Drug trials in children: problems and the way forward

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Introduction

The drug-licensing system was introduced with the Medicines Act of 1968, following the thalidomide disaster, with the aim of ensuring that medicines are safe, effective and of high quality. There is increasing concern from the pharmaceutical industry, paediatricians, paediatric pharmacists and the Government that many medicines routinely used in children have not been formally evaluated by this system. Such use is therefore not supported by the assurances that the process brings. A joint report was produced in 1996 by the British Paediatric Association (now the Royal College of Paediatrics and Child Health) and the Association of the British Pharmaceutical Industry. This described in detail the current unsatisfactory situation and made specific recommendations for a way forward [1]. Since then several studies have documented the extent of unlicensed and off-label drug use in critically ill children, paediatric medical and surgical inpatients and neonates [2–4]. These studies all show that unlicensed and off-label drug use is a frequent occurrence for children in hospital with up to 90% of newborn infants in intensive care receiving either unlicensed or off-label treatment.

Unlicensed medicines may be those compounded in a hospital pharmacy department or by a 'specials' manufacturer due to a lack of licensed alternatives. These medicines may not necessarily undergo the rigorous quality testing procedures that a licensed preparation must, and their quality may be variable. The term off-label refers to the use of a medicine outside the specifications of the product licence [5]. This covers medicines used at a different dosage to that recommended, in different age groups, by a different route or for a different indication. These off-label uses may be based on reliable published data, in which case prescribers can feel confident in using medicines in an off-label manner since this practice would be supported by peer review. In other instances they may rely more on the experience of the paediatrician or pharmacist, or drug information resources such as those of DIAL (Drug Information Advisory Line, Alder Hey Children's Hospital, Liverpool). They are less likely to be supported by extensive clinical trial information, as would the manufacturer's recommended uses of a licensed preparation.

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Are pharmaceutical companies reluctant to study drugs in children?

There are several reasons why the pharmaceutical industry may have been reluctant to study medicines in children. The market for the sale of many drugs for children is smaller than that for adults, and therefore investment in paediatric drug testing might be less attractive financially. Other reasons include ethical difficulties, problems with blood sampling and difficulties in recruiting sufficient numbers of children. We suggest that none of these hurdles are insurmountable reasons for not studying drugs in children.

It may be unrealistic to expect pharmaceutical companies to invest in the large randomized controlled trials, involving hundreds of patients, currently required by the licensing process in order to authorize new drugs which, however, clinically important in a specific patient group, have a very small market, e.g. neonates, drugs for rare diseases. A change in approach for such drugs and patient groups is probably needed. This may be to make the requirements of the regulatory bodies more flexible, to provide a financial incentive to the pharmaceutical industry to support the necessary studies and to concentrate such studies in specialist paediatric drug research centres. Important clinical questions can be answered in relation to efficacy and safety in clinical trials involving small numbers of patients [6, 7]. Recognition from the government that such research is essential and a commitment to developing a mechanism for it's funding is also urgently needed. The US has moved a long way down this road as described below and lessons should be learned from their experiences.

Which drugs should be studied?

Children have the same rights as adults to receive medicines that have been shown to be safe and effective.

They also have the right not to be tested with every new drug developed. Drugs used to treat clinical conditions that do not affect children clearly should not be tested in children. The drugs that should be tested are those likely to have a significant clinical impact upon the management of sick children, infants and neonates. A new European guidance on the clinical investigation of medicinal products in children came into force in September 1997 [8, 9]. This has a positive approach in relation to the encouragement of clinical trials for conditions in children where there is either no or inadequate treatment at present. The guidance divides drugs into four categories with the following recommendations:

Diseases affecting children exclusively. Clinical trials in children may start before any adult human exposure.

Diseases that mainly affect children, are of particular gravity in children or have a different natural history in children. Clinical trials in children are needed at an early stage in clinical development following demonstration of safety and reasonable evidence of efficacy in adults.

Diseases occurring in adults and children for which there is currently no treatment. Again clinical trials in children are needed at an early stage in clinical development following demonstration of safety and reasonable evidence of efficacy in adults.

Diseases occurring in adults and children for which treatment exists. In these situations clinical trials in children should usually follow completion of adult phase 3 trials.

It has been suggested that if this guidance is followed, the extent of unlicensed and off-label prescribing will fall, and the value of the resulting revised Summaries of Product Characteristics and Patient Information Leaflets will be enhanced in terms of paediatric prescribing [10]. However, the European Medicines Evaluation Agency (EMEA), is unlikely to be able to implement the changes on it's own. This is reinforced by a survey of the status of new medicines approved by the EMEA regarding paediatric use from January 1995 to April 1998 [11]. Of 45 new substances licensed, 29 (64%) were of possible use in children but only 10 (22%) were licensed for paediatric use.

Ethics

It is unethical for children to routinely receive medicines that have not been scientifically evaluated. Health professionals treating children have a responsibility to ensure that drugs are evaluated and that this is done in carefully controlled clinical trials. It is essential that any proposed clinical trial involving children is extensively reviewed. The revised guidelines for the ethical conduct of medical research involving children published by the then British Paediatric Association (BPA) suggests that researchers, funding and scientific bodies, research ethics committees, research assistants and nurses, children and their parents should be consulted [12]. In particular, any ethics committee considering a project or trial involving children must take advice from professionals familiar with working with children on a day to day basis in close practical terms, for example, Registered Sick Children's Nurses and Paediatricians. At the same time they must recognize that studies of drugs in children may involve placebo administration, or subtherapeutic doses of drugs being given to some children during the course of pharmacokinetic dosing studies. Such methods must be considered ethical in order for the paediatric population as a whole to benefit rather than every individual child. This issue presents a hurdle in the organization of clinical trials in children, and needs to be addressed by central leadership with the Medicines Control Agency and the Royal College of Paediatrics and Child Health producing advice for local and multicentre research ethics committees.

Blood sampling

In the original statement on ethics from the BPA, research involving procedures submitting children to more than minimal risk with only slight, uncertain or no benefit to themselves was considered to be unethical. Blood sampling was included in this. However, this statement has been revised in that it is now considered ethical to consider such procedures, if full informed consent is obtained from the carer or child (if more appropriate). This more helpful stance supports the recognition that attempts to protect children absolutely from the potential harms of research denies any of them the potential benefits.

Children, and their parents, may find blood sampling very distressing, although the use of topical local anaesthetic creams has greatly reduced this problem in paediatrics. It is therefore essential that the number of blood samples is kept to the minimum required. It is possible to calculate pharmacokinetic parameters from 4 blood samples taken at appropriate time points for drugs that are excreted by the kidneys, if there are data available from adults regarding the likely half-life [13]. For drugs that undergo hepatic metabolism, more blood samples are required, as there is likely to be more interindividual variation. It is, however, possible to collect opportunistically a reduced number of blood samples from an individual child but increase the total number of children studied [14, 15]. This approach is known as 'population kinetics'. A large number of patients will be needed to produce reliable data by this method. It is therefore, likely to be of use for drugs already being prescribed for

which more data are required to optimize use, but will be less useful for new drugs.

For children receiving an intravenous infusion of a drug, blood sampling at steady state allows the determination of plasma clearance. This has been shown to be of value in studying drug metabolism in children of different ages [13, 16, 17]. An additional problem especially in the newborn infant and young child relates to the volume of blood sample collected. The circulating blood volume in the newborn infant is much lower and it is important therefore to develop microassays.

Drug assay techniques from nonblood samples can be used in some circumstances in order to establish pharmacokinetic information. Approaches such as the use of saliva samples may be a possibility to reflect blood levels of certain drugs. Other noninvasive techniques such as the erythromycin breath test described below need to be developed and are likely to be useful tools to minimize blood sampling.

Drug toxicity

Adult data cannot be extrapolated to predict the toxic effects of drugs in children and infants for a variety of reasons [18]. Drug metabolism may involve different pathways. The hepatotoxicity of sodium valproate is thought to be due to altered drug metabolism in children under the age of 3 years [19]. The grey baby syndrome, in which neonates developed cyanosis and cardiorespiratory failure following chloramphenicol, was due to impaired metabolism of chloramphenicol in the newborn infant [20]. Altered drug metabolism may also have a protective effect. This is illustrated by paracetamol, which is less likely to cause liver damage following an acute overdose in a young child due to the increased capacity for sulphation of paracetamol [21]. Drug toxicity on developing tissues and organs should also be considered, for example, tetracyclines cause damage to teeth and bones if given in pregnancy or to children under 8 years of age.

In order to minimize drug toxicity it is important to understand the relationship between drug metabolism and age in more detail. In children, noninvasive methods of assessment should be used wherever possible. The collection of urine samples for the determination of 6β-hydroxycortisol has been useful in adults and in children to study enzyme induction [22]. Unfortunately, children may not like collecting urine samples and this can be technically difficult in infants who are not toilet trained. Breath tests such as the caffeine breath test have been used to study drug interactions and the effect of disease on drug metabolism [23–26]. This test involves the use of a stable nonradioactive isotope of caffeine that is given as an oral solution. The labelled methyl group undergoes biotransformation in the liver by the CYP1A2 pathway and is exhaled as labelled carbon dioxide. The 2 h cumulative exhaled carbon dioxide is determined by isotope ratio mass spectrometry and this correlates with the CYP1A2 activity. The caffeine breath test has been shown to be acceptable to children as young as 3 years of age and has also been used in the newborn infant. Its limitations are that the stable isotope is expensive but it avoids the need to collect blood samples in order to study drug interactions of clinical significance in children. Using similar methods an erythromycin breath test is under investigation which may examine the effects of drugs and disease on the CYP3A group of pathways. These are responsible for the metabolism of a wide array of clinically and toxicologically important agents [27].

A long-term issue regarding drug toxicity is that there is no defined framework to collect information on adverse drug reactions (ADRs) to unlicensed and off-label drugs. Licensed drugs are monitored by spontaneous reporting of ADRs by prescribers (in the Yellow Card scheme), and by postmarketing surveillance by the manufacturer [10]. There is currently no similar process to monitor ADRs to unlicensed and off-label drug use. Such drug use may be reported via the Yellow Card system but is not analysed separately or identified as unlicensed or off-label drug use. Prescribers may also be less likely to report ADRs to use of such medicines.

Formulations

A major practical problem for the pharmaceutical industry is that in order to use a drug in young children an acceptable liquid formulation is usually essential [28]. The development of such a formulation with an acceptable taste can be problematic but is crucial for the oral administration of drugs to children. With the introduction of controlled release oral preparations for adults it is important that the effect of splitting of tablets or capsules is assessed scientifically. The splitting of single unit systems like tablets or capsules to facilitate paediatric use can result in a reduction in drug effect or toxicity as it is difficult to accurately split such dose forms. The introduction of fast dissolving drug formulations and multiple unit systems with small sized particles are likely to facilitate the administration of lower doses to children [28]. The innovations may not have been originally developed for paediatric use but will have many practical benefits for the administration of new drugs to children. Such developments need to be encouraged. It may be necessary to introduce a financial incentive for pharmaceutical companies to provide such formulations since the paediatric market may be small. Developing such formulations, involving novel technology may require substantial investment. However, such formulations may also be

of benefit to the elderly and disabled populations therefore extending the potential market beyond paediatrics. Similarly, injection vials of appropriate quantities/strengths are essential to minimize the risk of medication errors. Tenfold errors are more likely to occur in newborn infants and young children, where one vial contains more than 10 times the dose [29]. The government must take some responsibility to facilitate a means to protect children from the harm caused by such errors.

American developments

There have been major changes in the United States law regarding licensing of drugs for children. The FDA can now make specific requests for the submission of paediatric use information if a drug is expected or known to be of use in paediatric patients or represents a safety hazard. If the pharmaceutical company fails to provide this information then the license for the drug can be withheld or revoked [30]. The law has also been changed so that if a condition or disease is similar in adults and children, and a drug is thought to behave the same in both populations, then the efficacy data from adequate, well-controlled trials in adults can be extrapolated to children. These adult data supplemented with necessary paediatric studies to address pharmacokinetic, pharmacodynamic and safety issues may be used as the basis for licensing the drug for use in children [31]. This will reduce the time and cost involved in the drug approval process. More recently, the US FDA has drawn up a 'Paediatric Priority List' of 493 drugs commonly used or of potential use in paediatric patients, which are not licensed for such use. If a drug is on this list and the FDA requests paediatric studies to be done, the pharmaceutical company's market exclusivity will be extended by six months if studies are performed to an acceptable standard [32]. This represents a major financial incentive for the pharmaceutical company to perform the paediatric studies necessary to allow the drug to be used in a safe and effective way in children.

Another major initiative in the US has been the government's funding of the Paediatric Pharmacology Research Unit Network [33]. Initially 7 centres were established where clinical trials in children were to be encouraged. The network has proved highly successful and further funding from the National Institutes of Health has resulted in the creation of a total of 13 centres throughout the USA.

European developments

A European Network for Drug Investigation in Children has been established. This network involves paediatricians and clinical pharmacologists with an interest in this field. The network at present includes members from the Netherlands, France, Germany, Italy, Sweden, Finland, the UK and Israel. Several of the members are involved in collaborative projects already and some have links with members of the Paediatric Pharmacology Research Network in the USA. This network does not have funding at present but it is hoped that either the European Union or the EMEA will facilitate this development so that pharmaceutical research in children is not driven solely by the United States of America.

Developments in the UK

The UK presently only has two paediatric clinical pharmacologists. It is clear that more needs to be done to develop research in this field in the UK. A Registrar Training Programme aiming to recruit new doctors into this speciality has been set up at Great Ormond Street Children's Hospital in London [32].

A national forum for the use of medicines in children has been established in order to facilitate research. This forum will try and raise the importance of this clinical area with the Department of Health, medical charities and the pharmaceutical industry. It is important that doctors work in conjunction with scientists and paediatric clinical pharmacists. A multidisciplinary Academic Division of Child Health has been established in the new Derbyshire Children's Hospital as part of the University of Nottingham. This Academic Division has a major focus on different aspects of drug therapy in children. It is currently involved in trials of anticonvulsants, pain control, aminoglycoside dosing in the neonate, adverse drug reaction surveillance, sedation in the critically ill, prescribing habits and licensing [4, 34]. This new Division is keen to facilitate clinical trials in children working in conjunction with other centres in the UK and Europe [11, 35]. The pharmaceutical industry in the UK has an excellent track record in supporting developments in clinical pharmacology in adults. It now needs to respond to the challenge of ensuring that the UK develops the field of paediatric clinical pharmacology and that clinical trials as recommended by the new European guidance are carried out in children. The Department of Health too needs to accept responsibility for improving the current situation. Co-operation between legislators, physicians, industry and consumers alike is essential to provide the changes needed to develop the way forward [10].

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