PAEDIATRIC ANAESTHESIA

Recent Advances in PAEDIATRIC ANAESTHESIA

Editors
Sukhminder Jit Singh Bajwa
Madhuri Kurdi
Indu M Sen
Suvarna Kaniyil
Mukesh Kumar Prasad
Ridhima Sharma

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CHAPTER 1

Recent Advances in Molecular Pharmacology in Paediatric Anaesthesia: Stay Ahead of the Curve and Provide the Best Care!

Sripriya R, Vanita Ahuja, Amrita Rath, Bhavna Gupta, Sukhminder Jit Singh Bajwa

ABSTRACT

The perioperative period requires the administration of multiple anaesthetic drugs, necessitating precise titration and careful management to ensure effective patient recovery. In paediatric patients, understanding pharmacokinetic and pharmacodynamic differences is crucial for optimising drug dosing and anaesthetic care. Advanced drug delivery systems, such as target-controlled infusion for intravenous drugs, have been developed based on paediatric-specific pharmacokinetic models. Additionally, pharmacodynamic variations and individual genetic differences significantly influence drug effects, emphasising the importance of personalising anaesthesia care. This chapter examines the pharmacokinetic differences in paediatric populations, recent innovations in pharmacogenomics, and advancements in drug delivery systems. It also explores the long-term effects of anaesthetic exposure during pregnancy and early childhood on neurodevelopment and neurocognition. Despite the challenges in conducting research in this vulnerable population, continued studies are crucial. Pharmacogenomics holds transformative potential for revolutionising the selection and dosing of anaesthetic drugs, paving the way for safer, more effective and individualised perioperative care.

Keywords: Anaesthetic, Drugs, Neonates, Paediatrics, Pharmacogenetics, Pharmacogenomics, Titration.

INTRODUCTION

Molecular pharmacology in paediatrics aims to enhance drug safety and efficacy by understanding molecular mechanisms of drug action, metabolism and interactions in children. Children cannot be regarded as 'small adults,' due to significant pharmacokinetic and pharmacodynamic differences. The pharmacokinetic and pharmacodynamic responses also vary among children of different ages. Pharmacogenetics and pharmacogenomics further influence the pharmacology of drugs in children.[1,2] Unlike the traditional 'one-size-fits-all' medicine, paediatric precision medicine can personalise medical care, based on an individual's genetic makeup, family history and environmental exposures, thereby ensuring that children receive the most appropriate care based on their unique genetic and biological characteristics.[1]

PHARMACOLOGY IN PAEDIATRICS

Pharmacokinetics

Pharmacokinetics encompasses four key processes: absorption, distribution, metabolism and clearance. Pharmacology in the paediatric age group depends on post-conceptual age or postmenstrual age, rather than post-natal age. Most neonatal drug dosing is weight-based (mg/kg or μg/kg), but increasing evidence confirms that there are many factors and variables beyond size that can be taken into consideration to optimise precision drug dosing in neonates. These variables include age, distribution (including plasma protein binding), route of elimination, isoenzyme maturation, renal development and transporter biology.[3,4] Ontogeny, age-related and development-related differences and changes in body size, composition, organ function, organ maturation and body chemistry, including enzyme activity and pharmacogenomics amongst children, can contribute to the variability in pharmacokinetics and pharmacodynamics. Changes in drug disposition at the level of tissues and cells with respect to drug transporter expression and function can affect drug efficacy and safety. Throughout childhood, from the time of birth to late adolescence, there is a 50-fold difference in drug disposition, most pronounced in the first year of life.[5]

Model-informed precision dosing (MIPD) is a novel and powerful tool to translate this updated knowledge of drug pharmacokinetics into dosing changes at the bedside.[6] It includes the use of pharmacokinetic models to tailor dosing to an individual patient's needs. It integrates mathematical models of drugs and diseases combined with individual patient characteristics such as genotype, anthropometric factors and organ function. This helps in attaining the therapeutic drug exposure targets and thereby improves the efficacy of the drug and reduces adverse events. It is used for drugs such as vancomycin in critically ill children.[7]

Absorption

In neonates, the pH in the stomach is neutral, which can affect the solubility and absorption of orally administered drugs. Additionally, gastric emptying and intestinal motility are slower, potentially prolonging drug absorption. By around 2 years of age, gastric pH, emptying time and motility generally approach adult levels, leading to more predictable absorption patterns. Rectal administration of drugs results in higher bioavailability due to avoidance of first-pass metabolism.[8]

The skin of neonates and infants is thinner and more hydrated, leading to higher absorption of topical medications. Blood flow to muscles and subcutaneous tissue can be erratic in neonates and infants, making absorption of intramuscular drugs unpredictable. Additionally, the lower muscle mass in young children can impact both the volume of distribution and the absorption rate.[9]

Distribution

Neonates have a higher total body water content (~75–90%) compared to adults (~60%), resulting in a larger volume of distribution for hydrophilic drugs compared to lipophilic drugs, necessitating higher weight-based dosing. Body fat increases from 3% in premature neonates to about 10% at birth and approximately 20% by the end of infancy. This affects the distribution of lipophilic drugs. For example, propofol exhibits lower distribution in infants than in adults.[9,10]

At birth, the plasma albumin and α-1-acid glycoprotein are 75–80% and 50% of adult levels, respectively. This may result in a high free fraction of drugs, enhancing pharmacological effects and increasing the risk of toxicity. For instance, the unbound concentration of diazepam is four times higher in neonates compared to adults, reaching adult levels by 1–3 years of age.[8-11] In premature neonates, the blood-brain barrier is immature, leading to increased drug transfer into the central nervous system.[12]

Metabolism

Neonates have immature liver enzyme systems, including cytochrome P450 enzymes, resulting in slower drug metabolism. Both phase I (oxidation, reduction and hydrolysis) and phase II (conjugation) reactions are affected, though they mature at different rates. The metabolism of drugs like thiopentone is dependent on phase I oxidative reactions.[8,9] Opioids, including morphine, fentanyl and other drugs such as amide local anaesthetics (LAs) and ketamine, are dependent on N-dealkylation of phase I metabolism. For phase II conjugation reactions, the main mechanism is glucuronamide reaction for morphine, fentanyl and naloxone. Cytochrome P450, family 3, subfamily A (CYP3A) has an effect in catalysing drug metabolism and increasing clearance with an increase in age. For example, hepatic extraction of midazolam is only 0.04 in neonates, as compared to 0.38 in adults. Other drugs affected by cytochrome P2D6 are selective serotonin reuptake inhibitors, morphine derivatives and prodrugs like tramadol. Cytochrome maturation occurs during the first months to years of life; however, esterase levels remain the same from neonates to adults. For example, remifentanil shows similar clearance in children aged 1 month to 9 years.[13]

Clearance

Renal clearance: Renal development starts at 5–9 weeks of gestation and is completed around 36 weeks. The glomerular filtration rate (GFR) is 5 ml/min in full-term neonates. In preterm neonates, it may be as low as one-fifth of that. GFR functions are non-linear with a maximum value at 48 weeks of postmenstrual age. On average, GFR is 30% of adult GFR at 8–12 weeks of age. Renal function continues to mature over the first year, approaching adult levels by around 6–12 months. The kidney eliminates water-soluble drugs

and metabolites. Age-dependent renal clearance, therefore, controls the drug dosing. Maturation of the kidney is independent of post-natal age and, hence, is a reliable method of clearance of a water-soluble drug.[1,5,8]

Hepatic clearance: Neonates also have immature biliary function, affecting both the binding and transport of bile salts, which limits the absorption of lipophilic drugs.[8,9,14] Intestinal enzyme cytochrome P450 family 3 subfamily A member 4 (CYP3A4) is present at lower levels in children compared to adults. In preterm infants, cytochrome P3A activity is also reduced, leading to decreased first-pass metabolism and increased bioavailability of certain drugs.[7,8]

The majority of the drugs used in anaesthesia, i.e. sedatives, hypnotics, benzodiazepines, opioids and neuromuscular blockers, are dependent on hepatic clearance. For drugs with a high extraction ratio, e.g. lignocaine, fentanyl, sufentanil and propofol, hepatic clearance is dependent on hepatic blood flow. For low-extraction drugs, e.g. diazepam and alfentanil, hepatic clearance is independent of hepatic blood flow and depends on intrinsic clearance for metabolism.[2,8]

Mechanism of Action of Drugs Used in Paediatric Anaesthesia

Intravenous Induction Agents and Sedatives

Propofol: The induction dose of propofol is 2.5–3.5 mg/kg in children aged > 3 years and 2 mg/kg in children aged 3–7 years. The dose is thus high compared to the dose of 2–2.5 mg/kg in adults. The intravenous infusion dose is 125–150 μg/kg/min for sedation and 1–3 mg/kg for emergence delirium. Propofol has rapid redistribution, short duration of action, large steady-state volume of distribution, slow elimination half-life and rapid clearance. Clearance of propofol exceeds liver blood supply, indicating that extra-hepatic sites such as lungs and intestines are involved in its metabolism. The loss of eyelash reflex is at 2 mg/kg in obese children as compared to 3.2 mg/kg in non-obese patients aged 3–17 years. Clearance attains mature adult values within 6 months of life. Context-sensitive half-life is 10.4 minutes for 1 hour's propofol infusion, and 19.6 minutes for 4 hours' infusion as compared to 6.7 and 9.5 minutes, respectively, in adults. Propofol reduces intraocular pressure and reduces emesis. Side effects of propofol include tolerance, pain on injection (more in infants, 50% and in children, 18%), spontaneous excitatory movements, anaphylactic reactions and propofol infusion syndrome (PRIS).[15]

Thiopentone sodium: Thiopentone sodium, an ultra-short-acting barbiturate, has an increased requirement in infants and children as compared to adults. There is a reduced requirement of thiopentone in premature neonates due to lower plasma protein binding, greater penetration of the brain or increased

sensitivity of receptors. The induction dose in neonates is 3–4 mg/kg; in infants: 5–8 mg/kg; in 1–12 years: 5–6 mg/kg; and in >12 years: 3–5 mg/kg.[16]

Etomidate: Etomidate is a potent, short-acting, non-barbiturate sedative-hypnotic agent used due to its cardiac stable function. The induction dose is 0.2–0.4 mg/kg for anaesthesia. Etomidate 0.4 mg/kg does not impair systemic or regional cerebral blood flow in neonates or infants with congenital heart disease. The onset of action is rapid, within 5–15 seconds, with peak effect at 60 seconds and a short duration of 3–5 minutes. Clearance is highly variable and is reduced in neonates and infants having cardiac disease. It has both anticonvulsant and pro-convulsant quantities. Myoclonic movements occur in 30–75% of patients at induction. Pain on injection is a common side effect due to etomidate being a fat emulsion of medium and long-chain triglycerides. Etomidate reduces cortisol levels during and at 24 hours following surgery and hence should be avoided in patients with adrenal-suppressed states.[17]

Ketamine: Intravenous ketamine has rapid distribution and onset of anaesthesia within 30 seconds. In infants <3 months old, the volume of distribution is similar, the elimination half-life is prolonged, and there is reduced clearance due to reduced metabolism and renal excretion as compared to older infants. Ketamine can be administered orally (3–10 mg/kg), intramuscularly (3–7 mg/kg) or intranasally (6–9 mg/kg) for premedication.[18,19]

The intravenous sedation dose of ketamine is 0.5–2 mg/kg, the analgesic dose is 0.1 mg/kg, and the analgesic infusion dose is 0.1–0.3 mg/kg/h. Propofol or midazolam can be combined with ketamine 0.5 mg/kg during cardiac catheterisation, anaesthesia induction and sedation procedures. A ratio of 1:5 of ketamine: propofol for 30-minute anaesthesia and 1:6.7 for 90 minutes of anaesthesia is suggested.[20] Ketamine causes an increase in intracranial pressure, intraocular pressure and nystagmus. Ketamine can cause hallucinations and vivid dreams, with an incidence of 5–10% in prepubescent children. This occurs due to depression of the inferior colliculus and medial geniculate nucleus, leading to misinterpretation of auditory-visual signals and musculoskeletal gravity perception.[20] Repeated uses of ketamine in neonates causes γ-aminobutyric acid type A ($GABA_A$) R-mediated excitation of neuronal tissue of immature brains. Studies done on animal models and a few preclinical studies have demonstrated that ketamine may cause neuroapoptosis, especially in the forebrain, anterior cingulate cortex and hippocampus. These effects may cause neurodegenerative changes, learning deficits and memory impairment due to synaptic plasticity later in life. These changes are of concern in children <3 years and anaesthetic and sedation duration of >3 hours or longer.[21,22]

Midazolam: Benzodiazepines act via gamma-aminobutyric acid (GABA) receptors. GABA is an inhibitory neurotransmitter in the brain, amygdala, limbic system and spinal internuncial neurons and produces sedation and hypnosis. In preterm infants, midazolam has a lower clearance rate due to the developmental immaturity of CYP3A4 metabolism as compared to older children and adults. Premedication dose of midazolam via oral route is 0.25–0.5 mg/kg, intranasal 0.2–0.3 mg/kg, and 0.05 mg/kg intravenously. Sedation dose of midazolam is 0.2–0.3 mg/kg via intranasal route, 0.1–0.15 mg/kg via intramuscular route, 0.05–0.1 mg/kg intravenously at 6 months to 5 years, and 0.025–0.05 mg/kg intravenously for the age group of 5–12 years. The sedation dose is 1 mg/kg per rectal. Intranasal administration is irritating to the nasal mucosa and has poorer acceptance than the sublingual route.[23]

Dexmedetomidine: Dexmedetomidine acts via hyperpolarisation of non-adrenergic neurons in the locus coeruleus, inducing sedation like natural sleep. Dexmedetomidine 0.3 μg/kg/hour has the longest context-sensitive half-life in neonates, followed by infants at 3 months, 6 months, 1 year and then reaches adult level at 10 years. Dexmedetomidine has a bioavailability of 80% by the transmucosal route and 73% with the intramuscular route. The elimination half-life of dexmedetomidine is 2 hours, and the distribution half-life is 6 minutes. Preterm neonates have lower clearance; larger volume of distribution and longer elimination time as compared to full-term neonates and older children.[1,9,17]

Dexmedetomidine has a neuroprotective effect. It is more useful during magnetic resonance imaging (MRI) than midazolam with an intravenous loading dose of 1–2 μg/kg over 10 minutes, followed by an infusion of 0.5–1 μg/kg/hour. The premedication dose of dexmedetomidine is 2 μg/kg intranasally, 0.5 μg/kg intravenously and 1–2 μg/kg intramuscularly. For emergence delirium and shivering, it can be administered intravenously at a dose of 0.3–0.5 μg/kg.

Inhalational Agents

The minimum alveolar concentration (MAC) of inhalational agents changes with age. MAC steadily increases until 2–3 months of age, but after 3 months, MAC starts declining with a slight increase during puberty. Uptake and elimination of inhalational agents are quicker in paediatric patients as compared to adults. This difference is seen as there is an increased respiratory rate and cardiac index in the paediatric population, with a greater distribution of cardiac output to vessel-rich organs. Changes in ventilation and cardiac output affect soluble inhalational agents more than less soluble anaesthetic agents, such as sevoflurane and desflurane.[8,9] Sevoflurane is widely used for induction during anaesthesia due to its low blood solubility and quick equilibration of alveolar and inspired concentrations.[1,24] Desflurane is

pungent and may trigger upper airway reflexes such as breath-holding and laryngospasm during induction in children. 1 MAC of desflurane is 9.16% in neonates, 9.42% in 1–6 months, 9.92% in 6–12 months, 8.72% in 1–3 years, 8.62% in 3–5 years and 7.98% in 5–12 years age-group as compared to 7% in an adult.[16,23]

Opioids

Remifentanil: Remifentanil is an ultra-fast-acting titratable opioid with a half-life of 3.2 minutes even after 3 hours of continuous intravenous infusion. Remifentanil has a strong affinity for mu receptors and less for kappa and delta-opioid receptors. The dose of remifentanil infusion is 0.05–0.1mg/kg/min with up to 0.5 mg/kg/min as mentioned in a recent study. It has predictable pharmacokinetics and an allometric exponent of 0.76. It has clinical application in short painful procedures due to its stable, haemodynamic and superior control of surgical stress response as compared to other opioids. Remifentanil can be combined with propofol with a clinical combination of 2.5, 5 and 10 mg of remifentanil combined per millilitre of propofol. Remifentanil has adverse effects of short duration. No dose adjustment is required in mild to moderate liver or renal disease.[25,26]

Fentanyl: Fentanyl is 50–100 times more potent than morphine. In premature infants, the half-life of fentanyl is 6–32 hours. The clearance of fentanyl is reduced in preterm neonates, resulting in respiratory depression. Fentanyl dosage via intravenous route is 1–2 μg/kg, continuous infusion 1–3 μg/kg/h, intranasal 1–2 μg/kg and oral transmucosal 5–15 μg/kg. Fentanyl may show variable kinetics (up to 17-fold variation in clearance) in preterm neonates after bolus or continuous infusion.[9,25,26]

Morphine: Morphine is 30–35% protein bound, but in neonates, it is 18–22% bound. Morphine-6-glucuronide metabolite is more potent than morphine. Morphine has a high hepatic extraction coefficient and is dependent on hepatic blood flow. Morphine is metabolised by sulfation rather than glucuronidation. The mean clearance of morphine is 32–52 ml/min/kg in children as compared to 2–16 ml/min/kg in neonates. Larger inter-individual variation has been observed with intravenous morphine in critically ill neonates and infants. Intravenous dose of morphine is 50 μg/kg in neonates and 100 μg/kg in infants and children up to 12 years of age. The dose of morphine as a continuous infusion in neonates is 5-20 μg/kg/h, in infants is 10–30 μg/kg/h, and in children is 20–30 μg/kg/h. Inter-individual variation in critically ill patients can prolong hepatic and renal clearance of morphine and lead to altered pharmacokinetics of morphine.[27]

Tramadol: Tramadol is a weak opioid with weak affinity to μ-opioid receptor. Polymorphism of the cytochrome P450 2D6 (*CYP2D6)* gene results in less conversion of tramadol to its active forms. The use of tramadol for pain relief

is contraindicated in children younger than 12 years, and for post-operative tonsil/adenoid surgery, it is contraindicated in children younger than 18 years as per the latest Food and Drug Administration (FDA) safety announcement. The dosage of intravenous tramadol is 1–2.5 mg/kg, and infusion is 0.1–0.25 mg/kg/h.[1,27] Breastfeeding mothers receiving tramadol for pain relief need to be warned regarding the occurrence of serious respiratory depression in neonates and infants.

Muscle Relaxants

The foetal acetylcholine receptors (AChRs) have 2α, β, γ and δ subunits. During development into adulthood, the γ subunit is replaced by ε subunit. Infants younger than 2 months have a lower train-of-four ratio, and infants > 2 months of age have increased fade. The volume of distribution is greater in children with water-soluble neuromuscular blocking drugs. So, increased dosages are required. Neonates and young infants have a large volume of distribution, and this results in altered response to depolarising neuromuscular agents, with dosage based on body weight. Neonates are resistant to depolarising neuromuscular agents when the administered dose of muscle relaxant is calculated based on body weight. However, when the dose of succinylcholine is calculated based on body surface area (which correlates with extracellular fluid) in neonates and young infants, the resistance to neuromuscular effect is not observed. In neonates, there is increased sensitivity to non-depolarising muscle relaxants due to reduced release of acetylcholine from immature motor nerves, but this effect is countered by the large volume of distribution. Hence, the dose calculations of non-depolarising muscle relaxants are calculated based on body weight.[8,28]

Succinylcholine: The dose is usually calculated based on weight. The dose is 1–3 mg/kg for infants and 2 mg/kg for children, with onset of action 30–60 seconds and duration of action 3–12 minutes.[28] Effective dose 90% (ED_{90}) of succinyl choline in neonates is 0.517 mg/kg and 8.24 mg/m^2.

Vecuronium: Vecuronium is a long-acting neuromuscular agent for infants and children. The dose in infants and children is 0.05–0.1 mg/kg. Onset is rapid in infants, 0.6–0.8 times that of a child and duration is increased by 1.7–2.9 times that of a child.[23,28]

Rocuronium: Rocuronium has a rapid onset and is longer acting in infants than in children. Both succinylcholine and rocuronium are of possible use in rapid sequence induction after ruling out any contraindication. The dose of rocuronium in infants and children is 0.3–1.0 mg/kg. The volume of distribution is larger in infants as compared to children, but clearance is slower in infants as compared to children.[28]

Cisatracurium: The dose of cisatracurium is similar to adults, with increased potency and greater specificity of drug action. Onset of action with intravenous cisatracurium 0.15 mg/kg occurs at 2 min in infants and 3 min in children. For cisatracurium, ED_{95} values are similar for infants, children and adults.[28]

Local Anaesthetics

Premature infants and neonates have a higher sensitivity to LAs due to their immature nervous system and increased sensitivity of sodium channels. Hence, reduced concentration and dose of LA are used in premature infants and neonates.[29] The larger volumes of distribution of water-soluble LAs in neonates and infants, as compared with older children, decrease the risk of high plasma concentrations after a single injection. However, the risk of drug accumulation after a continuous infusion or several injections is increased.[30]

Amino amide LA is metabolised in the liver. However, neonatal liver function is immature, with the maturation of cytochrome P450 enzyme systems occurring at different rates. For example, CYP3A4 typically matures within the first 9 months of life, whilst CYP1A2 may not reach full maturity until around 8 years of age.[31] In contrast, ester-type LA is metabolised by plasma cholinesterase, and the concentration and activity of plasma cholinesterase at birth are similar to those in adults.[29] This causes a higher risk of toxicity in neonates and infants with amide LA as compared to ester LA.

Infants have lower levels of LA-binding proteins, leading to a higher fraction of unbound LA and increased risk of toxicity. This risk is even greater before the age of 6 months when the liver is immature, and especially when continuous infusion or repeated bolus doses are used.[29] Clearance of these drugs is reduced in infants under 3 months, with adult levels reached by 8 months, resulting in longer elimination half-lives in neonates and infants compared to adults. Also, neonates and infants are at a higher risk of cardiac toxicity because of their higher heart rates and prolonged depolarisation phase.

When LA is used in peripheral nerve blocks, the duration of action is extended as compared to term neonates, as the premature neonates metabolise LA more slowly. However, when used for neuraxial anaesthesia, the duration of spinal block is shorter in infants than in adults, due to the larger volume of cerebrospinal fluid coupled with proportionally greater blood flow to the spinal cord, with more rapid uptake of drugs from the subarachnoid space. These phenomena are most pronounced in preterm infants compared with full-term infants.

Whilst using LA in fascial plane blocks, paediatric patients are at a higher risk of LA toxicity compared to adults due to the high vascularity of targeted tissue planes and the large volumes of anaesthetic required for effective spread in fascial planes.[32] Additionally, children's higher cardiac output and local blood flow elevate the likelihood of high plasma concentrations. To minimise risks, it is essential to adhere to dosing guidelines based on lean body weight, use dilute anaesthetic solutions, add epinephrine to reduce systemic absorption, select less cardiotoxic agents and monitor patients closely for 30–45 minutes after the block to observe peak plasma levels.

Furthermore, the concentration of LA used should be carefully selected, especially in children receiving general anaesthesia, where the block primarily provides analgesia. Lower concentrations (e.g., 0.125% levobupivacaine) are preferable for neonates to reduce the toxicity risk and to minimise complications such as masking compartment syndrome or delaying ambulation. However, higher concentrations (e.g., 0.5% levobupivacaine) are appropriate when a strong motor block is needed, such as in tendon transfer surgery for cerebral palsy. LA doses in children are calculated based on milligrams per kilogram, and not on volume as in adults. The recommended dosage of various LA drugs and adjuvants in paediatric patients is summarised in **Tables 1 and 2**.[33]

Synthetic opioids, such as fentanyl, lack evidence of efficacy as adjuvants in paediatric caudal blocks and do not enhance the effects of bupivacaine or ropivacaine.[33]

TABLE 1: Dosage of various local anaesthetic drugs in paediatrics.

Variables	*Bupivacaine*	*Ropivacaine*	*Levobupivacaine*	*Lignocaine with adrenaline*
Allowable dose (mg/kg)	2.5	2	2.5	7
Bolus for upper and lower extremity blocks(mg/kg)	0.5–1.5	0.5–1.5	0.5–1.5	—
Bolus for fascial plane blocks (mg/kg)	0.25–0.75	0.25–0.75	0.25–0.75	—
Concentration for infusions (%)	0.25	0.2	0.25	—
Allowable infusion dose in mg/kg/h	0.2	0.2	0.2	—

TABLE 2: Dosage of various local anaesthetic drug adjuvants in paediatrics.

Drug	*Intrathecal dose*	*Caudal epidural doses*	*Peripheral nerve block*	*Side effects*
Morphine	3 µg/kg	30–90 µg/kg		Nausea, vomiting and respiratory depression
Dexmedetomidine	0.5–1 µg/kg	1–2 µg/kg	0.25–0.75 µg/kg	Sedation, bradycardia and hypotension
Clonidine	0.5–1 µg/kg	1–2 µg/kg		Sedation, bradycardia and hypotension

EFFECT OF ANAESTHETIC EXPOSURE DURING CHILDHOOD ON THE DEVELOPING BRAIN

Animal studies suggest that anaesthetic exposure can harm the developing brain, leading to cognitive and functional impairments. Not only general anaesthetics but also hyperoxia can affect the developing brain. Hyperoxia is a well-known cause of cerebral white matter injury in preterm infants, with the male gender being an independent and critical risk factor for poor neurodevelopmental outcomes. Gender is therefore widely considered as one of the major decisive factors for the prognosis and treatment of these infants. Hyperoxia is a powerful trigger for the widespread apoptotic neuronal death and degeneration in the white matter tracts and periventricular regions in the developing brain. However, the molecular mechanisms and details regarding this still need to be uncovered.[34]

Recent research highlights the significant role of long non-coding ribonucleic acids (lncRNAs) in brain injury induced by hyperoxia.[35-37] For instance, the lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) has been identified as promoting neuroprotection during hypoxic/ischaemic injury. Additionally, studies have demonstrated that inhibiting lncRNA H19 can aid in the recovery from traumatic brain injury by activating the nuclear factor erythroid 2-related factor 2/heme oxygenase 1 (Nrf2/HO-1) pathway, facilitating both neuropathological and functional improvements.[36]

MECHANISMS OF NEUROTOXICITY

Inflammation and Immature Vascularisation

Systemic inflammation, potentially triggered by surgical stress or prenatal conditions, combined with hypoxia-ischaemia, activates microglia, releasing cytokines and free radicals and can lead to impaired cerebral flow. This

leads to excitotoxicity, damaging pre-oligodendrocytes and resulting in hypomyelination. Prolonged exposure to anaesthetics such as sevoflurane and propofol can cause mitochondrial injury, increasing reactive oxygen species (ROS) production and brain damage.[38] Isoflurane disrupts astrocyte development, further affecting brain maturation.[39]

Binding of Anaesthetics to N-Methyl-D-Aspartate and Gamma-Aminobutyric Acid Receptors

This binding disturbs intracellular calcium levels and mitochondrial function, thereby disrupting synaptic transmission and the excitatory-inhibitory balance essential for brain development.

Contrarily, sub-toxic doses of anaesthetics have been shown to confer neuroprotection. Isoflurane and sevoflurane preconditioning have been shown to improve outcomes in animal models through mechanisms such as protein kinase B activation, ROS release, and modulation of various signalling pathways.[40,41]

LONG-TERM NEUROCOGNITIVE OUTCOMES

Cognitive Deficits

Some studies suggest a risk of cognitive deficits, especially in language and abstract reasoning. However, the General Anaesthesia compared to Spinal anaesthesia (GAS) study found no increased neurocognitive impairment at 5 years.[42]

Behavioural Problems

Early anaesthesia exposure may be linked to behavioural issues, such as hyperactivity.[43] The GAS study found no increased risk of autism spectrum disorder or attention deficit hyperactivity disorder, though these conditions are typically diagnosed in older children.[42]

PRENATAL EXPOSURE TO ANAESTHETIC DRUGS AND EFFECTS ON THE FOETUS

Advanced medical and surgical technology has led to more frequent interventions during pregnancy. The mid-trimester of pregnancy is considered a safe period for surgery, but it is still a delicate phase for the foetus, as during this time, the central nervous system undergoes significant maturation, making it particularly susceptible to the anaesthetic drugs.

Understanding the anaesthetic transfer between the maternal and foetal systems is therefore crucial for minimising adverse effects. Although the placenta serves as a barrier to regulate the transfer of substances from the mother to the foetus, it is not completely effective in preventing the passage

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Salient Features

- It is the first book of the College of Indian Society of Anaesthesiologists (CISA), which is the academic wing of the Indian Society of Anaesthesiologists and aims to enhance the knowledge and practicing skills of both postgraduate students and practitioners.
- All chapters provide the latest and quality information on almost all basic aspects of paediatric anaesthesia and emergency situations in paediatric anaesthesia with an emphasis on patient safety.
- The book includes chapters on specialized topics such as molecular pharmacology, foetal surgery, anaesthesia for laparoscopy in children, paediatric airway surgery, regional anaesthesia in children including the latest nerve blocks, vasopressors and inotropes in children, and enhanced recovery after surgery, which provides the latest concepts to all the readers.
- It also has chapters dedicated to ethics, research, rights of children, curriculum, training and soft skills required in paediatric anaesthesia, which are not the regular features of standard textbooks of anaesthesia.
- It has a unique chapter which provides practical tips on anaesthetising children in resource-limited settings without compromising the clinical care and patient safety.
- Chapters are written by authors well experienced in paediatric anaesthesia from different states and cities of our country, which provide a good mix of clinical pearls practiced in different parts of our country.
- Each chapter has a rich information about the latest clinical knowledge, practical aspects, and expert opinions of different stalwarts in the field of paediatric anaesthesia.

Shelving Recommendation
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