with short duration of effect due to redistribution to deep, lipid-rich compartments. Fentanyl redistributes slowly from lipid-rich tissues after discontinuation of therapy, resulting in prolonged periods of sedation and respiratory depression (Koehntop et al. 1986). The context-sensitive half-time after 1 h infusion is ~20 min but, after 8 h is 270 min (Hughes et al. 1992).

**Side effects** Tolerance to synthetic opioids develops more rapidly (3–5 days) compared to morphine (2 weeks) and heroin (>2 weeks) (Arnold et al. 1991, Franck et al. 1998, Chana and Anand 2001). Fentanyl also has a propensity for muscular rigidity (Taddio 2002). Other drugs metabolized by CYP3A4 (e.g. cyclosporin, erythromycin) may compete for clearance and increase fentanyl plasma concentrations (Touw 1997, Tanaka 1998).

The respiratory depression caused by fentanyl (hours) may outlast its analgesic effect (35–45 min) due to the prolonged context-sensitive half-life and/or recirculation of fentanyl bound to the stomach’s acid medium (up to 20% of an IV dose) or delayed release from peripheral compartments (Stoeckel et al. 1979, Bjorkman et al. 1990).

**Non-opioid analgesics**

**Tramadol**

Tramadol is a moderately potent analgesic (Bamigbade and Langford 1998, Turturro et al. 1998). It is an analogue of codeine and its analgesic effect is mediated through norepinephrine re-uptake inhibition, both increased release and decreased re-uptake of serotonin in the spinal cord and a weak μ-opioid receptor effect (Poulsen et al. 1996, Bamigbade and Langford 1998, De Witte et al. 2001, Stamper and Stuber 2001).

**Pharmacodynamics** Tramadol’s affinity for opioid receptors is ~6000 times weaker than morphine, but the active o-demethyltramadol (+)-M1 metabolite has an affinity ~200 times greater than tramadol (Poulsen et al. 1996), thus mediating tramadol-attributed opioid effects. Both the μ-receptor effect and reduced serotonin uptake in descending spinal cord pathways may contribute to its emetic effect. A serum tramadol concentration above 100 ng/ml is associated with satisfactory postoperative analgesia after dental surgery (Payne et al. 2002). A higher target tramadol concentration of 300 μg/L has been suggested in adult patients given fentanyl 5 μg/kg intra-operatively or 600 (590) μg/L in adults not given other supplementary analgesics (Grond and Sablotzki 2004).

**Pharmacokinetics** The (+)-M1 is formed via the genetically polymorphic CYP2D6 iso-enzyme system responsible for codeine metabolism (Poulsen et al. 1996) and individuals may be classified as extensive or poor metabolizers of tramadol. Higher concentrations of the (+)-M1 metabolite and greater analgesic efficacy of tramadol are reported in extensive metabolizers with reduced nausea, vomiting and tiredness amongst
poor metabolizers (Poulsen et al. 1996). CYP2D6 activity has been observed in premature neonates as early as 25 weeks PCA (Allegaert et al. 2005a).

Tramadol clearance in neonates has been described using a two-compartment, zero-order input, first-order elimination linear model (Allegaert et al. 2005a). Clearance increased from 25 weeks postconception age (PCA) (5.52 L/h/70 kg) to reach 84% of the mature values (24 (CV 43.6%) L/h/70 kg) by 44 weeks PCA (standardized to a 70 kg person using allometric ‘1/4 power’ models). The mature value is similar to that described by others in older children and adults (Murthy et al. 2000, Payne et al. 2002). Central volume of distribution decreased from 25 weeks PCA (256 L/70 kg) to reach 120% of its mature value by 87 weeks PCA. Formation clearance to M1 contributed to 43% of the tramadol clearance (Allegaert et al. 2005a).

Side effects

Tramadol’s adverse effect profile includes nausea, vomiting, constipation, dizziness, somnolence, fatigue, sweating and pruritus. Tramadol has a greatly reduced potential for sedation, respiratory depression (<0.5% in children and neonates) (Bosenberg and Ratcliffe 1998) and dependence compared to conventional opioids (Broome et al. 1999). Tramadol is associated with the high incidence of postoperative nausea and vomiting (PONV) in adults and children (up to 50%) limiting its usefulness (Pang et al. 1999, 2000, van den Berg et al. 1999, Torres et al. 2001). PONV is generally managed with the anti-emetic, ondansetron. Ondansetron is a serotonin antagonist (anti 5-HT3) and the CYP2D6 iso-enzyme is also involved in the metabolism of ondansetron. Thus, concurrent use results in a mutual reduction of effect – tramadol less potent as an analgesic and ondansetron less effective as an anti-emetic. Tramadol does not cause histamine release, but its use has been associated with seizures (Tobias 1997, Gibson 1996).

Ketamine

The analgesic properties of ketamine are mediated by multiple mechanisms at central and peripheral sites. The contribution from N-methyl-D-aspartate (NMDA) receptor antagonism and interactions with cholinergic, adrenergic, serotonergic, opioid pathways and local anaesthetic effects remain to be fully elucidated.

Pharmacodynamics Ketamine is available as a mixture of two enantiomers – the S(+) enantiomer has four times the potency of the R(−)-enantiomer (Geisslinger et al. 1993). S(+)ketamine has approximately twice the potency of the racemate. The metabolite norketamine has a potency one-third that of its parent (Leung and Baillie 1986). Plasma concentrations associated with hypnosis and amnesia during surgery are 0.8–4 μg/ml; awakening usually occurs at concentrations lower than 0.5 μg/ml. Pain thresholds are elevated at 0.1 μg/ml (Grant et al. 1983).

Pharmacokinetics Ketamine has high lipid solubility with rapid distribution. Ketamine undergoes N-demethylation to form norketamine. Racemic ketamine elimination is complicated by R(−)-ketamine inhibiting the elimination of S(+)ketamine (Ihmsen et al. 2001). Clearance in children is similar to adult rates (80 L/h/70 kg, i.e. liver blood flow) within the first 6 months of life, when corrected for size using allometric models (Cook and Davis 1993, Anderson et al. 1997). Clearance in the neonate is reduced (26 L/h/70 kg) (Cook and Davis 1993, Hartvig et al. 1993). Vss decreases with age, from 3.46 L/kg at birth, to 3.03 L/kg in infancy, 1.18 L/kg at 4 years age, and 0.75 L/kg in adulthood (Cook and Davis 1993). There is a high hepatic extraction ratio and the relative bioavailability of nasal and rectal formulations were 50% and 30% respectively (Pedraz et al. 1989, Malinovsky et al. 1996).

Side effects Psycholergic emergence reactions can cause distress, but are not problematic under 5 years of age. These can be ameliorated by the benzodiazepines. An antisialagogue may be required to diminish copious secretions (Hollister and Burn 1974). Tolerance in children was described following the repeated use of ketamine (Byer and Gould 1981).

CONCLUSIONS

Neonates and infants are very different from adults. Their psychology, social structure, behaviour and disease spectrum are different. Growth and developmental aspects account for major pharmacokinetic differences between children and adults. Body size accounts for most of the pharmacokinetic differences between older children and adults. Additional differences in neonates and infants are largely attributable to developmental changes, which can be described by gestational age. Pharmacodynamic factors that may influence the clinical response to analgesics in early life remain poorly defined.
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