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Perspectives to Optimise Drug Therapy in Children in Germany

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Abstract

There are many different reasons for the lack of clinical trials in children: the greater cost, methodological difficulties, ethical issues and the relative lack of expertise in designing clinical trials specifically adapted for children. Detailed knowledge of the specific physiological conditions during the child's development, which leads to pharmacokinetic and pharmacodynamic peculiarities, is indispensable to plan a scientifically valid clinical trial in this age group. Knowledge of psychological development is required for the assessment of the pharmacodynamics of many drugs. A specific training course for paediatricians in the Department of Paediatrics of the Philipps-University in Marburg, Germany, was organised to assist in the planning and performance of clinical trials in children.

Key words: Pharmacotherapy – Clinical trials – Paediatrics

Introduction

Studies in children have shown that many medicines used in hospital are used in an unlicensed or off-label manner. A study in five European countries showed that in each country there was a significant degree of off-label or unlicensed prescribing ranging from 30% to 66% of all of the medicines used in children in hospital[1].

The only published studies of the extent of unlicensed and off-label drug use in children in Germany have been in Marburg. A study of 85 children showed that 46 (54%) of them received unlicensed or off-label medicines. 41% of the drug prescriptions were unlicensed or off-label with the majority being off-label (37%)[1].

The widespread use of unlicensed or off-label drug prescriptions may result in an increased risk

of adverse drug reactions[2]. The differences between children and adults in relation to drug metabolism have been extensively described previously[3]. Similarly, drug toxicity is different within the paediatric population.

There has been a reluctance by the pharmaceutical industry to study medicines in children because of the greater costs and ethical difficulties. This is a particular problem within Germany.

Judicial and Ethical Bases of Clinical Trials in Paediatrics

Children need special protection because they are unable to give informed consent. This protection is given by strong national legislative restrictions in the participation of children in clinical trials. They can only be performed with the informed consent of the parents or guardian and have to include a benefit for the patient. As a consequence, it is not possible to perform pure scientific studies with children. Healthy children cannot be included in clinical studies with the exception of trials for vaccines and diagnostics. Another legal requirement for clinical trials with children is previous data obtained from adults. There are, however, no more specific directives given by national law in Germany. The ethics committees in different universities or countries may therefore come to different judgements in relation to the same study protocol. This fact complicates clinical trials in paediatrics.

The current legislation in Germany prevents clinical trials in specific paediatric diseases where prior adult data are not available. The treatment of these diseases in an off-label or unlabelled manner is common. This is, however, therapy which is not based on valid scientific data regarding indication and dosage. Such therapy cannot lead to a scientific evaluation of efficacy and toxicity. A judicial and ethical framework which facilitates clinical trials in children is required.

Positive Developments

In order to improve the situation, there have been several positive developments. Firstly, the Paediatric Department of the University of Marburg, Germany has organised two workshops in relation to paediatric therapeutics. The first of these, in November 1999, attracted a small group of paediatricians. Twenty-six paediatricians and three paediatric clinical pharmacologists attended the week-long course that was organised in collaboration with the German Society of Paediatrics, the Department of Paediatrics of the University of Marburg and the Centre of Clinical Pharmacology, Tübingen, Stuttgart, Germany (Table 1). The essential components of the course are covered below.

Basics in Paediatric Clinical Pharmacology

One of the most important aspects of pharmacotherapy in paediatrics is the fact that children are not 'small adults'. They vary fundamentally in absorption, metabolism and excretion of drugs, leading to differences in

Table 1. Speakers at the first training course

Name	Institution
Professor J. van den Anker	Erasmus University, Rotterdam, The Netherlands
Professor I. Choonara	Derbyshire Children's Hospital, Derby, UK
Dr R. Ewald	Novartis Pharma GmbH, Nurenberg
Professor C. H. Gleiter	Eberhard-Karls-University, Tübingen
Professor T. Gudermann	Free University, Berlin
Professor U. Kern	BfArm, Berlin
Professor K. Hoppu	University of Helsinki, Finland
Dr B. Mühlbauer	Eberhard-Karls-University, Tübingen
Professor G. Pons	University René Descartes, Paris, France
Professor H. Schäfer	Philipps-University, Marburg
Dr M. Schwab	Dr Margarete Fischer-Bosch-Institute, Stuttgart
Dr J. Schwarz	Quintiles GmbH, Neu-Isenburg
Professor H. W. Seyberth	Philipps-University, Marburg
Professor I. Walter-Sack	Ruprecht-Karls-University, Heidelberg

pharmacokinetics, which represent a crucial parameter for the efficacy and safety of medicinal products. The evaluation of pharmacokinetic, and also pharmacodynamic, data in children is essential. In this context, attention was focused on analyses of population pharmacokinetics, which could help to reduce the numbers of participants[4]. It was demonstrated that dose-finding data from clinical trials in adults are not applicable to children. Therefore analyses of pharmacokinetics in children are of elemental importance for a valid, effective and safe pharmacotherapy in this age group[5,6]. In addition, dose finding in children is complicated by the physiological development of the enzyme and receptor systems, which should be taken into account in clinical trials[7].

There are five different developmental stages which have pharmacological relevance: preterm newborn infants, term newborn infants (0 to 27 days), infants and toddlers (28 days to 23 months), children (2 to 11 years) and adolescents (12 to 16–18 years). Each of these age groups has specific physiological and psychological characteristics, which should be reflected during the drug development process, if its use in paediatrics is anticipated. Furthermore, each of these groups includes specific methodological challenges to obtain scientific valid and age-related study results.

Organisation of Clinical Trials in Paediatrics

The more practical issues of planning, organisation and performing of clinical trials in paediatrics were discussed. In general, the planning of clinical trials in paediatrics regarding further statistical analyses is not different from the planning of clinical trials with adults. It is essential to define clearly target parameters before writing the study protocol. In paediatrics the estimate of numbers of patients is of special significance, because the recruitment of patients may be time consuming and is often much more complicated than it is in adults[8]. The limited number of patients in single centres makes multi-centre studies necessary. Therefore international co-operation regarding clinical trials becomes more important. The knowledge and application of the international standards of 'good clinical practice' is a crucial qualification in planning and performing clinical trials with children.

During the clinical trial, children may need to be hospitalised to ensure optimal monitoring. In these cases a child-friendly environment is essential. This can only be guaranteed by doctors and study nurses who have experience in paediatrics.

More recently a much larger workshop was organised (February, 2001) entitled Children in Clinical Trials: Limits of Medical Research. This meeting involved 100 health professionals from the pharmaceutical industry as well as children's hospitals. The conference was again assisted by the members of the European Network for Drug Investigation in Children[9] who had also been involved in the previous workshop. There was representation from nine university departments within Germany, which shows the increasing interest in this area.

There have been major developments within Germany over the last few years. In particular, the issue has been discussed in the German parliament with the viewpoint being given that clinical trials in children are appropriate if carried out scientifically for relevant medicines. Alongside the initiatives being undertaken in the European parliament and discussions regarding establishing a network in paediatric pharmacology within Germany, the situation is likely to improve dramatically.

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