Monotherapy of Essential Hypertension with a Converting-Enzyme Inhibitor

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SUMMARY The antihypertensive effectiveness of twice-daily dosing with the converting enzyme inhibitor, captopril, was examined in a multicenter study of 294 patients (181 white, 111 black, two oriental) with essential hypertension whose supine diastolic blood pressure (SDBP) was 95 mm Hg or higher after 4 to 6 weeks of preliminary placebo administration. In this double-blind study, the patients were randomized into one placebo and three captopril-treated groups: twice-daily placebo (n = 77) or twice-daily captopril 25 mg (n = 77), 50 mg (n = 71), or 100 mg (n = 69). The average decreases in SDBP after 8 weeks of treatment were 5.2%, 7.7%, 11.7%, and 10.5%, respectively. Only the two higher dose groups differed significantly from the placebo group; they also differed from the lowest dose group. The proportions of patients classified as having normalized pressures (SDBP < 90 mm Hg) in the four groups were 39%, 47%, 70%, and 50%. If the results were analyzed by race, all three captopril-treated groups differed significantly from the placebo-treated group in the white patients but not in the black patients. However, direct comparisons between the white and black groups showed a difference only at the low, 25 mg twice daily (b.i.d.), captopril dose. Thus, although conventionally given on a three-times daily basis, the twice-daily (12-hourly) administration of captopril provides effective antihypertensive treatment in doses of 50 or 100 mg b.i.d. Moreover, white patients also exhibit a significant response to captopril at doses as low as 25 mg b.i.d. This simplified approach appears to provide convenient and effective treatment in patients with milder forms of essential hypertension. (Hypertension 5 (supp III): III-108-III-113, 1983)

KEY WORDS hypertension • captopril • converting enzyme inhibitor • monotherapy

MUCH attention has been paid to the need for finding effective and simple pharmacologic treatment for the large number of patients who have mild to moderate essential hypertension. An important factor in achieving this goal is to regard essential hypertension from a mechanistic standpoint so that appropriate and specific treatment can be applied to the individual patient. This approach has led to modifications of the standard stepped-care approach to the treatment of hypertension in which therapy is always initiated with a diuretic. A number of the newer classes of antihypertensive agents, including beta-blockers, centrally-acting agents, and converting enzyme inhibitors, have been shown to be effective as single agents (monotherapy), although they still may require combination with a diuretic for maximal effectiveness in some patients.

Another desired property of the modern antihypertensive agent is that it facilitates treatment compliance by minimizing adverse effects and by having a convenient dosage schedule. Patients with mild, asymptomatic hypertension clearly are more likely to adhere to their treatment if it does not require dosing three or four times daily.

Captopril, which decreases blood pressure by inhibition of converting enzyme and perhaps by other mechanisms as well, is effective in treating hypertension of all degrees of severity. Because of the importance of minimizing adverse treatment effects in patients with milder forms of hypertension, we have been particularly interested in the effectiveness and acceptability of captopril in such individuals. Thus, in this study we have evaluated captopril, given as single-drug therapy on a twice-daily basis, in patients with mild-to-moderate essential hypertension.

Methods

Patients

The study was performed at 18 separate centers throughout the United States (for list, see appendix). A total of 411 patients was enrolled for the study, but
several were excluded prior to the start of active treatment, as explained in the Results section. The study was performed in men and women, over the age of 18 years, in whom a diagnosis of essential hypertension had been made by the exclusion of secondary forms of hypertension utilizing conventional clinical and laboratory methods. At entry into the study, patients had diastolic blood pressures (measured in the supine posture) in the range 95 to 115 mm Hg. Patients were excluded from entry if they had recently experienced a myocardial infarction or stroke, had evidence for congestive heart failure, renal insufficiency (creatinine clearance < 50 ml/min), proteinuria of > 0.5 g/24 hr, or a white blood count of < 3500 mm$^3$. Subjects with significant gastrointestinal disease or liver dysfunction, any evidence for allergy, drug hypersensitivity, or connective tissue disease, as well as women who were pregnant or were likely to become so, were also excluded from participation. All patients signed informed consents appropriate to the rules and standards of the institutions at which the study was performed.

The study was divided into two phases: a placebo lead-in period of 4 to 6 weeks duration, and an active treatment period of 8 weeks duration. Before entering the placebo phase, all patients who had previously taken antihypertensive treatment were discontinued from treatment and were then started on captopril placebo tablets administered twice daily (each 12 hours). They were seen every 2 weeks thereafter for 8 weeks. If after 2 and 4 weeks of placebo treatment the diastolic treatment blood pressure remained in the range of 95 to 115 mm Hg (in the supine posture), the patients then entered the active treatment phase. However, if after 2 weeks of placebo the diastolic blood pressure was outside that range, the placebo phase was extended by a further 2 weeks so that the patient would have an opportunity of having a blood pressure level within the desired range on two consecutive biweekly visits. Those patients whose blood pressures did not meet this criterion were excluded from the study and did not enter the active treatment phase.

The active treatment phase consisted of double-blind parallel groups and utilized fixed doses of captopril. The patients were randomized into four separate groups: placebo twice daily; captopril 25 mg twice daily; captopril 50 mg twice daily; and captopril 100 mg twice daily. The patients were seen every 2 weeks during the 8 weeks of active treatment. They were encouraged to take their medications once every 12 hours. Patients were excluded from the study during the active treatment period if they experienced severe adverse drug reaction, had a decrease in white blood count to < 3000 mm$^3$, or had a supine diastolic blood pressure of greater than 115 mm Hg on two occasions, gave evidence for poor treatment compliance, or became pregnant. The criteria for determining the effectiveness of treatments are given in the Results section.

### Results

Of the 411 patients who entered the study, 117 were dropped from the study because of: 1) a decrease in blood pressure (supine diastolic blood pressure < 95 mm Hg) during the placebo run-in phase (66 patients); 2) poor compliance with treatment or voluntary discontinuation from the study (30 patients); and 3) adverse treatment effects, concurrent illness, excessive blood pressure (supine diastolic blood pressure > 115 mm Hg), or late discovery of violations of inclusion criteria (21 patients).

Table 1 gives the demographic composition of the patients randomized to each of the four treatment groups, and the average blood pressures measured at the end of the placebo run-in phase, which were used as the baseline values for determining any treatment-induced changes. There were no statistical differences among any of the four treatment groups in the demographic or baseline characteristics of their patients.

Figure 1 shows the changes in supine diastolic blood pressure (measured at 2-weekly intervals) in each of the four treatment groups during the 8-week active treatment phase. When patients in the placebo group were compared with patients in the groups receiving either 50 or 100 mg b.i.d. of captopril, there were significant differences at each point of observation. Patients receiving 25 mg b.i.d. of captopril, however, differed from those receiving placebo only after 4 and 6 weeks of treatment. Indeed, the blood pressure decrements in the higher dose groups were significantly greater than those in the 25 mg b.i.d. group during the last 4 weeks of treatment. For the purposes of this study, a favorable outcome of treatment was defined as a fall in supine diastolic blood pressure to less than 90 mm Hg or a reduction in supine diastolic blood pressure of at least 10%.

Figure 2 shows that after the full 8 weeks of treatment, 39% of patients in the placebo group experienced favorable outcomes, whereas 47% of the patients in the captopril 25 mg b.i.d. group, 70% of the patients in the captopril 50 mg b.i.d. group, and 50% of the patients in the captopril 100 mg b.i.d. group experienced favorable outcomes. There were clearly no differences between the patients receiving 50 mg b.i.d. or 100 mg b.i.d. of captopril either with regard to...
Mean percentage changes in supine diastolic blood pressures in four groups of hypertensive patients during eight weeks of treatment with placebo (black circle, n = 77) or with captopril in doses of 25 mg b.i.d. (open circle, n = 76), 50 mg b.i.d. (open square, n = 71), and 100 mg b.i.d. (black square, n = 68). * = significantly different from placebo; † = significantly different from captopril 25 mg b.i.d.

In the four treatment groups (placebo, captopril 25 mg b.i.d., 50 mg b.i.d., and 100 mg b.i.d.), the average decrease in supine diastolic blood pressure (percent change) after 8 weeks treatment was 5.2%, 7.7%, 11.7%, and 10.5%, respectively, which was not different from the change in systolic blood pressure of 1.4%, 4.9%, 9.2%, and 9.1%, respectively. The decrease in diastolic blood pressure measured in the standing position also was similar to those given (above) for the supine position, 3.6%, 6.3%, 10.0%, and 10.7%, respectively. The corresponding change in standing systolic blood pressures was 0.4%, 4.3%, 9.4%, and 8.3%.

In comparing treatment responses of white and black patients (fig. 3), the white patients experienced significant decreases in supine diastolic blood pressure at all three dosage levels of captopril compared with the placebo group (p < 0.05 at least). In contrast, there were no significant changes in the black patients when compared with placebo. In the treatment group receiving captopril 25 mg b.i.d., the response of the white patients was significantly greater (p < 0.05) than that in the black patients; however, there were no differences between the two racial groups at the higher treatment doses. After 8 weeks of treatment, the proportion of white individuals with favorable responses (for the four groups respectively) was 39%, 61%, 77%, and 55%; for black patients, the proportion of favorable responses was 38%, 22%, 61%, and 41%.

Figure 4 shows the responses to treatment of the three groups receiving captopril expressed as a function of time following the last dose administered. After 8 weeks of treatment, there was clearly no difference at any of the captopril dosage levels among blood pressures measured between 9 and 15 hours after the last dose of captopril and those measured at less than 9 hours after the last dose. The proportions of patients exhibiting favorable responses were similarly close: for the 25, 50, and 100 mg b.i.d. groups, favorable responses were 49%, 77%, and 43%, respectively, for blood pressures measured between 9 and 15 hours after the last dose, and 45%, 63%, and 55% for pressures measured less than 9 hours after the last dose.

In general, symptomatic adverse effects of treatment were not severe, and included headache, minor rashes, pruritis, sexual dysfunction, change in taste sensation, and dizziness. For the four treatment groups (placebo, captopril 25, 50, and 100 mg b.i.d.), the incidence of adverse effects was 18%, 14%, 23%, and 15%, respectively; the differences among these groups in the incidence of adverse effects were not significant. The incidence of discontinuation from the study because of these adverse effects was 2.4%, 2.4%, 3.9%, and 4%. In three patients (all black men, aged 40, 47 and 58 years) transitory leucopenia (white blood count < 3000/mm$^3$) occurred, but the white blood count returned to its pretreatment value in each case while the captopril therapy was being administered. Despite the normalization of the white blood count, the patients were discontinued from the study. It is also likely that, in one instance, the low white blood count might have been due to a laboratory error (the low value could not be confirmed on a subsequent test), while in another, the temporary decrease in white blood count appeared to be secondary to an acute viral episode. There was no evidence for decreases in renal function or for protein-
CAPTOPRIL IN HYPERTENSION/Drayer and Weber

CAPTOPRIL

25 MG  BIO  50 MG  BID  100 MG  BID

FIGURE 3. Mean percentage changes in supine diastolic blood pressures after 8 weeks of treatment in white and black hypertensive patients divided into four groups receiving placebo or captopril in doses of 25, 50, or 100 mg b.i.d.

Discussion

Although combination antihypertensive therapy has often been required in patients with more severe forms of hypertension, a large proportion of patients with mild to moderate essential hypertension have responded satisfactorily to well-selected monotherapy. It seems reasonable to assume that single-drug therapy is generally convenient and may be a factor in achieving patient compliance. Traditional treatment strategies have been based on the use of a diuretic as the first step in treatment; but in many individuals, drugs other than diuretics may be more effective as monotherapy in controlling the blood pressure. Moreover, there has been some recent concern that the use of diuretic agents may be associated with adverse cardiovascular effects that are possibly related to diuretic-induced changes in blood biochemistries.

This study has shown that captopril is an effective, well-tolerated form of monotherapy for patients with mild to moderate essential hypertension. At least half the patients who received captopril experienced a favorable outcome of treatment; that is, their diastolic blood pressures (measured in the supine position) were decreased to less than 90 mm Hg or fell by at least 10%. There was no orthostatic component to captopril's action, for blood pressure fell at least as much in the supine position as in the standing position. Moreover, the diastolic blood pressure was decreased to at least the same extent as the systolic blood pressure.

FIGURE 4. Mean percentage changes in supine diastolic blood pressures (shown separately for measurements obtained between 9 and 15 hours after the last captopril dose and for those obtained at less than 9 hours after the dose) in hypertensive patients receiving captopril in doses of 25, 50, or 100 mg b.i.d.
This finding is consistent with the idea that captopril works primarily by decreasing peripheral vascular resistance, presumably by suppression of the vasoconstrictor actions of angiotensin II.4

This study revealed an interesting dose-response relationship during captopril treatment in patients with mild to moderate hypertension. In the lowest dose of 25 mg twice daily, captopril appeared to be only slightly superior to placebo in changing blood pressure or in bringing about favorable therapeutic outcomes. When 50 mg was given twice daily, however, captopril appeared to be far more effective, bringing about blood pressure decrements that were significantly greater than those observed both in the placebo group and in those patients receiving the lower 25 mg twice daily dosage. The highest captopril dose of 100 mg twice daily did not appear to offer any superiority over the 50 mg twice daily dosage. These findings raise the possibility that the relationship between the dose of captopril and its antihypertensive effectiveness may not be a continuous one, but instead may reflect a threshold phenomenon. Thus, it could be argued that the nature of captopril's action is such that it requires a certain minimum dosage in order to bring about a meaningful therapeutic response; however, having reached this critical dosage, further increases do not appear to bring about additional antihypertensive effects. Nevertheless, it should be pointed out that the parallel groups design of this study did not allow the nature of captopril's dose-response relationships to be fully evaluated, for it was not possible to determine the effects of differing doses of captopril within individual patients.

The question of dosage was also of interest in comparing the differing effects of captopril in white and black hypertensive patients. Overall, the white patients appeared to exhibit better antihypertensive responses than the black patients, but the only clear difference between the two groups was at the lowest (25 mg twice daily) dosage level. Indeed, at the higher dosage levels, there was only a slight (and not significant) difference in the frequency of favorable treatment outcome between the two groups. Thus, it is possible that black patients require a somewhat higher dose of captopril in order to achieve a satisfactory antihypertensive response.

A factor that made interpretation of the low-dose captopril response difficult was the relatively strong placebo response observed among both the black and the white patients. Of interest, this occurred in patients who had already been subjected to a preliminary placebo run-in period during which a large number of placebo responders had already been excluded from entering the active phase of this study. This finding appears to have some broad implications for patients with mild hypertension, for it suggests that an important proportion of these individuals might exhibit delayed decreases in blood pressure to normal levels in the absence of active therapy.

A better response to captopril by white than by black patients could have been predicted by previous studies. It was shown that black patients exhibited a greater antihypertensive response than white patients to diuretic therapy, whereas white patients appeared to respond better to other types of antihypertensive agents.2,9 In a large Veterans Administration Cooperative Study9 with captopril, it was found that black patients, as in the present study, had poorer antihypertensive responses than white patients. Of interest, when diuretic treatment was added to the captopril in that study, the antihypertensive response to the combination was the same in the black patients as in the white patients.

An important goal of this study was to determine whether captopril is an effective antihypertensive agent when given on a twice-daily basis. Although conventionally administered on a three-times daily basis, some recent studies have indicated that twice daily captopril is also effective.11,12 This study confirms those conclusions, and indicates that even the actual timing of the twice daily dosage administration may not be critical. Although it had been intended that blood pressures in this study be measured 12 hours after the last dose of captopril, a relatively large number of blood pressures were actually measured at fewer than 9 hours after the last dose. There was no difference, however, between the blood pressures measured after the shorter or longer post-dosing periods at any of the dosage levels. Thus, while it could be conjectured that high doses of captopril might be required to sustain antihypertensive effectiveness during a full 12-hour period, we found that even comparatively low doses were effective when given on a twice-daily basis.

In earlier studies using captopril for the treatment of more severe forms of hypertension, the high doses used were sometimes associated with adverse effects such as changes in renal function (including proteinuria) or decreases in the white blood count. With the doses of captopril used in this present large-scale study, however, there were no instances of proteinuria or of deterioration in renal function. Although three patients experienced transient leucopenia, the relationship of this effect to the treatment was not clear. In each case, the white blood count returned to baseline values despite continuation of the captopril treatment. Moreover, the three patients concerned were all black men; it is well established that such individuals are susceptible to spontaneous episodes of relatively low white blood counts.13 Other adverse effects in this study tended to be of only mild or moderate severity, and necessitated discontinuation of treatment in less than 4% of the patients. There was no difference in the incidence of side-effects between patients receiving placebo therapy and those receiving captopril.

This multicenter cooperative study has documented that captopril represents an effective form of monotherapy in patients with hypertension of mild to moderate severity. This effect is accomplished by dosage levels as low as 50 mg twice daily; in white patients, even 25 mg twice daily may be effective. A higher captopril dose of 100 mg twice daily does not appear to have any advantage over 50 mg twice daily.
References


Discussion

Discussants: G. MacGregor M. Weber E. Freis

MacGregor: One of the problems of parallel group studies is to be sure that the groups are homogeneous for all variables. Can you, for instance, tell us that the renin levels were the same in each group? From your slides I wondered whether the effect of 25 mg of captopril in whites was different from 50 mg. Would not a randomized crossover study have been better?

Weber: That's a fair point. After a longer period of treatment, the low dose might be as effective as the high dose, particularly with the white patients. The 50 mg or even the 100 mg twice daily dose would probably be no more effective in controlling blood pressure than the 25 mg dose twice daily.

MacGregor: I did not understand your timing of the measurements after each dose. You didn’t take each patient and measure the blood pressure at 2, 4, 6, and 12 hours after the last dose, which may be a better way of demonstrating the duration of action.

Weber: We made the measurements when the patients happened to turn up for their appointments. But ultimately the best way of showing the duration of captopril’s action is by 24 hours of ambulatory monitoring — which is a study that we’re just about to undertake.

Freis: In a similar study, we found that 25 mg was as effective as 50, but we measured the blood pressure 2 to 3 hours after the dose, whereas you measured it later. This probably accounts for the reason why our results are different. The major influence of these smaller doses seems to be on the duration of the antihypertensive effect rather than on the maximum decrease.

Weber: I agree. To some extent there is a threshold phenomenon — and as long as you have a concentration of drug above a certain level, you will have an effective response.
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