PHARMACEUTICAL RESEARCH IN PEDIATRIC PATIENTS

For many medicines, paediatric labelling and dosage forms are not available (1). Without these, physicians and pharmacists face ethical dilemmas. Often the selection of the medicine and the dose for paediatric patients must be estimated from adult data. Additionally, the dosage form for paediatric patients must often be prepared by manipulation of an adult dosage form (i.e., compounding). The use of untested medicines and dosage forms in paediatric patients increase the potential for undesirable outcomes (2). Where no paediatric preparation exists, the pharmacist may have to prepare an appropriate product extemporaneously. This is generally recognised as safe, but care must be taken to ensure that the preparation and dose are appropriate for the paediatric patient concerned.

Paediatric patients deserve to have the same access as adults to effective medicines. Although the exclusion of paediatric patients from clinical medicine trials has often be-

en based on a desire to protect children from the risk of experimentation, the use of medicines and doses unproven on paediatric patients should also be regarded as experimentation (3, 4). The absence of paediatric studies results in unacceptable choices; paediatric patients are either denied medicines for their illnesses or medicines are used without the benefit of rigorous study (3). The need to develop potentially valuable therapies for paediatric patients should be balanced against the need to protect them from useless trials with medicines that are abandoned part way through the medicine development process (5, 6).

The study of pharmaceuticals in neonates, infants, children, and adolescents requires knowledge of developmental differences in medicine disposition and pharmacodynamics, potential paediatric-specific toxicity of the pharmaceuticals and rational study design to incorporate validated end points that can be reliably measured in the study patients. For most pharmaceuticals, clinical studies in paediatric patients should be undertaken after the availability of toxicology data and after some evidence has been obtained of the effects of the agent in adults (3, 5,6,7,8,9). The research methods, including those used to recruit patients, should be transparent (10).

As more national bodies require paediatric medicine studies, it follows that more children will be recruited to them. Whereas most researchers recognise the legitimate right of a parent (or other legal guardian) to give consent for a child to serve as a research subject, fewer recognise the rights of a child to give informed assent free from coercion (11, 12, 13, 14,15). Assent is the child's affirmative agreement to participate in research; failure to object is not "assent." As compared with informed consent, informed assent may be overridden in circumstances where parents, investigators, and an institutional review board agree that the child's welfare would be significantly harmed by failure to participate (2). Both informed consent and assent rest on recognition of respect for the dignity of the individual with inherent rights of self-determination, an obligation to protect the individual from undue risk, fairness in distribution of the burdens and benefits of research, and recognition of the fact that the individual of whatever age must live with the outcomes of the research (3,16).

It is generally accepted that a competent child, usually 7 years, is capable of understanding the information needed to give informed assent (3). In addition to ethical and possible regulatory justifications for obtaining informed assent from children as potential patients in pharmaceutical research, informed assent may confer medical benefits.

Recommendations

For the reasons stated above FIP recommends that:

1. For most medicines with potential paediatric use, preliminary planning for paediatric studies should begin simultaneously with the planning of adult studies; however, paediatric studies should not usually be conducted until some evidence exists of safety and efficacy in adults. Paediatric studies should be well designed; it is not acceptable to involve children in poorly designed studies unlikely to result in measurable benefit or scientific advancement.

2. Patient age categories in paediatric pharmacokinetic studies should be based on developmental differences in the clearance mechanism of the medicine if known. Age categories in pharmacodynamic studies should be based on the age in which validated end points can be reliably measured. In neonates, gestational age (estimated age from conception) and weight should be considered.

3. The initial dose used in paediatric pharmacodynamic studies should be based on the information gained in adult pharmacodynamic studies and the known differences in developmental pharmacodynamics and pharmacokinetics.

4. International harmonisation of paediatric research requirements among regulatory agencies is necessary to facilitate the fullest use of paediatric studies performed and the fullest benefit of these studies to all children.

5. Programmes in paediatric clinical pharmacy and pharmacology must be available and be undertaken by investigators to qualify for the conduct of clinical studies in paediatric patients, because these studies require specialised skills and experience.

6. When studies with medicines in children are undertaken, the potential effects on endocrine and cognitive development and on growth should be considered in addition to the safety concerns relating to adults and adequate periods of time for long-term follow up should be incorporated into the design of the studies.

7. The support of the public should be gained through information about, and understanding of, the process involved in the development of safe and efficacious medicines for children, including the role of paediatric clinical trials.

8. Parents (or guardians) must be given sufficient information to give informed consent for their child to participate in pharmaceutical research and after they have given informed consent, competent children (usually 7+ years) given sufficient information to promote understanding before assent is sought; both parties must be reminded of their rights to withdraw at any time.

9. Methods used to recruit and obtain consent and assent for children to participate in pharmaceutical research should be transparent.

10. Institutional review boards (ethical committees) with oversight enforcement capabilities should be established to ensure that the rights of the parents and children in paediatric pharmaceutical research are observed.

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