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A long-term double-blind comparison of doxazosin and atenolol in patients with mild to moderate essential hypertension

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1 The efficacy and safety of doxazosin and atenolol were compared following once-daily administration for up to 1 year, with a minimum of 20 weeks' active treatment.

2 According to response, patients received doxazosin 1–16 mg day^{-1} or atenolol 50–100 mg day^{-1}. Mean daily doses at the final efficacy assessment (between 20 weeks and 1 year) were doxazosin 11.8 mg and atenolol 94.2 mg.

3 Atenolol produced somewhat greater falls in blood pressure than doxazosin. The differences were statistically significant in the supine but not in the standing position. A small mean reduction in heart rate was produced by doxazosin whereas atenolol produced a marked bradycardia. Analysis of the same patient group at 20 weeks revealed similar overall profiles of activity except that atenolol produced greater falls in blood pressure than in the longer term analysis.

4 Serum concentrations of HDL/total cholesterol ratio were raised in the doxazosin treatment group and lowered in the atenolol group. Triglyceride concentrations fell in the doxazosin group and rose in the atenolol group. Significant differences ($P < 0.001$) were observed between treatment groups for these parameters, all differences being in favour of doxazosin.

5 Pharmacokinetics of doxazosin, measured at steady state in 36 patients, showed dose-related plasma concentrations, a mean half-life of about 12 h and relatively low intersubject variation.

6 The incidence of side-effects was slightly greater for patients in the doxazosin group. Drug-related side-effects were mostly mild to moderate in severity with no serious drug-related occurrences in either treatment group.

7 No serious drug-related abnormalities in laboratory biochemistry and haematology tests were observed in either treatment group.

Keywords atenolol blood pressure doxazosin lipids pharmacokinetics

Introduction

Doxazosin is a selective peripheral α_1-adrenoceptor antagonist (Timmermans *et al.*, 1980) structurally related to prazosin and which, like prazosin, lowers blood pressure by reducing peripheral resistance (Singleton *et al.*, 1982; de Leeuw *et al.*, 1982). Pharmacokinetic studies in man (Elliott *et al.*, 1982; Vincent *et al.*, 1983) showed that the plasma half-life for doxazosin is 9–11 h, compared with approximately 2.5 h for prazosin, suggesting that a once-daily regimen might be appropriate. The purpose of this study was to compare the efficacy and safety of doxazosin with that of atenolol, a well-established drug for the treatment of essential hypertension, both drugs being given once daily. The parameters assessed were blood pressure, heart rate, plasma lipids and, for doxazosin only, steady state pharmacokinetics.

Methods

Patients

Patients aged 30–70 years with essential hypertension and an otherwise satisfactory medical

history entered a 4-week single-blind, placebo, run-in phase. Patients already receiving antihypertensive therapy had that treatment withdrawn for a 4-week period before entering the single-blind phase. Patients could then receive double-blind active study treatment, provided that the following blood pressure entry criteria were satisfied in both supine and standing positions during the 4-week single-blind run-in: (1) Phase V diastolic blood pressure (BP) immediately before double-blind treatment (week 4) of 90–114 mmHg (100 mmHg or higher in patients aged 60 years or more). (2) Average diastolic BP (over 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. Informed consent was obtained from all patients.

Excluded from the study were lactating women and women of child bearing potential. The use of concomitant antihypertensive agents was forbidden, except for thiazide diuretics, which could be given as additional therapy after 20 weeks if necessary.

Assessments

Ten centres were involved in the study, with a minimum of eight patients per centre, and all used a common protocol. Eligible patients were assigned to double-blind treatment with doxazosin or atenolol according to a randomization list. A double-dummy study design was employed and each patient's medication comprised an active (or placebo) doxazosin capsule and a placebo (or active) atenolol tablet.

Patients were instructed to take the medication once daily, at breakfast time. Starting doses were doxazosin 1 mg or atenolol 50 mg. Blood pressure and heart rate measurements were made 24 h after the previous dose. Blood pressure (phase V diastolic) to the nearest 2 mmHg 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 at 24 h post-dose, patients in the doxazosin group could receive 1, 2, 4, 8 or 16 mg once daily, whilst patients in the atenolol group could receive 50 or 100 mg once daily. Upward titration of dose occurred at 2 week intervals (6 weeks for penultimate step, doxazosin 8 mg) until either 'goal' blood pressure was achieved, or side-effects prevented further upward titration. 'Goal' BP was defined as a reduction from baseline diastolic BP of at least 10 mmHg, and to less than 90 mmHg in both supine and standing positions.

Patients were assessed double-blind at 2–4 week intervals for up to 20 weeks of active therapy and thereafter at 10–12 week intervals up to 1 year. The blinding code was not broken for the investigator until after the final patient review. Serum cholesterol, HDL cholesterol and triglyceride concentrations were measured at baseline and at intervals throughout the study.

Side-effects, observed or volunteered, were recorded at each review visit. Blood samples for haematology and biochemistry examination, together with urine samples, were taken at regular intervals throughout the study and monitored for possible drug-related changes. Other safety assessments included measurement of body weight, electrocardiography, ophthalmoscopy (including slit lamp examination) and chest X-ray.

Doxazosin pharmacokinetics

Steady state pharmacokinetics were assessed at two of the centres. At the Turku centre two pharmacokinetics investigations were performed using the same group of patients, investigations being separated by at least 3 months. The first investigation was conducted after patients had received active treatment for at least 3–4 months and a stable dose for at least 4 weeks. The double-blind code was broken in the assay laboratory and atenolol samples were discarded. At the Tampere centre a single investigation was performed at the end of the 1 year double-blind study, using only patients who had been receiving doxazosin. Patients were instructed to eat a normal (light) breakfast on the day of pharmacokinetic assessment but not to take the dose of the day until instructed. Blood samples for doxazosin analysis were taken pre-dose and at selected times after dosing. Doxazosin was assayed by h.p.l.c. using fluorescence detection (Rubin *et al.*, 1980).

Statistical methods

Results are expressed as mean values with standard errors of the mean changes. For BP, heart rate and body weight, analyses of changes from baseline were assessed by two-way analysis of variance with treatment, study centre and their interaction as factors. For the lipids similar analyses were performed on the logarithms of values with assay laboratory used as the blocking factor rather than study centre.

Table 1 Age, weight and sex of patients entering double-blind treatment phase

	Doxazosin			*Atenolol*		
	Male	*Female*	*Total*	*Male*	*Female*	*Total*
Number of patients	44	30	74	39	30	69
Age category (years)						
<15	0	0	0	0	0	0
15–44	19	10	29	14	14	28
45–64	24	19	43	25	16	41
≥65	1	1	2	0	0	0
Mean age (years)	45.2	50.0	47.1	47.0	48.0	47.4
Age range	31–65	36–66	31–66	32–64	36–62	32–64
Mean weight (kg)	87.7	68.3		82.4	68.2	
Weight range	69–110	59–99		61–108	54–88	

Results

Patients

Of 152 patients (76 per treatment group) entering the study nine dropped out before receiving double-blind study treatment and 143 patients (74 doxazosin, 69 atenolol) entered the double-blind treatment phase. The two patient groups were well matched for baseline characteristics. Details of age, weight and sex of patients are given in Table 1. In both treatment groups the mean duration of hypertension was 5–6 years and the baseline severity was moderate (average diastolic BP 100—<115 mmHg) in the majority of cases.

The efficacy analysis was performed on 120 patients (60 doxazosin, 60 atenolol). Of the 14 doxazosin patients excluded from analysis, six withdrew because of side-effects and eight were excluded for other reasons (four defaulted, one failed to satisfy BP entry criteria, three were given thiazide diuretics before completing 20 weeks). In the atenolol group nine patients were excluded from analysis; one withdrew because of side-effects and eight were excluded for other reasons (six failed to satisfy BP entry criteria, one defaulted, one was given concomitant hydrochlorothiazide before completing 20 weeks).

The mean final daily doses and duration of therapy for the efficacy sub-groups were doxazosin 11.8 mg, 307 days (range 140–393 days) and atenolol 94.2 mg, 338 days (range 140–410 days). For more than 80% of patients the recorded time of

Table 2 Blood pressures and heart rates. Changes from baseline after long-term treatment

Variable	*Treatment group*	*Baseline mean*	*Final mean*	*Mean change final-baseline ± s.e. mean*
Standing systolic BP (mmHg)	Doxazosin	153.5	142.3	−11.3±1.5
	Atenolol	153.5	140.2	−13.3±1.9
Standing diastolic BP (mmHg)	Doxazosin	106.2	97.4	−8.8±0.8
	Atenolol	105.6	95.4	−10.2±1.0
Standing heart rate (beats min^{-1})	Doxazosin	79.3	76.5	−2.8±1.2
	Atenolol	78.1	65.9	−12.2±1.3
Supine systolic BP (mmHg)	Doxazosin	156.1	148.6	−7.5±1.6
	Atenolol	156.2	142.8	−13.4±1.7
Supine diastolic BP (mmHg)	Doxazosin	101.8	95.3	−6.5±1.0
	Atenolol	101.3	91.1	−10.2±0.9
Supine heart rate (beats min^{-1})	Doxazosin	71.7	68.7	−3.0±1.1
	Atenolol	71.1	61.0	−10.1±0.9

n = 60 in each treatment group

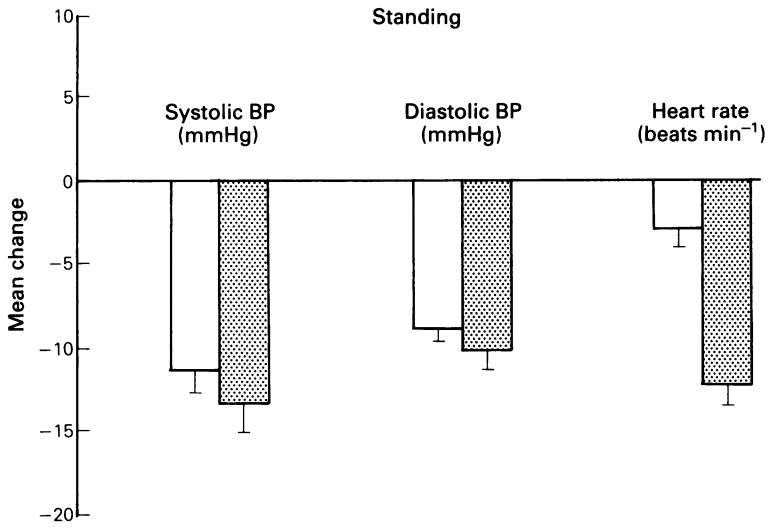

Figure 1 Mean (± s.e. mean) changes in standing BP (mmHg) and heart rate (beats min^{-1}) after long-term (up to 1 year) active treatment with doxazosin (□) or atenolol (▨).

last dose was 18–30 h prior to the final BP and heart rate evaluations. The mean times post-dosing of the final assessments for these patients were 24.4 h for doxazosin and 24.8 h for atenolol. The time of last dose was not recorded in the majority of remaining cases. The results were virtually identical for the patients with valid recorded times and the full efficacy evaluation group.

The lipid analysis was performed in 87 patients (39 doxazosin, 48 atenolol) who completed 1 year of double-blind treatment and for whom appropriate baseline and final measurements were available.

Blood pressure and heart rate

Efficacy was based on mean changes in blood pressure from baseline (average of readings from final two visits in the single-blind placebo run-in) to the final efficacy review visit, occurring after 20, 30, 40 or 52 weeks of double-blind treatment.

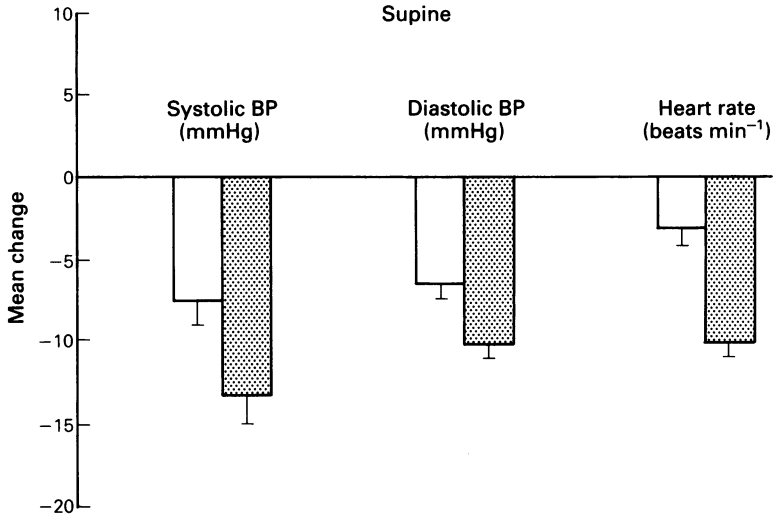

Figure 2 Mean changes (± s.e. mean) in supine BP (mmHg) and heart rate (beats min^{-1}) after long-term (up to 1 year) active treatment with doxazosin (□) or atenolol (▨).

Changes in heart rate were similarly assessed. For the 11 patients (nine doxazosin, two atenolol) in whom concomitant thiazide therapy was initiated after at least 20 weeks of single drug therapy, efficacy was assessed at the visit when administration of the thiazide was started. The results are shown in Table 2 and in Figures 1 and 2. In the standing position there was no statistically significant difference between the reductions in systolic and diastolic BP produced by the two agents, although atenolol produced numerically greater falls (11.3/8.8 mmHg doxazosin, 13.3/10.2 mmHg atenolol). However, in the supine position atenolol produced significantly greater ($P < 0.05$) falls in BP (7.5/6.5 mmHg doxazosin, 13.4/10.2 mmHg atenolol). Small mean reductions in heart rate (2.8 beats min^{-1} standing, 3.0 beats min^{-1} supine) were observed in the doxazosin treatment group. For atenolol the bradycardia was significantly greater ($P < 0.0001$) (12.2 beats min^{-1} standing, 10.1 beats min^{-1} supine).

Defining a responder as a patient with a fall in standing diastolic BP of (1) 10 mmHg or more, or (2) to below 90 mmHg and by 5 mmHg or more, then responder rates were doxazosin 27/60 (45%) and atenolol 30/60 (50%).

At the final assessment visit the investigator scored the overall efficacy of the treatment as excellent, good, poor or none. The total number of patients in the excellent and good categories were 37/60 (doxazosin, 62%) and 49/60 (atenolol, 82%).

An analysis performed after 20 weeks of double-blind therapy in the same population (less one doxazosin patient lacking a 20 week review visit) showed similar overall results to those reported above, except that the BP reduction for atenolol was greater than at final assessment. At 20 weeks all BP changes were significantly greater ($P < 0.05$) for atenolol, i.e. systolic and diastolic pressures in both supine and standing positions. The 20 week reductions in standing BP (mmHg) were 11.2/8.1 (doxazosin) and 16.6/12.6 (atenolol) and in supine BP were 7.3/6.4 (doxazosin) and 16.4/12.5 (atenolol).

Lipids

After 1 year, the percentage changes in total triglyceride concentration, derived from the geometric mean of final/baseline values, decreased (5.0%) in the doxazosin group and increased (42.7%) in the atenolol group (Table 3). The difference in the mean changes between the two groups was highly significant ($P = 0.0001$). In addition there were mean increases in both HDL cholesterol (3.9%) and the ratio HDL/total cholesterol (5.4%) with doxazosin whereas these values were decreased (7.4% and 9.9%, respectively) with atenolol. Again the difference in the mean changes between the groups was highly significant, $P = 0.001$ for HDL cholesterol and $P = 0.001$ for the HDL/total cholesterol ratio. Although total cholesterol concentrations were decreased (1.7%) with doxazosin compared with an increase (2.7%) with atenolol, the difference in the changes between the two treatment groups was not statistically significant. An analysis of changes for up to 20 weeks of active treatment in 42 patients from the Turku study centres is described separately (Lehtonen *et al.*, 1986).

Pharmacokinetics

The pharmacokinetic profile of doxazosin was investigated in 36 patients receiving stable doses, i.e. doses were fixed for at least 1 month. The results are shown in Figure 3 and indicate the close proportionality of dose (1–16 mg) to peak plasma concentration, minimum concentration (24 h post-dose) and average concentration during the 24 h between doses ($AUC_{(0-24)}/24$). In most patients the time to peak concentration was 2–3 h. For all patients the mean plasma elimination half-life was 11.8 h. A subset of 12 patients (Turku centre) had duplicate pharmacokinetic investigations, separated by at least 3 months. Average plasma concentrations of doxazosin during the 24 h between doses are shown in Figure 4 and were approximately proportional to dose and differed very little between the 2 study days. Mean half-lives were 11.2 and 11.1 h for the first and second study days.

Safety

A total of 49/74 doxazosin patients and 34/69 atenolol patients complained of side-effects, which were definitely or possibly related to treatment, at some time during the treatment period (in excess of 300 days in both groups). These were mainly mild to moderate in severity and disappeared or were tolerated on further treatment. There were similar proportions of patients in both treatment groups with postural side-effects (vertigo, dizziness, postural dizziness); 14/74 for doxazosin and 10/69 for atenolol. In the doxazosin group these postural-type effects were of mild or moderate severity, except in two cases where drug therapy was discontinued. In the atenolol group postural effects were also mild or moderate, except for one patient who experienced severe vertigo but continued in the trial, withdrawing later of her own volition.

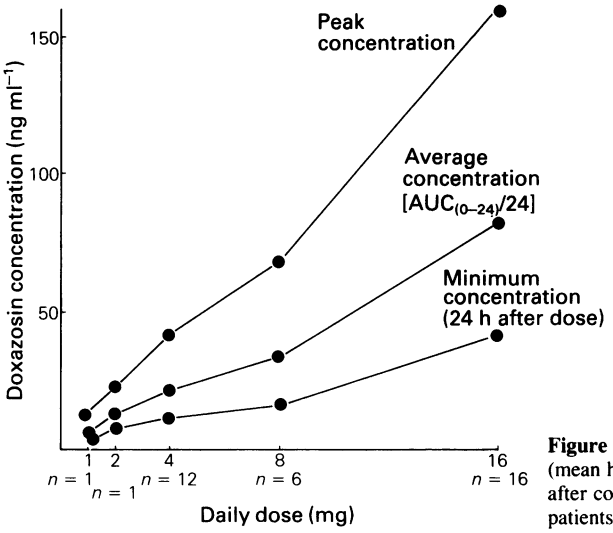

Figure 3 Mean plasma concentrations of doxazosin (mean half-life 11.8 h) in 36 patients at least 1 month after completion of dose titration, *n* = number of patients.

Other side-effects with a frequency of first occurrence greater than 5% were (number of patients with first occurrences): fatigue (15 doxazosin, 14 atenolol); palpitation/tachycardia (11 doxazosin, 0 atenolol); headache (eight doxazosin, five atenolol); leg, peripheral and other non-specified oedemas (six doxazosin, five atenolol).

Eleven patients were withdrawn due to side-effects possibly or definitely related to treatment in the doxazosin group and four in the atenolol group. In the doxazosin group the treatment-related withdrawals were postural side-effects (2), allergic rhinitis, pruritus, eczema (3), tachycardia (2), palpitations and hyperventilation (1), cold feeling (1), dyspnoea (1). The final doxazosin case was a patient who stopped the medication and fasted (lost 12 kg) for 2 weeks and suffered a transient collapse after taking a single dose of doxazosin 16 mg. In the atenolol group the reasons for withdrawal were nausea, dizziness and headache (1), impotence (1), bradycardia (1), patient unwilling to continue following earlier episode of vertigo (1).

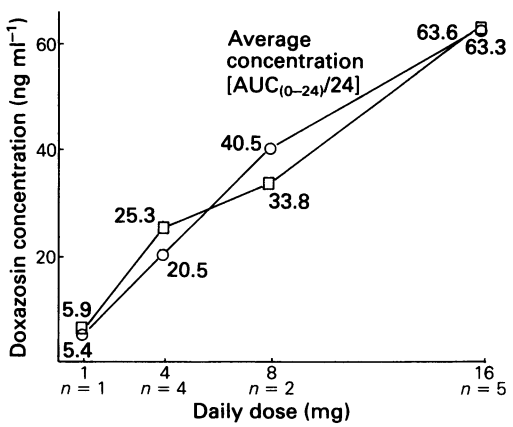

Figure 4 Average plasma concentrations of doxazosin in 12 patients on two occasions at least 3 months apart. □ first study day, ○ second study day. The mean half-life of doxazosin for the first study day was 11.2 h and for the second study day was 11.1 h.

During the course of the study two patients (one in each treatment group) suffered a myocardial infarction and one patient in the atenolol group died suddenly. None of these serious adverse events was considered to be due to drug treatment.

Mean body weight increased during the study in the doxazosin (+ 0.6 kg) and atenolol (+ 1.0 kg) groups, but there was no significant difference between treatments. No clinically relevant adverse trends occurred in either treatment group with respect to changes in ECG, ophthalmology or chest X-ray. No significant trend emerged in either of the treatment groups with respect to laboratory abnormalities possibly related to therapy. The overall incidence of such abnormalities was similar in the two groups (10 doxazosin, eight atenolol) but one patient in the atenolol group showed changes (marked eosinophilia, elevated LDH) and clinical signs (oedema of face and hands) consistent with drug hypersensitivity.

Discussion

In this study 120 patients, 60 per group, were evaluated for efficacy following long-term double-blind treatment with either doxazosin or atenolol. The mean duration of treatment was in excess of

Table 3 Serum lipids percentage change from baseline after 1 year of treatment with doxazosin and atenolol

	Doxazosin			*Atenolol*			
	n	Δ%	*s.e. mean*	n	Δ%	*s.e. mean*	P
Triglycerides	39	−5.0	7.0	48	42.7	9.5	0.0001
Cholesterol	39	−1.7	1.8	48	2.7	1.7	NS
HDL cholesterol	38	3.9	2.6	48	−7.4	2.0	0.001
HDL/total cholesterol	38	5.4	2.9	48	−9.9	2.2	0.0001

Δ% = Percentage change from baseline, derived from the geometric mean of final/baseline
P = Significance of difference between groups
NS = Not significant

300 days. Comparable reductions in 24 h post-dose standing blood pressures were achieved by the two agents. The responder rates for doxazosin and atenolol were similar. As anticipated from the different modes of action of the two drugs, atenolol produced significantly greater falls in supine BPs. Atenolol produced a marked bradycardia in both standing and supine positions compared with the small mean reductions in heart rate observed with doxazosin. An intermediate analysis of results obtained after 20 weeks of double-blind therapy showed similar falls in blood pressure for doxazosin compared with the long-term analysis, but for atenolol the falls were greater at 20 weeks. No explanation can be advanced for the apparent reduction in antihypertensive effect for atenolol between the 20 week and final long-term review.

In addition to raised blood pressure, plasma lipids have also been identified as a risk factor predisposing to coronary heart disease (CHD) (Kannel & Sorlie, 1975). The potentially adverse changes in the blood lipid profile produced by a number of antihypertensive agents have been reviewed (Miller, 1985; Weinberger, 1985; Leren, 1985). Increased plasma concentrations of HDL cholesterol relative to total cholesterol have been correlated with a beneficial effect on the atherogenic process, whilst increases in LDL cholesterol and triglycerides are deleterious (Miller, 1980). In this study highly significant changes in lipid profiles relative to atenolol were observed. After 1 year there was a mean 3.9% increase from baseline in HDL cholesterol in the doxazosin group compared with a 7.4% decrease in the atenolol group. The mean ratio of HDL/total cholesterol increased by 5.4% in the doxazosin group compared with a reduction of 9.9% in the atenolol group, whilst the mean total triglyceride concentration decreased by 5% in the doxazosin group and increased by 42.7% in the atenolol group. The antihypertensive action of doxazosin, coupled with its apparent lack of adverse effects on key lipid parameters, suggest that in susceptible patients the overall risk of CHD might be lowered by this agent.

A pharmacokinetic assessment of doxazosin was carried out in 36 patients who had been receiving a stable dose of doxazosin for at least 1 month. Absorption was rapid, with the peak concentration being observed 2–3 h after dosing. The mean elimination half-life was approximately 12 h and doxazosin was always present in the plasma pre-dose, i.e. 24 h following the previous dose. Plasma concentrations of doxazosin were proportional to dose. Twelve of the patients, maintained at constant dose, were assessed on two occasions 3 months apart. The pharmacokinetic responses were remarkably consistent, providing further evidence for the stable and predictable nature of the doxazosin pharmacokinetic profile. The results are in accord with those established earlier in single dose studies (Elliott *et al.*, 1982). The long half-life of doxazosin is fully compatible with the control of hypertension using a once-daily dosage regimen.

The relatively high incidence of side-effects found in both groups is a reflection of the length of the study (more than 300 days), the large number of review visits and the inclusion of side-effects possibly, but not definitely, related to treatment. There was a similar incidence of postural-type side-effects in both groups, mostly mild to moderate in severity. Of the 15 patients withdrawn due to side-effects possibly or definitely related to treatment, 11 were in the doxazosin group and four in the atenolol group. One patient from each treatment group suffered a myocardial infarction and one patient on atenolol died suddenly, but none of these cases was considered to be due to drug treatment.

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