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Original Contributions

A Double-Blind, Placebo-Controlled, Dose–Response Study of the Effectiveness and Safety of Lisinopril for Children With Hypertension

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Background: Despite widespread use in hypertensive children, the safety and effectiveness of lisinopril had not been previously tested in a controlled study.

Methods: This study explored the dose–response relationship and safety of lisinopril in 115 hypertensive children, aged 6 to 16 years. Patients were randomized in a double-blind fashion for 2 weeks to one of three doses by body weight at baseline: $<$50 kg: low (0.625 mg), middle (2.5 mg), high (20 mg), and $\geq$50 kg: low (1.25 mg), middle (5 mg), high (40 mg). The dose–response for lisinopril was evaluated by analyzing the change in slope in sitting diastolic and systolic blood pressure (BP) by dose after 2 weeks of therapy compared to baseline. Patients then entered a double-blind withdrawal, where patients were either switched to placebo or continued their current lisinopril treatment for up to 2 weeks. Patients completed period II when their BP returned to baseline. Antihypertensive effectiveness, between placebo and lisinopril was determined for all doses. Adverse events were carefully monitored.

Results: There was a dose–response relationship between the lowest and each of the higher doses of lisinopril. Blood pressure in the placebo group increased after withdrawal of lisinopril. The dose–response relationship was consistent across all subgroups (ie, age, Tanner stage, ethnicity, gender).

Conclusions: Lisinopril, once daily, is an effective and well-tolerated antihypertensive in children aged 6 to 16 years. An initial dose of 0.07 mg/kg, administered once daily, effectively lowered BP within 2 weeks. Blood pressure was reduced in a dose-dependent fashion. Am J Hypertens 2003;16:795–800 © 2003 American Journal of Hypertension, Ltd.

Key Words: Lisinopril, angiotensin converting enzyme inhibitor, hypertension, pediatric, children, adolescent.

Hypertension is an important risk factor for cardiovascular morbidity and mortality in adults and occurs in 1% to 9% of children and adolescents.[1] In the early years, hypertension is usually secondary to renal parenchymal or renovascular disease. During adolescence, essential hypertension is the most common form of hypertension and is often associated with obesity.[2,3]

In 1977, the National Heart, Lung, and Blood Institute commissioned the first Report of the Task Force on Blood Pressure Control in Children,[4] which reported a growing concern about the possible relationship between blood pressure (BP) patterns in youth and the subsequent development of adult essential hypertension. The second report of the Task Force[2] established guidelines for BP control in children and urged better detection and control of hypertension in children.

Angiotensin converting enzyme (ACE) inhibitors are used for the treatment of pediatric hypertension[5] due to efficacy in reducing BP, and possible beneficial effects on cardiac function, the peripheral vasculature, and end organ

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Some of the data presented in this article were previously published in abstract form in the *American Journal of Hypertension* and *Pediatric Research*.

A listing of the participants of the Lisinopril Pediatric Hypertension Collaborative Study Group appears in the Appendix.

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protection based on adult studies.[6–8] The ACE inhibitors are particularly effective treatment for hypertension in infants.[5] The reasons are not entirely clear, but may be related to increased activity of the renin-angiotensin system in infants. Despite widespread use of ACE inhibitors in children, there have been few prospective controlled studies in pediatric hypertension. One recently completed study, using enalapril, was the first, large controlled prospective study of an ACE inhibitor in children.[9]

In adults, lisinopril is a once daily antihypertensive medication that does not undergo metabolism and is excreted entirely unchanged in the urine. The present study explored the dose–response relationship, safety, and tolerability of lisinopril over a wide dose range in hypertensive children.

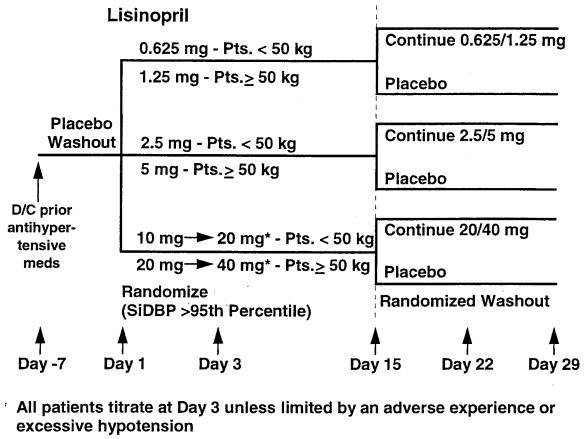

FIG. 1. Study design.

Methods

This prospective, randomized, double-blind multicenter study assessed the dose–response and tolerability of lisinopril in hypertensive children. Each site's Institutional Review Board or Ethical Review Committee approved the study protocol. Informed parental consent and patient assent, where appropriate, were obtained before patient participation.

BP Measurement

Trough BP was measured (24 h after the last dose of study therapy) at preselected study time points by trained site personnel, using the auscultatory method.[2] For patient safety, BP was measured at home and school with equipment provided, although only clinic measures contributed to study efficacy.

Patient Population

Male and female children, 6 to 16 years, ≥20 kg, with estimated glomerular filtration rate[10] of ≥30 mL/min/1.73 m^2, and documented hypertension (ie, sitting diastolic BP >95th percentile for age, gender, and height on two confirmatory measurements, each a mean of three)[11] were eligible to enter the study. All children had to be able to swallow tablets.

Study Design

The study design is shown in Fig. 1. The study began with an up to 7-day placebo washout for children on prior antihypertensive medication, during which their BP was monitored. When patients' BP increased to hypertensive levels on two consecutive measurements, they qualified for the randomized dose-ranging period (period I).

Period I: Randomized Dose Ranging

Eligible patients were randomized to receive one of three lisinopril doses (low, middle, and high) in period I, which lasted 14 days. Children <50 kg were randomly assigned to receive 0.625, 2.5, or 20 mg daily, whereas children ≥50 kg were randomly assigned to receive 1.25, 5, or 40 mg daily. The ratio of dosages, low-to-middle-to-high was 1:4:32 for each weight strata. Patients in the high dose group (20 mg or 40 mg) received a half dose for the first 2 days, then the full dose for the remainder of period I, unless limited by adverse effects or excessive hypotension (at the investigator's discretion). The low dose treatment groups (0.625 mg or 1.25 mg) received lisinopril in a suspension preparation.[12] The other treatment groups were dosed with standard tablets; however, to maintain the blind, the middle and high dose groups also received placebo suspension, and the low dose group also received placebo tablets. Patients took their study medication between 7 and 11 AM daily.

The primary hypothesis for this study was: At the end of the 14-day, double-blind treatment period, a dose–response relationship will be defined for lisinopril in children (aged 6 to 16 years) with hypertension.

Period II: Randomized Washout

After period I, all patients underwent a randomized washout to placebo or continued active lisinopril treatment (1:1) for up to 14 days, based on the original randomization at baseline. Patients were seen as often as the investigator considered necessary, but returned to the clinic for trough BP measurements at day 22 and day 29. Patients completed period II whenever their BP returned to or exceeded the baseline level. The secondary hypothesis was: At the end of the subsequent 14-day, double-blind, randomized, placebo-washout period, the mean change between the lisinopril and placebo groups for each assigned dose level will be positive.

Statistical Analysis

The intention-to-treat approach was used as the primary analysis, and included all patients having both baseline and post-randomization BP. Analysis was conducted using Statistical Applications Software (SAS Institute Inc., Cary,

Table 1. Baseline characteristics by dose

	Low Dose 0.625/1.25 mg (*N* = 33) *n* (%)	Middle Dose 2.5/5 mg (*N* = 24) *n* (%)	High Dose 20/40 mg (*N* = 58) *n* (%)	Total (*N* = 115) *n* (%)
Gender				
Male	21 (63.6)	15 (62.5)	39 (67.2)	75 (65.2)
Female	12 (36.4)	9 (37.5)	19 (32.8)	40 (34.8)
Ethnicity				
White	15 (45.5)	11 (45.8)	25 (43.1)	51 (44.3)
African American	4 (12.1)	3 (12.5)	5 (8.6)	12 (10.4)
Asian	0 (0.0)	0 (0.0)	1 (1.7)	1 (0.9)
Hispanic	14 (42.4)	10 (41.7)	27 (46.6)	51 (44.3)
Age (y)				
<6 to 12	17 (51.5)	11 (45.8)	26 (44.8)	54 (47.0)
13 to 16	16 (48.5)	13 (54.2)	32 (55.2)	61 (53.0)
SiDBP (mm Hg)				
Mean	87.9	91.0	90.4	89.8
SD	8.7	9.4	7.7	8.4
SiSBP (mm Hg)				
Mean	125.5	134.3	128.6	128.9
SD	12.7	15.1	11.6	12.9
Weight (kg)				
Mean	49.1	66.1	56.0	56.1
SD	19.0	34.3	27.2	27.3
Tanner stage				
≤3: number (%)	26 (78.8)	12 (50.0)	31 (53.4)	69 (60.0)
>3: number (%)	7 (21.2)	12 (50.0)	27 (46.6)	46 (40.0)

SiDBP = sitting diastolic blood pressure; SiSBP = sitting systolic blood pressure.

NC). All tests of significance were two-sided and performed at the 5% level of significance.

For period I, to demonstrate a dose–response relationship for lisinopril, a stratified simple linear regression model based on change in day 15 versus day 1 sitting diastolic BP was used with weight strata (<50 kg or ≥50 kg) and dose ratio (1:4:32) as covariates. The last-measurement-carried-forward approach was used for patients who did not have measurements on day 15. Sitting systolic BP was evaluated similarly in period I.

The primary end point for the secondary hypothesis in period II was the average difference between the lisinopril and placebo treated arms for all the three dose groups. This was estimated based on a one-way ANOVA with a factor of six levels (low–low, low–placebo, middle–middle, middle–placebo, high–high, and high–placebo), on change in trough BP at the end of the randomized placebo washout as compared to the end of period I (day 15).

Results

Patient Characteristics

Baseline characteristics for all 115 randomized patients are shown in Table 1. Baseline characteristics were balanced across the three dose groups.

Period I: Dose Response

During period I, 115 patients were randomly assigned to one of three doses (low, middle, or high); 33 patients to the low dose ($n = 15$ at 0.625 mg; $n = 14$ at 1.25 mg); 24 patients to the middle dose ($n = 11$ at 2.5 mg; $n = 12$ at 5 mg); and 58 patients to the high dose ($n = 27$ at 20 mg; $n = 25$ at 40 mg). Increasing doses of lisinopril resulted in greater reductions in sitting diastolic BP (low, −7.6 mm Hg; medium, −9.3 mm Hg; high, −16.4 mm Hg) (Table 2, Fig. 2). Using the intention-to-treat approach, the slope (SE) of sitting diastolic BP for the dose response was −0.28 mm Hg (+0.06) per unit increase in dose ratio ($P < .001$). The slopes were similar for the two weight strata (<50 kg and ≥50 kg). To support the dose–response finding, the antihypertensive effect of lisinopril on sitting systolic BP was also evaluated in period I (Table 2). Subgroup analyses demonstrated that the dose response to lisinopril was consistent across groups of age (≤12, >12 years old), Tanner stage (≤3, >3), gender (male, female), ethnicity (white, African American, Hispanic, Asian), and country (US, non-US).

Period II: Randomized Withdrawal to Lisinopril or Placebo

Of the 115 patients entered into the study, a total of 11 patients who discontinued in period I were excluded from the analysis. Among those remaining, 104 patients who entered period II were balanced between the lisinopril and placebo treated groups for each dose level (Table 3). In addition, Table 3 shows that the mean change (last dose versus day 15) in sitting diastolic BP increased in the

Table 2. Baseline to day 15 change in trough SiDBP and SiSBP (mm Hg) during period I by dose (intention-to-treat approach)

	N	Day 1	Day 15	Mean Changes	SD	95% Confidence Interval (for mean change)
SiDBP						
Low	33	87.9	80.3	−7.6	9.3	−10.9, −4.3
Middle	24	91.0	81.6	−9.3	8.7	−13.0, −5.7
High	58	90.4	74.1	−16.4	11.7	−19.5, −13.3
SiSBP						
Low	33	125.5	120.1	−5.4	9.9	−9.0, −1.9
Middle	24	134.3	122.1	−12.1	9.1	−16.0, −8.3
High	58	128.6	113.4	−15.2	12.1	−18.4, −12.0

N = patients with baseline (day 1) and postdose measurements; Mean change = measurement day 15 − measurement day 1. Other abbreviations as in Table 1.

middle and high dose groups of children who were randomized to placebo. The mean (±SE) difference between the lisinopril and corresponding placebo treatment was 6.19 ± 1.86 mm Hg over the three dose groups (P = .001), indicating that patients switched to placebo experienced an increase in BP.

Across all dose levels, patients who continued treatment with lisinopril during period II had no additional clinically important and statistically significant reduction in BP, demonstrating that 2 weeks was adequate to observe the antihypertensive effect of a specific dose of lisinopril. Similar results are shown for sitting systolic BP in Table 3.

Weight-Corrected Dose

Finally, in an attempt to determine a clinically useful dosing range, the relationship between weight-corrected dose and response was assessed. For low, middle, and high doses, the mean daily doses received when adjusting for body weight were 0.02 mg/kg, 0.07 mg/kg, and 0.61 mg/kg, respectively (Table 4).

Safety and Tolerability

Safety data, including clinical symptoms, changes in vital signs, and laboratory measurements were analyzed. Fourteen patients experienced clinical adverse events considered related to study drug by the investigators. Headache was the most common adverse event, occurring in 3 patients in the high dose and 1 patient in the low dose. Four patients reported adverse experiences believed to be related to lisinopril therapy by the investigators: 2 in the high dose experienced abdominal pain, diarrhea, nausea, and vomiting, and 2 in the middle dose experienced dizziness. Only 1 patient discontinued lisinopril due to clinical adverse effects. Two patients experienced serious adverse experiences considered unrelated to lisinopril, which did not cause study discontinuation: 1 patient had atypical pneumonia and 1 patient had gastroenteritis. Only one event of cough was reported, on high dose, and was considered not related to lisinopril therapy. There were no reports of angioneurotic edema.

Four patients experienced laboratory adverse events believed to be related to lisinopril by the investigators; 2 on the low dose (1 had decreased leukocytes and another had increased blood urea nitrogen and creatinine), and 2 on the high dose (1 had hyperkalemia and another had increased blood urea nitrogen and creatinine); none were considered serious. The elevation in serum creatinine (2.2 mg/dL from 1.7 mg/dL baseline) for the patient on the high dose was secondary to hypotension, and the patient was discontinued from the study.

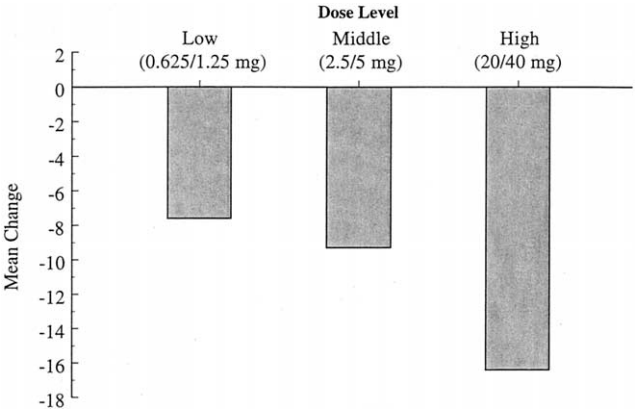

FIG. 2. Mean changes in trough in sitting diastolic blood pressure (mm Hg) in period I (day 15 *v* day 1).

Discussion

This study is the first prospective, controlled trial with the ACE inhibitor lisinopril in hypertensive children. Increasing doses of lisinopril resulted in greater reductions in BP after 2 weeks of lisinopril therapy taken once daily. The sitting diastolic BP was used as a primary measure, however, similar findings were also observed in systolic BP.

Randomized withdrawal of lisinopril using a placebo arm confirmed its antihypertensive effectiveness, especially in the middle and high dose groups. This effect was also observed in sitting systolic BP.

Until this time, no dosing recommendation has been available to pediatricians who prescribe lisinopril for chil-

Table 3. Mean changes and standard deviations in trough SiDBP and SiSBP (mm Hg) in by dose period II (intention-to-treat approach)

	N	Day 15	Last Dose	Mean Change (mm Hg)	SD	Group Difference	SE	95% CI
SiDBP								
Low–low	15	77.4	79.1	1.7	8.2	−0.2	3.3	−6.7, 6.3
Low–placebo	14	76.9	78.4	1.5	9.3			
Middle–middle	11	77.5	76.3	−1.2	7.3	9.7	3.2	3.3, 16.1
Middle–placebo	12	83.2	91.7	8.5	8.2			
High–high	27	71.1	72.5	1.4	9.1	9.1	2.6	3.8, 14.3
High–placebo	25	74.5	85.0	10.4	9.9			
SiSBP								
Low–low	15	115.9	117.7	1.8	7.8	−1.7	3.6	−8.8, 5.4
Low–placebo	14	119.8	119.9	0.1	11.1			
Middle–middle	11	120.7	121.2	0.5	9.4	10.4	4.4	1.7, 19.0
Middle–placebo	12	121.2	132.0	10.8	11.4			
High–high	27	113.0	112.2	−0.9	8.0	12.2	2.4	7.4, 17.0
High–placebo	25	112.3	123.7	11.4	9.3			

N = patients with Day 15 and postdose measurements; Group difference = Placebo − lisinopril; CI = confidence interval; other abbreviations as in Tables 1 and 2.

dren. This study included a wide range of doses (0.625–40 mg once daily). Because pediatricians are treating growing patients, they prefer to prescribe medicine on a weight-adjusted basis. The low dose level, when adjusted for patient body weight, resulted in a mean dosage of 0.02 mg/kg once daily, which was similar to placebo. The middle dose revealed a mean dosage of 0.07 mg/kg once daily. Based on the dose-dependent reduction in sitting diastolic BP during period I and an increase in BP in period II after discontinuation of lisinopril, a starting dose of lisinopril of 0.07 mg/kg (up to 5 mg) once daily offers consistent antihypertensive efficacy in children 6 to 16 years of age. The maximal weight-adjusted mean dosage in this study was 0.61 mg/kg once daily. The present study demonstrated that higher doses administered to children were associated with additional antihypertensive effectiveness. For patients not responding satisfactorily to the starting dose, upward titration should be considered to achieve sufficient antihypertensive effectiveness. Doses above 40 mg (0.61 mg/kg) have not been assessed and cannot be recommended.

The study groups were balanced with respect to age, gender, ethnicity, and sexual maturity (ie, Tanner stage). A wide age range was important for several reasons. Etiology of hypertension is different in different age groups. Our study population included many patients with hypertension due to underlying kidney diseases. We demonstrated a strong dose response in all patients and groups.

The safety of lisinopril was evaluated extensively. Lisinopril was well tolerated in children with hypertension. The number of adverse experiences was low across all groups, and there were no unusual or unexpected adverse experiences. Few significant adverse effects attributable to lisinopril were observed, and were similar to the types of adverse experiences reported in adults. Although this study was small and evaluated patients for a short duration, it is expected that the adverse experience profile will be similar to that reported in adults in larger clinical trials. It is important to note that because lisinopril blocks the renin-angiotensin-aldosterone system, similar to adults, hyperkalemia can occur in patients with reduced renal function. Because many of our patients had underlying kidney disease, increases in serum creatinine, especially when a patient has a decrease in intravascular volume, can be expected. In addition, although there were no reports of angioneurotic edema in this study, this has been reported in patients taking ACE inhibitors, including lisinopril. Furthermore, in this study there was only one report of

Table 4. Summary of weight-adjusted dose responses

	Dosage Group		
Statistics	Low (0.625/1.25 mg)	Middle (2.5/5 mg)	High (20/40 mg)
Number of patients randomized	33	24	58
Mean weight (kg)	49.1	66.1	56.0
Weight-adjusted dose (mg/kg)*	0.02	0.07	0.61

* Mean weight-adjusted dose at baseline: average of individual dose/weight (mg/kg).

cough, which was considered not drug related; however, cough has been reported in children and adults using ACE inhibitors.

In summary, lisinopril appears to be a highly effective and well-tolerated antihypertensive agent in children aged 6 to 16 years. An initial dose of 2.5 mg in children weighing <50 kg and 5 mg in children weighing ≥ 50 kg (mean = 0.07 mg/kg) administered once daily effectively lowered BP within 2 weeks in most patients. Blood pressure was reduced in a dose-dependent fashion. From these data we find that the dose of lisinopril may be increased in children who do not respond to lower doses with good tolerability. Doses above 40 mg (or 0.61 mg/kg) were not evaluated and are not recommended. Patients should be monitored carefully until the proper dose of lisinopril is established.

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Appendix:

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