

Challenges in conducting pediatric drug trials

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For many decades, and with the exception of the treatment of infections, drug use in children has been confined to symptom relief. But the emphasis in asthma treatment has now shifted to the use of antiinflammatory agents that prevent the process resulting in bronchoconstriction, thus removing a symptom's cause. Newer understanding from the use of antiinflammatory agents in adults has led to an appreciation of preventative therapy and a growing understanding that effective drug therapy during childhood could prevent changes in the disease process that lead to chronic symptoms during adulthood. Alongside these developments, and while the debate over conducting drug trials in children continues, a persistent gap remains in the knowledge about drug use in children. Challenges remain not only in the regulatory environment but also in research and in the identifying, recruiting, and fostering of pediatric investigators. (*J Allergy Clin Immunol* 2000;106:S125-7.)

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In his 1968 landmark editorial for the *Journal of Pediatrics*, Dr Harry Shirkey¹ coined the term *therapeutic orphan* to describe children who were not being included in drug trials. This description set in motion a campaign to convince the regulatory agencies and the pharmaceutical industry the importance of testing drugs in children. Over 30 years later, that campaign is still being waged. Indeed, the first challenge in a campaign for conducting drug trials in children is making a convincing argument that such trials are necessary.

On that point, pediatricians do not need convincing. They have always been interested in pediatric therapeutics. Nevertheless, with the important exception of antibiotic studies, children have been neglected in drug development until recent years.

Through its work with the Committee on Drugs (COD), the American Academy of Pediatrics has been actively involved in the issue of pediatric drug trials. In 1974, the Food and Drug Administration (FDA) published the COD's first version of its "Guidelines for Drug Testing in Children."² This document discussed the differences in physiologic features and drug branding (including absorption, distribution, metabolism, excretion, and pharmacodynamics) in infants and children

Abbreviations used

COD: Committee on Drugs
FDA: Food and Drug Administration
IRB: Institutional review board

from birth through adolescence. The COD submitted subsequent revisions to the FDA in 1982 and again in 1998. Then, because of growing concerns over testing in children under the age of consent, the COD in 1977 developed ethical guidelines for conducting drug trials in children³ that were reaffirmed and revised in 1995.⁴

On its end, the FDA in 1991 requested that the pharmaceutical industry initiate the Pediatric Page, which was to be a statement issued by a pharmaceutical company that was studying an investigational drug, that explained to the FDA the plans for including pediatric patients in drug studies. This initiative was not considered successful; there was no significant increase in the number of new drugs studied in children. In December 1994, the FDA requested that pharmaceutical companies submit existing pediatric data on drugs for which they have a patent.⁵ This also was not successful because the number of drugs for which pharmaceutical companies submitted data was disappointingly small. Then, in 1997, Congress passed the FDA Modernization Act, which allows the FDA to issue a written request for pediatric data for compounds which are, or may be, used in pediatric patients⁶ and allows for a patent extension for companies that are successful in conducting studies for pediatric labeling. The FDA's final ruling, in 1998, requires pediatric studies for certain new and already marketed drugs.⁷

Along with these changes in the regulatory environment, an important concept of pediatric therapeutics has evolved that will be challenging to appreciate and implement. For many decades, and with the exception of the treatment of infections, the use of drugs in children has been confined to symptom relief. However, when important drugs were developed for the adult population for conditions such as hypertension, cardiovascular disease, asthma, and neuropsychiatric conditions, it was logical to extend these important developments to the treatment of children. Additionally, the emphasis in treatment has shifted in recent years to drug therapy that modulates disease in addition to relieving symptoms, an emphasis especially true in the treatment of asthma. Initially, asthma treatment focused on providing bronchodilation and thus relieving a symptom. But the emphasis has now shifted to the use of antiinflammatory agents that prevent

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the process resulting in bronchoconstriction, thus relieving a symptom by removing its cause. The use of antiinflammatory agents has led to a new appreciation that, by modulating the disease process, this preventative therapy may change the course of the disease. It is probable that effective drug therapy during childhood could prevent changes in the disease process that lead to chronic symptoms during the adult years.

In fact, the underlying assumption of the 1994 FDA ruling for the labeling extension from adult drugs to pediatric drugs was that pediatric extension of labeling would be appropriate for diseases in adults, with corresponding diseases in the pediatric population.⁵ However, this assumes that the pediatric equivalent of adult disease is the same, which may not be true for all conditions. A current challenge for pediatric therapeutics is the investigation of this assumption. As an example, the pediatric cause of hypertension is usually based on abnormalities of renal structure or function, whereas in adults, it is caused by essential hypertension or an abnormal increase in systemic peripheral resistance. As greater understanding grows in the underlying pathophysiologic features, it is possible that antihypertensive drugs used in children will be a different group than those used for adults or that these drugs may overlap.

THE INVESTIGATOR'S ROLE

The most important key to pediatric studies is the investigator. A particular challenge for pediatric studies has been, and continues to be, finding adequately trained investigators with the necessary institutional support. Appreciating this need, the National Institutes of Health established the Pediatric Pharmacology Research Units Network in 1993. Originally involving 7 institutions, National Institutes of Health funding has expanded it to 13 sites. The Pediatric Pharmacology Research Units network, however, cannot study all the drugs that require pediatric studies; the continuing challenge will be to establish more centers for pediatric drug studies. A lofty but not impossible goal is to establish a pediatric pharmacology research unit in each of the 125 medical schools in the United States.

The pediatric investigator must understand the wide variety of pathophysiologic features in pediatric illnesses and appreciate how pathophysiologic features evolve with age. Yet, this is only 1 of many important attributes of an investigator who must also understand

- the adverse effects and drug interactions in the pediatric population and how they may differ with the patient's age,
- the influence of diet on drug absorption and drug action,
- the ethical conduct of drug trials and the clarification of the role of placebo therapy in the pediatric patient,
- the importance of the institutional review board (IRB) in the conducting of pediatric trials,
- the availability of a drug formulation that is palatable and shows adequate gastrointestinal absorption or

entry into the body by nontraditional means (ie, routes other than oral or parenteral),⁸ and

- the importance of making a reasonable effort to include members of all socioeconomic classes in drug trials.

For many investigators, the greatest difficulty in successfully carrying out protocols is obtaining approval through the IRB, which exists primarily to protect the pediatric patient. Another important issue for which an IRB should be responsible and about which the investigator should be knowledgeable is how to carefully explain a study to both the child and the family. The pediatric panel of the United States Pharmacopeia has developed *10 Guiding Principles for Teaching Children and Adolescents About Medicines*.⁹ Principle 10 states that, "Children asked to participate in clinical trials (after parents' consent) have a right to receive appropriate information to promote their understanding before assent and participation." Many protocols do not receive IRB approval because of a lack of clarity either in the protocol or in the consent form.

Attention must be paid to the importance of placebo or alternative therapy. The study drug is the first agent that may be effective. Placebos are acceptable for use in the pediatric patient for any of the following conditions:⁴

1. The study drug is the first agent that may be effective.
2. Other therapies are of questionable efficacy.
3. The commonly used therapy has a high frequency of adverse effects; the risk is greater than the benefit.
4. The placebo is used to identify adverse effects of an addition to an established regimen.
5. The disease process has frequent, unpredictable remissions and exacerbations, and a commonly used treatment is not established.

The investigator must be competent to design or conduct clinical trials, but first and foremost, the investigator must be a defender of the pediatric patient. This involves understanding the drug to be studied, protocol writing and adherence, the pharmacologic features of the drug, procedural safety, and risks. Most studies are multisite, and communication and cooperation skills are vitally important. The investigator must always be alert to conflicts of interest and scientific misconduct.

Identifying, recruiting, and fostering investigators is the most important challenge in carrying out the mandate to increase drug labeling and drug testing in the pediatric population. Even if all of the previously mentioned issues are satisfactorily addressed and overcome, pediatric drug studies will be impossible without imaginative, dedicated, and hard-working investigators who must combine an understanding of the pediatric patient with scientific acumen and persistence in ferreting out financial support, establishing institutional protected time, recruiting patients, and shepherding successful protocols through the IRB. The investigator must also be an effective communicator with the pharmaceutical industry, regulatory agencies, institutional committees, parents, and, most important of all, the pediatric patient. Today, there is no area in pediatrics that is more challenging yet holds greater hope for advancement and success than pediatric therapeutics.

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