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Multicentre 12-week double-blind comparison of doxazosin, prazosin and placebo in patients with mild to moderate essential hypertension

D. TORVIK[1] & H.-P. MADSBU[2]
[1]Telemark Sentralsjukehus, 3700 Skien and [2]Elverum Legesenter, 2400 Elverum, Norway

1 A 12-week double-blind study was performed to compare the safety and efficacy of doxazosin, prazosin and placebo in 172 patients with essential hypertension.
2 According to response, patients received doxazosin 1–16 mg once daily, prazosin 0.5–10 mg twice daily, or placebo. Mean final daily doses were doxazosin 11.3 mg and prazosin 13.8 mg.
3 Doxazosin once daily and prazosin twice daily both produced statistically significant reductions in both standing and supine blood pressures when compared with placebo. No significant differences between treatments were recorded for standing and supine heart rates.
4 Doxazosin, prazosin and placebo all had a similar effect on plasma lipid profiles, i.e. an increase in HDL/total cholesterol of approximately 10%. The differences between treatments were not statistically significant. The HDL/total cholesterol ratio significantly increased from baseline to the end of treatment for all three groups, the decrease in triglycerides being statistically significant only in the doxazosin-treated group.

Keywords doxazosin hypertension lipids prazosin

Introduction

Treatment of arterial hypertension has been shown to reduce the incidence of cerebrovascular accidents and heart insufficiency (Veterans Administration Co-operative Study Group on Antihypertensive Agents, 1967, 1970; US Public Health Service Hospitals Co-operative Study Group, 1977; Hypertension Detection and Follow-up Program Co-operative Group, 1979; Helgeland, 1980; Management Committee of the Australian Therapeutic Trial in Mild Hypertension, 1980). Arterial hypertension is also a coronary risk factor. However, antihypertensive treatment has not been shown to reduce the incidence of coronary heart disease, including myocardial infarction.

Various antihypertensive drugs affect the plasma levels of total cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL). A shift in plasma lipid levels toward the presumed more atherogenic components, and/or a reduction of anti-atherogenic components, could explain the apparent lack of effect on the coronary atherosclerotic process (Lees & Lees, 1982; Lasser *et al.*, 1984; Leren, 1984; Goto, 1984). In fact, epidemiological studies indicate that high HDL cholesterol levels are a strong negative risk factor (Miller *et al.*, 1977; Castelli, 1984).

Prazosin, a selective peripheral α_1-adrenoceptor antagonist which has been shown to be an effective first-line therapy in the treatment of essential hypertension (Stanaszek *et al.*, 1983), has a variable but consistently favourable effect on serum lipid levels (Helgeland *et al.*, 1978; Sirtori, 1981; Leren *et al.*, 1980; Kokubu *et al.*, 1981; Velasco *et al.*, 1981). Doxazosin is structurally related to prazosin but pharmacokinetic studies in man (Elliott *et al.*, 1982; Vincent *et al.*, 1983) have shown that the plasma half-life of doxazosin is 9–11 h compared with 2–3 h for prazosin, indicating that a once-daily dosing regimen might be appropriate with doxazosin. In order to ensure patient compliance and safety, a simple drug regimen is essential (Gatley, 1968; Ayd, 1974; Forsmann & Johnsson, 1982).

The objectives of this double-blind, multicentre study were to compare the efficacies of doxazosin once daily, prazosin twice daily and placebo in patients with essential hypertension. Safety and effect on plasma lipids were also assessed.

Methods

Patients

One hundred and seventy-two patients aged 26–71 years with essential hypertension and an otherwise

Table 1 Trial protocol

	Single-blind placebo run-in						*Double-blind treatment phase*	
Visit number	2	3	4	5	6	7	8	9
Study week	0	2	4	6	8	10	12	16
Assessment:								
BP/HR, body weight	X	X	X	X	X	X	X	X
Symptoms and physical findings	X		X					X
Side effects		X	X	X	X	X	X	X
ECG	X		X					X
Ophthalmology	X							X
Chest X-ray			X					X
Laboratory tests (safety)	X		X			X		X
Lipids	X		X			X		X

satisfactory medical history gave their informed consent to participate in the study. Patients already receiving antihypertensive therapy had their therapy withdrawn 4 weeks before the start of the study and could then enter a 4 week single-blind placebo run-in phase (Table 1). Patients not receiving antihypertensive therapy entered directly the 4 week single-blind, placebo, run-in phase. Patients entered the double-blind active treatment study provided that their blood pressures in both supine and standing positions during the 4 week run-in met the following criteria: (1) Phase V diastolic blood pressure (BP) immediately before double-blind treatment (week 4) of 95–114 mmHg (100 mmHg or higher in patients aged 60 years or more). (2) Average diastolic BP (during weeks 0, 2 and 4) of at least 90 mmHg. (3) Difference in diastolic BP between weeks 2 and 4 of run-in of 10 mmHg or less.

Lactating women, women of child bearing potential and patients on concomitant antihypertensive agents were excluded from the study.

Methods

Patients were randomly assigned to double-blind

Table 2 Demographic data for all patients

	Doxazosin			*Prazosin*			*Placebo*		
	Male	*Female*	*Total*	*Male*	*Female*	*Total*	*Male*	*Female*	*Total*
Number of patients	33	24	58	35	22	57	37	20	57
Age category (years)									
<15	0	0	0	0	0	0	0	0	0
15–44	12	4	16	5	1	6	12	3	15
45–64	20	17	37	26	19	45	23	13	36
>65	1	4	5	4	2	6	2	4	6
Mean age (years)	48.0	54.0	50.6	52.5	55.5	53.7	51.3	53.0	51.9
Age range (years)	26–67	31–69	26–69	29–71	39–70	29–71	33–68	30–70	30–70
Mean weight (kg)	82.8	68.5		84.3	69.0		83.8	68.8	
Weight range (kg)	67–110	45–102		60–108	52–88		61–102	48–92	
Caucasian	33	24	57	35	22	57	36	20	56
Oriental	0	1	1	0	0	0	1	0	1

treatment with doxazosin, prazosin or placebo. Each patient was instructed to take the medication twice daily, morning and evening. Patients in the doxazosin treatment group received placebo as the evening dose; patients in the prazosin treatment group received active drug as the morning and evening doses.

Blood pressure (random zero sphygmomanometer) and heart rate measurements were made approximately 24 h after the previous morning dose. Assessments were therefore made 12 and 24 h post-dose for prazosin and doxazosin, respectively. Blood pressure (phase V) and heart rate were recorded in duplicate after 5 min in the supine position and after 2 min in the standing position at each review visit.

According to response 24 h after the previous morning dose, patients in the doxazosin group received 1, 2, 4, 8 or 16 mg once daily, whilst patients in the prazosin group received 0.5, 1, 2, 4, or 10 mg twice daily. The dose was titrated upwardly at 2-weekly intervals until either target BP was achieved, or until side-effects prohibited further increases. The target BP was defined as a reduction from baseline diastolic BP to less than 90 mmHg, or by at least 10 mmHg for patients with a diastolic BP of less than 100 mmHg, in both supine and standing positions.

An ophthalmic examination, chest X-ray and 12-lead ECG were performed on entry into and completion of the study. In addition, haematological and biochemical examinations were performed at regular intervals and the results monitored for possible drug-related changes. Side-effects, observed or volunteered, were recorded at each review visit.

Statistical methods

Results are expressed as mean values with standard errors of the mean changes.

For BP, HR and body weight, analyses of changes from baseline were performed by two-way analysis of variance, with treatment, centre and their interaction as factors.

For the lipids, similar analyses were carried out on the logarithms of values, with laboratory used as the blocking factor rather than centre.

Results

One hundred and seventy-two patients (58 doxazosin; 57 prazosin; 57 placebo) entered the double-blind treatment phase. The three patient groups were well matched for baseline characteristics. Details of patients are given in Table 2. The mean duration of hypertension within each treatment group was between 5 and 7 years and the baseline severity was moderate (average diastolic BP 100—<115 mmHg) in the majority of cases.

The efficacy analysis was performed on 54 patients in the doxazosin group, and 49 and 56 patients in the prazosin and placebo groups respectively. The reasons for exclusion of four doxazosin patients from the efficacy analysis were: withdrawal due to side-effects unrelated to therapy (1); poor compliance (1), and BP measurements outside 18–30 h post-dose limits (2).

The reasons for exclusion of eight prazosin patients were: withdrawal due to intercurrent illness (1); withdrawal due to side-effects of nausea/dizziness (1); BP measurement outside 9–15 h post-dose limits (5), and error in dosing schedule (1). The patient excluded from the placebo group was withdrawn with side-effects of nausea and vomiting.

The mean final daily doses for the efficacy subgroups were doxazosin 11.3 mg and prazosin 13.8 mg. The duration of double-blind therapy was within a window of 10–16 weeks. The actual mean recorded times post-dosing of the final BP and HR evaluations were 25.1 h for doxazosin and 12.0 h for prazosin.

Blood pressure and heart rate

Efficacy was based on mean changes in BP and HR from baseline (average of readings from final two visits in the single-blind placebo run-in) to the end of double-blind treatment. The results are shown in Tables 3 and 4. In the standing position there was no significant difference between the mean reductions in BP produced by doxazosin (14.2/10.0 mmHg) and prazosin (12.0/10.4 mmHg) but both produced significantly greater mean falls in BP ($P < 0.05 - < 0.005$) when compared with placebo (5.2/4.0 mmHg). Similar results were obtained when the supine BPs of the three treatments were compared (Figure 1).

There was no statistically significant difference in HR between the three treatments, small mean reductions (0.7 – 3.1 beats min^{-1}) being recorded in both standing and supine positions.

Defining a responder as a patient with a fall in standing diastolic BP of either 10 mmHg or more, or to below 90 mmHg and by 5 mmHg or more, then responder rates were doxazosin 25/54 (46%), prazosin 29/49 (59%), and placebo 13/56 (23%).

At the final assessment visit the investigator

Table 3 Blood pressures and heart rates: change from baseline after 12 weeks' active treatment

Variable	*Treatment group*	n	*Baseline (mean)*	*Final (mean)*	*Change, final-baseline (mean ±s.e. mean)*
Standing systolic BP (mmHg)	Doxazosin	54	159.6	145.4	−14.2±1.7
	Prazosin	49	159.4	147.4	−12.0±1.3
	Placebo	56	157.6	152.4	−5.2±1.8
Standing diastolic BP (mmHg)	Doxazosin	54	106.7	96.7	−10.0±1.0
	Prazosin	49	106.8	96.4	−10.4±1.0
	Placebo	56	107.2	103.3	−4.0±1.0
Standing heart rate (beats min^{-1})	Doxazosin	54	76.9	75.7	−1.2±1.1
	Prazosin	49	77.9	76.8	−1.1±1.2
	Placebo	56	77.3	76.6	−0.7±1.1
Supine systolic BP (mmHg)	Doxazosin	54	161.6	150.1	−11.6±1.8
	Prazosin	49	161.5	151.8	−9.7±1.5
	Placebo	56	158.5	155.2	−3.3±1.8
Supine diastolic BP (mmHg)	Doxazosin	54	103.8	94.6	−9.1±1.0
	Prazosin	49	102.8	94.2	−8.6±0.9
	Placebo	56	103.5	98.8	−4.6±0.9
Supine heart rate (beats min^{-1})	Doxazosin	54	71.5	68.4	−3.1±0.9
	Prazosin	49	72.9	71.0	−1.9±1.0
	Placebo	56	71.6	70.0	−1.6±0.9

scored the overall efficacy of the treatment as excellent, good, poor or none. Combining the excellent and good categories, the results were: doxazosin 35/54 (65%), prazosin 28/49 (57%), and placebo 19/56 (34%).

Lipids

All three treatments resulted in changes in blood lipids (Table 5) with approximately a 10% increase in the HDL/total cholesterol ratio. No statistically

Table 4 Blood pressures and heart rates — difference between treatments[a]

	Doxazosin-placebo			*Prazosin-placebo*			*Doxazosin-prazosin*		
Variable	*Mean difference (mmHg)*	*95% confidence interval*	P	*Mean difference (mmHg)*	*95% confidence interval*	P	*Mean difference (mmHg)*	*95% confidence interval*	P
Standing SBP (mmHg)	−9.1	−14.7, −3.4	0.002	−6.8	12.6, −1.0	0.03	−2.2	−8.1, −3.6	NS
Standing DBP (mmHg)	−6.0	−9.4, −2.7	0.0002	−6.5	−9.9, −3.1	0.0002	0.4	−3.0, 3.9	NS
Standing heart rate (beats min^{-1})	−0.5	−4.3, 3.4	NS	−0.4	−4.3, 3.6	NS	−0.1	−4.1, 3.9	NS
Supine SBP (mmHg)	−8.3	−14.1, −2.5	0.003	−6.4	−12.3, −0.5	0.05	−1.9	−7.8, 4.1	NS
Supine DBP (mmHg)	−4.5	7.6, −1.4	0.003	−4.0	−7.2, −0.8	0.01	−0.5	−3.7, 2.7	NS
Supine heart rate (beats min^{-1})	−1.6	−4.8, 1.7	NS	−0.3	−3.6, 3.0	NS	−1.3	−4.6, 2.1	NS

NS = $P > 0.05$
[a]Corrected for centre effect
SBP = systolic blood pressure, DBP = diastolic blood pressure

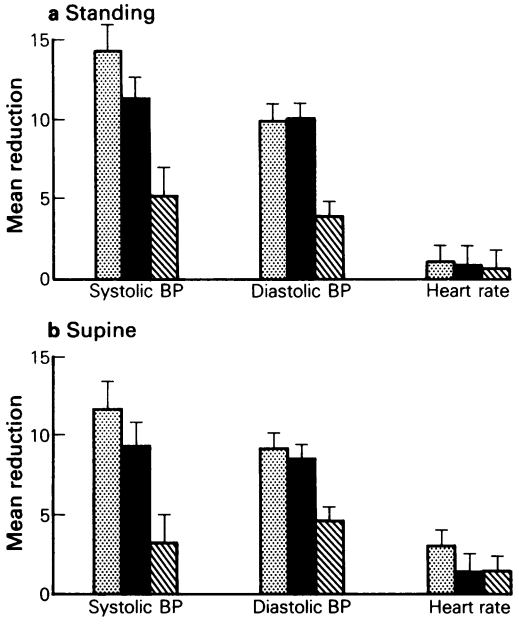

Figure 1 Mean ± s.e. mean reductions in (a) standing BP (mmHg) and heart rate (beats min^{-1}) and (b) supine BP (mmHg) and heart rate (beats min^{-1} after doxazosin (▨), prazosin (■) and placebo (▧).

significant differences between the active treatment and placebo groups were observed.

The HDL/total cholesterol ratio from baseline to the end of double-blind treatment was significantly ($P < 0.01$) increased for all three groups. The decrease in triglycerides from baseline to the end of double-blind treatment was statistically significant ($P < 0.05$) only for the doxazosin group.

Safety

Side-effects which were definitely or possibly related to treatment were reported by 31 doxazosin, 30 prazosin and 20 placebo patients. These were mainly mild to moderate in severity and either disappeared or were tolerated on further treatment. The number of patients with postural-type side-effects (vertigo, dizziness, postural dizziness) was similar on both active treatments: doxazosin 14, prazosin 12 and placebo 5. A greater incidence of headache/fatigue was reported for doxazosin (13) and prazosin (10) groups when compared with placebo (5). The incidence of other side-effects was similar for all three treatment groups.

Two patients were withdrawn from the study because of treatment-related side-effects. One patient receiving prazosin 4 mg twice daily withdrew owing to dizziness and nausea and one patient receiving placebo withdrew with nausea and vomiting.

The mean body weight of patients receiving doxazosin increased by 0.04 ± 0.20 kg and by 0.21 ± 0.2 kg for patients receiving prazosin. In the placebo group, however, the mean body weight gradually fell throughout the study, amounting to a loss of 1.18 ± 0.29 kg by the end of the study. The difference between the active and placebo groups was statistically significant ($P < 0.001$).

With respect to clinical chemistry no significant trend emerged in any of the treatment groups. There were possible treatment-related abnormalities in six, eight, and seven patients in the doxazosin, prazosin and placebo groups, respectively. Elevations of liver-related enzymes were seen in two patients receiving doxazosin and in one patient

Table 5 Lipid parameters: changes from baseline

Variable	*Treatment group*	n	*Geometric mean*		*% Change from baseline*[a] *(±s.e. mean)*
			Baseline	*Final*	
Total cholesterol (mmol l^{-1})	Doxazosin	46	6.78	6.52	−3.9±1.6
	Prazosin	49	6.48	6.07	−6.4±1.5
	Placebo	49	6.79	6.68	−1.6±1.6
HDL cholesterol (mmol l^{-1})	Doxazosin	44	1.19	1.26	6.3±3.1
	Prazosin	48	1.26	1.29	2.0±2.8
	Placebo	48	1.20	1.30	8.5±3.0
HDL/Total cholesterol	Doxazosin	44	0.176	0.194	10.3±3.5
	Prazosin	48	0.193	0.210	8.8±3.3
	Placebo	48	0.177	0.196	10.6±3.4
Triglycerides (mmol l^{-1})	Doxazosin	46	1.40	1.22	−12.6±5.0
	Prazosin	48	1.27	1.14	−10.1±5.1
	Placebo	48	1.25	1.16	−6.6±5.3

[a]Derived from the geometric mean of final/baseline

receiving placebo. None of the abnormalities was considered clinically relevant.

Analysis of changes in ECG, heart size and ophthalmological parameters revealed no evidence of clinically relevant differences between the treatment groups.

Discussion

Doxazosin once daily and prazosin twice daily both proved to be effective in reducing the BP of patients with mild to moderate hypertension. The BP reductions were significantly greater ($P < 0.05$) than those obtained with placebo. However, placebo also resulted in a reduction in BP when compared with baseline values, a result in accordance with previous studies (Bauer, 1980; Gould *et al.*, 1981; Meland, 1983).

An increase of approximately 10% in the HDL/total cholesterol ratio and a decrease in triglycerides were observed in all three treatment groups, although the differences between groups were not statistically significant. For all three groups a significant increase in HDL/total cholesterol ratio was noted at the end of double-blind treatment compared with baseline.

A significant increase in HDL levels in patients subjected to caloric restriction/weight reduction has been observed (Wolff & Grundy, 1983) and this cannot be excluded as a possible cause in this study. Other investigators have shown that prazosin (Leren *et al.*, 1980) and doxazosin (Lehtonen *et al.*, 1985) have a positive effect on plasma lipid profiles. Further long-term investigations are needed to determine if these effects on plasma lipid profiles are of clinical benefit during prolonged use.

The decrease in weight of 1.18 kg (voluntary or involuntary calorific and/or sodium reduction) in the placebo treated group may also partly explain the BP reduction and changes in lipid parameters observed. The lack of weight reduction observed in the active treatment groups may be due to increased plasma volume (McNair *et al.*, 1980).

The incidence of reported side-effects for doxazosin and prazosin was very similar and these were mainly mild to moderate in severity, including postural type side-effects, headache and lethargy. A reduction in the dosage regimen was necessary only for two doxazosin patients, three prazosin patients and one placebo patient. The treatments were generally well tolerated and clinical abnormalities were minimal.

In conclusion, the results of this study show that doxazosin once daily and prazosin twice daily are both effective first-line antihypertensive therapies. A significant increase in HDL/total cholesterol ratio over the 12 week study period was observed for all three treatment groups. In addition, a significant decrease in triglycerides was noted in the doxazosin treated group.

Future studies of antihypertensive agents, including α_1-adrenoceptor antagonists, should be concerned not solely with their BP lowering effects and safety but also with their effects on the atherosclerotic (and metabolic) processes. The effect on the heart, i.e. left ventricular hypertrophy, and effects on fluid dynamics (heart rate) and blood platelets are also important aspects.

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