Once vs twice daily administration of a fixed combination of captopril plus hydrochlorothiazide in essential hypertension: a double-blind crossover study in known responders to a standard combination

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The purpose of this randomized, double-blind, crossover trial was to compare the hypotensive effects of a fixed combination of captopril (C) 50 mg and hydrochlorothiazide (HCTZ) 25 mg (C 50/HCTZ 25) once daily with those of a fixed combination of C 25 mg and HCTZ 12.5 mg (C 25/HCTZ 12.5) twice daily. We studied 199 patients (108 M, 91 F) with mild to moderate essential hypertension whose BP was already controlled by the co-administration of C 25 mg and HCTZ 12.5 mg twice daily. They were randomly assigned to either C 25/HCTZ 12.5 twice daily during the first 6 weeks and C 50/HCTZ 25 once daily during the second 6 weeks or C 50/HCTZ 25 once daily followed by C 25/HCTZ 12.5 twice daily. Both regimens showed comparable efficacy on office diastolic BP (91.6 vs 91.3 mm Hg). Systolic BP was slightly but significantly higher ($P = 0.02$) with the once daily formulation (141.2 vs 139.1 mm Hg). Fixed combinations once daily and twice daily resulted in identical working ambulatory BP ($133.7 \pm 13/83.6 \pm 8$ mm Hg vs $132.4 \pm 11/83.3 \pm 7$ mm Hg) without affecting heart rate. Adverse events were reported by 16% of patients and cough was the most common occurring in 7%. In conclusion, these results indicate that the fixed combination of C 50/HCTZ 25 given once daily controls office and working BP as well as the fixed combination C 25/HCTZ 12.5 given twice daily in patients with mild to moderate hypertension.

Keywords captopril hydrochlorothiazide hypertension working blood pressure

Introduction

Previous preliminary studies have reported that the use of a fixed combination of captopril (C) 50 mg + hydrochlorothiazide (HCTZ) 25 mg administered once daily produces adequate 24 h control of blood pressure in a small number of patients (Asmar *et al.*, 1987; Meijer *et al.*, 1987). However, there are presently no randomized studies available comparing its antihypertensive effect on office and ambulatory blood pressure with those of a fixed combination administered twice daily. The present double-blind, randomized, crossover study was thus designed to compare the effectiveness of the fixed combination of C 50 mg + HCTZ 25 mg (C 50/HCTZ 25) administered once daily with the fixed combination of C 25 mg plus HCTZ 12.5 mg (C 25/HCTZ 12.5) twice daily in hypertensive patients already controlled by the co-administration of C 25 + HCTZ 12.5 mg twice daily.

Methods

Patient selection

This multicentre study was conducted in Quebec city area under the supervision of the hypertension research unit at the Centre Hospitalier de l'Université Laval, in Quebec, Canada.

Previously treated and newly-diagnosed untreated outpatients of both sexes between 18 and 70 years of age with seated diastolic blood pressure between 95 and 114 mm Hg inclusive and seated systolic blood pressure lower than 220 mm Hg were eligible for inclusion in the study. Most patients had been previously identified by the investigators as requiring a drug combination to control their blood pressure. In all subjects secondary causes of hypertension were ruled out by routine screening tests. Exclusion criteria included significant cardiac,

pulmonary, renal, cerebrovascular, hepatic, haematologic or allergic disease and childbearing potential. All centres received approval from their respective institutional review board. Informed consent was obtained from each subject. In all patients current antihypertensive medication was withdrawn gradually at least 2 weeks before the beginning of the study.

Trial design

This study was a 20-week, randomized, double-blind, crossover clinical trial performed after a 2- to 4-week single-blind placebo run-in period. Only patients with the mean of two seated diastolic blood pressures between 95 and 114 mm Hg inclusive on two consecutive weekly visits within 4 weeks of their initial visit and evidence of compliance higher than 80% qualified for the entire study. After this placebo run-in period, patients entered the evaluation phase in which they were randomized in a double-blind fashion to treatment with either C 25 mg or HCTZ 12.5 mg twice daily. After 4 weeks patients with seated diastolic blood pressure ≥ 90 mm Hg received combination of C 25 mg and 12.5 mg twice daily for another 4 weeks. However, responders defined as having seated diastolic blood pressure < 90 mm Hg or a decrease greater than 20% were withdrawn from the study. To qualify for the comparison between the fixed combination of C 50/HCTZ 25 administered once daily in the morning for 6 weeks and the fixed combination of C 25/HCTZ 12.5 administered twice daily for 6 weeks, patients had to present blood pressure normalized (seated diastolic < 90 mm Hg) or decreased by more than 10% at the end of evaluation period. Patients eligible for the comparison period were randomly assigned in a double-blind fashion (without regard to the treatment administered by the first randomization), to receive either the once daily or the twice daily regimen of the fixed combination during the first part of the crossover and the alternate regimen during the second part of the crossover. No wash-out period was implemented between the two parts of this period. A double-dummy technique was used to preserve the blindness during the whole study.

Clinical procedures

At all visits during the study, blood pressure, heart rate and body weight were measured. Clinic visit blood pressure was measured by a single observer with a standard mercury sphygmomanometer and recording phase V Korotkoff sound as diastolic blood pressure. Measurements were taken on the same arm throughout the study 12 h after the previous evening dose of medication. Blood pressure was defined as the mean of two readings taken 3 min apart with the patient in the sitting position. Side effects reported voluntarily were noted at each visit, and patients also completed a symptom questionnaire during the placebo run-in period, each monotherapy treatment, combination therapy twice daily and at the end of once daily and twice daily regimens of the fixed combination. Routine laboratory tests were also performed on each patient at the same time points. Ambulatory working blood pressure profiles were recorded using a portable automated device (Spacelabs system model 90202, Spacelabs INC REDMOND

WASH USA) after 6 weeks of the fixed drug combination administered once daily and twice daily in 88 randomly selected patients. All evaluations were done during working days and the recorder was fitted between 07.00 h and 07.30 h. Blood pressure was recorded at 30 min intervals during 12 h from 08.00 h to 19.00 h inclusive. Patients were instructed to stop muscular activity and keep their arms entirely still during blood pressure measurements. Monitor accuracy was validated against a conventional mercury sphygmomanometer using a T-tube connector (Graettinger *et al.*, 1988).

Statistical analysis

Statistical analysis was performed using Student's *t*-test for characteristics of treatment groups and the Chi-square test for contingency tables. The comparison of once daily and twice daily regimens was based on office seated systolic and diastolic blood pressure at the end of the two phases of the crossover comparison periods and the analysis of variance for split-plot designs was used. Drug effects on ambulatory blood pressure were compared using an analysis of variance for a cross-over design. All *P* values were based on two-tailed tests. Tests of hypothesis to assess comparability and efficacy were declared statistically significant if *P* was lower than or equal to 0.05. Data are given as mean $\pm$ s.d.

Results

Patient population

A total of 256 Caucasian patients were recruited for the study. Fifteen (15) were withdrawn during the placebo run-in period (13 because of blood pressure normalization and 2 because seated diastolic blood pressure exceeded 114 mm Hg). Of the 241 patients who entered the double-blind evaluation period, 42 dropped out from the study (normalization of blood pressure during monotherapy (5 patients), goal diastolic blood pressure not reached with bitherapy (26 patients), adverse events (5 patients), poor compliance with treatment (2 patients), personal reasons (3 patients) and intercurrent disease (1 patient). Of the 199 patients randomized to the comparison phase of the study, similar demographic characteristics were achieved among the groups hereafter referred to as twice daily/once daily and once daily/twice daily groups.

Blood pressure

Mean clinical blood pressure decreased from $159.3 \pm 16.1/104.4 \pm 5.1$ mm Hg on placebo to $152.8 \pm 15.6/98.1 \pm 6.1$ mm Hg after 4 weeks of C 25 mg twice daily and to $142.5 \pm 15.5/92.9 \pm 7.3$ mm Hg on C 25 mg + HCTZ 12.5 mg twice daily. HCTZ 12.5 mg twice daily decreased mean blood pressure from $156.3 \pm 15.3/102.9 \pm 5.1$ mm Hg to $145.7 \pm 12.6/96.4 \pm 4.8$ mm Hg; with HCTZ 12.5 mg + C 25 mg twice daily it was reduced to $139.1 \pm 13.8/90.5 \pm 5.6$ mm Hg. It may be noted that baseline diastolic blood pressure was significantly higher in the captopril group compared with hydrochlorothiazide (*P*

≈ 0.02). This difference was still present at the end of evaluation period. Blood pressure was normalized or decreased by more than 10% in 88% of subjects at the end of this period. In patients who entered the comparison period, mean blood pressure reduction from baseline during the 4 weeks of monotherapy was 9.1/6.2 mm Hg (95% confidence intervals 6.3, 11.9/5.3, 7.1). The addition of the second drug produced a further decrease of 9.6/7.3 mm Hg (95% confidence intervals: 6.9, 12.3/6.4, 8.2). At the end of 4 weeks of bitherapy, blood pressure reduction was comparable in both groups of patients. There were no significant changes in heart rate in both groups with mean values at week 8 being identical to placebo readings.

Of the 199 patients who entered the comparison period six dropped out because of adverse events. At the end of this study, 97 patients were left for analysis in the once daily/twice daily group and 96 in the twice daily/once daily group for a total of 193 patients. Mean office blood pressure for all patients (Figure 1) decreased significantly from $157.3 \pm 15/103.5 \pm 5.1$ mm Hg on placebo to $138.5 \pm 13/90 \pm 4.3$ mm Hg ($P < 0.001$ for both systolic and diastolic blood pressure) after 4 weeks of treatment with C 25 mg + HCTZ 12.5 mg twice daily. There was no statistical difference in blood pressure reduction between that regimen at the end of titration period and the fixed combination of C + HCTZ administered once or twice daily. However, while once and twice daily fixed combinations showed comparable efficacy on diastolic blood pressure at 3 weeks (90.4 vs 90.7 mm Hg) and 6 weeks (91.6 vs 91.3 mm Hg), mean seated systolic blood pressure was slightly but significantly higher (141.2 vs 139.1 mm Hg; $P = 0.02$) with the once daily fixed combination at week 6. No significant carry-over effect was observed between both treatment phases ($P = 0.21$ for systolic and $P = 0.72$ for diastolic blood pressures). Heart rate did not change significantly with either regimen.

The results of the ambulatory blood pressure measurements during working hours after 6 weeks of fixed combinations of C 50/HCTZ 25 once daily and C 25/

HCTZ 12.5 twice daily are shown as hourly mean values in Figure 2. In comparing the two regimens, no significant differences in the daily course and levels of systolic and diastolic pressures were observed. Moreover, mean work ambulatory blood pressure was similar with the fixed combination administered once daily and twice daily; $133.7 \pm 13.3/83.6 \pm 8.4$ mm Hg vs $132.4 \pm 11.1/83.3 \pm 7.6$ mm Hg. Mean heart rate was not significantly reduced with either treatment during ambulatory recordings (84.5 ± 9.0 vs 84.3 ± 9.4 beats min^{-1}).

Adverse events

Adverse events remotely, possibly or probably related to therapy that occurred during evaluation period were reported in 14 patients (5.8%) receiving C monotherapy, 15 patients (6.2%) receiving HCTZ monotherapy and 52 patients (21.6%) receiving C + HCTZ combination. The most frequent adverse events during C therapy were cough, fatigue and frequent micturition: each appeared in three patients (2.5%). During hydrochlorothiazide therapy, the most common adverse events were dizziness, tachycardia and frequent micturition reported by 4, 3 and 3 patients respectively. The co-administration of C + HCTZ increased the incidence of dizziness (13 patients or 5.6%). There was no significant difference in the frequency or severity of adverse events reported during once daily (10.6%) and twice daily (13.1%) administrations of the fixed combination. The most common adverse event during this maintenance period was cough reported by 14 (7%) patients and considered to be related to C therapy since it disappeared after study completion. The incidence of withdrawals due to adverse events was 4% (11 patients) during the entire study and 3% (6 patients) during the comparison period.

Laboratory data

No significant changes occurred in haematology, glucose, lipid, creatinine and urinary values during the trial. Clinically small but statistically significant ($P < 0.01$)

Figure 1 Mean office sitting blood pressure during the placebo period □, at the end of evaluation period ■ and after 3 and 6 weeks of fixed combination of C 50/HCTZ 25 once daily ▨ or C 25/HCTZ 12.5 mg twice daily ▩. * $P < 0.05$ in comparison with C 50/HCTZ 25 once daily, *** $P < 0.001$ in comparison with placebo run-in.

Figure 2 Comparison of working ambulatory systolic (upper part) and diastolic blood pressure (lower part) after 6 week treatment with C 50/HCTZ 25 once daily (■, ●) and C 25/HCTZ 12.5 twice daily (□, ○).

decreases in sodium (142 ± 2.0 vs 140 ± 2.2 mmol l⁻¹) and potassium (4.1 ± 0.3 vs 3.8 ± 0.4 mmol l⁻¹), and rise in uric acid (350 ± 81 vs 399 ± 95 mmol l⁻¹) were observed compared with baseline.

Discussion

Angiotensin-converting enzyme (ACE) inhibitors have gained increasing acceptance for the treatment of essential hypertension either as monotherapy or with concomitant diuretics (Joint National Committee, 1988; Williams, 1988). The results of this multicentre trial of mild to moderate essential hypertension show that the fixed combination of C 50/HCTZ 25 once daily provided an antihypertensive effect equal in magnitude to that of the fixed combination of C 25/HCTZ 12.5 twice daily in patients already controlled by the co-administration of C 25 mg and HCTZ 12.5 mg twice daily. Moreover this study confirms previous reports (Weinberger, 1982, 1983, 1985) demonstrating the additive effect of the two agents on blood pressure. Indeed, beneficial blood pressure response (normalized blood pressure or decreased by 10% or more) was seen in 88% of the patients as reported by Clementy *et al.* (1988). The average decrease in diastolic blood pressure during once-daily therapy was comparable with the blood pressure reduction achieved during twice-daily therapy.

There is increasing awareness that single measurements of blood pressure in the clinic may not accurately reflect blood pressure levels throughout the rest of the day (Pickering *et al.*, 1985). Numerous studies have showed that ambulatory blood pressure monitoring is a reliable method for evaluating whether medication can control blood pressure over 24 h (Weber, 1988). In our study, ambulatory blood pressure monitoring illustrated the similar antihypertensive efficacy of both once daily and twice daily regimens of fixed C + HCTZ combination during regular working activities. These findings may be clinically relevant since available studies have shown that the correlation between blood pressure during work and left ventricular mass was much closer than was the correlation of either the 24 h blood pressure or office blood pressure with left ventricular mass (Devereux & Pickering, 1988). Such a correlation would thus favour

the use of antihypertensive agents effective in reducing clinic and ambulatory blood pressure (O'Brien *et al.*, 1989). In this regard, the combination of low doses of captopril and hydrochlorothiazide appears most appropriate since both ACE inhibitors and hydrochlorothiazide reduce ambulatory work pressure (Lacourcière & Provencher, 1989).

Side effects are important factors in the clinical uses of drugs. The proportion of patients reporting adverse reactions during the active treatment was greater (21.6%) when patients were treated with C + HCTZ than when treated with C (5.8%) or HCTZ (6.2%) alone. However, it should be noted that the incidence of adverse reactions decreased by nearly 50% following the fixed combination administered once or twice daily. Moreover, there was no difference in nature, frequency or intensity of reported side effects between once daily and twice daily regimens of the fixed combination. The most commonly encountered adverse effect during the comparison period was cough, which now is often mentioned as a common complaint, even at low doses of ACE inhibitors (Hood *et al.*, 1987). Indeed, cough occurred in 14 patients (7%) taking the fixed combination. Nevertheless, as previously described (Boulet *et al.*, 1989), cough resolved within 2 weeks after the withdrawal of the fixed combination therapy.

The mean decrease in sodium and potassium and the rise in uric acid were likely to be due to the thiazide component of the combination since captopril has not been shown to cause metabolic alterations (Weinberger, 1985). However, our results demonstrate that the administration of C did not appear to offset the adverse metabolic effects of HCTZ contrary to claims by Weinberger (1983).

In conclusion, the efficacy and safety profile of the fixed combination of C 50 mg and HCTZ 25 mg makes it an alternative therapeutic agent for the once daily management of mild and moderate hypertension.

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