

## COMPARISON OF CAPTOPRIL AND HYDROCHLOROTHIAZIDE ALONE AND IN COMBINATION IN MILD TO MODERATE ESSENTIAL HYPERTENSION

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1 A placebo-controlled, randomised double-blind comparison of captopril 25 mg three times a day, hydrochlorothiazide 15 mg three times a day, and the combination was conducted in 207 patients with essential hypertension with supine diastolic blood pressures of 92-110 mm Hg. Significant decreases in blood pressure were seen in all three groups; the magnitude of decrease seen with captopril and hydrochlorothiazide was similar, while the combination produced an additive response greater ( $p < 0.001$ ) than captopril or hydrochlorothiazide alone.

2 The major side effect reported was a rash in fewer than 6% of patients taking captopril alone or in combination. Loss of taste or proteinuria was not observed.

3 The addition of captopril to hydrochlorothiazide blunted the hypokalaemia and hyperuricaemia observed with hydrochlorothiazide alone in addition to its antihypertensive synergy. These observations indicate that this relatively low dose of captopril is safe and efficacious in the treatment of mild to moderate hypertension alone and particularly when combined with a thiazide diuretic.

### Introduction

Captopril, an orally effective angiotensin-converting-enzyme inhibitor is efficacious in treating severe hypertension (Bravo & Tarazi, 1979; Case *et al.*, 1978; Gavras *et al.*, 1978). In patients who are refractory to conventional multiple-agent antihypertensive treatment doses of captopril as high as 600 mg/day, often in addition to diuretics and  $\beta$ -adrenergic blocking drugs, are required to control blood pressure adequately (Havelka *et al.*, 1982; Raine & Ledingham, 1982; Weinberger, 1982). At such dose levels side effects such as pruritic rash, loss of taste, and proteinuria have been reported in some patients. While these side effects are generally transitory, even with continuation of the drug, they have none the less limited the widespread use of captopril in less severely hypertensive patients.

The present multicentre trial was designed to examine the efficacy and side effects of lower doses of captopril in milder forms of essential hypertension and to compare these effects to those of hydrochlorothiazide alone and in combination.

### Methods

These studies were performed by the 13 investigators listed in the appendix. All studies had been approved by the appropriate institutional review committee

and informed consent was obtained from each subject after explanation of the studies to be performed. All antihypertensive drugs were withdrawn 2 weeks before entry to the placebo phase (255 patients). Supine diastolic blood pressure was required to be  $\geq 92$  mm Hg and  $< 110$  mm Hg for entry. Patients with child-bearing potential, secondary forms of hypertension, recent history of myocardial infarct or cerebral vascular accident, significant renal dysfunction (creatinine clearance  $< 50$  ml/min; serum creatinine  $> 2.0$  mg/100 ml or urinary protein excretion  $> 0.5$  g/24 h), systemic lupus erythematosus, or significant hepatic dysfunction were excluded from study.

At the end of four weeks of placebo treatment 207 patients were entered into the active drug period (six weeks) if they had supine diastolic pressures of  $\geq 92$  mm Hg and  $\leq 110$  mm Hg on each of two biweekly visits and evidence of compliance (by pill counts) indicating ingestion of between 80% and 110% of predicted placebo tablets. Patients were randomly assigned to receive: captopril 25 mg three times a day plus hydrochlorothiazide 15 mg three times a day, captopril 25 mg three times a day plus placebo three times a day, or placebo three times a day plus hydrochlorothiazide 15 mg three times a day. A double-blind design was used for the six weeks of active treatment completed by 198 patients. Patients were evaluated every two weeks throughout the study. A complete

physical examination, chest radiography, and electrocardiography were performed on entry to the study and the physical examination and electrocardiogram were repeated on the last visit of the placebo and active treatment periods.

Patients were examined at three to eight hours after the last dose of drug. Body weight and temperature were recorded at each visit as well as pulse rate and systolic and diastolic blood pressure (Korotkoff 1 and 5) after five minutes of supine posture and again after three minutes of standing. Laboratory studies, including a complete blood count, urine analysis with quantitative 24-hr urine protein measurement, and routine blood chemistry estimations (albumin, alkaline phosphatase, bilirubin, blood urea nitrogen, calcium, chloride, cholesterol, carbon dioxide content, creatine phosphokinase, creatinine, glucose, lactic dehydrogenase, phosphorus, potassium, total protein, glutamic oxalacetic transaminase, glutamic pyruvic transaminase, sodium, triglycerides, and uric acid) were obtained at entry to the study, at the end of the placebo period, and every two weeks (complete blood count) or at the end of the active treatment period (urine studies, routine blood chemistry). Patients were withdrawn from the study because of a severe adverse reaction, an absolute neutrophil count of  $1 \times 10^9/l$ , at the patient's request, or on the judgment of the investigator.

Data were analysed in comparison to baseline (last placebo visit) using linear statistical models and Duncan's multiple range tests.  $\chi^2$  analyses were also used and statistical significance determined with Bonferroni critical values. Absolute and relative (%) changes were evaluated. Mean arterial pressure was calculated as diastolic pressure plus 1/3 (systolic-diastolic). The effect on supine diastolic blood pressure was also evaluated by classifying observations as: normal ( $< 90$  mm Hg and  $> 5\%$  decrease from baseline), response ( $> 90$  mm Hg and  $> 10\%$  decrease from baseline), and non-response ( $< 10\%$  decrease from baseline).

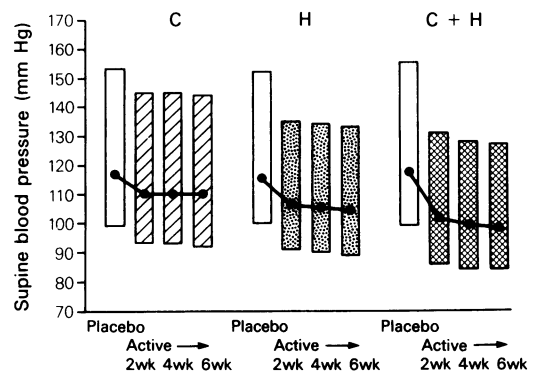
## Results

Of the 255 patients initially entered into the placebo period, 48 were withdrawn before the active treatment period, largely because supine diastolic pressure

was  $< 92$  mm Hg at the last placebo visit. Of the 207 patients randomised to the active treatment phase, similar distributions of sex, number of patients, average age, and body weight were achieved among the groups (Table 1). Among the 198 patients completing six weeks of active treatment (66 on captopril and hydrochlorothiazide; 71 on captopril; and 70 on hydrochlorothiazide) no significant differences in the racial proportions of the treatment groups were seen.

## Blood pressure

Figure 1 depicts average supine systolic, diastolic, and mean arterial pressure at the end of the placebo period (baseline) for each treatment group. There were no significant differences in average baseline systolic, diastolic or mean pressure among the three groups. There were also no significant changes between pressures at entry or after two weeks of placebo and those at the last placebo visit. All three treatment groups showed significant ( $p < 0.05$ ) decreases in supine systolic, diastolic, and mean pressure at each active treatment visit (two, four, and six weeks) when compared with baseline. The proportionate decrease for each group at each treatment period is shown in Table 2. The decrease with captopril and hydrochlorothiazide was significantly ( $p < 0.001$ ) greater than



**Figure 1** Average supine blood pressure during the placebo period and at two, four, and six weeks of active treatment in the three groups. Mean arterial pressure is indicated by dots connected by lines.

**Table 1** Demographic characteristics of the groups studied

Treatment group (n)	Sex		Age (years)	Weight (kg)
	Men	Women		
Captopril and hydrochlorothiazide (66)	37	29	50	82.1
Captopril (71)	41	30	50	84.9
Hydrochlorothiazide (70)	42	28	48	84.5

Table 2 Proportionate changes in supine blood pressure during active treatment

	Systolic			Diastolic		
	Captopril and hydrochlorothiazide	Captopril	Hydrochlorothiazide	Captopril and hydrochlorothiazide	Captopril	Hydrochlorothiazide
Week 2	-12.0%	-2.4%	-8.0%	-12.2%	-5.9%	-7.2%
Week 4	-15.3%	-3.5%	-9.1%	-15.5%	-6.2%	-9.0%
Week 6	-15.7%	-3.9%	-10.2%	-15.2%	-6.4%	-9.1%

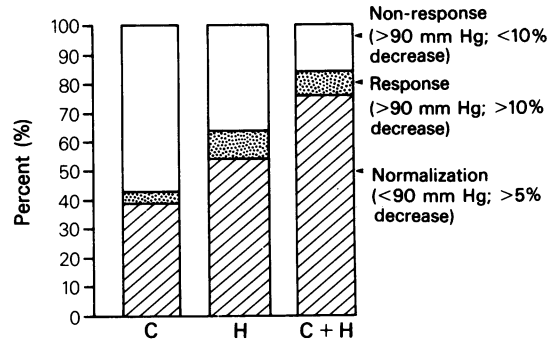


Figure 2 Response of supine diastolic blood pressure to six weeks of active treatment in the three groups.

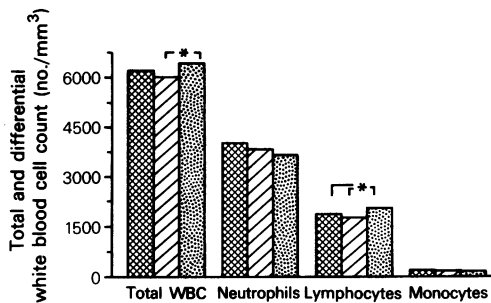
that observed with either drug alone at each visit. Similar changes in standing pressures were observed. When the supine diastolic blood pressure response was evaluated in terms of normalisation, response, and non-response (Figure 2) the benefit of combined treatment was most evident. More than three-quarters of those receiving captopril plus hydrochlorothiazide had normal blood pressures and 84% had a favourable response to the combination therapy. Pressures in over half of the hydrochlorothiazide group returned to normal, and an additional 10% of patients were classified as responders.

**Heart rate**

Heart rate, both supine and standing, increased slightly (1.4–4.7%) but significantly ( $p < 0.05$ ) in both groups receiving hydrochlorothiazide but not in the group receiving captopril alone, where slight (-1.7%–0.7%) but non-significant decreases in heart rate were observed.

**Laboratory changes**

A significant ( $p < 0.05$ ) decrease in white blood cell count (baseline mean  $6.46^9 \times 10^9/l$  treatment mean  $5.993 \times 10^9/l$ ) was seen in the group treated with captopril alone (Figure 3). This was associated with a decline in mean lymphocyte count from  $2.046 \times 10^9/l$  to  $1.795 \times 10^9/l$  in this group. This change was not seen in the captopril and hydrochlorothiazide group and was not deemed to be of medical importance during the study. No other significant haematological changes were observed after treatment in any of the groups. The other statistically significant laboratory changes from baseline which were observed during the study were those often seen with hydrochlorothiazide treatment. These included significant ( $p < 0.05$ ) increases in glucose (7.2%), calcium (1.3%), serum aspartate transaminase (8.5%),

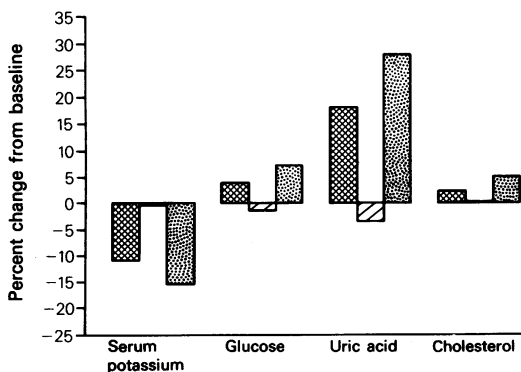


**Figure 3** The effect of six weeks of active treatment on total white blood cell count, absolute neutrophil, lymphocyte and monocyte count in the three groups. ■ Captopril and hydrochlorothiazide, ▨ captopril, ▩ hydrochlorothiazide. \* $p < 0.05$ .

cholesterol (5.0%), and albumin (0.7%) and decreases in potassium (15.2%) and chloride (5.0%) in the group receiving hydrochlorothiazide alone. No such changes were observed with captopril alone and the addition of captopril to hydrochlorothiazide resulted in a significantly ( $p < 0.05$ ) higher mean serum potassium and lower uric acid concentration than with hydrochlorothiazide alone. The proportionate (percentage) changes in potassium, glucose, uric acid, and cholesterol concentrations for the three groups during active treatment are shown in Figure 4. None of the groups showed significant amounts of protein in 24 hour urine samples.

#### Adverse reactions

Treatment was discontinued in five patients because of adverse reactions—three receiving captopril and



**Figure 4** Proportionate (% change from baseline) change in serum potassium, glucose, uric acid, and cholesterol levels after six weeks of treatment in the three groups. ■ Captopril and hydrochlorothiazide, ▨ captopril, ▩ hydrochlorothiazide.

hydrochlorothiazide and two captopril alone. These reactions included pruritus or rash in three; muscle cramps, myalgia, and malaise in one and paraesthesiae in the other. No patient in any treatment group had proteinuria, leucopenia or taste alterations. During the placebo period 21 patients (8%) reported adverse reactions and in five of these (2%) the study was discontinued in the placebo period because of adverse effects. The proportion of patients reporting adverse reactions during the active treatment period was greater in the captopril plus hydrochlorothiazide group (22%) than those treated with captopril (16%) or hydrochlorothiazide (14%) alone. The most commonly encountered adverse effects during active treatment were rashes, which occurred in four (5.8%) patients taking captopril and hydrochlorothiazide, four (5.6%) on captopril alone, and none on hydrochlorothiazide alone, and dizziness, which occurred in six (8.7%) on captopril and hydrochlorothiazide, one (1.4%) on captopril alone and one (1.4%) on hydrochlorothiazide alone. No other side effects were reported by more than two patients in any treatment group.

#### Discussion

The results of this multicentre trial of mild to moderate essential hypertension show that captopril 25 mg three times a day provided an antihypertensive effect equal in magnitude to that of hydrochlorothiazide 15 mg three times a day. Most studies using hydrochlorothiazide have shown a flat response at doses greater than those used in the present study. An additive antihypertensive effect was observed when captopril was combined with hydrochlorothiazide, and in over 75% of these patients blood pressure returned to normal, a significantly greater proportion than with either compound alone. The evidence thus indicates that captopril is an effective antihypertensive agent in this population, particularly when combined with modest doses of thiazide diuretic.

Previous studies using much higher doses of captopril in the treatment of severe, refractory, and complicated patients have reported the occurrence of side effects, most often rash, loss of taste, and proteinuria (Bravo & Tarazi, 1979; Case *et al.*, 1978; Gavras *et al.*, 1978; Havelka *et al.*, 1982; Raine & Ledingham, 1982; Weinberger, 1982). While these side effects have tempered the enthusiasm for captopril, it has none the less proved to be a very effective antihypertensive agent in such difficult patients. The observation of a much lower rate of side effects in the present study, in which we used lower doses of captopril than those used in the treatment of severe hypertension, confirms the suggestion of previous studies that side effects of captopril are dose dependent. None of the subjects in the current study showed proteinuria,

**Table 3** Response of supine diastolic blood pressure to 6 weeks of active treatment

Treatment group (n)	Normal*	Response†	No response <sup>a</sup>
Captopril and hydrochlorothiazide (62)	47 (76%)	5 (8%)	10 (16%)
Captopril (69)	27 (39%)	3 (4%)	39 (57%)
Hydrochlorothiazide (67)	36 (54%)	7 (10%)	24 (36%)

\* < 90 mm Hg; > 5% decrease; † > 90 mm Hg; > 10% decrease; <sup>a</sup> > 90 mm Hg; < 10% decrease.

taste disturbance, or significant neutropenia. The incidence of rash, the least troublesome of reported side effects, was also considerably lower in the current study.

Indeed, 8% of the subjects in our present study experienced side effects during the placebo phase and in 2% these symptoms were so severe that they were withdrawn from the study before receiving the active drug. In five patients experiencing side effects during the active treatment period symptoms led to their withdrawal from the study. A rash was reported in fewer than 6% of those receiving captopril alone or with diuretics. The other major side effect, dizziness, may have reflected the antihypertensive effectiveness of treatment since it occurred most often (8.7%) in the group treated with captopril + hydrochlorothiazide but was also noted with each agent alone.

While intermediate-acting diuretics such as hydrochlorothiazide have been the keystone of treatment in the uncomplicated, mild to moderate hypertensive population, this agent is not without important side effects. The most common of these are hypokalaemia and increases in uric acid concentrations, with precipitation of gout in those predisposed to this abnormality. Even at submaximal doses of hydrochlorothiazide, such as the dose of 15 mg three times a day used in this study, a significant decrease in serum potassium (4.14 to 3.54 mmol/l) and increase in uric acid (5.78 to 7.39 mg/100 ml) were seen. Serum

cholesterol concentration also increased in the thiazide-treated group by 5% ( $p < 0.05$ ). In addition to the synergistic antihypertensive effect observed when captopril was added to hydrochlorothiazide, it is important to recognise that the potassium loss (4.22 to 3.74 mmol/l) and increases in uric acid (5.73 to 6.79 mg/100 ml), and cholesterol (2.4%) were blunted (Figure 4). Thus, as well as enhancing the antihypertensive efficacy of moderate doses of diuretic, captopril minimises the magnitude of significant biochemical alterations induced by diuretic therapy.

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## Appendix

### Investigators

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