Concentration-effect relationships and individual responses to doxazosin in essential hypertension

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1 This study investigates aspects of the pharmacokinetics, pharmacodynamics and concentration-effect relationships in 10 patients with essential hypertension during acute and chronic treatment with doxazosin, an α_1 -adrenoceptor antagonist.

2 Following the first dose of doxazosin (2 mg) there were significant reductions in blood pressure, increases in heart rate and in plasma noradrenaline, and parallel rightward shifts of the phenylephrine pressor response curves, consistent with α -adrenoceptor antagonism. There was no significant change in the pressor response to angiotensin II.

3 Using an integrated kinetic-dynamic model, individual blood pressure responsiveness was characterised as the fall in blood pressure (mm Hg) per unit drug concentration. Responsiveness to the first dose of doxazosin was directly correlated with the responsiveness after 1 and 6 weeks treatment although there was a systematic reduction (of approximately 30%) which occurred during the first week of treatment.

4 Neither the acute nor long-term responsiveness to doxazosin was related to age, plasma renin activity, plasma noradrenaline or the pretreatment sensitivity to phenylephrine. There was a significant relationship between responsiveness and the height of the initial (pretreatment) blood pressure.

5 Integration of pharmacokinetic and pharmacodynamic data provides a reproducible index of responsiveness which can be used to investigate the consistency of the long-term anti-hypertensive response, to identify factors which influence the magnitude of the response, and to optimise the choice of dose and dose interval.

Keywords doxazosin pharmacokinetics concentration-effect

Introduction

The α_1 -adrenoceptor antagonist doxazosin, which is a quinazoline derivative related to prazosin, has been shown to lower blood pressure in patients with essential hypertension (Frick *et al.*, 1986; Baez *et al.*, 1986; Cox *et al.*, 1986). In comparison with prazosin, doxazosin has a longer terminal elimination half-life (Cubeddu *et al.*, 1987; Elliott *et al.*, 1987) and, even after intravenous administration, a more gradual onset of antihypertensive effect (Elliott *et al.*, 1982) and so appears to be suitable for once daily dosing (Elliott *et al.*, 1987). The blood pressure

fall after the first dose of prazosin has been shown to be directly correlated with drug concentrations in blood (Bateman *et al.*, 1979; Seideman *et al.*, 1981; Larochelle *et al.*, 1982) but for doxazosin no comparable relationship was observed between plasma concentration and the fall in blood pressure (Elliott *et al.*, 1982; Vincent *et al.*, 1983; Cubeddu *et al.*, 1987). Using integrated kinetic-dynamic modelling the acute hypotensive effect of doxazosin in normotensive subjects has been shown to correlate with drug concentrations in the 'effect'

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compartment (Vincent *et al.*, 1983). Such concentration-effect relationships have not been previously described in hypertensive patients.

This study in patients with essential hypertension evaluates the pharmacodynamic effects, including α_1 -adrenoceptor antagonist activity, and the pharmacokinetics of doxazosin after acute and chronic administration and, using an integrated kinetic-dynamic model (Holford & Sheiner, 1981), characterises the concentration-effect relationships and antihypertensive responses in individual patients.

Methods

Outline of study

Ten patients (four male, six female) with mild to moderate essential hypertension (160/90–210/115 mm Hg), age range 47–70 years, gave informed consent to participate in this study which was approved by the Research and Ethics Committee of the Greater Glasgow Health Board. Patients were either newly diagnosed and untreated essential hypertensives or patients in whom current therapy was ineffective or poorly tolerated. Each patient discontinued all medication and at the end of a drug-free run-in period of at least 6 weeks the average entry blood pressure $\pm$ s.d. was 180/103 $\pm$ 11/4 supine and 174/102 $\pm$ 8/5 mm Hg erect. In a single-blind design a matching placebo tablet was then administered for 3 weeks, followed by doxazosin 2 mg once daily for 6 weeks. Each patient attended four 8 h study days in the Clinical Pharmacology Research Unit (CPRU) to evaluate the effects of placebo, first dose doxazosin and after 1 week and 6 weeks doxazosin treatment. On each occasion, following an overnight fast, baseline blood pressure and heart rate measurements were recorded, an indwelling cannula was inserted into a forearm vein and placebo or doxazosin 2 mg was administered orally with 100 ml water at approximately 08.00 h. At frequent intervals during each study day, and at 24 h after dosing, blood pressure and heart rate were measured supine after not less than 10 min recumbency and erect after 5 min standing using a Datascope Accutorr semi-automatic sphygmomanometer. At corresponding times venous blood samples were collected for the measurement of plasma doxazosin concentration and additional samples were collected at 1.5 and 6 h for plasma renin activity, aldosterone and catecholamines. A standard light lunch was provided after 4 h.

Additional (short) study day

On the third day of doxazosin treatment patients were instructed to take their dose at 08.00 h and attend the CPRU 5 h later. They rested supine for 1 h and at 6 h after dosing a venous cannula was inserted, blood pressure and heart rate recorded and a blood sample collected for doxazosin concentration. The pressor effect of intravenous phenylephrine was then measured according to the method described below.

Pressor responses to intravenous phenylephrine

During each full study day, between 1.5–3 h (early) and at 6 h (late), and at 6 h after drug administration on the short study day, pressor responses to an intravenous infusion of the α_1 -adrenoceptor agonist phenylephrine were measured. Early and late pressor responses were timed to coincide with the anticipated peak plasma concentration of doxazosin and the maximum hypotensive effect respectively. To assess the effect of doxazosin on non-adrenergic pressor mechanisms the responses to angiotensin II were also measured during the early period of each full study day using a similar method.

In each case the agonist was administered intravenously in incremental doses, using a Braun Perfusor pump, to produce a controlled progressive rise in blood pressure, with a target increase of 20 mm Hg in mean arterial pressure. For safety reasons the infusion was terminated if increases in blood pressure above 45 mm Hg systolic or 30 mm Hg diastolic blood pressure occurred. Each dose was infused for 8 min and the mean of the final five sequential blood pressure and heart rate measurements (recorded at 1 min intervals between minutes 3–8) was calculated for each dose level (Sumner *et al.*, 1982). Administered doses were within the range 2.5–15 ng kg⁻¹ min⁻¹ for angiotensin II and 0.5–9.0 μ g kg⁻¹ min⁻¹ for phenylephrine.

Laboratory methods

Plasma concentrations of doxazosin were measured by h.p.l.c. with fluorescence detection (Rubin *et al.*, 1980). The inter- and intra-assay coefficients of variation for the drug assay were 7.5% and 5.8% respectively over a concentration range 1–40 ng ml⁻¹. Plasma renin activity and plasma aldosterone concentrations were measured by radioimmunoassay (McKenzie *et al.*, 1974; Derkx *et al.*, 1979), and plasma catecholamines by radioenzymatic assay (Da Prada & Zurcher, 1976).

Pharmacokinetics and concentration-effect analysis

A hierarchy of pharmacokinetic models was fitted to the plasma concentration data and the most appropriate model, as assessed by the general linear test, was a one compartment model with first order input and inverse weighting of the concentration data. Measurements derived from fitting this model to the concentration-time profiles for individual patients on each study day were the elimination half-life, area under the curve (AUC), $C_{\max}$ and $t_{\max}$.

For the concentration-effect analysis the standard pharmacokinetic model was augmented by an 'effect' compartment as described previously (Holford & Sheiner, 1981). Effect, in this case blood pressure reduction, was then related to the drug concentration in the effect compartment by means of both linear and non-linear ($E_{\max}$) functions. In each case, after both acute and chronic dosing, the data were most appropriately described by the linear model which defines the relationship between drug concentration and effect as:

$$E = mC_c + i$$

where E is the measured effect, C_c the drug concentration in the effect compartment and i the intercept. The slope of this relationship, m , represents the responsiveness to the drug in terms of effect (in mm Hg) per unit drug concentration. The first order rate constant of the effect model, K_{eq} , describes the removal of drug from the effect compartment and characterises the temporal discrepancy for the plasma concentration-effect relationship (Holford & Sheiner, 1981).

The pharmacokinetic and pharmacodynamic data for doxazosin were sequentially fitted to the linear effect model using a non-linear least squares fitting procedure and the responsiveness, m , for individual patients on each study day was calculated in terms of the (placebo-subtracted) change in both erect systolic and diastolic blood pressure per unit change in drug concentration.

Statistical analysis

The blood pressure and heart rate data and the measurements of plasma renin activity, aldosterone and catecholamines were evaluated by repeated measures analysis of variance. The pharmacokinetic parameters for individual patients were compared between study days by repeated measures analysis of variance.

All data points in each individual patient for

the pressor responses to PE and AII were fitted to a quadratic function according to the method of Sumner *et al.* (1982). The derived PD_{20} values represent the dose of agonist required to raise mean arterial pressure by 20 mm Hg and the logarithmic transformations of these measurements were compared between study days by repeated measures analysis of variance. The dose ratio was calculated as the ratio PD_{20} treatment/ PD_{20} placebo.

The concentration-effect parameters, m and K_{eq} , were compared between study days by Student's paired t -test with appropriate correction for multiple comparisons. Linear regression analysis was used to evaluate the relationship between the responsiveness to doxazosin (m) acutely and the responsiveness after 1 week and 6 weeks treatment, and for the correlations between m and factors such as starting blood pressure, the phenylephrine dose ratio and changes in heart rate. Results throughout are expressed as mean $\pm$ s.d.

Results

Blood pressure

There were significant reductions in both supine and erect blood pressure following the first dose of doxazosin and the lowest blood pressures were recorded at 5–6 h after dosing (Figure 1). For example, supine blood pressure fell from a baseline of $170/102 \pm 13/5$ to $128/77 \pm 14/11$ mm Hg at 6 h, compared with a corresponding change from $175/105 \pm 16/7$ to $147/88 \pm 7/8$ mm Hg at 6 h after placebo. The corresponding changes for erect blood pressure were from a baseline of $165/102 \pm 15/8$ to $114/69 \pm 18/12$ mm Hg at 6 h, compared with $173/107 \pm 13/6$ to $151/93 \pm 11/6$ mm Hg at 6 h after placebo.

Continued treatment with doxazosin significantly reduced predose blood pressures. Supine blood pressure recorded 24 h after the last dose was $155/94 \pm 13/6$ mm Hg after 1 week and $157/95 \pm 17/8$ mm Hg after 6 weeks, compared with $175/105 \pm 16/7$ mm Hg following placebo. Blood pressure levels were particularly satisfactory during the 8 h of each study day, with average blood pressures (calculated from all the readings throughout the 8 h) of $137/82$ supine and $133/82$ mm Hg erect after 1 week, and $140/85$ supine and $135/84$ mm Hg erect after 6 weeks.

Heart rate

The fall in blood pressure following the first dose of doxazosin was associated with a signifi-

Figure 1 Mean profiles ($\pm$ s.d.) for erect systolic and diastolic blood pressure and heart rate after placebo ($\circ$), first dose doxazosin 2 mg ($\bullet$), and after 1 week ($\triangle$) and 6 weeks ($\blacktriangle$) doxazosin treatment.

cant increase in heart rate, particularly in the erect position 4–5 h after drug administration (Figure 1). Erect heart rate increased from a baseline of 79 ± 10 to 92 ± 10 beats min^{-1} 4 h after the first dose compared with a change from 79 ± 13 to 77 ± 11 beats min^{-1} following placebo. After 1 week of treatment with doxazosin the heart rate increase was attenuated, although still significant, from a baseline of 81 ± 9 to 87 ± 11 beats min^{-1} at 4 h but after 6 weeks of doxazosin the heart rate profiles were not significantly different from placebo (Figure 1).

Symptoms and adverse reactions

Doxazosin was generally well tolerated by all patients. There were symptoms of dizziness and light-headedness at peak drug effect (5–6 h) after the first dose of doxazosin in four out of ten patients. However, the initial dose used (2 mg) was higher than that recommended in practice and selected in this study to ensure that a substantial measurable effect on blood pressure was achieved. No patient had any other significant symptoms or side effects attributable to doxazosin and all patients recruited completed the study.

Hormone measurements

There were significant increases in plasma noradrenaline at 6 h after the first dose of doxazosin (5.1 ± 2.6 nmol l^{-1} compared with 2.8 ± 0.9 after placebo) (Table 1) and also after 1 week's treatment (4.4 ± 2.0 nmol l^{-1}). Measurements at 6 weeks were not significantly different from placebo. Doxazosin had no significant effect on plasma renin activity or aldosterone (Table 1).

Pressor responses

Doxazosin produced parallel rightward shifts of the phenylephrine pressor dose-response

Table 1 Plasma renin activity, aldosterone and noradrenaline 6 h after oral dosing with placebo or doxazosin 2 mg daily. Mean $\pm$ s.d.

	Placebo	First dose	1 week	6 weeks
Plasma renin activity (ng AI ml^{-1} h^{-1})	2.2 ± 1.6	2.8 ± 1.5	2.8 ± 3.0	2.2 ± 1.9
Plasma aldosterone (pg ml^{-1})	117 ± 73	117 ± 28	101 ± 33	87 ± 40
Plasma noradrenaline (nmol l^{-1})	2.8 ± 0.9	$5.1 \pm 2.6^{**}$	$4.4 \pm 2.0^{*}$	3.3 ± 1.6

** $P < 0.001$, * $P < 0.01$.

Figure 2 Pressor dose-response curves for phenylephrine in a representative patient, fitted to a quadratic function, after placebo ($\circ$), first dose doxazosin 2 mg ($\bullet$), and after 1 week ($\triangle$) and 6 weeks ($\blacktriangle$) doxazosin treatment.

Table 2 Pressor responses to phenylephrine and angiotensin II (mean $\pm$ s.d.) expressed as dose to raise mean blood pressure by 20 mm Hg (PD_{20}) after placebo or doxazosin 2 mg daily

	Placebo	First dose	3 days	1 week	6 weeks
<i>Phenylephrine</i> ($\mu\text{g kg}^{-1} \text{min}^{-1}$)					
Early (1.5–3 h)	1.9 ± 0.7	$5.7 \pm 3.0^*$	—	$8.7 \pm 4.3^{**}$	$6.2 \pm 3.4^{**}$
Late (5–6 h)	1.4 ± 0.7	$3.9 \pm 1.6^*$	$8.3 \pm 4.4^{**}$	$7.2 \pm 3.8^{**}$	$5.6 \pm 2.8^{**}$
<i>Angiotensin II</i> ($\text{ng kg}^{-1} \text{min}^{-1}$)					
Early (1.5–3 h)	4.9 ± 2.2	4.7 ± 1.8	—	4.3 ± 1.0	5.9 ± 3.7

Comparison with placebo * $P < 0.0005$, ** $P < 0.0001$.

Comparison with 1 week $^x P < 0.02$.

curves as illustrated for a representative patient (Figure 2), and there were significant increases in PD_{20} for early and late infusions (Table 2). For the whole group the mean PD_{20} for the early period for phenylephrine increased from 1.9 (placebo) to 5.7 (first dose), 8.7 (1 week) and $6.2 \mu\text{g kg}^{-1} \text{min}^{-1}$ after 6 weeks. On each study

day there was no significant difference in pressor responses to phenylephrine between the early and late infusions. The maximum α_1 -adrenoceptor antagonist effect of doxazosin was observed during the first week of treatment after 3 and 7 days. α -adrenoceptor blockade was less prominent after 6 weeks. The mean PD_{20}

for phenylephrine was significantly reduced ($P < 0.02$) at $5.6 \mu\text{g kg}^{-1} \text{min}^{-1}$ after 6 weeks compared with 7.2 after 1 week.

Doxazosin had no significant effect on pressor responses to angiotensin II (Table 2).

Pharmacokinetics

The mean pharmacokinetic parameters obtained by fitting a one compartment model to the individual data sets are shown in Table 3. Analysis of variance revealed a significant difference in terminal elimination half-life when comparing the first dose with steady state therapy, with

mean values of 12.5 ± 3.3 and 12.3 ± 2.5 h at 1 and 6 weeks respectively compared with 8.8 ± 2.3 h on first dosing (Table 3). The apparent increase in half-life with chronic therapy is paralleled by a significant increase in AUC (and thereby a reduction in oral clearance assuming consistent absorption) from 287.2 ± 104.8 to 372.6 ± 136.3 and $369.4 \pm 133.2 \text{ ng ml}^{-1} \text{h}$ at 1 and 6 weeks respectively (Table 3). No significant changes in maximum concentration (C_{max}) or time to attain C_{max} (t_{max}) were observed (Table 3).

There was no relationship between patient age and the pharmacokinetics of doxazosin.

Table 3 Doxazosin pharmacokinetics. Summary of derived parameters. (Mean $\pm$ s.d.)

	First dose	1 week	6 weeks
AUC ($\text{ng ml}^{-1} \text{h}$)	287.2 ± 104.8	$372.6 \pm 136.3^*$	$369.4 \pm 133.2^*$
$t_{1/2}$ (h)	8.8 ± 2.3	$12.5 \pm 3.3^*$	$12.3 \pm 2.5^*$
C_{max} (ng ml^{-1})	18.6 ± 6.5	17.9 ± 5.1	18.9 ± 6.4
t_{max} (h)	3.2 ± 1.8	3.2 ± 1.9	2.4 ± 1.5

* $P < 0.03$: comparison with first dose.

Figure 3 Pharmacodynamic modelling in a representative subject (patient 3) after the first dose doxazosin 2 mg (a, b) and after 6 weeks (c, d), illustrating the observed ($\blacktriangle$ — $\blacktriangle$) and fitted ($\triangle$. . . $\triangle$) effect of doxazosin on systolic (a, c) and diastolic (b, d) blood pressure.

Concentration-effect relationships

In individual patients, there was no simple direct relationship between the plasma doxazosin concentration and the fall in blood pressure. However, using the linear effect model, doxazosin concentrations were well correlated with changes in both systolic and diastolic blood pressure, as illustrated for a representative patient in Figure 3. The derived m and K_{eq} values for reductions in systolic and diastolic blood pressure in individual patients are shown in Table 4. There was a significant reduction ($P < 0.03$) in the responsiveness to doxazosin during chronic compared with acute administration: for example, the mean responsiveness in terms of the change in systolic blood pressure was -2.1 mm Hg $\text{ng}^{-1} \text{ml}^{-1}$ following the first dose, -1.5 after 1 week and -1.4 after 6 weeks (Table 4). There was, on average, a 30% fall in the responsiveness during chronic treatment and most of this change occurred during the first week. For individual patients however there was still a significant correlation between the responsiveness to the first dose of doxazosin and the

responsiveness after 1 week ($r = 0.65$) and 6 weeks ($r = 0.63$) treatment (Figure 4). In addition, there were significant correlations between the responsiveness (m) calculated in terms of systolic blood pressure and the responsiveness for reduction in diastolic blood pressure ($r = 0.85$).

There was a trend towards a relationship between the responsiveness to doxazosin after the first dose and the degree of peripheral α_1 -adrenoceptor antagonism (expressed as the phenylephrine dose ratio) but this did not achieve statistical significance ($P < 0.055$). There was a significant positive correlation between the responsiveness to doxazosin after the first dose and the baseline (pretreatment) blood pressure (Figure 5b) and there was a negative correlation between responsiveness acutely and the placebo-corrected maximal change in heart rate (Figure 5a).

There was no relationship between the responsiveness to doxazosin and patient age, plasma renin activity and plasma catecholamine levels. There was no significant change in K_{eq} between the 3 study days.

Table 4 Concentration-effect parameters, m (mm Hg $\text{ng}^{-1} \text{ml}^{-1}$) and K_{eq} (h^{-1}) for changes in erect systolic and diastolic blood pressure in individual patients after doxazosin 2 mg daily

Patient	First dose		1 week		6 weeks	
	m	K_{eq}	m	K_{eq}	m	K_{eq}
<i>Systolic blood pressure</i>						
1	-3.2	0.4	-1.1	0.6	-1.0	0.8
2	-3.2	8.5	-4.3	0.3	-3.1	0.2
3	-2.3	1.6	-1.8	0.4	-1.9	0.7
4	-1.1	4.2	-0.6	2.3	-0.6	2.3
5	-3.2	3.9	-1.7	2.4	-1.7	6.0
6	-2.0	1.0	-2.0	1.1	-1.5	0.6
7	-1.3	1.1	-0.7	0.5	-0.7	0.5
8	-1.3	4.5	-0.7	0.8	-0.6	1.8
9	-2.1	2.1	-1.2	0.7	-0.9	1.0
10	-1.4	2.4	-1.1	4.7	-1.6	2.2
Mean s.d.	-2.1 ± 0.8	3.0 ± 2.4	$-1.5 \pm 1.1^*$	1.4 ± 1.4	$-1.4 \pm 0.8^*$	-1.6 ± 1.7
<i>Diastolic blood pressure</i>						
1	-2.2	0.3	-0.6	0.8	-0.7	1.0
2	-2.2	3.1	-1.0	0.7	-1.9	0.2
3	-1.2	3.3	-1.1	0.4	-1.6	0.4
4	-0.9	0.6	-0.5	1.2	-0.4	3.8
5	-1.6	8.3	-0.6	19.7	-0.8	4.1
6	-1.2	1.3	-0.6	0.7	-0.7	1.0
7	-0.9	0.6	-0.7	1.8	-0.6	1.0
8	-1.1	1.8	-0.8	0.9	-0.8	1.0
9	-1.9	1.0	-0.6	0.6	-0.5	1.2
10	-1.1	2.6	-0.7	7.3	-1.2	1.0
Mean s.d.	-1.4 ± 0.5	2.3 ± 2.4	$-0.7 \pm 0.2^*$	3.4 ± 6.1	$-0.9 \pm 0.5^*$	1.5 ± 1.3

Figure 4 Correlation between the responsiveness (m) to the first dose doxazosin and the responsiveness after 6 weeks.

Discussion

It has been well established that doxazosin lowers blood pressure (Frick *et al.*, 1986; Baez *et al.*, 1986; Shionoiri *et al.*, 1987) and this study has confirmed that the antihypertensive effect during longterm treatment is sustained for 24 h with a dosage regimen of 2 mg once daily. For

the purposes of this research study the dose of doxazosin was fixed at 2 mg to ensure an adequate and measurable response to the first dose. This is larger than the starting dose of 1 mg recommended for routine clinical use. Although doxazosin was generally well tolerated throughout the study, four patients experienced orthostatic symptoms at the peak of action after the first dose. Adverse effects after the first dose of an α_1 -adrenoceptor antagonist are partly dose dependent (Rosendorff, 1976) and in routine clinical practice the lower starting dose of 1 mg doxazosin appears to be well tolerated (Cox *et al.*, 1986).

The pharmacokinetic profile of doxazosin is compatible with a single daily dosing regimen (Elliott *et al.*, 1987). There was a further significant increase in the elimination half-life and AUC of doxazosin during chronic compared with acute administration. Similar reductions in drug clearance and prolongation of half-life during chronic doxazosin treatment have been described by others (Shionoiri *et al.*, 1987) and also were reported in a study that sampled drug levels for up to 72 h after dosing (Cubeddu *et al.*, 1987). The explanation for this apparent reduction in clearance is uncertain. In part it may reflect the schedule of sampling times and achieved plasma concentrations after the first dose but additionally it may reflect saturation of hepatic metabolic activity since doxazosin is ex-

Figure 5 First dose doxazosin. There was a negative correlation between responsiveness (m) and the maximal increase in erect heart rate (placebo and baseline subtracted) (a), and a positive correlation between responsiveness and the height of the pretreatment blood pressure (b).

tensively metabolised in the liver (Kaye *et al.*, 1986). There is some evidence with prazosin, which undergoes metabolism by the same demethylation pathway, that age, and the presumptive decline in hepatic function, leads to a significant change in drug disposition (Rubin *et al.*, 1981). This has not been a consistent finding (McNeil *et al.*, 1987) and in this relatively small study there was no relationship between age and the pharmacokinetics of doxazosin.

The pharmacodynamic profile of doxazosin, in contrast to that of prazosin (Seideman *et al.*, 1981), is clearly out of phase with plasma drug levels and therefore no simple direct relationship exists between plasma concentration and the fall in blood pressure (Elliott *et al.*, 1982; Vincent *et al.*, 1983; Cubeddu *et al.*, 1987). With prazosin, consistent concentration-effect relationships have been identified after acute intravenous dosing (Bateman *et al.*, 1979; Seideman *et al.*, 1981; Larochelle *et al.*, 1982) but studies of oral dosing, particularly where group data have been analysed, have been less successful (MacCarthy *et al.*, 1980; Grahnen *et al.*, 1981). With doxazosin Vincent *et al.* (1983) defined concentration-effect relationships in individual subjects for both blood pressure reduction and α -antagonism and the present study has extended these observations to chronic oral treatment in hypertensive patients.

There was a significant reduction (of approximately 30%) in the responsiveness (m) to doxazosin during longterm treatment. This was clearly apparent after 1 week with little change between 1 and 6 weeks therapy. Despite the reduction during chronic treatment in antihypertensive responsiveness and the changes in the extent of α -adrenoceptor blockade, there were significant correlations between the responsiveness to the first dose of doxazosin and that after 1 week and 6 weeks treatment. This may have potential clinical application in that the response to the first dose, for an individual patient, may be used to forecast the response (albeit 70% magnitude) during longterm treatment and thereby allow prompt identification of poor or non-responders.

Very little is known about factors which determine the response to treatment with an α -adrenoceptor blocker (MacCarthy *et al.*,

1980; Stokes *et al.*, 1980; Donnelly *et al.*, 1989) but variability in kinetic as well as dynamic parameters accounts for much of the inter-individual differences in antihypertensive effect. The fall in blood pressure is related to antagonism of α_1 -adrenoceptors in the peripheral vasculature but, acutely, reflex increases in heart rate tend to counteract the fall in blood pressure and if the heart rate response is attenuated, for example with a β -adrenoceptor antagonist, the acute hypotensive effect of prazosin is enhanced (Elliott *et al.*, 1981). In this study there was a significant negative correlation between the responsiveness to the first dose of doxazosin and the maximum reflex rise in heart rate. Although it has been claimed that α_1 -adrenoceptor antagonists produce greater haemodynamic effects in the elderly (Stokes *et al.*, 1984) this however takes no account of possible age-related differences in pharmacokinetics (Rubin *et al.*, 1981; McNeil *et al.*, 1987). In this study, although the age range studied was not wide (47–70 years), there was no relationship between age and the fall in blood pressure per unit drug concentration.

In contrast, starting blood pressure may be an important determinant of the magnitude of the response to treatment with an α -adrenoceptor blocker (Sumner *et al.*, 1988) and in this study there was a significant correlation between the responsiveness to doxazosin acutely and the pre-treatment systolic blood pressure.

In conclusion, the pharmacokinetics and pharmacodynamics of doxazosin are consistent with 24 h blood pressure control using a single daily dose. Concentration-effect relationships can be derived for both systolic and diastolic blood pressure in individual hypertensive patients during acute and long-term treatment. This approach incorporates kinetic and dynamic information and additionally takes account of placebo effects and changes in drug concentration and blood pressure during the dosage interval. The responsiveness to doxazosin appears to be related to its α_1 -adrenoceptor antagonist activity. The attenuation in responsiveness observed probably occurs within a few days and is not progressive. The predictability of the long-term response to doxazosin from the response to the first dose appears to be independent of treatment duration.

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