Successes and Shortcomings of the Food and Drug Modernization Act

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As is true for many pediatric illnesses, the treatment of hypertension in childhood has been hampered by a paucity of data regarding antihypertensive drug pharmacokinetics and efficacy in children. Although nearly all antihypertensive agents have been used to treat hypertensive children,¹ until recently only a few of these agents had been systematically studied in children, and few drug manufacturers included pediatric dosing recommendations in their published prescribing information.² If a physician wishes to use a new drug or a drug without a manufacturer’s pediatric dose recommendation, he or she must adapt adult doses, a practice that is fraught with numerous potential problems.³ Hypertensive children in need of pharmacologic treatment could truly be considered “therapeutic orphans,”³,⁴ with each prescription written an experiment with a single subject.

Fortunately, two recent developments have produced large quantities of new data that should rectify this situation and improve the treatment of hypertensive children. The first of these has been the publication of several relatively large single-center experiences with the use of newer antihypertensive agents in children.⁵,⁶ Although such studies suffer from important design flaws, including selection bias and lack of control groups, these “real-life” experiences add important information that may be lacking in industry-sponsored trials, especially use of a greater variety of doses and long-term tolerability. It may be necessary to combine the results of these studies with those of industry-sponsored trials to gain full understanding of how a particular antihypertensive should be used in children.

The second development is the passage of the Food and Drug Modernization Act of 1997 (FDAMA) in the US,⁷ which amended the Federal Food, Drug and Cosmetic Act. Section 111 of FDAMA created incentives for pharmaceutical companies to conduct clinical trials in children. The mechanism established by FDAMA and later extended by the Best Pharmaceuticals for Children Act (BPCA)⁸ calls on the Food and Drug Administration (FDA) to determine whether a drug has potential health benefits in children, and pharmaceutical companies in response to these requests have sponsored dozens of clinical trials. With respect to antihypertensive compounds, nearly two dozen written requests have been issued by the FDA, and pediatric clinical trials have been completed or are underway in response to nearly 75% of these requests (Table 1). Furthermore, nearly every completed study has resulted in granting of additional market exclusivity. More important, dissemination of the results of these studies by publications in scientific journals should provide valuable guidance to physicians who prescribe these medications to children.

However, the FDAMA process will not necessarily produce the types of data that pediatricians require, nor will it answer all of the scientific questions of interest. For example, although manufacturers are required to conduct pediatric studies, they are not required to develop age-appropriate drug formulations, meaning that some drugs will be proven effective in the context of a trial but impossible to administer in practice.² Drug doses and


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Published by Elsevier Inc.
dosing regimens used in the trials are controlled to some extent by the study sponsors, meaning that the higher doses and unique dosing regimens reported to be necessary for children in single-center studies will never be rigorously tested. Furthermore, it has been common practice for industry-sponsored trials to exclude young (<<6 years old) children and children with severe hypertension from participation, meaning that the efficacy of these compounds in children with secondary hypertension, who tend to be younger and to have more significant hypertension than children with primary hypertension, will remain unknown. Finally, several of the initial trials were relatively short in duration, which leaves questions of long-term efficacy and safety unanswered.

The pediatric lisinopril study conducted by Soffer and colleagues and published in this issue of the American Journal of Hypertension, illustrates many of the FDAMA-related issues discussed above. Lisinopril, an angiotensin-converting enzyme inhibitor with proven efficacy in the treatment of hypertension in adults, was studied in a multicenter clinical trial co-sponsored by Merck and AstraZeneca in 115 children with hypertension, defined as seated diastolic blood pressure (BP) >95th percentile for age, gender, and height. Lisinopril was administered once-daily as either a standard tablet or suspension specifically prepared for use in the study. After stratification by weight (50 kg and ≥50 kg), subjects were randomized to treatment with low, medium, or high doses of lisinopril for 2 weeks; after this, subjects were randomized in a 1:1 fashion to receive either placebo or continued treatment with lisinopril for 2 additional weeks. The results of the study demonstrated that lisinopril reduced BP in a dose-dependent manner and was superior to placebo.

This study can be viewed from a number of perspectives. From the sponsors’ perspective, the trial was clearly a success as it fulfilled the requirements of the FDA’s written request and resulted in 6 additional months of market exclusivity for lisinopril. Although it is likely that the trial was expensive to conduct—22 collaborating sites on three continents were needed to complete it—it is also likely that the economic gain was considerable.

From a scientific perspective, the results of the trial are mixed. It is true that this was the first large-scale clinical trial of an angiotensin-converting enzyme inhibitor previously unstudied in children, which is likely to have considerable application in the treatment of hypertensive children, particularly those with renal disease who may gain unique benefits from treatment with lisinopril (ie, reduction of proteinuria). Unfortunately, the investigators do not specifically identify the causes of hypertension of the subjects enrolled in the trial—although at one point they do state that “many” of their subjects had “underlying kidney diseases,” knowing the exact percentage of subjects with renal or other forms of secondary hypertension would have been useful information to future prescribers of lisinopril. In addition, they did not report the results of lisinopril treatment in a clinically useful manner. Instead of reporting BP reduction in mm Hg, it would have been more helpful to know the percent BP reduction produced by lisinopril, or perhaps the percentage of subjects whose BP decreased to <95th percentile with lisinopril treatment.

Establishment and publication of an effective dosing range for lisinopril will undoubtedly make the results of this study helpful to pediatric nephrologists and other pediatricians who treat hypertensive children. However, although starting and maximal doses are recommended, there is no guidance on how to best up-titrate lisinopril, and no information on the effect of lisinopril doses between 5 and 20 mg. Both of these problems could have been solved had the investigators chosen to publish their linear regression graph of lisinopril dose versus BP reduction.

Similarly, it is useful to know that it is possible to prepare a suspension formulation of lisinopril for administration of this drug to children too young to be able to swallow commercially available tablets. Publication of the compounding instructions and stability data for the suspension will allow physicians who care for young children with hypertension to use lisinopril. It is unfortunate,
however, that the manufacturers have no plans to bring their suspension to market—while the difficulties in such an endeavor from the manufacturer’s perspective are readily appreciated—lack of a commercially available suspension means that it will have to be compounded by patients’ pharmacists, increasing the chances of adverse effects related to mistakes in preparation of the suspension. As noted, this is a clear failure of the FDAMA process, and one that will not be rectified by the recent modifications to FDA written requests and other initiatives discussed below.

Finally, from a patient safety perspective, the results of this study leave much to be desired. The trial was of just 4 weeks in duration, and half of the children in the study received lisinopril for only 2 weeks.9 The fact that few adverse experiences were reported while subjects were receiving lisinopril is essentially meaningless—What patient is treated with an antihypertensive agent for just 2 to 4 weeks? Again, this is a consequence of the FDAMA process in that study sponsors only had to fulfill the requirements of the written requests issued by the FDA. Early written requests issued by the FDA did not require long-term treatment to establish safety; fortunately, the written requests issued more recently have included requirements for long-term, open-label extensions of 6 to 12 months in duration. Studies that include long-term extensions will be much richer sources of information regarding drug safety than the present study and will represent a significant advance in the process of expanding our knowledge about treatment of childhood hypertension.

Perhaps the most significant shortcoming of FDAMA with respect to the study of medications in children is that the market exclusivity provision is only applicable to drugs that have remaining patent protection. Older antihypertensive drugs commonly used in children such as atenolol, nifedipine, and clonidine will never be studied in children, as they are well beyond their period of patent protection—perhaps this explains the lack of pediatric studies of some of the drugs listed in Table 1. Fortunately, the BPCA addresses this issue—Section 3 mandates that the Secretary of Health and Human Services issue an annual list of drugs with potential health benefits to children that lack patent protection, and establishes a mechanism by which the FDA can issue contracts to drug manufacturers for pediatric clinical trials of such drugs.3 Of note, the first list included one intravenous antihypertensive agent, sodium nitroprusside, and two diuretics occasionally used in complicated hypertension, bumetanide and furosemide.12 Although no pediatric clinical trials have yet emerged as a result of this process, it is encouraging that Congress has taken action to rectify the omission of children (as well as other neglected populations) in drug development.

Finally, as noted, the FDA is also taking steps internally to improve how clinical trials are being conducted in children. In March of 2003, representatives of the International Pediatric Hypertension Association met with the Division of Cardio-Renal Drug Products of the FDA to discuss the successes and shortcomings of FDAMA and how the process of pediatric drug development could be improved through the written request process. Changes currently under consideration by the Cardio-Renal Division include expansion of written requests to require that children <6 years old be included in future trials, and that in addition to safety and efficacy, the effects of antihypertensives on cognition, growth, and development be included as trial endpoints (personal communication from Douglas Throckmorton, MD, Director, Division of Cardio-Renal Drug Products, March 17, 2003). Further improvement in the treatment of hypertension in children will depend on such ongoing collaboration of pediatric investigators with industry and government, all working to ensure that children with hypertension and other significant health conditions receive drugs that are safe, effective, and appropriate to their unique needs.

Acknowledgments
The author thanks Dr. Adrian Spitzer for his thoughtful review of this manuscript.

References
5. von Vigier RO, Franscini LMD, Bianda NDF, Patti R, Casal
ta Aebischer C, Bianchetti MG: Antihypertensive efficacy of amlo