Pharmacologic Management of Childhood Hypertension: Current Status, Future Challenges

Joseph T. Flynn

The treatment of childhood hypertension has been hampered by several factors, including a lack of extensive scientific data regarding drug efficacy and pharmacokinetics in children, a lack of manufacturer’s recommendations for the use of antihypertensive agents in children, and a lack of age-appropriate drug formulations. These problems have forced clinicians either to rely on limited data from older studies of agents empirically no longer considered first-line choices for use in children, or to adapt agents studied in adults for pediatric use. Recent developments, including publication of single-center studies of newer agents and the proliferation of industry-sponsored trials spurred by the Food and Drug Administration Modernization Act, have increased the amount of data available. Investigators involved in such studies must ensure that the unique aspects of using antihypertensive drugs in children are adequately addressed.

Key Words: Children, hypertension, drug therapy, clinical trials, Food and Drug Administration Modernization Act.

The pharmacologic management of childhood hypertension has been characterized by a lack of extensive data on how best to use antihypertensive drugs in children, and about whether there are significant differences in drug metabolism or adverse effects in children compared to adults. This article reviews the deficiencies in our current knowledge regarding the use of antihypertensive agents in children, presents some of the recently published information in this field, and highlights the issues that should be addressed by future clinical trials of antihypertensive drugs in children.

Limitations of Current Knowledge

Lack of Controlled Studies

Until recently, organized trials of antihypertensive agents in children have been rare, and have not been sponsored by industry. The agents that had been prospectively studied in children included only a handful of compounds: captopril, minoxidil, propranolol, short-acting nifedipine, and some diuretics. Although these drugs have been proven to be effective antihypertensives, problems with each agent limit their usefulness in the modern management of childhood hypertension.

Captopril, for example, was prospectively studied in 73 hypertensive children from several centers, most of whom had renal or renovascular disease. Efficacy was demonstrated in approximately 60% of the children studied, with a relatively low incidence of side effects. In other studies, most either single center or retrospective, captopril was also shown to be an effective agent in both children and infants with hypertension. Although the efficacy of captopril in pediatric hypertension appears to be reasonably well established on the basis of these data, the drug has a relatively short duration of action and usually must be given three times daily to achieve sustained blood pressure (BP) control. Thus, except for certain clinical situations (for example, the treatment of hypertensive infants), captopril has been largely replaced by longer acting angiotensin converting enzyme (ACE) inhibitors, most notably enalapril, none of which had been prospectively studied in children until very recently.

For minoxidil and propranolol, the problems are slightly different. Minoxidil, which has been demonstrated to be an effective agent in children with severe hypertension, is usually not included as first-line therapy in children because of its well-known side effect of hypertrichosis. Propranolol, which has been studied in hypertensive children both alone and in comparison to chlorthalidone, has also fallen out of favor because of its adverse effects on athletic performance, mental concentration, and plasma lipids.

Short-acting nifedipine represents yet another problematic agent. Several reports dating back to 1983 have dem-
onstrated this drug to be effective in children with acute, severe hypertension.9–11 Investigators in these early reports noted that short-acting nifedipine tended to reduce BP by about 30% after a single dose, that it had a shorter duration of effect than expected, and that a potential for additive hypotension existed if repeat doses were given. More recently, reports have appeared regarding significant adverse neurologic sequelae caused by the rapid decrease in BP after the administration of short-acting nifedipine.12 Thus, although the exact incidence of such events is unknown at the present time, it has been recommended that children with severe hypertension be treated with alternative agents.13

It should be clear from these examples that one of the major impediments to rational, evidence-based pharmacologic management of childhood hypertension is the limited amount of available data. Fortunately, as will be discussed, data published more recently has expanded somewhat the number of antihypertensive agents that have been reasonably well studied in children.

### Lack of Manufacturers’ Dosing Recommendations

The practitioner who relies on information supplied by pharmaceutical companies to guide the use of antihypertensive agents in children will find few published dosing recommendations. A quick review of the current issue of the *Physicians Desk Reference*, for example, reveals that for antihypertensive medications, manufacturers’ information usually includes statements to the effect that “Safety and effectiveness have not been established in children.”14 Although pediatric dosing recommendations can be found in the manufacturers’ information for a handful of antihypertensive medications (Table 1), these are clearly exceptions from the norm. Furthermore, as noted previously, many of these are medications that have fallen out of favor in the modern management of childhood hypertension.5

Table 1. Manufacturers’ pediatric dosing recommendations for antihypertensive medications*

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
<th>Manufacturer’s Recommendations (dose or other comments)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>Captopril</td>
<td>Suggested dosage comparable or less than that used in adults</td>
</tr>
<tr>
<td>Beta-adrenergic</td>
<td>Enalapril</td>
<td>Initial dose: 0.08 mg/kg/day (up to 5 mg); maximum dose: 0.58 mg/kg/day (up to 40 mg)</td>
</tr>
<tr>
<td>antagonist</td>
<td>Propranolol</td>
<td>Initial dose: 1 mg/kg/day divided BID; usual dose 2–4 mg/kg/day; maximum dose: 16 mg/kg/day</td>
</tr>
<tr>
<td>Central-adrenergic</td>
<td>Methyldopa</td>
<td>Initial dose: 10 mg/kg/day, divided BID–QID; maximum dose: 65 mg/kg/day, up to 3 g/day</td>
</tr>
<tr>
<td>agonists</td>
<td>Diazoxide</td>
<td>Per-kg doses same as for adults</td>
</tr>
<tr>
<td>Direct vasodilators</td>
<td>Hydralazine</td>
<td>Initial dose: 0.75 mg/kg/day, divided QID; maximum dose 7.5 mg/kg/day up to 200 mg/day</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Minoxidil</td>
<td>Initial dose: 0.2 mg/kg/dose once daily; effective range: 0.25–1.0 mg/kg/day up to 50 mg/day</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide</td>
<td>10–20 mg/kg/day divided BID up to 1 g/day; up to 30 mg/kg/day in infants &lt;6 months old</td>
</tr>
<tr>
<td></td>
<td>Furosemide</td>
<td>2 mg/kg/day once daily; increase up to 6 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide</td>
<td>1 mg/pound/day, divided BID, maximum 50 mg/day for HTN; 1.5 mg/pound/day in infants &lt;6 months old</td>
</tr>
<tr>
<td></td>
<td>Spironolactone</td>
<td>1.5 mg/pound/day (3.3 mg/kg/day)</td>
</tr>
</tbody>
</table>

ACE = angiotensin converting enzyme; HTN = hypertension.
* Information derived from Reference 14.

Lack of Age-Appropriate Drug Formulations

A problem that affects not only antihypertensives, but also all medications originally designed for use in adults, is the lack of suspensions or other age-appropriate drug formulations.15 Of the many antihypertensive agents on the market, commercially available suspensions exist only for propranolol, and a few diuretics.14 Pediatricians, therefore, have long had to instruct parents to crush tablets and administer the medication mixed in food, or have had to
instruct pharmacists to compound tablets or capsules into suspensions.

Although stability data for “extemporaneous” suspensions of enalapril, isradipine, and amlodipine have recently been published, many such suspensions have inherent problems, including limited stability, questionable uniformity, and unknown bioavailability, that make their use problematic at best. The optimal solution to this problem, development of a wider assortment of commercially available suspension formulations for the most commonly used antihypertensive agents, is unlikely to be pursued by industry because of the prohibitive costs involved and the lack of incentive to undertake such development. This is one area in which publication of single-center data by interested investigators will likely remain the major method by which better information will become available.

Recent Developments

Publication of Efficacy Data for Newer Agents

The amount of published information regarding the pediatric use of antihypertensive medications has been bolstered over the past 5 to 10 years by the publication of empirically derived data for newer antihypertensives. Frequently representing single center or retrospective studies, such publications have helped other physicians to learn how to use these drugs, and have helped to identify important research questions for subsequent prospective, multicenter trials.

The best examples of this trend are the calcium-channel blocking agents. Results of pediatric studies of amlodipine, felodipine, isradipine, intravenous nicardipine, and nitrendipine have been published. Amlodipine, for example, has been studied by at least five groups of investigators. Although most of the children in these studies have had secondary forms of hypertension, amlodipine has been repeatedly demonstrated to be an effective antihypertensive agent, capable of reducing both systolic and diastolic BP, with adverse effects similar to those commonly seen in adults. Interestingly, an inverse relationship between effective amlodipine dose and patient age has been identified, as well as a possible need to dose amlodipine twice daily in children to achieve effective BP control. These findings, which have not been seen in studies of amlodipine conducted in adults, have helped to shape the recently completed industry-sponsored pediatric amlodipine pharmacokinetic study. The results of this study, as well as the pediatric amlodipine efficacy trial, should lead to improved understanding of the effects of amlodipine in hypertensive children, thereby helping clinicians to use this medication more effectively.

The major drawback to these recently published data are the inherent limitations of the single-center, retrospective study designs that have characterized many of these publications. However, as illustrated by the amlodipine studies cited, such data are clearly helpful in identifying research questions for later study. They also provide practical guidance with respect to dosing ranges and expected adverse effects to practitioners who consult these publications.

Proliferation of Industry-Sponsored Clinical Trials

Passage of the Food and Drug Administration Modernization Act in 1997 has been the greatest single stimulus for the recent proliferation of industry-sponsored trials of antihypertensive agents in children. This legislation mandates that the Food and Drug Administration identify drugs with potential health benefits in children and then requests that manufacturers conduct pediatric trials. In exchange, manufacturers can receive an additional 6 months of market exclusivity.

Although pediatric trials have been completed or are underway for many antihypertensive medications, results for just two compounds are available at this time: the ACE inhibitor enalapril and the combination β-blocker/diuretic bisoprolol/hydrochlorothiazide. Two pediatric enalapril studies were conducted, one a safety and efficacy trial, and the other a pharmacokinetic trial. The safety and efficacy trial enrolled 110 children aged 6 to 16 years with diastolic hypertension (defined as diastolic BP above the 95th percentile) and demonstrated that enalapril lowered BP in a dose-dependent manner with a low incidence of adverse effects. The pharmacokinetic trial demonstrated similar results for enalapril in infants and children compared to adults, a somewhat surprising finding given the common clinical practice of dosing this agent twice daily in children.

The multicenter pediatric trial of bisoprolol/hydrochlorothiazide (Ziac) was designed to examine not just drug efficacy and safety, but also dose–response and pharmacokinetics. It was also the first trial of a combination antihypertensive product in children. As with the pediatric enalapril trial, this study demonstrated efficacy with respect to BP reduction, although not as great as that seen in adults treated with this combination.

Although it is likely that such industry-sponsored trials will add important knowledge to our use of antihypertensive medications in children, there are many important scientific questions that will not be addressed. Chief among these are issues pertaining to the long-term use of these drugs in children: how will 10 to 15 years of treatment with a calcium-channel blocker affect the growth and development of a child’s cardiovascular system? Similarly, will treatment of hypertensive children with these drugs have any significant health benefits beyond reduction of BP? The long-term studies needed to answer such questions will not be conducted under the auspices of the Food and Drug Administration Modernization Act.

Furthermore, except for angiotensin receptor antagonists and newer antihypertensives not yet on the market, it
is unlikely that pediatric data will ever be generated for the many other drugs that continue to find widespread use in the treatment of hypertensive children. Clinicians involved in industry-sponsored trials need to take the responsibility of pursuing these and other important research questions, either within the confines of trials proposed by industry, or by designing appropriate trials themselves and seeking funding from industry.

In conclusion, at present, the state of knowledge regarding use of antihypertensive drugs in children is limited but improving. Collaboration between investigators and industry has enormous potential to increase our knowledge of how to treat childhood hypertension, but investigators must be proactive so that useful, pediatric-specific data will be generated.

References