Br. J. clin. Pharmac. (1986), **21**, 63S–67S

Antihypertensive effect of doxazosin in hypertensive patients: comparison with atenolol

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1 The antihypertensive effect of doxazosin 1–16 mg once-daily was compared with that of atenolol 50–100 mg once-daily, and placebo, utilizing a double-blind parallel group (12 patients each) design.

2 Blood pressure (BP) and pulse rate were determined in out-patients who returned for clinic visits every 2 weeks for 14 weeks. During the first 4 weeks, all patients received single-blind placebo therapy. During the subsequent 10 weeks, patients were randomized to placebo, atenolol or doxazosin treatment.

3 After 2 weeks of doxazosin therapy 16 mg daily, there was a significant decrease from baseline (single-blind placebo period) in supine diastolic BP ($P < 0.01$) and standing diastolic BP ($P < 0.001$). The decreases in supine and standing diastolic BPs in the doxazosin 16 mg daily group were significantly ($P < 0.01$) different from the corresponding BPs of the placebo group. At weeks 12 and 14, heart rates in the doxazosin group were not significantly different from baseline or from those in the placebo group.

4 After 4 and 6 weeks of atenolol 100 mg daily, there was a significant decrease from baseline in both supine ($P < 0.001$ and $P < 0.05$) and standing ($P < 0.05$) diastolic BPs and heart rates ($P < 0.05$). However, when the atenolol group was compared with the placebo group, a significant decrease occurred only with supine diastolic BP at week 12 ($P < 0.01$) and not at week 14; but significant decreases occurred in supine and standing heart rates at weeks 12 and 14 ($P < 0.05$). Furthermore, there were no significant decreases in standing diastolic BP with atenolol when compared with placebo.

5 There were no significant differences between the doxazosin and atenolol groups in systolic and diastolic BPs in either the supine or standing positions. However, the supine and standing heart rates in the atenolol group were significantly lower than those in the doxazosin group at weeks 12 and 14 ($P < 0.05$).

Keywords atenolol doxazosin hypertension

Introduction

Doxazosin is a quinazoline α_1-adrenoceptor antagonist that has been investigated as an antihypertensive agent (Singleton *et al.*, 1982); it is chemically related to prazosin, a widely used α_1-adrenoceptor antagonist. Doxazosin has a half-life of 9–11 h and long duration of action, and therefore may be suitable for once-daily administration (Vincent *et al.*, 1983; Elliott *et al.*, 1982).

The purpose of this study was to compare the antihypertensive effects of doxazosin with those of atenolol and placebo in parallel groups of hypertensive patients.

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Methods

Patients

Adult patients with stable mild or moderate essential hypertension 'according to the criteria of

the Veterans Administration Co-operative Study Group on Antihypertensive Agents (1970)' participated in this study. Patients with significant haematological, renal, hepatic, gastrointestinal, autoimmune or cardiac disease and pregnant or nursing women were excluded. Institutional review board approval was obtained, and each patient gave written informed consent.

Thirty-six hypertensive patients of both sexes (24 males and 12 females) with a mean (± s.d.) weight of 81 ± 16 kg and aged 33–68 years, participated in this study. There were 28 Caucasian and eight Black patients. The duration of known hypertension ranged from 1 month to 22 years. Eleven patients had been treated previously with various antihypertensive agents. All antihypertensive drugs and diuretics were discontinued at least 4 weeks before the placebo phase of the study. For entry into the study, patients were required to have a baseline diastolic BP > 95 mmHg in both supine and standing positions at weekly clinic visits during the first 3 weeks (washout period) of the study. In addition, patients were required to have diastolic BPs > 90 mmHg in both supine and standing positions at the two clinic visits during the 4-week single-blind placebo period that preceded the double-blind therapy period. Patients were excluded if diastolic BPs were persistently greater than 114 mmHg or if there was a difference of more than 10 mmHg between diastolic pressures obtained in supine or standing positions at three visits.

Study design

This study was a double-blind, parallel group, 10-week comparison of doxazosin, atenolol and placebo: after the initial 3-week washout period, placebo was given single-blind for 4 weeks. Patients had clinic visits every 2 weeks during the study, except during the initial 3-week washout period and the last 3 weeks of double-blind therapy, when the visits were weekly.

Blood pressure (Korotkoff phases I and V) and pulse rate were recorded after 5 min in the supine position and after 2 min standing. The measurements were always made in triplicate 24 h after the last dose of medication. A 'double-dummy' technique was used for blinding purposes, with patients taking medication orally once daily from each of two bottles. Thirty-six patients were randomized into three parallel treatment groups (each 12 patients) and received doxazosin, atenolol or placebo. Upon completion of the single-blind placebo period (week 4), the doxazosin dose was titrated every 2 weeks in the following ascending order: 1, 2, 4, 8 and 16 mg daily; patients were at each dose level for 2 weeks. The atenolol group was started with 50 mg daily and continued for 4 weeks (end of week 8); at that time the daily dose was increased to 100 mg for the next 6 weeks. Upward titration of doxazosin and atenolol proceeded as described unless goal blood pressure was achieved, i.e., a reduction of standing diastolic blood pressure to <90 mmHg and by ⩾10 mmHg measured 24 h after the last dose. In the event that goal blood pressure was achieved, the same daily dose of drug was continued under double-blind conditions without further upward titration.

The presence of adverse effects was recorded at each clinic visit. A complete laboratory evaluation was done at the end of weeks 4, 8 and 14. Within-group differences (between final efficacy evaluation and the single-blind placebo evaluation) were subjected to a one-way analysis of variance using drug as the treatment factor. Tukey's multiple comparison procedure for honest significant difference was then used to assess differences between treatments.

Results

Effects on blood pressure and heart rate

The mean supine and standing diastolic BPs (SuDBP and StDBP) after doxazosin 8 mg (week 12) and 16 mg (week 14) treatment are compared with placebo values in Table 1. Diastolic BPs were not significantly different at the 8 mg doxazosin dose, but were significantly different at the 16 mg dose. Supine and standing systolic BPs (SuSBP and StSBP) in the doxazosin group were lower than the BPs in the placebo group, but the differences were not significant. At weeks 12 and 14, the mean supine and standing heart rates (SuHR and StHR) in the doxazosin group were not significantly different from baseline or from those in the placebo group.

Table 1 also shows the general and progressive decremental response in systolic and diastolic BPs in both supine and standing positions as the doxazosin dose was increased. In contrast, the BP response to atenolol was not a continuous decremental reduction in systolic and diastolic BPs. The systolic and diastolic blood pressures decreased 2 weeks after treatment with atenolol 50 mg daily; and although the decrease in diastolic BPs was sustained 2 weeks later (week 8), there was a trend toward a return to baseline in systolic BPs. An increase in the dose of atenolol to 100 mg daily resulted in a sustained decrease in diastolic and systolic BPs in the standing but not in the supine

Table 1 Blood pressure lowering effects of doxazosin and atenolol treatment compared with baseline values and placebo treatment (mean ± s.d.)

Baseline (week 4)	*Week*					
	6	*8*	*10*	*12*	*14*	
Placebo ($n=12$)						
SuSBP	150±14	148±10	150±15	154±12	149±11	148±15
SuDBP	100±6	96±8	96±5	98±6	99±7	97±7
StSBP	151±16	148±14	151±16	150±14	144±11	146±16
StDBP	108±7	106±9	106±8	108±6	104±9	105±12
Doxazosin ($n=12$)						
SuSBP	152±11	150±10	150±8	148±12	152±9	146±14
SuDBP	99±8	96±12	97±13	94±7	94±12	90±5**a,b
StSBP	152±14	149±11	148±12	141±11	151±14	142±16
StDBP	106±7	102±10	101±9	99±8	98±11	93±7***a,**b
Atenolol ($n=12$)						
SuSBP	154±9	138±10	142±16	139±14	138±15	142±14
SuDBP	103±6	93±6	93±8	90±9	90±7***a,**b	95±10*a
StSBP	150±11	134±9	142±15	140±17	141±14	142±20
StDBP	109±7	100±8	102±7	99±8	101±9*a	99±12*a

Doxazosin daily dosages: weeks 4–6, 1 mg; weeks 6–8, 2 mg; weeks 8–10, 4 mg; weeks 10–12, 8 mg; weeks 12–14, 16 mg
Atenolol daily dosages: weeks 4–8, 50 mg; weeks 8–14, 100 mg
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$
[a]Compared with baseline, [b]Compared with placebo

position. In the latter case, there was a trend for pressures to return toward baseline at week 14.

The supine and standing diastolic BPs for the atenolol 100 mg and placebo groups (weeks 12 and 14) are presented in Table 1. The only significant difference between placebo and atenolol groups occurred with the supine diastolic BP at week 12; the standing diastolic BPs at week 12 were not significantly different between the 2 groups. Neither the supine nor the standing diastolic BPs at week 14 were significantly different between the 2 groups; but significant decreases occurred in SuHR and StHR in the atenolol group at weeks 12 and 14 ($P < 0.05$). When the supine and standing diastolic BPs and HRs for the atenolol 100 mg group after 4 weeks (week 12) and 6 weeks (week 14) are compared with baseline, the BPs (Table 1) and HRs ($P < 0.05$) are significantly lower. A comparison of the doxazosin and atenolol groups in systolic and diastolic BPs in the supine and standing positions revealed no significant differences at either week 12 (doxazosin 8 mg and atenolol 100 mg) or week 14 (doxazosin 16 mg and atenolol 100 mg). However, the supine and standing HRs in the atenolol group were significantly lower ($P < 0.05$) than in the doxazosin group at weeks 12 and 14.

Adverse effects

A partial list of adverse effects thought to be drug-related or possibly drug-related is presented in Table 2; only those adverse effects that occurred more than once in any of the treatment groups are listed. Most of the adverse effects were mild. One patient who received doxazosin 16 mg daily had

Table 2 Number of patients reporting adverse effects during active drug treatment (weeks 5–14)

	Doxazosin	*Atenolol*	*Placebo*
Postural dizziness	5	3	1
Headache	4	2	6
Abdominal discomfort	3	3	1
Blurred vision	3	2	0
Oedema	2	1	0
Lack of energy	2	2	1
Chest discomfort	2	0	0
Sedation	2	1	1
Constipation	3	1	0
Dry mouth	2	2	2

$n = 12$ in each group

moderately severe orthostatic hypotension which disappeared when the dose was reduced to 8 mg daily. One patient who was receiving doxazosin 2 mg daily developed right bundle branch block on ECG. It did not appear that this event was drug-related and the titration sequence continued until the patient was normotensive. There was no increase in frequency of adverse effects with increased doses of doxazosin. No patient was discontinued from active drug treatment. No clinically significant laboratory toxicity for either doxazosin 16 mg or atenolol 100 mg was observed. In general, doxazosin therapy was associated with a higher frequency of adverse effects than atenolol therapy. The increased frequency of adverse effects with doxazosin could presumably be attributed to the more aggressive doxazosin titration.

Discussion

The findings in this study indicate that doxazosin 16 mg once-daily was consistently effective in lowering systolic and diastolic BPs in both supine and standing positions in mild to moderate hypertension. The BPs with doxazosin 16 mg were, on average, at or near normotensive levels and significantly lower than those of the placebo group. In contrast, the BPs in the atenolol group at the 100 mg level were only significantly different from the placebo group in the supine diastolic BP at week 12, but not at week 14; and the standing diastolic BPs were not significantly different from placebo at either weeks 12 or 14.

In the present study, the treatment goal was a standing diastolic BP of 90 mmHg or less. At the end of the study (week 14), 25% of the patients in both the doxazosin and atenolol groups had reached this goal. A common treatment goal of physicians who are treating hypertensive patients in their general practice of medicine is a supine diastolic BP of 90 mmHg or less. At the end of the study, 66% of the doxazosin group and 16% of the atenolol group had reached this therapeutic goal. Possible reasons for these findings are as follows: (1) higher baseline BP levels in the atenolol group; (2) differences in the mechanisms of action between doxazosin and atenolol; and (3) possible use of non-equivalent antihypertensive doses of doxazosin and atenolol.

However, it is of interest to note that the recommended maximum dose of atenolol is 100 mg daily (Physicians Desk Reference, 1985). Assuming then, that in this study both atenolol and doxazosin were used in equivalent antihypertensive doses, the results may indicate that doxazosin 16 mg daily may be more effective than atenolol 100 mg daily in BP control. Alternatively, the study results may indicate that a re-examination of the maximum recommended dose of atenolol is needed.

The incidence of side-effects among the 36 patients in the three treatment groups of this study requires comment. Headache may not be an important side-effect of either doxazosin or atenolol treatments, because the incidence of headaches in the placebo group was greater than in either the doxazosin or atenolol groups. The incidence of postural dizziness or orthostatic hypotension was higher with doxazosin therapy than with atenolol therapy. Postural dizziness is directly related to the degree of blood pressure lowering and the latter effect is the therapeutic goal of treatment. Blurred vision, abdominal discomfort, lack of energy and dry mouth appear to be genuine side-effects of both doxazosin and atenolol therapy; these side-effects occurred in 25% or less of patients in these treatment groups and occurred about equally in both groups. Oedema, sedation and constipation occurred in both the doxazosin and atenolol groups; chest discomfort was reported only in the doxazosin group. These effects are probably drug-related. Other adverse effects that occurred only once in the study were not listed in Table 2 and are much less likely to be drug-related. The side-effects are comparable with those seen with other commonly used antihypertensive agents.

In summary, there were no significant differences between the doxazosin and atenolol groups in systolic or diastolic blood pressures in either the supine or standing positions. Doxazosin appears to be an effective and well-tolerated antihypertensive agent when administered once-daily.

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