Clinical pharmacology

Principles of dosing in young children

Several drugs that are marketed and prescribed are not registered for use in children owing to a limited number of pharmacokinetic studies done in infants and children. Drug doses are usually derived from studies in adults. However, the pharmacokinetics and pharmacodynamics of drugs in children are different from those in adults due to the impact of development physiology. Age-based dosing results in errors due to variability in the weight and lean body mass of children of the same age. In this article we discuss the effect of developmental changes in young children on drug absorption, distribution, metabolism and excretion which form the basis for recommended dose estimation.

Developmental changes in pharmacokinetics

Absorption and first-pass metabolism

Most drugs are absorbed after oral, intramuscular, rectal or percutaneous administration.

Oral route

The rate and extent of absorption are affected by many factors including the physicochemical properties of the drug, and factors which vary between and within individuals such as concomitantly administered drugs and food, co-morbid disease and disease severity, gastric pH and the rate of gastric emptying, intestinal transit time, maturity of the intestinal mucosa, biliary function, intestinal and hepatic first-pass metabolism, the expression of drug transporters and microbial colonisation.

Gastric pH is neutral at birth. It decreases to about 3 within 48 hours and thereafter returns to neutral for 10 days. The pH then slowly declines until it reaches adult values at about 2 years of age. Hence, acid-labile drugs (e.g. amoxicillin and erythromycin) are more efficiently absorbed in young children, and the absorption of weak organic acids (like phenytoin) is reduced. Gastric emptying is delayed in the period immediately after birth. Thus the rate of drug delivery to intestinal sites of absorption is retarded. Consequently, the time taken for a drug to reach a maximum concentration is prolonged in neonates and the peak drug concentration might be lowered as a result, as with paracetamol. Gastric emptying approaches adult rates within 6 - 8 months. Intestinal transit time is prolonged in neonates and reduced in older infants as a result of changes in intestinal motility. Shorter transit times are associated with decreased absorption of certain sustained release formulations, e.g. theophylline. Immaturity of the intestinal mucosa in neonates leads to increased permeability to certain drugs. Practical issues involving oral absorption include frequent feeding which might interact with some drugs.

Intramuscular route

Intramuscular absorption of drugs is often erratic in neonates, because in the first 2 - 3 weeks of life, blood flow to the muscles is very variable. Drug delivery after intramuscular injection can therefore be unreliable in very young patients.

Rectal route

Absorption of drugs via the rectal route is not much changed by maturation. Drugs administered high in the rectum are delivered to the portal vein; they may be affected by first-pass metabolism (on passing through the gastrointestinal membranes and liver) and enterohepatic circulation. Drugs placed low in the rectum are delivered directly into the systemic circulation by the haemorrhoidal veins. Frequent defaecation in neonates and infants, compared with older children and adults, can reduce absorption.

Percutaneous route

Percutaneous absorption of drugs is faster and more extensive in neonates and infants because of the relatively larger surface area, and because they have thin, poorly keratinised and well-hydrated skin which is more permeable. Systemic toxicity can occur with topical use of steroids or lignocaine.

Distribution

After absorption, drugs are distributed by arterial blood to the tissues including the organs of elimination. The apparent volume of distribution (V_d) is the volume of plasma required to account for the total amount of drug in the body, at the plasma concentration, when in equilibrium. V_d is a function of lipid v. water solubility and the plasma and tissue-binding properties of the drug. V_d may be altered in children owing to differences in body composition, plasma protein-binding capacity and high membrane permeability.

Body composition and apparent volume of distribution of the drug

In very young infants, the total body water is high (80 - 90% of body weight) while the fat content is low (10 - 15% of body weight). By adulthood the total body water decreases to 55 - 60% of body weight. The extracellular water content is approximately 45% of the body weight in neonates compared with 20% in adults. The extracellular fluid volume correlates with body surface area (BSA) in children. Hence several hydrophilic drugs such as gentamicin and linezolid have a larger V_d in neonates than in infants or adults.

Plasma protein-binding

Neonates have a low plasma protein-binding capacity, for several reasons. Firstly the concentration of the binding proteins is low. Moreover, these proteins are qualitatively different with lower affinities for binding certain drugs. The concentration of albumin at birth may be as low as 35 - 37 g/l; this slowly rises to reach normal adult values of 45 - 48 g/l by 1 year of age.

For drugs that are highly protein bound (> 90%), lower doses are required in neonates who have a low plasma protein-binding capacity. For example, decreased protein binding of theophylline in neonates allows the use of low doses for the treatment of neonatal apnoea, while higher doses may elicit adverse effects. As the drug has a narrow therapeutic index, therapeutic drug monitoring (TDM) is advised.

Membrane permeability

The immaturity of the blood-brain barrier in neonates renders it relatively permeable, allowing higher drug concentrations to reach the central nervous system (CNS). The volume of the CNS reaches 80 - 90% of adult values by age 4 - 6 years, but BSA does not reach adult values until about 16 - 18 years. Thus, the relatively larger CNS volume found in younger children does not correlate with BSA. Therefore, dose adjustment for intrathecal administration of some drugs, e.g. methotrexate, should be done according to age rather than BSA.

Metabolism

The liver is the principal site of metabolism for most drugs. Drug biotransformation reactions are usually classified as phase I or II

reactions. Phase I reactions such as oxidation, reduction and hydrolysis transform drugs into inactive or active metabolites. Typically, these metabolites are then conjugated by phase II reactions such as glucuronidation, sulphation or methylation to form less toxic metabolites which are more readily excreted due to their increased polarity. Both phase I and II metabolic pathways are immature at birth. Individual enzyme isoforms involved in these pathways have unique maturational profiles. Neonatal drug metabolism rates are approximately 20 - 70% those in adults due to altered hepatic enzyme activity. Cytochrome P-450 enzyme activity increases to adult levels by 6 - 12 months, and exceeds that of adults during years 1 - 4. It then declines back to adult levels by the end of puberty. Glucuronidation is depressed at birth and reaches adult values by the age of 3 years. Serious toxicity from chloramphenicol administration leading to circulatory collapse and the 'grey baby syndrome' may occur as a result of deficient glucuronidation. Sulphation and methylation activities are higher in children than in adults. The rate of drug metabolism is also dependent on liver growth. Children have a higher liver volume than adults for their body weight. The liver volume, blood flow and biliary function correlate well with BSA.

Excretion

Renal elimination of drugs depends on three processes: glomerular filtration, tubular secretion and tubular reabsorption. The developmental increase in glomerular filtration rate (GFR) relies on the existence of normal nephrogenesis. This process, beginning at 9 weeks' gestation, is complete by 34 - 36 weeks and is followed by postnatal changes in renal and intrarenal blood flow. Table I shows the approximate GFR depending on age, weight and BSA. After maturation of renal function at approximately 2 years, the GFR correlates well with BSA. The GFR of a child less than 12 years of age can be estimated from the following formula of Schwartz:

$$\text{GFR (ml/min/1.73m}^2) = \frac{\text{Height in cm X 40}}{\text{Serum creatinine in µmol/l}}$$

The GFR in children older than 12 years can be more accurately estimated from the Cockcroft-Gault formula used in adults:

For females multiply the answer by 0.85.

Creatinine clearance (ml/min) =
$$\frac{(140 - \text{age in years})(\text{weight in kilograms})}{(72)(\text{serum creatinine in µmol/l})}$$

Tubular secretion is an energy-dependent process. It is reduced at birth and mature by 1 year of age. Tubular reabsorption is usually developed at birth, but further maturation is completed at 3 years of age.

Table I. Approximate GFR depending on age, weight and BSA according to Fawer (Daschner M)			
Age	Approximate weight (kg)	BSA (m²)	GFR (ml/min/1.73 m²)
Premature infant	2.0	0.15	6.0
Term neonate	3.2	0.2	13.0
1 month	4.0	0.25	52
1 year	9.2	0.45	115.0
10 years	30	1.0	120
Adult	70	1.73	120

Dose estimation

There is no universal formula that can be recommended for adjusting an adult dose to the paediatric patient. Age-based dosing may result in errors due to variability in weight and lean body mass of children of the same age. Dose should be calculated by body weight rather than age. This can be done as follows:

$$\text{Infant dose} = \frac{\text{adult dose x body weight infant}}{70 \text{ kg}}$$

where 70 kg is the average body weight for a healthy adult male. The maximum dose should not exceed the adult dose. Doses based on body weight may result in under- or overdosing of small or obese infants and children.

BSA, which correlates well with many physiological parameters that are important for drug distribution and elimination, gives a better estimate for adjusting doses in small infants and children. The dose estimation can be done as follows:

$$\text{Infant dose} = \frac{\text{adult dose x BSA infant}}{1.73 \text{ m}^2}$$

where 1.73 m² is an average BSA of a 70 kg adult.

For drugs that are metabolised mainly by the liver, reduced doses are indicated in hepatic disease. Signs of clinical toxicity should be sought and TDM done where applicable. In patients with renal disease, the doses of drugs that are excreted mainly via the kidneys should be adjusted according to the GFR. Drug doses usually require reduction when the GFR is less than 30 - 40 ml/min/1.73 m². TDM should be done where applicable.

These broad dosing guidelines need to be considered in conjunction with individual factors such as the physical state of the patient (e.g. malnutrition, dehydration), the indication for the drug and the presence of concomitant medications with potentially significant drug interactions. Some drugs with a large V_d need a loading dose to achieve the desired concentration. For example, neonates require a loading dose of aminoglycosides (e.g. amikacin, gentamicin and tobramycin)

to achieve adequate bactericidal activity. However, due to renal immaturity in neonates, and hence decreased clearance, the dosing interval should be increased from 24 to 36 hours and TDM is recommended to guide further dosing after 48 hours.

Conclusion

In clinical practice, the ultimate goal is to provide infants and children with safe and effective therapy. As 'children are not merely small adults', the impact of maturational changes on drug metabolism and disposition should be considered. Dose estimation depends on the age of the child, the indication for the drug, drug properties, disease state and concomitant medication. Body weight and body surface area, rather than age, should be used to estimate the dose. Drug information package inserts are useful resources for calculating the correct dose.

Further reading

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