Today's Treatment

Clinical pharmacology

Drugs in children

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Children are not "little adults" but rather immature individuals whose bodies and organ functions are in a continuing state of development. More particularly, the newborn infant has to adapt very rapidly to a new environment by going through a series of rapid and continuous anatomical and physiological changes. It is not surprising, therefore, that the pharmacokinetics and toxicity of most drugs vary considerably throughout the paediatric age range and may differ profoundly from findings in adults.

Drug absorption

The rate of drug absorption into the systemic circulation depends on both the route of administration and the drug's physicochemical properties—molecular weight, pKa, and lipid solubility. The latter primarily determine the rate and extent of a drug's passage across membranes and apply equally to all ages. Tissue perfusion is an important factor relating to the route of administration. There are no functional differences between the older infant, child, and adult that should affect gastrointestinal absorption, although the rate, but not extent, of absorption may be increased by using liquid preparations of many drugs, and these formulations are often preferred in the young child.

In the newborn period, and after the first day of life, gastric contents are less acidic, and the gastric emptying time and intestinal transit time are considerably slower than at any other age. Consequently, drugs such as penicillin G and ampicillin, which are partially inactivated by a low pH, have greater overall absorption when swallowed.^{1,2} The slow gastric emptying time reduces the absorption of some drugs, while others may achieve greater absorption because of prolonged contact with the bowel wall during the longer transit period through the intestine.

Absorption from intramuscular and subcutaneous sites depends mainly on tissue perfusion, and if this is adequate it is similar in children and adults. The vasomotor instability in the newborn period might theoretically cause delay in absorption from peripheral sites, although in practice the therapeutic effectiveness of drugs given via these routes suggests that this is not an important factor.

Drug distribution and protein binding

The distribution process regulates the amount of drug reaching specific body compartments or tissues and hence the concentration of the drug at the receptor site. It is mainly influenced by the tissue mass, fat content, blood flow, membrane permeability, and degree of protein binding.

The relative body fat content is lowest in the newborn, particularly in preterm and light-for-dates babies. Thereafter, the relative mass of subcutaneous tissue rises to a maximum at 9 months of age, decreases until 6 years, and subsequently increases towards adolescence. The relative proportions of body water compartments also vary with age. As a percentage of total body weight the total body water falls from 87% and 77% in the preterm and term newborn baby respectively to 73% at 3 months, 59% at 1 year, and 55% in the adult. Similarly, extracellular water falls from 45% of the total body weight in the term newborn infant to 33% at 3 months, 28% at 1 year, and 20% in the adult.³ Most drugs are bound to intracellular components but in addition are distributed evenly throughout the total and extracellular body water and, to some extent, body fat. The variability with age in concentrations of water-soluble and fat-soluble drugs at the receptor sites arising from these changes in compartment volumes and resulting from similar weight-related drug doses are obvious.

In addition the blood-brain barrier appears to be more permeable in the newborn period and thereby allows increased passage of some drugs across it, a fact that may be advantageous in the antibacterial treatment of meningitis at this age.

Extracellular binding to plasma proteins depends on the amount of binding proteins and the drug affinity constant for proteins, and these are directly or indirectly modified by pathophysiological conditions and by other drugs and compounds. A quantitative and qualitative reduction in plasma protein binding occurs in the newborn period. At this stage, babies, and particularly preterm babies, have lower plasma albumin concentrations than at other ages (30-40 g/l), and the albumin is qualitatively different and has a lower affinity for drugs. Further modification of plasma protein binding by the higher free fatty acid and bilirubin concentrations and the lower blood pH is likely to occur at this age.⁴

Information on drug protein binding in older children is limited, but from indirect evidence of cerebrospinal fluid and saliva levels, similar degrees of binding have been observed for carbamazepine, phenobarbitone, and phenytoin.⁵⁻⁷ An increase in the free drug allows greater availability for metabolism and excretion, and the net effect of change is not wholly predictable.

The few studies reporting drug volumes of distribution in children suggest that there is greater variability in these subjects, there being generally the greatest values in the newborn period, progressively reducing but remaining relatively greater than

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in adults through childhood until equivalence is reached in adolescence.

Elimination

Elimination of a drug is effected by metabolism or excretion, or both, of the parent drug. Drug elimination rates vary considerably in the newborn, infants, older children, and adults.

METABOLISM

The liver is quantitatively the most important organ for drug metabolism at all ages. The overall rate of metabolism probably depends on both the size of the liver and the metabolising ability of the appropriate microsomal enzyme system. Liver volume relative to body weight decreases from birth to adulthood, the relative volume in the first year of life being twice that at 14 years.⁸ This may explain why rates of drug metabolism are greatest in late infancy and early toddlerhood and become progressively less rapid through childhood to adolescence and adulthood. In the newborn period the microsomal enzyme systems are immature, and at this time the relative contributions of hepatic size and immaturity of the enzyme system probably determine drug metabolising rates. For most drugs in this period the rates of elimination appear to be slower than in later childhood. In older children the microsomal enzyme system activity per unit volume of liver is similar to that in adults,⁹ although there is probably wide variability.

EXCRETION

The ultimate route of elimination of most drugs is via the kidney. Developmental changes affecting the glomerular filtration and tubular secretory excretion processes are therefore important. The former attains adult values per unit surface area from about 2½–5 months of age, but in the newborn period it is only 20–40% of that in adults.¹⁰ Tubular secretory and reabsorptive mechanisms reach adult capacity by about 7 months.¹⁰ Consequently, drugs excreted by glomerular filtration—for instance, digoxin and gentamicin—and those for which tubular secretion is important—for example, penicillin—are eliminated less rapidly in the newborn than in older infants and children.

The generally larger volumes of distribution and faster rates of elimination of drugs in children compared with adults necessitate the higher weight-related doses in order to reach similar plasma drug concentrations. Not only are there pronounced differences in kinetic values between children and adults, but there is pronounced variability among individuals in childhood, particularly in the younger age groups.

Adverse effects

The overall incidence of adverse drug reactions in children varies in published data from 6% to 17%^{11 12} and is similar to that reported for adults.¹³ A higher rate (24.5%) has been reported in newborn infants,¹⁴ which may reflect the slower rates of drug elimination and the greater magnitude of drug exposure in the newborn period.

As in adults most reactions relate to the gastrointestinal tract, followed by the haematological, cutaneous, neurological, metabolic, cardiovascular, and respiratory systems.^{11 12} In the newborn hypertension, cardiac arrhythmias, renal failure, gastrointestinal reactions, and hypoglycaemia are the most frequent moderate/major adverse reactions.¹⁴

Drug interactions

Most children given drugs in hospital receive more than one and drug-drug interactions therefore need to be considered in prescribing. Many of the known interactions reported from adult practice, however, concern drugs not commonly used in paediatric practice, such as warfarin and the oral hypoglycaemic agents. In children interactions involving anticonvulsant drugs, either with each other or with other drugs, are likely to be those most commonly seen.

Children often receive "over the counter" drugs for minor ailments, but the problems of interactions resulting from these medications are not known.

Drug-concentration monitoring

The indications for monitoring drug concentrations in body fluids are the same for children as adults. The practice, however, is likely to be of particular relevance in children for several reasons. Inter- and intra-individual variation in drug response in childhood is greater than at any other time, and titration of dose to the therapeutic response is unsuitable for most of the commonly prescribed drugs in children (antimicrobials, anti-convulsants, anti-inflammatory agents). In addition the therapeutic index of some drugs appears narrower in the young.

Nevertheless, few therapeutic ranges for drugs have been reported, specifically in children, and if, as seems likely, there are pharmacodynamic differences for some drugs between children and adults, establishing relevant therapeutic ranges is mandatory. In most cases monitoring drug concentrations in blood is the most appropriate approach, but children generally dislike its invasive nature. The problem may be offset by using saliva as the body fluid for drug assay, although this considerably reduces the scope and possibly the accuracy of the drug monitoring.

The large fluctuation in blood or saliva concentrations between doses and possible contamination of saliva by drug retained in the mouth make interpretation of drug concentrations particularly difficult in children.

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