Ethical aspects of pediatric therapeutic clinical trials

Pr. Evelyne Jacqz-Aigrain

Department of Pediatric and Perinatal Clinical Pharmacology, Hôpital Robert Debré, Paris, France.

The therapeutic clinical trials include studies on the efficacy, safety and disposition of drugs given for the treatment of a disease and they form the basis for therapeutic decisions by all physicians. They must be conducted in children to make rational drug therapy available to themselves and to others. The "Déclaration d'Helsinki 1964" is the accepted basis for clinical trials ethics, which must be fully known and followed by all engaged in research on human beings (1,2,3).

Trials testing drugs are needed in children

Children cannot be considered as young adults. They respond to drugs differently depending on their age and in relation to their stage of development.

1. Pharmacokinetic differences are important in the premature and term newborn, related primarily to unpredictable absorption, differences in distribution and immaturity of metabolic and renal functions. Faster rates of metabolism may be observed during infancy and childhood.
2. Pharmacodynamic responses may be affected by delayed development of receptor functions and effector systems.
3. Drugs might alter physical and mental growth.
4. Drugs may be required for a pathology occurring only in children or for diseases which differ from adults because of severity or increased frequency.

They must be conducted under high scientific standards — A poorly designed trial is unethical

In order to maximize the likelihood that the clinical trials will result in useful information (4) :

1. The objectives of the trial should be clearly defined.
2. The design should be appropriate : a controlled trial comparing the drug under investigation and either a reference product or a placebo will demonstrate the efficacy of the new product. A randomized double blind control study is the most effective as the accuracy of diagnostic and severity of the disease must be comparable in the groups being compared. Such a design is impossible to use in the investigation of rare or very severe disorders and in such cases, the trial will be non-controlled.
3. An homogenous group and appropriate control group must be selected and sample size should be estimated prior to beginning the clinical trial.
4. The dosage of drugs must be chosen in order to compare the relative efficacy and toxicity between the different groups of treatment.
5. The outcome of therapy should be recorded and well-defined clinical endpoints, which might differ in adults, should be used.

The scientific data required and chronology in relation to trials conducted in adults

Before pediatric clinical trials are started, animal studies including repeated toxicity studies should be performed and analyzed. Reproductive toxicity and genotoxicity studies should be completed. Safety data from adult human studies, when available, are the most relevant safety data for pediatric populations. In order to avoid an excessive delay in obtaining relevant pharmacological data, the clinical trials should be conducted as soon as ethically possible. Two situations may be discussed :

1. The drug has been evaluated in adults and is to be given for a similar disease in children. The main purpose of the clinical trial in such situations is to determine an appropriate dosage schedule in the different age groups, based on pharmacokinetic and safety studies. If therapeutic alternatives are available in children, efficacy studies are also required. Such trials should be performed at the end of the evaluation in adults, i.e Phase III trials.
2. The drug is to be administered for a disease occurring only in children, for diseases different from those in adults or for serious diseases without satisfactory alternatives. In such cases, the clinical trials should be performed earlier, i.e Phase II. This is for example the case of phase II trials for cytotoxic drugs in pediatric oncology (5).

Specific aspects of clinical trials in children

1. The evaluation of the potential use. If a drug appears to have important advantages for a disease in childhood, it is important to perform studies in children, rather than either contra-indicate the drug or use the drug without having adequate evaluation i.e, pharma-

cokinetic and efficacy data. In addition, it is important to obtain a suitable form, even if the prescription are likely to be small.

2. The determination of benefits and risks. Children are very vulnerable and should obtain a benefit from the trial for themselves and/or for children of their age group. The risks should be limited. The determination of the risks of a planned study should include the predictable effects of the drug, based on animal studies, adult data and observations from clinical use. The assurance of safety and efficacy are of major importance during vaccination programs for the individuals and for the whole population.

3. A placebo should be use in pediatric clinical trials, even in neonates, when there is no reference drug (6).

4. The age and maturity, the selection of paediatric subgroups and individuals. When a trial is planned in children, it is preferable to begin with older children and then to extent the study to younger children. The newboms either term or premature, are at high risks because of renal and hepatic immaturity at birth and rapid physiological development. Adolescence is characterized by sexual maturation which can be influenced by many diseases but also by drugs. Special pediatric populations should be even more protected : handicapped, children with a chronic disease separated from their family, sometimes in medical care centers, etc.

5. The information and informed consent. Information related to the trial should be given in oral form and in usual words but also in a written form. It should include the evaluation of pain and fright associated with the study. The informed consent should be obtained from the child as a responsible individual and from his/her parents. In addition, it should be stated that the child cannot be obliged to participate and that refusal will be without disadvantages for him. And the decision of a child not to participate in a trial must be accepted. No financial benefit should be offered to the parents and/or the child for participating (7,8,9).

6. Investigator and sponsor. The investigator is a qualified person, trained in pediatrics and in the clinical area of the trial, known to have high ethical standards and professional integrity. The investigator must respect confidentiality, including identity, medical information and information on the deroulement of the trial, response to treatment and occurrence of adverse events. The sponsor is responsible for conducting the trial following the recommendations of Good Clinical Practice.

7. The Medical Research and Ethics Committees are constituted by medical professionals and non medical members. They should verify that the safety integrity and human rights of the subjects participating in the trials will be respected. The Ethics Committee should ask the opinion of the paediatricians and specialized nurses, as long as pediatric clinical trials are examined. Children must not be entered into a trial until the Ethics Committee has given its favourable opinion. In addition, the Ethics Committee should verify the following aspects : insurance to cover the liability of the investigator, compensation/treatment in the case of injury, death. The analysis of the protocols rejected by the Pediatric Ethics Committee of Toronto (10) has shown that the most common reasons for rejection were scientific, with according to the Committee an inability of the study to answer the question posed by the investigators.

Conclusion

Ignorance has risks but there are largely unseen. Increasing knowledge has risks which are noticed and is costly. This probably explains why maintaining ignorance often seems more attractive than increasing knowledge.

References

1. Déclaration d'Helsinki de l'Association Médicale Mondiale — Recommandations à l'adresse des médecins dans le domaine de la recherche biomédicale portant sur les sujets humains Adoptée par la 18ème Assemblée Médicale Mondiale 6 Helsinki (Finlande) Juin 1964.
2. American Academy of Pediatrics — Committee on drugs. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. *Pediatrics*, 1977, **60** : 91-101.
3. CPMP working party on efficacy of medicinal products. EEC note for guidance : good clinical pratice for trials on medicinal products in the european community. *Phannacol. Toxicol.*, 1990, **67** : 361-372.
4. NIES A.S., SPIELBERG S.P. Principles of therapeutics. *In* : GOODMAN and GILMAN's the pharmacological basis of therapeutics 9th ed., 1996, pp. 43-62.
5. PRATT C.B. The conduct of phases 1-11 clinical trials in children with cancer. *Med. Pediatr. Oncol.*, 1991, **19** : 304-309.
6. JACQZ AIGRAIN E., DAOUD P., BURTIN P., DESPLANQUES L., BEAUFILS F. Placebo-controlled trial of midazolam sedation in mechanically ventilated newborn babies. *Lancet*, 1994, **344** : 646-650.
7. SILVENNAN W.A. The myth of informed consent in daily pratice and in clinical trials. *J. Med. Ethics.*, 1989, **15** : 6-11.
8. ROBINSON R.J. Ethics committees and research in children. *Br. Med. J.*, 1987, **294** : 1243-1244.
9. DAWSON J. Randomised trials and informed consent in neonatal medicine. *Br. Med. J.*, 1986, **292** : 1373-1374.
10. KOREN G., PASTUSZAK A. Medical research in infants and children in the eighties : analysis of rejected protocols. *Pediatr. Res.*, 1990, **27** : 432-435.