Once-Daily Fosinopril in the Treatment of Hypertension


This multicenter, dose-ranging study evaluated the antihypertensive effectiveness of once-daily administration of fosinopril sodium in 220 patients with supine diastolic blood pressure of 95–115 mm Hg. After a 4-week placebo period, patients were randomly assigned to double-blind therapy with either placebo or 10, 40, or 80 mg fosinopril once daily for 4 weeks. If treatment goals were not met, chlorthalidone 25 mg/day was added for weeks 5 to 8. Thereafter, patients could enter the long-term, open-label phase and receive 10–80 mg/day fosinopril plus chlorthalidone, if needed. After 4 weeks of monotherapy, the average decreases in supine diastolic blood pressure were 9% (10 mg), 11.5% (40 mg), and 12.5% (80 mg) compared with 6% in the placebo group. After 8 weeks, the average decreases, with or without diuretic therapy, were 12.5–18.2%, compared with 10.8% with placebo. Blood pressure continued to be well controlled, and the patients showed no evidence of tachyphylaxis or tolerance through 12–15 months of treatment. Fosinopril was well tolerated. During the short-term phase, no patient withdrew because of adverse events possibly related to fosinopril; during the long-term phase, nine of 148 patients (6.1%) withdrew for that reason. In patients with mild-to-moderate hypertension, once-daily fosinopril (40 and 80 mg) provided significant antihypertensive effects with or without diuretic therapy. The 10 mg dose was effective in some patients and may be considered a starting dose. (Hypertension 1991;17:636–642)

The efficacy of oral angiotensin converting enzyme (ACE) inhibitors in the treatment of hypertension has been well documented in numerous clinical studies.1,2 Captopril, the first orally active ACE inhibitor, was first marketed in 1981. Since then, two other ACE inhibitors, enalapril maleate and lisinopril, have been marketed in the United States. These agents are believed to exert their pharmacological effects by preventing the formation of angiotensin II, a potent vasoconstrictor. Other possible mechanisms include the generation of vasodilatory compounds (i.e., bradykinin and prostaglandins).3 Fosinopril sodium (hereafter referred to as fosinopril) is a member of a new class of phosphorus-containing ACE inhibitors. During and after absorption from the gastrointestinal tract (i.e., within 40 minutes after drug administration to healthy subjects4), fosinopril, a prodrug, is hydrolyzed primarily to the pharmacologically active diacid fosinoprilat and one other minor metabolite, which is inactive.4 Fosinoprilat, a potent ACE inhibitor, is cleared almost equally by both renal and hepatic routes.4 This balanced, dual route of elimination may prevent significant accumulation of the drug in patients with impaired or diminished kidney function.5 Twenty-four hours after oral administration of fosinopril in healthy subjects fosinoprilat was detected in serum,4 suggesting that this drug may be an effective antihypertensive agent when administered once daily. The purpose of the large multicenter study described here was to evaluate the safety and efficacy of once-daily fosinopril with or without diuretic therapy in patients with mild-to-moderate hypertension.

Methods

The dose-ranging study performed at nine centers throughout the United States consisted of a short-term (3-month), double-blind segment and a long-term (10–13-month) open-label segment. A total of 276 men and women with a primary diagnosis of essential hypertension, that is, untreated supine dia-
systolic blood pressure (SDBP) between 95 and 115 mm Hg, were enrolled in the trial. Excluded were women who were pregnant or lactating or of childbearing potential and not practicing adequate contraception. Other reasons for exclusion were history of major allergy or serious sensitivity to other medications, abnormal liver function test results, recent (less than 6 months) myocardial infarction, serious illness or disease, or other conditions that would make the patient unsuitable for the study. Each investigator obtained approval from an institutional review board and written, informed consent from each patient enrolled.

**Short-term Segment**

The short-term segment of the study design used a double-blind, placebo-controlled, parallel-group format. The study segment was divided into three phases: a placebo lead-in period that lasted 4 weeks and two active treatment periods lasting 4 weeks each. Patients were monitored weekly during all three phases. Blood pressure was measured with a standard sphygmomanometer after the patient had rested in the sitting position for 20 minutes; the average of three determinations was recorded and analyzed.

Before the placebo period began, all antihypertensive treatment was discontinued. At the conclusion of that period, patients with SDBP between 95 and 115 mm Hg were randomly assigned to four groups, which received 10, 40, or 80 mg fosinopril or matching placebo every 24 hours for 4 weeks. Adherence to therapy was monitored by tablet count at each return visit. During the second 4-week active-treatment period, patients with SDBP of 90 mm Hg or less continued their original regimens, while patients whose SDBP was more than 90 mm Hg received their original regimens plus 25 mg chlorthalidone daily.

At the beginning of the first active-treatment period, the patients were admitted to the hospital for 1 day, during which their supine and standing blood pressures and heart rate were determined at 1, 3, 6, 12, and 24 hours after the first dose of double-blinded medication. All patients returned to the center weekly, 24±3 hours after the last dose of medication. Supine and standing blood pressures and heart rate were determined at each visit. If SDBP was more than 90 mm Hg at the end of 4 weeks, the cardiovascular responses to the first dose of combined fosinopril or placebo with chlorthalidone were similarly monitored for 24 hours.

Patients had chest x-ray and slit-lamp eye examinations at enrollment. Complete physical examinations, including funduscopy and 12-lead electrocardiograms, were done at enrollment and at the conclusion of each period. Hematology, serum chemistry, routine urinalysis, and 12-hour urine protein were determined at enrollment, at the conclusion of the placebo period, and biweekly thereafter.

At each weekly visit, all adverse events and other medication consumed were recorded. Adverse events were defined as untoward clinical or laboratory events that were temporally related to study drug administration, but not necessarily caused by the drug. Adverse events included both adverse drug experiences and concomitant events. Adverse drug experiences are untoward clinical or laboratory events temporally related to study drug administration and believed by the investigator to be caused by or possibly caused by the study drug or of unknown relation to the study drug. Concomitant events are untoward clinical or laboratory events that were temporally related to study drug administration but are believed by the investigator to be caused by factors other than the study drug.

Patient characteristics, including mean age, weight, duration of previous antihypertensive medications, and baseline vital signs, were evaluated using standard two-way (drug x investigator) analysis of variance techniques. Distributions of patients by race, sex, and Keith-Wagner funduscopy grades were evaluated with use of $\chi^2$ statistics. Change from baseline within treatment groups was assessed by Student's t test using the logarithm of the posttreatment-to-pretreatment ratio. A value of $p<0.05$ was considered to be statistically significant. If the drug effect as derived from the analysis of covariance model was statistically significant, Duncan's multiple comparison procedure was used to test for statistically significant differences between treatments.

**Long-term Segment**

Immediately after completion of the short-term segment of the study, patients who had received fosinopril and whose SDBP was 90 mm Hg or less or had decreased 10% or more from pretreatment had the option of enrolling in the long-term, open-label segment of the study for an additional 10–13 months. The dose of fosinopril could be titrated up to a maximum of 80 mg/day to reduce the patient's blood pressure to normal (SDBP 90 mm Hg or less). Chlorthalidone (37.5 mg/day or less) could be added for additional blood pressure control.

Standing and supine blood pressures and heart rates were recorded biweekly during month 4 and monthly from months 4 to 12 or 15. Physical examinations and the previously described clinical laboratory tests were performed monthly until month 6 and bimonthly thereafter. Electrocardiograms were done at the end of months 3, 6, and 12, and slit-lamp eye examinations and chest x-ray examinations were repeated at month 12.

Patients who had not received fosinopril during the short-term phase, but whose SDBPs were 90 mm Hg or more at the end of that period, were also eligible to participate in the long-term segment of the study. In those patients, laboratory tests were performed at least monthly during the long-term segment. Physical examinations were done and electrocardiograms were evaluated monthly until month 4. Patient visits and evaluations were scheduled as they were for the fosinopril patients during months 4–12 or 15.

The analysis of vital signs was based on mean percentage changes from baseline after 1–12 or 15
TABLE 1. Demographic Characteristics and Baseline Measurements in Patients Randomly Assigned to the Four Treatment Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (n=54)</th>
<th>Fosinopril (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>10 (n=55)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>46.7±1.5</td>
<td>49.8±1.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>86.9±2.4</td>
<td>88.2±2.2</td>
</tr>
<tr>
<td>White (%)</td>
<td>85</td>
<td>91</td>
</tr>
<tr>
<td>Supine blood pressure (mm Hg)</td>
<td>153.1/100.2</td>
<td>157.7/101.6</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

months of fosinopril therapy. A paired Student's t test was used to determine if the differences were statistically significant at the p≤0.05 level. Geometric means were used throughout the study.

Patients were considered to have had a favorable response to treatment if they were classified as either "normalized" (decrease in SDBP to 90 mm Hg or less) or "responders" (SDBP decreased by 10% or more).

Results

Short-term Segment

Of the 276 patients enrolled, 56 were excluded before the start of active treatment. The reasons for exclusion were a decrease in SDBP to less than 95 mm Hg during the placebo lead-in period (27 patients); an increase in SDBP to more than 115 mm Hg (six patients); violations of inclusion criteria (12 patients); and poor compliance, lost to follow-up, or voluntary withdrawal (11 patients).

Table 1 describes the demographic characteristics of the 220 randomized patients (139 men, 81 women) and the average blood pressures measured at enrollment in each of the four treatment groups. The groups' age, sex, weight, or racial distributions did not differ significantly. Patients in the 10-mg fosinopril group had slightly higher average supine blood pressure than patients in the 40-mg fosinopril group. Duration of hypertensive disease or funduscopy ratings did not differ among the groups.

During the double-blind portion of the study, 15 patients withdrew for various reasons (lost to follow-up, protocol violations, concurrent medical illness). No patient was withdrawn from that portion of the study because of an adverse event attributed to fosinopril (i.e., adverse drug experience). Mean supine blood pressure during the 24 hours after the first dose of placebo or fosinopril is shown in Figure 1. The mean SDBP at 24 hours was 9 or 10 mm Hg less than baseline in the three fosinopril-treated groups (p<0.001) and 4 mm Hg less in the placebo group (p<0.05). Mean 24-hour change in supine systolic blood pressure (SSBP) from baseline was 9-13 mm Hg for the three fosinopril groups (p<0.001) versus 1 mm Hg in the placebo group (NS). At 24 hours, all doses of fosinopril reduced SDBP more than placebo (p<0.05), and the 40- and 80-mg doses reduced SSBP more than placebo (p<0.05). Mean heart rate did not change in any treatment group.

Figure 2 shows the blood pressure response at week 4 in patients whose supine blood pressures were measured within 24±3 hours after taking their last doses. The mean reductions in SDBP from baseline were 6.0%, 9.0%, 11.5%, and 12.5% in the placebo and 10-, 40-, and 80-mg dose groups, respectively. The percentage decreases from baseline in both supine systolic and diastolic blood pressures were significantly (p<0.01) greater in the fosinopril
40- and 80-mg treatment groups than in the placebo group; for the 10-mg group, the percentage reduction of systolic blood pressure was significantly ($p<0.05$) greater than in the placebo group. Neither fosinopril nor placebo significantly affected heart rate.

Mean SDBP and SSBP in patients who did not require chlorthalidone during the double-blind phase of study (week 4 SDBP 90 mm Hg or less) are shown in Figure 3. Statistically significant ($p<0.001$) reductions from baseline at week 8 occurred in all treatment groups except for SSBP in placebo-treated patients. Comparisons between treatment groups were not performed because of bias that could have been introduced by the selection criteria for this subpopulation (i.e., all patients had responded).

Figure 4A illustrates mean SDBP of all patients throughout the 8-week trial, and Figure 4B summarizes the blood pressure responses of patients who required chlorthalidone (week 4 SDBP more than 90 mm Hg). SDBP were consistently lower in the 40- and 80-mg fosinopril groups than in the other two treatment groups. After addition of chlorthalidone at week 4, blood pressure decreased further in all treatment groups. At week 8, changes from baseline were statistically significant ($p<0.001$) in all treatment groups of patients who had not responded at week 4 (Figure 4B).

The mean percentage decreases in SDBP and SSBP of all patients (with or without chlorthalidone) whose blood pressure was measured 24 ±3 hours after dose were 10.8% and 7.0% (placebo), 12.5% and 9.8% (10 mg), 15.6% and 12.1% (40 mg), and 18.2% and 16.4% (80 mg) (Figure 5). Significantly ($p<0.01$) greater percentage reductions in SDBP and SSBP occurred in the 40- and 80-mg fosinopril treatment groups than in the placebo or 10-mg fosinopril groups. In all groups, mean change in heart rate was clinically insignificant (i.e., 1–3 beats/min) with no relation to dose.

**FIGURE 2.** Bar graph showing mean percentage change from baseline in supine blood pressure and heart rate in a subset of patients at week 4. Data were collected 24 ±3 hours after the last dose of fosinopril or placebo monotherapy.

**FIGURE 3.** Line graph showing effect of fosinopril or placebo on supine diastolic blood pressure in patients who did not require chlorthalidone ($n=19–30$ patients/group at week 8). Fosinopril 10 mg □; fosinopril 40 mg △; fosinopril 80 mg ▽; placebo ○.
The proportions of patients who did not require the addition of the diuretic were 46% in the placebo group, and 41%, 58%, and 57% in the 10-, 40-, and 80-mg fosinopril groups, respectively. At 4 weeks, the proportions of patients whose SDBP was 90 mm Hg or less or was reduced 10% were 40% in the placebo group and 50%, 72%, and 67% in the 10-, 40-, and 80-mg fosinopril groups, respectively. Significantly more patients responded favorably to therapy with 40 (p<0.01) and 80 (p<0.05) mg/day fosinopril than responded favorably to placebo. After the full 8 weeks of treatment, 64% of patients receiving the placebo with or without chlorthalidone, the usual dose of which was 25 mg/day. The antihypertensive effects of fosinopril alone or with chlorthalidone in those patients are summarized in Figure 6. Throughout the long-term segment of the study, mean supine systolic and diastolic blood pressures were consistently lower than at baseline (p<0.001). Mean SDBP and SSBP remained relatively constant throughout long-term treatment. Average supine heart rates essentially did not change from baseline (i.e., change of less than 3 beats/min). Fosinopril alone or with chlorthalidone also effectively reduced standing blood pressure. In a cohort of 89 patients with data recorded at all evaluation intervals (months 1, 2, 3, 6, 9, and 12), the average reductions from baseline ranged from 8% to 14% in systolic blood pressure and 11% to 17% in diastolic blood pressure (p<0.001). Heart rate remained essentially constant except for slight but statistically significant (p≤0.05) increases at months 2 (3.7%) and 9 (2.6%). No evidence of tolerance to the treatment regimen was observed. During the long-term portion of the study, 15 patients discontinued because of personal reasons (9), concomitant illness (3), inadequate blood pressure control (2), or unwillingness to take the diuretic (1). Fifty-five adverse events were reported by 35 (24%) of the 148 patients. The most common adverse

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**Figure 4.** Panel A: Line graph showing effect of fosinopril or placebo reflected by decreases in geometric mean supine diastolic blood pressure (mm Hg) in each of four treatment groups. For the first 4 weeks, patients received monotherapy; after week 4, chlorthalidone could be added for patients who did not reach goal for supine diastolic blood pressure. Panel B: Line graph showing reductions in supine diastolic blood pressure only among patients receiving chlorthalidone (n=18-26 patients/group at week 8). Fosinopril 10 mg □; fosinopril 40 mg △; fosinopril 80 mg ▽; placebo ○. Before the addition of chlorthalidone, the 40 mg dose of fosinopril caused the greatest reductions. CT, chlorthalidone.
drug effects that were considered by the investigator to be possibly related to fosinopril were lightheadedness/dizziness, cough, and gastrointestinal disturbance. Seven patients (5%) were discontinued because of cough, sexual dysfunction, asthma, or flatus. Two additional patients discontinued because of transient elevations of laboratory values. One of those patients had a mild increase in serum glutamic-pyruvic transaminase (SGPT) (1.5 times above the upper limit of normal); however, his SGPT concentration had fallen to within the normal range by the last day of treatment. The other patient had elevated serum glutamic-oxaloacetic transaminase and other values up to five times normal limits; however, in the opinion of the investigator, those elevations were secondary to a recent viral illness. Results of other laboratory tests, physical examinations, electrocardiograms, slit-lamp eye examinations, and chest x-rays did not disclose any serious abnormalities that were unequivocally related to fosinopril.

Two patients with significant coronary artery disease died suddenly during treatment with fosinopril. The investigators did not consider either death to be related to fosinopril.

Discussion

The study described here demonstrated that fosinopril given once daily, alone or with a diuretic, safely and effectively controls blood pressure in patients with mild-to-moderate essential hypertension. The average reductions in SDBP were similar to those with other ACE inhibitors,6-8 diuretics,9,10 β-adrenergic blocking agents,11 and calcium antagonists12 administered as monotherapy. Furthermore, in approximately 60% of the patients, SDBP decreased to 90 mm Hg or less after 4 weeks of therapy with either 40 or 80 mg/day fosinopril. This finding is consistent with the results of studies6-12 with other antihypertensive agents in patients with mild-to-moderate hypertension.

At weeks 4 and 8, blood pressure in the standing and supine positions was reduced to a similar extent. This suggests that fosinopril does not produce orthostatic hypotension, and that like captopril, fosinopril primarily lowers peripheral vascular resistance by
suppressing the vasoconstrictor activity of angiotensin II. Like other ACE inhibitors, fosinopril reduces blood pressure without causing tachycardia.

Fosinopril gradually reduced blood pressure after the first dose. The greatest reductions in blood pressure occurred approximately 3 hours after the first dose. This is consistent with the results of a previous study, which showed that peak levels of fosinoprilat were attained approximately 3 hours after administration to healthy subjects. With chronic fosinopril administration, blood pressure fell continuously throughout week 4, when it was appreciably lower than at baseline. Among the patients who responded to 40 and 80 mg fosinopril, SDBP remained constant or decreased further at 8 weeks. The addition of diuretic therapy in patients not responding fully reduced blood pressure further. During the long-term portion of the study, blood pressure continued to be well controlled with no evidence of tolerance or tachyphylaxis.

This study also demonstrated that in patients with mild-to-moderate hypertension, there is a dose-response relation with fosinopril treatment, up to a dose of 40 mg/day. Significant reductions from baseline occurred with 10–80 mg/day fosinopril (p<0.05 compared with baseline). Although the results with the 10 mg dose fosinopril in this study were not consistently different from placebo for all parameters, significant antihypertensive effects of fosinopril (compared with placebo) have been reported with this dosage in other trials, which suggests that 10 mg is effective in some patients and may be a reasonable starting dose for most patients.

Adverse drug experiences were generally mild and transient and did not appear to be dose-related. There was no appreciable difference in the incidence of adverse drug experiences between patients treated with fosinopril and patients who received placebo. Within 24 hours after the initial dose, one patient in the placebo and the 10- and 40-mg fosinopril treatment groups and two patients in the 80-mg group reported dizziness/lightheadedness. During week 1 of monotherapy, mild dizziness was reported by one patient in the 10-mg fosinopril group and by two patients in the 80-mg fosinopril group. These complaints, which have been reported with other ACE inhibitors, as well, occur more commonly when these agents are administered to patients with renin-dependent hypertension or those maintained on a low salt diet. In the present study, the intravascular volume status of the patients with these complaints was not recorded. Each patient recovered without sequelae and did not report any additional occurrences during continued treatment with fosinopril.

No patient who received fosinopril withdrew from the short-term segment of the study. In the long-term segment of the study, the discontinuation rate from fosinopril treatment, secondary to adverse drug experiences, was nine in 148 (6.1%) and is comparable with the incidence associated with other ACE inhibitors.

Serum potassium decreased slightly in patients who received chlorthalidone. The average decrease in serum potassium concentration was greater among patients receiving placebo or 10 mg fosinopril daily than in patients treated with 40 or 80 mg fosinopril daily. This suggests that the higher doses of fosinopril might have exerted a mild blunting effect on the kaliuresis induced by chlorthalidone. This action of fosinopril resembles that of other ACE inhibitors and is probably related to the suppression of aldosterone levels. During the long-term segment of the study, only moderate elevations in liver function test values in two patients were observed.

On the basis of the data we are reporting and the published results of clinical trials, fosinopril with or without chlorthalidone is a safe and effective treatment for mild-to-moderate essential hypertension.

References

KEY WORDS • essential hypertension • fosinopril • angiotensin converting enzyme inhibitors • diuretic therapy
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