New Drugs

Prescribing for infants and children

GEORGE W RYLANCE

Rational drug treatment for infants and children requires an understanding of the wide variability in drug handling and response in the early years of life. Such understanding without knowledge of the many and varied practical aspects of drug administration during this period is, however, insufficient, and treatment therefore depends on a comprehensive theoretical and practical approach to prescribing.

Drug handling

The main changes in drug handling with age occur in the first three or four years of life and particularly in the first few months. The table summarises these changes which form the basis for altering the dosage of relevant groups of patients who may be affected. Often several determinants of dosage—for example, increased distribution of water soluble drugs in neonates who have diminished excretion—may be altered simultaneously. In some instances these work in opposite directions, producing no overall change in drug concentration.

ABSORPTION

Physiological changes during infancy and childhood have little effect on the rate or extent of gastrointestinal absorption. Though the rate of absorption may be increased by using liquid preparations that do not require any time for dissolution, the widespread use of such preparations in young children has little clinical importance except in the long term use of drugs that are eliminated rapidly—for example, carbamazepine, theophylline. Adverse effects relating to higher peak concentrations, and also reduced control of symptoms or signs owing to lower trough concentrations at the usual intervals between doses, may be more prevalent in the young as a result of this increased rate of absorption.¹ The rate and extent of absorption of drugs administered intramuscularly varies little with age and is far more dependent on other factors—for example, perfusion.²

The newborn baby born at full term has a mature skin with barrier properties similar to those of the child or adult. Infants born before 33 weeks of gestation, however, have a poorly developed epidermal barrier, but this has limited therapeutic possibilities owing to the lack of a convenient and reliable method of transdermal

drug delivery, though some success has been achieved with theophylline.³ Modifying the transdermal systems used for delivering nitroglycerine and clonidine may also be useful.

DISTRIBUTION

The total volumes of body water and extracellular fluid related to body weight are the greatest during the neonatal period and infancy. These values decrease with age most appreciably during the first three months of life and thereafter more gradually. Water soluble drugs that are distributed mainly in extracellular water therefore have the largest volumes of distribution in the newborn and young infants.⁴ Furthermore, the blood-brain barrier may be functionally incomplete in the neonate, allowing increased penetration of some drugs.

Though there are small differences in the extent of protein binding with age throughout childhood (lower values in newborns and young infants),² these are generally not clinically important. The displacement of bilirubin from albumin by sulphonamides and some other drugs in the newborn is well recognised,⁵ and it should not be forgotten that the transfer of drugs in breast milk may be a source of inadvertent treatment to the neonate.

BIOTRANSFORMATION

The rates of biotransformation of most drugs proceed comparatively slowly in the first few weeks of life (table). This is particularly so in preterm infants and relates to the comparative immaturity of the hepatic microsomal enzyme systems.^{6,7} Oxidation and glucuronidation are particularly slowed. After a few weeks (about two to 12, and the time varies according to the process of biotransformation) the rates increase rapidly and remain fairly high for most drugs for the first two or three years of life. After this they reduce gradually until adolescence. There are, however, several exceptions to these general changes—for example, conjugation by sulphation does not seem to be altered.⁸

EXCRETION

The glomerular filtration rate increases steadily in early infancy to reach "adult" values related to surface area at between 2 and 5 months of age. Tubular secretion and reabsorption matures over a similar period.⁹ Thus most drugs that are primarily excreted unchanged by the kidney are eliminated more slowly in the first few months of life. Again, this is a particular feature in preterm babies, in whom the glomerular filtration rate may be less than one sixth of that of the normal older child and adult.¹⁰ The reported higher clearance rates of some drugs that are primarily eliminated by the kidney in young children compared with adult rates are probably due to enhanced extrarenal biotransformation (few drugs are totally eliminated by renal excretion). There are therefore considerable

Pharmacokinetics of drugs in children compared with "normal" adults (↑ = increased, ↓ = decreased, ↔ = unaltered)

	Age of child					Comments
	Newborn preterm	Term (0-4 weeks)	Infancy	1-4 years	5-12 years	
Absorption	↓	↔	↔	↔	↔	No clinical relevance
Distribution:						
Body water	↑ ↑ ↑	↑ ↑	↑	↑	↑	Weight related doses produce lower blood concentrations of water soluble drugs in the newborn
Body fat	↓ ↓	↓	↓ Slight	?↔	?↔	Minimal clinical effect
Plasma albumin	↓	↓	↓ Slight	↔	↔	Minimal clinical effect
Biotransformation:						
Oxidation/hydrolysis	↓ ↓ ↓	↓ ↓	↑ ↑ (After some weeks)	↑	↑ Slight	Reduce dosage for newborn and early infancy; increased dosage subsequently
N-demethylation	↓ ↓ ↓	↓	↑ ↑	↑	↔	Applies to theophylline, caffeine
Acetylation	↓ ↓ ↓	↓	↑	↑	↔	Reduce dose in newborn—for example, sulphonamides
Conjugation-glucuronidation	↓ ↓ ↓	↓	↑	↑	↔	Reduce dose in newborn—for example, chloramphenicol
Renal excretion:						
Glomerular filtration	↓ ↓ ↓	↓	↓ ↓ Slight to 6 months	↔	↔	Reduce dose in first few months
Tubular secretion	↓ ↓	↓		↔	↔	

differences in the rates of drug biotransformation among infants and children of a similar age but less appreciable differences in the rates of elimination of those drugs that are primarily excreted unchanged by the kidney.

Receptor sensitivity

Differences in the sensitivity of receptors related to age that have been seen in animal studies may also be present in humans, but to date this has not been shown. There is, however, indirect evidence of some differences as shown by the higher doses of digoxin, related to weight (or surface area), required in infancy compared with those at other ages. Infants have higher myocardium:plasma and erythrocyte:plasma concentration ratios of digoxin.¹¹

The paradoxical effects of some drugs (for example, hyperkinesia with phenobarbitone), previously considered to be peculiar to childhood, also occur in some adults and may not represent a difference in drug sensitivity related to age.

Prescribing

The difference in drug handling and response among infants and children of different ages and among children and adults as described above needs to be considered carefully at each stage of prescribing.

CHOICE OF DRUG

Though drugs that have been widely used without undue untoward effects for many years may be considered to be the safest, this assumption should be regularly reviewed and questioned. The comparatively recent evidence of the relation between aspirin and some cases of Reye's syndrome supports this approach.¹²

ROUTE OF ADMINISTRATION AND DRUG FORMULATION

Most children aged 5 years or more will successfully take solid preparations. The use of liquids, with a greater chance of spillage and therefore less accurate dosage, is thus inappropriate for an older child. Some liquid preparations still contain sucrose, with no alternative sweetener available. The long term use of medicines that contain sucrose increases the incidence of tooth caries and gingivitis.¹³

Sustained release preparations that reduce fluctuations in drug concentration between doses should be particularly useful in children who will metabolise drugs rapidly. Young children aged under 4 years, however, who might be expected to benefit most in this respect, cannot generally swallow large solid preparations.

Accommodating the needs of young children by crushing or cutting the tablets usually destroys the sustained release properties.

Some liquid medicines and tablets contain dyes and colouring agents. Sensitivity to these—for example, tartrazine—is much commoner in children than in adults, though the number who react adversely is probably small.

Children have difficulty coordinating their breathing, so taking drugs by inhalation from aerosols is particularly difficult for them, though modifications—for example, providing reservoirs—are helpful. Even powdered formulations that depend on self inhalation are seldom effectively given to children aged under 4 years.

The topical application of drugs to the skin is appropriate only for skin conditions except possibly for the limited purpose of delivering theophylline to preterm newborns.³ Inflamed or broken skin is a poor barrier to drug absorption, and topical agents used to treat diseased areas may therefore cause systemic effects. Such treatment, leading to drug absorption through the skin, may therefore have toxic consequences. Extensive nappy rashes, eczema, and blistered skin conditions are examples of conditions in which the risk of toxicity from the repeated use of topical agents is enhanced. Problems have been reported after the percutaneous absorption of alcohol, iodine, salicylic acid, oestrogens, steroids, hexachlorophene, antibiotics (for example, neomycin), and urea.

Intramuscular injections are often painful. Hydrocortisone, aminophylline, and paraldehyde are particularly irritating. There is generally little advantage in giving drugs by this route. Where indicated, and temporary use in a vomiting child may be considered to be an appropriate indication, the quadriceps muscle is the safest site; the upper and outer quarter of the buttock should not be used (the course of the sciatic nerve is more transverse in this area in children than in adults). Babies of low gestational age have little muscle bulk, and intramuscular injection is therefore generally inappropriate in preterm babies.

DOSAGE

The larger volumes of distribution in young children, particularly in the first few months of life, mean that single doses of drugs according to weight need to be comparatively larger at this age to produce similar drug concentrations in the blood. In repeated dosing the total daily doses according to weight vary widely with age. In the newborn and particularly preterm infants daily doses of drugs that are metabolised in the liver should be lower, as drug clearance is slow at this time owing to immaturity of the microsomal enzymes.^{6,7} After a few weeks the appropriate dose changes rapidly over a fairly short period, so that daily doses according to weight in early infancy are higher than at any other time of life. Subsequently the relative daily dose decreases gradually throughout childhood until it reaches that normal in the adult. Weight related daily doses of drugs that are primarily eliminated by the kidney are similar at all ages after renal function has matured at about 6 months of age.

Measuring drug concentrations in plasma may provide information useful for determining the appropriate dosage and dosage interval. The time taken to reach a steady state is usually shorter for most metabolised drugs after the first few weeks of life because of the shorter half life in children.

Mistakes in administered doses occur in children as in other ages, and some of these relate to difficulties in measurement. Small errors in the volumes of liquids containing drugs in high concentration particularly designed for "adult" markets can be important in the very young.

FREQUENCY OF DOSING

Most hepatically metabolised drugs have a shorter elimination half life in young children. At "standard" intervals between doses that are accepted for adults fluctuations in the drug concentration may be great and clinically unacceptable.¹ For example, children receiving carbamazepine at the same treatment intervals as adults may show evidence of toxicity at peak concentration times and breakthrough convulsions immediately before dosing. Increasing the frequency of dosing during the child's shorter wakeful day (about 12 hours) is a compromise that has little effect on the total fluctuation over 24 hours.

For drugs for which there is no relation between concentration and effect the frequency of dosing is governed by other considerations. Compliance should be improved by reducing the number of daily doses. Dosing with steroids once a day produces less toxicity than using divided doses.

COMPLIANCE

The definition of compliance used in reported studies varies widely. It is therefore difficult to compare rates of compliance in children and other age groups. About one half of children taking long term and short term treatment, however, take drugs according to the advice of the prescriber.¹⁴ This is similar to that reported in other groups. Most children are not responsible for their own treatment, and it might be expected that the requirement for a third party (usually a parent) and the tendency for young children to refuse to comply at the time of administration would increase the incidence of poor compliance.

Other aspects of prescribing

NEW DRUGS

The fact that children are growing and developing mentally and physically, and that late adverse effects of drugs are most likely to be seen in those who live for a considerable time after the introduction of new drugs, suggests that additional caution is necessary when treating children with new drugs. The balance between extreme and inappropriate caution and allowing children to be therapeutic orphans and therefore disadvantaged is a fine one.

INTERACTIONS

Infants and children are apparently no more likely to show the clinical effects of interactions between drugs than other age groups. Though the microsomal enzyme systems of infants and young children have a greater capacity for induction, and neonates and infants have generally less drug protein binding, the effects of interactions that are clinically relevant are few. The apparent problems with lower rates of interaction in children probably reflects the fairly low exposure of children to many of the commonly

implicated drug groups and the lower incidence of treatment with multiple drugs at this age. Anticonvulsants, theophylline, and erythromycin are the drugs most likely to be implicated in clinically relevant interactions.

ADVERSE EFFECTS

The incidence of adverse reactions of drugs in newborn infants (25%) is higher than that reported in infants and children, both in hospital and in the community (5.2-12.2%).¹⁵⁻¹⁷ The nature of these adverse effects varies according to the circumstances of drug use. In "everyday" use in the community, the most commonly reported effects are drowsiness, diarrhoea, and abdominal pains.¹⁸ These contrast with rash, drowsiness, vomiting, and suppressed bone marrow activity as the most commonly reported reactions in studies in hospitals. The types of adverse reactions due to prescribed drugs in children in the community are not significantly different from those due to drugs obtained "over the counter."

DRUGS IN SCHOOLS

Most commonly used drug treatment does not need to be given during school hours. Even for commonly used antibiotics administration three times daily is acceptable for all conditions treatable during continued school attendance. Some drugs, however, need to be used at school, and this presents problems for the child, family, and teachers. Teachers are naturally reluctant to accept third party responsibility for the safe storage and administration of medicine, particularly when they consider the stringent regulations of the not so dissimilar circumstances of medicine administration to hospital inpatients by nurses. Close liaison among parents, the child, the teacher, the school nurse, and the doctor should allow a code of conduct acceptable to all parties to be formulated. Doctors clearly have a responsibility to consider this specific problem when they advise on and prescribe drugs.

References

- Rylance GW, Moreland TA, Butcher GM. Carbamazepine dose frequency requirement in children. *Arch Dis Child* 1979;54:454-8.
- Morselli PL, Franco-Morselli R, Bossi L. Clinical pharmacokinetics in newborns and infants. *Clin Pharmacokinet* 1980;5:485-527.
- Evans NJ, Rutter N, Parr G, Hadgraft J. Percutaneous theophylline administration to the preterm neonate. *Br J Clin Pharmacol* 1985;19:125P.
- Friis-Hansen B. Bodywater compartments in children: changes during growth and related changes in body composition. *Pediatrics* 1961;28:169-81.
- Rylance GW. Neonatal pharmacology. In: Robertson NRC, ed. *Textbook of neonatology*. Edinburgh: Churchill Livingstone, 1986:223-38.
- Aranda JV, MacLeod SM, Renton KW, Eade NR. Hepatic microsomal drug oxidation and electron transport in newborn infants. *J Pediatr* 1974;85:534-42.
- Rane A, Tomson G. Prenatal and neonatal drug metabolism in man. *Eur J Clin Pharmacol* 1980;18:9-15.
- Miller RP, Roberts RJ, Fischer LJ. Acetaminophen elimination kinetics in neonates, children and adults. *Clin Pharmacol Ther* 1976;19:284-6.
- Gladtko E, Heimann G. The rate of development of elimination function in kidney and liver of young infants. In: Morselli PL, Garattini S, Sereni F, eds. *Basic and therapeutic aspects of perinatal pharmacology*. New York: Raven Press, 1975:393-403.
- Arant B. Developmental patterns of renal function maturation compared in the human neonate. *J Pediatr* 1978;92:705-12.
- Park MK, Ludden T, Arom KV, et al. Myocardial vs serum digoxin concentrations in infants and adults. *Am J Dis Child* 1982;136:418-22.
- Hurwitz ES, Barrett MJ, Bregman D, et al. Public Health Service study on Reye's syndrome and medication. *N Engl J Med* 1985;313:849-67.
- Roberts IF, Roberts GJ. Relation between medicines sweetened with sucrose and dental disease. *Br Med J* 1979;iii:14-6.
- Shope JT. Medication compliance. *Pediatr Clin North Am* 1981;28:5-21.
- Boston Collaborative Drug Surveillance Programme. Drug surveillance: problems and challenges. *Pediatr Clin North Am* 1972;19:117-30.
- Whyte J, Greenan E. Drug usage and adverse drug reactions in paediatric patients. *Acta Paediatr Scand* 1977;66:767-75.
- Choonara IA, Harris F. Adverse drug reactions in medical patients. *Arch Dis Child* 1984;59:578-80.
- Woods CG, Rylance ME, Cullen RE, Rylance GW. Adverse reactions to drugs in children. *Br Med J* 1987;294:869-70.