Safety of Placebo Controls in Pediatric Hypertension Trials

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Abstract—Many clinical trials, including those in pediatric populations, use a placebo arm for medical conditions for which there are readily available therapeutic interventions. Several short-term efficacy trials of antihypertensive medications performed in response to Food and Drug Administration–issued written requests have used a placebo arm; whether the use of a placebo arm is safe in children with hypertension is unknown. We sought to define the rates of adverse events in 10 short-term antihypertensive trials to determine whether these trials resulted in increased risk to pediatric patients receiving placebo. We combined patient-level data from 10 antihypertensive efficacy trials performed in pediatric patients that were submitted to the Food and Drug Administration from 1998 to 2005. We determined the number and type of all of the adverse events reported during the placebo-controlled portion of the clinical trials and compared these numbers between the patients who received placebo and those who received active drug. Among the 1707 children in the 10 studies, we observed no differences in the rates of adverse events reported between the patients who received placebo and those who received active drug. Only 5 patients suffered a serious adverse event during the trials; none were thought by the investigators to be related to study drug, and only 1 occurred in a patient receiving placebo. Short-term exposure to placebo in pediatric trials of antihypertensive medications appears to be safe. (Hypertension. 2008;51:829-833.)

Key Words: pediatric drug therapy ■ hypertension ■ placebo-controlled clinical trials ■ adverse events ■ medical ethics

In response to a paucity of clinical trials in the pediatric population, Congress passed the Food and Drug Administration Modernization Act in 1997 providing for an additional 6-month period of marketing exclusivity to a drug company that responds to a Food and Drug Administration (FDA)–issued written request for studies of their drug in pediatric patients.1,2 The program was extended in January 2002 when Congress passed the Best Pharmaceuticals for Children Act and was renewed recently in September 2007. This program has been very successful in stimulating drug studies in children, and, as a result of the program, 139 drug labeling changes have been made for children.2–4

In the written requests for antihypertensive drugs, the FDA allows for 4 efficacy trial designs (Figure). Three of these designs (Figure, parts A, C, and D) involve a placebo-controlled phase. The placebo-controlled phase of the trial design raises both ethical and recruitment problems for these trials.5–8 Parents may be reluctant to enroll their hypertensive children in a clinical trial where they may receive only placebo. In addition, some investigators and ethicists believe it to be unethical to enroll patients in a placebo-controlled trial when a therapeutic intervention is available.8 Other investigators have argued that withholding active therapy for a short time in patients with a low incidence of adverse events (AEs) may be acceptable9 and that enrolling patients in studies that provide poor data are equally ethically questionable.5 Finally, there are recommendations that placebo not be used in children with hypertensive target organ damage or with secondary hypertension.10

Randomized placebo-controlled trials are considered the gold standard for clinical research in academics, industry, and by government agencies including the FDA and the European Medicines Agency. However, it is unknown whether these antihypertensive trials expose pediatric patients to increased rates of AEs. The European Medicines Agency has recently started to require drug studies in children and has begun to receive pediatric investigational plans for new molecular entities, including antihypertensive products. We sought to determine the AE rate in 10 short-term antihypertensive trials submitted to the FDA for pediatric exclusivity. In so doing, we sought to determine the short-term risks associated with the use of placebo in antihypertensive trials.

Methods

Study Cohort

Between January 1, 1998, and December 31, 2005, data from 10 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. The data, protocols, case report forms, and all of the documents necessary for submission from these 10 trials were submitted to the FDA electronically. These were multicenter trials approved by the institutional review boards of the participating sites. The trials excluded patients with severe hypertension or significant renal disease.
Data Management
We obtained the study data sets from the FDA electronic document room. Patient-level data were combined to obtain 1 observation per AE (or per patient, if no AEs occurred). From each trial, we assembled the following common variables: study drug, study identification number, age, sex, race, height, weight, body mass index, AE preferred terms, body system Medical Dictionary for Regulatory Activities terms, investigator’s opinion of the causal relationship between the study drug and AE, severity of AE, phase of study in which AE occurred, and therapy received during placebo-controlled phase of the study (placebo or active drug). We used a categorical variable of “white/black/other” for race, because several trials used this format to report race, and more specific information was not available.

Serious AE (SAE) determination was made by the trial investigators, and a dichotomous variable was used to classify the AE as serious or not. We examined the percentage of patients with AEs (AE prevalence), the mean number of AEs per patient (rate of AEs), and identified patients with SAEs. Although several trials contained dose-response phases in which all of the patients received drug or prolonged open-label safety phases, we limited our analysis to the placebo-controlled trial period.

Analysis
We report 2-tailed P values calculated by Fisher’s exact test, t test, logistic regression, or Poisson regression for count outcomes. Statistical significance was determined by a P<0.05. Analysis was performed using Stata 9.

Table 1. Patient Demographics

<table>
<thead>
<tr>
<th>Trait</th>
<th>Total</th>
<th>Aml</th>
<th>Ben</th>
<th>Ena</th>
<th>Fel</th>
<th>Fos</th>
<th>Irb</th>
<th>Lis</th>
<th>Los</th>
<th>Qui</th>
<th>Ram</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>1707</td>
<td>258</td>
<td>85</td>
<td>101</td>
<td>133</td>
<td>235</td>
<td>295</td>
<td>104</td>
<td>165</td>
<td>112</td>
<td>219</td>
</tr>
<tr>
<td>Age, mean, y</td>
<td>12.1</td>
<td>12.9</td>
<td>11.6</td>
<td>12.1</td>
<td>12.1</td>
<td>12.1</td>
<td>12.5</td>
<td>12.0</td>
<td>12.0</td>
<td>12.1</td>
<td>11.8</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>62</td>
<td>70</td>
<td>60</td>
<td>56</td>
<td>60</td>
<td>66</td>
<td>67</td>
<td>66</td>
<td>54</td>
<td>59</td>
<td>57</td>
</tr>
<tr>
<td>White race, %</td>
<td>55</td>
<td>62</td>
<td>56</td>
<td>38</td>
<td>50</td>
<td>60</td>
<td>86</td>
<td>42</td>
<td>55</td>
<td>37</td>
<td>30</td>
</tr>
<tr>
<td>BMI z score, mean</td>
<td>1.40</td>
<td>1.42</td>
<td>1.49</td>
<td>0.83</td>
<td>1.85</td>
<td>1.69</td>
<td>1.11</td>
<td>0.93</td>
<td>1.12</td>
<td>1.71</td>
<td>1.69</td>
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<tr>
<td>Median change in diastolic blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>3.0</td>
<td>2.7</td>
<td>0.0</td>
<td>2.8</td>
<td>2.0</td>
<td>1.7</td>
<td>2.3</td>
<td>6.2</td>
<td>4.8</td>
<td>6.7</td>
<td>6.0</td>
</tr>
<tr>
<td>Low dose</td>
<td>3.9</td>
<td>1.7</td>
<td>9.5</td>
<td>1.7</td>
<td>2.7</td>
<td>4.0</td>
<td>1.7</td>
<td>6.8</td>
<td>3.2</td>
<td>4.3</td>
<td>4.5</td>
</tr>
<tr>
<td>Medium dose</td>
<td>4.7</td>
<td>4.0</td>
<td>9.0</td>
<td>4.5</td>
<td>4.7</td>
<td>3.8</td>
<td>4.0</td>
<td>9.2</td>
<td>10.0</td>
<td>3.7</td>
<td>5.0</td>
</tr>
<tr>
<td>High dose</td>
<td>7.8</td>
<td>NA</td>
<td>7.0</td>
<td>18.5</td>
<td>1.3</td>
<td>4.7</td>
<td>6.0</td>
<td>13.5</td>
<td>10.5</td>
<td>5.3</td>
<td>7.0</td>
</tr>
<tr>
<td>Median change in systolic blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>5.0</td>
<td>3.3</td>
<td>3.0</td>
<td>0.5</td>
<td>5.3</td>
<td>6.3</td>
<td>7.2</td>
<td>3.5</td>
<td>3.3</td>
<td>4.0</td>
<td>9.0</td>
</tr>
<tr>
<td>Low dose</td>
<td>6.3</td>
<td>5.7</td>
<td>9.0</td>
<td>3.0</td>
<td>5.3</td>
<td>6.7</td>
<td>11.0</td>
<td>7.2</td>
<td>3.0</td>
<td>6.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Medium dose</td>
<td>8.0</td>
<td>8.5</td>
<td>11.0</td>
<td>3.5</td>
<td>3.3</td>
<td>9.2</td>
<td>9.3</td>
<td>8.5</td>
<td>10.8</td>
<td>6.0</td>
<td>9.0</td>
</tr>
<tr>
<td>High dose</td>
<td>10.3</td>
<td>NA</td>
<td>7.0</td>
<td>17.0</td>
<td>4.7</td>
<td>13.0</td>
<td>15.3</td>
<td>13.7</td>
<td>9.0</td>
<td>7.3</td>
<td>10.0</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; Aml, amlodipine; Ben, benazepril; Ena, enapril; Fel, felodipine; Fos, fosinopril; Irb, irbesartan; Lis, lisinopril; Los, losartan; Qui, quinapril; Ram, ramipril; NA, not applicable.
Blood and lymph & 1.3 (0.06 to 2.5) & 1.3 (0.7 to 2.2) & 0.55 \\
Cardiac & 0.7 (0.2 to 1.7) & 1.0 (0.9 to 2.5) & 0.09 \\
Congenital/genetic & 0.0 (0.0 to 0.5) & 0.1 (0.0 to 0.5) & 0.60 \\
Ear and labyrinth & 0.7 (0.2 to 1.7) & 0.3 (0.1 to 0.9) & 0.18 \\
Eye & 0.3 (0.0 to 1.1) & 0.8 (0.3 to 1.5) & 0.33 \\
Gastrointestinal & 6.4 (4.7 to 8.5) & 6.9 (5.5 to 8.7) & 0.70 \\
General disorders & 11.8 (9.5 to 14.5) & 11.7 (8.8 to 13.9) & 1.00 \\
Hepatobiliary & 0.1 (0.0 to 0.8) & 0.0 (0.0 to 0.4) & 0.40 \\
Immune & 0.1 (0.0 to 0.8) & 0.4 (0.1 to 1.0) & 0.65 \\
Infections & 6.0 (4.3 to 8.0) & 5.2 (4.0 to 6.8) & 0.59 \\
Injury & 0.7 (0.2 to 1.7) & 0.7 (0.3 to 1.4) & 1.00 \\
Investigations/laboratory & 1.6 (0.8 to 2.9) & 1.3 (0.7 to 2.2) & 0.68 \\
Metabolism/nutrition & 2.3 (1.3 to 3.8) & 1.6 (0.9 to 2.5) & 0.28 \\
Musculoskeletal & 1.7 (0.9 to 3.0) & 3.3 (2.3 to 4.6) & 0.07 \\
Nervous & 11.7 (9.4 to 14.3) & 13.4 (11.4 to 15.6) & 0.30 \\
Psychiatric & 0.1 (0.0 to 0.8) & 0.5 (0.2 to 1.1) & 0.41 \\
Renal/urinary & 0.9 (0.3 to 1.9) & 1.3 (0.7 to 2.2) & 0.49 \\
Reproductive-breast & 0.3 (0.0 to 1.1) & 0.2 (0.0 to 0.7) & 1.00 \\
Respiratory & 11.1 (8.8 to 13.7) & 13.0 (11.0 to 15.2) & 0.26 \\
Skin & 2.6 (1.6 to 4.1) & 2.7 (1.8 to 3.9) & 1.00 \\
Vascular & 0.4 (0.1 to 1.3) & 0.7 (0.3 to 1.4) & 0.75 \\

**Table 3. Number of Reported Pediatric AEs**

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Placebo, n (%)</th>
<th>Active Drug, n (%)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>3 (1.2)</td>
<td>1 (0.3)</td>
<td>0.19</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0 (0.0)</td>
<td>3 (0.8)</td>
<td>0.13</td>
</tr>
<tr>
<td>Cardiac*</td>
<td>8 (3.4)</td>
<td>16 (4.2)</td>
<td>0.50</td>
</tr>
<tr>
<td>Neuro/psych†</td>
<td>13 (5.5)</td>
<td>26 (6.8)</td>
<td>0.48</td>
</tr>
<tr>
<td>Headache</td>
<td>113 (48.1)</td>
<td>179 (46.9)</td>
<td>0.68</td>
</tr>
<tr>
<td>Syncope‡</td>
<td>15 (6.4)</td>
<td>31 (8.1)</td>
<td>0.35</td>
</tr>
<tr>
<td>Gastrointestinal§</td>
<td>54 (23.0)</td>
<td>90 (23.6)</td>
<td>0.51</td>
</tr>
<tr>
<td>Asthma/SOB</td>
<td>11 (4.7)</td>
<td>12 (3.1)</td>
<td>0.58</td>
</tr>
<tr>
<td>Elevated LFTs</td>
<td>7 (3.0)</td>
<td>7 (1.8)</td>
<td>0.51</td>
</tr>
<tr>
<td>Muscle aches</td>
<td>11 (4.7)</td>
<td>17 (4.6)</td>
<td>0.94</td>
</tr>
<tr>
<td>Total</td>
<td>235 (100.0)</td>
<td>382 (100.0)</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Ethics**

We received a waiver of review from the Duke University Medical Center Institutional Review Board and a letter of exempt status from the FDA Research Involving Human Subjects Committee, because none of the patient-level data in any of the 10 trials had associated patient identifiers.

**Results**

The placebo-controlled phase of these 10 trials ranged from 2 to 4 weeks. Trial size ranged from 85 to 295 patients, and a total of 1707 patients entered the placebo-controlled phase of the trials (Table 1). There were 685 patients randomly assigned to placebo and 1022 randomly assigned to active drug. The trials enrolled patients from 6 to 17 years of age. The majority of patients in the studies were white (55.5%) and male (62.1%).

Over the course of the placebo-controlled phase of the 10 studies, the median diastolic blood pressure decreased 5.6 mm Hg in the active drug treatment group and 3.0 mm Hg in the placebo group (\( P < 0.001 \)). Median systolic blood pressure decreased 8.5 mm Hg in the active drug treatment group and 5.0 mm Hg in the placebo group (\( P < 0.001 \)). For patients receiving low, medium, and high doses of antihypertensive drugs, the median changes in diastolic blood pressure were \(-3.9\) (interquartile range [IQR]: \(-9.0\) to 1.5), \(-4.7\) (IQR: \(-10.3\) to 0.3), and \(-7.8\) (IQR: \(-14.0\) to \(-1.3\)) mm Hg, respectively (Table 1). For patients receiving low, medium, and high doses of antihypertensive drugs, the median changes in systolic blood pressure were \(-6.3\) (IQR: \(-13.0\) to \(0.0\)),

-8.0 (IQR: \(-15.0\) to \(-1.0\)), and \(-10.3\) (IQR: \(-17.5\) to \(-4.0\)) mm Hg, respectively.

During the placebo-controlled phase of the trial, 263 (38.4%) of 685 of the patients in the placebo arm and 402 (39.3%) of 1022 patients in the active drug arm had \(\geq 1\) AE (\( P = 0.72\)). The mean number of AEs per patient was 0.76 in the placebo cohort (519 AEs total) and 0.83 in the active drug cohort (851 AEs total; \( P = 0.37\)). The mean numbers of AEs per patient in the low-dose, medium-dose, and high-dose groups were 0.79, 1.07, and 0.61, respectively. No difference was observed in the percentage of patients in either group suffering an AE in 21 different body system Medical Dictionary for Regulatory Activities categories (Table 2).

We examined the number of AEs occurring in 10 categories of AEs that are common to antihypertensive medications (Table 3). No significant differences in the number of AEs between patients receiving placebo and active drug were noted in any of these categories. There were 3 reported episodes of hypotension (2 episodes in 1 patient) in the group of patients receiving active drug and no episodes in patients receiving placebo. Hypertension was recorded as an AE in only 4 patients over the 10 studies (Table 3). Three (1.2%) of these patients received placebo, and 1 (0.3%) received active drug.

One patient receiving placebo (0.1%) and 4 patients (0.4%) receiving active drug suffered a SAE (\( P = 0.65\)). The patient receiving placebo suffered a rejection of a transplanted kidney. A patient receiving irbesartan experienced an episode of diabetic ketoacidosis, and a second patient had a syncopal event. A patient receiving lisinopril experienced 2 separate SAEs (gastroenteritis and pyuria). Finally, a patient receiving losartan broke a clavicle after a fall. None of these SAEs were felt by the investigators to be related to study drug. The AE relationship to the study drug was determined by the investigators at each of the study sites. All of the 167 AEs identified as definitely related to study drug were from the amlodipine trial (Table 4).
The reason for subject dropout was available for 8 of the 10 studies. The total number of dropouts from beginning of study to end of the placebo-controlled phase was 149 (11.0%) of 1355. However, only 30 (2.2%) of 1355 patients left the study because of AEs. There were 76 dropout subjects identified in the published reports of the 5 trials for which we had dropout data versus 81 identified in the original data. In a regression model using treatment received during the placebo-controlled phase (drug versus placebo), sex, body mass index, and age to predict a patient experiencing an AE, we observed no effect for treatment ($P=0.82$) or sex ($P=0.88$). Higher body mass index and younger age were associated with increased risk of AEs ($P=0.025$ and $<0.001$, respectively).

### Discussion

The present version of the Declaration of Helsinki states that “the benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best present prophylactic, diagnostic, and therapeutic methods.” However, a controversial 2002 clarification by the World Medical Association states that a placebo may be acceptable in a clinical trial for a “minor condition and the patients who receive placebo will not be subject to any additional risk or serious irreversible harm.” The American Academy of Pediatrics guidelines allow for use of placebo-controlled groups in clinical trials if the use of the placebo does not place the child at any increased risk. In addition, the FDA continues to support the use of placebo-controlled trials in selected populations.

There are several reasons that investigators, drug companies, and the FDA prefer placebo-controlled trials. Placebo-controlled trials may be accomplished with a smaller overall sample size than trials comparing a new drug with an active therapeutic agent. This may potentially expose fewer patients to experimental therapy and can substantially decrease the overall cost of the study. Placebo-controlled trials are also important for conditions in which an intervention carries a high placebo effect. In an adult antihypertensive trial, 58 (31%) of 187 patients treated with placebo achieved goal blood pressures, and a significant placebo effect has been noted in pediatric trials of antihypertensive medications.

Proponents of placebo-controlled trials argue that withholding short-term treatment for some clinical conditions is unlikely to result in harm (ie, allergic rhinitis). Patients in placebo-controlled trials are typically under close medical supervision, high-risk patients can be excluded from the study, and exposure to placebo can be limited to short periods. Finally, placebo use is often justified by investigators, because first-line intervention for some conditions, including hypertension, may be nonpharmacologic.

Although we discovered a marked difference in the number of AEs attributed to 1 drug (amlodipine) compared with the other drugs, we found no difference in AEs between patients receiving placebo and those receiving active drug and very few SAEs in either arm. The case report form for the amlodipine efficacy trial only gave investigators 2 options for association of the study drug with the AE (yes or no). The case report forms for the other 9 studies offered 4 levels of association (no, possibly, probably, or yes). This difference resulted in a dramatic inconsistency in how AE association to study drug was reported (Table 4). We observed no differences between the 2 cohorts in any of the Medical Dictionary for Regulatory Activities system organ classes. Even after separating out several commonly reported AEs, we observed no difference in the number of these AEs reported between the 2 groups (Table 3). The difference in AE association with drug observed with amlodipine was likely the result of differences in the way in which the case report forms captured this information for amlodipine versus the other 9 drugs.

Overall, the frequency of AEs was remarkably low and consistent with a previous review of 25 short-term antihypertensive trials in adults. The authors of this study found no difference in the study end points (death, stroke, myocardial infarction, and congestive heart failure) between the placebo and active drug arms. However, the duration of the trials and exposure to placebo was short. Any serious outcomes might be expected to occur after months to years of exposure to increased blood pressures. We found that children with higher body mass index and younger age are more likely to have AEs. This finding may result from improper dosing at extremes of age and body mass index. However, because of data limitations, we could not identify reasons for this; further studies are needed to identify why these groups of patients are at higher risk for AEs.
The low number of AEs observed may have resulted from the low-risk patients enrolled who received placebo or the relatively good adverse effect profiles of the antihypertensive agents given to patients receiving active therapy. Obviously, active therapy can often result in increased rates of AEs in patients receiving active drug if placebo is being given to low-risk populations, such as those enrolled in the pediatric hypertension trials reviewed here.

Our findings might also be explained by the short duration of the placebo-controlled phases of the 10 studies (2 to 4 weeks). Although it is still unknown whether childhood hypertension leads to increased cardiovascular morbidity, long-term hypertension in adults clearly leads to long-term morbidity. However, these morbidities could only be observed over years or decades of surveillance. Finally, the lack of SAEs observed in this study may have resulted from the exclusion of pediatric patients with severe hypertension and the close monitoring of patients during the clinical trial. However, even with the combined data of 10 trials, we would have only 70% power to detect a 1% difference in SAE rates between the 2 groups given the overall low rate of SAEs reported.

**Perspectives**

Opinion on the ethics of placebo-controlled trials continues to be divided, even in short-term trials like those examined here. Long-term trials with comprehensive follow-up are needed to best determine the overall risks to patients. Unfortunately, the time and cost to undertake these types of studies are prohibitive. However, we found no evidence in this review to suggest that pediatric patients receiving placebo are at an increased risk for AEs during short-term, placebo-controlled hypertension trials. Based on these findings, short-term exposure to placebo in pediatric trials of antihypertensive medications appears to be safe.

**Acknowledgments**

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**Disclosures**

None.

**References**
