Double-Blind Comparison of Captopril and Enalapril in Mild to Moderate Hypertension

PETER H. VLASSES, PHARMD, DALE P. CONNER, PHARM D, HESCHI H. ROTMENSCH, MD, RICHARD J. FRUNCILLO, MD, PhD, JANICE R. DANZEISEN, RN, KENNETH J. SHEPLEY, BS, ROGER K. FERGUSON, MD, FACC

Philadelphia, Pennsylvania

To compare the antihypertensive and humoral effects of the angiotensin-converting enzyme inhibitors captopril and enalapril, 20 patients with essential hypertension, not receiving treatment for 2 weeks and consuming a prescribed sodium ion intake, were randomly assigned to two parallel, double-blind treatment groups with stratification based on race and untreated seated diastolic blood pressure. These groups received a placebo (day -1) followed by either captopril, 200 mg every 12 hours (n = 9), or enalapril maleate, 20 mg every 12 hours (n = 11), alone (days 1 to 14) and then with hydrochlorothiazide, 25 mg every 12 hours (days 16 to 28). Captopril and enalapril were coadministered alone (day 15) and with hydrochlorothiazide (day 29) to assess whether further decreases in blood pressure would occur. Captopril and enalapril alone caused comparable decreases (p < 0.05) in the mean 12 hour time-averaged seated diastolic blood pressure from values on day -1 (placebo), on day 1 (11 and 9 mm Hg, respectively) and day 14 (8 and 7 mm Hg, respectively). The addition of hydrochlorothiazide further decreased (p < 0.05) blood pressure in each group (7 and 8 mm Hg, respectively) from values on day 14. Combined use of captopril and enalapril did not result in further reduction.

Coupled with the comparable changes observed in each treatment group in serum angiotensin-converting enzyme activity, plasma renin activity and plasma aldosterone concentration, these data support the view that captopril and enalapril have similar antihypertensive effects and mechanisms.

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Angiotensin-converting enzyme inhibitors are a new class of antihypertensive agents. Captopril, the first orally active agent in this class, was marketed in the United States in 1981. Enalapril (MK-421), a more potent orally active converting enzyme inhibitor, will soon be marketed in the United States (1). Enalapril differs structurally from captopril by the absence of a mercapto or sulfhydryl group. This chemical group, although initially deemed necessary for adequate converting enzyme inhibition, has been suggested to have a causal role in some of the adverse effects of captopril (2).

Although captopril and enalapril clearly inhibit angiotensin-converting enzyme, the precise mechanisms responsible for their blood-pressure-lowering effects are controversial (1-3). Other activities that have been suggested to contribute include the potentiation of kinins, alterations in vasoactive prostaglandins and an interaction with the sympathetic nervous system through the decrease in angiotensin II formation. It has also been suggested (3) that inhibition of converting enzyme in various tissues, such as arteriolar vessel walls, may be of more importance than inhibition of the circulating enzyme.

Investigators have wondered whether captopril and enalapril might differ not only in potency but also in their antihypertensive effects as a result of dissimilarities in ancillary properties or tissue penetration, or both. Comparative studies in animals (4-10) have suggested either comparable effects or potential differences in the blood-pressure-lowering or other actions of these agents. A difference between the effects of these agents on vasoactive prostaglandins in humans was noted by the same laboratory (11,12). Third et al. (13) recently reported that in a double-blind parallel study of enalapril and captopril in 32 patients with moderate to severe hypertension receiving hydrochlorothiazide, enalapril was somewhat more effective than captopril in lowering blood pressure, acutely and chronically. In con-
trast, Lewis et al. (14), in 24 hypertensive patients treated with hydrochlorothiazide in a trial of nearly identical design, reported that captopril was more effective than enalapril in the short term, but the two agents had comparable blood pressure-lowering effects after long-term treatment. Moreover, Chrysant et al. (15) noted no difference between these agents in 20 hypertensive patients studied under a similar protocol.

The purpose of this study was to compare the antihypertensive effects of captopril and enalapril, both alone and in combination with a thiazide diuretic agent, in patients with mild to moderate essential hypertension. To assess possible mechanistic differences, doses of captopril and enalapril near the upper recommended ranges were selected, and the agents were coadministered to determine whether a further decrease in blood pressure would occur.

**Methods**

**Patients.** Twenty patients with essential hypertension and normal renal function qualified to participate in the study. These patients were recruited from our hypertension clinic population, on a sequential basis, if they were: 1) previously shown to be hypertensive (seated diastolic pressure >95 mm Hg) while not receiving medications; 2) in otherwise good health based on their medical history, physical examination, electrocardiogram and laboratory organ function test evaluations; and 3) willing to participate in the study after a careful explanation of its purpose and their requested time commitment. All patients who volunteered gave written consent to participate after the trial was approved by the Jefferson University Institutional Review Board.

**Trial design (Fig. 1).** All patients entered an initial 2 week no drug period. During this time, they were instructed on a "no added salt" diet. Urinary excretion was monitored to exclude marked sodium restriction or excessive consumption. On study day -1, patients were admitted to the clinical pharmacology unit at 8 AM, having fasted from the previous evening. An intravenous catheter was placed in an arm vein to allow blood sampling for humoral measurements. Approximately 1 hour later, baseline determinations of supine and seated blood pressure and pulse rate were determined. For the purpose of objectivity and elimination of observer variation and fatigue, this and all other blood pressure and pulse rate measurements were made by a stationary, automated device that uses the Doppler principle (DINAMAP, Critikon, Inc.). In a single-blind manner, patients then received a placebo while fasting, and had blood pressure and pulse rate determined hourly for 12 hours. Food was withheld for 3 hours after dosing. The frequent evaluations were undertaken to minimize the effect of the known hour to hour within-subject variability in blood pressure on the assessment of overall treatment effects. Blood samples for determination of serum angiotensin-converting enzyme activity, plasma renin activity and aldosterone concentration were collected, after the patients had been seated for at least 30 minutes, before dosing and at 1, 4, 8 and 12 hours after dosing; blood samples were assayed at the completion of the trial. Urine was collected for 24 hours after placebo administration in two 12 hour fractions.

At the end of the placebo day, the average seated diastolic blood pressure from 1 to 12 hours after dosing, that is, the mean of 12 separate readings, was computed for each patient. Patients continued on to the captopril/enalapril comparison (Fig. 1) if this mean value was between 94 and 120 mm Hg. Because other investigators had suggested that the antihypertensive response of converting enzyme inhibitors might vary between black and white patients (16) or as a function of the level of the initial untreated blood pressure (17), patients were allocated study medications in a randomized, double-blind manner to allow stratification for both of these variables into two comparable, parallel treatment groups.

Figure 1. Study protocol. Refer to text for doses. Cap = captopril; Enal = enalapril; HCTZ = hydrochlorothiazide; PL = placebo.
Table 1 depicts the demographic characteristics of the two treatment groups (C for the group initially receiving captopril and E for the one initially receiving enalapril). In general, the groups were well matched except for sex; however, this variable has not been noted to be a determinant of the blood pressure response to converting enzyme inhibitors. The unequal number of subjects in the two treatment groups was the result of the stratification procedure. One patient in group E was eliminated from the study on day 25 and one patient in group C did not participate on day 29 because of an excessive decrease in blood pressure (see Results section, Adverse effects). The data from these patients were included for comparisons before these days.

The treatment sequences are shown in Figure 1. Each group received one of the converting enzyme inhibitors alone for 14 days, with inpatient evaluations and collection of study data similar to the placebo day (day − 1) on the first and last day of monotherapy (days 1 and 14). The doses of captopril (200 mg every 12 hours) and enalapril maleate (20 mg every 12 hours) were selected to approximate the maximal daily dosage recommended by the respective manufacturers. This was done to minimize the effects of the known potency difference between the two compounds in the efficacy comparison. All doses were prescribed for use on an “empty stomach." On study day 15, also an inpatient evaluation day, the other converting enzyme inhibitor was coadministered with the agent that the patient had been receiving; that is, the patients received both converting enzyme inhibitors, to test whether an additional hypotensive effect could be elicited.

From day 16 to day 28, the patients received their original converting enzyme inhibitor in combination with hydrochlorothiazide, 25 mg every 12 hours, with an inpatient evaluation on the last day of treatment. A few patients were allowed to proceed to the diuretic phase even if the mean seated diastolic pressure was somewhat below 90 mm Hg (and they, thus, might not have received the drug under clinical circumstances), to allow the pharmacologic assessment of the hypotensive activity of each converting enzyme inhibitor with the diuretic agent. On the next inpatient day (day 29), each subject received his or her original converting enzyme inhibitor, hydrochlorothiazide and a single dose of the other converting enzyme inhibitor to again test whether an additional hypotensive effect could be elicited.

Patients were carefully evaluated during the study for drug-related side effects or changes in laboratory screening tests. Medication diaries, pill counts and retrospective evaluation of serum angiotensin-converting enzyme activity were used to assess compliance.

Analyses. Plasma renin activity at pH 7.4 (Roche Diagnostics) and plasma aldosterone concentrations (Abbott Laboratories) were measured by radioimmunoassay methods. Angiotensin-converting enzyme activity was measured based on the percent of a known quantity of radiolabeled substrate (1H)-hippuryl-glycyl-glycine which was hydrolyzed in the presence of a known volume of a patient’s serum per unit time (18). Sodium metabisulfite (50 μl of a 5% solution) was added to all blood samples for converting enzyme activity determinations to prevent degradation of captopril. Interassay variation was assessed daily using plasma or serum from normal subjects. Serum and urine electrolyte concentrations were determined by flame photometry.

Statistical analysis. The overall treatment effect for each group during the dosing interval on each inpatient study day was characterized by calculating the mean of each patient’s time-averaged 1 to 12 hour seated systolic and diastolic blood pressures and pulse rate. Within each treatment group separately, the differences in the means of these variables between study days were assessed using an analysis of variance procedure. The statistical model employed partitioned the error term to evaluate the effects of day (differences between study days during each treatment sequence), race, day \times race interaction and subjects. If day (that is, treatment regimen differences on a given day [Fig. 1]) effects were significant, Duncan’s multiple range test was used to compare mean values by day in each treatment sequence. The differences between treatment groups for each study day were assessed by unpaired Student’s \( t \) tests. When significant differences in mean time-averaged diastolic blood pressures either within or between the randomized treatment regimens were not observed, the differences that could have been detected with 80% power based on a \( t \) distribution were calculated.

Statistical analysis of the humoral values was performed in a similar manner with the exception that, because of the unequal blood collection intervals, the average value for a patient on a treatment day was assessed by calculating the area under the respective variable time curve and dividing

| Race (no. of patients) | | |
|------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                        | C (captopril sequence) | E (enalapril sequence) |
| No of patients         | 9                | 11              |
| Age (yr)               |                  |                 |
| Mean (± SD)            | 47 ± 8           | 54 ± 9          |
| Range                  | 39 to 61         | 42 to 64        |
| Sex                    |                  |                 |
| Female                 | 5                | 1               |
| Male                   | 4                | 10              |
| Time (1 to 12 hour)-Averaged Seated Diastolic Blood Pressure on Placebo Day (mm Hg) | | |
|                        | 94 to 105        | 106 to 120      | 94 to 105       | 106 to 120      |
by the time interval. The relations between the acute (day 1) and chronic (day 14) blood pressure responses in each treatment group and various study variables (for example, pretreatment blood pressure and plasma renin activity) were evaluated by linear regression analysis. All statistical evaluations were made using a computer software package (Statistical Analysis Systems). Data are presented as the mean ± SD. All statistical tests were two-tailed and evaluated at a probability (p) of less than 0.05 level of significance.

Results

Blood pressure. The means (± SD) of the time-averaged systolic and diastolic pressures for each treatment group on each inpatient study day are depicted in Figure 2. The two treatment groups were well matched with regard to seated diastolic pressures on day -1 (placebo day): group C (captopril sequence) 101 ± 6 mm Hg versus group E (enalapril sequence) 102 ± 8 mm Hg (p = 0.78). Systolic pressure was higher in group E than in group C but this difference was not quite significant (p = 0.08). The remainder of the Results section will only address effects on diastolic blood pressure.

Both captopril and enalapril alone lowered mean time-averaged, seated diastolic blood pressure on days 1 and 14 in comparison with day -1 (placebo). Values on day 1 (group C 90 ± 9 mm Hg versus group E 93 ± 9 mm Hg) and day 14 (group C 93 ± 8 mm Hg versus group E 95 ± 10 mm Hg) within and between groups were comparable. The t test comparing the mean diastolic pressure on captopril or enalapril on day 14 could detect a 12 mm Hg difference with 80% power.

Comparison of the time course of the hourly mean blood pressure values for each group on study days -1 and 1 (data not shown) revealed that both agents had a prompt onset of action with a duration that extended throughout the 12 hour dosing interval. Both onset of effect (1 versus 2 hours) and maximal effect (2 versus 3 hours) were achieved slightly earlier with captopril than with enalapril. Comparison of the time-averaged seated diastolic blood pressure for individuals receiving placebo (day -1) versus their values on the last day of monotherapy (day 14) revealed that 7 of 9 patients in group C (captopril sequence) and 7 of 11 patients in group E (enalapril sequence) had at least a decrease in mean time-averaged blood pressure of 5 mm Hg greater than the placebo response.

Combined administration of captopril and enalapril on day 15 did not decrease mean time-averaged seated diastolic pressure significantly from values observed on day 14: group C 93 ± 8 versus 91 ± 9 mm Hg, respectively, and group E 95 ± 10 versus 92 ± 11 mm Hg, respectively. Differences of 8 mm Hg (group C) and 9 mm Hg (group E) could be detected with 80% power for a paired comparison of the day 14 versus day 15 response.

The addition of hydrochlorothiazide (Fig. 2) resulted in significant further decreases in mean time-averaged seated diastolic pressure within each group on day 28 (group C 86 ± 12 mm Hg versus group E 87 ± 10 mm Hg), but differences between groups on this day were not statistically significant.

With converting enzyme inhibitor plus diuretic therapy (day 28), 6 of 9 patients in group C and 7 of 10 patients in group E had time-averaged seated diastolic pressures less than 90 mm Hg. On day 29, when both converting enzyme inhibitors and hydrochlorothiazide were coadministered, the mean time-averaged seated diastolic pressure was similar for group C (82 ± 9 mm Hg) and for group E (82 ± 9 mm Hg).
mm Hg). From day 28 to 29 within groups, however, seated diastolic blood pressure was significantly decreased in group E (p < 0.05) and nearly as decreased for group C.

Heart rate. There were no significant changes in the mean time-averaged seated pulse rates on days −1, 1, 14 or 15 within either treatment group. The respective mean values (beats/min) in group C (captopril sequence) were 69, 68, 69 and 70 whereas those in group E (enalapril sequence) were 67, 68, 68 and 70. Addition of hydrochlorothiazide (days 28 and 29) resulted in small (6 to 11 beats/min) but significant (p < 0.05) increases in mean pulse rate from day −1 in each group.

Laboratory values. After dietary counseling, mean sodium excretion on day −1 was 86 mEq in group C and 125 mEq in group E; these values were not quite significantly different and, overall, reflected compliance with the dietary prescription. Sodium excretion on day 1 in both groups was nearly identical to day −1 values but was somewhat increased, although not significantly, on days 14 and 15. On day 28, after 13 days of combined converting enzyme inhibitor plus hydrochlorothiazide treatment, mean urinary sodium excretion was 169 mEq in group C and 192 mEq in group E. Because urine was collected for only 12 hours on day 29, evaluation of mean 12 hour (9 AM to 9 PM) urine collections on days 28 and 29 revealed sodium values of 104 and 77 mEq for group C (NS) and 105 and 66 mEq for group E (p < 0.05). Mean serum potassium did not change significantly from day −1 to days 1, 14 and 28 in either group; values in group C were 4.0, 4.2, 4.1 and 3.9 mEq/liter whereas those in group E were 4.2, 4.3, 4.2 and 4.0 mEq/liter.

The values for mean (± SD) time-averaged serum angiotensin-converting enzyme activity, plasma renin activity and plasma aldosterone concentration for each treatment group are depicted in Figure 3. On day −1 (placebo), mean angiotensin-converting enzyme activity (Fig. 3, top panel) was somewhat greater in group C than in group E (p = 0.16). In comparison with the placebo day, both captopril and enalapril markedly suppressed mean converting enzyme activity on all subsequent days. No significant difference was observed between the two treatment sequences on any day.

Mean time-averaged plasma renin activity (Fig. 3, middle panel) increased slightly though not significantly after both captopril and enalapril alone (days 1 and 14 in each group) versus placebo (day −1). No significant change from day 14 was observed on day 15 (combined converting enzyme inhibitor administration) in either group. Addition of hydrochlorothiazide resulted in a marked increase (p < 0.05 from all other days) in mean plasma renin activity in both groups on days 28 and 29; no significant change was observed in either group when the alternate converting enzyme inhibitor was added to double therapy of converting enzyme inhibitor plus hydrochlorothiazide (day 28 to day 29).

Mean time-averaged plasma aldosterone concentration on day −1 (placebo) (Fig. 3, bottom panel) was greater in group C than in group E. Both captopril and enalapril tended to decrease mean plasma aldosterone concentration on days 1, 14 and 15 in comparison with their respective placebo days, although the changes did not always achieve statistical significance. No significant change in either group was seen with the addition of the alternate converting enzyme inhibitor to chronic monotherapy. After the addition of hydrochlorothiazide, mean aldosterone values increased to the respective baseline (day −1) on days 28 and 29 in group C and somewhat above the baseline (p < 0.05) in group E.

Adverse effects. In group C (captopril sequence), one patient developed a marked alteration in taste sensation on day 20 of the study while receiving captopril and hydrochlorothiazide. The patient continued in the study through day 28 and the taste alteration persisted. She was excluded from day 29 because of low blood pressure (124/64 mm Hg) and light-headedness on day 28. The taste disturbance dissipated slowly after drug discontinuation. Another patient in group C developed dizziness, weakness and hypotension on day 29 for a 6 hour period. In group E (enalapril sequence), one patient complained of light-headedness for a short period of time, 2 to 3 hours after dosing, on both days 14 and 15; this was not accompanied by profound hypotension. One patient, a black woman, was eliminated from the study because of hypotension while receiving enalapril and hydrochlorothiazide. She had a marked response to enalapril on day 1 (from a mean time-averaged seated diastolic blood pressure of 110 mm Hg with placebo to 86 mm Hg with enalapril). By day 14, however, her blood pressure had returned to near baseline (106 mm Hg) and her urinary sodium excretion had increased by 50 mEq from day −1 and day 1 values. The addition of captopril on day 15 did not result in a further decrease in blood pressure (mean 106 mm Hg). With the addition of hydrochlorothiazide, the patient developed marked dizziness, diaphoresis and nausea on day 18 (3 days of combined treatment) and her blood pressure was 86/50 mm Hg. Her drugs were withheld for 2 days during which time her blood pressure returned to baseline values and treatment with enalapril and hydrochlorothiazide was restarted. Four days later (day 25), she again developed dizziness, nausea and hypotension and was withdrawn from the study.

No significant changes in laboratory screening tests for organ function were observed during the study. No treatment-related changes in white blood cell counts or urinary protein were observed in these patients with normal renal function during the month of converting enzyme inhibitor treatment.

Response predictors. The analysis of variance procedures in both groups C (captopril) and E (enalapril) identified a significant racial effect in mean seated diastolic blood
Figure 3. Mean (+ 1 SD) serum angiotensin-converting enzyme (ACE) activity (A), plasma renin activity (B) and plasma aldosterone concentration (C) on inpatient study days in group C (captopril sequence, closed bars) and group E (enalapril sequence, open bars). Within group comparisons, p < 0.05 for: * = from day -1 (placebo); † = from days -1, 1, 14 and 15; and ‡ = from day 28.
Converting enzyme inhibitors in this study. Other factors that were either poor or inconsistent individual predictors of acute or chronic blood pressure response in both groups were pretreatment plasma renin activity, change in plasma renin activity from pretreatment, pretreatment plasma aldosterone concentration and change in plasma aldosterone concentration from pretreatment.

**Discussion**

Before entry into this double-blind randomized study, the 20 hypertensive patients with normal renal function were classified into a treatment group (captopril or enalapril) according to the degree of their blood pressure elevation and their race, because these factors had been identified by others (16,17) as possibly influencing a comparison of drug effects. Before the study, moderate sodium intake was prescribed and complied with based on evaluations of urinary sodium excretion. The doses were purposely selected near the upper recommended ranges for the two oral converting enzyme inhibitors to minimize differences in effects due strictly to dissimilar potencies. Comparable blood pressure reduction might have been achieved with lower doses of both agents. Although enalapril has been given once daily in patients with hypertension (2), some patients require twice daily dosing and, for this reason, twice daily dosing was selected for our protocol.

**Antihypertensive effects.** Under these study conditions, no clinically or statistically significant differences between the antihypertensive effects of captopril and enalapril were apparent. On day 14, both agents decreased mean seated diastolic blood pressure by 7 or 8 mm Hg from the value with placebo in their respective group. No additional decrease in blood pressure was observed when a single dose of enalapril was added after chronic captopril therapy or vice versa (day 15), suggesting that these agents may have a similar mechanism of action. Because the acute and chronic hypotensive effects of these agents were similar, it is unlikely that continued administration of these agents in combination would have resulted in a further decrease in blood pressure. When captopril or enalapril was combined with hydrochlorothiazide, however, a further decrease in blood pressure was achieved in each group; the effect of this combination therapy in each group was comparable (that is, an additional 7 to 8 mm Hg decrease in mean seated diastolic blood pressure in each group by day 28). Finally, after the alternate converting enzyme inhibitor was added to either combination (converting enzyme inhibitor plus diuretic agent), there was no difference in the antihypertensive response between the two groups of patients, although there was a further decrease in blood pressure compared with the blood pressure measured with each drug regimen alone. This further decrease in blood pressure on day 29 merits further consideration.

**Role of sodium intake and excretion.** The hypotensive response to the angiotensin-converting enzyme inhibitors is dependent on the sodium and volume status of the patient (12,19). On study days -1, 1, 14 and 15, the subjects had similar 24 hour urinary excretion, indicating moderation in their sodium intake and no notable natriuresis. When our patients were studied in the clinical pharmacology unit, they were given a sodium-restricted diet. After beginning diuretic treatment, urinary sodium excretion increased markedly and remained increased before readmission to the unit on day 28. On the basis of other trials (20) with diuretic drugs we have undertaken in which sodium consumption was monitored, this increase in sodium excretion after 12 days of combination therapy was thought to be, in large part, a reflection of increased sodium intake rather than continued diuretic-induced natriuresis. In the unit, the patients were again placed on a prescribed diet for 2 days, which resulted in a marked decrease in sodium excretion on day 29 in comparison with the same period on day 28. This change in sodium intake probably accounted for the additional decrease in blood pressure observed on this day (day 29) on addition of the alternate converting enzyme inhibitor in each group. This explanation is more plausible than a mechanistic difference existing between these agents that was only manifested when the patients were receiving a diuretic drug, and it further demonstrates the ability of increased sodium intake to counteract the antihypertensive effect of converting enzyme inhibitors (12,19). This was also evident by evaluation of the urinary sodium excretion in the black woman in group E who initially had a marked decrease in blood pressure in response to enalapril with a return to near baseline value by day 14, only to have hypotension develop when diuretic treatment was added.

Captopril versus enalapril: animal studies. Mechanistic differences between captopril and enalapril have previously been postulated, mainly on the basis of animal studies (4-10). In the spontaneously hypertensive rat, enalapril (MK-421) was more potent than captopril in decreasing blood pressure, yet equally active in its ability to block angiotensin I pressor responses (4). In the pithed spontaneously hypertensive rat, captopril significantly inhibited pressor responses to sympathetic nerve stimulation and noradrenaline, whereas enalapril did not (5). Because both drugs were antihypertensive in this rat model, it was suggested that only captopril was interfering with sympathetic responses. Such differences in the antihypertensive activity...
of the converting enzyme inhibitors in animals has been proposed (5) to result from differential penetration and inhibition of converting enzyme activity in the arterial vascular wall as opposed to the serum alone. This hypothesis appeared to be confirmed in intact spontaneously hypertensive rats and in the isolated perfused kidney, where captopril abolished vascular responsiveness to norepinephrine in the renal artery to a much greater extent than did enalapril (6,8,9). Differences in potency among converting enzyme inhibitors in pressor responses to infusion of angiotensin I also have been reported (10) in the conscious spontaneously hypertensive rat, even though their hypotensive effect was similar. On the other hand, in normotensive men both captopril and enalapril were equally effective in blocking pressor responses to exogenous angiotensin I, although with a different milligram potency (20).

**Captopril versus enalapril: human studies.** In a double-blind, parallel comparison study of 32 patients receiving hydrochlorothiazide, 50 mg/day, Thind et al. (13) recently reported that enalapril, 5 to 20 mg twice daily, was superior to captopril, 25 to 100 mg three times daily, in decreasing supine and upright diastolic blood pressure. These findings are in contrast to those of our study. The study of Thind et al. can be criticized because 1) the investigators did not specify at what time blood pressure measurements were made in relation to the previous dose; 2) no evaluation of dietary sodium intake was made, which could have led to apparent treatment differences; 3) more patients in the enalapril group than in the captopril group were hypokalemic on treatment with hydrochlorothiazide alone (n = 5 and n = 1, respectively), perhaps indicating a greater stimulation of the renin-angiotensin-aldosterone system in this group, which could affect the response to converting enzyme inhibition; and 4) there was no assessment of biochemical correlates of the blood pressure response, as performed in our study.

In contrast, Lewis et al. (14), in a very similar study, reported a greater initial response with captopril than with enalapril added to hydrochlorothiazide but reported equivalent efficacy with more prolonged treatment. Moreover, Chrysant et al. (15) noted no difference between these agents in 20 patients studied under essentially the same protocol. Furthermore, in a review article on enalapril, Davies et al. (22) discussed an unpublished, large-scale, comparative trial in 161 patients with supine diastolic blood pressures of 100 to 120 mm Hg initially treated with 50 mg/day of hydrochlorothiazide. Doses of enalapril in this study were 10 to 40 mg/day, whereas those of captopril were 75 to 300 mg/day, which is similar to the doses in the studies of Thind (13), Lewis (14), Chrysant (15) and coworkers. The results reported by Davies et al. indicate that captopril and enalapril produced very similar and not significantly different antihypertensive effects in combination with hydrochlorothiazide. On the basis of the similarity of the reported study designs, it appears that the study groups of Thind (13), Lewis (14), Chrysant (15) and coworkers were subgroups of the larger study (21) and that the reported differences were not confirmed by total group analysis. Our data on day 28 (hydrochlorothiazide plus angiotensin-converting enzyme inhibitor) agree with those reported by Davies et al. (22). In addition, our trial evaluated these agents as monotherapy and also found no apparent differences in efficacy.

**Factors affecting hypotensive response to either agent.** Thus, despite results suggesting mechanistic differences in animal and human studies, on the basis of our study captopril and enalapril appear to be equally effective in decreasing blood pressure in hypertensive patients as long as maximal inhibition of serum angiotensin-converting enzyme activity is achieved. In this regard, our own initial suggestion, based on a retrospective comparison (23,24), that these agents may have dissimilar antihypertensive activity in humans was more than likely due to differences in converting enzyme inhibitor potency or the sodium status of the patients. Control of these variables led to a more precise evaluation of drug effects in the present study.

Our study also suggests no essential difference in the mechanism (or mechanisms) by which captopril and enalapril decrease the blood pressure. This conclusion is further substantiated by their similar effects on serum converting enzyme and plasma renin activities and plasma aldosterone concentrations, whether alone or in combination with a diuretic agent. The observed changes are compatible with those noted to occur with converting enzyme inhibitors (1,2). In addition to indicating similar effects of the two inhibitors, our data, as well as those of others (25), support two general concepts about these agents. One is that maximal suppression of the renin-angiotensin system, through inhibition of serum angiotensin-converting enzyme, corresponds with the maximal antihypertensive effect of the inhibitors. Second, if other mechanisms are involved in the antihypertensive effect of the angiotensin-converting enzyme inhibitors, they are probably secondary effects. For example, a decrease in angiotensin II concentrations by captopril could thereby have produced decreased vascular responsiveness to endogenous norepinephrine (26,27).

**Other findings.** Additional aspects of our study are worthy of note. As expected, heart rate did not change after treatment with either converting enzyme inhibitor. The increases noted on days 28 and 29 were those commonly observed with diuretic agents alone. There was an overall statistical difference in the antihypertensive effect of the converting enzyme inhibitors in the black as compared with the white patients, compatible with our prestudy assumption (16). Pretreatment plasma renin activity, however, was not predictive of the magnitude of the hypotensive response to either converting enzyme inhibitor. In this regard, the sodium and volume status of black patients may be a more important factor than the level of plasma renin activity. In
contrast to data in a previous report (17), the level of pre-
treatment blood pressure did not correlate with the magni-
tude of blood pressure reduction after administration of either
converting enzyme inhibitor and diuretic treatment, suggesting potas-
sium-sparing effects of this combination, similar to our pre-
vious findings (23). Finally, the changes in plasma renin activity
and plasma aldosterone concentrations from pre-
treatment values after the two converting enzyme inhibitors
were administered did not correlate well with their anti-
hypertensive effects, suggesting that other factors affecting
these biochemical indexes make them less than desirable in
evaluating the effectiveness of these agents.

Conclusions. We found that captopril, 200 mg twice
daily, and enalapril, 20 mg twice daily, decreased blood
pressure to a comparable degree in patients with mild to
moderate essential hypertension. This was true whether the
agents were used alone or in combination with hydrochloro-
thiazide. Combining captopril and enalapril did not result
in a further decrease in blood pressure. There was a greater
blood pressure reduction in white than in black patients with
the converting enzyme inhibitors. The apparent lack of dif-
fences in blood pressure effect was paralleled by similar
changes in measured humoral factors after administration
of either drug. Both drugs were well tolerated. Although
there were a few more side effects (for example, loss of
taste) with captopril than with enalapril, careful interpri-
tation of these results is suggested because of the small
sample size, the low incidence of adverse effects and the
absence of renal dysfunction, which has been implicated as
a risk factor for captopril side effects (1). Finally, large
scale trials would not be expected to show significant dif-
fences between the efficacy of these two converting en-
zyme inhibitors used either alone or in combination with
hydrochlorothiazide.

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