Comparative study of once-daily administration of captopril 50 mg, hydrochlorothiazide 25 mg and their combination in mild to moderate hypertension

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1 Two hundred and eleven patients with mild or moderate hypertension, mean age 53.5 ± 9.5 years (range 24-70) were randomised double-blind to treatment with either captopril 50 mg (C50), hydrochlorothiazide 25 mg (HCTZ25), the fixed combination of captopril 50 mg and hydrochlorothiazide 25 mg (C50/HCTZ25) or placebo.

2 Blood pressure, heart rate, body weight and side effects were assessed at the end of the run-in period on placebo and after 4, 6, 8 weeks treatment at the same time, 20-24 h after the last dosing. Routine biochemical examinations were carried out on all patients after the placebo period as well as after 4 and 8 weeks.

3 Blood pressure significantly decreased in all groups, but the mean percentage change from baseline was highly statistically significant at 8 weeks, for C50 and C50/HCTZ25 groups.

4 The incidence of clinical side effects was low and not statistically different for the four groups with few specific adverse effects (one transient alteration of taste in captopril group). No patient was withdrawn from the study due to side effects.

5 A better anti-hypertensive efficacy was obtained with the fixed combination captopril 50 mg/hydrochlorothiazide 25 mg once daily compared to placebo or each component alone, and without any difference in side effects.

Keywords arterial hypertension captopril diuretics

Introduction

Since 1979, the angiotensin converting enzyme inhibitor captopril has been used successfully alone, or combined with a diuretic in mild hypertension (Reyes *et al.*, 1985). The combination of low doses of captopril with diuretics in a long term study seems to minimise the adverse reactions of chronic diuretic therapy (Weinberger, 1983).

The aim of our study was to assess whether the fixed combination captopril-hydrochlorothiazide, given once daily, would be valuable in the treatment of essential mild or moderate hypertension.

Thus we carried out a placebo-controlled study of 2 months duration to assess efficacy and safety of the fixed combination of 50 mg captopril plus 25 mg hydrochlorothiazide in a single daily dose.

Methods

Patients

This multicentre study was performed in patients aged 20 to 70 years, with essential mild to

moderate hypertension. At entry into the study, patients had a systolic blood pressure (SBP) between 160 and 200 mm Hg and diastolic blood pressure (DBP) between 95 and 120 mm Hg at two consecutive measurements.

Patients with secondary forms of hypertension, recent history of myocardial infarction or stroke, renal insufficiency, proteinuria or a white blood cell count $< 3500 \text{ mm}^3$ were excluded from the study. All the patients were withdrawn from other anti-hypertensive therapy two weeks before entry to the placebo phase.

Trial design

The study was divided into two phases: a placebo run-in period of 2 weeks' duration and an active treatment period of 8 weeks duration when the patients were randomised in four groups:

captopril 50 mg, hydrochlorothiazide 25 mg combination (C50/HCTZ25) once daily, captopril 50 mg alone (C50) once daily, hydrochlorothiazide 25 mg alone (HCTZ25) once daily or placebo once daily. A double-blind design was used for the 8 weeks of active treatment.

Blood pressure, heart rate, body weight, side effects were assessed at the end of the run-in period on placebo and after 4, 6, 8 weeks treatment at the same time, 20–24 h after the last dosing. Routine biochemical examinations were carried out on all patients after placebo period as well as after 4 and 8 weeks.

Clinical and biological assessments

Blood pressure assessment was made by a cuff mercury type manometer. Diastolic blood pressure was noted at the Korotkoff phase 5. The average of three measurements made by the same physician, at the same arm, over a short time, 20–24 h after the last medication, was noted. Blood pressure was recorded at the end of a 10 min rest and after 5 min of standing posture.

Laboratory studies including a complete blood count and routine biochemical estimation were obtained at entry to the study and every 4 weeks.

Statistical analysis

Mean $\pm$ s.d. were calculated using standard methods. The statistical methods used were paired *t*-test for intragroup comparisons. The intergroup comparisons were made by Dunnett's test (Dunnett, 1964).

Results

Patient population

Of the 221 patients who entered the study, 10 dropped out from the study because of (1) a decrease of blood pressure during the placebo run-in phase (four patients), (2) poor compliance with treatment during placebo period (four patients) and (3) violation of inclusion criteria (two patients).

At the end of this study, 45 patients were left for analysis in group C50/HCTZ25, 42 patients in group C50, 41 patients in group HCTZ25 and 83 patients were included in the placebo group. The number of patients in placebo was two times greater than the active groups to allow more valid statistical comparisons to be made.

Table 1 gives the demographic characteristics of the 211 patients who entered the study according to the inclusion criteria at the end of the placebo run-in phase. Similar distributions of sex, average age and body weight were achieved among the groups.

Blood pressure

All the treatment groups showed significant ($P < 0.01$) decreases in systolic and diastolic blood pressure in supine and standing position at each visit when compared to baseline.

The decrease with the fixed combination C50/HCTZ25 was significantly greater than that observed with either drug alone (Figures 1 and 2).

The percentage change in systolic blood pressure at the end of the study was significantly higher for the C50/HCTZ25 group (-15.3%)

Table 1 Demographic characteristics of the groups studied

	Placebo	HCTZ25	C50	C50/HCTZ25
Number of patients	83	41	42	45
Age (years)	52.8 ± 9.0	55.1 ± 10.7	52.8 ± 10.6	53.8 ± 9.2
Weight (kg)	68.9 ± 13.0	71.7 ± 16.2	74.5 ± 14.2	72.1 ± 13.4
Male/Female	47/36	21/20	23/19	27/18

Figure 1 Average ($\pm$ s.d.) supine systolic blood pressure during the placebo period and at 8 weeks of active treatment. Baseline vs 8 weeks, * $P < 0.01$, ** $P < 0.001$.

Figure 2 Average ($\pm$ s.d.) supine diastolic blood pressure during the placebo period and at 8 weeks of active treatment. Baseline vs 8 weeks, *** $P < 0.001$.

compared with the C50 group (-11.1%), the HCTZ25 group (-10.3%) or placebo (-6.3%). The same results were observed with the diastolic blood pressure, respectively -18.1% , -14% , -11.7% and -8.7% .

When the supine diastolic blood pressure response was evaluated in terms of normalisation (supine DBP ≤ 90 mm Hg), response (supine DBP not normalised but decreased $\geq 10\%$) or non-response, the benefit of the fixed combination was most evident (Figure 3).

Seventy eight per cent of those receiving the fixed combination were normalized, 20% responded and only one patient was a non-responder; with captopril 50 mg alone, 72.5% of patients showed normalisation of their blood pressure and the others remained non-responders; with hydrochlorothiazide 25 mg alone, the normalisation rate was 67.5%, the response and non-response were 7.5% and 25%; for the placebo group there were 45% normalisations, 3.7% responders and 51% non-responders.

Figure 3 Response of supine diastolic blood pressure at the end of 8 weeks: $\square$ % normalised patient: supine DBP ≤ 90 mm Hg and decreased $\geq 5\%$; ▨ % responder: supine DBP > 90 mm Hg and decreased $\geq 10\%$; ░ % non-responder: supine DBP > 90 mm Hg and decreased $< 10\%$.

Of the 211 patients who entered the double-blind phase of the study, six withdrew from the treatment because of (1) inefficacy (two patients on placebo, one on C50, one on HCTZ25) or (2) loss of follow-up (one placebo, one HCTZ25). Heart rate, both supine and standing did not change significantly with either treatment.

Laboratory changes

A decrease in serum potassium (from 4.2 ± 0.4 mmol l^{-1} to 4.1 ± 0.4 mmol l^{-1}) was seen in the group treated with hydrochlorothiazide alone; this change was not seen in the other groups.

The other statistically significant laboratory change from baseline which was observed during the study was an increase in uric acid concentration (7%) in the C50/HCTZ25 and HCTZ25 groups.

There were no significant haematological changes, and we did not notice a decrease in white blood cell count. No proteinuria was noted.

Adverse reactions

No patient discontinued the study because of adverse effects. The proportion of patients reporting adverse reactions during the active treatment period was greater in the hydrochlorothiazide group (20%) and placebo group (16%) than those treated with captopril alone (10%) or with the fixed combination of captopril plus hydrochlorothiazide (13%). Furthermore these proportions were lower than those we observed during the run-in placebo period (29.8%). The most commonly encountered adverse effect during the active treatment period was transient

gastrointestinal upset, which occurred in six patients taking C50/HCTZ25, four on C50 alone, eight in HCTZ alone and ten on placebo. One patient treated with captopril alone, noticed a transient taste alteration. No patient experienced orthostatic hypotension.

Discussion

In this double-blind study, patients with mild-to-moderate hypertension were treated either with the fixed combination captopril 50 mg hydrochlorothiazide 25 mg, or with each component alone, or placebo given once daily. A synergistic effect upon hypotensive efficacy has previously been reported between these two compounds (Stumpe, 1984).

On a pathophysiological, pharmacological and clinical basis, the most logical supplement to captopril is the administration of a diuretic agent such as hydrochlorothiazide. The respective mechanisms of action of the two drugs are different but complementary, and captopril is more active when the renin-angiotensin system is stimulated.

The results obtained in this study show a synergistic effect of this combination on the systolic and diastolic blood pressure.

In a previous study, Lederle (1985), used a fixed combination of 25 mg captopril plus 25 mg hydrochlorothiazide twice daily. If blood pressure was not lowered satisfactorily, this author in-

creased the dosage to a fixed combination of 50 mg captopril plus 25 mg hydrochlorothiazide twice a day. The results obtained were the same as ours but with a twice daily regimen.

In addition, Andersen *et al.* (1986) reported the long-term efficacy and safety of a fixed combination of captopril 50 mg and hydrochlorothiazide 25 mg administered once a day. The anti-hypertensive efficacy recorded in this trial persisted at 24 h and is in agreement with our results.

In conclusion, this study confirms that a fixed combination of captopril and hydrochlorothiazide at low doses, and in once daily regimen lowers blood pressure and may be of value by increasing patient compliance.

Appendix

The study investigators

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