Pharmacology in the Very Young: Anaesthetic Implications

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Introduction

Neonates and infants include those from birth up to the age of 2 years of life. Consequently, postmenstrual age (PMA) may range from extreme preterm birth at 22 weeks up to 780 weeks PMA with a corresponding weight range from 0.5 to 20kg. Maturation of anatomical and physiological systems distinguishes this group as a specific population with major pharmacological differences from their older counterparts. Morbidity and mortality associated with anaesthesia is highest in this age group, attributable in part, to a poor understanding of developmental pharmacology.

Pharmacokinetic differences

Absorption

Anaesthetic drugs are mainly delivered intravenously or through inhalation, but premedication and postoperative pain relief are commonly administered enterally. Drug absorption after oral administration is slower in neonates than in children due to delayed gastric emptying [1]. Slow gastric emptying and reduced clearance may dictate reduced doses and frequency of administration (Figure 1).

The larger relative skin surface area, increased cutaneous perfusion and thinner stratum corneum in neonates increase systemic exposure of topical drugs (e.g. corticosteroids, local anaesthetic creams, antiseptics). Neonates have a tendency to form methaemoglobin (due to reduced methaemoglobin reductase activity and a tendency for greater oxidation of fetal haemoglobin) with prilocaine.

The nature of the epidural space in infants is different from adult with increased vascularity and a smaller absorptive surface for local anaesthetics. Anatomical studies have shown that the epidural fat is spongy and gelatinous in appearance with distinct spaces between individual fat globules. With increasing age, fat becomes more tightly packed and fibrous. The consequent absorption half time of epidurally administered local anaesthetics decreases from birth until 6-months postnatal age (PNA). This, combined with reduced clearance (mediated by cytochrome P450, CYP3A4), causes the time to maximum plasma concentration (Tmax) to be delayed in neonates (Figure 2).

Figure 1. Simulated mean predicted time-concentration profiles for a term neonate, a 1-year-old infant and a 5-year old child given paracetamol elixir. The time to peak concentration is delayed in neonates due to slow gastric emptying and reduced clearance. The slow absorption and reduced clearance dictate a greater dose interval and smaller daily dose (from Anderson BJ et al. Anesthesiology 2002; 96:1336-45).
Figure 2. The time to peak concentration (Tmax) after epidural levobupivacaine 2 mg/kg, standardized to a 70 kg person, decreases from 2.2 h at 1-month PNA with a maturation half-life of 1.2 months to reach 80% of the mature value (0.75 h) by 6-month PNA (From Chalkiadis G. Pediatric Anaesthesia 2006; 16: 275-82).

Neonates and infants have an increased alveolar ventilation to functional residual capacity ratio compared with adults, primarily the result of an increased metabolic demand for oxygen, which drives an increase in alveolar ventilation. Consequently, the alveolar to inspired fractions and therefore the blood to inspired partial pressure of anaesthetics reach equilibration more rapidly in neonates than in children and adults [2]. The higher cardiac output and greater fraction of the cardiac output distributed to vessel rich tissues (i.e. a clearance factor) and the lower tissue/blood solubility (i.e. a volume factor) further contribute to the more rapid wash-in of inhalational anaesthetics in early life [3].

Analgesic medications and delivery systems commonly used in adults may not be possible or practicable in children. Preschool children are unable to use patient controlled analgesia devices. Sublingual administration in children requires prolonged exposure to the mucosal surface. Younger children find it difficult to hold drug in their mouth for the requisite retention time (particularly if taste is unfavourable) and this results in more of the drug being swallowed or drug spat out than in adults. If the drug has a high first pass effect then its lower relative bioavailability results in lower plasma concentrations.

Distribution

Distribution is influenced by body composition, protein binding, haemodynamics (e.g. regional blood flow) and membrane permeability.

Body composition:

Total body water and extracellular fluid (ECF) [4] are increased in neonates and reduction tends to follow PNA while the percentage of body weight contributed by fat is 3% in a 1.5 kg premature neonate and 12% in a term neonate. This proportion further doubles by 4-5 months of age. These body component changes affect volumes of distribution of drugs. Polar drugs such as depolarising and non-depolarising neuromuscular blocking drugs (NMBDs) distribute rapidly into the ECF, but enter cells more slowly. The initial dose of such drugs is consequently higher in the neonate compared to child or adult. In contrast, morphine is a hydrophilic drug and has a reduced volume of distribution in neonates. Neonates have low body fat and muscle content and so less propofol is apportioned to these ‘deep’ compartments. Delayed awakening occurs because CNS concentration remains higher than that observed in older children as a consequence of reduced redistribution.

Plasma Proteins:

Albumin and alpha-1 acid glycoprotein (AAG) concentrations are reduced in neonates, albeit with a broad range of scatter (0.32-0.92 g/l), but are similar to those in adults by 6 months PNA [5]. Alpha-1 acid glycoprotein is an acute phase reactant that increases after surgical stress. This causes an increase in total plasma concentrations for low to intermediate extraction drugs such as bupivacaine. The unbound concentration, however, will not change because clearance of the unbound drug is affected only by the intrinsic metabolizing capacity of the liver. Any increase in unbound concentrations observed during long term epidural drug delivery is attributable to reduced clearance rather than AAG concentration. Total bupivacaine concentrations increase in the first 24 h after surgery in neonates given...
analgesia by continuous epidural infusion. This increase is attributable to an increase of AAG. This increase, combined with reports of seizures in infants given epidural bupivacaine infusion has lead to recommendations to stop epidural infusions at 24 hours. However, it is the unbound bupivacaine that is responsible for effect and this unbound concentration may not change, implying that the infusion could be run for a longer duration. Clearance is the key parameter and this is reduced in neonates. Unfortunately, clearance is associated with large between-subject variability and this means that unbound bupivacaine concentrations may continue to rise in some infants with very low clearance. Plasma albumin concentrations approximate to adult values by 5 months PNA and are lowest in preterm neonates. Binding capacity approaches adult values by 1 year of age. In addition, free fatty acids and unconjugated bilirubin compete with acidic drugs (e.g. ibuprofen, ceftriaxone) for albumin binding. Neonates also have a tendency to develop a metabolic acidosis that alters ionization and binding properties of plasma proteins. The induction dose of thiopentone is lower in neonates than children, possibly due to decreased binding of thiopentone to plasma albumin; 13% of the drug is unbound in newborns compared with 7% in adults.

Regional blood flows:

The initial phase of distribution after intravenous administration reflects regional blood flow. Consequently, the brain, heart and liver, are exposed first. The drug is then redistributed to other relatively well perfused tissues, such as skeletal muscle. There is a much slower tertiary distribution to relatively under-perfused tissues of the body that is noted with long term drug infusions. These changes alter the context sensitive half-time in neonates and infants. Perinatal circulatory changes (e.g. ductus venosus, ductus arteriosus) alter drug disposition. Blood flow, relative to cardiac output, to kidney and brain increases with age, while that to the liver decreases through neonatal life. Cerebral and hepatic mass as a proportion of body weight are much higher in the infant than in the adult. Reduced cardiac output and cerebral perfusion in neonates means that onset time after intravenous induction of anaesthesia is slower in neonates, although reduced protein binding may counter this observation for some drugs. Offset time is also delayed because redistribution to well perfused and deep under-perfused tissues is more limited.

The Blood-brain barrier:

The Blood-brain barrier (BBB) is a network of tight junctions to restrict paracellular diffusion of compounds between blood and brain. The 'leaky BBB theory' was initially proposed to explain reduced respiratory depression observed with pethidine compared with morphine in neonates [6]. However, respiratory depression could have been the result of higher morphine concentrations due to a smaller volume of distribution in neonates. The respiratory depressive effects of morphine are similar from 2 to 570 days of age when the concentration of morphine in blood is the same [7]. The BBB may influence drug effects in other ways. Small molecules access foetal and neonatal brains more readily. Blood-brain barrier function improves gradually, possibly reaching maturity at term age. Kernicterus, for example, is more common in premature neonates. Drugs bound to plasma proteins will not normally cross the BBB. However, unbound lipophilic drugs passively diffuse across the BBB to achieve equilibrium very quickly. This may contribute to bupivacaine’s propensity for seizures in neonates. Decreased protein binding in neonates results in a greater proportion of unbound drug. Besides passive diffusion, there are also specific active transport systems. Pathological CNS conditions can cause BBB breakdown and alterations in these transport systems. Fentanyl is actively transported across the BBB by a saturable ATP-dependent process, while ATP-binding cassette proteins such as P-glycoprotein actively pump out opioids such as fentanyl and morphine. P-glycoprotein modulation significantly influences opioid brain distribution and onset time, magnitude and duration of analgesic response. Modulation may occur with disease processes, fever, or drugs (e.g. verapamil). Genetic polymorphisms affecting P-glycoprotein-related genes may explain differences in CNS-active drug sensitivity.

Elimination

The main routes by which drugs and their metabolites leave the body are the hepatobiliary, renal and respiratory systems. The liver is the primary organ for clearance of most drugs, although the lungs have a major role for anaesthetic vapours. Although the metabolism of a given drug most frequently results in inactive compounds, metabolism may also result in transformation to a more potent drug (e.g. codeine to morphine by CYP2D6) or into a toxic compound (halothane to trifluoroacetyl chloride by CYP2E1 causing halothane hepatitis).

Two major considerations influencing drug action in children are growth and maturation. How these factors interact is not necessarily transparent from simple clinical observations because they correlate very closely. One approach is to standardise for size before incorporating a factor for maturation and organ function.
Size and maturation

There is a non-linear relationship between clearance and size. Clearance in children 1-2 years of age, expressed as l/h/kg, is commonly greater than that observed in older children and adolescents. This ‘artefact of size’ disappears when allometric scaling is used (Figure 3). Allometry is a term used to describe the nonlinear relationship between size and function.

This nonlinear relationship is expressed as: \( y = \text{BodyMass}^{PWR} \).

Where \( y \) is the variable of interest (e.g. basal metabolic rate) and \( PWR \) is the allometric exponent. The value of \( PWR \) has been the subject of much debate. Basal metabolic rate (BMR) is the commonest variable investigated and camps advocating for a \( PWR \) value of 2/3 (i.e. body surface area) are at odds with those advocating a value of 3/4. A great many physiological, structural and time related variables scale predictably within and between species with weight \( (W) \) exponents \( (PWR) \) of 3/4, 1 and 1/4 respectively.

Figure 3. The clearance maturation profile of dexmedetomidine expressed using the per kilogram model and the allometric ¾-power model. This maturation pattern is typical of many drugs cleared by the liver or kidneys. (Adapted from Potts AL. Pediatric Anaesthesia 2009; 19: 1119-29)

Formulæ used to determine fresh gas flows for the anaesthetic T-piece breathing system relate to BMR. Flows increase with age when expressed as per kilogram. However, the minute volume and alveolar ventilation do not increase with age when standardised to a 70 kg human using allometric models; they are approximately 8 l/min/70kg and 4.5 l/min/70kg respectively. The fresh gas flow formulæ all standardise to a flow 1-1.5 times the minute volume [8].

These allometric exponents \( (PWR) \) have applicability to pharmacokinetic \( (PK) \) parameters such as clearance \( (CL) \) exponent of 3/4), volume \( (V) \) exponent of 1) and half-time \( (T_{1/2}) \) exponent of 1/4) [9].

Remifentanil and atracurium are degraded by non-specific esterases in tissues and erythrocytes. Clearance, expressed per kilogram, is increased in younger children, and is likely to be attributable to size because clearance is similar when scaled to a 70 kg person using allometry [10]. Nonspecific blood esterases that metabolise remifentanil and atracurium are mature at birth.

The equilibration half-times \( (T_{1/2keo}) \) for propofol distribution to the effect compartment increases with age [11], contributing to rapid onset in infants. Similarly, the observed speed of onset of intermediate duration neuromuscular blocking drugs (e.g. atracurium) is faster as age decreases, but can be scaled using a 1/4 power to approximately 3 min for a standard 70 kg person [8].

Unlike remifentanil clearance, allometry alone is insufficient to predict clearance in neonates and infants from adult estimates for most drugs. The addition of a model describing maturation is required. The sigmoid hyperbolic or Hill model has been found useful for describing this maturation process (MF).

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MF = \frac{PMA^{Hill}}{TM^{Hill}_{50} + PMA^{Hill}}
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The TM_{50} describes the maturation half-time, while the Hill coefficient relates to the slope of this maturation profile. Maturation of clearance begins before birth, suggesting that post-menstrual age (PMA) would be a better predictor of drug elimination than postnatal age (PNA) [9].

**Hepatic metabolic clearance**

Phase 1 reactions are typified by the CYP iso-enzymes. These, with the exception of CYP3A7, have a low phenotypic activity until birth. CYP2E1 activity surges after birth, CYP2D6 becomes detectable soon thereafter, CYP3A4 and CYP2C appear during the first week, whereas CYP1A2 is the last to appear [12, 13]. Neonates depend on the immature CYP3A4 for levobupivacaine clearance and on CYP1A2 for ropivacaine clearance, dictating reduced epidural infusion rates in this age group. Formation of the M1 metabolite of tramadol, reflecting that CYP2D6 activity appeared rapidly around term and reached 84% of mature values by 44 weeks PMA. This enzyme has genetic polymorphisms altering phenotypic expression, which have different maturation rates in the very young [14].

Some phase II iso-enzymes are mature in full term neonates (e.g. sulphate conjugation), while others are not (acetylation, glycination, glucuronidation) [15]. A failure to appreciate immaturity of uridine diphosphate-glucuronosyltransferase (UGT) resulted in cardiovascular collapse of neonates given chloramphenicol in the late 1950s. Additionally, UGT is also important for the metabolic clearance of drugs such as paracetamol, morphine, propofol and dexametomidine. Allometric body-size scaling complimented by maturation models [9] have been used to describe clearance maturation of these drugs [16]. Clearance is immature in the preterm 24 week PMA neonate and matures to reach adult rates by the end of the first year of life (Figure 4). These maturation profiles closely match that of glomerular filtration rate (GFR); the elimination pathway of the water soluble metabolites matches their production by UGT. While UGT is the major metabolic pathway for propofol, multiple CYP iso-enzymes (CYP2B6, CYP2C9, CYP2A6) also contribute to its metabolism and cause a faster maturation profile than expected from UGT alone.

![Clearance maturation, expressed as a percentage of mature clearance, of drugs where glucuronide conjugation (paracetamol, morphine, dexmedetomidine) plays a major role. These profiles are closely aligned with GFR. In contrast, cytochrome P450 isoenzymes also contribute to propofol metabolism and cause a faster maturation profile than expected from glucuronide conjugation alone. Tramadol and levobupivacaine clearance maturation (CYP2D6, CYP3A) is also rapid. (Adapted from Anderson BJ. Pediatric Anaesthesia 2011; 21:222-37)](image)

The influence of illness is exemplified by morphine clearance that is reduced in very sick neonates who are candidates for extracorporeal membrane oxygenation (ECMO); clearance increases dramatically a few days after ECMO is started.

**Pulmonary elimination**

The factors determining anaesthetic absorption through the lung (alveolar ventilation, FRC, cardiac output, solubility) also contribute to elimination kinetics. We might anticipate more rapid wash-out in neonates for any given duration of anaesthesia because there is less distribution to fat and muscle content.
Renal elimination

Renal elimination of drugs and their metabolites is determined by three processes: glomerular filtration, tubular secretion and tubular reabsorption. Glomerular filtration rate (GFR) is only 10% that of mature value at 25 weeks, 35% at term and 90% of the adult GFR at 1 year of age (Figure 4) [17]. Aminoglycosides are almost exclusively cleared by GFR and maintenance dose is predicted by PMA because it predicts the time course of renal maturation. Similarly the clearance of the neuromuscular blocking drug, d-tubocurare, can be directly correlated with GFR [18].

Pharmacodynamics

Altered Pharmacodynamics in infants

Children’s responses to drugs have much in common with the responses in adults once developmental pharmacokinetic (PK) aspects are considered. The perception that drug effects differ in children arises because these drugs have not been adequately studied in paediatric populations who have size and age related effects as well as different diseases. However, neonates and infants do have altered pharmacodynamics (PD). A common example is bronchodilators; these are ineffective in infants <1 year because of the paucity of bronchial smooth muscle that can cause bronchospasm. Conversely, neonates have an increased sensitivity to the effects of neuromuscular blocking drugs [18], possibly due to reduced release of acetylcholine from the phrenic nerve. Cardiac calcium stores in the endoplasmic reticulum are reduced in the neonatal heart because of immaturity. Exogenous calcium has greater impact on contractility in this age group than in older children or adults. Conversely, calcium channel blocking drugs (e.g. verapamil) can cause life threatening bradycardia and hypotension.

The minimal alveolar concentration (MAC) is commonly used to express anaesthetic vapour potency. The MAC for almost all these vapours is less in neonates than in infancy [3]. Typically MAC values peak at 1-6 months of age before decreasing to adult values in adolescence. Changes in regional blood flow may influence the amount of anaesthetic going to the brain. Changes in gamma-aminobutyric acid (GABA<sub>A</sub>) receptor numbers or developmental shifts in the regulation of chloride transporters in the brain also change with age, contribute to altered responses (e.g. midazolam).

Catecholamine release and response to vasoactive drugs vary with age. Dopaminergic receptors are fewer in the pulmonary than in the systemic vasculature and this enables the use of dopamine in neonates with known pulmonary hypertension after cardiac surgery. Signs of cardiovascular α-receptor stimulation may occur at lower doses than β-receptor stimulation because β-receptor maturation lags behind α-receptor maturation during the development of the adrenergic system. Maturation changes in PK (e.g. reduced elimination) and PD may contribute to dopamine’s continued popularity in the neonatal nursery while its popularity wanes in the adult population.

Measurement of pharmacodynamics in infants

Outcome measures are commonly more difficult to assess in neonates and infants than in children or adults. The common effects measured in anaesthesia are neuromuscular blockade, depth of anaesthesia, and sedation or pain. A common effect measure used to assess depth of anaesthesia is a modified EEG signal, but the EEG in infants is fundamentally different from the EEG in older children; there remains a need for specific neonate-derived algorithms if EEG-derived anesthesia depth monitors are to be used in neonates.

There are an extensive number of sedation or pain scales. Most scores are validated for the acute, procedural setting and perform less well for subacute or chronic pain. Future research may provide us with objective tools to quantify pain and sedation, but will have to take maturational aspects of the infant into account.

Adverse Drug Effects

Neonates and young children may suffer permanent effects resulting from a stimulus applied at a sensitive point in development. For example, the incidence of vaginal carcinoma is high in children of mothers treated with stilboestrol during pregnancy. There are concerns that neonatal exposure to some anaesthetic agents (e.g. ketamine, midazolam) may cause widespread neuronal apoptosis and long-term memory deficits.
Anaesthesia, however, generally involves examination of immediate adverse effects such as PONV, hypotension or respiratory depression. Therapeutic use of all drugs balances their beneficial effects against adverse effects. Morphine dose in the very young was traditionally limited by fears of respiratory compromise; postoperative arterial oxygen desaturation continues to be reported with sedative drugs in neonates. The use of propofol in neonates has recently been associated with profound hypotension [19], questioning our understanding of the dose-effect relationships of this common drug. Such information allows informed dosing.

Conclusions
An understanding of pharmacology in the very young is important in order to achieve anaesthesia effect. Many facets of this knowledge in young children remain unknown, even for common drugs (e.g. propofol) hindering the use of target controlled infusion (TCI) pumps in that population [20]. A better understanding of pharmacokinetic and pharmacodynamic maturation in the very young is needed for dose approximation.

Key Learning Points
- Neonates and infants represent a diverse group of children. They range from the extreme premature neonate through to 2 years of age, encompass diverse pathologies, maturation states and weight ranges.
- Drug absorption through skin and lungs is increased, orally it is slowed by reduced gastric emptying times and rectal absorption is variable.
- Distribution is influenced by body composition, protein binding, regional blood flow and membrane permeability.
- The main routes of elimination are the hepatobiliary system, kidneys and lungs. Size and maturation are the major covariates influencing clearance. The liver and kidneys are immature at birth, maturing over the first two years of life. Postmenstrual age rather than postnatal age is a better marker of maturation.
- Neonates display altered pharmacodynamics e.g. differences in MAC of gaseous vapours, altered effectiveness of neuromuscular blocking drugs, bronchodilators and the inotropic effects of calcium.
References