Pediatric Antihypertensive Trial Failures
Analysis of End Points and Dose Range

Daniel K. Benjamin, Jr, P. Brian Smith, Pravin Jadhav, Jogarao V. Gobburu, M. Dianne Murphy, Vic Hasselblad, Carissa Baker-Smith, Robert M. Califf, Jennifer S. Li

Abstract—Historically, drugs prescribed for children have not been studied in pediatric populations. Since 1997, however, a 6-month extension of marketing rights is granted if manufacturers conduct Food and Drug Administration–defined pediatric trials. In nearly half of the drugs studied, there were unexpected results in dosing, safety, or efficacy compared with adult studies, including failure of half of the antihypertensive dose-response trials, which are pivotal for deriving dosing recommendations. We sought to define design elements that might have contributed to these trial failures by combining patient-level data from 6 dose-ranging antihypertensive efficacy trials completed for pediatric exclusivity and submitted to the Food and Drug Administration from 1998 to 2005. We evaluated dosing, primary end point, and other components to assess underlying reasons for failure to show efficacy in children. Of 6 trials examined, 3 showed a dose response; 3 did not. Eligibility criteria were similar across studies, as were subject demographics. Successful studies showed large differences in doses, with little or no overlap between low, medium, and high doses; failed trials used narrow dose ranges with considerable overlap. Successful trials also provided pediatric formulations and used reduction in diastolic, not systolic, blood pressure as the primary end point. Careful attention to pediatric pharmacology and selection of primary end points can improve trial performance. We found poor dose selection, lack of acknowledgement of differences between adult and pediatric populations, and lack of pediatric formulations to be associated with failures. More importantly, our ability to combine data across trials allowed us to evaluate and potentially improve trial design.

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Key Words: pediatrics ▪ antihypertensive agents ▪ dose-response relationship ▪ clinical trials ▪ randomized ▪ pediatric epidemiology

Historically, 75% of drug products used in pediatric populations have had insufficient labeling information for pediatric dosing, safety, or efficacy.1 The Food and Drug Administration Modernization Act of 1997 authorized an incentive of 6 months of marketing exclusivity for drug manufacturers who agreed to perform pediatric studies specifically defined in a “written request” issued by the US Food and Drug Administration (FDA). The Pediatric Exclusivity Program has been successful, resulting in >130 labeling changes to date.

Since the program’s inception, approximately half of the products studied have been found to have substantive differences in dosing, safety, or efficacy in children when compared with adult populations.2 Twenty-nine of 131 drugs examined were found to be ineffective when studied in children. Several products that did not work (or for which a statistically significant dose response was not observed) were oral antihypertensive agents known to be effective in adults.3–10 These trial failures have significant public health implications, because systemic hypertension occurs in ∼2% of the pediatric population and is rising concomitantly with obesity in children and adolescents.11

The FDA allows for several types of trial designs in the written request for an antihypertensive agent. The written request, generally issued by FDA before initiation of pediatric exclusivity studies, contains the required elements of the requested studies, including indication, number of studies, sample sizes, trial design, and age ranges.12 The most common antihypertensive trial design (type C; please see the online data supplement available at http://hyper.ahajournals.org for study schematic) was used for 6 antihypertensive agents. Type C design includes a lead-in period of ∼10 days, an initial randomization phase into ≥2 active treatment arms (eg, low, medium, and high dosage), a second randomization to double-blind withdrawal to placebo, and an open-label “safety” phase. The primary end point for these trials was to
establish a dose response of sitting blood pressure to the agent.

Of the 6 type C trials, 3 (enalapril, lisinopril, and losartan) were successful, whereas 3 (amlodipine, fosinopril, and irbesartan) did not show a statistically significant dose response. As a pattern of failed pediatric antihypertensive trials emerged, we sought to determine why these trials failed to show dose response in children and hypothesized that difficulties in dosing might be the cause of trial failure.

Methods

Study Cohort

Between January 1, 1998, and December 31, 2005, efficacy data from 12 antihypertensive products were submitted to the FDA Division of Cardiovascular and Renal Products. One efficacy trial and ≥1 pharmacokinetic trial were completed for each agent. These trials did not indicate differential dosing from adult data and did not suggest differences in absorption, bioavailability, clearance, or differential response by age or development. Pharmacokinetic-pharmacodynamic samples were not obtained in these trials, but rather for each product in the pharmacokinetic-pharmacodynamic trials; therefore, we did not include specific pharmacokinetic-pharmacodynamic results in our analysis.

Of the 12 efficacy trials, 6 were of type C design and included 3 products of which the trials demonstrated efficacy and 3 products of which the trials did not demonstrate efficacy in pediatric populations. The primary end point was prespecified by the sponsor as either change from baseline in systolic blood pressure (n=3 trials) or diastolic blood pressure (n=3). The data, protocols, case report forms, and all of the documents necessary for submission from these 6 trials were submitted electronically to the FDA. We documented inclusion and exclusion criteria and other key aspects of study design for each trial (please see the data supplement for study eligibility criteria).

Data Management

We obtained study data sets through the FDA electronic document room repository. Source data were available in SAS data sets, which we converted to Stata data sets via STAT Transfer. We then combined patient-level data to obtain 1 observation per patient, as defined by the protocol for primary analysis.

From each trial we assembled 30 common variables: antihypertensive product, unique patient identification number, age, sex, race, height, weight, body mass index (BMI), baseline sitting systolic blood pressure, baseline sitting diastolic blood pressure, and amounts of drug in milligrams and per dosing stratum (low, medium, or high) to which the subject was randomly assigned. We used forward selection to add the covariates listed above; covariates were retained if they were associated (P<0.05) with trial failure.

A significant dose response was concluded if the slope of the regression line differed from 0 at the 0.05 significance level. We reported 2-tailed P values and 95% CIs from the analyses. We presented the project to the Duke University Medical Center Institutional Review Board and received a waiver of review for this analysis, because none of the patient-level data in any of the 6 trials had associated patient identifiers in the data sets.

Results

Trials

Inclusion and exclusion criteria among trials were similar. The studies enrolled children 6 to 16 years of age; 5 of 6 trials accepted either systolic or diastolic blood pressure >95th percentile for age, sex, and height. The trials excluded children with severe hypertension (because of the randomized withdrawal phase), as well as children with low glomerular filtration rates, electrolyte abnormalities, renal disease, and other substantive medical problems.

Subject demographics among trials were also similar (Table 1). The fraction of male children and the age distribution of enrolled subjects were similar among trials. The enalapril and lisinopril trials enrolled a lower proportion of white children: 39% and 44%, respectively (compared with a mean of 65%), because the distribution of race was prespecified by protocol for these 2 trials. The distribution of weight and BMI of subjects varied among trials. The median BMI z score of subjects enrolled in the enalapril and lisinopril trials was 1.0 and 1.1, respectively; median BMI z score was 2.0 in the fosinopril trial. Three trials (amlodipine, enalapril, and fosinopril) distributed subjects equally between dosing arms (Table 1).

Dose Selection

The range in amount of agent received by subjects randomly assigned to low- and high-dosage groups was extremely variable among trials (Table 2). In the amlodipine trial, there was a 2-fold difference between the high-dosage and low-dosage groups (5 mg/2.5 mg=2). In the fosinopril and irbesartan trials, dosing ranges were also small, at 6- and 9-fold, respectively. The enalapril, lisinopril, and losartan trials had considerably higher dosing ranges, at 32-fold, 32-fold, and 20-fold, respectively.
Dose by Weight

Weight-based dosing strategies were inconsistent among trials. The amlodipine trial did not incorporate individual subject weight in dosing (Table 2) but rather gave all of the subjects in the low-dosage arm 2.5 mg of product and all of the subjects in the high-dosage arm 5 mg of product. This dosing strategy resulted in the following paradox: a 100-kg subject randomly assigned to “high” dosage received 0.05 mg/kg, and a 20-kg subject randomly assigned to “low” dosage received 0.125 mg/kg. In the low-dosage group, one fourth of subjects received >0.06 mg/kg, and one fourth of the high-dosage group received <0.06 mg/kg (Figure 1). Although blood pressure did not show a dose response to amlodipine as randomized (Figure 2) and despite not being approved by the FDA for treatment of hypertension in pediatric populations, increased dosage on a milligram per kilogram basis was associated with a decrease in blood pressure.

Table 1. Demographics of Patients Enrolled in the Trials

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Combined</th>
<th>Amlodipine</th>
<th>Enalapril</th>
<th>Fosinopril</th>
<th>Irbesartan</th>
<th>Lisinopril</th>
<th>Losartan</th>
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<tr>
<td>Randomized, n</td>
<td>1241</td>
<td>268</td>
<td>110</td>
<td>253</td>
<td>318</td>
<td>115</td>
<td>177</td>
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<tr>
<td>Mean age (SD), y</td>
<td>12.1 (3.0)</td>
<td>12.1 (3.3)</td>
<td>11.7 (3.1)</td>
<td>12.1 (2.6)</td>
<td>12.5 (2.8)</td>
<td>12 (2.9)</td>
<td>12 (3.1)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>795 (64)</td>
<td>177 (66)</td>
<td>64 (58)</td>
<td>166 (66)</td>
<td>214 (67)</td>
<td>75 (65)</td>
<td>99 (56)</td>
</tr>
<tr>
<td>Female, n</td>
<td>446</td>
<td>91</td>
<td>46</td>
<td>87</td>
<td>104</td>
<td>40</td>
<td>78</td>
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<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>White, n (%)</td>
<td>782 (63)</td>
<td>163 (61)</td>
<td>43 (39)</td>
<td>152 (60)</td>
<td>275 (86)</td>
<td>51 (44)</td>
<td>98 (55)</td>
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<td>Black, n</td>
<td>209</td>
<td>70</td>
<td>23</td>
<td>52</td>
<td>32</td>
<td>12</td>
<td>20</td>
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<td>Other, n</td>
<td>250</td>
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<td>44</td>
<td>49</td>
<td>11</td>
<td>52</td>
<td>59</td>
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<td>Missing, n</td>
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<tr>
<td>Mean height (5%, 95%), cm</td>
<td>155 (119, 182)</td>
<td>154 (116, 183)</td>
<td>146 (112, 175)</td>
<td>157 (127, 181)</td>
<td>160 (128, 184)</td>
<td>150 (111, 181)</td>
<td>151 (113, 180)</td>
</tr>
<tr>
<td>Mean weight (5%, 95%), kg</td>
<td>65 (23, 116)</td>
<td>66 (24, 120)</td>
<td>53 (20, 110)</td>
<td>74 (29, 136)</td>
<td>65 (28, 115)</td>
<td>56 (21, 102)</td>
<td>58 (22, 102)</td>
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<td>BMI z score</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Mean</td>
<td>1.44</td>
<td>1.44</td>
<td>0.82</td>
<td>1.69</td>
<td>1.06</td>
<td>0.96</td>
<td>1.09</td>
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<tr>
<td>Median</td>
<td>1.62</td>
<td>1.00</td>
<td>2.00</td>
<td>1.17</td>
<td>1.11</td>
<td>1.2</td>
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<tr>
<td>25%, 75%</td>
<td>0.69, 2.29</td>
<td>−0.17, 1.07</td>
<td>1.2, 2.49</td>
<td>0.29, 2.06</td>
<td>0.09, 1.92</td>
<td>0.37, 2.04</td>
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<tr>
<td>Enrolled, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Low</td>
<td>446 (36)</td>
<td>127 (47)</td>
<td>30 (27)</td>
<td>83 (33)</td>
<td>103 (32)</td>
<td>33 (29)</td>
<td>70 (40)</td>
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<tr>
<td>Medium</td>
<td>431 (35)</td>
<td>141 (53)</td>
<td>30 (27)</td>
<td>87 (34)</td>
<td>108 (34)</td>
<td>24 (21)</td>
<td>41 (23)</td>
</tr>
<tr>
<td>High</td>
<td>364 (29)</td>
<td>...</td>
<td>50 (45)</td>
<td>83 (33)</td>
<td>107 (34)</td>
<td>58 (50)</td>
<td>66 (37)</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure.
The fosinopril trial also failed to demonstrate a dose response, although it incorporated individual subject weight into the dosing. This was probably because the trial limited dosage to a maximum of 40 mg. In this trial, subjects randomly assigned to medium dosage who weighed >30 kg received more fosinopril (in milligrams per kilogram) than the heaviest subjects randomly assigned to high dosage. Similar to the amlodipine trial, blood pressure dose response was not associated with product as randomized, but increased dosing on a milligrams per kilogram basis was associated with blood pressure reduction (Table 3).

**Primary End Point**
The 3 successful studies were trials of enalapril, lisinopril, and losartan, all of which demonstrated a dose-response reduction in sitting blood pressure. These 3 successful trials used change in diastolic blood pressure as the primary end point. The 3 unsuccessful studies (trials of amlodipine, fosinopril, and irbesartan) used change in sitting systolic blood pressure as the primary outcome (Table 2). Sample sizes ranged from 110 to 318 subjects randomly assigned to the dose-response phase. Larger sample size did not predict success: the 3 successful trials were the smallest. Dosing for 5 of the 6 agents was divided into low, medium, and high dosages (Table 2), but there was considerable variability among trials regarding how much agent a subject in the high-dosage arm received compared with a subject in the low-dosage arm.

The 3 successful trials had the largest differences in dosing ranges: 32-, 20-, and 32-fold differences between low- and high-dosage groups for the enalapril, losartan, and lisinopril trials, respectively, compared with 2-, 6-, and 9-fold for the amlodipine, fosinopril, and irbesartan trials, respectively ($P=0.049$, rank sum test).

We evaluated the reduction in systolic and diastolic blood pressures related to each agent (Table 3). A reduction in diastolic blood pressure was more closely related to the dosage of agent administered. In the enalapril trial, the dosage was more closely related to a reduction in diastolic blood pressure than systolic blood pressure (coefficient 0.19...
We also observed a closer relationship between diastolic blood pressure reduction and dosage in the lisinopril trial (coefficient 0.12 [P<0.001] versus coefficient 0.08; P<0.05). Weight-based (milligrams per kilogram) exposure was associated with a reduction in blood pressure.

**Discussion**

We were provided access to individual patient data for each of the type C efficacy trials submitted for pediatric exclusivity from 1998 to 2005, inclusive. The primary end point for these trials was a dose-response change in sitting blood pressure among low-, medium-, and high-dosage groups. We found that 3 trials (enalapril, lisinopril, and losartan) were successful. These trials had several design components in common: all used diastolic blood pressure as the primary end point, were characterized by a larger range in amount of agent given to low-dosage versus high-dosage groups, and used a pediatric formulation in their efficacy trial.

Pharmaceutical companies continue to apply for pediatric exclusivity in the United States for antihypertensive agents, and an analogous program is now in place in the European Union. We believe that these results have several important implications for the design of future pediatric antihypertensive trials.

**Study Design**

These data support the use of reduction in sitting diastolic blood pressure, rather than systolic blood pressure, as the primary study end point. Diastolic blood pressure has less physiological variability among observations within a subject than does systolic blood pressure in children. This reduction in variability may have contributed to the success of diastolic blood pressure as the primary end point. Systolic hypertension is 3-fold more common than diastolic hypertension, and the motivation to use systolic blood pressure as the primary end point derives from feasibility, a common problem in conducting pediatric drug trials. However, the underlying causes of systolic and diastolic hypertension may differ (eg, abnormal aortic compliance versus elevated systemic vascular resistance), and this may become a significant factor depending on the patient population (eg, systolic hypertension is more common in elderly patients). A primary study end point of mean arterial blood pressure that incorporated both systolic and diastolic blood pressure values might prove advantageous, and this possibility should be explored in future trials.

The incentives in place for the Pediatric Exclusivity Program are designed to encourage trial completion; sponsors are given exclusivity if the trials are completed, and the decision to grant exclusivity is not dependent on product safety or efficacy. Feasibility is, therefore, of far greater importance to sponsors than optimal trial design. Eligibility for exclusivity regardless of outcome is a major advantage of type C trial design, because it is considered interpretable regardless of outcome; avoiding the use of an explicit placebo arm makes this type of trial more appealing to parents of potential subjects and institutional review boards.

Our results indicate that future pediatric antihypertensive trials should incorporate a wide range of doses and use information from adult trials to account for potential pharmacological differences between adult and pediatric populations. For example, the lowest clinical trial dose should be lower...
than the lowest approved dose in adults, and the highest clinical trial dose should at least be 2-fold higher than the highest approved dose in adults, unless contraindicated for safety concerns.

None of the failed trials investigated dose ranges higher than the corresponding adult doses. For example, the highest irbesartan dose was 4.5 mg/kg, whereas adult data indicate that most adults need doses up to 150 to 300 mg (=2 to 4 mg/kg for a 75-kg child) for better blood pressure control. Data obtained from irbesartan use in adults showed that effects on blood pressure increase at doses ≤600 mg (=8 mg/kg for a 75-kg child), and the maximum irbesartan dose studied in adults was 900 mg.

In contrast, the 3 successful trials provided large differences among low-, medium-, and high-dose strata. All 3 of the successful trials used doses much lower (nearly placebo) than the doses approved in adults. For example, the recommended initial lisinopril dose in adults is 10 mg, and the usual dose range is 20 to 40 mg. The lowest dose used in the clinical trial was 0.625 mg, thus providing a wider range for exploring dose response. The selection of wide dose ranges is important for pharmacokinetic reasons, because closely spaced doses yield overlapping exposures among dose groups. If overlap is substantial, the dose response could appear flat and, thus, fail to demonstrate a significant dose-response relationship.

Furthermore, 3 of these orally administered antihypertensive agents (those used in the failed trials) did not develop a pediatric (eg, liquid) formulation and, thus, exhibited a wide range in exposure within each weight stratum. Development of a liquid formulation is often challenging: bioavailability can be unreliable, and dissolving the agent in liquid can require high concentrations of alcohol. Stability and bioequivalence testing of liquid formulations also require additional time and expense. Still, pediatric formulations should be requested in the Pediatric Exclusivity Program whenever possible. Development of these formulations is now more economically feasible because of benefits provided to companies for successfully completing trials requested by FDA as part of this program.

It is possible that the failed trials were unsuccessful because the agents do not work (or do not work well) in children. Each trial had a placebo-withdrawal stage to address this concern. Amlodipine and fosinopril, neither of which showed a dose response, both reduced blood pressure compared with placebo. The third agent that failed, however (irbesartan), did not show a clinically meaningful reduction in blood pressure in the placebo-withdrawal stage.

One potential flaw in the conduct of these studies is the overall approach of study sponsors to compliance with FDA Modernization Act requirements: these studies are often designed and executed at the end of the product’s period of marketing protection. This problem is not limited to antihypertensive agents but exists across all products and can result in trials that fail to provide optimal data for the practicing clinician.

Failure to document dose response has been noted in other FDA-approved study designs and is not confined to type C trials. One solution might be to encourage lowering of blood pressure compared with placebo (eg, over a 4-week period) with subsequent follow-up studies to determine long-term safety. This would eliminate reliance on dose-response findings and put greater emphasis on long-term safety exposure.

**Study Limitation**

Our study is limited by the fact that we conducted a posthoc analysis of only 6 trials. However, there are very few pediatric efficacy trials, and if we are to improve trial design, posthoc analyses will need to be completed after relatively few studies.

In conclusion, access to protocols, final study reports, and individual patient data for each trial was crucial to our investigation. Our analysis highlights potential improvements in trial design, accurate assessment of product efficacy, and improved public health when access to data across trials is granted to investigators.

**Perspectives**

Poor dose selection, failure to fully incorporate pediatric pharmacology into trial design, lack of pharmacokinetic information, and use of systolic blood pressure as the primary end point likely led to the failure of several antihypertensive pediatric exclusivity trials. Complete access to patient-level data allowed us to fully examine trial results and may result in better design for future studies. Our data may be applicable to efforts to improve pediatric clinical trial design by government agencies, clinicians, and pharmaceutical sponsors in both North America and Europe. In the future, we recommend that pediatric antihypertensive trials do the following: (1) develop an exposure-response model using adult data and published pediatric data and use this model to perform clinical trial simulations of pediatric studies and to explore competing trial designs and analysis options; (2) work with FDA to design pediatric trials by leveraging previous quantitative knowledge; and (3) routinely collect blood samples at informative time points to assess the pharmacokinetics in each subject to ascertain exposure response analysis.

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References

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Supplemental Material:

Table S1: Inclusion and Exclusion Criteria from 6 Type C Pediatric Antihypertensive Efficacy Trials

Figure S1: Type C Antihypertensive Trial Design

Corresponding author:
Daniel K. Benjamin, Jr., MD, PhD, MPH
PO Box 17969
Duke Clinical Research Institute
Durham NC 27705
Tel: 919-668-8295; FAX: 919-668-9457
E-mail: danny.benjamin@duke.edu; daniel.benjamin@fda.gov
Table S1. Inclusion and Exclusion Criteria from 6 Type C Pediatric Antihypertensive Efficacy Trials

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Amlodipine</th>
<th>Enalapril</th>
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<th>Irbesartan</th>
<th>Lisinopril</th>
<th>Losartan</th>
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<td>SBP or DBP</td>
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*Plus positive history. BP indicates blood pressure; DBP, diastolic blood pressure; GFR, glomerular filtration rate; SBP, systolic blood pressure.
Figure Legend

Figure S1. Type C Antihypertensive Trial Design. Type C design includes a lead-in period of up to 10 days, an initial randomization phase into at least 2 active treatment arms, a second randomization to double-blind withdrawal to placebo, and an open-label “safety” phase.
Figure S1. Type C Antihypertensive Trial Design

Study Schematic

High

Placebo

Medium

Placebo

Low

Placebo

Load In
Double Blind
Double Blind Withdrawal
Open Label