The Efficacy and Safety of the Novel Aldosterone Antagonist Eplerenone in Children with Hypertension: A Randomized, Double-Blind, Dose-Response Study

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Objectives To determine the efficacy and safety of eplerenone therapy in children with hypertension.
Study design A total of 304 children age 4-16 years with systolic blood pressure (SBP) ≥95th percentile were randomized to low-dose (25 mg daily), middle-dose (25 mg twice daily), or high-dose (50 mg twice daily) eplerenone (phase A), then rerandomized to active therapy or placebo for another 4 weeks (phase B). The primary endpoint was change in SBP in phase B.
Results During phase A, mean SBP decreased from baseline by 8 mm Hg, and diastolic blood pressure (DBP) decreased by up to 3.8 mm Hg; no dose-response relationship was demonstrated. Mean differences in SBP from placebo during phase B were -2.61 for the low-dose group, +2.32 for the middle-dose group, and -2.76 mm Hg for the high-dose group; only the reduction in the high-dose group was statistically significant (P = .048). No significant effects on DBP of eplerenone therapy relative to placebo were detected. Eplerenone was well tolerated, with a rate of adverse events comparable to that of placebo.
Conclusions Short-term treatment with eplerenone reduced blood pressure in children with hypertension and had acceptable tolerability. *(J Pediatr 2010;157:282-7)*.

Although hypertension in young children may be secondary to an underlying disorder, primary or essential hypertension accounts for most cases in adolescents.[1] Hypertension in this age group is often linked to risk factors associated with the metabolic syndrome. This is of concern, given the rising prevalence of overweight children and adolescents.[2] Hypertension in childhood often persists into adulthood and is a known risk factor for coronary heart disease.[3,4] Based on these trends, the number of children receiving antihypertensive medications is likely to increase. Therapy is hampered by uncertainties regarding the efficacy and safety of antihypertensive medicines in children, however. The use of agents that have been extensively tested and used in adults often is not supported by data obtained in children.[5,6]

Eplerenone is a novel competitive aldosterone antagonist that reduces systolic blood pressure (SBP), diastolic blood pressure (DBP), and ambulatory blood pressure in a dose-dependent manner in adults.[7] Eplerenone also is effective as add-on therapy in patients receiving angiotensin-converting enzyme (ACE) inhibitor therapy.[8] Eplerenone has been approved to treat adult hypertension and shows promise in children. This double-blind, placebo-controlled study evaluated the antihypertensive efficacy and safety of eplenerone in children with hypertension.

Methods

The primary study objective was to compare the effects of eplerenone and placebo on SBP. Secondary objectives included to compare the effects of eplerenone and placebo on DBP, evaluate the effect of eplerenone on SBP and DBP as a function of dose and body size, and evaluate of the safety of eplenerone therapy. The study was a double-blind, randomized, placebo-controlled, dose-response trial with a placebo-withdrawal phase, carried out in accordance with the Declaration of Helsinki and in compliance with International Conference on Harmonization Good Clinical Practice guidelines. The final study protocol and informed consent documentation were approved by an institutional review board and/or independent ethics committee at each participating site. Written, informed, and witnessed consent was obtained from a parent or

ACE	Angiotensin-converting enzyme
ANCOVA	Analysis of covariance
BP	Blood pressure
DBP	Diastolic blood pressure
LVH	Left ventricular hypertrophy
SBP	Systolic blood pressure

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legal guardian of each enrolled child, along with the assent of the child where appropriate (ClinicalTrial.gov identifier: NCT00147589).

Inclusion criteria included age 4-16 years, granting of consent, and a history of seated SBP ≥95th percentile for age, sex, and height[9] at screening. Subjects were allowed to be taking another necessary concomitant antihypertensive medication, provided that the dosage had been stable for 3 weeks before study entry and remained unchanged throughout the study period. Exclusion criteria included body weight <20 kg, concomitant therapy with a potassium supplement or potassium-sparing diuretic within the 7 days preceding phase A, concomitant therapy with a potent CYP3A4 inhibitor (eg, clarithromycin, ketoconazole), unstable hypertension, clinically unstable underlying disease, a National Kidney Foundation Kidney Disease Outcomes Initiative CKD classification[10] of >3, potassium level >5.5 mEq/L, and inability to tolerate or absorb the study medication.

The trial was divided into 2 phases and was carried out in 43 centers in the United States, India, South Africa, Russia, and the Dominican Republic. After a screening and washout period, subjects were randomized to receive 1 of 3 doses of eplerenone (low dose: 25 mg once daily; medium dose: 25 mg twice daily; high dose: 25 mg twice daily for 2 weeks, then 50 mg twice daily for 4 weeks) in a 1:1:3 ratio for 6 weeks during phase A (Figure 1), after which they were rerandomized on a 1:1 basis within each group to either continued active therapy or to placebo for 4 weeks (phase B). Randomization was stratified by age (up to 12 years, and 13-16 years) and race (with enrollment prespecified so that at least 25% of subjects would be African-American). Primary endpoints were measured from baseline of phase B to the end of study.

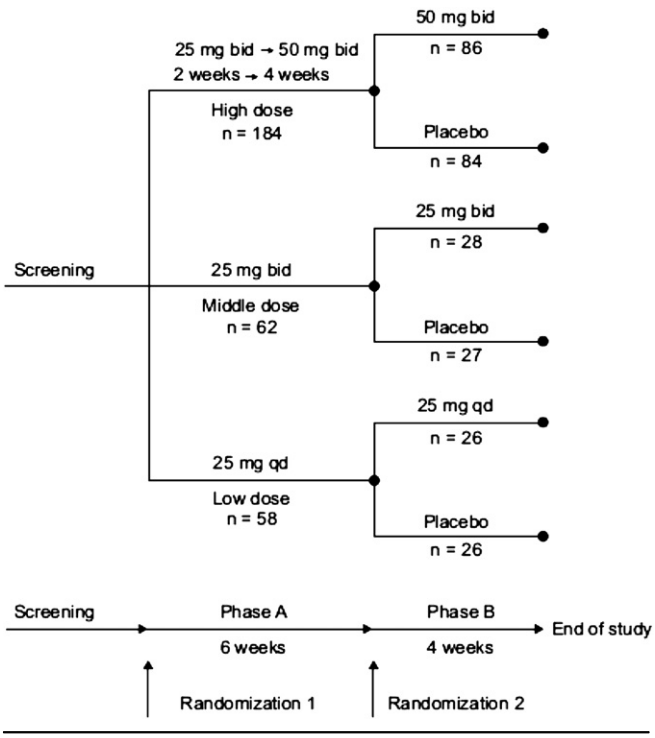

Figure 1. Study flowchart. Subjects were randomized to 1 of 3 doses of eplerenone during phase A after screening, after which they were rerandomized within their dose groups in phase B to carry on with active therapy or to receive placebo.

Blood pressure was measured with a Dinamap automated device (Critikon, Tampa, Florida). Pressures were recorded from the right arm every 2 minutes for 8 minutes in total while the subject was seated. The recorded blood pressure (BP) was the mean of the last 3 of a set of 4 determinations. A full medical history was obtained and physical examination performed at the screening visit, and blood pressure was measured on 3 separate occasions 1 or more days apart. Blood pressure and adverse events were recorded weekly. Laboratory testing for safety variables was undertaken at screening, at the start of phase B, and at the end of study, and potassium levels were measured biweekly and as clinically indicated. Pregnancy tests were performed in adolescent girls with child-bearing potential at screening and at the end of the study. Compliance was assessed by pill counts at study visits.

Adverse Events

Adverse events included drug reactions, illnesses with onset during the study, and exacerbations of previous illness. Investigators graded these as mild, moderate, or severe. Serious adverse events were those that resulted in death, were life-threatening, required hospitalization or prolonged existing hospitalization, or resulted in persistent or significant disability. Laboratory safety tests included complete blood chemistry evaluations and complete blood counts. Pregnancy tests were obtained as appropriate, and results indicative of above-normal potassium level (defined as serum or whole blood potassium >5.5 mEq/L) were repeated to validate hyperkalemia. Severe worsening of hypertension was defined during phase A as a persistent increase in SBP of 15% over that at the start of phase A, and during phase B as a persistent increase in SBP of 10% over that at the start of phase A. If severe worsening of hypertension occurred, the investigator could permanently discontinue the study medication and withdraw the subject.

Statistical Methods and Data Analysis

Approximately 300 subjects were needed in this study to give the study 90% power to detect a statistically significant effect of at least 1 of the 3 doses of eplerenone on SBP relative to placebo with the skewed randomization of 1:1:3. It was assumed that subjects assigned to the high-dose group who were randomized to placebo would have an average SBP increase of 7 mm Hg during phase B, that subjects assigned to the middle-dose group would have an average increase of 5 mm Hg, and that subjects assigned to the low-dose group would have an average increase of 3 mm Hg. These were conservative estimates based on data suggesting that adults treated with eplerenone 50-200 mg daily exhibit changes in SBP with differences from placebo of 6-13 mm Hg.[7] Grouping together all phase B placebo arms, there was 90% power to detect an