Pharmacokinetics and Pharmacodynamics in the Pediatric Population

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Introduction

Children still remain therapeutic orphans [1]. New regulations encouraging paediatric investigation of new drugs are rectifying this situation, but for many commonly used medicines the lack of well-conducted pharmacokinetic-pharmacodynamic (PK-PD) studies is replaced with extrapolation from adult or non-human data. While neonates, infants and children have different psychology, social structure, behaviour and disease spectrum from adults, they also share many similarities. Growth and developmental aspects account for major differences between neonates and infants and adults. However, once out of infancy, body size alone can account for many of the pharmacokinetic differences between children and adults. Pharmacodynamic factors that may influence response in early life remain poorly defined. Most PK and PD differences occur in the first few years of post-natal life with major changes occurring during the neonatal period that are mature by the end of infancy. Knowledge of paediatric PK-PD and of changes seen during growth and maturation is essential for dosing sedatives in children.

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PK Differences in the First Year of Life

Absorption

The rate at which most drugs are absorbed when given by the oral route is slower in neonates than in older children because gastric emptying is delayed and normal adult rates may not be reached until 6–8 months [2–5]. Slow gastric emptying and reduced clearance may dictate both reduced doses and reduced frequency of administration. This has been demonstrated for both cisapride [6] and acetaminophen [7]. Enteral administration through the rectum (e.g. thiopentone, methohexitone) takes approximately 8 min in children but is speedier for neonates undergoing cardiac catheter study or radiological sedation [8, 9].

The larger relative skin surface area, increased cutaneous perfusion and thinner stratum corneum in neonates [10] increase absorption and exposure of topically applied drugs (corticosteroids, local anaesthetic creams, antiseptics). Neonates have a tendency to form methaemoglobin because they have reduced levels of methaemoglobin reductase and foetal haemoglobin is more readily oxidised compared to adult haemoglobin. This, combined with increased absorption through the neonatal epidermis, resulted in reluctance to use lidocaine–prilocaine cream for repeated use in this age group [11, 12].

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Anaesthetic delivery to the alveoli is determined largely by alveolar ventilation and functional residual capacity (FRC). Neonates have increased alveolar ventilation. They also have a smaller FRC compared to adults because of increased chest wall compliance; this causes an increase in the speed of delivery. Pulmonary absorption is generally more rapid in infants and children than in adults [13]. The greater cardiac output and 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 effect the more rapid wash-in of inhalational anaesthetics in the younger age group [14]. Solubility determines 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 solubility in blood of halothane, isoflurane, enflurane and methoxyflurane are 18% less in neonates than in adults [15], attributable to altered serum albumin, globulin, cholesterol and triglyceride concentrations. The solubility of these same agents in the vessel-rich tissue group in neonates is approximately one half of that in adults [15]. The latter may be due to the greater water content and decreased protein and lipid concentration in neonatal tissues. Infants with their decreased solubility would be expected to have a shorter time to reach a predetermined F_E–F_I ratio because of a smaller volume of distribution. Age has little effect on the solubility of the less soluble agents, nitrous oxide and sevoflurane [16].

Induction of anaesthesia may be slowed by right-to-left shunting of blood in neonates suffering cyanotic congenital cardiac disease or intrapulmonary conditions. This slowing is greatest with the least soluble anaesthetics [17]. Left to right shunts usually have minimal impact on uptake because cardiac output is increased so that systemic tissue perfusion is maintained at normal levels. The flow of mixed venous blood returning to the right heart ready for anaesthetic uptake is normal. If cardiac output is not increased and peripheral perfusion is reduced, then there will be less anaesthetic uptake in the lung. Although alveolar anaesthetic partial pressure may be observed to rise rapidly, there is a slower rise in tissue partial pressure and anaesthetic effect is delayed.

Bioavailability

The oral bioavailability may be affected by interactions with food when feeding is frequent in the neonate (e.g. phenytoin [18]), use of adult formulations that are divided or altered for paediatric use (nizatidine [19]) and by lower cytochrome P450 enzyme activity in the intestine. The latter may cause an increased bioavailability of midazolam because CYP3A activity is reduced [20]. The use of adult vials for paediatric use may result in dose inaccuracy, causing a relative increase or decrease in assumed bioavailability [21].

The frequent passage of stools in the neonate may render suppository use ineffective. Variable absorption and bioavailability have resulted in respiratory arrest when repeat opioids are administered through the rectal route to children [22].

Distribution

Body Composition

Total body water and extracellular fluid (ECF) [23] are increased in neonates and reduction tends to follow post-natal age (PNA). Polar drugs such as the non-depolarising neuromuscular blocking drugs (NMBDs) and aminoglycosides distribute rapidly into the ECF, but enter cells more slowly. The initial dose of such drugs is consequently higher in the neonate compared to the infant, older child or adult.

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 infants start walking and protein mass increases (20% in a term neonate, 50% in an adult). These body-component changes affect volumes of distribution of drugs. Volume of distribution influences initial dose estimates. Fentanyl has an increased volume of distribution in neonates. The volume of distribution at steady-state is 5.9 (SD 1.5) L/kg in a neonate under 1 month of age compared

to 1.6 (SD 0.3) L/kg in an adult [24]. This may contribute to the reduced degree of respiratory depression seen after single doses as high as 10 μg/kg in older term neonates.

Reduction of propofol concentrations after induction is attributable to redistribution rather than rapid clearance. Neonates have low body fat and muscle content, and so less propofol is apportioned to these tissues. Delayed awakening occurs because CNS concentration remains higher than that observed in older children as a consequence of reduced redistribution.

Plasma Proteins

Albumen and alpha-1 acid glycoprotein (AAG) concentrations are reduced in neonates but are similar to those in adults by 6 months, although between-patient variability is high (0.32–0.92 g/L) [25, 26]. AAG is an acute phase reactant that increases after surgical stress. This causes an increase in total plasma concentrations for low to intermediate extraction drugs such as bupivacaine [27]. The unbound concentration, however, will not change because clearance of the unbound drug is affected only by the intrinsic metabolising capacity of the liver. Any increase in unbound concentrations observed during long-term epidural is attributable to reduced clearance rather than AAG concentration [28].

Plasma albumin concentrations are lowest in premature infants, and other foetal proteins such as alpha-fetoprotein (synthesised by the embryonic yolk sac, foetal gastrointestinal tract and liver that has 40% homology with albumin) have reduced affinity for drugs. In addition, increased concentrations of free fatty acids and unconjugated bilirubin compete with acidic drugs for albumin binding sites. Neonates also have a tendency to manifest a metabolic acidosis that alters ionisation and binding properties of plasma proteins. Serum albumin concentrations approximate adult values by 5 months of age and binding capacity approaches adult values by 1 year of age. The induction dose of thiopentone is lower in neonates than older children. It is possible that this is related to decreased binding of thiopentone to plasma albumin; 13% of the drug is unbound in newborns compared to 7% in adults [29].

Regional Blood Flows

The initial phase of distribution after intravenous administration reflects regional blood flow. Consequently, the brain, heart and liver are the tissues first exposed to the drug. The drug is then redistributed to other relatively well-perfused tissues, such as skeletal muscle. There is a much slower tertiary distribution to relatively underperfused tissues of the body that is noted with long-term drug infusions.

Apart from the neonatal circulatory changes that occur at birth (e.g. secondary to functional closure of the ductus venosus and ductus arteriosus), there are differences in relative organ mass and regional blood flow change with growth and development during the first few months of life. Blood flow, relative to cardiac output, to the kidney and brain increases, while that to the liver decreases through the neonatal period [30]. Cerebral and hepatic mass as a proportion of body weight are much higher in the infant than in the adult [31].

Mean cerebral blood flow is highest in early childhood (70 mL/min/100 g) at about 3–8 years of age [32]. It is reduced before this age in neonates and later in adults, where flows are similar (50 mL/min/100 g) [33]. The highly lipophilic induction agents diffuse rapidly across the blood-brain barrier (BBB) to achieve concentration equilibrium with brain tissue. Reduced cardiac output in neonates and reduced cerebral perfusion means that onset time after intravenous induction is slower in neonates that in early childhood. Offset time is also delayed because redistribution to the well-perfused and deep, underperfused tissues is less.

Blood–Brain Barrier (BBB)

The BBB is an elaborate network of complex tight junctions between specialised endothelial cells that restricts the paracellular diffusion of hydrophilic molecules from the blood to the brain substance. Confusion over the importance of this barrier in the neonate exists, partly because of early studies comparing respiratory depression caused by the opioids, morphine and pethidine. Greater respiratory depression was evident in neonates after morphine given as an adult equipotent

dose of pethidine [34]. This finding is consistent with pethidine, unlike morphine, being lipid soluble and, therefore, crossing the immature or mature BBB equally [34]. However, plasma opioid concentrations were not measured in that study, and the increased neonatal respiratory depression observed after morphine could be due to reduced volume of distribution of morphine in term neonates 1–4 days (1.3 L/kg) compared to those at 8–60 days (1.8 L/kg) 61–180 days (2.4 L/kg) and adults (2.8 L/kg) [35]. Consequently, we might expect initial concentrations of morphine to be higher in neonates than in adults and consequent respiratory depression greater. Respiratory depression, as measured by carbon dioxide response curves or by arterial oxygen tension, is similar in children from 2 to 570 days of age at the same morphine concentration [36].

The BBB may have an impact in other ways. There are specific transport systems selectively expressed in the barrier endothelial cell membranes that mediate the transport of nutrients into the CNS and of toxic metabolites out of the CNS. Small molecules access foetal and neonatal brains more readily than they do adult brains [37]. BBB function improves gradually throughout foetal brain development, possibly reaching maturity at term [37]. Kernicterus, for example, is more common in the premature neonate than the term neonate. Pathological conditions within the CNS can cause BBB breakdown or alterations in transport systems play an important role in the pathogenesis of many CNS diseases. Proinflammatory substances and specific disease-associated proteins often mediate BBB dysfunction [38].

Fentanyl is actively transported across the BBB by a saturable ATP-dependent process, while ATP-binding cassette proteins such as P-glycoprotein actively pump out opioids such as fentanyl and morphine [39]. P-glycoprotein modulation significantly influences opioid brain distribution and onset time, magnitude and duration of analgesic response [40]. Modulation may occur during disease processes, increased temperature, or other substances (e.g. verapamil, magnesium) [39]. Genetic polymorphisms affecting P-glycoprotein-related genes may explain some individual differences in CNS-active drug sensitivity [41].

Drug Metabolism

The main routes through which drugs and their metabolites leave the body are the hepatobiliary system, the kidneys and the lungs. The liver is the primary organ for clearance of most drugs, although the lungs have a major role for anaesthetic vapours. Non-polar, lipid-soluble drugs are converted to more polar and water soluble compounds. Water soluble drugs and metabolites rendered water soluble by the liver are excreted by the kidneys. Both hepatic and renal systems are immature in the neonate and mature within the first year of life. The impact of birth as an accelerator or temporal switch in the maturation of these processes remains uncertain. Maturation of these processes is commonly measured against post-menstrual age (PMA), although PNA may also have impact [42, 43] on maturation and longitudinal PK studies are required to distinguish the separate influences of these two age types.

Descriptors for Metabolism Maturation

Three descriptors (size, maturation and organ function [OF]) have been used to describe changes in clearance with age [44, 45]. Size is commonly standardised using body surface area (BSA), although 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. This is different to the BSA exponent of 2/3. Fractal geometry is used to mathematically explain this phenomenon [46]. A great many physiological, structural and time-related variables scale predictably within and between species with weight (W) exponents (PWR) of 3/4, 1 and 1/4 respectively [45].

These exponents have applicability to pharmacokinetic parameters such as clearance (CL), volume (V) and half-time [45]. The factor for size (F_{size}) for total drug clearance may be expected to scale weight with an exponent of 3/4:

$$F_{size} = \left(\frac{W}{70}\right)^{3/4}.$$

Remifentanil clearance in children 1 month to 9 years is similar to adult rates when scaled using an allometric exponent of 3/4 [47]. Remifentanil

is hydrolysed by non-specific tissue and plasma esterases that do not appear to be influenced by age after scaling for size.

The effect of size on the dose of remifentanil tolerated during spontaneous ventilation under anaesthesia has been investigated in children undergoing strabismus surgery ($n=45$, age 6 months to 9 years). The propofol infusion was titrated using state entropy as a pharmacodynamic end point and remifentanil infused, using a modified up-and-down method, with respiratory rate depression as a pharmacodynamic end point. A respiratory rate of just greater than 10, stable for 10 min, determined the final remifentanil infusion rate [48]. This influence of age on the remifentanil infusion requirement is shown in Fig. 9.1. Superimposed on this figure are clearance estimates for age, determined by size using an allometric model with a standardised clearance of 2,790 mL/min for a 70 kg person. Clearance mirrors infusion rate in children over the age of 1 year. There is a divergence between clearance estimate and infusion rate in those children in infancy. The higher infusion rates recorded in those infants can be attributed to greater suppression of respiratory drive in this age group than the older children during the study; a respiratory rate of 10 breaths/min in an infant is disproportionately slow compared to the same rate in a 7-year-old child, suggesting excessive dose.

For most drugs, however, allometry alone is insufficient to predict clearance in neonates and infants from adult estimates. The addition of a model describing maturation with age is required. The sigmoid hyperbolic function (also known as the Hill equation) [49] has also been found useful for describing this maturation process (MF).

$$\mathrm{MF} = \frac{\mathrm{PMA}^{\mathrm{Hill}}}{\mathrm{TM}_{50}^{\mathrm{Hill}} + \mathrm{PMA}^{\mathrm{Hill}}}.$$

The TM_{50} describes the maturation half-time, while the Hill coefficient relates to the slope of this maturation profile. The maturation profile for dexmedetomidine expressed using allometric scaling, and this maturation model is shown in Fig. 9.2.

OF remains the other major covariate influence on clearance. While renal pathology may be reflected by assessment such as creatinine clearance, distinguishing this from normal physiology in infants may be difficult unless ordinary renal maturation is understood [44]. Although specific organ dysfunction of the kidney or liver are well

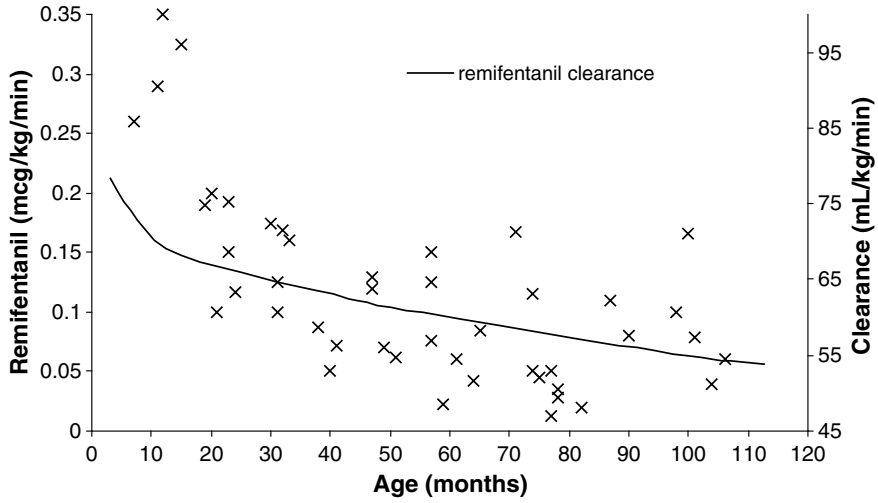

Fig. 9.1 The effect of age on the dose of remifentanil tolerated during spontaneous ventilation under anaesthesia in children undergoing strabismus surgery [48]. Superimposed on this plot is estimated remifentanil clearance determined using an allometric model [151]. There is a mismatch between clearance and infusion rate for those individuals still in infancy (from Anderson [150] with permission from Wiley-Blackwell)

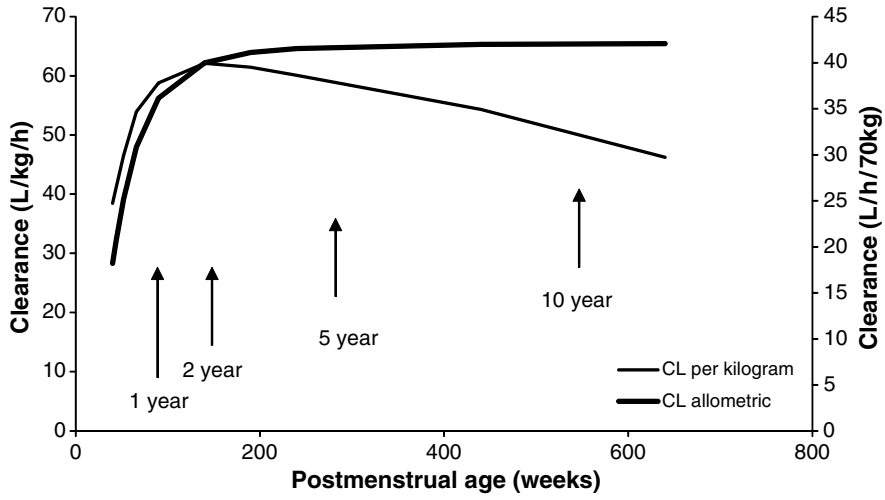

Fig. 9.2 Dexmedetomidine clearance changes with age, expressed both as per kilogram and using allometric scaling with a maturation model. The per kilogram model (L/h/kg) demonstrates an increased clearance in infants that explains the observed increased infusion (mg/min/kg) required for sedation in this age group. Use of the allometric model allows better understanding of the clearance maturation process. Data from Potts et al. [152]

recognised as having effect on clearance, other processes (sepsis, malnutrition, disease severity scores) can also be used as markers of reduced clearance.

Pharmacokinetic parameters (P) can be described in an individual as the product of size (F_{size}), maturation (MF) and OF influences where P_{std} is the value in a standard size adult without pathological changes in OF:

$$P = P_{std} \cdot F_{size} \cdot \text{MF} \cdot \text{OF}.$$

Hepatic Elimination

Phase 1

The mixed-function P450 oxidases are reduced in neonates [50, 51]. CYP2E1 activity surges after birth [52], CYP2D6 becomes detectable soon thereafter CYP3A4 and CYP2C family appear during the first week, whereas CYP1A2 is the last to appear [53]. Neonates are dependent on the immature CYP3A4 for levobupivacaine clearance and CYP1A2 for ropivacaine clearance, dictating reduced epidural infusion rates in this age group [54–56].

If a drug has a high extraction ratio then intrinsic clearance may be very much greater than liver blood flow and in these situations hepatic clearance is primarily determined by liver blood flow characteristics. Fentanyl clearance (CYP3A4) is 70–80% of adult values in term neonates and, standardised to a 70-kg person, reaches adult values within the first few weeks of life [28]. Omphalocele repair may be associated with raised intraabdominal pressure (an OF effect), resulting in reduced fentanyl clearance attributable to decreased hepatic blood flow.

Phase 2

Some phase II pathways are mature in term neonates at birth (sulphate conjugation), while others are not (acetylation, glycination, glucuronidation) [57]. Allometric body-size scaling complemented by maturation models [45, 58] have been used to unravel the developmental PK of morphine [59, 60] and paracetamol [61, 62]. Paracetamol and morphine are cleared by individual isoforms of glucuronosyl transferase (UGT1A6 and UGT2B7), as is bilirubin (UGT1A1). Clearance of both drugs is immature in the premature 24 week PMA neonate and mature to reach adult rates by the first year of life. Dexmedetomidine is also cleared predominantly by the UGT system and has a similar maturation

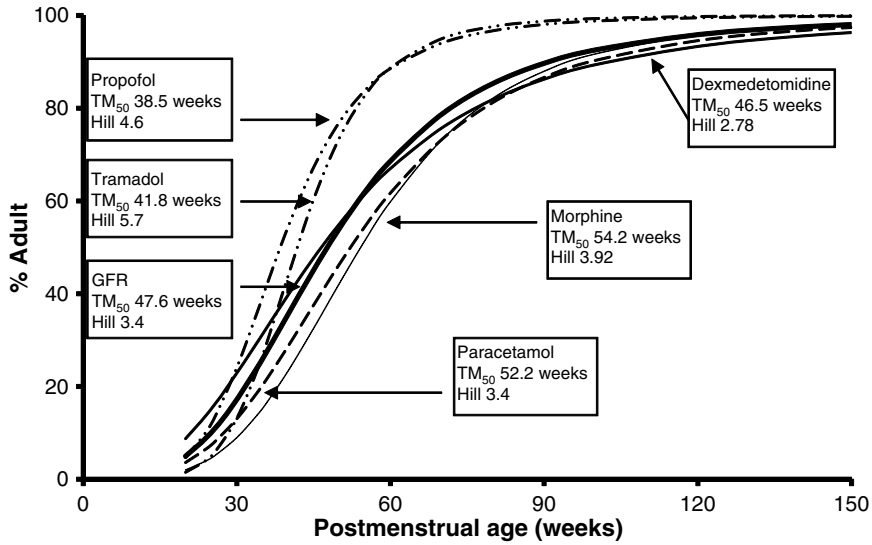

Fig. 9.3 Clearance maturation, expressed as a percentage of mature clearance, of drugs where glucuronide conjugation (paracetamol, morphine, dexmedetomidine) plays a major role. These profiles are closely aligned with Glomerular filtration rate (GFR). By contrast, cytochrome P450 isoenzymes also contribute to propofol metabolism and cause a faster maturation profile than expected from glucuronide conjugation alone. Tramadol clearance maturation (Phase I, CYP2D6, CYP3A) is also rapid. Maturation parameter estimates were taken from refs. [58, 60, 63, 69, 75, 153]

profile [63]. Glucuronidation is also the major metabolic pathway of propofol metabolism, although multiple cytochrome P450 isoenzymes, including CYP2B6, CYP2C9 or CYP2A6, contribute to its metabolism and cause a faster maturation profile (Fig. 9.3) than expected from glucuronide conjugation alone [43].

The impact of OF has been demonstrated on morphine clearance. Clearance is greater in infants undergoing non-cardiac surgery than in those undergoing cardiac surgery [64], or in those receiving extracorporeal membrane oxygenation [65] or positive pressure ventilation [60]. Similarly, clearance of propofol was reduced after cardiac surgery in children admitted to a paediatric intensive care [66]. A circadian night rhythm effect was noted in an investigation of infant propofol sedation after major craniofacial surgery [67].

Renal Elimination

Drugs and their metabolites are excreted by the kidneys by two processes – glomerular filtration and tubular secretion that mature at different rates [68]. Glomerular filtration rate (GFR) is only 10% that of mature value at 25 weeks, 35% at term and 90% of the adult GFR at 1 year of age [69]. Tubular secretion maturation lags behind that of GFR [68]. Aminoglycosides are almost exclusively cleared by renal elimination and maintenance dose is predicted by PMA because it predicts the time course of development of renal function [70]. The clearance of the old NMBD, d-tubocurare, can be directly correlated with GFR [71].

Immaturity of clearance pathways can be used to our advantage when managing apnoea after anaesthesia in the premature nursery graduate. N_7-methylation of theophylline in the newborn to produce caffeine is well developed, whereas oxidative demethylation (CYP1A2) responsible for caffeine metabolism is deficient and develops over the ensuing months. Theophylline is effective for the management of post-operative apnoea in the premature neonate, partly because it is a prodrug of caffeine, which is effective controlling apnoea. Caffeine can only be slowly cleared by the immature kidney.

Pulmonary Elimination

The factors determining anaesthetic absorption (alveolar ventilation, FRC, cardiac output, tissue/

blood solubility) also contribute to elimination. We might anticipate more rapid wash-out in neonates than adults for any given duration of anaesthesia because there is less distribution to fat and muscle content. The greater decrease in cardiac output induced by halothane in neonates might be expected to speed elimination, but brain perfusion will also be reduced and this slows recovery. Halothane, in particular, and to a far lesser extent isoflurane and sevoflurane undergo hepatic metabolism, but contribution is small compared to pulmonary elimination [72].

Metabolites

Many drugs have active metabolites that contribute to effect. Examples include norketamine from ketamine [73], 4′-hydroxydiclofenac from diclofenac [74], *O*-demethyl tramadol from tramadol [75], hydroxymidazolam from midazolam [76] and morphine 6-glucuronide (M6G) from morphine [59].

Contributions to both the desired effect (analgesia) and the undesired effects (nausea, respiratory depression) of M6G are the subject of clinical controversy [77]. M6G has been explored in adults using pupil size as a measure of central opioid effect, but results are confusing. Effect compartment modelling suggested that M6G was apparently 22 times less potent than morphine [78, 79]. Contrarily, other authors have suggested that M6G was 4 times more potent than morphine in producing meiosis [80], half as potent as an analgesic [81] and with reduced respiratory depressive effects [82]. The relative ratios of morphine to M6G vary in neonates and early infancy, depending on relative maturation of UGT2B7 (formation of M6G) and GFR (elimination of M6G). Term neonates less than 7 days old have a lower ratio of plasma morphine/M6G than those over 1 year despite similar doses [83]. The impact of this is uncertain.

Pharmacogenomics

Pharmacogenomics (PGs) is the investigation of variations of DNA and RNA characteristics as related to drug response that incorporates both PK and PD. There is large between individual PK variability that is contributed to by polymorphisms of the genes encoding for metabolic enzymes [84]. Genetic variability influencing plasma cholinesterase activity and its influence on succinylcholine is a well-known example. Another example is the CYP2D6 single nuclear polymorphism (SNP) that 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 metabolisers have reduced morphine production from codeine [85, 86]. Tramadol is also metabolised by *O*-demethylation in the liver (CYP2D6) to *O*-desmethyl tramadol (M1) and the M1 metabolite has a mu-opioid affinity approximately 200 times greater than tramadol.

A SNP may only be important if it contributes greater than 50% metabolism, has an active metabolite, a steep dose–response relationship and a narrow therapeutic index. These polymorphisms may have little impact during the neonatal period when metabolism is developmentally limited [6, 75, 87–89]. SNPs will certainly have impact in infants and children. Impact will be dependent on the rate of maturation of the specific enzyme system.

PG differences also have impact on PD. Candidate genes involved in pain perception, pain processing and pain management such as opioid receptors, transporters and other targets of pharmacotherapy are under investigation. Genetic differences (G118 allele) may explain why some patients need higher opioid doses and the adverse effects profile may be modified by these mutations [90]. Some genes (e.g. foetal haemoglobin) are expressed much more in early life than in adults, and gene switching may mean that a drug is effective at one age and not another.

In adults, gene testing may prove valuable for reducing adverse drug effects [91, 92]. However, most drug responses involve a large number of proteins regulated by multiple genes. Genotype does not equate with phenotype; environment, concomitant therapy and disease have impact, and allele prevalence varies among ethnic groups.

The situation in children is more complex. Allelic variants may remain unchanged throughout life but transcriptomonic, proteomic and metobonomic data in children are continuously changing throughout development.

PD Differences in the First Year of Life

Children's responses to drugs have much in common with the responses in adults [93]. The perception that drug effects differ in children arises because the drugs have not been adequately studied in paediatric populations who have size and maturation related effects as well as different diseases. Neonates and infant, however, often have altered pharmacodynamics.

The minimal alveolar concentration (MAC) for almost all anaesthetic vapours is less in neonates than in infancy, which is in turn greater than that observed in children and adults [14]. MAC of isoflurane in preterm neonates less than 32 weeks gestation was 1.28%, and MAC in neonates 32–37 weeks gestation was 1.41% [94]. This value rose to 1.87% by 6 months before decreasing again over childhood [94]. The cause of these differences is uncertain and may relate to maturation changes in cerebral blood flow, gamma-aminobutyric acid ($GABA_A$) receptor numbers or developmental shifts in the regulation of chloride transporters.

Neonates have an increased sensitivity to the effects of NMBDs [71]. The reason for this is unknown, but it is consistent with the observation that there is a threefold reduction in the release of acetylcholine from the infant rat phrenic nerve [95, 96]. The increased volume of distribution, however, means that a single NMBD dose is the same as that in the older child; reduced clearance prolongs duration.

Cardiac calcium stores in the endoplasmic reticulum are reduced in the neonatal heart because of immaturity. Exogenous calcium has greater impact on contractility in this age group than in older children or adults. There are some data to suggest greater sensitivity to warfarin in children, but the mechanism is not determined [97]. Amide local anaesthetic agents induce shorter block duration and require a larger weight scaled dose to achieve similar dermatomal levels when given by subarachnoid block to infants. This may be due, in part, to myelination, spacing of nodes of Ranvier, and length of nerve exposed as well as size factors. There is an age-dependent expression of intestinal motilin receptors and the modulation of gastric antral contractions in neonates. Prokinetic agents may not be useful in very preterm infants, partially useful in older preterm infants, and useful in full-term infants. Similarly, bronchodilators in infants are ineffective because of the paucity of bronchial smooth muscle that can cause bronchospasm.

Measurement of PD End Points

Outcome measures are more difficult to assess in neonates and infants than in children or adults. Measurement techniques, disease and pathology differences, inhomogeneous groups, recruitment issues, ethical considerations and end-point definition for establishing efficacy and safety confuse data interpretation [98].

Common effects measured include anaesthesia depth, pain and sedation and neuromuscular blockade. A common effect measure used to assess depth of anaesthesia is the electroencephalogram or a modification of detected EEG signals (spectral edge frequency, bispectral index, entropy). Physiological studies in adults and children indicate that EEG-derived anaesthesia depth monitors can provide an imprecise and drug-dependent measure of arousal. Although the outputs from these monitors do not closely represent any true physiological entity, they can be used as guides for anaesthesia and in so doing have improved outcomes in adults. In older children, the physiology, anatomy and clinical observations indicate that the performance of the monitors may be similar to that in adults. In infants, their use cannot be supported yet in theory or in practice [99, 100]. During anaesthesia, the EEG in infants is fundamentally different from the EEG in older children; there remains a need for specific neonate-derived algorithms if

EEG-derived anaesthesia depth monitors are to be used in neonates [101, 102].

The Children's Hospital of Wisconsin Sedation Scale [103] has been used to investigate ketamine in the emergency department [104]. However, despite the use of such scales in procedural pain or sedation studies, few behavioural scales have been adequately validated in this setting [105, 106]. Inter-observer variability can be high [107]. Most scores are validated for the acute, procedural setting and perform less for subacute or chronic pain or stress.

Population Modelling

Models describe systems in simple terms, although some models may be quite sophisticated. They are used to describe, predict and explain observations. Pharmacokinetic (PK) and pharmacodynamic (PD) models are used to improve paediatric anaesthetic and sedation management. They quantify the exposure–response relationship, often providing clarity and insight into complex systems as well as a mechanistic understanding of the drug effect. Dose selection can be rationalised. Models may enable extrapolation beyond observed data. Modelling is a knowledge management tool; it captures and integrates data from all studies. Models can also be used for hypothesis testing and can drive decision-making during drug development.

Population PK and PD modelling using nonlinear mixed effects models has had enormous impact in adult anaesthetic pharmacology. This methodology has particular applicability in children where the blood volume available for sampling is limited. Sparse data from multiple subjects can be used. Sampling times are not crucial for population methods and can be fitted around clinical procedures or outpatient appointments. Sampling time bands rather than exact times are equally effective and allow flexibility in neonates. Sampling cannulae for PK studies may become obstructed, parents may refuse repeat sampling and repeat venepuncture is frowned upon. Missing data, however, can still be used in a paediatric population analysis. Data from different studies can be pooled [108, 109].

The Target Concentration Approach

The goal of treatment is the target effect. A pharmacodynamic model is used to predict the target concentration given a target effect. Population estimates for the PD model parameters and covariate information are used to predict typical PD values in a specific patient. Population estimates of PK model parameters estimates and covariate information are then used to predict typical PK values in a typical patient. For example, a dexmedetomidine steady-state target concentration of 0.6 μg/L may be achieved with an infusion of 0.33 μg/kg/h in a neonate, 0.51 μg/kg/h in a 1-year-old and 0.47 μg/kg/h in an 8-year-old [63]. This target concentration strategy is a powerful tool for determining clinical dose [110]. Monitoring of serum drug concentrations and Bayesian forecasting may be used to improve dosing in individual patients.

This target effect approach is intrinsic to paediatric anaesthesiologists using target controlled infusion (TCI) systems. These devices target a specific plasma or effect site concentration in a typical individual, and this concentration is assumed to have a typical target effect. The target concentration is one that achieves target therapeutic effect (e.g. anaesthesia) without excessive adverse effects (e.g. hypotension). Effect monitoring (e.g. Bispectral index, BIS) can be used to refine the target effect.

Pharmacokinetic Models

Compartment models dominate the anaesthetic literature. Standard compartment models may be unable to accurately describe drug concentrations immediately after bolus administration of an anaesthetic induction agent because mixing in the central compartment is not instantaneous, making it difficult to model the fast blood-to-brain concentration equilibrium [111] and pulmonary uptake may also occur [112]. Recirculatory models help explain these early phase PK [113]. Such models have proved valuable determining anaesthetic induction doses [114] and NMBD pharmacodynamics [115]. Physiologically based pharmacokinetic (PBPK) modelling has been used to assist with first-time dosing in children. A general PBPK model for drug disposition in infants and children,

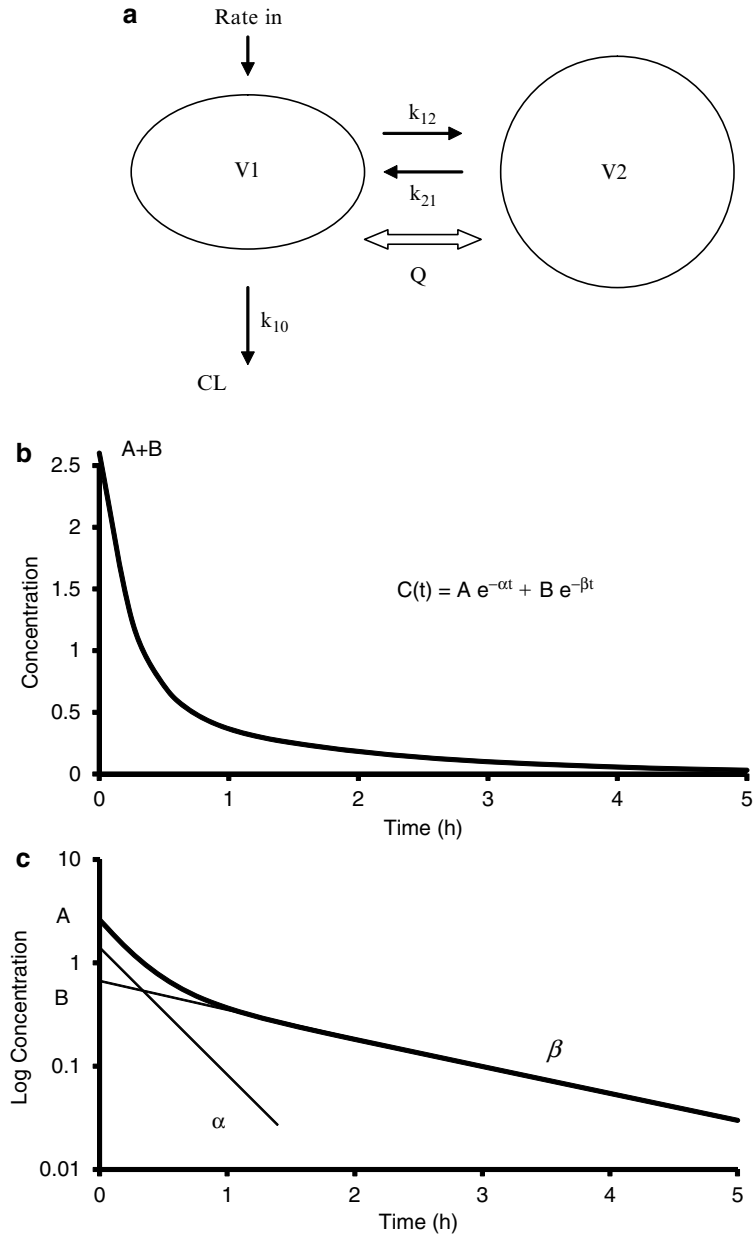

Fig. 9.4 (**a**) A mammillary two-compartment PK model. (**b**) Time–concentration profile for a two-compartment model. (**c**) Conversion of concentration to a log scale allows estimation of elimination constants and compartment volumes

covering the age range from birth to adulthood, has been successfully evaluated using theophylline and midazolam as model drugs [30].

A single compartment is often insufficient to characterise the time–concentration profile and further compartments are required (mammillary models). Drug is administered into a central compartment (V_1) and redistributes to peripheral compartments (V_2, V_3, etc., Fig. 9.4a). In a two compartment model transfer of drug between the central and peripheral compartment is relatively fast compared with the rate of elimination. A plot of the natural log of concentration after bolus reveals two distinct slopes (rate constants, *a* and *b*, Fig. 9.4b). Consequently, the time–concentration profile is commonly described using a polyexponential function.

$$C(t) = A \cdot e^{-\alpha \cdot t} + B \cdot e^{-\beta \cdot t}.$$

These polyexponential parameters have little connection with underlying physiology and an alternative parameterisation is the use of a central volume and three rate constants (k_{10}, k_{12}, k_{21}) that describe drug distribution between compartments. Another common method is to use two volumes (V_1, V_2) and two clearances (CL, Q). Q is the inter-compartment clearance.

Students are commonly taught to estimate compartment model PK parameters through interpretation of graphs representing time–concentration profiles. Conversion of concentration to a log scale allows estimation of elimination constants and compartment volumes (Fig. 9.4c). Integration of the function describing this profile yields an AUC (area under the curve), from which CL can be determined

$$CL = \frac{Dose}{AUC}.$$

Computers have enabled the use of non-linear regression to directly estimate parameters through iterative techniques using least squares curve fitting. Models with two or more compartments are now commonly solved using differential equations.

Parameter estimates (CL, Q, V_1, V_2) can be used to predict dose. A loading dose raises concentration in the plasma to target concentration promptly and may be desirable in anaesthesia when rapid effect is required. In a one-compartment model, the volume of distribution is the proportionality factor that relates total amount of drug in the body to plasma concentration (TC = target concentration)

$$\text{Loading dose} = V \cdot TC.$$

This calculation may not be applicable to many sedative drugs that are characterised using multi-compartment models. The use of V_1 results in a loading dose too high; too high a dose may cause transient toxicity.

An alternative technique is to use the target effect dose. The time to peak effect (T_{peak}) is dependent on clearance and effect site equilibration half-time ($T_{1/2keo}$). At a submaximal dose, T_{peak} is independent of dose. At supramaximal doses, maximal effect will occur earlier than T_{peak} and persist for longer duration. The T_{peak} concept has been used to calculate optimal initial bolus doses [116].

Clearance is the most important parameter when defining a rational steady-state dosage regimen. At steady state

$$\text{Dosing rate}_{ss} = \text{rate of elimination}_{ss} = CL \cdot TC.$$

When a drug is given intermittently

$$\text{Maintenance dose} = \text{dosing rate} \times \text{dosing interval}$$

When a drug is given by constant infusion

$$\text{Infusion rate}_{ss} = \text{dosing rate}_{ss}.$$

Once the target concentration of a drug is defined, the infusion rate is determined by CL at steady state. Many sedative drugs distribute to peripheral compartments, and steady state may not be achieved during the time of infusion. Dose adjustment is required to achieve constant effect until steady-state conditions are reached.

Propofol PK are usually described using a three-compartment mammillary model. In order to achieve steady state 3 μg/mL in children of 3–11 years, dosing changes are required, e.g. a loading dose of 2.5 mg/kg followed by an infusion rate of 15 mg/kg/h for the first 15 min, 13 mg/kg/h from 15 to 30 min, 11 mg/kg/h from 30 to 60 min, 10 mg/kg/h from 1 to 2 h and 9 mg/kg/h from 2 to 4 h. TCI pumps are capable of finer-tuning by making adjustments at 10 s intervals [117].

The PK of drug disposition confined to a one-compartment model is often expressed in terms of half-life. Half-life ($T_{1/2}$) is the time required to change the amount of drug in a body compartment by one half.

$$T_{1/2} = \ln(2) \cdot \frac{V}{CL}.$$

This half-life is related to the elimination rate constant (k), a parameter representing the slope of the exponential decay curve.

$$k = \frac{CL}{V}.$$

Elimination half-life is of no value in characterising disposition of intravenous anaesthetic drugs with multiple compartments during dosing periods relevant to anaesthesia. A more useful concept is that of the context-sensitive half-time

where "context" refers to infusion duration. This is the time required for the plasma drug concentration to decline by 50% after terminating infusion [118]. The context-sensitive half-time is the same as the elimination half-life for a one-compartment model and does not change with infusion duration.

Context-sensitive half-time may be independent of infusion duration (e.g. remifentanil 2.5 min); moderately affected (propofol 12 min at 1 h, 38 min at 8 h); or display marked prolongation (e.g. fentanyl 1 h at 24 min, 8 h at 280 min). This is due to return of drug to plasma from peripheral compartments after ceasing infusion. Peripheral compartment size differs in children from adults so that at termination of infusion more drug may remain in the body for any given plasma concentration than in adults. The context-sensitive half-time for children given propofol, for example, is longer [117]. The context-sensitive half-time gives an insight into the PK of a hypnotic drug, but the parameter may not be clinically relevant because the percentage decrease in concentration required for recovery is not necessarily 50%.

Pharmacodynamic Models

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 effect site and its target. Drugs may exert effect at non-specific membrane sites, by interference with transport mechanisms, by enzyme inhibition or induction or by activation or inhibition of receptors.

The Sigmoid E_{max} Model

The relation between drug concentration and effect may be described by the Hill equation (see maturation model above), well known to anaesthesiologists through the oxygen dissociation curve [49], according to the equation

$$\text{Effect} = \text{E}_0 + \frac{(\text{E}_{max} \cdot \text{Ce}^{\text{N}})}{(\text{EC}_{50}^{\text{N}} + \text{Ce}^{\text{N}})},$$

where E_0 is the baseline response, E_{max} is the maximum effect change, Ce 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. Efficacy is the maximum response on a dose or concentration–response curve. EC_{50} can be considered a measure of potency relative to another drug provided N and E_{max} for the two drugs are the same. A concentration–response relationship for acetaminophen has been described using this model. An EC_{50} of 9.8 mg/L, $N = 1$ and an E_{max} of 5.3 pain units (VAS 0–10) was reported [119]. Midazolam PD in adults have been similarly defined using EEG response [120, 121].

Quantal Effect Model

The potency of anaesthetic vapours may be expressed by MAC and this is the concentration at which 50% of subjects move in response to a standard surgical stimulus. MAC appears at first sight to be similar to EC_{50}, but is an expression of quantal response rather than magnitude of effect. There are two methods of estimating MAC. Responses can be recorded over the clinical dose range in a large number of subjects and logistic regression applied to estimate the relationship between dose and quantal effect; the MAC can then be interpolated. Large numbers of subjects may not be available, and so an alternative is often used. The "up-and-down" method described by Dixon [122, 123] estimates only the MAC rather than the entire sigmoid curve. It involves a study of only one concentration in each subject and, in a sequence of subjects, each receives a concentration depending upon the response of the previous subject; the concentration is either increased if the previous subject did not respond or decreased if they did. The MAC is usually calculated either as the mean concentration of equal numbers of responses and no-responses or is the mean concentration of pairs of "response–no response".

Logistic Regression Model

When the pharmacological effect is difficult to grade, then it may be useful to estimate the probability of achieving the effect as a function of plasma concentration. Effect measures such as

movement/no movement or rousable/non-rousable are dichotomous. Logistic regression is commonly used to analyse such data and the interpolated EC_{50} value refers to the probability of response. For example, an EC_{50} of 0.52 mg/L for arousal after ketamine sedation in children has been estimated using this technique [104].

Linking PK with PD

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 half-life of the drug may correlate closely with the half-life of drug effect. Observed effects may not be directly related to serum concentration. Many drugs have a short half-life but a long duration of effect. This may be attributable to induced physiological changes (e.g. aspirin and platelet function) or may be due to the shape of the E_{max} model. 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 a considerable effect. There may be a delay due to transfer of the drug to effect site (NMBD), a lag time (diuretics), physiological response (antipyresis), active metabolite (propacetamol) or synthesis of physiological substances (warfarin).

A plasma concentration–effect plot can form a hysteresis loop because of this delay in effect. Hull et al. [124] and Sheiner et al. [125] 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. It has a negligible volume and contains negligible blood. A single first-order parameter ($T_{1/2keo}$) describes the equilibration half-time. This mathematical trick assumes concentration in the central compartment is the same as that in the effect compartment at equilibration, but that a time delay exists before drug reaches the effect compartment. The concentration in the effect compartment is used to describe the concentration–effect relationship [126].

Adult $T_{1/2keo}$ values are well described, e.g. morphine 16 min, fentanyl 5 min, alfentanil 1 min, propofol 3 min. This $T_{1/2keo}$ parameter is commonly incorporated into TCI pumps to achieve a rapid effect site concentration. The adult midazolam $T_{1/2keo}$ of 5 min [127] may be prolonged in the elderly, resulting in overdose if this is not recognised during dose titration.

The $T_{1/2keo}$ for propofol in children has not been described. We might expect a shorter $T_{1/2keo}$ with decreasing age based on size models [128], and this is exactly what has been described by Jeleazcov et al. [129]. Similar results have been demonstrated for sevoflurane and BIS [130]. If unrecognised, this will result in excessive dose in a young child if the effect site is targeted and peak effect (T_{peak}) is anticipated to be later than it actually is because it was determined in a teenager or adult. Unfortunately, integrated PK-PD studies in children are lacking. Available paediatric propofol $T_{1/2keo}$ values have been determined by the application of published PK data to PD observations only [131, 132].

Adverse Effects

Neonates and young children may suffer permanent effects resulting from a stimulus applied at a sensitive point in development. For example, congenital hypothyroidism, if untreated causes lifelong phenotypic changes. The incidence of vaginal carcinoma is high in children of mothers treated with stilboesterol during pregnancy [133]. There are concerns that neonatal exposure to some anaesthetic agents (e.g. ketamine, midazolam) may cause widespread neuronal apoptosis and long-term memory deficits [134, 135].

Anaesthesia, analgesia or sedation, generally involves examination of immediate adverse effects such as PONV, hypotension or respiratory depression. A dose–response curve for intravenous morphine and vomiting was investigated in children having day-stay tonsillectomy. Doses above 0.1 mg/kg were associated with a greater than 50% incidence of vomiting [136]. These data are similar to those in children undergoing inguinal herniorrhaphy [137]; suggesting that

lower doses of morphine are associated with a decreased incidence of emesis after day stay surgery, and encourage the use of alternative analgesic drugs.

Drug Interactions

Drug interactions can increase or decrease response mediated through either PK or PD routes. Phenobarbitone induces glucuronide conjugation maturation in neonates. An increase in the $T_{1/2keo}$ of d-tubocurarine with increasing inspired halothane concentrations has been demonstrated [138]. Halothane is a negative inotrope [139] and reduces skeletal muscle blood flow [140], so it seems reasonable to interpret changes in $T_{1/2keo}$ as due to changes in blood flow. Inhalation anaesthetic agents can also prolong duration of block and this effect is agent specific. Sevoflurane potentiated vecuronium more than halothane; when compared to balanced anaesthesia, the dose requirements of vecuronium were reduced by approximately 60 and 40%, respectively [141].

Anaesthetic drug interactions traditionally have been characterised using isobolographic analysis or multiple logistic regression. Minto et al. [142] has proposed a model based on response-surface methodology. Computer simulations based on interactions at the effect site predicted that the maximally synergistic three-drug combination (midazolam, propofol and alfentanil) tripled the duration of effect compared with propofol alone. Response surfaces can describe anaesthetic interactions, even those between agonists, partial agonists, competitive antagonists and inverse agonists [142].

Synergism between propofol and alfentanyl has been demonstrated using response-surface methodology. Remifentanil alone had no appreciable effect on response to shaking and shouting or response to laryngoscopy while propofol could ablate both responses. Modest remifentanil concentrations dramatically reduced the concentrations of propofol required to ablate both responses [143]. When comparing the different combinations of midazolam, propofol and alfentanil, the responses varied markedly at each end point assessed and could not be predicted from the responses of the individual agents [144]. Similar response-surface methodology has been taken for investigation of the combined administration of sevoflurane and alfentanil [145] and remifentanil and propofol [146] on ventilation control. These combinations have a strikingly synergistic effect on respiration, resulting in severe respiratory depression in adults. These synergistic associations can be extended to paediatric sedation techniques. It is little wonder that the use of three or more sedating medications compared with 1 or 2 medications was strongly associated with adverse outcomes [147].

Defining Target Concentration

An effect site target concentration has been estimated for many drugs used in anaesthesia, analgesia and sedation. For example, a propofol target concentration of 3 mg/L in a typical patient can be achieved using pre-programmed TCI devices. A BIS monitor can then be used to manually adjust infusion rate to achieve a desired target effect in the specific individual. The luxury of such a feedback system is not available for most drugs.

A target concentration of 10 μg/L is used for morphine analgesia. Observations in children after cardiac surgery suggested that steady-state serum concentrations greater than 20 mg/L resulted in hypercarbia ($PaCO_2 > 55$ mmHg) and depressed CO_2 response curve slopes. During wash-out, morphine concentrations more than 15 μg/L resulted in hypercarbia in 46%, whereas concentrations less than 15 μg/L were associated with hypercarbia in 13% of children. No age-related differences in respiratory effect were seen in these studies at the same serum morphine concentration [36]. Observation or self-reporting pain scales are used as part of the feedback loop for dose incremental changes.

The target concentration may vary, depending on the desired target effect. The target concentration for ketamine analgesia (0.25 mg/L) is quite different from that of anaesthesia (2 mg/L) [148].

Conclusions

Children can be considered as small adults; size factors alone can explain many differences between children and adults. Neonates are developing children; maturation processes over the first few years of life have dramatic impact on both PK and PD. Size, age and OF models can be used to characterise PK changes in the paediatric population. Although PD differences between neonates and children are recognised, there is little information describing maturation of these PD differences. Achievement of a target effect with minimal adverse effect is the key to anaesthetic, analgesic and sedation drug use. Pharmacodynamic models are useful tools to identify a target effect and concentration at which that occurs. Pharmacokinetic models, in turn, point to dose that will achieve that target concentration. The population approach to modelling has proven beneficial to exploring PKPD differences in children. The impact of other drugs, active metabolites, stereoisomer interactions and PGs on the concentration–response relationship remains undefined for many drugs.

An understanding of PK and PD of drugs commonly used in children of all ages is vital for sensible sedation regimens. Simple infusion regimes for morphine, targeting a plasma concentration of 10 μg/L, that vary with age have been proposed [59]. Ketamine regimens that target an effect (e.g. arouses slowly to consciousness with sustained painful stimulus) are reported [149]. TCI pumps are dependent on an accurate knowledge of PK and PD parameters. Currently, this technique is unavailable for even propofol and remifentanil in infants under 2 years of age because such information is lacking. Once this information is available, it will be possible to programme these TCI pumps to deliver any adequately investigated drug to any specific target concentration in either plasma or effect site [150]. However, even with a good knowledge of PK and PD parameters estimates, there remains considerable between-patient variability of both PK and PD parameters. This variability can result is some patients not achieving the desired sedation level because they are “too light” or “too deep.” Concentration monitoring (e.g. propofol in expired breath) may reduce target concentration scatter attributable to PK parameter variability. Infusions can be increased or decreased to achieve the desired target. Unfortunately, the concentration–response curve is also associated with considerable variability, and target effect monitoring (e.g. modified EEG signalling) can be used to further modulate drug delivery for the individual. Modified EEG signalling and feedback loops that automatically regulate infusion rates to achieve desired effect are already available in adult practice and widely used for propofol. Children should not be denied similar levels of sophistication. This level of sophistication will only come once we have elucidated and understood paediatric PK and PD and the factors that contribute to their variability (e.g. age, size, PGs).

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