

Paediatric Pharmacology

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Definitions

Premature neonate – baby born less than 37 weeks post conception

Neonate – baby less than 44 weeks post conception

Infant – child up to twelve months of age

Child - over 12 months of age up to adolescent

Pharmacokinetics – describes the absorption, distribution, metabolism and elimination of drugs. Another way of describing it is “the effects of the body on drugs”.

Pharmacodynamics – describes the effects of drugs on the body.

Phase I metabolism – biotransformation to render the drugs more polar (to prepare for elimination) by means of oxidation, reduction or hydrolysis.

Phase II metabolism – biotransformation to render the drug more polar (to prepare for elimination) through conjugation reactions such as glucuronidation, sulfation and acetylation.

Bioavailability – Describes the extent (and rate) of uptake of an active drug into the body. It is expressed as a percentage when compared to intravenous administration of the same drug. If an orally administered drug has is poorly absorbed or has a high first-pass metabolism it will have a low bioavailability.

First-Pass Metabolism – this usually refers to the liver metabolism after oral administration. A high first-pass metabolism will reduce the bioavailability of a drug e.g. Morphine, midazolam, propranolol. Sublingual or rectal administration can bypass the liver and hence increase the drug bioavailability. Some drugs undergo first pass metabolism in the gut mucosa e.g. methyl dopa.

pK – the pH at which 50% of the drug is ionized.

Volume of Distribution (V_d) – a theoretical term to quantify the distribution of a drug. It is the volume in which the amount of drug would need to be uniformly distributed to produce the observed blood concentration. Therefore:

$$\underline{V_d \times \text{Drug concentration in blood} = \text{total amount of drug in the body}}$$

Introduction

When administering drugs to children it is vital to understand the developmental pharmacology of neonates, infants and children. Many aspects of pharmacodynamics and pharmacokinetics differ between the adult and paediatric population. Failure to appreciate these differences can result in preventable serious morbidity or even mortality. Many of these differences are particularly important in the neonatal or premature neonatal group.

Pharmacokinetics

a) Absorption

Oral administration

Most drugs for children are administered orally. Oral preparations are cheaper to manufacture and are more acceptable to children than using the painful intramuscular route.

Many factors alter the degree of absorption of a drug through the gut wall. Small, lipid soluble unionized molecules with favourable dissolution characteristics in gastric fluid are better absorbed than larger ionized molecules. The degree of ionization is dependent on the pK of the drug and the pH of the environment. For example, a drug which is a weak base (e.g. morphine, pK 8.0, pethidine pK 8.5) will be more ionized as the pH is reduced i.e. when the environment becomes more acidic. An acidic drug such as penicillins, salicylates however will become less ionized as the environment becomes more acidic.

Therefore the pH and volume of acidic gastric acid will determine the absorption characteristics and hence bioavailability of many drugs. The gastric acid secretion is decreased in the neonate. This makes the absorption of many drugs variable in this group.

Delayed gastric emptying and reduced gut motility may also occur in the neonate which further alters drug absorption.

Mucosal Administration

To bypass the hepatic first pass metabolism, some drugs may be given to be absorbed through the oral or nasal mucosa. An example is midazolam, where the bioavailability is 57% when given nasally, compared to 30% when given orally. The dose therefore needs to be adjusted accordingly. Some drugs can be given as a lozenge (or “lolly”) for transmucosal absorption, such as fentanyl. It is rapidly absorbed and bypasses the liver. The bioavailability has been found to be higher when compared to adults and the current preparations are expensive.

Rectal Administration

The rectum has a rich blood supply, supplied by plexuses of the superior, middle and inferior rectal arteries, which represent anastomoses between portal and systemic circulations. Some of the first pass metabolism of the liver may therefore be bypassed. Many drugs can be given rectally, particularly if the oral route is not possible. Commonly, paracetamol (acetaminophen) can be given rectally, however it must be remembered that absorption in children via this route is variable, and the lag time to detectable blood levels can be 40 minutes. Oral administration produces rapid and more reliable absorption; this is often within 10 minutes.

Skin Patch administration

Some drugs are given via a skin patch e.g. fentanyl, however this must be done with extreme caution in children as the absorption is dependent on skin thickness and blood flow. A fever for example may increase skin blood flow and increase the rate of absorption. As the skin acts as a reservoir for the drug, absorption will continue for many hours after removal of the patch.

Intramuscular Administration

It is very easy to lose the trust of a child if we cause pain. It is for this reason that despite the high bioavailability of the intramuscular route, this method of administration is almost always avoided in children if at all possible.

b) Distribution

The determinants of drug distribution can largely be classified in terms of **drug factors** and **patient factors**.

Drug Factors

Most of the drug factors determining whether a drug crosses membranes are similar to that discussed in the absorption section; highly lipid soluble small unionized molecules will easily cross membranes such as the blood-brain barrier. A further drug factor which is extremely important is protein binding. The higher the protein binding of a drug, the less 'active' free drug is available to cross cell membranes and have a pharmacological effect. A drug with high protein binding will therefore have a lower volume of distribution. Protein binding for a particular drug is altered in the neonate and is discussed below.

Patient factors

There are differences between adults and children in terms of drug distribution; body composition and protein binding are responsible for many of these differences. Premature and full term neonates have a much greater proportion of body weight in the form of water compared to older children (Table 1).

Age	Premature neonate	Neonate	1 year old	Adult (male)
Total Body Water (%)	85	80	60	60
Intracellular Water (%)	25	35	35	40
Extracellular Water (%)	60	45	25	20

Table 1: The developmental changes in body water composition. Note the overall total body water is as high as 85% in the premature neonate compared to 60% at one year. The percentage of extracellular water reduces in the first few months of life, while the intracellular value increases. The one year old is very similar to an adult in terms of water composition and distribution.

The implication of this is that water soluble drugs will have a greater volume of distribution in the neonate. Sometimes the neonate may require a greater loading dose per kg compared to the older child to have a similar effect. Examples would be suxamethonium or theophylline. One must remember however, that neonates are often sensitive to medications that affect the respiratory, cardiovascular and nervous systems. Other factors are important however; the neuromuscular junction is less well developed in the neonate, so in practice one does not require as much of an increase in dose of non-depolarising blocker as one may expect from distribution alone (e.g. curare or atracurium).

Muscle and fat content as a proportion of total body mass is smaller in neonates compared to older children. Therefore, anaesthetic drugs that redistribute to muscle and fat would be expected to have a prolonged clinical effect. Thiopentone is an example of this.

Protein binding alters during (approximately) the first 6 months of life. The neonate has a lower concentration of albumin and alpha-1-acid glycoprotein (AAGP). Acidic drugs tend to bind to albumin (e.g. phenytoin, thiopentone) and basic drugs tend to bind to AAGP (e.g. local anaesthetics, alfentanil). Not only is the concentration of

proteins reduced in the neonate, but the affinity of these proteins for drug binding is reduced. The effect of reduced quantity and quality of protein binding has a marked effect on the concentration of 'free' active drug as well as its ability to cross membranes. It is of particular importance in those drugs which are highly protein bound, such as phenytoin, diazepam, bupivacaine, barbiturates, many antibiotics and theophylline.

Furthermore, albumin binds to bilirubin. Some drugs compete with bilirubin for protein binding, so rendering the neonate susceptible to kernicterus (if the unbound bilirubin fraction is increased) or drug toxicity (if the fraction of free drug is increased). Drugs which can compete with bilirubin in this way include phenytoin and caffeine.

Other factors which alter distribution include regional blood flow and the maturation of the blood-brain barrier. The neonatal brain is relatively large and receives a higher percentage of the cardiac output (25%) compared to the adult. This is one reason induction agents act so quickly in the neonate. The blood-brain barrier (BBB) is immature in the neonate and therefore drugs which are relatively lipid insoluble (e.g. morphine) can reach the central nervous system easier than in the older brain. Fentanyl on the other hand is more lipid soluble and therefore the effect of a maturing BBB has less of an impact on its ability to reach the brain.

c) **Metabolism**

The metabolism of many drugs are dependent on the liver and its blood flow. The hepatic blood flow is reduced in the neonate and increases as a proportion of the cardiac output as the infant matures. Pathology may alter blood flow, such as any cause of raised intra-abdominal pressure e.g. post exomphalos reduction.

The complex enzyme systems involved in drug metabolism mature at differing rates in the paediatric population. Many drugs undergo Phase I metabolism, and are metabolised by enzymes of the cytochrome p450 system. The important gene families of these isoenzymes are CYP1, CYP2 and CYP3. The enzymes of these families develop at very different rates. The development is also variable between individuals, which emphasizes the need to titrate drugs to effect or to concentration levels if available. As an example of this variability, the enzyme CYP2D6 is responsible for transforming codeine into its active form of morphine. The activity of this enzyme is very low in neonates and can take more than 5 years to develop adult levels. A study of 3-12 year olds showed 46 percent were poor metabolisers of codeine.

In contrast, CYP3A4 is has an important role in the metabolism of many drugs eg midazolam, diazepam, paracetamol; however it matures rapidly to adult levels in the first 6-12 months of life.

As a result of these hepatic factors, the $T_{1/2\text{Beta}}$ (half life of the drug after the initial rapid redistribution has taken place) is often markedly prolonged in the neonate; however the older child frequently has a shorter $T_{1/2\text{Beta}}$ than the adult (reflecting the large hepatic blood flow in the child). A good example is thiopentone, where the $T_{1/2\text{Beta}}$ in the adult is 12 hours. The child $T_{1/2\text{Beta}}$ is approximately half of this

value, however the neonate is around 18 hours, due to hepatic blood flow and enzyme factors.

d) Excretion

The renal efficiency in neonates is considerably reduced compared to the adult. This is due to a combination of factors:

- Incomplete Glomerular development with immature glomerular filtration and tubular function
- Low renal perfusion pressure
- Inadequate osmotic load to produce full counter-current effects.

Drugs reliant on glomerular filtration or tubular function are particularly affected by these differences and result in prolonged half life e.g. aminoglycoside or cephalosporin antibiotics. Premature neonates are particularly susceptible.

The Glomerular Filtration Rate develops to full maturity by the age of 2 years (*Table 2*).

GFR (%of adult value corrected for size)	15%	25%	50%	60%	80%	100%
Age	1 day	1 week	3 months	6 months	12 months	2 years

Table 2. The development of GFR compared to full adult values (size corrected). (Adapted from Cote C et al 3rd Ed. 2001).

Pharmacodynamics of individual drug groups.

When considering the overall effects of individual drugs, one needs to consider the often conflicting pharmacokinetic factors as well as the pharmacodynamic effects of the drug on the child. Below is a discussion of some commonly used drugs in anaesthesia.

a) Inhalational Anaesthetic Agents

Inhalational inductions are more common in children than in adult practice with either halothane or sevoflurane. The MAC values for all anaesthetics vary with maturation. The MAC in a neonate is relatively low and increases to peak at 6-12 months of age before decreasing to adult values after a few years. For example the peak MAC of isoflurane in a 6 month old may be over 2% before reducing to adult values over 5-10 years.

It has been suggested that neuronal density, metabolic rate, oxygen consumption and brain water have contributed to this alteration from birth; however the precise mechanism remains unclear.

Desflurane is preferred in neonates in some centres as maintenance of anaesthesia as it is associated with rapid wake-up and reduced post-operative apnoeas.

b) Intravenous Anaesthetics

i) Propofol

In young children, the induction dose is 3-4 mg/kg compared to 1-2mg/kg in adults. The dose for maintenance of anaesthesia is higher compared to adults. The reason for this is the very rapid redistribution and rapid metabolic clearance. It must be noted that propofol is not licensed for sedation in children due to the risk of propofol infusion syndrome (metabolic acidosis, refractory bradycardia, rhabdomyolysis and hepatomegaly with lipaemic plasma).

Up to 60% of children experience significant pain on injection of propofol into a peripheral vein. The incidence may be reduced with the administration of a small dose of lignocaine (with or before the propofol) or injecting into a large vein. Newer preparations of propofol are more expensive but also appear to have a lower incidence of pain.

Propofol undergoes extensive hepatic and extrahepatic clearance, which accounts for children with biliary atresia having similar pharmacokinetics to control groups.

ii) Thiopentone

The reduced protein binding in the neonate would suggest a reduced dose is required. The immature cortical function further reduces this requirement. Furthermore, the reduced fat and muscle content in the neonate may prolong the expected duration of action. Infants on the other hand require a larger dose which is mostly dependent on the rapid redistribution of the drug. The $T_{1/2\text{Beta}}$ of thiopentone has been discussed in the pharmacokinetic section.

Both propofol and thiopentone appear to produce similar reductions in blood pressure, although the relative bradycardia with propofol potentially could have a profound effect on the cardiac output of the neonate or young infant. They both have a similar incidence of apnoea after administration.

iii) Ketamine (see TOTW “Ketamine in Anaesthetic Practice”)

The analgesic properties of ketamine make it suitable for many patients for procedural sedation. It can also be used as a premedicant before general anaesthesia or as an anaesthetic agent. Children require a greater dose (per kg) of ketamine than adults. The more rapid degradation is responsible for this; however there is a large amount of variability. Post operative nausea and vomiting is common (1/3 of patients) after ketamine anaesthesia. Post operative hallucinations and dreaming are more common in older children compared to younger children. The effect can last for weeks and even months. Benzodiazepine co-administration may reduce the incidence of this.

The salivation caused by ketamine may necessitate an antimuscarinic such as glycopyrrolate to avoid laryngospasm.

Ketamine should not be used in patients with intracranial hypertension. It also can increase pulmonary artery pressures if the ventilation is not controlled to normocapnoea.

c) Benzodiazepines

i) Diazepam

Oral absorption is very rapid in children. It can also be used successfully by rectal administration when the oral route is not possible, such as during a seizure.

It must be remembered that the $T_{1/2}$ Beta is very prolonged (up to 100 hours) in neonates due to low hepatic blood flow and immature hepatic excretion. The intermediate metabolite (N- desmethyldiazepam) is very active with an even longer half life. It is therefore not a suitable drug for neonates or for short procedures requiring rapid wake-up – particularly in children under 12 months of age.

i) Midazolam

Midazolam is the most commonly used benzodiazepine in paediatric anaesthesia. The anterograde amnesia is a useful effect as well as the calming nature of the drug. The method of administration has been discussed above; however the bitter taste is often disguised with the addition of flavours.

Despite the shorter half-life of midazolam compared to diazepam, the $T_{1/2}$ Beta is still 6-12 hours in the neonate. Older children (2-3 hours) clear the drug slightly quicker than adults. Metabolism is more dependent on hepatic blood-flow than hepatic function. It is less fat soluble than diazepam so the peak effect of midazolam is slower. Unlike diazepam, the metabolite has minimal clinical activity.

Unfortunately, some children exhibit excitatory effects with midazolam which is an unwanted effect when used as a premedication in the anxious child.

d) Neuromuscular blockers (see also TOTW “Pharmacology of Neuromuscular Blocking Drugs and Anticholinesterases”)

Overall, the neuromuscular blockers have a higher volume of distribution in young children; the clinical implication of this depends on the individual drug, the clearance rate and the maturity of the neuromuscular junction. In general, the clearance is reduced in neonates and much higher in children – often higher than adult values.

Suxamethonium is discussed above. The high volume of distribution necessitates a higher dose per kg (2mg/kg) compared to adults. It must be remembered that a bradycardia after suxamethonium is relatively common and is poorly tolerated in neonates (who also have a high vagal tone).

Of the non-depolarising neuromuscular blockers, atracurium is a suitable agent to use in infancy due to its predictable duration of action of about 30 minutes. The high volume of distribution is offset by the increased plasma clearance in infancy. The implication is that recovery of neuromuscular function varies very little with age (Bell

S and Monkhouse D 2005). Some people use a smaller dose in neonates and a higher dose in older children; however this does not appear to be important in clinical practice (Black A and McEwan A 2004).

Pancuronium is a longer acting neuromuscular blocker which is renally excreted; there is delayed excretion in neonates. It is often used for prolonged procedures; particularly where post operative ventilation is planned. It is vagolytic; the associated tachycardia is well tolerated in neonates.

It must be remembered that residual neuromuscular blockade in neonates and infants may have a profound effect on the balance between the body oxygen supply and demand during the recovery phase; the smaller functional residual capacity, the potential for small airway collapse and neuromuscular weakness in the presence of high basal oxygen demand may quickly lead to tissue hypoxia.

e) **Local Anaesthetics.**

One needs to take care to avoid high plasma levels of local anaesthetic with the resultant risk of cardiac and CNS toxicity. Neonates and infants absorb local anaesthetics well due to high tissue blood flow and cardiac output (Black A and McEwan A 2004). As well as this the low quality and quantity of protein binding in the neonate potentially expose the neonate to higher levels of free drug. Metabolism is reduced due to enzyme immaturity. During infusions of epidural bupivacaine for example, the plasma levels continue to rise even after 48 hours in neonates, whereas in adults they would have reached steady state levels in a much shorter time.

(Analgesics are discussed in TOTW “Perioperative Analgesic Pharmacology in Children”)

Key points

- There are many pharmacokinetic and pharmacodynamic changes as a child develops.
- In general, caution is particularly needed in the premature and term neonatal population to avoid pharmacological errors.
- The pharmacological variation amongst neonates and infants emphasize the need to titrate many drugs to effect.
- Physiological and Pathological factors can alter drug handling.
- Hepatic metabolism is determined by developing hepatic enzyme systems and by blood flow.
- Enzyme systems in the developing child are variable and complex. This gives reduced predictability of how a drug will affect a young child.
- The paediatric patient’s ability to clear a drug changes rapidly in the first few months of life; often a child can clear drugs faster than an adult.
- Oral administration is far more acceptable to children compared to the intramuscular route.

Further Reading

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