

Paediatric pharmacokinetics and drug doses

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SUMMARY

The pharmacokinetics of many drugs are different in children compared to adults. The pharmacokinetic processes of absorption, distribution, metabolism and excretion undergo changes due to growth and development.

Finding the correct doses for children is complicated by a lack of pharmacokinetic studies. Children's doses cannot always be extrapolated directly from adult studies.

Many paediatric doses are based on the child's age or weight. These may need adjustment depending on the child and the clinical response.

It is important to check dose calculations. The calculated childhood dose should not usually exceed the adult dose.

Introduction

While the adage that children are not small adults has existed for some time, most paediatric doses are still extrapolated from adult studies. Children experience large amounts of growth and development during early childhood which can dramatically affect the pharmacokinetics of different drugs. The lack of paediatric clinical trials and dosing information has been highlighted by the US Food and Drug Administration (FDA) and the European Medicines Agency as areas of clinical need, and there is now a requirement for more paediatric data in the evaluation of new drugs.¹

In the absence of data, the use of many drugs in children, especially neonates, is often off label. The off-label use of drugs is associated with an increased risk of adverse effects, particularly in patients under the age of two years.² It is particularly difficult to predict pharmacological effects in neonates as development occurs quickly, resulting in rapid changes in drug metabolism over short periods of time which create difficulty in predicting doses.^{3,4}

Understanding the differences in physiology at different stages of development (Table 1), compared to adults, assists with designing dose regimens. The different drug effects seen in children can be toxic, as seen with valproate hepatotoxicity and tetracycline-stained tooth enamel, or enhanced, as seen with some treatments for leukaemia.⁵ Drugs with a wide safety margin are good options for treating children as pharmacokinetic changes are unlikely to result in toxicity or ineffectiveness. For drugs with narrow safety margins, such as gentamicin or phenytoin, even small changes can cause serious toxicity. Table 2 shows examples of the differences between dosing children and adults.

Absorption

The composition of intestinal fluids and the permeability of the gut vary during childhood. Absorption of orally administered drugs is affected by changes in gastric pH which decreases during infancy to reach adult values by two years of age.⁶ Infants are at higher risk of toxicity via skin absorption due to a larger surface area to volume ratio and they also absorb more of a drug across skin due to their thinner stratum corneum.⁷ This explains why infants have an increased risk of methaemoglobinaemia with topical anaesthetics.⁸

Distribution

The volume of distribution changes throughout childhood as stores of fat and water change. Infants have a higher percentage of extracellular water, and stores of body fat increase throughout childhood. Changes in volume of distribution can alter the drug's half-life, requiring adjustment of the dosing interval, as seen with digoxin.

Table 1 Childhood age classes

Class	Age
Neonate	0-28 days
Infant	>28 days - 12 months
Toddler	>12-23 months
Preschool child	2-5 years
School age child	6-11 years
Adolescent	12-18 years

Table 2 The effect of paediatric physiology on pharmacokinetics of common drugs

Drug	Pharmacokinetic differences	Effect
Gentamicin	Volume of distribution decreases throughout childhood along with percentage of total body water	Higher mg/kg doses used in younger children to ensure therapeutic peaks
Codeine	Conversion to morphine difficult to predict along with reduced clearance	Accumulation more likely. Not recommended for children due to safety concerns
Theophylline	Increased clearance	Higher mg/kg doses required in infants and children
Phenytoin	Decreased oral absorption due to high stomach pH and decreased protein binding in infants	Decreased bioavailability, however lower serum concentrations required due to lower protein binding
Benzyl alcohol (common excipient)	Decreased clearance	Accumulation in infants leading to fatal 'gaspings syndrome'
Levetiracetam	Increased clearance	Higher mg/kg dose required in patients up to 12 years of age
Methylphenidate	Decreased clearance	Lower dose required in children (6–12 years) compared to adolescents

Dosing information for obese children is limited and has been identified as an area for research. Obese children can be dosed using ideal body weight and the dose adjusted based on clinical effect. They are at higher risk of toxicity from drugs such as paracetamol that do not distribute into fat, if actual weight is used to calculate the dose.

Infants have lower concentrations of circulating plasma proteins reducing protein binding.⁷ This results in higher distribution and lower peak concentrations of protein-bound drugs such as cefazolin.⁸

Metabolism

The metabolism of drugs is the most complex difference between adults and children. Cytochrome P450 (CYP) enzymes are active in the fetus. Enzyme activity begins to increase during the later stages of pregnancy with different rates of individual enzyme development seen in infants who are born preterm.⁹ The pattern of active enzymes changes over the first few months of life to reach or exceed adult levels at around two years of age.⁷ While most enzymes increase in activity over the first few months of life, some such as CYP3A7 are replaced by other enzymes, in this case CYP3A4. The development of metabolic processes, such as glucuronidation, is less clear, but is thought to take at least three years to achieve full activity.⁹

Liver blood flow may be relatively high in infants. This could affect first-pass metabolism particularly for drugs with a high extraction ratio, like propranolol.

Elimination

Excretion is an important step in the final removal of the drug and any metabolites from the body. It relies on effective renal and hepatic function that develop over time. Preterm neonates develop renal

excretion pathways more slowly than term neonates.¹⁰ Glomerular filtration rates reach adult levels by about two years of age.¹¹

Dosing and development

The change from treating children and neonates as little adults has occurred gradually. Previously size and gestational age were viewed as the main determinants of drug clearance, but this has been replaced with the view that the capacity and functions of individual organs and the development of biochemical pathways are of greater importance.⁹ The development of drug metabolism and clearance pathways begins in the fetus and continues throughout childhood.¹² A study by the FDA examined different methods of predicting paediatric clearance of drugs based on adult values, and concluded that no single method of prediction is suitable for all drugs or age groups.⁴

Dosage regimens based entirely on age are often inaccurate and may lead to adverse effects, toxicity or lack of clinical effect. There is a lack of pharmacokinetic studies in children of different ages. Dosing information is difficult to determine in children as traditional pharmacokinetic studies are hard to conduct in children and are subject to a greater range of ethical considerations. These studies require large amounts of blood to be taken over periods of time and this is not considered ethical in children. The development of population pharmacokinetic modelling has allowed paediatric-specific dosing information to be developed.¹³ These new techniques will assist in developing safer dosing information for children over time by reducing the burden of pharmacokinetic studies. Although improving, no mathematical method of dose estimation can replace clinical studies using actual outcomes, surrogate measures or therapeutic drug monitoring.¹⁴

Weight-based and surface-area-based dosing regimens are simple and are used in most clinical situations. However, with the lack of specific paediatric data, these dosing equations are often based on adult data and then scaled based on size and age as an approximation for drug activity in children. Paediatric growth and development is not a linear process. Scaling from adult doses based on weight alone is not adequate for determining doses across the range of developmental processes that occur throughout childhood.⁷ While this method may have some value in older children and adolescents, who have similar values to adults for body composition and organ function, it lacks utility in toddlers and neonates.

Therapeutic drug monitoring in conjunction with clinical review can be used to assess effectiveness and safety, but only when information about the safe and effective concentrations in children is available. Even for vancomycin, for which therapeutic drug monitoring is commonly performed, this information is not available.¹⁵ More information is available regarding the safe and effective concentrations of antiepileptic drugs in children, although therapeutic drug monitoring cannot predict all adverse effects, such as hepatotoxicity with sodium valproate.

Practical advice

When prescribing for children it is appropriate to use a paediatric reference source. Use a reputable dosing reference, such as the AMH Children's Dose

Companion.¹⁶ As many doses are given in mg/kg, knowing the child's weight is important. In some cases the dose may have to be based on the ideal weight. Children on long-term treatment will need dose adjustments as they grow.

An incorrect dose, particularly in infants, could have catastrophic adverse effects. It is good practice for two people to double check dose calculations, such as the prescriber and dispensing pharmacist. Usually the calculated dose should not exceed the adult dose.

The recommended dose may not be the optimum dose for some children. It may then be necessary to adjust the dose according to the clinical response.

Ensure the calculated dose is able to be administered safely to the child. Doses can be rounded to ensure they are able to be measured by parents and carers accurately.

Conclusion

There is often a lack of pharmacokinetic studies in children of different ages. This can make it difficult to know what the optimum dose is for a child. Many doses are based on the child's age or weight. This does not always allow for the different rates of childhood development. It may be necessary to adjust doses according to the clinical response. ◀

Conflict of interest: none declared

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