Paediatric anaesthetic pharmacology

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It is ethically and practically more difficult to undertake pharmacological research in children compared with adults. As a result, there are less data available regarding many drugs commonly used in paediatric practice. Indeed, a number of commonly used drugs are unlicensed for use in children. It is important to realise that children are not merely small adults. There are numerous reasons for the altered pharmacokinetics and pharmacodynamics seen in the paediatric population. These differences are most marked in the first year of life but persist to about 10 years of age.

In the first section of this article, some of the reasons for the different pharmacological properties of drugs in children are examined; in the second section, these differences are highlighted using some of the drugs commonly used in paediatric practice as examples.

Most drugs administered in adult anaesthetic practice are used in children. Many are given for a particular application without a specific product licence and much of the evidence, even for basic dosage, is anecdotal.

General pharmacology

Absorption

Gastric emptying rate is reduced in the neonate. This may reduce the rate of absorption of orally administered drugs (if they are mainly absorbed distal to the stomach) and bioavailability if they are inactivated by low pH. Drugs administered intra-muscularly in children exhibit a more rapid onset of action than in adults because of the relatively higher cardiac output and increased muscle blood flow. However, this route of administration is not commonly used in paediatric practice. Drug absorption by the rectal route can be erratic and depends on the quantity of faeces in the rectum, whether the drug is administered high or low into the rectum, duration of retention of the suppository and pH of the preparation. Premedics such as midazolam have been administered intra-nasally but this can be distressing for the child.

Inhalational agents are taken up and eliminated more rapidly in children. For nitrous oxide, an F1:F A ratio of 1.0 is achieved in 25 min in infants, 30 min in children and 60 min in adults. This occurs because tidal volumes remain relatively constant throughout life at approximately 7 ml kg–1 but the ratio of alveolar ventilation to the functional residual capacity is 5:1 in infants compared with 1:4:1 in adults. Additionally, the tissue:gas and blood:gas solubility of volatile agents is reduced in infants. The increased cardiac output in infants might be expected to reduce the speed of inhalational induction but this is offset by the greater proportion of cardiac output directed to the vessel-rich tissues and the reduction in fat and muscle mass in the infant (Table 1). Minimum alveolar concentration (MAC) is inversely related to age in children.

Distribution

Distribution is influenced by plasma protein binding, blood volume, solubility coefficient

Table 1  Age-related estimates of gas and tissue volumes and blood flow

<table>
<thead>
<tr>
<th>Tissue volume</th>
<th>Gas and tissue volume (ml kg–1)</th>
<th>Tissue blood flow (% cardiac output)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td>Infant</td>
<td>Adult</td>
</tr>
<tr>
<td>Tidal volume</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Functional residual capacity</td>
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<td>25</td>
</tr>
<tr>
<td>Blood volume</td>
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<td>70</td>
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<tr>
<td>Viscera</td>
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<td>175</td>
</tr>
<tr>
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<td>180</td>
</tr>
<tr>
<td>Fat</td>
<td>150</td>
<td>100</td>
</tr>
<tr>
<td>Poorly perfused tissue</td>
<td>270</td>
<td>270</td>
</tr>
</tbody>
</table>

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Based on Cook DR and Marcy JH (1988).

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and tissue blood-flow. Infants have reduced plasma protein binding, thereby increasing the plasma concentration of unbound drug. Neonatal albumin is present in a reduced concentration and has a lower affinity for drugs. Neonates also have reduced $\alpha_1$-acid glycoprotein (AAGP), which is the major binding protein for many alkaline drugs (including local anaesthetics and opioids). Increased total body water, extracellular fluid volume and blood volume all serve to increase the volume of distribution ($V_D$), particularly for highly ionised (water soluble) drugs. Increased cardiac output allows a more rapid delivery of drugs to the target tissues, with a greater proportion being directed to the vessel rich tissues such as the brain. Reduced muscle mass and fat stores mean there is a smaller amount taken up into inactive sites and a smaller reservoir for fat-soluble drugs. The blood–brain barrier is immature at birth, allowing greater uptake of partially ionised drugs (e.g. morphine).

**Metabolism**
The liver is the principal site of drug metabolism. Hepatically metabolised drugs may exhibit a prolonged half-life compared with adults. Phase I reactions convert the drug to a more polar metabolite, whilst phase II reactions involve processes (e.g. conjugation) that render the drug or its metabolite more hydrophilic and renally excretable. Microsomal activity requires the cytochrome P450 system, which is incomplete or absent in the neonate. Phase I reactions reach adult levels a few days after birth, whilst phase II reactions mature by 3 months. Metabolism reaches a maximum level during the latter part of the first decade, often exceeding adult rates.

**Excretion**
The excretion of drugs and their metabolites from the kidneys is influenced by the glomerular filtration rate (GFR), clearance and proximal tubular secretion. All of these are reduced in infants, particularly premature neonates. GFR approaches adult values by 1 month, clearance by 3 months and proximal tubular secretion by 5 months. The dose requirements of renally excreted drugs (e.g. penicillins and aminoglycosides) may need to be reduced, particularly in neonates.

**Pharmacology of some drugs commonly used in anaesthetic practice**

**Intravenous induction agents – propofol**
Propofol was first used in children in 1985. A higher induction dose than is usually required in adults (typically 2.5–3.5 mg kg$^{-1}$) is needed, particularly in younger children. Pharmacokinetic studies in children show the central volume of distribution ($V_c$) to be 50% greater (0.34–1.03 litre kg$^{-1}$) and the clearance (34.3 ml kg$^{-1}$ min$^{-1}$) to be 25% greater than adult values. Children require approximately 50% more propofol than adults for the maintenance of anaesthesia. The Diprufusor is not licensed for use in children (16 years or less). A number of regimens have been devised for TIVA. The UK Committee on Safety of Medicines specifically prohibits propofol infusion for sedation on intensive care units in children < 16 years of age due to concerns over increased mortality and morbidity resulting from lactic acidosis. Propofol is licensed for use as an induction agent for children of 1 month and over and for the maintenance of general anaesthesia in children of 3 years and above. However, it is not recommended for sedation during surgical and diagnostic procedures in children, as safety and efficacy have not been demonstrated.

The pattern of recovery from propofol is similar to adults; recovery is more rapid when compared with thiopental as an induction agent, awakening following induction and maintenance with propofol is more rapid than with halothane, but slower than with sevoflurane. There is little difference between any of the agents in time-to-discharge from recovery or hospital. Propofol may have an anti-emetic effect in children.

Following induction of anaesthesia, mean arterial pressure is reduced to a greater degree than with thiopental. There is no compensatory tachycardia and bradycardia may occur, particularly if anaesthesia is maintained with propofol in combination with vagotonic drugs or vagally stimulating surgical procedures in children aged 2 years or less. The systemic vascular resistance is reduced by 15–20% and the cardiac index falls by 13%. Apnoea occurs more commonly and airway reflexes are suppressed to a greater degree than with thiopental. As with adults, involuntary movements may occur at any time during propofol anaesthesia.

**Volatile agents – sevoflurane**
Sevoflurane is widely used for inhalational induction in children. It has a relatively pleasant smell and a blood gas solubility coefficient of 0.68 allowing rapid induction and recovery. MAC falls with increasing age (Fig. 1). Unlike other volatile agents, there is no increase in MAC in the first few months of life. Tracheal intubation is possible with an end-tidal concentration of 1.3 MAC, whilst LMA insertion is achievable with end-tidal concentrations of 1 MAC. The low blood:gas solubility coefficient allows a more rapid recovery
than with halothane, but early postoperative pain scores are higher. There is an increased incidence of agitation during recovery, particularly if used as a maintenance agent.

Sevoflurane is relatively cardiostable, causing less tachycardia than isoflurane and less myocardial depression, fewer arrhythmias and less sensitisation to catecholamines than halothane. Sympathetic nervous system activation and coronary steal do not occur with sevoflurane anaesthesia. As with other volatile anaesthetic agents, there is dose-dependent depression of tidal volume, a reduction in respiratory rate and shifting of the carbon dioxide response curves. Effects on intra-cranial pressure are similar to those seen with isoflurane. There is little effect on the cerebral blood flow, cerebral metabolic requirement for oxygen, or cerebral autoregulation. There may be seizure-like activity on induction. Neuro-muscular block is potentiated.

Opioids – morphine

Several opioids are routinely used in paediatric practice and a number of generalisations can be applied to their pharmacological disposition in children:

- $V_c$ tends to be greater in the young child than the adult
- Steady-state volume of distribution ($V_{ss}$) stays the same or decreases with age
- Clearance increases with age
- The elimination half-life is greatest in the neonate, decreasing to its lowest level in the young child and then increasing to adult levels

Morphine is the most widely studied opioid in the paediatric population. Plasma protein binding is age dependent – 28% in the neonate as compared with 50% in the adult. It is used at a dose of 100 µg kg⁻¹ as an intravenous bolus, 200 µg kg⁻¹ intramuscularly and approximately 20 µg kg⁻¹ h⁻¹ as an intravenous infusion. Following long infusions, plasma and CSF morphine concentrations approach equilibration.

Morphine is metabolised in the liver to inactive morphine-3-glucuronide and active morphine-6-glucuronide. Glucuronide metabolism is proportional to age for the first 2.5 years of life. In neonates, about 20% of morphine is excreted unchanged via the kidneys compared with the adult value of 10%. Clearance is age dependent, being maximal in pre-school age children (20–40 ml kg⁻¹ min⁻¹). In premature neonates, this value may be as low as 0.5–3 ml kg⁻¹ min⁻¹. Consequently, elimination half-life is lowest in pre-school children.

Morphine is used for analgesia or sedation. The plasma concentration required for adequate analgesia and sedation is age dependent. Following orthopaedic thoracic surgery, mean concentration in infants for adequate analgesia was 26 µg litre⁻¹ versus 4 µg litre⁻¹ in 2–6-year-olds. Neonates may require concentrations of up to 125 µg litre⁻¹ for adequate analgesia and sedation.

The side-effects of opioids in children are similar to those seen in adults, i.e. nausea and vomiting, sedation, pruritus, urinary retention and respiratory depression. Some degree of respiratory depression has been reported with plasma concentrations of morphine > 20 µg litre⁻¹. It has traditionally been thought that infants are at a higher risk of respiratory depression but a study of the ventilatory effects of IV morphine in 30 patients aged 2–570 days found no age-related differences in respiratory effects at the same plasma concentrations. However, the neonate may be more susceptible to morphine accumulation because of differences in pharmacological disposition. Doses of opioids should always be titrated to effect.

Local anaesthetic agents – bupivacaine

There are a limited amount of paediatric data available and this relates mainly to bupivacaine. There are marked differences compared with adults. The clearance of bupivacaine is approximately 10 ml kg⁻¹ min⁻¹ in neonates compared with 3 ml kg⁻¹ min⁻¹ in adults. However, $V_D$ differs similarly, being greater in neonates (4.5 litre kg⁻¹) than adults (1–2 litre kg⁻¹),
Elimination half-life is greater in neonates (7 h versus ~3 h). Therefore, doses of bupivacaine, given on a mg kg\(^{-1}\) basis, have greater potential for toxicity in neonates and infants than in adults. In the neonate, the blood–brain barrier is not fully formed, thus allowing free drug to pass more easily into the central nervous system. In plasma, local anaesthetics are bound to AAGP. The concentration of AAGP increases 3–5-fold in the first year of life and by a further 25% during childhood. Thus, there will be substantially more free drug in the neonatal plasma than in the older child or adult.

Practical considerations play a great part in the increased toxicity of local anaesthetic agents in babies and children. Small size increases the likelihood of inappropriate injection. In particular, the potential for accidental intrathecal injection during caudal anaesthesia is recognised because the dural sac extends down to S3 in the neonate compared with S2 in adults. Most local anaesthetic administrations are performed following a general anaesthetic rendering the ‘test dose’ uselessness and obtunding several signs of toxicity (e.g. drowsiness and convulsions).

Ropivacaine exhibits less toxicity. Studies in infants and children under 5 years demonstrate an age-related decrease in peak plasma concentration of drug following caudal administration of a 2 mg kg\(^{-1}\) bolus, with mean concentrations of 0.73 µg ml\(^{-1}\) in those under 1 year compared with 0.49 µg ml\(^{-1}\) in those aged 1–5 years. This difference may be explained by increased tissue perfusion, reduced tissue uptake and reduced metabolism. Studies have demonstrated that ropivacaine administered epidurally has a plasma half-life of 4.9 h in children, which is similar to that in adults.

Several non-depolarising relaxants exhibit a prolonged elimination half-life when compared with the adult. This results in slower recovery and a real risk of accumulation following repeated, non-monitored, administration. For renally excreted drugs, this is related to reduced GFR. Hepatically excreted drugs (e.g. vecuronium) exhibit a larger V\(_D\) but no age-related change in clearance and, therefore, prolonged excretion. Atracurium and mivacurium are the exceptions to this as they undergo inactivation by hydrolysis or Hoffman degradation and plasma cholinesterase, respectively, prior to excretion. Atracurium and vecuronium are used at bolus doses of 500 µg kg\(^{-1}\) and 100 µg kg\(^{-1}\), respectively.

The neonate is relatively resistant to succinylcholine, thereby completing the picture of a myasthenic response. This is due to the greater extracellular fluid volume in these patients resulting in a lower plasma concentration of drug (from a weight calculated dose) rather than any property of the neonatal neuromuscular junction. Succinylcholine has side-effects similar to those seen in adult practice. It is used at a dose of 1–2 mg kg\(^{-1}\). Myalgia is experienced from approximately 9 years of age. Bradycardia is seen after a single dose in some children. Cardiac arrest has been reported in several patients, some of whom were found to have a previously undiagnosed muscular dystrophy. Children with muscular dystrophy develop severe hyperkalaemia in response to succinylcholine. These cases have led to a recommendation (from the FDA in the US) that succinylcholine be reserved for emergency intubation only. No such recommendation is in place in the UK.

**Muscle relaxants**

The neuromuscular junction in the neonate is immature; specifically, it has smaller reserves of acetylcholine than the older patient. Neonates are said to have a myasthenic response to muscle relaxants, exhibit tetanic fade in the absence of relaxants, and are proportionally more sensitive to non-depolarising relaxants than infants and children.

Diaphragmatic muscle in infants and children differs from that of adults in that there are proportionally fewer (slow) type 1 fibres and more (fast) type 2 in younger subjects. Type 2 fibres are more easily fatigued than type 1 which may explain an apparent sensitivity of the infant diaphragm to non-depolarising relaxants.