Clinical Pharmacology of Anesthetic Drugs in Neonates

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17.1 Introduction

Neonates include preterm, term, and former preterm neonates (who may now be older than 28 days in age). This heterogenous group of patients consists of newborns with postmenstrual age (PMC) ranging from 22 weeks (severe preterm) to 50 weeks (post term), and birth weight ranging from 500 g to 5000 g. The leading indication for surgery is correction of congenital defects or malformations (seen in nearly 3% of newborns and occurring due to defective embryogenesis). These congenital defects contribute to around 15% of the perinatal mortality in India [1].

The neonatal period is characterised by immaturity and underdevelopment of all organ systems, affecting drug pharmacokinetics, pharmacodynamics, drug responses, and long-term effects. Effective and safe administration of drugs in the neonate depends on their evolving physiological characteristics, such as age, weight and size, comorbidities, coadministration of other drugs, genetic susceptibilities, and pharmacokinetics and pharmacodynamics of the drug being used.

Since neonates are a vulnerable population and, therefore, not usually added to studies by pharmaceutical companies for ethical or logistical reasons, such as technical issues, lack of self-reporting, lack of specific formulations etc., there is limited drug data in neonates. Outcome measures are also difficult to assess. Many of the medications are used 'off label', with only three anesthetic drugs; sevoflurane, remifentanil, and rocuronium having received food and drug administration (FDA) approval for use in neonates and none for preterm neonates born before 30 weeks of gestation [2].

This chapter will take the reader through the pharmacological principles of drug action in neonates, such as developmental pharmacology, neurodevelopmental

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U. Saha (ed.), *Clinical Anesthesia for the Newborn and the Neonate*,
https://doi.org/10.1007/978-981-19-5458-0_17

effects, pharmacokinetics and pharmacodynamics, body composition (plasma protein, Fetal Hb), cardiac output and regional blood flow, drug elimination (hepatic and extrahepatic), anesthetic drugs, local anesthetic, miscellaneous and resuscitative drugs, their doses, and anesthetic implications or considerations.

Note: Oxygen, nitrous oxide. Air, IV fluids, Blood and blood products, also are drugs in technical terms, as they deserve same care, precautions and considerations, as all chemical drugs, because low and high doses will have less or more effect, side effects and adverse or toxic effects on the developing organs, especially the brain. These are discussed elsewhere in this book.

17.2 General Pharmacological Definitions and Terms

17.2.1 Pharmacology

Pharmacology is a branch of medicine that is concerned with drug or pharmacon defined as any artificial, natural, or endogenous molecule with biochemical or physiological effects. It studies the interactions between living being and chemicals, and includes neuro, renal, cardiovascular, endocrine, and immune pharmacology, central and peripheral nervous system, and drug metabolism and regulation. This requires intimate knowledge of the biological system affected, and cell biology and biochemistry.

The two main areas of pharmacology are:

(a) Pharmacodynamics (effect of a drug on biological systems)
(b) Pharmacokinetics (effects of biological systems on the drug)

17.2.2 Clinical pharmacology

Clinical pharmacology is application of pharmacological principles to patient care, and **posology** is the study of medicine dosing. Modern pharmacology is a biomedical science that uses genetics, molecular biology, biochemistry, and other advanced tools to understand molecular information which is transformed into therapies directed against disease and pathogens or for diagnostic, preventive, and therapeutic care [3].

17.2.3 Therapeutic index

Therapeutic index describes the safety profile of a drug. It is the ratio of the desired to the toxic effect. A narrow therapeutic index (close to one) means that the desired effect of a drug occurs at a dose close to the toxic dose, while a wide therapeutic index (>5) means that the desired effect occurs at a dose much below the toxic dose.

17.2.4 Drug approvals

In the US, the FDA is responsible for creating guidelines for approval and use of drugs, with the condition that all approved drugs fulfill two requirements:

1. **Efficacy**: must be effective against the disease for which it is seeking approval
2. **Safety**: must meet safety criteria (animal and controlled human testing)

17.3 Developmental Pharmacology

The major reasons for pharmacokinetic variabilities in neonates are due to age, weight, and organ function. Although the most common variable used to calculate drug requirement is weight, it is not sufficient to predict drug clearance, which is important for drug infusion or maintenance rates. The gestational age/maturity plays a significant role in determining metabolism and clearance from the body. Compromised organ (liver and kidney) development and function due to illness may further impact drug clearance.

17.4 Pharmacokinetics

Pharmacokinetics describe the effect of the body or the biological systems on the drug or chemical (e.g., half-life and volume of distribution). **LADME** describes the pharmacokinetic properties of the API (active pharmaceutical ingredient), i.e., Liberation (for oral drugs), Absorption, Distribution, Metabolism and Excretion. The pharmacokinetics of drugs is very different in neonates when compared to infants and older children [4, 5].

17.4.1 Drug Absorption

Drug absorption and its effects depend on the route of administration.

Most anesthetic drugs are administered through the intravenous or the inhalational route.

17.4.1.1 Oral

O**ral** route is employed for premedication (in liquid form), and for postoperative analgesia. The absorption of oral medications is slow due to reduced gastric emptying and poor GI motility, especially if associated with abdominal pathologies, such as duodenal atresia and necrotising enterocolitis (NEC) or due to coadministration of opioids. Slow gastric emptying and absorption means inadequate or delayed desired effect. This, along with delayed clearance means that both onset of action and excretion will be slow, and hence, the interval between doses must be increased and frequency reduced, e.g., the dose of paracetamol ranges from 25 mg/kg/day in

a preterm neonate to 60 mg/kg/day in a term neonate, at 8–12 h interval instead of 4–6 h interval in older children and adults.

17.4.1.2 Rectal

Rectal route has been frequently used for agents such as thiopentone and methohexitone for induction of anesthesia in the pediatric age group. In neonates, rectal administration of anesthetics can also lead to speedy induction; however, due to variability in absorption, altered bioavailability, and gastrointestinal diseases, this is not a very suitable route for administration of drugs.

17.4.1.3 External Application

A relatively large body surface area, thinner stratum corneum layer of skin, and more vascularity, predispose neonates to greater absorption of local anesthetics applied to the skin as compared to older children. EMLA ointment (eutectic mixture of lignocaine and prilocaine) applied before placement of intravenous (IV) or intra-arterial cannulae has a quicker onset of action, but is associated with risk of methemoglobinemia because of prilocaine. Higher amounts of fetal hemoglobin (fHb) with reduced methemoglobin reductase activity mean that neonates have a higher tendency to form methemoglobin. Hence, use of this ointment is better avoided. A study by Shahid et al. on 907 infants under the age of 3 months, published in 2019, reported minimal benefits of EMLA in terms of reduction of venipuncture pain and no benefit in comparison with sucrose and/or breastfeeding. Moreover, it produced elevation in methemoglobin levels and skin blanching [6].

17.4.1.4 Inhalation Route

Absorption of inhaled anesthetics and speed of induction depends on functional residual capacity (FRC), alveolar ventilation, cardiac output, and tissue blood solubility of the agent. It is more rapid in neonates because of higher alveolar ventilation-to-FRC ratio, higher cardiac output, lower blood gas solubility, and lower tissue solubility of volatile anesthetics. Even while FRC is small, but because of increased alveolar ventilation, pulmonary absorption is rapid, with faster induction of anesthesia.

This is further facilitated by high cardiac output, better distribution of blood to highly vascular areas, such as brain, and lower tissue blood solubility. In neonates suffering from cyanotic heart disease or lung diseases, or in conditions with greater right to left (R–L) shunt, induction may be slowed, while left to right (L–R) shunt has minimal impact.

17.4.1.5 Intravenous Route

Intravenous route: IV route is a sure and direct method of drug administration, that bypasses hurdles faced by other routes in drug absorption. The onset of action is quick, effect is more predictable and clearance is also faster. In neonates with R–L intracardiac shunt, the onset of action is faster, because it bypasses the pulmonary circulation and reaches the brain earlier, compared to L–R shunt, where onset is slower and effect is less because of greater dilution of the drug in the heart.

17.4.2 Drug Distribution

Distribution of drugs in the body compartments depends on the **body composition, protein binding, and regional blood flow.**

17.4.2.1 Body Composition

Neonates have relatively higher total body water (TBW) and larger extracellular fluid (ECF) volume, lower muscle mass and less fat as compared to older children. This affects their volume of distribution (V_D) for drugs. Distribution is also affected by the nature of the drug, whether hydrophilic or lipophilic. The V_D of hydrophilic drugs is greater (higher TBW and ECF) than that in older children and adults. Hence, the initial dose of **polar (hydrophilic) molecules and drugs** (Table 17.1) (such as neuromuscular blocking (NMB) agents, which are rapidly distributed in the ECF and have slow cellular uptake), will be higher than in older children or adults on per kg body weight basis. In some cases, this leads to larger volume of free drug, which can increase risk for toxicity, especially that of local anesthetics, especially because of their slow metabolism and poor clearance. Premature babies have even greater body water and lower fat content as compared to term neonates, and all these effects are more pronounced in them, requiring greater care and precision during IV drug administration.

Termination of action of drugs such as **thiopentone** and **propofol** is by redistribution rather than clearance. The lesser fat and muscle content in neonates means that they have a lower volume for redistribution into the tissues, and CNS concentration remains high for a longer period of time. Thus, they have prolonged duration of action and delayed awakening as compared to older children.

Fentanyl has a higher volume of distribution, so initially, there is less respiratory depression with the standard dose. However, since clearance by redistribution is reduced higher or repeated dosing can lead to a prolonged effect and greater or delayed respiratory depression.

Table 17.1 Polar and nonpolar molecules

Polar molecules	Nonpolar molecules
• Water—H_2O • Ammonia—NH_3 • Sulfur dioxide—SO_2 • Hydrogen sulfide—H_2S • Ethanol—C_2H_6O • NaCl (sodium chloride) • Neuro muscular blockers	• Noble gasses: He, Ne, Ar, Kr, Xe • Homonuclear diatomic elements: H_2, N_2, O_2, Cl_2 • Carbon dioxide—CO_2 • Benzene—C_6H_6 • Carbon tetrachloride—CCl_4 • Methane—CH_4 • Ethylene—C_2H_4 • Hydrocarbon liquids, such as gasoline, toluene • Most organic molecules • Volatile anaesthetic agents • Opioids

17.4.3 Plasma Proteins and Protein Binding

Changes in concentration and composition of circulating plasma proteins also influence the distribution of highly protein bound drugs. Total serum proteins and albumin fraction are low in neonates and reach adult values by 6 months of age. They also tend to have metabolic acidosis which can affect the ionization and binding of drugs to plasma proteins. The ability to bind to drugs can take from 6 months to 1 year to reach adult values. This implies that the loading dose of drugs has to be modified accordingly. Diazepam and barbiturates bind to albumin, and lignocaine binds to alpha-1 acid glycoprotein, and will have higher free level and greater effect.

The presence of fetal albumin, which is functionally immature, has been postulated to explain the **reduced ability of newborn plasma to bind bilirubin and various drugs,** resulting in higher free fraction of protein bound drugs.

For hydrophilic drugs, higher dose by body weight is required to reach therapeutic levels. This leads to more free form of drugs with increased risk of toxicity, especially that of local anesthetics.

Highly lipophilic drugs such as propofol have a lower volume of distribution potentially resulting in a higher drug concentration because of limited distribution in the reduced fat tissue. The free level of thiopentone is higher in neonates (13%) as compared to older children and adults (7%); hence, induction dose should be reduced.

Fetal albumin also affects binding of bilirubin and fatty acids. These also compete with drugs for binding sites on albumin and further increase the free drug levels. Besides, displacement of bilirubin from protein binding sites increases the risk of kernicterus, especially in sick neonates.

Protein binding has a significant effect on drug clearance. The desired effect of a drug is proportional to its free form in the plasma, and that bound to plasma proteins acts as a reservoir. Clearance occurs of the free ionized form in the plasma. Because of high protein binding of some drugs, though the plasma concentration may be low, it will continue to be maintained as more and more drug is released from the binding site to replace that cleared. This causes prolongation of effect. However, high protein binding may also be beneficial by maintaining clearance by keeping plasma concentration constant.

17.4.3.1 Regional Blood Flow

Distribution of regional blood flow to the brain determines the onset of action, whereas redistribution to tissues such as the skeletal muscle determines the termination of action of many drugs. This distribution can be further affected by persistence of embryonic circulation, such as a patent ductus arterioles (PDA). The brain in neonates is large in relation to the total body weight, but receives a relatively lesser proportion of cardiac output. Redistribution is also limited. Hence, onset as well as termination of IV induction agents is slower than older children.

The blood–brain barrier (BBB) is a network of junctions that limit diffusion of compounds between the blood and the brain. It is underdeveloped at birth and more immature in preterm babies. The transport of water soluble and lipophilic drugs

(such as morphine) across the BBB depends on its maturation. Protein bound drugs usually cannot cross the BBB in term neonates, while unbound lipophilic drugs can cross over easily. The higher brain concentrations of morphine and greater respiratory depression seen with it in neonates are explained by the higher permeability of the BBB to morphine. Pathological conditions of the CNS, fever or other drugs may alter the permeability of the BBB and modify the responses to drugs, such as opioids.

Bupivacaine, similar to lignocaine, also binds to alpha 1 acid glycoprotein, which is low in neonates, and hence results in higher free concentration of this drug. Due to its lipophilic nature, bupivacaine can cross the immature BBB, with tendency to cause seizures in the neonate.

17.4.4 Drug Elimination

Elimination of drugs from the body depends on their clearance and excretion. A few definitions are important to understand elimination of drugs from the body, and will help the reader understand how this affects the neonate. **Clearance** is defined as the volume of plasma from which a substance is completely removed per unit time (L/h or ml/min) and **excretion** is the amount of substance removed from the body per unit time, expressed in mg/min, μg/min. The sum of clearance of a substance by all the routes must be considered for calculating **total body clearance.** It must be kept in mind that while a constant amount of drug is eliminated per unit time, this amount keeps changing with the changes in the blood levels of the drug. Another important term is **intercompartmental clearance** which refers to the redistribution of drug or substance between body compartments, e.g., plasma, muscle, and fat.

The primary routes of elimination of all compounds, substance, drugs, and their metabolites, whether exogenous or endogenous, are through the **hepatic (hepatobiliary) and extrahepatic (renal, pulmonary, and enzymatic)** routes. At birth, especially in premature babies, these are immature and adult levels are not achieved until the age of 2 years.

17.4.4.1 Hepatic Elimination

Liver is the primary organ for inactivation and metabolic clearance of drugs and substances. Most compounds are usually metabolized by more than one enzyme systems. The presence of genetic polymorphism is responsible for variations in drug metabolism in different individuals. Chromosomal and genetic abnormalities in a neonate increase chances of this polymorphism and affect drug metabolism. Drug metabolism occurs in two phases: **Phase 1 reactions** (oxidation, reduction, and hydrolysis) and **Phase 2 reactions** (conjugation–sulphuration, glucuronidation, and acetylation). While some substances undergo either one of the two reactions, others undergo both reactions, one after the other.

Plasma clearance of drugs metabolized in the liver is age dependent, such that drug elimination by biotransformation is slower in neonates than in infants and older children. Phase II sulfate conjugation is fully developed at term, but

glucuronidation and acetylation are not. Anesthetic drugs such as propofol, dexmedetomidine, morphine, and paracetamol depend on glucuronidation for their clearance. Their duration of action is prolonged in newborns, especially the preterm neonate, and only nears adult values after the first year of life. Nondepolarizing muscle relaxants (NDMR)s, vecuronium, and rocuronium are also metabolized in the liver and excreted in the bile. Enzyme systems, cytochrome P 450 and noncytochrome P 450, both are involved in metabolism and these too are immature at birth, but by 44 weeks of postmenstrual age, their activity reaches 85% of adult values. Hence, less frequent dosing and lower infusion rates must be used soon after birth and in premature neonates.

17.4.4.2 Extrahepatic Drug Elimination

17.4.4.2.1 Renal Elimination

Renal elimination of drugs and their metabolites occurs through two mechanisms: **glomerular filtration or tubular secretion.** Almost all substances pass through the kidneys for elimination by filtration, secretion or for reabsorption. Besides, kidneys also have enzymes that metabolize many substances.

Renal function in the neonates is lower than expected on basis of the body weight or body surface area, due to reduced renal blood flow and GFR, decreased capacity of the renal tubules to concentrate or acidify urine, and poor transport of organic ions for active tubular secretion.

Glomerular filtration is the main mechanism by which substances are removed from circulation. At birth, GFR is only 35% of adult values in a term newborn and much lower in a preterm newborn. It attains 90% of adult activity by 1 year of life. This influences clearance of drugs excreted via the kidneys, with increase in the half-life and duration of action of drugs principally eliminated by renal clearance, in neonates, and especially in preterm. Anesthetic drugs eliminated through the kidneys include milrinone, which is commonly used after congenital cardiac surgery in neonates, theophylline, antibiotics (aminoglycosides, penicillin, cephalosporin, and tetracycline), cardiac drugs (beta-blockers, digoxin, procainamide, and diuretics), lithium, antacids (cimetidine, ranitidine), and phenobarbital.

Urinary pH, by influencing the ionization of compounds excreted, affects their renal elimination. Many drugs are weak acids or bases, and are in both ionized and nonionized forms. The ionized component, being water soluble or hydrophilic, is easily cleared. Phenobarbital is a weak polar acid, and moderately binds to proteins, but instead of being eliminated, it is reabsorbed in the renal tubules, with low clearance and prolonged duration of action. Morphine and paracetamol are metabolized by the kidneys.

Several drugs can themselves cause renal damage, such as antibiotics (ciprofloxacin, methicillin, vancomycin, and sulphonamides) and NSAID analgesics (aspirin, naproxen, and ibuprofen). They can reduce the GFR by nearly 20%, especially in the preterm neonate, and reduce renal elimination of other drugs so should be administered with care.

All these factors affect drug excretion in the neonates and the premature. This necessitates a change in drug schedules, dosing intervals and infusion rates.

17.4.4.2.2 Pulmonary Elimination

Alveolar ventilation, FRC, cardiac output, and blood gas solubility are the main factors that affect anesthetic drug absorption through the lungs, and these are the very factors that also affect their elimination and washout. The increase in alveolar ventilation, high alveolar ventilation-to-FRC ratio, reduced solubility of volatile anesthetics, and higher percentage of the cardiac output being delivered to the brain leads to higher uptake of volatile agents, in neonates as compared to older children and adults. The minimum alveolar concentration (MAC) of inhalation agents is characteristically reduced in preterms, peaks at 1–6 months of age and then falls to reach adult values by adolescence. Lower concentration of inhalational agents is also required, because they produce greater myocardial depression in the neonate. However, the MAC of sevoflurane (3.2%) is not reduced in preterm or neonates, and is comparable to older children.

17.4.4.2.3 Enzymatic Metabolism/Hydrolysis

Many drugs are not metabolized in the liver nor cleared by the kidneys and lungs. They undergo hydrolysis in the plasma by esterases, leading to the termination of their effect, and hence their elimination depends on the maturity and concentration of esterases. Esterases are of two types: **acetyl or erythrocyte or true cholinesterase (ACHE) and pseudo or plasma or butyryl or false cholinesterase or cholinesterase2 (BCHE). Colloquially, cholinesterase refers to pseudocholinesterase.**

(a) **ACHE** is present at the neuromuscular junction (NMJ), in the RBC membrane, and at other neural sites. It hydrolyses acetylcholine more quickly into choline and acetic acid. High levels in amniotic fluid are predictive of abdominal wall and neural tube defects. Drugs such as **atracurium, succinylcholine, and remifentanil** are metabolized by ACHE and are not dependent on the liver or kidney for their elimination. Since these enzymatic reactions are mature at birth, even in preterm neonates, dose modification is not required, rather clearance of these drugs may be increased as compared to adults.
(b) **BCHE** is present in the plasma, and it hydrolyses butyrylcholine more rapidly. It is synthesized in the liver and immediately released into the plasma, with a half-life is 10–14 days. It hydrolyses succinylcholine, atracurium, and cis-atracurium (benzylisoquinoline diesters).

Pseudocholinesterase deficiency occurs in 1:3,200–5,000 people, and may be genetic (gene mutation) or acquired. Deficiency or reduced activity of BCHE results in significant prolongation of effect of ester local anaesthetics (procaine, chloroprocaine, and tetracaine) and increases in sensitivity of muscles to scoline- and mivacurium-induced neuromuscular blockade. In neonates, BCHE is deficient because of immature hepatic production. Pseudocholinesterase deficiency is silent and is not discovered until an abnormal drug reaction occurs.

Causes of BCHE Deficiency:

i. **Genetic** or inherited—BCHE gene mutation
ii. **Acquired**—neonates, elderly individuals, and pregnancy, chronic infections (tuberculosis), extensive burns, liver and kidney disease, uraemia, heart failure, malignancy, malnutrition, organophosphate poisoning, collagen diseases, hypothyroidism, plasmapheresis, and **medications** like cholinesterase inhibitors—chlorpromazine, cyclophosphamide, ecothiophate eye drops, esmolol, glucocorticoids, and pancuronium, and benzodiazepines (temazepam).

Clinical Implication in Neonates:

(a) **Dose of scoline** in neonates is higher than in children (3–4 mg/kg), but caution needs to be exercised because of inability to establish the deficiency of BCHE. Neonates have low plasma levels of BCHE because of reduced hepatic production. Because of potential risk of prolonged duration, Phase 2 block, and availability of shorter acting nondepolarizing muscle relaxants (**NDMR**), anaesthetists are moving away from using scoline for intubation.
(b) **Avoid use of ester local anaesthetics** as prilocaine has an additional risk of causing methemoglobinemia. It is preferred to use amide local anaesthetics in this age group.

17.5 Pharmacodynamics

Pharmacodynamics is defined as how the body reacts to the drug or the effect of the drug on the body (desired or toxic).

Pharmacodynamics of drugs is altered in neonates, but there are large gaps in our knowledge about the pharmacodynamics of anesthetic drugs in neonates. Outcome measures such as effect on circulation, respiration, and neuromuscular blockade can be assessed, but variables such as pain, memory, and unconsciousness are hard to evaluate:

i. The MAC of **inhalational agents** is less in neonates than that in infants.
ii. Their brain is more sensitive to the effects of **sedatives**.
iii. There is increased sensitivity to depolarizing **drugs**.
iv. Reduced duration of regional block with **amide local anesthetics**.
v. Prolonged effect with **ester local anesthetics**.
vi. For **spinal anesthesia**, the weight to dose requirement of local anesthetics is more and the duration of action is shorter. This might be due to incomplete myelination.
vii. Some drugs are **ineffective** in neonates, e.g., bronchodilators, due to underdeveloped bronchial smooth muscle or drugs that affect intestinal motility.

17.6 Anesthetic Agents

17.6.1 Inhaled Anesthetic Agents

Inhalation induction is commonly used technique for neonates due to its rapid onset. The absorption as well as elimination of drugs via the respiratory system depends on many factors, such as inspired concentration, alveolar ventilation, FRC, cardiac output, and blood gas solubility. Neonates have a high alveolar ventilation to FRC ratio of 5:1 which is nearly three times that of adults. The increase in alveolar ventilation in neonates leads to a higher volatile agent uptake. The solubility of volatile anesthetics is reduced in the newborn, so there is less uptake of anesthetic by the tissues, allowing partial pressures in the FRC to rise rapidly. Furthermore, a higher percentage of the cardiac output is delivered to vessel rich organs, especially brain, allowing rapid equilibration of alveolar and cerebral partial pressures of the agent. All these factors lead to rapid inhalational induction in newborns. In neonates with cyanotic heart disease or lung diseases, where there is a greater right to left shunt, induction may be slowed, while left-to-right shunts have a minimal impact.

The MAC of inhalational anesthetic agents in children is age dependent. (Table 17.2) It is lower in preterm than term neonates [7, 8]. Lower concentration of inhalational agents must be used in newborns as they produce greater depression of myocardium, greater hypotension, and depression of respiration, with inhibition of the ventilatory response to CO_2. This requires respiration to be assisted early during induction, which increases the potential for overdose of inhalation agent, while attempts are being made to establish an IV line. While myocardial depression is most often seen with halothane, it can occur with sevoflurane also. Recovery from inhalation agents is slower than expected. The effect of inhalational anesthetics on various organ systems in the neonate has not been studied but is thought to be similar to those seen in infants and older children.

a. **Halothane:** Before sevoflurane, halothane was the agent of choice for induction of anesthesia in neonates. It is a relatively potent agent, but because of its higher blood gas solubility, induction and recovery are slower as compared to sevoflurane. Its MAC is low in neonates, and causes profound myocardial depression, hypotension, with sensitization of the myocardium to both exogenous and endogenous catecholamines, and high risk of arrythmias, especially if accom-

Table 17.2 Comparative MAC for modern inhalational agents [10]

	Sevoflurane	Desflurane	Isoflurane	Nitrous oxide
MAC adult	2.05%	7.0%	1.2%	104%
MAC neonate (full term)	3.2%	9.2%	1.6%	–

panied with hypoxemia and hypercarbia. This is believed to be due to lesser number of myocardial contractile elements, less sensitivity of the myocardium to calcium, and incomplete cardiac sympathetic innervation. Cardio depressant effects of halothane can be attenuated by maintaining the heart rate and preload; hence, atropine is frequently used at induction, more so if scoline is used for intubation [9].

b. **Sevoflurane:** Sevoflurane is less pungent than isoflurane and desflurane, has low blood solubility, hence causes rapid induction and emergence from anesthesia. It is the anesthetic agent of choice for induction in neonates. It is not associated with vomiting or emergence delirium seen in children. Unlike other agents, the MAC of sevoflurane (3.3%) is the same in term, preterm neonates and infants under 6 months of age.
c. **Isoflurane:** Isoflurane has blood solubility intermediate of halothane and sevoflurane. It is more potent than sevoflurane, but its unpleasant smell leads to a higher risk of airway complications, such as breath holding, laryngospasm, and bronchospasm, thus making it unsuitable for induction. However, it can be used for maintenance of anesthesia.
d. **Desflurane:** Just like the other agents, MAC of desflurane is low in neonates. Its blood solubility is lower than isoflurane and sevoflurane, which facilitates rapid induction and emergence from anesthesia. It is suitable for maintenance. It is not suitable for induction due to its noxious smell, high incidence of laryngospasm, and high cost.
e **Nitrous oxide:** Nitrous oxide has low solubility, low potency and is a weak analgesic. It can be used along with other inhalational agents for increasing the speed of induction and to reduce their requirement during maintenance. Neonates, especially preterm, are at high risk of O_2 toxicity and retinal damage and use of N_2O avoids high oxygen tensions. However, any difficulty with the airway can lead to rapid desaturation so, air is a better option than N_2O and should be preferred if available.

17.6.2 Intravenous Anesthetic Agents

The dose–response relationship for intravenous agents has not been well-studied in neonates; thus, dosage guidelines are generally extrapolated from adult data or that from older children. In neonates, there is delayed awakening from IV induction, and termination of action is by redistribution which is slow due to less fat and muscle mass. Hence, brain concentration stays high for a longer period.

a. **Propofol:** Although there is paucity of literature regarding neonates, propofol has been used in them. The induction dose is less than that for older children (1–2 mg/kg) and clearance is longer. It tends to cause profound myocardial depression which leads to hypotension, especially in sick neonates, so should be used with caution. Furthermore, as an infusion, there is a risk of metabolic acidosis, organ failure, and death. Though the induction dose of propofol in neonates is relatively higher than in adults/kg body weight due to a larger volume of distribution, but the dose and duration of propofol need to be limited,

especially in early postnatal life. Reduction in systemic vascular resistance, caused by propofol in acidotic or hypoxemic newborns, can cause return of circulation to fetal type transiently.

b. **Thiopentone:** Dose requirement of thiopentone is much lower in neonates than in infants. There are many reasons postulated. It crosses the BBB more easily and its clearance by redistribution is also slower hence causes prolonged effect. The cerebral cortical function is more immature with fewer synapses, making the brain more susceptible to the action of thiopentone. It may be used for induction in a reduced dose (2–4 mg/kg).
c. **Ketamine:** Ketamine is used very infrequently for induction in neonates. Since it does not cause myocardial depression and maintains systemic vascular resistance, it has been used for premedication and induction in neonates with cyanotic congenital heart disease. It is a potent analgesic, but is considered controversial, because ketamine has been shown to cause neuronal apoptosis in newborn rats. The initial requirement is higher than in older children, and clearance is also reduced. There is no merit in routine use of ketamine in neonates, except in very sick, hemodynamically unstable, and bradycardic neonates.
d. **Etomidate:** Etomidate suppresses adrenal function and corticoid secretion, and has limited indication in neonates. Its volume of distribution is large, so initial dose requirement is high.

17.6.3 Analgesics

17.6.3.1 Alpha 2 Agonists

a. **Clonidine:** An increase in clearance time has been observed with clonidine in neonates, which reaches adult levels by 1 year of age. Clonidine has been used for sedation in the NICU, for management of neonatal abstinence syndrome, and as an additive to caudal and epidural anesthesia. It prolongs the duration of analgesia in children, but not much data is available in neonates [11]. It can lead to apnea in neonates [12, 13], has not received FDA approval.
b. **Dexmedetomidine:** There has been limited use of this agent in neonates. As with many other agents, it shows reduced clearance. It has been used as an additive to neuraxial block and though it has still not received FDA approval for use in neonates. Its uses in children include procedural sedation, opioid withdrawal, prevention of emergence delirium, and postoperative analgesia, but studies in neonates are limited.

17.6.3.2 Opioids (Table 17.3)

a. **Morphine:** Morphine is a long-acting opioid which has been used in neonates, for both intraoperative and postoperative analgesia, as bolus or infusion, especially in those requiring assisted ventilation. Apart from the IV route, oral, rectal, and caudal routes have also been used. It is metabolized in the liver and is eliminated after glucuronidation and sulfonation. Although sulfonation plays a minor role in adults, it is an important pathway for drug clearance in neonates.

Table 17.3 Recommended analgesic dosing for neonates

Medication	Intermittent dose	Infusion dose	Adverse effects
Acetaminophen	10 mg/kg IV/PO	N/A	None reported[a]
NSAIDS	Not recommended	N/A	Unwanted ductal closure, gastropathy, nephropathy, NEC, IVH, surgical bleeding
Morphine	0.05–0.1 mg/kg IV	0.005–0.03 mg/H	Respiratory depression, decreased gastrointestinal motility, hypotension, urinary retention
Fentanyl	1 mcg/kg IV	0.5–2 mcg/kg/H	Respiratory depression, hypotension, muscle rigidity, hypothermia
Ketamine	0.5–2 mg/kg IV	0.5–1 mg/kg/H	Respiratory depression, increased secretions

[a]No reported adverse effects in therapeutic doses. Known hepatotoxicity with overdosing. *NSAIDS* Nonsteroidal anti-inflammatory drugs, *NEC* Necrotizing enterocolitis, *IVH* Intraventricular hemorrhage

The metabolites of morphine are dependent on renal elimination. Hence, prolongation of action of morphine is seen due to immature liver function and reduced renal excretion. Furthermore, it causes severe respiratory depression, especially in preterm, probably due to immaturity of the BBB. It is, therefore, better to avoid morphine in this age group or to use it with extreme caution.

b. **Codeine:** Codeine, especially in combination with paracetamol or NSAIDS, has been used in infants. Its analgesic effect is due to its metabolism to morphine. It can be used in term neonates, but is not useful in preterm neonates as its conversion to morphine is limited. Intravenous use can lead to hypotension and is not recommended. It can be used orally, rectally or intramuscularly [14].
c. **Pethidine:** Pethidine is more lipophilic than morphine and lesser amounts cross the BBB, so it can be used in newborns. Even though it is less metabolized in neonates than adults, it should not be used for long periods or repeated administration due to risk of accumulation of its toxic metabolite norpethidine, which can lead to seizures. Elimination of pethidine is greatly reduced in neonates with prolongation of its action.
d. **Fentanyl:** The introduction of fentanyl has allowed safer and more effective pain management in the neonates. Its advantages include rapid onset due to high penetration of BBB, short duration of action, hemodynamic stability, suppression of neonatal stress response and better outcome after surgery. The volume of distribution is high, clearance is reduced, elimination half-life is longer, compared to older children and adults. Hence, the dose needs to be modified accordingly. It has a short duration of action is due to redistribution. In high doses, it behaves like a long-acting narcotics, producing respiratory depression, muscle rigidity, cholinergic effects and bradycardia, and mild vasodilatation leading to hypotension. The dose is 1–3 μg/kg, but higher doses have been used in cardiac surgery. Common routes of administration are intravenous and caudal, and there are hardly any studies about transdermal and transmucosal use in neonates.

e. **Alfentanyl and sufentanyl**: have a similar profile to fentanyl. Alfentanil causes muscle rigidity and is recommended to be used with muscle relaxants in newborns.
f. **Remifentanil:** Remifentanil has very favorable pharmacokinetics in neonates. It is degraded by plasma and tissue esterase, which are mature even in preterms and hence its metabolism is independent of hepatic or renal functions. It has a very short half-life and neonates can clear the drug more rapidly than older children. Hence, it has a higher safety profile than any other narcotic agent, and can be safely used in neonates without risk of cardiovascular or prolonged respiratory depression. Side effects such as respiratory depression and muscle rigidity are seen at higher concentrations.
g. **Tramadol:** Tramadol is a weak opioid with less chances of respiratory depression. However, it has reduced clearance and is not of much use in neonates.

Respiratory depression due to narcotics can be treated with naloxone 0.1 mg/kg.

17.6.3.3 Other Analgesics

a. **Paracetamol** (acetaminophen) has a central analgesic effect, mediated through activation of descending serotonergic pathways. In neonates, it has a higher volume of distribution. The metabolism is different from adults, the major pathway being sulphate conjugation and limited metabolism by glucuronidation. Thus, it has a lower initial peak concentration with less effective analgesia, but repeated administration can lead to accumulation. There are no known adverse effects at therapeutic dosing. Hepatotoxicity is rare, probably due to decreased activity of cytochrome P-450. It can be used intravenously in small doses. Although rectal bioavailability is higher than in children, oral and rectal routes do not provide adequate postoperative analgesia.
(b) **NSAIDS** are effective analgesics in children; however, not much data is available for neonates. They have been used for ductal closure. Side effects such as gastropathy, nephropathy, necrotising enterocolitis and intraventricular haemorrhage and surgical bleeding are similar as in older children.

17.6.4 Muscle Relaxants

At birth, the neuromuscular junction (NMJ) is immature, muscle mass is less, and volume of distribution is high due to higher ECF volume. Muscle relaxants behave differently in newborns than in adults.

a. **Succinylcholine (scoline):** The only depolarizing muscle relaxant in clinical use is scoline. It was very popular as a component of rapid sequence intubation (RSI), but its side effects such as arrythmias, hyperkalemia and risk of malignant hyperthermia have led to its disrepute. Scoline has a very high volume of distribution and the recommended dose is 3 mg/kg as compared to older children, where it 2 mg/kg. However, its action is not prolonged due to rapid clearance by plasma esterase. Malignant hyperthermia is not generally seen, and

increase in potassium is not significant to warrant being termed hyperkalemia, which in neonates is defined as serum potassium more than 6 mEq/L. Adequate relaxation for intubation can be obtained without using muscle paralysis, by deepening the plane of anesthesia with inhalational anesthetics or propofol use of opioids (fentanyl or remifentanil), and assisted ventilation.

(b) **Nondepolarizing muscle relaxants (NDMR):** The response to NDMRs is more unpredictable in neonates, The NMJ is very sensitivity to NDMRs, even though their volume of distribution is high. The duration of action is prolonged due to slow metabolism and poor elimination due to immature hepatic and renal function. **Atracurium** and **cisatracurium** are not dependent on the kidney or liver for excretion, (they undergo ester hydrolysis and Hofmann elimination), hence are preferred in newborns and neonates [15]. **Rocuronium** behaves similar to adults in neonates. **Vecuronium** is metabolized in the liver, which is still immature, prolonging the duration of action: 0.1 mg/kg dose of vecuronium and 1 mg/kg of rocuronium maintain paralysis for almost an hour in neonates [16]. Pancuronium is a long acting nondepolarizing neuromuscular blocking agent, with a prolonged duration of action. It has a sympathomimetic effect and causes tachycardia, which is beneficial to neonates, but prolonged duration of action with delayed excretion precludes its use in neonates [17]. Mivacurium is a NDMR which is administered in doses of 0.1–0.2 mg/kg with rapid onset of blockade, lasting 15–30 minutes. It undergoes ester hydrolysis and is ideal for short surgical procedures. In plasma cholinesterase deficiency, duration of action of mivacurium is prolonged.

Reversal of NM blockade: Neuromuscular blockade should always be antagonized in neonates, even if they appear to have completely recovered, because the smallest increase in work of breathing can cause fatigue and respiratory failure. **Neostigmine** and **atropine** or **glycopyrrolate** combination is commonly used. Data regarding **sugammadex** are limited.

17.6.5 Sedatives

a. **Benzodiazepines:** It is difficult to quantify sedation in neonates. Benzodiazepines have an increased half-life due to reduced drug clearance and can result in prolonged sedation.
b. **Midazolam** is the only benzodiazepine approved by FDA for use in neonates, with a half-life of 6–12 h. The IV dose is 0.05–0.10 mg/kg. When given in combination with fentanyl, it can cause severe hypotension and respiratory depression. Discontinuation of midazolam after long use in the ICU can cause withdrawal symptoms, such as agitation in children, though difficult to quantify in neonates.
c. **Diazepam** has an extremely long half-life (80 h) in neonates and should not be used.

17.6.6 Anticholinergic Drugs

The decision whether to routinely premedicate neonates with anticholinergics (**atropine**, **glycopyrrolate**) is controversial and this use is declining. Current use is limited to treatment of bradycardia or sometimes to reduce secretions, e.g., in oral surgeries. Hypoxia is the most common cause of bradycardia and should be managed by ensuring oxygenation, and not by anticholinergics, which will induce tachycardia at the expense of increase in myocardial O_2 consumption and myocardial damage. However, anticholinergics must always be given with neostigmine at the time of reversal of NM blockade. Clearance of both atropine and glycopyrrolate is reduced due to hepatic and renal immaturity.

17.6.7 Local Anesthetics (Table 17.4)

Both lignocaine and bupivacaine can be used in neonates and help to reduce the dose of opioids given to them. Lignocaine is used for local anesthesia in reduced doses of 1–1.5 mg/kg, since its clearance is reduced and there is risk of accumulation. Cardiac toxicity is more common that neurotoxicity, though that could be due to masking of symptoms during anesthesia. In addition, unlike adults, toxicity manifests less as cardiac arrest and more in the form of arrythmias, convulsions, and respiratory arrest [14].

Bupivacaine is usually bound to alpha 1 acid glycoprotein, which is low in neonates, and hence the free level of drug is high. Due to its lipophilic nature, it can cross the underdeveloped BBB and hence can cause seizures in the neonate. For local anesthesia, it is used up to a maximum dose of 1 mg/kg. The dose of bupivacaine for spinal anesthesia in infants is 0.6–1 mg/kg which is higher than the adult requirement because of a larger CSF volume of circulation, myelination, and rapid drug clearance due to higher heart rate and cardiac output. Use of

Table 17.4 Commonly used local anaesthetics and doses in neonates

S no.	LA drug	Maximum dose[a]	Neonatal dose	Use/Comments
1	Bupivacaine	2.5 mg/kg	1 mg/kg	Field block, wound infiltration
2	Ropivacaine	3 mg/kg	1.5 mg/kg	Less motor block and cardiotoxicity than bupivacaine
3	Lidocaine	5 mg/kg	2.5 mg/kg	Avoid digital and penile blocks with addition of vasoconstrictor
4	Prilocaine	Not recommended		Risk of methemoglobinemia
5	Chloroprocaine	14 mg/kg	7 mg/kg	Short T1/2, no accumulation
6	EMLA	1 g/5 kg	1 g	Maximum skin contact—1 h, risk of methemoglobinemia

[a]Maximum doses are additive and not independent of each other; local anaesthetic dosing should be decreased by 50% in neonates [10].

adjuvants such as fentanyl or clonidine can result in respiratory depression and apnea and is not recommended. Ropivacaine may be used as a local anesthetic up to a dose of 1.5 mg/kg. It has less chances of cardiotoxicity and motor block. If given as an infusion, ropivacaine can also accumulate and cause seizures in neonates due to low clearance.

When EMLA is used in neonates, due to higher body surface area compared to body weight, and high skin permeability, there is higher absorption of the local anesthetics. Since they have high amounts of fetal hemoglobin and reduced methemoglobin reductase activity, these children have a higher tendency to form methemoglobin. Hence, the use of this ointment is better avoided in neonates.

17.6.8 Miscellaneous Drugs

a. **Calcium** has a greater impact on myocardial contractility as their endogenous calcium stores are low.
b. **Catecholamine:** Response to catecholamines in the neonates is variable and depends on the myocardial structure, number of contractile elements, sympathetic innervations, and development of adrenergic receptors which are underdeveloped, and on noradrenaline stores which are low. Alpha receptors get stimulated at lower doses compared to beta receptors, because they develop earlier.
c. **Dopamine** infusion is accepted in neonates especially after cardiac surgery or in pulmonary hypertension as it causes more systemic than pulmonary vasoconstriction. The initial requirement may be higher. However, the action is usually prolonged due to reduced metabolism.

Some drugs are ineffective in neonates such as drugs affecting **intestinal motility or bronchodilators** and **xanthines**, as neonates have underdeveloped smooth muscle [18, 19].

Neonates have a developing brain and the impact of anesthesia and possibility of neurodevelopmental harm is a topic of active research especially in premature babies and those needing multiple surgeries. This topic is discussed in a separate chapter.

17.7 Anesthetic Implications of Clinical Pharmacology in Neonates

Note: An important point to be kept in mind while diluting drugs for neonates is that the volume of drug which is given contributes to the total volume replacement with intravenous fluids during surgery.

Both general anesthesia and spinal anesthesia have been successfully used in neonates and former premature infants, who are at risk of postoperative apnea, bradycardia, and desaturation [20, 21].

Premedication: the decision whether to routinely premedicate neonates with **anticholinergic drugs** are controversial [22]. Many anesthetists have abandoned routine premedication with no negative consequences, pointing out that bradycardia is almost always due to hypoxia, for which the treatment is O_2 and not drugs. However, advocates of routine premedication with anticholinergics believe that since the parasympathetic system is fully developed, incidence of bradycardia, especially with scoline is high. In addition, delivery of IV medication is delayed during bradycardia and hence must be given in advance. **Benzodiazepines** have an increased half-life due to reduced drug clearance and can result in prolonged sedation and must be avoided in neonates. However, the role they play as anxiolytic and sedative is debatable and cannot be quantified. (Table 17.5)

As regards **intravenous agents,** the dose response relationship has not been well-studied in neonates, and dosage guidelines are extrapolated from adult data. Although **propofol** has been used in neonates, it leads to hypotension, especially in sick patients. In addition, its redistribution and delayed clearance leads to prolonged recovery. Furthermore, its use as an infusion has been shown to cause metabolic acidosis and organ failure leading to death, so the dose and duration of propofol need to be limited.

NMB **agents** are commonly used during surgery. In general, the NMJ in neonates is resistant to depolarizing NMBs, and sensitive to nondepolarizing NMBs. Their response is similar to myasthenia gravis patients. All relaxant drugs are polar and water soluble, and hence have a high volume of distribution. This means that the initial dose must be high to achieve a target effect, but supplements will be smaller in dose or at longer intervals. Depolarizing NMBs are hydrolyzed by plasma cholinesterase and so there is not much prolongation of effect, unless there is deficiency of the enzyme. Nondepolarizing NMBs are metabolized in the liver and excreted in urine, hence will have prolonged action, even in absence of hepatic or renal disease.

The pharmacology and side effects of **narcotics** are better understood than that of induction agents. Morphine is generally avoided as it causes hypotension and prolonged respiratory depression due to its dependance on renal metabolism and elimination. Fentanyl, introduced in the 1980s, with its better safety profile and shorter duration of action has replaced morphine and pethidine in neonates for

Table 17.5 Preoperative medications, routes, and doses in neonates

Drug	PO	Nasal	IV	IM
Midazolam	0.5–1.0 mg/kg (max 15 mg)		0.05–0.1 mg/kg	No
Fentanyl			1–3 μg/kg	No
Morphine			0.05–0.10 mg/kg	No
Sufentanil		0.25–0.5 μg/kg		No
Ketamine	2–4 mg/kg		1–2 mg/kg	8–10 mg/kg
Methohexital	25–30 mg/kg per rectal (max 500 mg)		1–2 mg/kg	No

surgical analgesia. It has a minimal cardiovascular effect, is able to suppress the stress response, with improved outcome. However, prolonged use and in high doses, it can cause respiratory depression, bradycardia (cholinergic action), and hypotension (vasodilator effect). Because of its potential to cause rigidity, monitoring of respiration is essential in neonates on spontaneous respiration. Though morphine has limited use in neonates, but its potent analgesic effect is most beneficial in and after major surgeries, with large volume shifts, long duration (>2 h), and where postoperative ventilatory support may be anticipated or planned.

Paracetamol has a higher volume of distribution with limited metabolism (immature glucuronidation). Thus, it has a lower initial peak concentration with less effective analgesia, and repeated administration can lead to accumulation (Table 17.3).

Bupivacaine has lower protein binding capacity and clearance which leads to increased free form in the plasma, with risk of adverse effects. The dose for spinal anesthesia is 0.6–1 mg/kg, higher than in adults, because of a larger CSF volume (4 mg/kg vs 2 mL/kg in adults). **Adjuvants** (fentanyl, clonidine) should be used cautiously because of risk of delayed respiratory depression and apnea, and are best avoided in neonates not on respiratory support.

EMLA has been used in neonates, but due to larger body surface area and high skin permeability, LA absorption is high, with risk of LA-induced seizures and methemoglobinemia.

The possibility of neurodevelopmental harm by anesthetics is a topic of active research, to the developing brain of the neonate. This can influence long term neurological outcome especially in premature babies and those needing multiple surgeries and anesthesia exposures.

Resuscitation medications: (Box 17.1) all resuscitative medications should be kept available when anesthetizing neonates. They should be diluted appropriately and loaded in syringes, labelled for use in an emergency intraoperatively. Their volume adds on the IV fluid volume, and should be considered when calculating fluid requirements.

Box 17.1 Resuscitation medication in children

Epinephrine = 10–100 μg/kg for arrest (100 μg/kg in ETT), 1–4 μg/kg for hypotension
Atropine = 0.01–0.02 mg/kg (0.3 mg/kg in ETT)—actual dose 0.1–1 mg
Adenosine = 0.1 mg/kg (max 6 mg)
Lidocaine = 1–1.5 mg/kg
Scoline = 2–3 mg/kg
Rocuronium 1 mg/kg
Calcium chloride = 10–20 mg/kg (dilute to 10 mg/cc or else veins will sclerose, prefer central vein)
Bicarbonate = 1 mEq/kg (dilute to 1 mEq/cc or else veins will sclerose)
Naloxone = 0.1 mg/kg
DEFIBRILLATION = 2 J/kg (can increase up to 4 J/kg)

17.8 Conclusion

Anaesthetising the neonate is fascinating, but challenging even for experienced anaesthesiologists. Neonates differ from other paediatric patients not only anatomically and physiologically but also pharmacologically. For successfully managing this group of patients, it is essential to have knowledge about their pharmacological variations and exercise extra caution while anaesthetising them, keeping in mind their developing physiology, coexisting pathologies and pharmacokinetics and pharmacodynamics of any given drug.

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