Chapter

2 Pharmacological Issues Affecting Anaesthesia in Neonates and Young Children*

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Introduction

Paediatric patients differ significantly from adults in the way that drugs affect them for several reasons:

- Size: There is a more than 100-fold difference in weight between a premature neonate and a healthy adult, but weight alone is an inadequate indicator of dosage because of changes in body composition.
- Physiology: Developmental changes, particularly during the first few months of life, profoundly affect both the pharmacokinetics and pharmacodynamics of anaesthetic drugs.
- Comorbidities: The range of conditions requiring anaesthesia in children is different. Whilst age- and lifestyle-related conditions may be rare or absent, congenital abnormalities may be more frequent. In addition, local/regional anaesthesia and/or sedation are less likely to be used.

This chapter provides a general overview of these considerations, followed by a more detailed discussion of individual drugs commonly used in paediatric anaesthetic practice.

Size and Paediatric Drug Dosing

Calculating the correct dose of a drug for a neonate or young child invariably involves scaling the dose according to the patient's size. Scaling for size (allometrics) has been based on weight, surface area and power models based on surface area, but no single model is appropriate for all drugs. Figure 2.1 illustrates some of the difficulties of using size models to predict paediatric doses. The variation in the dose of thiopental required to produce sleep in 50% of subjects (ED50) with age is biphasic, which cannot be modelled by a single mathematical function. Power models are not generally practical to use, and any method which entails a complex calculation is more likely to result in errors. Drug doses are much less predictable in infants aged less than one year owing to immaturity of organs and enzyme systems, and reduced doses are frequently required in this age group.

The first years of human life are characterised by rapid growth, differentiation and maturation. In the first six weeks, the birth weight will increase by 50% and double in the first three to four months. By approximately one year of age, the birth weight will have tripled. Over the same period, body length and body surface area increase by 50% and 100% respectively, whilst caloric expenditure increases fourfold. Predictably, these developmental changes lead to significant variation in how neonates, infants and children respond to medications, and age-appropriate adjustments in drug doses are necessary.

Physiology

Developmental changes, particularly during the first few months of life, profoundly affect both the pharmacokinetics and the pharmacodynamics of anaesthetic drugs.

Factors Affecting Pharmacokinetics

Absorption

Drugs administered by routes other than intravenous must overcome chemical, physical, mechanical and/or biological barriers to achieve their effect. The gastrointestinal tract, skin and pulmonary tree all undergo developmental changes which affect the absorption of drugs across their surfaces and thus their bioavailability. Oral absorption of drugs

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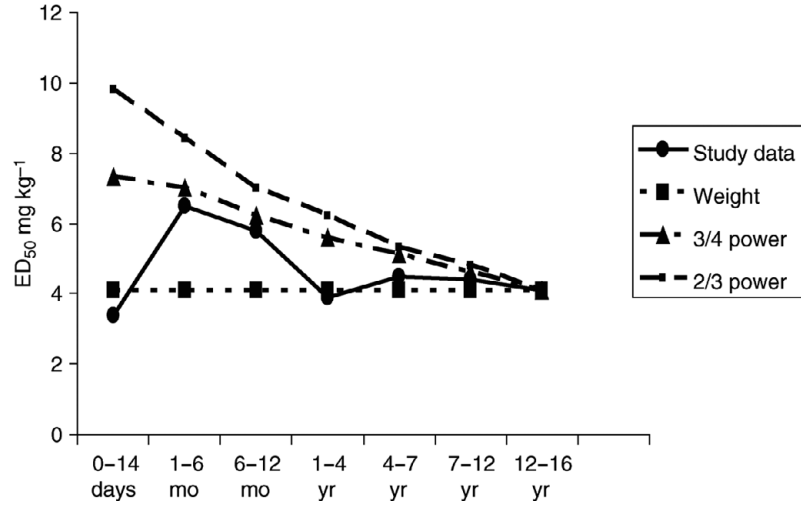

Figure 2.1 Biphasic variation in the ED50 sleep dose of thiopental with age presented as a solid line. The broken lines represent paediatric doses of thiopental predicted from the adult dose of 4 mg kg^{-1} using one of three size models (weight, 3/4 power and 2/3 power). The weight model predicts the lowest doses, the 2/3 power model the highest; the 3/4 power model predicts doses intermediate between the other two and provides the best fit to the data in children aged one to six months and older.
Source: Data taken from Jonmarker C, Westrin P, Larsson S et al. Thiopental requirements for induction of anesthesia in children. *Anesthesiology* 1987; 67:104–7; and Westrin P, Jonmarker C, Werner O. Thiopental requirements for induction of anesthesia in neonates and in infants one to six months of age. *Anesthesiology* 1989; 71:344–6.

is affected by changes in intraluminal pH, biliary function, gastric emptying time and intestinal motility. At birth, gastric pH is roughly neutral, and within 48 hours it decreases to approximately pH3 before returning to neutral over the subsequent 24 hours, where it remains for the following 10 days. It then decreases gradually to reach adult pH values by two years. Differences in intestinal motility at different stages of development influence the gut transit time, resulting in prolonged transit times in neonates compared to older children and adults but faster transit times in infants. The ability of neonates to absorb lipophilic drugs may be altered due to immature biliary function leading to a reduction in the solubility effect of bile.

Few studies have investigated the effects of developmental changes in absorptive function in children; however, the absorption of oral paracetamol has been shown to be significantly lower in the first few days of life. Greater absorption following cutaneous application of a drug in neonates is because of their proportionally higher body surface area and more permeable skin. Percutaneous absorption in preterm infants is inversely related to gestational age, with permeability rates 100−1,000 greater before 30 weeks of gestation compared to term neonates, and only three to four times increased permeability beyond 32 weeks. There is some evidence that the increased permeability in preterm infants is short-lived, lasting only two weeks postnatally even in the most immature infants. Topical use of the local anaesthetic cream EMLA (lidocaine/prilocaine) for pain relief may lead to methaemaglobinaemia in neonates due to higher systemic absorption and an increased susceptibility of fetal haemoglobin to prilocaine.

Distribution

Distribution of drugs to body compartments, tissues and cells is affected by:

- Body composition (e.g. total body water and fat percentage)
- Cardiac output and regional blood flow
- Protein binding
- Blood–brain barrier

Body composition: Total body water accounts for 85–90% of body weight in very immature and preterm infants and their total fat content is only 10–15%. This ratio declines gradually into adulthood, where total body water accounts for 55–60% of body weight. In neonates the extracellular water content is approximately 45% of body weight, whereas in adults it is only 20% (Figure 2.2).

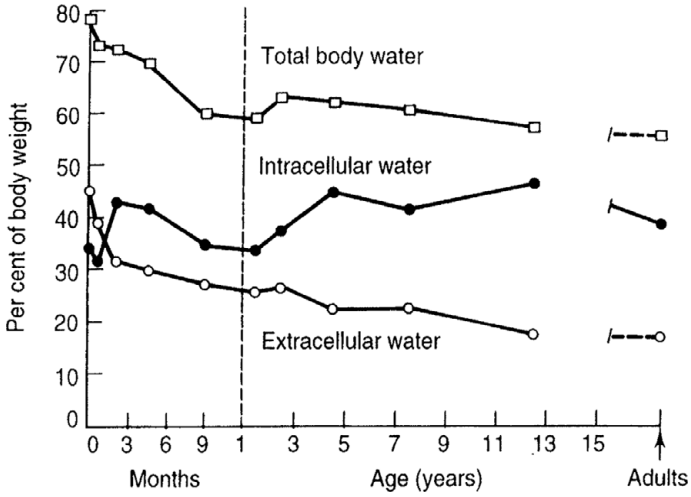

Figure 2.2 Variation in body water compartments with age.
Source: Adapted from Friis-Hansen B. Body water compartments in children: changes during growth and related changes in body composition. *Pediatrics* 1961; 28:169–81.

Higher initial bolus doses (mg kg^{-1}) of water-soluble drugs are required to achieve similar plasma concentrations in neonates compared to older children and adults. The effect of age on the distribution of lipophilic drugs in children is less clear. During infancy, the total body fat content increases steadily, which is likely to influence the volume of distribution of lipophilic drugs such as propofol.

Cardiac output and regional blood flow: The initial phase of distribution from the central compartment reflects regional blood flow. Redistribution from the brain, heart, liver and kidneys to other relatively well-perfused tissues such as skeletal muscle follows, with much slower distribution to the less perfused tissues, such as fat. These less well-perfused areas become important in relation to long-term drug infusions. Relative organ mass and regional blood flow alter as infants mature. During the neonatal period, blood flow as a proportion of the cardiac output increases to the kidneys and brain, whereas that to the liver decreases. Relative to their body weight the cerebral and hepatic mass in infants is much higher than in adults. Both the increased cardiac output and cerebral perfusion mean that the onset time after intravenous induction is shortened in neonates.

Protein binding: Drug distribution is influenced by the concentration of circulating plasma proteins such as albumin and α-1-acid glycoprotein (AAG). Neonates and young infants often display a reduction in both the quantity and the binding affinity of circulating plasma proteins. Plasma albumin concentration approximates adult values by five months and binding capacity by one year of age. Neonates also tend to a metabolic acidosis that alters the ionisation and binding properties of plasma proteins.

Blood–brain barrier (BBB): It is thought that BBB permeability to water-soluble drugs changes with maturation; the BBB is less well developed in neonates than older children and is therefore more permeable to partially ionised drugs (e.g. morphine, bupivacaine). Besides passive diffusion, there are specific transport systems within the BBB that mediate active transport. These include the adenosine triphosphate (ATP)–dependent processes that transport opioids such as fentanyl and morphine. Modulation of transporter proteins (e.g. p-glycoprotein) will have a significant influence on brain distribution and onset time as well as the magnitude and duration of analgesic response of opioids.

Elimination

The main routes of drug elimination are either through metabolism (mainly hepatic) or excretion of the parent compound or its metabolites (mainly renal). Both hepatic metabolism and renal clearance mature in early life.

Metabolism: Metabolic processes mainly transform lipid-soluble drugs into water-soluble metabolites, which can be excreted more readily by the kidney. The concentrations and activities of microsomal enzymes are reduced or absent in the newborn. In particular, elements of the mixed oxidase or cytochrome P450 system are less than half as active as in adults and may take from a few weeks to several years to mature. This results in

reduced metabolism of many drugs, including barbiturates, diazepam and amide local anaesthetics. Similarly, the ability to form glucuronide conjugates is impaired owing to a reduction in the activity of glucuronyl transferase and uridine diphosphate glucose (UDPG) dehydrogenase. This is of major importance in the metabolism of morphine, which is greatly reduced in the neonate and takes over six months to approach adult levels.

Many drugs are metabolised at extrahepatic sites, frequently by esterases. Studies with neonatal plasma have shown that the rate of hydrolysis of procaine by butyryl-cholinesterase (plasma cholinesterase) is half of that in adults. However, the reduction in butyryl-cholinesterase activity has no effect on the duration of action of suxamethonium in the newborn, which seems to be influenced more by the rapid redistribution of the drug from its site of action.

Excretion: Drugs and their metabolites are excreted principally by the kidney, involving glomerular filtration and tubular secretion. Some drugs are simply filtered, in which case their rate of elimination will depend upon the glomerular filtration rate (GFR). GFR is lower in newborns and infants than in adults, and when related to body surface area it achieves adult values at three to five months of age. However, when related to body weight, GFR reaches adult values at one to two weeks, which reflects more accurately the age at which the half-times of unmetabolised drugs approach adult values. Proximal tubular secretion is important for the elimination of some conjugated drugs; it reaches adult levels by about seven months of age.

Pharmacodynamics

Developmental pharmacodynamics describes the impact of maturation of biologic systems on responses to drugs. The pharmacodynamic outcomes commonly measured in anaesthesia are pain, neuromuscular blockade and depth of anaesthesia or sedation. Age-related pharmacodynamic variation may be influenced by developmental changes in receptor number, type, affinity and the availability of endogenous ligands. Beyond drug-receptor interactions, drug responses may be significantly impacted by the child's developing physiology. For example, neonates have increased postnatal expression of the μ-opioid receptor, and this, coupled with differences in their tendency to apnoeas, contributes to this age group being more sensitive to morphine. Further examples of pharmacodynamic considerations are covered later in discussions of specific drugs.

Comorbidities

The presence of certain congenital abnormalities and syndromes will affect responses to some medications. Patients with genetic conditions affecting organ systems (e.g. heart, liver, kidney) may need to be monitored more closely for adverse reactions. Caution should be taken with the use of specific drugs in patients with liver disease and those at risk of decreased drug clearance. Drugs that may enhance the neuromuscular blocking action of suxamethonium should be noted, including several medications that may be prescribed for patients with genetic disorders. These may include aminoglycoside antibiotics, β-blockers, procainamide, lithium carbonate, glucocorticoids, metoclopromide, terbutaline and monoamine oxidase inhibitors. Those with inherited metabolic disorders and myopathies may be particularly susceptible to certain side effects, and some drugs should be avoided entirely in certain patients (see Chapter 8 for further details).

Intravenous Anaesthetic Agents

Propofol

Propofol is the most widely used IV anaesthetic agent and can be used for both induction and maintenance of anaesthesia in infants and children but is less commonly used in neonates. It can also be used for sedation. Propofol has largely replaced thiopental as the intravenous induction agent of choice because of its rapid, clear-headed recovery and antiemetic effect. Propofol also suppresses laryngeal and pharyngeal reflexes, thereby facilitating laryngeal mask airway insertion and tracheal intubation.

The faster and more clear-headed recovery following a single dose of propofol compared with thiopental is due to propofol's shorter distribution half-time and more rapid plasma clearance. The rapid elimination of propofol (plasma clearance approximately six times as fast as thiopental in paediatric studies) reduces the potential for accumulation, making the drug suitable for the maintenance of anaesthesia. Induction and maintenance doses of propofol are greater in

children than in adults because the volume of the central compartment is 50% larger and the plasma clearance 25% faster in children. Average induction doses (1.3 × ED50) in unpremedicated patients are as follows:

- Infants: 4 mg kg^{-1}
- Children: 3 mg kg^{-1}
- Adults: 2 mg kg^{-1}

When given with an opioid, the average infusion dose of propofol for maintenance of anaesthesia in children is 0.1–0.2 mg kg^{-1} min^{-1}, approximately twice the dose required in adults.

The use of propofol for prolonged sedation (>48 hours) in paediatric intensive care units has been associated with a rare syndrome comprising lipaemia, metabolic acidosis, heart failure, rhabdomyolysis and death. The cause of this syndrome is unknown, but attention has focused mainly on impairment of fatty acid oxidation by propofol as a possible cause. In view of these reports, the drug regulatory authorities of the United Kingdom, Canada and the United States have recommended that propofol should not be used for intensive care sedation of children under 16 years.

Thiopental

Thiopental is a barbiturate with a rapid onset of action following intravenous administration. In the newborn, plasma protein binding of thiopental is reduced, so that the fraction of unbound drug is almost twice that found in older children and adults. In addition, the elimination half-time is more than three times as long in neonates as in older children; however, as recovery depends primarily on redistribution, the effect of an induction dose is not significantly prolonged.

The usual induction doses of thiopental are:

- Healthy neonates: 4–5 mg kg^{-1}
- Infants: 7–8 mg kg^{-1}
- Children: 5–6 mg kg^{-1}

The lower dose for thiopental in neonates compared with infants may be explained by decreased plasma protein binding, greater penetration of the neonatal brain and increased responsiveness of neonatal receptors.

The increased dose for thiopental in infants and children compared with adults (average dose 4 mg kg^{-1}) may be due to the increased cardiac output in younger patients, which should reduce the initial concentration of thiopental arriving at the brain.

Ketamine

Ketamine is a unique drug with anxiolytic, analgesic, amnesic and dissociative properties and a wide safety margin. As an induction agent, it causes less hypotension than propofol or thiopental and can be used for procedural sedation for children undergoing short, painful or frightening procedures in the emergency department. Ketamine can cause hallucinations, nightmares and other transient psychotic effects; these can be reduced by co-administration of a benzodiazepine such as midazolam.

Neonates and young children require lower doses of ketamine of 1–2 mg kg^{-1} for induction of anaesthesia compared to older children (>12 years) (1–4.5 mg kg^{-1}). Ketamine can also be administered via intramuscular injection with neonates requiring a reduced dose of 4 mg kg^{-1} in comparison to infants and older children, where doses of 4–13 mg kg^{-1} are required.

Sedatives

Dexmedetomidine

Dexmedetomidine has anxiolytic, sedative and analgesic properties and is notable for its ability to provide sedation without risk of respiratory depression. It was launched in the United Kingdom in 2011, with marketing authorisation for sedation of adult intensive care patients only. However, due to its unique pharmacological profile its clinical use has expanded to unlicensed applications in children. It is the S-enantiomer of the veterinary sedative medetomidine and a highly selective α2-adrenoceptor agonist, and administration is possible via multiple routes (oral, nasal, buccal, IV).

Dexmedetomidine induces sedation that resembles physiological sleep in terms of electroencephalography (EEG). Its use can reduce emergence delirium as well as acute postsurgical pain and opioid requirement. Disadvantages include transient hypertension, hypotension and bradycardia.

Dexmedetomidine can be used as an infusion or as a bolus dose intraoperatively. An infusion is given at a dose of 0.2–0.7 mcg kg^{-1} hr^{-1} and the bolus dose in children is 0.5–1 mcg kg^{-1}.

Midazolam

Midazolam is a water-soluble benzodiazepine associated with profound sedation when high doses are given intravenously or when it is used with certain other drugs. It may be used to provide sedation, anxiolysis and amnesia prior to diagnostic, therapeutic or endoscopic procedures, before induction of anaesthesia or as a sedative agent in mechanically ventilated patients in intensive care. Midazolam is the only benzodiazepine approved by the US Food and Drug Administration (FDA) for use in neonates; in this population, the half-life is much longer (6–12 hours). Severe hypotension has been reported with midazolam in neonates after bolus administration, and this effect appears to be compounded in those also receiving fentanyl. When used as a sedative and analgesic in neonates in intensive care, a loading dose is avoided, and continuous intravenous infusions depending on gestation are recommended:

- <32 weeks' gestation: 30 mcg kg^{-1} hr^{-1} adjusted according to response
- >32 weeks' gestation: 60 mcg kg^{-1} hr^{-1} adjusted according to response
- Dose may be gradually increased up to 150 mcg kg^{-1} hr^{-1}

As with older children and adults, neonates can become tolerant to midazolam, thus abrupt withdrawal after prolonged use should be avoided.

Opioids

Until the late 1980s, the use of opioids was avoided in newborns and young infants because of their increased susceptibility to respiratory depression. However, attitudes changed following the demonstration that neonates mount a significant stress response to surgery which can be modified by opioids.

The susceptibility of newborns to opioid-induced respiratory depression may be due to:

- Increased central nervous system (CNS) penetration by opioids
- Reduced capacity for opioid elimination
- Developmental changes in the relative proportions and affinities of opioid receptors

Morphine

Morphine remains the drug of choice for the management of severe postoperative pain in infants and children. It is usually administered by continuous infusion or by nurse- or patient-controlled analgesia (NCA/PCA). In view of the long time constant of morphine, a loading dose is required to achieve an effective plasma concentration within a reasonable time.

Following an intravenous injection of morphine, brain uptake is slow owing to poor lipid solubility. Similarly, the decay of CNS concentration is slow as it depends on elimination of the drug by the liver. Conjugation with glucuronide produces both active and inactive metabolites which are excreted by the kidneys. Morphine clearance in neonates is only 25% of that in adults and takes six months to approach adult values. Accordingly, the elimination half-time of morphine is significantly prolonged in young infants. The fraction of protein-bound morphine is similar in all age groups (~20%).

For children and infants aged over six months, a loading dose of 100 mcg kg^{-1} followed by a maintenance infusion rate of 10–30 mcg kg^{-1} h^{-1} should achieve and maintain an adequate target concentration of 10–25 ng ml^{-1}.

In newborns, a plasma concentration of morphine of 10–25 ng ml^{-1} should be achieved with a loading dose of 25 mcg kg^{-1} followed by an infusion rate of 5–10 mcg kg^{-1} h^{-1}. All infants and children receiving morphine infusions should be monitored with continuous pulse oximetry, and infants aged less than one month should be nursed in a high–dependency unit.

Fentanyl

Fentanyl is a synthetic opioid with a high lipid solubility that confers increased potency, rapid onset and short duration of action. After a dose of 1–3 mcg kg^{-1}, the clinical effects of fentanyl are terminated by redistribution and its duration of action is limited to 20–30 minutes. However, after repeated doses or a continuous infusion, progressive saturation of peripheral compartments occurs, and its effects may last for several hours.

The mean plasma clearance of fentanyl in infants is greater than that in adults, although there is great inter-patient variability due to age and the type of surgery. Fentanyl clearance increases during the first two weeks of life, reflecting rapid maturation of the cytochrome P-450 3A4 enzyme. During the same period, the volume of distribution of fentanyl is two to three times that in adults, and

there is a corresponding increase in the half-time of elimination. Accordingly, single doses of fentanyl in neonates should be reduced (e.g. 0.5–1 mcg kg^{-1}).

Remifentanil

Remifentanil is an ultra-short acting, ester-linked synthetic opioid introduced into clinical practice in 1996. Following intravenous infusion, it is rapidly hydrolysed by non-specific blood and tissue esterases to produce a virtually inactive carboxylic acid compound. As remifentanil is not a substrate for butyrylcholinesterase (plasma cholinesterase), its elimination is not affected by a deficiency in this enzyme.

The volume of distribution (Vd) is greatest in infants under two months old and decreases with age, and clearance is more rapid in the younger age groups. Thus, half-life is similar in all age groups (means of 3.4 to 5.7 minutes). The short time constant frequently makes a loading dose unnecessary and facilitates control of the infusion. Unlike other opioids, its duration of action does not increase with increasing dose or duration of infusion, because its volume of distribution is small and its clearance is fast. The usual infusion rate of remifentanil is 0.1–0.5 mcg kg^{-1} min^{-1}. Its use in neonatal and infant anaesthesia is associated with a reduction in the requirements for volatile anaesthetic agents, stable cardiovascular conditions and a low incidence of postoperative apnoea.

Muscle Relaxants

Suxamethonium

Suxamethonium is the only depolarising neuromuscular blocking drug in clinical use. A unique combination of rapid onset and short duration of action makes it especially useful for emergency tracheal intubation. Elimination depends on hydrolysis by butyrylcholinesterase, hence a deficiency in this enzyme may result in prolonged block.

Studies during thiopental–fentanyl–nitrous oxide anaesthesia showed that the doses of suxamethonium for 90% depression of the twitch response (ED90) in neonates, infants and children were 0.52, 0.61 and 0.35 mg kg^{-1} respectively. These values were all greater than that obtained in a comparable adult study (0.29 mg kg^{-1}; see Figure 2.3). It was recommended that neonates and infants should be given 3 mg kg^{-1} and children 2 mg kg^{-1} of suxamethonium for tracheal intubation. The duration of action of these doses was about the same as or less than that produced by 1 mg kg^{-1} in adults (six to eight minutes), reflecting the shorter half-times of suxamethonium in infants and children.

When intravenous access is not available, suxamethonium may be given by intramuscular injection. In this case, doses of 5 mg kg^{-1} for infants and 4 mg kg^{-1} for children produces 85–100% twitch depression. Maximum block will be achieved at 3 to 4 minutes, and full recovery will occur after 15–20 minutes (see Figure 2.3).

The increased dose requirement of suxamethonium in younger patients probably results from its distribution into a larger extracellular fluid (ECF) volume rather than an altered response to the action of the drug at acetylcholine receptors. The unique mode of action of suxamethonium (sustained depolarisation) and its activity at muscarinic acetylcholine receptors are responsible for

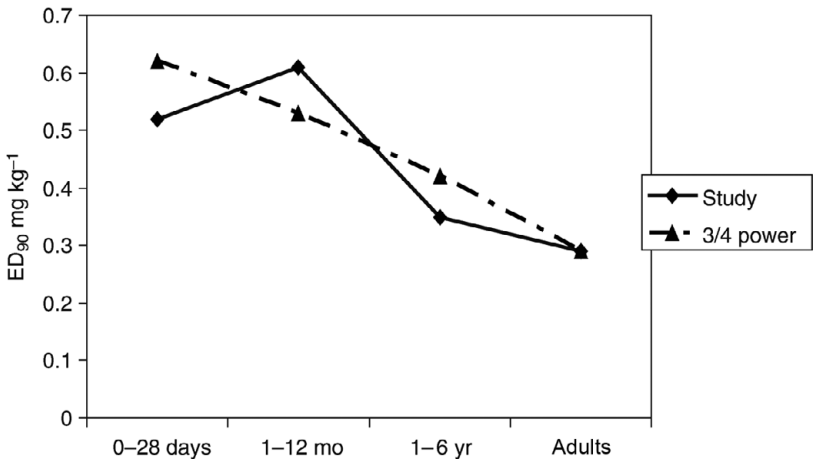

Figure 2.3 Monophasic variation in the ED90 dose of suxamethonium with age (solid line). The broken line represents paediatric doses of suxamethonium predicted from the adult dose of 0.3 mg kg^{-1} using the 3/4 power size model.
Source: Data taken from Meakin GH, McKiernan EP, Morris P et al. Dose-response curves for suxamethonium in neonates, infants and children. *British Journal of Anaesthesia* 1989; 62:655–8; and Smith CE, Donati F, Bevan DR. Dose–response curves for succinylcholine: single versus cumulative techniques. *Anesthesiology* 1988; 69:338–42.

many adverse effects. Of greatest concern have been reports of rare, but often fatal, hyperkalaemic cardiac arrests in boys with undiagnosed muscular dystrophy. As a result of these reports, the FDA recommends that the use of suxamethonium in children should be reserved for emergency intubation and instances where immediate securing of the airway is necessary (e.g. laryngospasm, difficult airway, full stomach) or for intramuscular use when a suitable vein is not available.

Non-depolarising Neuromuscular Blocking Drugs

Clinical studies in the 1960s and 1970s produced conflicting results about the sensitivity of paediatric patients to non-depolarising neuromuscular blocking drugs (NMBDs). The question was largely resolved in 1982 by a study which demonstrated that the steady-state concentration of tubocurarine corresponding to 50% depression of EMG twitch (Cpss50) in neonates was only one-third of that in adults, whilst that of infants was about one-half. However, when the dose corresponding to 50% depression of EMG twitch (D50) was determined for each patient by multiplying the Cpss50 by the volume of distribution (Vdss), there were no significant differences between the groups (Table 2.1). It was concluded that whilst neonates and infants were more sensitive to tubocurarine in terms of the lower plasma concentration required to produce a given effect, this was countered by an increased volume of distribution (ECF volume), such that the dose did not vary significantly with age. The same appears to be true of other NMBDs.

Experimental data from young rats suggest that the increased sensitivity of the neuromuscular junction of the human neonate and infant to NMBDs is due to a reduction in the release of acetylcholine (ACh) from developing motor nerves. A prejunctional locus for the weakness in neuromuscular transmission in human infants is also consistent with the mature appearance of the motor endplate from 31 weeks gestational age, the absence of fetal acetylcholine receptors (AChRs) after this time and the apparently normal response of the motor endplate to suxamethonium in newborns.

Table 2.1 Steady state concentration of tubocurarine for 50% depression of EMG twitch (C_{pss50}), steady state volume of distribution (V_{dss}) and dose for 50% depression of twitch (D_{50}) calculated from the other two parameters.

	C_{pss50} (mcg ml^{-1})	V_{dss} (l kg^{-1})	D_{50} (mcg kg^{-1})
Neonates	0.18	0.74	155
Infants	0.27	0.52	158
Children	0.42	0.41	163
Adults	0.53	0.30	152

Adapted from Fisher DM, O'Keefe C, Stanski DR *et al.* Pharmacokinetics and pharmacodynamics of D-tubocurarine in infants, children and adults. *Anesthesiology* 1982;**57**:203–8.

Atracurium

Atracurium is a bis-quaternary benzylquinolinium diester with an intermediate duration of action.

It is metabolised by non-enzymatic cleavage at body temperature and pH (Hofmann elimination) as well as by hydrolysis. Plasma clearance of atracurium is therefore independent of organ function and, when normalised for body weight, is greater in infants than in older children.

When compared during thiopental–nitrous oxide–narcotic anaesthesia, the ED95 of atracurium has been shown to be significantly lower in neonates and infants than in children (119 and 163 vs 195 mcg kg^{-1}). Following a standard intubating dose of atracurium 0.5 mg kg^{-1} (~2 × ED95), 95% depression of twitch occurred more rapidly in neonates than in children (0.9 vs 1.4 min), whilst recovery to 10% of control twitch height occurred more rapidly in neonates compared with the other two groups (22.7, 29.7 and 28.6 minutes; for neonates, infants and children respectively). Prompt, predictable recovery in all age groups is a major advantage of atracurium when used for paediatric anaesthesia.

The adverse effects seen with atracurium relate mainly to histamine release. Commonly, this results in a macular rash or erythema along the course of the vein of injection, which may subsequently spread peripherally. Occasionally the rash may be accompanied by more serious histamine effects such as hypotension, tachycardia or bronchospasm. The cardiovascular changes are dose related and usually occur at doses greater than twice the ED95.

Cisatracurium

Cisatracurium is 1 of 10 stereoisomers that make up the commercially available atracurium mixture. The ED95 of cisatracurium is 45 mcg kg^{-1}, therefore it is approximately three times as potent as atracurium. The increased potency of cisatracurium compared with atracurium confers greater specificity of action and fewer histamine-related side effects. The main disadvantage of increased potency is a slower onset of action. Consequently,

a dose of ~3 × ED95 of cisatracurium (0.15 mg kg^{-1}) is required to produce intubating conditions at two minutes comparable to those obtained with 2 × ED95 of atracurium. Following a dose of cisatracurium 3 × ED95, 25% recovery time was shown to be longer in infants than in children (43 vs 36 minutes), which could have clinical importance in infants undergoing short surgical procedures.

Vecuronium

Vecuronium is a monoquaternary aminosteroid relaxant of intermediate duration of action, which is largely eliminated unchanged by the liver. As with other non-depolarising relaxants, the variation in effective dose of vecuronium is biphasic with the ED95 in infants being like that in adolescents whilst the maximum effective dose occurs in children aged five to seven years. Significantly, a standard intubating dose of 100 mcg kg^{-1} of vecuronium (~2 × ED95) maintains over 90% neuromuscular blockade for almost an hour in newborns and infants compared with only 18 minutes in children. Vecuronium is therefore a long-acting muscle relaxant in neonates and infants, reflecting its dependence on hepatic function for elimination.

Rocuronium

Rocuronium is an analogue of vecuronium with a more rapid onset of action, making it a suitable for rapid sequence induction. Rapid onset is the result of reduced potency, which necessitates an increase in dose. When compared during nitrous oxide–opioid anaesthesia, the ED95 of rocuronium was significantly lower in infants than in children (248 vs 396 mcg kg^{-1}), whilst the duration of clinical effect following a standard intubating dose of 0.6 mg kg^{-1} (~2 × ED95) was much longer (42 vs 27 minutes). These results confirm that rocuronium, like vecuronium, is longer acting in infants than in children. However, unlike vecuronium, rocuronium retains the characteristics of an intermediate-acting muscle relaxant in infants.

Antagonism of Non-depolarising Relaxants

Any residual non-depolarising neuromuscular blockade at the end of anaesthesia should be antagonised with a cholinesterase inhibitor. This is especially important in infants because of their reduced respiratory reserve. Neostigmine is the most used agent. In the presence of 10% recovery of twitch height, 35 mcg kg^{-1} of neostigmine has been shown to provide maximal antagonism in both paediatric and adult patients. Recovery after neostigmine was faster in paediatric patients compared with adults. For convenience, a somewhat larger dose of 50 mcg kg^{-1} of neostigmine is usually given, in combination with glycopyrrolate to prevent muscarinic effects.

Sugammadex

Sugammadex reverses neuromuscular blockade with a mechanism that differs from the commonly used acetylcholinesterase inhibitors like neostigmine. It is a modified gamma-cyclodextrin that selectively binds the aminosteroid muscle relaxants, rocuronium and vecuronium. It forms a complex with the muscle relaxants, which leads to a decrease in the concentration of drug available to bind to the nicotinic receptor in the neuromuscular synapse. Sugammadex is only recommended for routine reversal of rocuronium-induced blockade in children and adolescents over the age of two (dose 2 mg kg^{-1}). It is not recommended for use in children and adolescents for recovery after vecuronium or for rapid recovery after any muscle relaxant.

Inhaled Anaesthetics

The commonly used inhalational agents in paediatric anaesthesia worldwide are halothane, sevoflurane, isoflurane, desflurane and nitrous oxide. Halothane is no longer commercially available in the United Kingdom or the United States but remains on the World Health Organisation's List of Essential Medications for both adults and children. Sevoflurane has mostly replaced halothane as the induction agent of choice in children because of its non-pungent odour, rapid induction characteristics and relative cardiostability.

Uptake and elimination of inhaled anaesthetics occur more rapidly in paediatric patients than in adults, primarily because of an increased level of ventilation in relation to functional residual capacity (FRC) and a corresponding increase in weight-normalised cardiac output. The increased rate of uptake of inhaled anaesthetics in infants correlates with more rapid induction of anaesthesia and earlier development of adverse cardiovascular events.

Halothane

Halothane is a halogenated alkane with a non-pungent odour, making it suitable for inhalation

induction in infants and children. Induction of anaesthesia is rapid owing to its relatively low blood–gas partition coefficient and high potency (Table 2.2). In newborns, the minimum alveolar concentration (MAC) of halothane is 0.9%, but it increases rapidly to a maximum of 1.2% at age one to six months and thereafter declines gradually to 0.8% in the adult. The reduced MAC of halothane in neonates compared with infants may relate to immaturity of the CNS or attenuation of the pain response due to increased plasma concentrations of endorphins. The higher MAC in infants compared with older children and adults may be due to reduced solubility of inhaled anaesthetics in brain tissue owing to an increased water content. Neonates and young infants are more sensitive to the myocardial depressant and vagotonic effects of inhaled anaesthetics than older children.

Sevoflurane

Sevoflurane is trifluoromethyl isopropyl ether; fluorination decreases solubility in fat and blood, thereby reducing anaesthetic potency whilst increasing the rate of uptake and elimination. Because of its lower blood solubility (Table 2.2), induction and recovery are more rapid with sevoflurane than with halothane.

The MAC of sevoflurane varies with age, being higher in neonates and young children than in adults (Table 2.2). Sevoflurane produces less myocardial depression and bradycardia than halothane; however, significant hypotension may still occur in neonates.

Although an estimated 5% of the inhaled dose of sevoflurane is metabolised producing inorganic fluorides, peak concentrations of fluoride in paediatric studies have not exceeded two-thirds of the suggested nephrotoxic level of 50 mmol l^{-1}, and there have been no reported cases of sevoflurane nephrotoxicity.

Emergence agitation is a significant problem with sevoflurane. The reported incidence varies (30–80%), affecting mainly preschool children. Episodes typically last for ~10 minutes during which the child appears to be agitated, restless, combative, frightened and inconsolable. It cannot be attributed solely to pain or rapid emergence from anaesthesia and has been described as a short-lived acute organic mental state of uncertain aetiology. It may be the result of different washout times between excitatory and inhibitory centres in the CNS. Its incidence can be reduced using sedatives and short-acting opioids, e.g. intravenous induction with propofol and administration of 1 mcg kg^{-1} of fentanyl 10 minutes before the end of anaesthesia.

Table 2.2 Properties of volatile anaesthetics

	Halothane	Isoflurane	Sevoflurane	Desflurane
Odour	Non-pungent petrolic	Pungent ethereal	Non-pungent ethereal	Pungent ethereal
Blood–gas coefficient				
Neonates	2.1	1.2	0.7	–
Adults	2.3	1.4	0.7	0.4
MAC (%)				
Neonates	0.9	1.6	3.3	9.2
Adults	0.8	1.2	2.0	6.0
Rate of metabolism (%)	20	0.2	2.0	0.02
Myocardial depression	++	+	+	+
Peripheral vasodilation	+	++	++	++
Respiratory depression	+	++	++	++

Source: Adapted from Meakin G. Neonatal anaesthetic pharmacology. In: Hughes DG, Mather SJ, Wolf AR, eds. *Handbook of Neonatal Anaesthesia*. Saunders. 1996; 18–54.

Isoflurane

Isoflurane is a halogenated methyl-ethyl ether with irritant properties rendering it unsuitable for inhalational induction. The potency of isoflurane varies with age in a similar manner to that of halothane; the MAC is approximately 1.6% in neonates, 1.9% at age one to six months and thereafter declines gradually to about 1.2% in adults. The MAC of isoflurane is further reduced in premature infants: at 32 weeks gestational age, it is approximately 1.3% whilst at 32–37 weeks it is 1.4%. Equipotent concentrations of isoflurane and halothane produce similar reductions in blood pressure in infants and children, although heart rate and myocardial function are better preserved with isoflurane.

Desflurane

Desflurane is synthesised by the replacement of the single chlorine atom of isoflurane with fluorine. Like isoflurane, desflurane has a pungent odour making it unsuitable for inhalation induction. However, because of its lower blood solubility (Table 2.2), recovery after desflurane anaesthesia is faster than that after halothane or sevoflurane. The MAC of desflurane varies with age in a way similar to most other volatile anaesthetics, being 9.2% in newborns, 9.9% in infants aged 6–12 months and thereafter declining gradually to 6.0% in adults. The cardiovascular profile of desflurane is like that of halothane; metabolism is negligible, and the drug resists degradation by soda lime. The rapid recovery seen after desflurane may be of special benefit in neonates and ex-premature infants in view of their increased susceptibility to postoperative apnoea and ventilatory depression. Increasing awareness of desflurane's potent greenhouse gas effect (approximately 26 times that of sevoflurane) has led to a recent reduction in its usage.

Nitrous Oxide

Nitrous oxide is a sweet-smelling, non-irritant, anaesthetic gas with a low blood–gas partition coefficient (0.47) resulting in rapid uptake and elimination. When used as a carrier gas with oxygen, it speeds the uptake and elimination of potent volatile anaesthetics by the second gas effect and reduces their MAC requirement for anaesthesia. The low potency of nitrous oxide may be an added safety factor when the agent is used in neonates who generally tolerate anaesthetics poorly.

In recent years there have been calls for the abandonment of nitrous oxide in routine anaesthesia owing to a greater appreciation of its disadvantages (e.g. potential for delivering a hypoxic mixture, distension of air pockets in the body, increase in intracranial pressure, contribution to greenhouse gas effect). Although paediatric anaesthetists still find nitrous oxide useful for inhalation induction of anaesthesia, its use for maintenance of anaesthesia is declining in line with recent trends in adult anaesthetic practice.

Local Anaesthetics

Local anaesthetics are commonly used for wound infiltration, perioperative nerve blocks and neuraxial blockade as part of a multimodal approach to analgesia. Drugs of the amino-amide type are used most frequently. Lower concentrations of α-1-acid glycoprotein in young infants increase the amount of unbound local anaesthetic and the potential for CNS and cardiovascular toxicity. Total body clearance is also reduced in young infants because of the limited oxidising capacity of the liver, which, together with an increase in the volume of distribution, leads to a prolonged elimination half-time. Accordingly, the maximum permitted single and infusion doses of local anaesthetics should be reduced in young infants. Bupivacaine is a racemic mixture of R (+) and S (–) enantiomers. Its chief advantage is its long duration of action (e.g. four to six hours after a single epidural injection). For patients aged over six months, the maximum single injection dose (plain or with adrenaline) is 2.5 mg kg^{-1}, and the maximum epidural infusion rate is 0.5 mg kg^{-1} h^{-1} for a maximum of 36 hours. In infants aged less than six months, these doses should be halved, and consideration should be given to reducing the rate of infusions by a further one-third after 24 hours as there is evidence of drug accumulation even with the reduced doses.

Bupivacaine toxicity is a particular concern in children since most blocks are carried out under anaesthesia when early signs of impending catastrophe are absent. Demonstration in the 1970s that the S (–) enantiomer of bupivacaine was significantly less cardio-depressant than the R (+) enantiomer led to the development of ropivacaine and

levobupivacaine. In view of their wider safety margins, these S (–) enantiomer drugs should be the local anaesthetics of choice for paediatric anaesthetic practice. In comparative trials, ropivacaine, levobupivacaine and bupivacaine were found to be equally effective when given in equal doses and concentrations to children for caudal and epidural analgesia, but ropivacaine and levobupivacaine were associated with less motor block.

Further Reading

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