

## **Chapter 5. Paediatric Drug Research**

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## **I. INTRODUCTORY REMARKS**

Studies in Europe (1) and Australia (2) have shown that a significant number of children, both in hospital and the community, receive unlicensed and off-label medicines. Unlicensed medicines are where the medicine has been modified from that specified in its product license (3). This may involve crushing a tablet in order to make it into a suspension so that a young child can take the medicine orally. Off-label medicines are those that are used in a different manner than recommended in the product license. This may involve using the medicine in a different age group, for a different indication, at a different dose or by a different route to that recommended (3).

## **II. PAEDIATRIC DRUG RESEARCH**

### **II.1. Why?**

The licensing process was introduced in response to drug toxicity that affected children and adults. In particular, the Medicines Act (UK 1968) and the Kefauver-Harris amendment (USA 1962) were passed following 1) drug toxicity in the newborn infant – e.g. the grey baby syndrome due to chloramphenicol and 2) drug toxicity in the developing fetus – e.g. phocomelia due to thalidomide. It is ironic that legislation introduced following drug toxicity in the newborn infant and the developing fetus has failed to ensure that medicines used in paediatric patients are fully tested in relation to efficacy and toxicity. The use of unlicensed and off label medicines is thought to be associated with a greater risk of drug toxicity (4).

An additional problem associated with the widespread use of off label medicines is the lack of appropriate formulations for young children. Young children cannot swallow tablets and they therefore require liquid formulations. Recent studies have shown that many young children are prescribed tablets or capsules even though they are too young to swallow them (5).

Drug toxicity in children is different to that in adults (6). One therefore needs to study medicines in paediatric patients in order to prevent future cases of drug toxicity. Different mechanisms of drug toxicity in children are illustrated in Table 1.

### **II.2. Who?**

Paediatric drug research needs to involve the pharmaceutical industry working in partnership with paediatric health professionals. The latter group consists of doctors, pharmacists and nurses with paediatric expertise. Ideally paediatric clinical pharmacologists, who have both the expertise of other paediatric health professionals and an understanding of clinical pharmacology should be involved, especially in relation to the design of the clinical trials.

The pharmaceutical industry has previously been reluctant to become involved in drug research in children. The legislative changes that have been introduced in the USA (the FDAMA and the Pediatric Rule) have provided a significant financial incentive to study medicines (7). Discussions are currently taking place in Europe with regards to introducing some financial incentive for the European pharmaceutical industry.

**Table 1 Major adverse drug reactions in paediatric patients**

<b>Year</b>	<b>Drug / Compound</b>	<b>Age group</b>	<b>ADR</b>	<b>Mechanism</b>
1886	Aniline dye	Neonates	Methaemoglobinemia	Percutaneous absorption
1956	Sulphisoxazole	Neonates	Kernicterus	Protein displacing effect on bilirubin

1959	Chloramphenicol	Neonates	Grey baby syndrome	Impaired metabolism
1979	Sodium valproate	Young children (< 3 years)	Hepatic failure	Abnormal metabolism?
1980	Salicylate	Children	Reye's syndrome	Unknown
1990	Propofol	Children	Metabolic acidosis	Unknown Dose related?
1996	Lamotrigine	Children	Skin reactions	Unknown Associated with comedication with sodium valproate

(Reproduced with permission from Paed Perinatal Drug Ther (6))

### **II.3. Where?**

One cannot perform a paediatric clinical trial in an adult clinical trials unit. It is accepted that sick children need to be treated by paediatric health professionals. Similarly for clinical trials involving children, paediatric health care professionals need to be involved, ideally within a paediatric unit. It is important to recognise that clinical trials and other aspects of paediatric drug research can be performed in district general hospitals (8). For general paediatric conditions, these units are probably preferable to tertiary centres where one is more likely to see a highly selective patient group that is not representative of children throughout the community.

For those clinical trials that involve children as outpatients, it is important that the children are assessed in a child friendly location, i.e. safe with toys and play therapists available. It may also be appropriate to assess the child at home.

### **II.4. Which Medicines?**

The success of any clinical trial is related to the clinical need for the medicine. Investigators are more likely to participate in a study of a medicine which is likely to result in significant clinical benefit to children than one where there is already satisfactory treatment. The clinical need of the medicine will also be taken into account by the ethics committee. Ethics committees are more likely to recognise that a clinical trial is appropriate in children if there is no current treatment available. This does not mean, however, that the clinical trial will automatically be approved as the design of the study may be inappropriate.

The International Conference on Harmonisation, which includes representatives from the European Medicines Evaluation Agency (EMA), the Food and Drug Administration (FDA) and Japan have issued ICH E11, Clinical Investigation of Medicinal Products in the Paediatric Population (7). This guidance categorises medicinal products and their value in children into three categories. These are shown in Table 2. The aim is to encourage the study of medicines in the first two groups where there is the greatest potential clinical benefit.

**Table 2 ICH Classification of medicinal products for children**

Medicinal products for diseases predominantly or exclusively affecting paediatric patients
Medicinal products intended to treat serious or life threatening diseases occurring in both adults and paediatric patients for which there are currently no or limited therapeutic options
Medicinal products intended to treat other diseases and conditions

## **II.5. When?**

The timing of studies in children is clearly dependent upon several factors. These include whether one is dealing with a serious or life-threatening disease for which there is currently no or limited treatment available. In this situation early paediatric studies are essential. However, where existing treatment is available then clinical trials in children should only be conducted after initial safety data has been established in adults.

## **II.6. Which paediatric patients?**

The clinical nature of the medicine will determine whether it needs to be studied in neonates, infants or children. It is important that investigators are aware of the ICH Guidance in relation to the classification of the five different age groups in relation to paediatric patients. These are shown in Table 3.

**Table 3 ICH Classification of children by age**

<b>Category</b>	<b>Age</b>
Preterm neonates	<36 weeks gestation, 0 – 27 days
Full-term neonates	0 – 27 days
Infants and toddlers	28 days – 23 months
Children	2 – 11 years
Adolescents	12 – 17 years

## **II.7. How?**

### **II.7.A. Study design**

The study design is crucial in that a poorly designed study will fail to attract investigators, obtain ethical approval and recruit children. Investigators need to ask the following questions:

- a. Which paediatric age group is most likely to benefit from the medicine?
- b. Should a placebo be included in the trial design? (Placebo is appropriate if there is no existing treatment for the condition. If however, effective therapy is available, then the use of a placebo is neither appropriate nor ethical.)
- c. How will the pharmacodynamic effect be studied?
- d. Which pharmacokinetic parameters, if any, need to be determined?
- e. What is the likelihood of significant drug toxicity?

Regulatory authorities are more likely to raise questions about clinical trials in children than in adults (9). The duration of clinical trials in adult and paediatric patients is similar (in Finland two thirds completed within 12 months) (9). Clinical trials in healthy adult volunteers, however, are significantly shorter (over two thirds completed within 6 months) (9).

### **II.7.B. Pharmacokinetics**

It is important to ensure that the minimum number of samples, involving the smallest amount of blood possible is collected from each patient. Microassays may need to be developed to measure drug concentrations in small volumes of blood. Information regarding the metabolic pathway and pharmacokinetic parameters in adults is essential before commencing pharmacokinetic studies in paediatric patients.

The use of population pharmacokinetics whereby a larger number of children are involved but fewer samples are collected from each patient should be considered (10). It is usually appropriate to carry out pharmacokinetic studies in a subgroup of the children recruited for the clinical trial. It should not be made

a precondition for entry into the clinical trial as this may result in the loss of a significant number of children from the study.

### **II.7.C. Non-invasive methods**

Consideration needs to be given to the use of non-invasive techniques such as the caffeine breath test. The caffeine breath test has been used as a probe for CYP1A2 enzyme activity (11). It involves the use of a stable isotope of caffeine and the collection of breath samples for two hours after administration of the caffeine. It has been used to study drug interactions (induction and inhibition) and also the effect of disease on drug metabolism<sup>11</sup>.

### **II.7.D. Pharmacodynamics**

It is often difficult to study pharmacodynamic effect in younger patients. For certain conditions, measuring the pharmacodynamic effect is not difficult, e.g. seizures in patients with epilepsy (12), mortality in children with leukaemia. For other conditions, however, it is more difficult to assess pharmacodynamic effect, e.g. bronchodilators in infants under the age of 18 months, assessing pain relief in pre-verbal children and neonates. There are validated pain scales appropriate for use in paediatric patients of different ages (13). It is, therefore, essential that one uses a validated pain scale if one is studying an analgesic drug.

### **II.7.E. Pharmacovigilance**

Drug toxicity in children is different to that in adults (6). This may be due to impaired drug metabolism or altered protein binding, but may also be idiosyncratic. As the child is developing they may be prone to different toxicities to adults. The principles of pharmacovigilance in children are similar to that in adults. Consideration should be given to setting up an Independent Safety Monitoring Board if there is the potential for significant toxicity.

## **III. CONCLUSIONS**

Paediatric drug research is more difficult than similar studies in adults. Paediatric drug research involves patients whereas many adult studies involve volunteers. It is up to paediatric health professionals and the pharmaceutical industry to work together to ensure that we study the right medicines with an appropriate design to ensure that children receive medicines that are fully evaluated scientifically. Such an approach will increase efficacy and hopefully reduce toxicity.

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