Preface

Children form a large percentage of the patient population, but they have been a neglected group where medicines are concerned. It is not that children do not have access to medicines, but that few products have been designed and tested specifically for paediatric use. Children are not simply small adults and, although numerous, are not a homogeneous population. The change in the metabolism and pharmacokinetics of drugs in children is rapid in the first few weeks and months of life and even as the child grows the methodology of calculating doses is not precise.

Because of these factors, markets for children's medicines tend to be small and the range of doses used may be wide for any drug formulation, leading to a lack of attention to paediatric medicines. Because of the paucity of medicines designed and researched specifically for children, the normal regulatory processes for approval of safety and efficacy have been circumvented. Many children are treated with adult medicines used 'off-licence', employing to the full the skill and judgement of physicians and pharmacists to ensure appropriate drug, dose form and dosing regimen. The notion that it is unethical to trial drugs in children holds no force against the ethical issues raised by the use of medicines that have not undergone the same rigorous licensing that adult medicines have to undergo by law.

The situation is changing, and not before time. In the USA incentives are provided to manufacturers through patent extensions for products trialled in children. In the UK, the recent institution and publication of the *BNF for Children* has codified knowledge on the safe use of medicines in children.

This new textbook, not least because it deals with the pharmacokinetics and pharmacodynamics of drugs and formulations in children of different ages, also provides a timely discussion of pharmacogenomics and addresses the real problem of medication errors in paediatric practice, often caused by the need to manipulate adult dose forms to deliver drugs to very young people. There are many challenges in the formulation of established, new and orphan drugs for use in paediatric

Conclusion: practical applications of developmental changes to treatment

The known variations in pharmacokinetics and the significant gaps in knowledge that exist mean that it is not possible to use simple formulae or allometric scaling to determine the appropriate safe and effective dose for a child from a known adult dose.

Developmental changes produce differences in the absorption, metabolism and excretion of drugs. These age-related changes in pharmacokinetics have been used as determinants in the development of age-specific dose recommendations.

Most doses for children are based on weight as it is an easily measurable parameter, although body surface area may reflect physiological differences more accurately.

Age-related changes in pharmacokinetics can result in a variable and unpredictable response to drugs, particularly in preterm neonates, term neonates and young infants. Dose recommendations should generally be regarded as a good starting point. Knowledge of the influence of development on the factors that may affect the response to drugs is essential in adjusting treatment to maximise efficacy and minimise adverse effects.

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3

Medication errors in children

Ian K Wong

Introduction

Miss Hartigan, a mother of a 9-week-old baby, checked the label on her son's repeat prescription and realised that each pill contained 25 mg instead of 2 mg of captopril. The hospital that had prescribed the drug following surgery confirmed the mistake. She was initially shocked but relieved. Miss Hartigan said 'I understand people do make mistakes but then it happened a second time. I was really upset and angry that something so serious could have happened and was happening again' (BBC News, 2004). Thankfully, Miss Hartigan's experience is not frequent; however, many cases of tenfold medication errors in children have been reported in the literature and many have tragic outcomes. In this chapter you will be introduced to the definition, epidemiology, nature and prevention of medication errors in children.

Definitions of medication error

'Medical error' is an umbrella term given to all errors that occur within the healthcare system, including mishandled surgery, diagnostic errors, equipment failures and medication errors. As medicines are the most common interventions in the healthcare system, medication errors are probably one of the most common types of medical error. Research suggests that approximately 7000 patients a year are killed by medication errors in the USA (Kohn *et al.*, 1999), and in British hospitals the incidence and consequences appear to be similar (Cowley *et al.*, 2001; Dean *et al.*, 2002).

Prescribing, dispensing and administration of medicines for children pose a unique set of risks, predominantly because of the wide variation in body mass, which requires doses to be calculated individually based on patient age, weight or body surface area, and their clinical condition. This increases the likelihood of errors, and tenfold errors, as

Table 3.5 Description of the steps involved in root cause analysis

1. Classifying the incident	The NHS uses the 5 × 5 matrix with colour coding or textual descriptors
2. Setting the team	Includes experts, specialists and those who were in contact with the incident
3. Scoping the incident	Acute episodes analysed completely while chronic can be explored at any point where incident happened and worked backwards to track data
4. Data gathering	Sources of information are clinical staff, the patient and the carers, medical records, policies and procedures
5. Information mapping	Different templates such as timeline, tabular timeline or narrative chronology
6. Identifying problems	Done naturally at the gathering and mapping steps, problems noted as either care delivery problem or service delivery problem
7. Analysing problems for contributory factors	Using contributory factor framework, cause and effect method, tree diagram, barrier analysis and 'the five why's' technique. Each contributory factor identified in the analysis could be a causal factor or an influencing factor
8. Agreeing the root causes	This can be done using nominal group technique or brainstorming
9. Recommending and reporting	Actions should prevent or reduce the occurrence of an event resourced; they should be implemented and evaluated for effectiveness through barrier analysis

Application in the accident causation model

In this section, a real case is presented so that the accident causation model can be applied to identify the root cause of the errors (BBC News, 1999a–g).

Case: morphine injection fatal medication errors

Background

Baby LW was given a dose of morphine which was 100 times stronger than it should have been. The death certificate said Baby LW died from a brain disease and breathing difficulties.

Baby LW, who was born 7 weeks prematurely and had difficulty breathing, was given the morphine to sedate her. Dr HE (Senior House Officer) is alleged to have miscalculated the amount of morphine that

options available to administer oral medicines to children who cannot swallow whole solid dosage forms.

Ideally, if there is no appropriate dosage form for a drug, another drug with the same therapeutic spectrum but adequate formulation, such as liquid, effervescent, dispersible tablets, is recommended in accordance with the prescriber.

The term 'OL medicine' may be used to describe a drug in an adequate dosage form for administration to children (e.g. liquid formulation) but which is being used outside the specification terms of the product licence (or marketing authorisation). For example, in the UK, there is an adult licensed liquid preparation of atenolol but it is not licensed for children. OL may also be given:

- by an unlicensed route of administration (e.g. lorazepam injection given orally)
- for an unlicensed indication (e.g. sildenafil for pulmonary hypertension)
- at an unlicensed dose (e.g. salbutamol nebules are licensed for adult use at up to 40 mg a day but can be given to children at up to 60 mg a day)
- outside the age limits stated in the licence (e.g. diazepam rectal solution, although not licensed for children under 1 year, is used in infants)
- even if contraindicated for use in children (e.g. aspirin used in Kawasaki's disease and some cardiac patients but generally not recommended for children because of its association with Reye's syndrome).

UL medicines are medicines under an unlicensed dosage form obtained after manipulation of the original dosage form (e.g. crushing/cutting tablets, extemporaneous preparations, 'special'). Sometimes the drug itself may have no licence at all (e.g. chemicals used in metabolic diseases, such as betaine to treat homocystinuria, and novel medicines). Imported medicines become unlicensed in the country into which they are imported.

In general, it is not necessary to obtain the explicit consent from children, parents or carers to prescribe or administer UL or OL medicines. Nevertheless, a clear explanation should be given.

When a company supplies a product for which no product licence exists, it is usually supplied on a named patient basis, meaning that the consultant's name, patient's name and the conditions that the drug is being used to treat are all recorded.

Table 4.2 E colours and food additives classification

Additives	*E numbers*
Colours	100–181
Preservatives	200–290
Acids, antioxidants, mineral salts	300–390
Vegetal gums, emulsifiers, stabilisers, etc.	400–485, 500–585
Flavour enhancers	620–640
Miscellaneous (contains sweeteners)	>900

colouring agents should be consulted to choose acceptable additives in the country where the product is intended for use.

Vehicle composition

After water, ethanol is most commonly used in the formulation of oral liquids and is not without risk of acute overdose or chronic intoxication in children. There are still many extemporaneous and commercial preparations containing ethanol as co-solvents administered to children. Adverse effects to the central nervous system because of high blood–brain barrier permeability in children are reported, along with drug interactions linked with acute or chronic exposure. In the USA, the limits are set to a maximum of 10% alcohol in products for 12 year olds and over, a maximum of 5% alcohol in products intended for children aged 6–12 years and less than 0.5% alcohol content in products intended for children under 6 years of age. Nevertheless, further long-term research is needed to evaluate safety when this excipient is present in the drug formulation.

Propylene glycol (propane-1,2-diol), used in the formulation of lipid-soluble oral, topical and intravenous drugs (phenytoin, diazepam, digoxin and vitamins), is a less viscous liquid and a better solvent than glycerol, but practically tasteless. It has been widely demonstrated to cause osmotic laxative effects and contact dermatitis, and to increase the risk of serum hyperosmolality with a marked osmolar gap, lactic acidosis, seizures and cardiac arrhythmias when the patients received high-dose, long-term administration. Concern about propylene glycol toxicity prompted the World Health Organization (WHO) to establish a maximum daily intake limit of 25 mg/kg per day, although there is no known toxic dose. Propylene glycol toxicity is a potentially life-threatening iatrogenic complication (Wilson *et al.*, 2005). Propylene

such as tablets or strips/films/wafers, stand on the periphery of solids and liquids. They all have the advantages of solids in that they are compact and more stable but they also have the same palatability issues as liquids, with the particular challenge that the quantity of excipients available to improve the taste is limited. Literature suggests that chewable tablets provide a safe, well-tolerated alternative in children over 2 years of age who have teeth (Michele *et al.*, 2002). Unlike fast-dissolving/disintegrating tablets (FDDTs) and films, they can be spat out easily and, unlike effervescent preparations, powders and granules but like FDDTs, they do not require food or drink for administration.

Buccal and sublingual routes

For local but also systemic delivery, the oromucosal route might be suitable if safety is established. Mucoadhesive preparations, especially films, semi-solids and liquids, might be of interest if they do not interfere with suction and frequent feeding. Nevertheless, one of the major issues remains the taste of the preparation and the willingness as well as the ability of the child to retain buccal or sublingual tablets in the mouth, thus ensuring that sufficient absorption takes place.

Rectal route

Rectal administration of solids is not dose flexible and absorption is poorly reproducible. It is affected by active non-compliance (poorly accepted by older children or caregivers) or passive non-compliance (premature ejection when it should be retained for at least 20/30 minutes). Lubricants are sometimes used to ease insertion, although it is unclear whether the release and absorption of the drug are modified when using this method. Water could be a valuable lubricant. If the appropriate size/dose of suppository is not available, as illustrated in Figure 4.4, splitting the suppository is not recommended (see under Solid dosage forms, page 47).

Other semi-liquid or liquid preparations can be used rectally (gel, enemas). Rectal drug delivery should not be overlooked in certain therapeutic situations, when oral and parenteral routes are not available, or when the child is unconscious (e.g. postoperative), vomiting or on continuous suction. The absorption is usually rapid and may avoid first-pass metabolism.

medicines. Under the BPCA, the National Institutes of Health (equivalent to the Medical Research Council in the UK) provide public funding to conduct research on those medicines that manufacturers opted not to test in children.

The BPCA also established an Office of Paediatric Therapeutics within the FDA to oversee and coordinate paediatric activities and programmes, and the reporting of all adverse events for one year after exclusivity has been granted. Furthermore, the results of completed paediatric studies must be made public.

Pediatric Research Equity Act

In October 2002 the Washington DC Federal District Court overturned the Pediatric Rule. The court pointed out that the US Congress never intended the FDA to have the statutory authority to require paediatric drug studies. In 2003, the Pediatric Research Equity Act (PREA) was enacted (Food and Drug Administration, 2003). The PREA stipulated that all applications for new active ingredients, indication, dosage form, dosing regimen or route of administration must contain a paediatric assessment unless a deferral or waiver of paediatric studies has been obtained. The paediatric assessment must contain data adequate to assess a drug's safety and effectiveness, including dosing regimens in children. Deferrals may be granted in situations where a drug is ready for approval for use in adults before paediatric studies are complete or paediatric studies should be delayed until additional safety or effectiveness data are made available. Waivers from a paediatric assessment may be applied (see section above). In the case of a waiver, the PREA could require manufacturers to include in the PI a statement indicating that waivers from a paediatric assessment have been granted because the drug was found to be ineffective or unsafe for children. The PREA has the sunset date of 10 January 2007.

Network of paediatric pharmacology research units in the USA

The most commonly cited reasons for lack of research into paediatric medicines are (Wong *et al.*, 2003):

1. High cost compared with potential return
2. Complex ethical issues including consent, accents and the use of placebo

To comply with the new legislation the sponsor needs to develop a set of standard operation procedures (SOPs) to cover all areas of trial activities. A quality system should be in place to ensure record-keeping and verification of data entry or extraction of data from the case report form (CRF), capture adverse events (AEs), serious adverse events (SAEs) and unexpected serious adverse reactions (SUSARs) and report in an expedited manner data transfer from source data to database and archiving of the source data for audit purpose. GCP and trial specific training should be carried out and recorded in a timely manner.

Ethics committee

An ethics committee is an independent body constituted of medical/scientific professionals and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of humans involved in a trial. It provides public assurance of that protection by, among other things, reviewing and approving/providing favourable opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial participants.

In the UK, the United Kingdom Ethics Committees Authority (UKECA) is responsible for establishing, recognising and monitoring ethics committees. The Authority may establish ethics committees to act for the entire UK or for each area of the UK and the description or class of clinical trial in relation to which it may act. The categories are listed in Table 6.3.

Clinical trials of medicinal products for gene therapy are subject to separate arrangements for ethical review. Applications relating to such trials should be submitted to the Gene Therapy Advisory

Table 6.3 Types of ethics committee in the UK

Types of ethic committees	*Expertise*
1	Phase I clinical trials of medicinal products in healthy volunteers throughout the UK
2	Investigational medicinal products (other than phase I trials in healthy volunteers) to take place only at sites within an area defined by the geographical remit of their own appointing authority
3	As in type 2 but at any site in the UK

researcher has the option of approaching the local research ethics committee directly. A domain is an area covered by a strategic health authority (England), a health board (Scotland), a regional office of the NHS Wales Department or the whole of Northern Ireland. Once a validation letter is received by the chief investigator from the main REC, a site-specific assessment for the suitability of the investigation, site and facilities may be submitted to a relevant REC by the principal investigator.

Types of paediatric clinical trials

Researchers need to justify the need to conduct the study concerned. The need of the investigation should be weighed against the prevalence of the condition to be treated, the seriousness of the condition, the availability of alternative treatments, the novelty of the compound, uniqueness of the conditions in paediatrics, the age ranges of the children, unique safety concerns in paediatrics and the unique requirement of paediatric formulations that serve the needs of the population.

Paediatric formulation

The lack of suitable formulations in paediatrics has been highlighted by various authors in various countries ('t Jong *et al.*, 2004; Chui *et al.*, 2005; Nunn and Williams, 2005). The suitability includes palatability, appropriate strength and dose volume, favour and colours and route. Young children cannot swallow tablets, and liquids, suspensions, chewable tablets and suppositories may be needed for children of different age groups.

The concentrations of licensed medications may be too high, necessitating further manipulation in the form of dilution with an excipient. However, when the concentration is low, the dose volume may be too large for some children. The excipients in many liquid formulations may not be suitable for selected patient groups. For example, the propylene glycol content in amprenavir liquid formulation makes it unsuitable for children under 4 years of age. Severe delayed-onset hypersensitivity reaction was associated with formulation of amoxicillin liquid; the reaction may have been caused by the exicipent (Chopra *et al.*, 1989). Sweeteners, dyes and other excipients may cause adverse reactions and should be identified and restricted in paediatric formulations (Kumar *et al.*, 1996). Some clinical studies have been directed to ascertain the effect of drug concentration and frequency of

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