Comparative effects of zofenopril and hydrochlorothiazide on office and ambulatory blood pressures in mild to moderate essential hypertension

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1 Thirty-eight patients with mild to moderate essential hypertension (seated diastolic 95–110 mm Hg) were randomized double-blind to treatment with either zofenopril ($n = 19$) or hydrochlorothiazide ($n = 19$) over a period of 12 weeks.

2 Office blood pressure, heart rate, side effects and metabolic changes were assessed at the end of the run-in period on placebo and after 4, 8, 12 weeks treatment at the same time, 22–24 h after the last dosing. Ambulatory recordings over 14 h (8 h to 22 h) were performed at the end of placebo period and after active treatment for 12 weeks.

3 The two regimes reduced office blood pressures equally with minimal additional effect seen on increasing the dose. Both zofenopril and hydrochlorothiazide lowered average baseline ambulatory blood pressure, but zofenopril had greater efficacy in reducing BP during some working hours.

4 Adverse reactions were mild and transient with both drugs. There were no significant changes in laboratory values.

5 Thus hydrochlorothiazide and zofenopril given once daily at low dosage both reduce office and ambulatory blood pressures and are well tolerated.

Keywords essential hypertension ambulatory pressures zofenopril hydrochlorothiazide

Introduction

The superiority of ambulatory pressure readings over casual readings obtained in the office in predicting long term hypertensive vascular complications has been suggested (Perloff *et al.*, 1983). Numerous studies have since showed that ambulatory blood pressure monitoring is a reliable method for evaluating whether medication can control blood pressure over 24 h (Pickering *et al.*, 1985). In recent studies it was demonstrated that angiotensin converting enzyme (ACE) inhibitors captopril and enalapril

significantly reduce 24 h blood pressure (Meijer *et al.*, 1987; Gradman *et al.*, 1985) and this effect is more pronounced when captopril or enalapril are combined with hydrochlorothiazide (Assmar *et al.*, 1987; Meijer *et al.*, 1987; Baumgart *et al.*, 1986).

Although hydrochlorothiazide (HCTZ) has been used for three decades in the treatment of essential hypertension, there are presently no data available comparing its antihypertensive effect on ambulatory pressures with those of

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other antihypertensive agents. Zofenopril calcium, a second generation ACE inhibitor is an analogue of captopril. Its chief distinguishing features are a fivefold greater potency than that of enalapril *in vivo*, greater stability, higher absorption, longer duration of action at equivalent dose and a dual route of excretion via kidney and liver (Mackanness, 1985).

The purposes of this study were to evaluate by a non-invasive ambulatory blood pressure monitoring method the antihypertensive effects of zofenopril calcium (SQ 26,991), and hydrochlorothiazide given once daily in low dosages in mild to moderate essential hypertension.

Methods

Patients

This study was a double-blind randomized investigation with parallel groups of white patients who were recruited from the hypertension clinic at the Centre hospitalier de l'Université Laval in Quebec, Canada.

Previously treated and newly-diagnosed untreated outpatients of both sexes between 20 and 70 years of age with mild to moderate essential hypertension WHO stages 1–11 were eligible for inclusion in the study. In all patients secondary causes of hypertension were ruled out by routine screening tests. Informed consent was obtained from each participant and the study was approved by the local hospital ethics committee. Exclusion criteria included cerebral or myocardial infarction within the last 6 months, insulin dependent diabetes, congestive heart failure, angina pectoris, renal impairment, serious allergy, history of drug hypersensitivity, collagen diseases, a total leucocyte count below 3000 mm^3 , and childbearing potential. Concomitant medication known to interfere with the study medication was not permitted. In all patients previous therapy was discontinued for at least 2 weeks before the beginning of the study.

Trial design

After inclusion in the study the patients entered a 4–6 week single-blind placebo period. Only patients with the mean of three seated diastolic blood pressures between 95 and 110 mm Hg on two consecutive 2-week visits within 6 weeks of their initial visit qualified for the entire study. After this placebo period patients were randomized double-blind to treatment with either zofenopril 30 mg once daily or hydrochlorothia-

zide 25 mg once daily. Active treatment and placebo tablets were identical and patients were not aware that their treatment was being changed. After 4 weeks patients with normalized office blood pressure (seated diastolic blood pressure < 90 mm Hg) had their medication continued at the same dose for 8 more weeks. Zofenopril was increased to 60 mg and hydrochlorothiazide to 50 mg daily in those patients who remained hypertensive. Subjects were given this dosage for another 8 week period.

Upon enrolment in the study patients were seen once every 2 weeks during placebo period and then monthly. Visits were scheduled so that blood pressure and pulse rate could be assessed approximately 24 h after the previous morning dose of zofenopril and hydrochlorothiazide. Office blood pressure was taken by the same trained observer, utilizing a standard mercury sphygmomanometer and recording phase V Korotkoff sound as diastolic blood pressure. Blood pressure was defined as the mean of three readings taken in the seated and standing positions after 15 min of rest. At each visit body weight was measured, pill counts were conducted and new medication was dispensed. The following procedures were also completed for each patient at the same time points: routine laboratory tests, electrocardiography and blood lipids. Non invasive ambulatory blood pressure monitoring using an automated device (Space-labs System model 5200) was carried out on each patient on the last day of the placebo period and again at the end of the active period. Recordings were performed every 30 min from 08.00 h to 22.00 h, the patients working as usual during the day and then going home normally in the evening. Patients were instructed to have their arms raised to the level of the heart and to stop muscular activity during blood pressure measurements. The reliability of this technique was determined previously (Assmar *et al.*, 1987). Mean ambulatory blood pressures were defined as an average of all nonartifactual measurements obtained during the entire recording examination. Results at each hour are the average of two measurements on each patient. Criteria for artifact have been reported previously (Kennedy *et al.*, 1979). At the end of the placebo period and at each visit during the active treatment phase patients were asked to report any adverse effects experienced.

Statistical analysis

For comparison of age and weight, a one-way analysis of variance was performed. Changes in

office sitting and standing blood pressures from placebo treatment were evaluated using an analysis of variance with one grouping factor (drugs) and two repeated factors (sitting *vs* standing; placebo *vs* taking drug). At each individual time the ambulatory pressures were evaluated using an analysis of variance with one grouping factor (drugs) and one repeated factor (placebo *vs* taking drug). Data are given as mean $\pm$ standard deviation. The null hypothesis was rejected when $P < 0.05$.

A power calculation was made employing the mean office blood pressure measurement on the last day of the placebo period and the last day of the maintenance phase (Andersen & Holm, 1984). Diastolic blood pressure: the power was 80% to detect a 6.3 mm Hg difference between the two drugs. Systolic blood pressure: the power was 80% to detect a 13.5 mm Hg difference between the two drugs.

Results

Of the 45 patients who entered the study seven dropped out because blood pressure fell during

the placebo run-in-phase. At the end of this study, 19 patients were left for analysis in the zofenopril group and 19 in the hydrochlorothiazide group. The treatment groups were similar with regard to baseline characteristics such as sex, age, weight, office sitting blood pressure and duration of hypertension (Table 1). At the end of the placebo period 32 patients had mild while six patients had moderate hypertension.

All 38 patients completed the double-blind study and had two ambulatory blood pressure monitorings, one while taking placebo, and a second after 12 weeks of active medication (zofenopril or hydrochlorothiazide). Both treatment groups showed decreases in office systolic and diastolic blood pressures in sitting position after 4, 8 and 12 weeks compared with baseline (Table 2). Twelve patients had their blood pressure controlled with zofenopril 30 mg daily and in seven patients the dose was increased to 60 mg daily. The hydrochlorothiazide group including 10 patients taking 25 mg once daily and nine patients on 50 mg daily, demonstrated a similar decrease in office blood pressure to that observed with zofenopril therapy. Only two patients on zofenopril and three patients on

Table 1 Demographics and baseline data (mean $\pm$ s.d.)

Characteristics	Zofenopril (n = 19)	Hydrochlorothiazide (n = 19)
Sex		
Male	8	8
Female	11	11
Age (years)	52 $\pm$ 10	57 $\pm$ 9
Weight (Kg)	72.6 $\pm$ 11.1	71.9 $\pm$ 14.6
Blood pressure (mm Hg)		
Systolic	155 $\pm$ 22	157 $\pm$ 21
Diastolic	98 $\pm$ 6	98 $\pm$ 6
Duration of hypertension (years)	9.4 $\pm$ 5	9.9 $\pm$ 4

Table 2 Clinical and monitoring blood pressure levels during the study (mean $\pm$ s.d.)

		Clinical BP (mm Hg)				Monitoring BP (mm Hg)	
		After placebo	After 4 weeks	After 8 weeks	After 12 weeks	After placebo	After 12 weeks
Group ZOFE	SBP (mm Hg)	151 $\pm$ 14	140 $\pm$ 16	140 $\pm$ 18	137 $\pm$ 18	141 $\pm$ 18	125 $\pm$ 18
	DBP (mm Hg)	98 $\pm$ 3	90 $\pm$ 8	87 $\pm$ 8	89 $\pm$ 7	89 $\pm$ 11	80 $\pm$ 11
Group HCTZ	SBP (mm Hg)	154 $\pm$ 15	144 $\pm$ 19	139 $\pm$ 17	139 $\pm$ 15	150 $\pm$ 26	137 $\pm$ 20
	DBP (mm Hg)	100 $\pm$ 4	91 $\pm$ 7	88 $\pm$ 5	89 $\pm$ 6	94 $\pm$ 13	84 $\pm$ 10

Figure 1 Non invasive 24 h ambulatory blood pressure measurements by the spacelabs monitor. For every hour, data on zofenopril and hydrochlorothiazide are compared with placebo. (○---○ placebo, ●—● active treatment). Data are given as means. ● = $P < 0.05$, ●● = $P < 0.01$, ●●● = $P < 0.001$.

Figure 2 Comparison of ambulatory systolic and diastolic blood pressure reductions after 12 week treatment with hydrochlorothiazide (○---○) and zofenopril (●—●). * $P < 0.05$, ** $P < 0.01$.

hydrochlorothiazide became normotensive when the dose was increased. There were no significant changes in heart rate in both groups with mean sitting and standing values at week 12 being identical to placebo readings. When we compare average blood pressure change over the two 14 h observation periods, both systolic and diastolic pressures were decreased with either zofenopril or hydrochlorothiazide (Table 2). Automatic blood pressure monitoring also demonstrated that both zofenopril and hydrochlorothiazide given once daily reduced systolic

and diastolic blood pressure every single hour during the daytime (Figure 1) and these reductions were statistically significant. This effect was slightly more pronounced with zofenopril for some hours (Figure 2). Mean heart rate was not significantly reduced with either treatment during ambulatory recordings. In both groups weight remained stable during the study.

No patient discontinued the study because of adverse effects. The only significant alteration in laboratory values which was observed during the study was a moderate increase in serum glutamic

oxaloacetic and serum glutamic pyruvic transaminases (SGOT, SGPT) in a patient treated with zofenopril. However liver enzymes decreased to normal value in this patient 2 weeks after cessation of zofenopril. Electrocardiographic changes were not seen with either treatment.

Discussion

This double-blind study compared the effects of zofenopril a new ACE inhibitor and hydrochlorothiazide on office and ambulatory blood pressures in patients between 20 to 70 years of age with mild to moderate essential hypertension. Treating patients with zofenopril or hydrochlorothiazide given alone resulted in a decrease in office sitting and standing blood pressures 24 h after drug ingestion. The reduction of blood pressures was similar with both drugs as reported in studies comparing captopril or enalapril with hydrochlorothiazide (Weinberger, 1982, 1985; Fergusson *et al.*, 1982). Blood pressure control in 50% of the hydrochlorothiazide group and in 63% of the zofenopril group with low starting doses is consistent with previous observations and supports the conclusion that low-dose diuretic and ACE inhibitor therapies are often effective in treating hypertension regardless of the age of the patient (Kaplan, 1984; Jenkins *et al.*, 1985). Moreover increasing the dose of zofenopril or hydrochlorothiazide was shown to have a small additional effect and to normalize blood pressure only in a few more patients, as has also been shown by others (VA cooperative Study Group, 1982; McVeigh *et al.*, 1988).

Non-invasive ambulatory blood pressure monitoring was introduced a few years ago to better define blood pressure in patients with

borderline, mild to moderate hypertension and to assess the effects of antihypertensive therapy, as well as to quantify variability of blood pressure (Pickering *et al.*, 1985). This non-invasive procedure has been used in recent years to assess the efficacy of new drugs such as ACE inhibitors, calcium antagonists, β -adrenoceptor blockers or drug combinations in lowering ambulatory pressures. Numerous studies have shown good control of ambulatory pressures with ACE inhibitors given as monotherapy and better control when combined with thiazides (Assmar *et al.*, 1987; Meijer *et al.*, 1987; Baumgart *et al.*, 1986). However studies comparing the effects of ACE inhibitors and thiazide diuretics that are still commonly used first-step drugs as a monotherapy were not available so far. In our study, automatic blood pressure monitoring demonstrated the diurnal hypotensive efficacy of both zofenopril and hydrochlorothiazide given once daily (Figure 1). Moreover zofenopril therapy produced significantly greater reductions in systolic and diastolic blood pressures for some hours during working time. These findings may be relevant since work blood pressure could have a disproportionate effect on target organ damage (Devereux *et al.*, 1983; Parati *et al.*, 1987).

Side effects are important factors in the clinical uses of drugs. During this study, no serious clinical adverse experiences were noted, but because of the small number of patients it is not possible to make any interpretation of the side-effects reported.

In summary, both the new ACE inhibitor zofenopril and hydrochlorothiazide given once daily at low doses provided equivalent office blood pressure reduction. In addition both treatments significantly reduced ambulatory blood pressure at every hour during the daytime with a greater effect observed in the zofenopril group.

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