Determination of the optimal dosage regimen of captopril + hydrochlorothiazide in the treatment of moderate arterial hypertension

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1 A multicentre controlled trial was carried out to determine the optimal dosage of a 2/1 combination of captopril plus hydrochlorothiazide (HCTZ) in mild hypertension at three doses against placebo in a 6 week double-blind trial. The number of patients was 111: 27 received placebo; 26 were treated with captopril 25 mg plus HCTZ 12.5 mg (25/12.5); 25 with captopril 50 mg plus HCTZ 25 mg (50/25); and 33 with captopril 100 mg plus HCTZ 50 mg (100/50).

2 A significant fall in blood pressure was seen in all four groups, but was greater with the active treatments. The percentage of patients who were normalized [diastolic blood pressure (DBP) less than or equal to 90 mm Hg] or good responders (10% fall in DBP) increased as a function of the dose. At Day 21, the antihypertensive effect of 50/25 was similar to that of 100/50, but greater than that of captopril 25-HCTZ12.5. At Day 42, the antihypertensive effects of the three doses were similar.

3 Tolerance data showed a higher incidence of side-effects with 100/50 than with the other dosages.

4 Thus, 50/25 appeared to be the optimal dosage for the control of mild hypertension.

Keywords captopril hydrochlorothiazide moderate arterial hypertension dose-finding

Introduction

Captopril is an angiotensin-I converting enzyme (ACE) inhibitor which is effective in the management of arterial hypertension. Like all antihypertensive drugs, captopril does not normalize all hypertensive patients. It is for this reason that drug combinations to treat hypertension are under investigation. Among these combinations, captopril + a thiazide appears to be a safe and effective treatment for mild to moderate essential hypertension. It appears that this combination is more effective than either drug given separately indicating a synergistic effect (Andren *et al.*, 1982; Murakami, 1985; Weinberger, 1982, 1985; Wicker *et al.*, 1984; Veterans Administration

Cooperative Study Group on Antihypertensive Agents, 1984). The different possible dosage regimens would appear to favour the 2/1 dosage ratio of captopril to hydrochlorothiazide (HCTZ).

The present study sought to evaluate the therapeutic efficacy of captopril + HCTZ in three doses, to determine the optimal drug dosage and to assess patient tolerance. Therapeutic efficacy was evaluated by measuring the decrease in diastolic blood pressure compared with baseline readings.

The different dosage regimens investigated in this study were as follows: captopril 25 mg + HCTZ 12.5 mg, captopril 50 mg + HCTZ 25 mg

and captopril 100 mg + HCTZ 50 mg *vs* a placebo group administered as a single daily dose.

Methods

This study was a multicentre double-blind randomized investigation with parallel groups of patients who were examined in hospital out-patient departments (OPD) and in general practice.

Patient population was selected according to the following inclusion criteria:

111 patients, male or female, with mild to moderate essential hypertension, defined as diastolic BP between 95 to 115 mm Hg after a 15 day wash-out period were selected.

Patients were 18 to 60 years of age (mean 39 years).

The four study groups of patients were comparable for height, weight, duration of the hypertension and type of previous antihypertensive therapy.

Exclusion criteria were the following:

- hypertension secondary to specific organic disorder,
- severe hypertension complicated by stage III or IV retinopathy,
- congestive heart failure (Stage III or IV of NYHA),
- hypertensive vascular disease (including myocardial infarction),
- impaired renal function (serum creatinine $> 135 \mu\text{mol l}^{-1}$),
- proteinuria $> 0.50 \text{ g } 24 \text{ h}^{-1}$,
- recent history of cerebrovascular accident,
- severe impaired liver function tests (prothrombin time $< 60\%$),
- a history of adverse reactions to captopril or HCTZ,
- a history of immunological disorders, leucopenia, or white blood cell count $< 2000/\text{mm}^3$,
- treatment with immunosuppressor or other leucopenia-inducing drugs,
- patients on other antihypertensive drug regimen, pregnant women or nursing mothers.

The principal criterion for therapeutic efficacy was the normalization of diastolic BP in the supine position, as measured three times in succession after a 3 min rest period. Patients were classified as normalized if diastolic BP was equal to or below 90 mm Hg; responders if diastolic BP was above 90 mm Hg but decreased at least 10% compared with baseline or as non-responders.

Other measurements were the systolic, diastolic and mean BP in supine position and heart

rate. The systolic and diastolic BP and heart rate were recorded after standing for 1 min. All readings were recorded at the same time of the day, approximately 24 h after the previous day's recordings. Mean BP was calculated as $2\text{DBP} + \text{SBP}/3$.

Adverse reactions were sought and graded according to three stages of intensity, by means of a questionnaire.

Laboratory values were recorded at Day 0 (baseline) and at Day 42 including: blood count including platelet count, serum creatinine, sodium, potassium, uric acid, fasting blood sugar, serum cholesterol and triglycerides; proteinuria was tested using reagent-strips.

Therapeutic efficacy and overall tolerance were assessed by a physician at the conclusion of the study.

Evaluation of efficacy was made after 3 weeks' (D 21) and 6 weeks' (D 42) treatment. The study was conducted for 8 weeks' duration (2 weeks placebo and 6 weeks of active treatment).

For quantitative items, statistical treatment of data was done with the following statistical tests:

t-test for paired samples: this test was done in order to appreciate the longitudinal efficacy of each treatment;

one way analysis of variance followed by analysis of contrasts by Scheffe method. These tests were done in order to compare the four groups of treatment.

Qualitative items were treated by the chi-square test.

Dosage

Patients were assigned to one of four possible treatment groups:

- Group 1: placebo: 27 patients,
- Group 2: captopril 25 mg + HCTZ 12.5 mg: 26 patients,
- Group 3: captopril 50 mg + HCTZ 25 mg: 25 patients and
- Group 4: captopril 100 mg + HCTZ 50 mg: 33 patients.

Treatment was given once a day. No other antihypertensive drugs or potassium supplements were authorized during the investigation. Immunosuppressor or leucopenia-inducing drugs were contra-indicated. A normal amount of dietary sodium was authorized.

Treatment was withdrawn if a patient developed any of the following conditions: systolic BP above 210 mm Hg, diastolic BP above 120 mm Hg, stroke or evidence of ischaemic heart disease, any serious side-effects due to therapy, symptomatic orthostatic hypotension or serious electrolyte imbalances.

Results

Significant falls in BP occurred in all four study groups (see Table 1). However, BP reduction in the placebo group was slight and of short duration.

At Day 21, the decrease of systolic, mean and diastolic BP were 10–12, 10–18 and 13–20 mm Hg after the three captopril + HCTZ dosages 25/12.5, 50/25 and 100/50 respectively. At Day 42, they were 16–20, 13–20 and 15–24 mm Hg respectively.

According to the principal criterion of the therapeutic efficacy, normalization of diastolic BP, it is evident that by Day 21 there was a significant difference due to captopril + HCTZ therapy, after patients were classified as responders or non-responders ($P = 0.022$). The percentage of normalized or responders in the treatment groups was higher than in the placebo group and increased with increasing dosage. Thus 50% of patients were normalized or responded with regimen 25/12.5, 64% with 50/25 and 73% with 100/50 (Figure 1, Day 21).

On day 42, normalization and response was 68% for the 25/12.5 regimen, 72% with 50/25 and 81% for the 100/50 regimen (Figure 2, Day 42).

Monitoring of systolic BP in the supine position demonstrated a difference due to the effect of therapy as evidenced by analysis of variance on Day 21 ($P = 0.006$) and on Day 42 ($P = 0.002$). On Day 21 only drug regimen 3 (50/25) was different from the placebo. On Day 42, all

Figure 1 Percentage of normalized (□), responders (□) and non responders (▨) in the four groups of patients at D 21.

three captopril + HCTZ regimens were different from the placebo group.

Analysis of variance demonstrated an effect due to treatment on diastolic BP on Day 21 ($P = 0.001$, treatment 4 different from placebo) and on Day 42 ($P = 0.001$, treatment 2 and 4 different from placebo).

On mean BP here again, analysis of variance showed a highly significant treatment effect at Day 21 ($P = 0.004$, treatment 3 and 4 different from placebo) and at Day 42 ($P = 0.055$, all three active treatments different from placebo). Compared with Day 0, the effect of treatment is not significant at Day 21 although the decline of BP increased with the dosage of captopril + HCTZ. At Day 42, the treatment effect was significant ($P = 0.05$). The results are expressed in Figure 3.

Heart rate varied little from one group of patients to another.

Table 1 Evolution of systolic, diastolic and mean BP (mm Hg) in the four groups of patients during the 6 week treatment period

		Day 0	Day 21	Day 42	Significance according to t-test		
		Mean (s.d.)	Mean (s.d.)	Mean (s.d.)	Day 21/Day 0	Day 42/Day 0	Day 42/Day 21
Placebo							
Systolic	BP	180.0 (17.4)	169.6 (17.7)	167.8 (18.4)	0.001	0.001	NS
Diastolic	BP	104.8 (6.2)	97.1 (9.4)	96.2 (11.5)	< 0.001	0.002	NS
Mean	BP	129.8 (9.2)	121.3 (11.0)	120.1 (12.3)	< 0.001	< 0.001	NS
C 25/HCTZ 12.5							
Systolic	BP	171.0 (16.2)	160.1 (20.4)	151.1 (20.2)*	< 0.001	< 0.001	0.012
Diastolic	BP	103.4 (5.9)	93.0 (10.5)	87.2 (11.3)*	< 0.001	< 0.001	0.014
Mean	BP	126.2 (8.2)	115.4 (13.0)	108.5 (13.6)*	< 0.001	< 0.001	0.01
C 50/HCTZ 25							
Systolic	BP	170.2 (12.5)	151.4 (17.0)*	150.2 (17.5)*	< 0.001	< 0.001	NS
Diastolic	BP	101.6 (5.1)	91.5 (8.3)	88.6 (9.0)	< 0.001	< 0.001	0.08
Mean	BP	124.5 (5.9)	111.5 (10.1)*	109.1 (10.8)*	< 0.001	< 0.001	NS
C 100/HCTZ 50							
Systolic	BP	175.5 (18.3)	155.3 (20.9)	151.9 (19.4)*	< 0.001	< 0.001	NS
Diastolic	BP	101.6 (6.3)	88.7 (9.4)*	87.0 (10.2)*	< 0.001	< 0.001	NS
Mean	BP	126.2 (8.7)	110.9 (11.5)*	108.7 (11.5)*	< 0.001	< 0.001	NS

*Statistically different from corresponding placebo values according to analysis of variance.

Figure 2 Percentage of normalized (□), responders (▨) and non responders (■) in the four groups of patients at D 42.

Figure 3 Evolution with time of mean BP (□ D 0, ▨ D 21 and ■ D 42) in the four groups of patients.

An overall evaluation of efficacy was made by physicians participating in the study. They graded any possible exacerbation of the patient's condition on a rating scale from -1 to -4. In case of an improvement, this was scored from 1 to 4. Absence of modifications was scored 0. The score increased with the dosage of captopril + HCTZ used (placebo = 1.06; 25/12.5 = 2.08; 50/25 = 2.40; 100/50 = 2.50).

Thus, the highest dosage of captopril + HCTZ (100/50) produced the best therapeutic results. However, analysis of patients' tolerance showed that there were more clinical side-effects in this group of patients ($n = 44$ at D 21 and 32 at D 42). The lower dosage of captopril + HCTZ produced a number of side-effects ($n = 17$ at D 21 and 20 at D 42) very similar to the number observed with the placebo ($n = 15$ at D 21 and 14 at D 42). With captopril + HCTZ 50/25, 22 side-effects were seen at D 21 and D 42. Dizziness (six cases), asthenia (six cases), muscular cramps (four cases) were most frequent with the highest dosage of captopril + HCTZ (100/50). At D 21, with the medium dosage (50/25), nausea (three cases), asthenia (three cases), dizziness (two cases), taste distortion (two cases) were noticed. Similar side-effects were seen with the low dosage of captopril + HCTZ and placebo. At D 42, the

most frequent adverse reactions were nausea with the medium dosage (50/25) and dizziness with the high dosage (100/50). The number of muscular cramps decreased between D 21 and D 42.

The following results were seen on laboratory tests values.

Mean plasma creatinine did not change between D 0 and D 42 in all four groups of treatment. One subject of the placebo group had a value of $150 \mu\text{mol l}^{-1}$ at D 0 which decreased to normal at D 42. Four moderate increases were seen (one in placebo group, one in 50/25 and two in 100/50) but they did not reach pathological values.

There was no modification of mean sodium and potassium values and no pathological decrease of potassium values below 3.3 mmol l^{-1} .

Mean glycaemia, cholesterolaemia, triglyceridaemia and uricaemia were not modified by any of the four treatments.

Haematological tolerance was good although a significant treatment effect appeared ($P = 0.03$) for leucocytes. With the highest dosage of captopril + HCTZ (100/50), the mean decrease of leucocytes reached $1000 \text{ elements/mm}^3$ whereas with the low dosage of captopril + HCTZ (25/12.5) the increase was of 63 elements/mm^3 .

On neutrophilic polynuclears, a significant treatment effect is also noticed, but no difference between groups could be pointed out.

However, there was no individual pathological decrease of leucocytes or neutrophilic polynuclears.

Other elements of the blood count were not modified by either treatment.

Discussion

This study had as a main objective to choose the optimal dose of the fixed association captopril + HCTZ. The results showed a better efficacy of each active treatment when compared with placebo.

A choice based on the efficacy only would consider the highest dose as the best. However, the tolerance of this dose would not allow a safe use in the first attempt of treatment in ambulatory moderately hypertensive patients.

On a tolerance basis, the comparison between the lower (25/12.5) and intermediate dosage (50/25) does not show any difference between these two groups. But it appears, in spite of a significant efficacy of the low dosage (25/12.5) at Day 42, that the 50/25 mg dosage provided a more regular and earlier (D 21) improvement. Moreover, this dosage led to the normalization of

hypertension in 70% of patients as compared to 50% for the lower dosage. Therefore, the authors propose the 50/25 dosage as the one providing the best risk/benefit ratio.

Conclusion

This study, which sought to determine the therapeutic efficacy of three different dosage regimens of combinations of captopril + HCTZ to treat mild essential hypertension, showed that all dosage regimens tested were effective in de-

creasing BP, especially the diastolic value. In almost half of the patients, BP returned to normal or thereabout after 3 weeks' treatment with the 25/12.5 regimen and in about 70% of patients who received the 50/25 regimen.

In general, only mild adverse drug reactions occurred and this number increased with increasing dose. Because of the good therapeutic efficacy of the 50/25 mg regimen and the relatively low percentage of side-effects, this study suggests that this 2/1 captopril-HCTZ ratio represents the optimal treatment for moderate essential hypertension.

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