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Neonatal pharmacology

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Neonatal physiology differs from that of older children and adults and has a direct implication on the use of anaesthetic drugs. Their clinical pharmacology is dynamic and diverse as there is ongoing maturation of enzymes, anatomical and physiological systems which leads to drug response variability. In order to properly dose anaesthetic drugs in this patient population it is important to appreciate their unique physiological characteristics, pharmacokinetics, pharmacodynamics and consider potential drug adverse effects. The use of postmenstrual rather than postnatal age has been shown to be a valid measure for maturation. In this article, the unique neonatal pharmacological features pertaining to anaesthesia will be reviewed.

Keywords: neonate, anaesthesia pharmacology, pharmacokinetics, pharmacodynamics

Introduction

While specifically defined as birth to one month of age, neonates are in practice a heterogenous group including extreme pre-term babies born at 22 weeks up to those 50 weeks post menstrual age (PMA) and weights varying from 0.5–5kg.[1] They have well recognised pharmacological differences from older children and adults and their biological systems evolve with maturity. This variability is a core component of their clinical pharmacology. Providers caring for neonates should pay close attention to factors contributing to variability specifically patient size, maturation and, to a lesser extent, organ function.[2,3] Pharmacokinetic (PK) and pharmacodynamic (PD) variability is also due to differences in patient age, genetic polymorphisms, inter-individual variation, comorbidities and drug co-administration. Appreciation of these differences is essential to provide safe and effective pharmacotherapy.

Disasters due to poor understanding of neonatal pharmacology (chloramphenicol and gray baby syndrome; benzyl alcohol toxicity and gasping syndrome) historically remind us how critical it is to pay close attention to differences in neonates.[1] Unfortunately, evidence-based pharmacotherapy in neonates is still limited. Clinical studies in this population remain restricted by difficulties with ethics, recruitment of adequate numbers, technical challenges, perceived high vulnerability, and concerns of potential adverse effects later in life. Advances in population-based modelling, micro-sampling, pooling of data from multiple institutions, and improved computer programs have helped address some of these challenges.[4] This article will attempt to summarise our understanding of PK and PD in neonates undergoing anaesthesia. Appreciation of these differences may help to improve pharmacological safety and further research in neonatal anaesthesia.

Pharmacokinetics (PK) and the neonate: *"What the body does to the drug"*

By definition PK is the study of drug disposition by patients. It considers absorption (a), distribution (d), metabolism (m), and elimination (e) of administered drugs.[4]

Absorption

Absorption links a drug's physicochemical properties and patient considerations that influence translocation from its exposure site to either the blood stream or effect compartment.[2] Absorption can occur via various routes.

Enteral route: Administration by mouth is a common route for drug administration in neonates. Gastric pH and volume of secretions is variable after birth, and absorption is therefore often delayed. Gastric emptying and motility do not mature until six to eight months. This can directly affect the ability of a drug to dissolve, altering the ionised/unionised components.[2] This is worsened by feeds that are calorie dense or containing long-chain fatty acids and in congenital gastrointestinal abnormalities such as pyloric stenosis and duodenal atresia. Slower gastric emptying and reduced clearance may influence dosing of medications commonly administered enterally. For example, paracetamol should be administered in decreased doses and frequency in neonates. Co-administration of opioids can further slow down emptying.

Transdermal route: Compared to older children neonates have increased absorption. Exposure to commonly administered drugs such as corticosteroids, local anaesthetic creams, and antiseptics like betadine can easily reach toxic levels. This is due to a greater relative skin surface area, higher cutaneous perfusion, and thinner stratum corneum. Lidocaine-prilocaine creams can be especially toxic as neonates are predisposed to forming higher amounts of methaemoglobin due to reduced methaemoglobin reductase activity and the presence of foetal haemoglobin which is more readily oxidised. This has resulted

in a general unwillingness to use lidocaine-prilocaine cream in neonates.[5]

Rectal route: In neonates, administration via this route results in variable plasma concentrations because of irregular motility of the lower gastrointestinal tract and inconsistent depth of drug insertion. Varying depth of insertion affects plasma concentration because absorption via the upper rectal veins undergoes first pass metabolism unlike the middle and inferior veins which bypass this.[2]

Inhalational and intramuscular route: Anaesthetic delivery by the inhalational route is determined by functional residual capacity (FRC) and alveolar ventilation. In the neonate there is higher minute ventilation (MV) to FRC (MV:FRC) ratio and alveolar ventilation. Rapid wash-in is further supported by the presence of higher cardiac output with a greater proportion distributed to the vessel-rich organs. In the presence of cardiac right-left shunt (intrapulmonary or cyanotic heart disease), inhalational induction is slower especially with the least soluble agents like sevoflurane and nitrous oxide. However, left-right shunting has a minimal effect on induction unless there is reduced cardiac output or peripheral perfusion.

Drug effect after intramuscular administration is faster because of increased neonatal muscle capillary density and higher cardiac output.[5,6]

Epidural route: The epidural space in infants compared to adults has increased vascularity and a smaller absorptive surface for local anaesthetics. Epidural levobupivacaine absorption T ½ decreases from birth till six months of age. There is also reduced levobupivacaine clearance (via CYP3A4) leading to delayed time to maximum plasma concentration (T_{max}). In combination, this may contribute to increased rostral spread and subsequent longer duration of caudal analgesia seen in this population.[7] Chloroprocaine is a potentially safer alternative to bupivacaine in neonates because of its much shorter elimination T ½.

Distribution (V_d)

Distribution relates to transfer of a drug from one location in the body to another.[6,8]

$$V_d(\text{l/kg}) = \frac{\text{total amount of a given drug}}{\text{concentration}}$$

V_d is a theoretical value and does not necessarily represent uniform drug distribution throughout the body. Maturational physiological changes that occur in body composition, regional blood flow, organ size and plasma protein concentration can all affect distribution. Many of the drugs used in anaesthesia do not have one simple volume of distribution.[6,8]

Body composition: For preterm and term neonates the V_d of water-soluble drugs is larger as compared to older children and a larger loading dose is required (e.g. aminoglycosides, cefazolin, paracetamol and neuromuscular blocking drugs [NMBD]).[8] (See Table I for the fluid composition of neonates compared to adults).

Despite having a higher initial dose, reduced clearance capacity results in lower maintenance dose to avoid accumulation. Fentanyl (lipophilic) will have a much higher V_d compared to total body volume because fat holds more drug compared to the same volume of blood. If V_d is large then the dose required to achieve a target concentration is also large. However, larger doses may cause more significant adverse effects and are not given because a prolonged effect can result from reduced clearance.[2]

Table I. Fluid composition in neonates compared to adults[2]

	Preterm	Term	Infant (1 year)	Adult
TBW*	85%	80%	60%	60%
ECF†	60%	45%	25%	20%
ICF‡	25%	35%	35%	30%

* Total body water
† Extracellular fluid
‡ Intracellular fluid
All as % of total body weight

Fat contributes 3% of total body weight in a 1.5 kg premature neonate and 12% at term. By the time the infant is four to five months old this would have doubled.[5] Drugs relying on redistribution to fat and muscle like thiopentone and propofol can have prolonged and higher concentration in plasma in the preterm.

Cerebrospinal fluid contributes a greater proportion of body composition in neonates as compared to older children explaining the larger doses of spinal anaesthesia drug required in this population (1 mg/kg in infants < 5 kg compared to 0.3 mg/kg for those > 15 kg).[9]

Protein binding: Protein binding is decreased in neonates. Concentrations of albumin and α_1-acid glycoprotein (AAG) are lower in neonates (0.32–0.92g/l) but by six months values are similar to adults.[10,11] Decreased quantity of drug-protein binding results in increased free drug concentrations and subsequent enhanced effect for drugs with typically high protein binding.

Albumin concentrations are lowest in preterm neonates. Drugs such as thiopentone that typically bind to albumin, have lower induction doses in neonates than children due to less protein binding (13% unbound drug in newborns versus 7% in adults).[12] Jaundice is also common in premature infants. Elevated bilirubin competes with drugs like phenytoin for protein binding. Phenytoin administration in jaundice may lead to higher free drug concentration and increased risk of kernicterus (immature blood-brain barrier).[12]

Bupivacaine is typically highly bound to AAG. With the decreased levels in neonates, a higher proportion of the drug is unbound; therefore, bolus epidural dosing is lower (1.5–2 mg/kg vs 2.5 mg/kg) to decrease the risk of toxic levels. AAG is an acute phase reactant and will increase after surgical stress hence, bupivacaine concentration in the first 24 hrs post-surgery may increase in neonates on continuous epidural infusion but theoretically the unbound fraction should remain the same.[13] However, there have been reports of seizures in infants on continuous bupivacaine epidural infusions leading to the recommendation to discontinue infusions at 24 hrs.[14] For bupivacaine, clearance

(CYP3A4) is the main parameter reduced in infants and there is more inter-individual variability in concentration as compared to reduced protein binding. In neonates, continuous epidural infusions will not generally run beyond 48 hrs (dose of 0.2 mg/kg/hr less than 0.4 mg/kg/hr in older children).[13,14]

Blood-brain barrier (BBB): The integrity of the BBB improves gradually with age. Foetal and neonatal brains may be more easily accessed by small molecules and even more so with certain disease states such as sepsis, hypoxia, and acidosis. Unbound lipophilic drugs such as bupivacaine can passively diffuse across the BBB.[2] Combined with reduced protein binding, this may explain the increased risk of toxic levels leading to seizures in neonates.

Fentanyl is actively transported across the BBB by an ATP-binding cassette protein like P-glycoprotein. Modulation of this glycoprotein can influence onset of action, maximum effect, and duration of analgesic response.

Metabolism and elimination

Significant covariates, when considering neonatal drug metabolism are size, maturation and the effect of disease on organ function. Allometry describes the non-linear relationship between size and function. Use of allometric models enables prediction of paediatric doses from adult ones and target-controlled infusions have the potential to use allometric scaling.[1,5] With the exception of remifentanil, allometry alone is insufficient in predicting clearance of most drugs in neonates and infants and there is a need to add a model accounting for maturation. Since maturation of clearance starts before birth, PMA is probably the better predictor than postnatal age (PNA) for drug elimination.[5] For example, CYP2D6, CYP3A4, CYP1A2 display ontogeny in the second and third trimester of pregnancy.[15] Organ function changes associated with normal growth and development can be determined from pathological changes as function decreases with disease.[1] Organ function may be increased by enzyme inducers like phenobarbitone (CYP1A2, CYP2C9, CYP2C19, CYP3A4, UDP glucuronsyltransferase [UGT]).[1]

The hepato-biliary (metabolic clearance) and renal (elimination clearance) systems are the main routes of clearance for drugs and metabolites. Immaturity in these two systems has an effect on neonatal drug handling.

Hepatic metabolic clearance: Hepatic elimination is governed by phenotypic variation and relates to inherent, disease-related and genetic factors. During infancy the main determinant is age-dependent phenotypic enzymatic activity. Development of these systems can alter drug clearance significantly.

There are three categories of isoenzymes in neonates with most being in class iii[16-18]:

i. Mature at birth with decreasing activity with age (CYP3A7, SULT1A3/1A4)
ii. Moderate maturation at birth with increased activity with increasing age (CYP3A5, CYP 2C19, SULT1A1)
iii. Little to modest maturation at birth with increasing activity with age (CYP2D6, CYP3A4, CYP2C9, CYP1A2)

Metabolising enzymes are divided into Phase I (non-synthetic reactions like oxidation, reduction and hydrolysis) and Phase II reactions (synthetic or conjugation reactions making water soluble compounds excreted in urine).

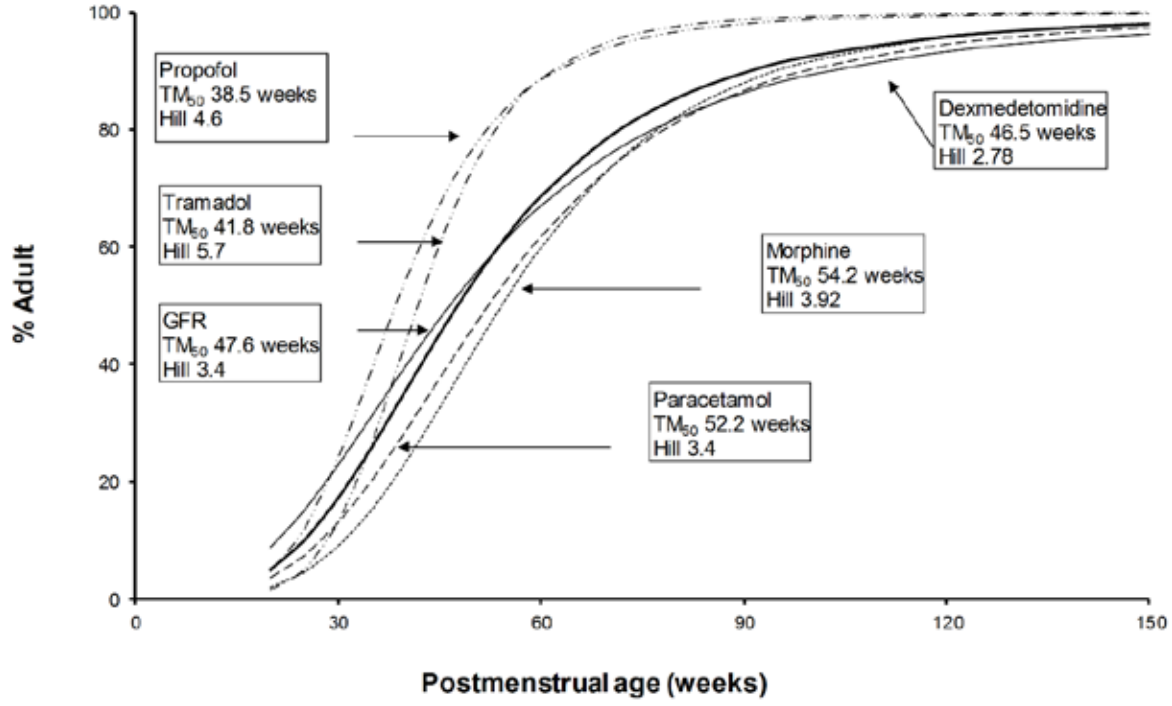

Figure 1. Clearance maturation, expressed as a percentage of mature clearance, of drugs for which glucuronide conjugation (paracetamol, morphine, dexmedetomidine) plays a major role. (Note how the profiles correlate to glomerular filtration rate [GFR]). Cytochrome P450 isoenzymes also contribute to propofol metabolism as shown by the faster maturation profile than expected from glucuronide conjugation alone. Tramadol and levobupivacaine clearance maturation (CYP2D6, CYP3A) is also rapid.[5] Reproduced with permission.

Important for the Phase I reactions are the cytochrome P450 group of enzymes which are often not fully mature in the neonate and also subject to variation due to genetic polymorphisms. Clearance of levobupivacaine depends on CYP3A4 and CYP1A2 for ropivacaine which are both immature in the neonate. This means this population requires reduced epidural infusion rates of these drugs.[7] Altered phenotypic expression of CYP2D6 enzymes affects tramadol metabolism and formation of the major (M1) metabolite.[19] Plasma cholinesterase activity influencing succinylcholine metabolism is also influenced by genetic polymorphism.[5]

Phase II reactions show limited activity during foetal life and some reactions like acetylation, glycination and glucuronidation are not mature at birth.[2] These systems are complicated. For example, UGT clearance is immature at PMA 24 weeks but reaches maturity by the first year of life. UGT has isoforms maturing at different rates (see Figure 1 showing clearance maturation profiles of drugs mainly metabolised by UGT).[5] Lack of understanding of UGT maturity led to gray baby syndrome with chloramphenicol in the 1960s.

Maturation processes can also be affected by illnesses. Morphine clearance is reduced in the very sick neonate and propofol clearance is lower in children after cardiac surgery. Concomitant drug use also affects metabolism. Ketamine's sedative effects are less in children on long term phenobarbitone (CYP3A4 induction).

Renal clearance: Renal elimination is reflected by diuresis, GFR and renal tubular activity. At PMA of 25, GFR is only 10% of the mature value, 35% at term, and by one year it is 90% of the adult value.[4] Renal inefficiency in the neonate is due to low perfusion pressure, incomplete glomerular development and inadequate osmotic load for the counter-current mechanisms. Drugs almost exclusively cleared by GFR (cephalosporins, aminoglycosides, D-tubocurarine) have lower maintenance dose which is predicted by PMA. PMA is used because it more accurately estimates the time course of renal maturation. Immaturity of clearance has some therapeutic use in the management of apnoea. When using theophylline, N7-methylation development to produce caffeine is well developed. However, oxidative demethylation (CPY1A2) is deficient. The produced caffeine is effective in controlling apnoea.[20]

Pulmonary elimination: In the lungs, anaesthetic absorption is determined by alveolar ventilation, FRC, blood-gas solubility and cardiac output. These also have a bearing on elimination kinetics. Washout will be more rapid due to reduced distribution to fat and muscle.

Some agents undergo hepatic metabolism (halothane much more than isoflurane and sevoflurane). However, hepatic elimination is very small at typical anaesthetic concentrations.[5]

Table II summarises some PK considerations in neonates.[4]

Table II. Illustrations of the impact of neonatal physiology on the pharmacokinetics (absorption, distribution, metabolism, elimination) of specific drugs commonly administered to neonates[8]

Compound	Pharmacokinetics	Relevance
Iodine disinfectant	Skin more permeable, skin surface per kg weight higher (a)	Higher absorption may suppress thyroid function
Inhalational gases	Higher alveolar ventilation/FRC ratio (a)	Faster wash-in
Cefazolin	Lower protein-binding capacity results in higher distribution volume (d) and higher free plasma fraction (e) Lower GFR (e)	Peak concentration is lower Bactericid effect relates to free concentration Lower clearance, prolonged duration of bactericid effect
Bupivacaine	Lower protein-binding capacity (d) Lower clearance (e)	Free concentration related to adverse effects Accumulation during continuous administration
Propofol	Lipophilic compound, lower distribution volume (d) Glucuronidation for metabolic clearance (m)	Peak concentration is lower, redistribution more limited Accumulation during continuous or repeated administration More profound hypotension due to immature (para) sympathetic balance
Paracetamol	Water soluble compound, higher distribution volume (d) Glucuronidation for metabolic clearance (m)	Peak concentration is lower, less effective analgesia likely Accumulation during repeated administration possible
Midazolum	Clearance to metabolite (1-hydroxy) is low (m) Elimination clearance of (1-hydroxy) midazolam is low (e)	Metabolite is also sedative Lower clearance results in prolonged sedation
EMLA cream	Skin more permeable, skin surface/kg higher (a)	Higher absorption, may induce local anaesthetic related seizures Increased risk of methaemoglobinaemia
Codeine	Clearance to metabolite (morphine) is low (m) Elimination of codeine and metabolite is low (e)	Shorter or reduced analgesic effect Accumulation of codeine or metabolite more likely, prolonged or more pronounced analgesia
NMBD	Increased distribution volume (d) Lower clearance (m)	Lower concentration at end plate, compensated by lower acetylcholine Prolonged effect

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Table III. Inhaled anaesthetic agents' pharmacology[1]

	Halothane		Enflurane		Isoflurane		Sevoflurane		Desflurane	
	A*	N†	A	N	A	N	A	N	A	N
MAC	0.75	0.87	1.7	–	1.2	1.6	2.05	3.2	7.0	9.2
Solubility: Blood-gas	2.4	2.14	1.9	1.78	1.4	1.19	0.66	0.66	0.42	–
Solubility: Brain-blood	1.9	1.5	1.3	0.9	1.6	1.3	1.7	–	1.2	2.7

*adult †neonate

Pharmacodynamics (PD) and the neonate: "What the drug does to the body"

Pharmacodynamics is the study of the drug effects (therapeutic and adverse) on patients. Despite there being significant differences in this population, drug responses in children have some commonalities with adults once developmental PK characteristics are considered.[21]

MAC for volatile anaesthetics is generally less in neonates than infants. Peak is at six months and then decreases to adult values by adolescence (see Table III). The variability in drug responses among the different volatile agents is influenced by the change in number of $GABA_A$ receptors and developmental shifts in the regulation of chloride transporters in the brain.[2]

Response to vasoactive drugs is also age-dependent. PD differences can be attributed to developmental changes in myocardial structure, cardiac function, and receptor function.

Table IV highlights some of the PD differences in neonates.

Components of ideal general anaesthesia include unconsciousness, analgesia and muscle relaxation. Measuring these pharmacodynamic outcomes in neonates is harder compared to children or adults. For example, unconsciousness is assessed by monitoring the anaesthesia depth with

Table IV. Pharmacodynamic differences of common drugs used in anaesthesia[5,23-26]

Drug	PD difference	Reason	Comments
Propofol	Profound hypotension of about 20 minutes in neonates given 3 mg/kg	Unclear	Needs further PD and PK investigation
Morphine	Increased sensitivity	Functional expression of mu receptors is developmentally regulated	–
Local anaesthetics	Amide agents induce shorter block duration Need higher dose for subarachnoid block (see text)	Myelination, spacing of nodes of Ranvier and length of nerve exposed	–
NMBD	Increased sensitivity to effects Succinylcholine induces bradycardia	Immature neuromuscular junction	–
Inotropes	Dopamine can be used in the presence of pulmonary hypertension Signs of α-receptor stimulation may occur at lower doses than β-receptor stimulation	Fewer dopamine receptors in pulmonary vs systemic vasculature β receptor maturation lags behind α maturation	Dopamine popular in the neonatal population compared to adults
Sedatives	Bolus midazolam associated with hypotension (especially if given with fentanyl)	–	–
Thiopentone	Dose 3.4 mg/kg (compared with 6.3 mg/kg in infants and 4-7 mg/kg in adults)	Uncertain PK and PD Uncertain cause ? immature cerebral cortical function ? rudimentary dendritic abnormalities ? relatively few synapses	–
Paracetamol	Poorly defined PD Early exposure may be related to later development of atopy-related syndromes ? early PDA closure	Unknown link	–
Prokinetics	Not very useful in very preterm neonates but useful at full term	Age-dependent expression of intestinal motilin Modulation of antral contractions in the neonate	–
Bronchodilators	Ineffective	Paucity of bronchial smooth muscle that can cause bronchospasm	–
Calcium channel blockers	Can cause life-threatening bradycardia and hypotension	Cardiac calcium stores in the endoplasmic reticulum are lower because of immaturity	Exogenous calcium has greater impact on contractility

electroencephalogram (EEG) or bi-spectral index in adults. However, use of these devices cannot yet be supported in children and EEGs are different in the various categories of paediatric patients.[22]

Adverse drug effects (ADE): Drug dosage errors are more common in children with the problem being further aggravated by narrow error margins in delivery and dilution.[27] Off-label drug administration in neonates is still common with limited evidence-based pharmacotherapy. Therefore, it is requisite to design and participate in trials in the PK and PD of compounds commonly used by paediatric anaesthetists using suitable formulations and assessment methods.

In addition to the potential ADE that can occur in adults, neonates are potentially prone to particular effects because of immaturity of their physiology. Exposure to stimuli at a sensitive point of development may result in permanent effects. There are concerns that exposure of neonates to anaesthesia may cause increased neuronal apoptosis and long-term memory deficits. Implicated drugs are N-methyl D-aspartate antagonists (ketamine and nitrous oxide) and $GABA_A$ agonists (benzodiazepines, propofol, all volatile anaesthetic agents and barbiturates).[28] Translating these observations to humans has proven difficult. The FDA issued a warning on drugs used for anaesthesia in 2016 raising concerns among parents of children undergoing anaesthesia. The General Anaesthesia Spinal (GAS) study indicated that a sevoflurane-based anaesthetic of less than an hour does not increase the danger of adverse neurological outcome at two years of age.[29] The Paediatric Anaesthesia Neuro-Development Assessment (PANDA) study showed no significant differences in full-scale IQ at 10 years of age between exposed (general anaesthesia) and unexposed siblings. Scores assessed memory, language, attention, motor processing speed and behaviour among other things.[30] The area of long-term effects of anaesthesia in children is one of ongoing research and debate.

Conclusion

Neonates have significant pharmacological differences compared to adults due to rapidly maturing physiological systems. Paediatric anaesthetists have to be knowledgeable in the PK and PD of neonates through studying available literature and participating in ongoing research in this area.

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