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Editorial Comment

Clinical Research on Children in The 1990s*

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In the 1970s and 1980s, a great deal of clinical research was published (my own work included) that might be viewed differently in the 1990s. It is worthwhile to examine the research principles that have evolved, and especially their application to children, before assessing the report by Mehta and Chidambaram (1) in this issue of the Journal.

Clinical research on children. Children *are* little adults in some ways, and not in others. Some clinical research on children, especially studies of drugs and devices, is based on findings demonstrated previously in adults. Therefore, the original research question can be as simple as, What differences are observed between the responses of children and adults? However, in providing such a narrow focus for an investigation, we miss the opportunity to learn about children. Any research project, especially one involving invasive testing, should provide data that not only are specific to the question being studied, but also can be generalized to other childen. For example, from a drug study, one should learn how children of different ages absorb, metabolize, distribute and excrete drugs in general, using a specific drug as a model.

When the research question involves testing specific hypotheses based on data presented in other investigations, such as those performed in adults, it is important to conduct a truly prospective study (a retrospective study identifies areas for future prospective studies). In undertaking a prospective study, there is a certain responsibility to obtain from every patient, if at all possible, every piece of data that is sought. Therefore, the data to be evaluated must be chosen carefully and based on hypotheses (one might say that the difference between fishing and hypothesis testing is that with hypothesis testing, you guess what kind of fish you are going to catch). In assessing the specific data to be collected, one must choose the control group carefully. In children especially, the confounding variables of growth and development must be considered. Rarely are historical control subjects acceptable because, in the space of 1 year or less, a problem such as supraventricular tachycardia may disappear or worsen spontaneously in response to a child's growth and development. In planning a prospective study, the number of subjects necessary to answer each question must be calculated and the calculation must be based on a straightforward formula of estimated variance.

We owe it to the children to perform rigidly controlled protocols. In conducting clinical research studies on antiarrhythmic drugs in children, I have found that it is not the patients or the parents who are noncompliant but the doctors who "let it go." We can and must perform double-blind, placebo-controlled studies. Although the children may not know the difference between drug and placebo, parents often understand the difference and influence their children in subtle ways. Parents must be taught by the nursing and physician staff to be careful, objective observers. They need to understand that children may show subtle signs of toxicity such as irritability or listlessness (it is difficult for 14-month old children to tell parents that they have a headache). Reliance for evaluation on the presence or absence of symptoms even through the teenage years may be inadequate in children. More objective methods of evaluation should be sought, including more frequent observation by trained professionals and more frequent laboratory testing. Parallel study designs are more likely than sequential designs to yield meaningful results because the natural history of any disease changes with growth and development.

Assessment of the need for invasive studies such as blood drawing or even electrophysiologic study should be based on the risk/benefit ratio in a manner similar to that used in adults. If sequential blood drawing for measurement of pharmacokinetic variables in necessary to answer a question, and the pharmacokinetic data are needed to answer a specific question about a specific child as well as for general use in learning about children, the data should be obtained. In plannning such invasive studies, however, it should be remembered that children are impressionable and have extremely good memories, but they may not understand the relation of the testing to their overall benefit or to the benefit to human understanding. Therefore, in children the discomfort of testing must be weighed more importantly on the risk side of the risk/benefit ratio.

We have been extremely fortunate to have access to one of several Clinical Research Centers supported by the National Institutes of Health and designed specifically for children. Because the entire nursing staff in such centers is oriented toward making the children who are being studied as comfortable as possible, the adverse effects of hospitalization and testing are minimized. These centers are vital to the performance of safe and productive research in children. These centers provide the important atmosphere of concern for the patient; they also require patients or parents, or both, to sign a consent form, thus forcing physicians to declare when they are doing research and to demonstrate to the parents (and in many cases to the child) the exact nature of the research and its costs and its benefits.

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We have a responsibility to the children and their parents to make valid conclusions based on the data obtained. A study should not be completed or reported if it is based on small subgroups of patients that are too small to allow meaningful comparisons. The inferences based on these small groups may be misleading and the data subject to a type II error.

The present study. The major conclusion in the study of Mehta and Chidambaram (1) is that nadolol is a safe and effective agent in the management of supraventricular tachycardia in children; the arrhythmia in 23 of 26 patients was well controlled. It is likely that such good results were the result of the administration of nadolol; nonetheless, a more rigorous study design with a parallel placebo group might have improved the study. The second conclusion—that the long-term efficacy can be predicted by the short-term response to intravenous nadolol or propranolol—may require more data. Of the 27 children, 7 received intravenous nadolol and 6 received intravenous propranolol. The concordance of results again supports the conclusion, but in a prospective study, the inclusion of larger numbers in each subgroup would have been helpful.

Conclusions. In recent years, the art of designing a prospective clinical research study has become a science. There are numerous examples of extremely well done studies that have allowed us to reach important conclusions that have helped many people. Many of these studies have been in adult patients and some have been in children. If we as pediatric cardiologists are to be taken seriously as members of the scientific community, we must follow the examples of excellence in clinical research. We are being judged by a new standard.

Reference

1. Mehta AV, Chidambaram B. Efficacy and safety of intravenous and oral nadolol for supraventricular tachycardia in children. J Am Coll Cardiol 1992;19:630–5.