Antihypertensive Therapy in Children
Implications for Future Studies
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This issue of Hypertension includes the results from a double-blind, randomized, placebo-controlled antihypertensive drug trial with valsartan in children. It takes the study of hypertension in children another step forward by extending controlled drug trials into the preschool age group (3 to 6 years old).

Historically, blood pressure and hypertension as independent disciplines within pediatrics date only to the 1977 publication of the first report of the Task Force on Blood Pressure in Children. The task force report provided standards for normal and elevated blood pressure in children, based on national population studies, and arbitrarily defined hypertension as blood pressure greater than the 95th percentile of the distribution according to age and sex. As a result of that report and 3 subsequent revisions, measurement of blood pressure and recognition of hypertension as a childhood health care issue have become integral to the practice of pediatrics.

Associated with the rising interest in hypertension was the realization that little was known about the use of antihypertensive drugs in children. The primary concern among pediatricians was related to potential adverse effects, in particular, developmental effects, of using adult drug doses and dosing schedules. At that time there was little incentive for the pharmaceutical companies to test drugs in children, and studies were investigator initiated by a telephone call to the company medical director, with the expense in the low 6 figures. Despite including crossover designs comparing 2 or 3 drugs, washout periods, and dose-response data, those protocols probably would not be funded today because of the small cohort size that combined patients spanning the pediatric age range and the lack of any placebo. Nevertheless, those studies demonstrated a degree of drug efficacy and safety and produced pediatric doses and schedules that are still used and effective.

The major impact on clinical evaluation of antihypertensive drugs in children came from federal legislation, with passage of the Food and Drug Administration Modernization Act. In addition to a mandate to the pharmaceutical industry to evaluate drugs in children, the legislation was sweetened by providing the companies with extended patent exclusivity as a reward for conducting the childhood trials. The result has been a flurry of activity. It seems reasonable to now ask whether these studies are providing the most useful data and whether future studies can be modified to provide additional information. The valsartan study provides a model for these considerations.

The general goal of drug studies in children is to obtain information on efficacy, dosing, and safety. It might be asked why efficacy data are needed for drugs that are effective in adults and have usually been used regularly in children before the trials are conducted. In fact, of 108 drugs relabeled in response to recent pediatric studies, 19 did not show efficacy, including the angiotensin receptor blocker irbesartan. Pediatricians have been reluctant to use a placebo in drug studies because of the perception that it threatens the safety of hypertensive children. However, recent data show that the risk with a placebo is minimal in childhood antihypertensive studies. Although this may be related, in part, to exclusion of patients with severe hypertension, who are likely to have the greatest antihypertensive response, it may be time to design childhood protocols with randomization to active drug versus placebo at the beginning of the study, ie, the design traditionally used in adult studies, in an attempt to maximize the opportunity to identify a treatment-placebo difference. Although statistically significant, the drug-placebo difference was small in the valsartan study and was achieved only after pooling the 3 treatment groups. This is in contrast to the highly significant percentage of reduction in blood pressure observed with each of the treatment groups after the start of therapy.

Drug dosing in children cannot be simply extrapolated from dosing recommendations in adults. This is because of potential age-related differences in drug uptake, clearance, and metabolism, recognizing that, in some cases, pharmacokinetic data in children are similar to adults. The valsartan study did not show a dose-response relation, as also reported in other recent childhood antihypertensive studies. The most likely explanation is the failure to use a broad enough dosing range. The traditional method used by pediatricians for drug dosing is based on dose per weight (milligrams per kilogram), but the valsartan study used 3 fixed amounts of drug (high, middle, and low doses). Although the percentage of reduction in blood pressure was similar with the 3 doses, it is disappointing that the response was not expressed in terms of weight-adjusted dosing (milligrams per kilogram). This is complicated by the failure to provide dosing recommendations. It seems reasonable to recommend starting no higher than the lowest dose tested (5 to 10 mg), and it needs to be
asked whether this recommendation was not made because it would require the company to produce a child-specific drug formulation.

Neonates, children with the most acute differences in drug metabolism because of immature organ and biological systems and rapid developmental change, have been excluded from almost all studies. Yet, antihypertensive drugs frequently are used in the neonatal intensive care nursery. A number of years ago we were able to show the profoundly exaggerated effect of Captopril in neonates (ie, long periods of blood pressure reduction in response to very small drug doses), but neonatal data for other drugs are scarce. Now that the valsartan study has moved drug trials into the preschool age range, consideration should be given to trials in the youngest children, recognizing the extra effort involved in recruiting and conducting trials in this age group.

The valsartan study recruited small numbers of children from many pediatric practices, including internationally. The result was blood pressure measurement with a variety of instruments that must have limited the quality control and reduced measurement precision. This type of recruitment is related to the need of the pharmaceutical companies to complete studies within the shortest period of time, because the studies are almost always conducted at the end of the drug patent life, increasing the importance of the exclusivity extension. Initiating childhood trials coincident with, or very shortly after, adult trials should be compatible with extending the period of recruitment, resulting in larger numbers of subjects from any given center and overcoming some of these issues.

Some of the important ongoing questions relate to which children should be treated and which drugs should be used. Most of the patients in the valsartan study had renal-related secondary hypertension, the most prominent cause of hypertension until children reach junior high school age and essential hypertension becomes prevalent. Few would argue with antihypertensive treatment of children with renal disease or target organ disease, most often represented by left ventricular hypertrophy. However, the best approach to essential hypertension is less clear. Studies of the natural history of blood pressure through adolescence and into young adulthood show strong cross-sectional correlations with body mass index. However, the longitudinal tracking effects are much lower for blood pressure than body mass index. Implicit with starting antihypertensive drugs during childhood is the prospect of ongoing therapy for 60 to 70 years. Pediatricians need better information than is currently available to feel confident about when treatment should begin, the effectiveness of specific agents or classes of agents, and how to treat specific disease states (eg, obesity versus chronic renal hypertension).

Finally, there continues to be other treatment-related issues left to address, beginning with a clearer understanding of the natural history of blood pressure, identifying the mechanisms leading to the early development of hypertension, and a better grasp of effective preventive and therapeutic strategies.

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References
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