Br. J. clin. Pharmac. (1982), **14**, 97S–101S

RACIAL DIFFERENCES IN RESPONSE TO LOW-DOSE CAPTOPRIL ARE ABOLISHED BY THE ADDITION OF HYDROCHLOROTHIAZIDE

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1 In a randomised study, 475 men with diastolic blood pressures of 92–109 mm Hg received either placebo or captopril 37.5 mg, 75 mg or 150 mg/day for 7 weeks.

2 After 7 weeks patients taking placebo were given hydrochlorothiazide 25 mg twice daily, as were two-thirds of each group taking captopril and they were observed for 7 additional weeks.

3 Captopril reduced blood pressure by 12.2 ± 0.8/9.4 ± 0.4 mm Hg at 7 weeks (n = 323) and captopril plus placebo reduced it by 10.3 ± 1.9/10.2 ± 0.9 mm Hg at 14 weeks (n = 83); placebo by 2.0 ± 1.7/3.4 ± 0.8 mm Hg (n = 76); and captopril plus hydrochlorothiazide by 24.4 ± 1.1/16.2 ± 0.6 mm Hg (n = 173). The effect of low-dose captopril was similar to that of high doses.

4 White patients responded better than blacks, with a blood pressure reduction of 14.7 ± 1.1/10.7 ± 0.6 mm Hg (n = 170) v 9.1 ± 1.2/8.0 ± 0.7 mm Hg (n = 151). This difference was abolished by the addition of hydrochlorothiazide.

5 Only 15/384 (3.9%) of patients were dropped from the study because of adverse effects.

6 The prescription of low-dose captopril might be extendable to patients with mild to moderate hypertension.

Introduction

Captopril, an oral angiotensin-converting-enzyme inhibitor, has been shown to be effective in lowering arterial pressure of hypertensive patients (Rubin *et al.*, 1978; Gavras *et al.*, 1978). It does not seem to be associated with the adverse effects of the sympatholytic drugs. Captopril may, however, cause rash, neutropenia, and proteinuria, which has resulted in initial use being restricted to severely ill patients and these patients with severe hypertension resistant to multiple drug combinations (Waeber *et al.*, 1981). In general, very high doses (450 mg or more) of captopril have been used. We studied patients with mild uncomplicated hypertension to determine whether captopril could be effective as a hypotensive agent in much lower doses and to determine whether lower doses would be associated with fewer adverse effects. We also investigated the degree of further reduction of blood pressure induced by the addition of hydrochlorothiazide to captopril. Finally, we examined the racial differences in drug response because previous studies by our group had shown important differences in response to propranolol and hydrochlorothiazide (Materson *et al.*, 1981).

Methods

We enrolled 722 ambulatory male veterans whose diastolic (Korotkoff phase 5) blood pressure was 92–109 mm Hg and who met other qualifying criteria. All patients gave fully informed written consent before they were enrolled. The protocol had been approved by a central human studies committee and similar committees at each of the seven participating centres. Patients were withdrawn from current treatment at least two weeks before entering the study and then placed on a placebo (CINONE A). If the patient met the blood pressure entry criteria, and compliance requirements (checked by counting pills remaining in a special blister pack), they were randomised to CINONE B, which was identical in appearance to CINONE A but contained one of the following: placebo or captopril 12.5 mg, 25 mg, 37.5 mg, or 50 mg. All of these medications were taken three times a day, except for captopril 37.5 mg, which was taken twice daily; the blind was preserved by placing a placebo as the mid-day dose on the blister pack. After seven weeks (phase A), all patients were given ERYX, which was either hydrochlorothiazide 25 mg twice daily or placebo. All patients previously taking

0306–5251/82/100097–05 $01.00

placebo were given active ERYX so that beyond this point there were no patients left in the study taking placebo alone. All other patients taking captopril were randomised such that one-third of each dose group received placebo and two-thirds active ERYX. The patients were followed for an additional seven weeks (phase B), after which they were either put back on placebo for two weeks or entered into a long-term trial of captopril. The twice daily dose regimen was tested by placing a known placebo on the blister card in place of the morning dose of active drug on one designated visit in each of the two phases. The blood pressure obtained on this visit was compared with that obtained on the visits before which active drug had been taken. Appropriate tests of white blood cells, blood chemistry, and urine protein excretion were made.

Results

Of the 722 men enrolled 475 (65.8%) qualified for randomisation; 399 have completed phase A and 315 have finished phase B. They are the basis for the data which follow. The racial distribution was: 248 (52.2%) white, 222 (46.7%) black, and five (1.1%) other. Their average age was 55.0 and 58.4% of them had been treated for hypertension.

Blood pressure results are presented in Table 1. During phase A all doses of captopril were effective in reducing blood pressure and the effects were no different from each other. The twice daily dose was as good as the thrice daily and the percentage of patients whose blood pressures reached the goal pressure of < 91 mm Hg diastolic was the same on each dose. During phase B the 83 patients who were randomised to have placebo added to captopril maintained about the same level of effect except for loss of systolic effect at the lowest dose and a slight additional pressure reduction at the 37.5 mg and 50 mg doses. The remaining 173 patients taking captopril who received hydrochlorothiazide had a pronounced further reduction in both systolic and diastolic blood pressure. There was no difference in the response of the two 75 mg/day captopril groups.

This study was not designed for titration to a predetermined goal blood pressure. It is interesting, however, to examine the percentage of patients in each group whose diastolic blood pressure was reduced to less than 90 mm Hg. During phase A white patients tended to respond to captopril better than black patients (Table 2). Figure 1 shows the phase A results separated by race. Placebo appears to have been effective because the lowest entry diastolic blood pressure was 92 mm Hg and there was a 3.4 mm Hg decline in diastolic pressure associated with placebo treatment. In general, white patients achieved goal blood pressure more often than did blacks. As shown in Figure 2, the addition of hydrochlorothiazide abolished this racial difference.

In the phase A twice daily test, when placebo was given instead of the active drug on one visit to the clinic, systolic pressure on placebo rose by 0.9 mm Hg compared with 5.6 mm Hg on captopril 25 mg and 5.3 mm Hg on 37.5 mg; diastolic pressure on placebo rose 1.4 mm Hg compared with 4.1 on 25 mg of captopril

Table 1 Blood pressure reduction achieved by captopril and captopril plus hydrochlorothiazide*

	Phase A					*Phase B*				
	Placebo	*Captopril*				*Captopril plus hydrochlorothiazide*				
		12.5 mg	25 mg	37.5 mg	50 mg	Hydrochlorothiazide	12.5 mg	25 mg	37.5 mg	50 mg
No	76	79	78	85	81	59	44	41	39	48
Baseline systolic blood pressure	146.0 ±1.6	147.6 ±1.7	147.6 ±1.3	149.3 ±1.5	147.4 ±1.8	145.6 ±1.8	146.1 ±2.4	148.1 ±1.7	148.8 ±1.9	146.8 ±2.3
Reduction in systolic blood pressure	2.0 ±1.7	9.9 ±1.7	11.6 ±1.6	13.7 ±1.7	13.3 ±1.5	11.6 ±1.7	23.3 ±2.6	26.5 ±2.2	25.8 ±2.6	22.5 ±1.8
Baseline diastolic blood pressure	97.8 ±0.5	97.0 ±0.4	98.1 ±0.5	97.5 ±0.5	97.9 ±0.5	97.6 ±0.6	96.2 ±0.6	98.2 ±0.7	97.5 ±0.7	98.4 ±0.7
Reduction in diastolic blood pressure	3.4 ±0.8	8.6 ±0.9	9.2 ±0.9	9.5 ±0.9	10.3 ±0.8	8.2 ±1.0	16.6 ±1.1	15.5 ±1.2	14.5 ±1.2	17.6 ±1.1

*All blood pressures are reported in mm Hg ± SE. Captopril doses are recorded by mg given thrice daily except 37.5 mg, which was given twice daily. All blood pressure reductions were different from placebo ($p < 0.05$), but there were no significant differences between the captopril dose groups within each phase.

Table 2 Blood pressure response by race*

	Phase A		*Phase B*			
			Captopril alone		*Captopril plus hydrochlorothiazide*	
	White	*Black*	*White*	*Black*	*White*	*Black*
No.	170	151	46	37	89	80
Baseline systolic blood pressure	148.2 ±1.1	147.6 ±1.2	148.4 ±2.4	148.5 ±1.9	146.7 ±1.2	147.8 ±1.8
Baseline diastolic blood pressure	97.4 ±0.3	97.8 ±0.4	97.1 ±0.6	98.2 ±0.8	97.3 ±0.4	97.8 ±0.5
Experimental systolic blood pressure	133.5 ±1.2	138.5† ±1.2	134.1 ±2.8	143.2‡ ±2.7	122.7 ±1.3	123.1 ±1.5
Experimental diastolic blood pressure	86.7 ±0.6	89.9§ ±0.7	86.0 ±1.3	89.1 ±1.6	81.6 ±0.8	81.4 ±0.9

*Blood pressure is expressed as the mean ± SE (mm Hg). Blood pressure was determined with the patients seated. The baseline and experimental values are for the groups of patients who completed each phase.

† $p < 0.005$; ‡ $p < 0.025$; § $p < 0.001$.

and 4.6 mm Hg on 37.5 mg. During the phase B test, systolic blood pressure increased 2.1 mm Hg in patients on hydrochlorothiazide, 8.6 mm Hg in those on diuretic plus captopril 25 mg, and 10.2 mm Hg in those on 37.5 mg. Diastolic blood pressure increased by 3.8 mm Hg in patients on hydrochlorothiazide compared with 6.1 mm Hg in those taking diuretic plus captopril 25 mg and 6.5 mm Hg in those taking 37.5 mg. For those patients taking captopril and placebo or hydrochlorothiazide, systolic blood pressure rose 10.2 mm Hg in the 25 mg group compared with 8.2 mm Hg in the 37.5 mg group and the corresponding increases in diastolic pressure were 5.1 mm Hg and 5.8 mm Hg.

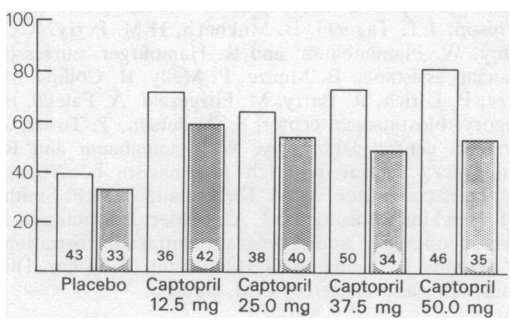

Figure 1 Percentage of patients who achieved goal blood pressure (< 91 mm Hg diastolic) by the end of phase A. The captopril doses were given thrice daily except for 37.5 mg, which was given twice daily. The numbers in the bar indicate the number of subjects in each group. □ white ▩ black.

During phase A 2.6% of patients taking placebo and 3.1% taking captopril developed rashes. During phase B 1.7% of the placebo plus hydrochlorothiazide, 3.6% of the captopril plus placebo, and 1.2% of the captopril plus hydrochlorothiazide groups had a rash. Among the total captopril group of 384 patients 15 (3.9%) had a rash, of whom five patients were receiving the 150 mg/day dose.

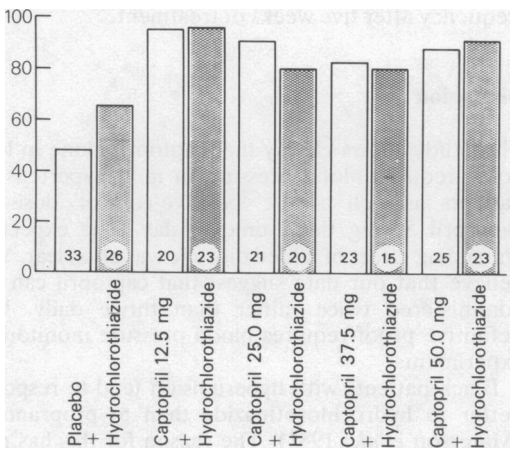

Figure 2 Percentage of patients who achieved goal blood pressure (< 91 mm Hg diastolic) by the end of phase B. The captopril doses were given thrice daily except for 37.5 mg, which was given twice daily. Hydrochlorothiazide 25 mg twice daily was added to each group during phase B. The numbers in the bar indicate the number of subjects in each group. □ white ▩ black.

Therefore the incidence in the low-dose group was 2.4%.

A total of 18 patients were withdrawn for drug intolerance. These were evenly distributed across all of the groups. Two patients taking captopril 37.5 mg and 50 mg were withdrawn because of urticaria; three taking diuretic plus captopril 12.5 mg, 25 mg, and 50 mg had a maculopapular rash; two taking diuretic plus 25 mg and 37.5 mg captopril had loss of taste, which returned after discontinuation of the drugs; two taking diuretic plus captopril 12.5 mg and 25 mg had nausea and vomiting. Proteinuria occurred in three patients. In one patient, who was taking captopril 12.5 mg, protein concentrations rose from a baseline 24-hour urinary excretion of 126 mg to 665 mg after five weeks of captopril and back to baseline after captopril was discontinued. One patient with proteinuria initially (over 453 mg/day) excreted 1600 mg/day after 12 weeks of captopril 50 mg. He was later discovered to be an abuser of ethanol and intravenous heroin and amphetamine. One patient who was randomised to placebo excreted 800 mg/day and 1200 mg/day four days later. He returned to normal within one month without intervention. Three patients were withdrawn for intolerable hypotension; two were taking 50 mg captopril and one was associated with the addition of diuretic to 25 mg captopril. One patient taking 37.5 mg of captopril complained of intolerable headaches. Two patients taking placebo were withdrawn for drug intolerance. One complained of weakness, dizziness, and dry mouth after the first dose and refused to return. One complained of headache, impotence, dysuria, and urinary frequency after five weeks of treatment.

Discussion

This study shows clearly that captopril alone in low doses reduces blood pressure in mild hypertensive patients as well as the 'positive-control' dose of captopril 50 mg three times a day. The expected enhancing effect of added diuretic was also clear. We believe that our data suggest that captopril can be administered twice rather than thrice daily, but definitive proof requires blood pressure monitoring experiments.

Black patients with hypertension tend to respond better to hydrochlorothiazide than to propranolol (Materson *et al.*, 1981). The reason for this has not been established, but as a group black patients have lower plasma renin activity than age-matched white patients (Chrysant *et al.*, 1979). One hypothesis holds that patients with low plasma renin activities have volume-dependent hypertension and should respond better to diuretic drugs. In contrast, patients with normal or high plasma renin may respond better to drugs, such as beta-adrenergic blocking agents, that lower plasma renin activity (Laragh, 1976). One might predict that black patients would respond less well to captopril than whites. One might also predict that this differential effect would be abolished by the addition of a diuretic drug to the therapeutic regimen. Both predictions were fulfilled in this study. It is important to note that these results are derived from observations of groups of patients. Although such information may be important in guiding therapy, it cannot be used to predict the response of a given individual patient.

Withdrawals because of adverse effects were very low and in the range of withdrawals we have experienced in previous studies of diuretics and β-blocking agents. That is not to imply that such effects as rash did not occur, but that they usually did not require discontinuation of the drug. It was also very difficult to be certain whether rashes were due to captopril or to diuretic or to the combination.

We believe that the results of this short-term study shows that the use of captopril in low doses, especially when combined with a diuretic, may be extendable to the general population of hypertensive patients and might no longer need to be restricted to those with severe or resistant hypertension.

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