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DOXAZOSIN, AN α_1-ADRENOCEPTOR ANTAGONIST: PHARMACOKINETICS AND CONCENTRATION-EFFECT RELATIONSHIPS IN MAN

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1 The effects of single doses of doxazosin, a quinazoline derivative similar to prazosin, were studied in six normotensive volunteers.

2 Both 1 mg (i.v.) or 2 mg (oral) doxazosin caused a fall in blood pressure which was most apparent in the erect posture at 5–6 h following drug administration. The maximum fall in blood pressure following i.v. doxazosin was from 123/81 to 106/69 mm Hg associated with a rise in heart rate from 81 to 107 beats/min.

3 The terminal elimination half-life following oral and intravenous doxazosin was about 9 h.

4 Pressor responsiveness to the α_1-adrenoceptor agonist, phenylephrine, showed no significant difference between oral and i.v. doxazosin suggesting that the route of administration did not influence α_1-adrenoceptor antagonism at the doses used.

5 Using a pharmacodynamic modelling technique in individual subjects, there was a significant correlation between the change in doxazosin concentration in the effect compartment and its hypotensive effect.

6 With the modelling technique it was possible to show a significant correlation between the pressor responsiveness to the α_1-adrenoceptor agonist phenylephrine and the concentration of doxazosin in the effect compartment. This is consistent with the concept that the hypotensive effect of doxazosin is mediated by α_1-adrenoceptor blockade.

Introduction

Doxazosin is a quinazoline derivative related to prazosin. Like prazosin it has α-adrenoceptor antagonist properties with a relatively selective peripheral α_1-adrenoceptor antagonist effect in animals (Karamat *et al.*, 1980; Timmermans *et al.*, 1980;) and in man, (Singleton *et al.*, 1980).

The hypotensive effect of prazosin after the first dose has been shown to correlate with drug concentrations in blood (Bateman *et al.*, 1979; Seidman *et al.*, 1981; Elliott *et al.*, 1981; Larochelle *et al.*, 1982) but in preliminary studies with doxazosin in volunteers, the maximum hypotensive effect occurred at 6 h after intravenous (i.v.) administration and was therefore out of phase with peak whole blood drug concentrations (Elliott *et al.*, 1982).

This study defines the clinical pharmacokinetics of doxazosin after oral and intravenous dosing in normal volunteers and investigates the relationship of drug concentrations to hypotensive effect and α-adrenoceptor blockade.

Methods

Six healthy normotensive male volunteers, aged 23–39 years, gave written informed consent to receive 1 mg i.v. and 2 mg oral doxazosin on separate study days at least 1 week apart in a randomised cross-over design. The study was approved by the local Research and Ethical Committee. At frequent intervals throughout the study period, blood samples were withdrawn from an indwelling intravenous cannula for subsequent measurement of whole blood or plasma doxazosin by h.p.l.c. assay using fluorescence detection with a limit of detection of 1 ng/ml and an average coefficient of variation of 5.1% (Rubin *et al.*, 1980). At corresponding times, blood pressure and heart rate were measured after 10 min resting supine and then on standing for 2 and 5 min. Blood pressure was measured with a semi-automated sphygmomanometer (Roche Arteriosonde model 1225) and heart rate was measured on a continuous ECG recording from standard arterior chest leads displayed on a Grass Polygraph Model 7D.

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Pressor responses to graded intravenous doses of the α_1-adrenoceptor agonist, phenylephrine, were performed at 2.5 and 6.5 h after drug administration and also on a separate control day under comparable study conditions. The infusion was commenced at 0.5 $\mu g\ kg^{-1}\ min^{-1}$ and the dose rate was increased at 5 min intervals until a maximum rise of 45 mm Hg systolic or 30 mm Hg diastolic pressure was achieved. Pressor dose–response curves were constructed by plotting the rise in mean arterial pressure from baseline against the log–dose of the pressor agent. The results were analysed as described by Sumner *et al.* (1982) and all data points fitted to a quadratic function. The dose required to raise the mean arterial pressure by 20 mm Hg (PD_{20}) was derived.

Estimates of pharmacokinetic parameters were obtained by computer assisted non-linear least squares regression analysis with an inverse weighting of drug concentration.

The inter-relationship between drug concentration and drug effect following intravenous doxazosin was examined by the pharmacodynamic modelling technique described by Whiting & Kelman (1980). Using this effect model the pharmacokinetic data were related to the fall in systolic blood pressure (after 5 min standing). With this method the standard pharmacokinetic model was augmented by an effect compartment which was governed by a first order process, but which was deemed small enough not to influence the pharmacokinetics. The measured effect (in this case change in blood pressure) was then related to the concentration of drug in the effect compartment. The relationship between drug effect (E) and concentration of drug in the effect compartment (*Ce*) was examined in the simplest form using the linear equation:

$$E = mCe\ (t) + i$$

where m, the slope, described the 'sensitivity' parameter that expressed the change in systolic blood pressure for a given change in the drug concentration in the effect compartment and i was the intercept. The concentration of drug in the effect compartment (*Ce*) can be described as

$$Ce = \frac{Ak_{eq}}{k_{eq}-\alpha}(e^{-\alpha t} - e^{-k_{eq}t}) + \frac{Bk_{eq}}{k_{eq}-\beta}(e^{-\beta t} - e^{-k_{eq}t})$$

where k_{eq}, a first order rate constant, characterises the blood concentration–effect discrepancy. The three parameters m, i, k_{eq} were determined by non-linear least squares fitting.

Statistical analysis was by repeated measured ANOVA for heart rate and blood pressure and by the Student's *t*-test for paired data for the pressor responses and pharmacokinetic parameters.

Results

Drug levels and pharmacokinetic analysis

Representative whole blood concentration–time profiles for both oral and i.v. doxazosin are shown in Figure 1.

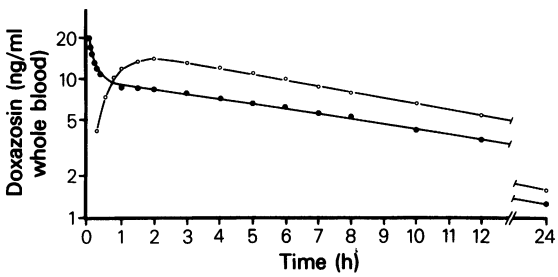

Figure 1 Representative concentration-time profile (subject 6) of whole blood doxazosin concentration after oral administration of 2 mg (○——○) or i.v. dosing with 1 mg (●——●).

The pharmacokinetic data were most appropriately fitted to a two compartment model following i.v. doxazosin and to a one compartment model following oral doxazosin administration.

The values obtained by fitting i.v. and oral whole blood doxazosin data to the appropriate equations are summarised in Table 1. The mean calculated bioavailability of doxazosin was 63 ± 13% and the terminal elimination half-lives were not significantly different at 562 ± 92 and 534 ± 101 min (9.4 and 8.9 h) following i.v. and oral administration respectively. Doxazosin clearance from whole blood was 139 ± 30 ml/min following i.v. administration.

The parameter values obtained by fitting plasma doxazosin concentrations were not significantly different from those obtained with whole blood. Bioavailability was 64.5 ± 13.9% and the intravenous and oral terminal elimination half-lives were 574 ± 64 and 571 ± 85 min respectively. Clearance calculated from plasma levels was significantly less at 88 ± 19 ml/min than that from whole blood (Table 2).

Blood pressure and heart rate

The effects of doxazosin on supine systolic and diastolic blood pressure and heart rate are illustrated in Figure 2 which shows the average systolic pressure and heart rate (± s.d.) after oral dosing. The mean maximal changes in supine blood pressure were from 124/76 (± 11/8) to 122/65 (± 15/8) after i.v. doxazosin and from 121/78 (± 9/7) to 115/72 (± 6/4) after oral administration. The fall in blood pressure was more pronounced in the erect posture (Figure 3) with mean maximal changes in 5 min erect blood pressure from 123/81 (± 11.7/10.1) to 106/69) mm Hg (± 14.9/14.9)

Table 1 Pharmacokinetic parameters of doxazosin in whole blood after i.v. (1 mg) and oral (2 mg) administration

	i.v. doxazosin (1 mg)			*Oral doxazosin (2 mg)*			
Subject	$t_{½,z}$ (*min*)	*AUC* (*ng ml^{-1}min*)	*Clearance* (*ml/min*)	$t_{½,z}$ (*min*)	t_{lag} (*min*)	*AUC* (*ng ml^{-1}min*)	*Bioavailability* (%)
1	460	5410	185	608	12	8263	76.4
2	504	7579	132	437	20	10462	69.0
3	572	7101	141	527	24	8516	60.0
4	571	7776	129	448	3	8508	54.7
5	535	6628	151	485	3	9705	7.32
6	729	10700	94	697	48	9285	43.4
Mean ± s.d.	562 ± 92		139 ± 30	534 ± 101			62.8 ± 12.5

with an associated increase in heart rate from 81.8 ± 6 to 107 ± 15 beats/min for i.v. doxazosin and from 116/77 (± 22/23.3) to 97/62 mm Hg (± 20.3/24.1) for oral doxazosin, with a corresponding increase in heart rate from 97 ± 24 to 106 ± 14 beats/min. With both oral and i.v. doxazosin, it was observed that the maximum fall from baseline blood pressure did not occur until about 5–6 h.

Comparison of the blood pressure and heart rate responses to i.v. and oral doxazosin showed no significant difference in the average effects throughout the study day. There was, however, a difference in the pattern of response with the fall in blood pressure due to i.v. doxazosin being greater than that due to oral doxazosin in the first hour, whereas the fall due to oral doxazosin was greater between 2–6 h.

Pressor responsiveness to intravenous phenylephrine

There was a parallel shift to the right of the log–dose pressor response curves after administration of doxazosin indicating α-adrenoceptor antagonism after both oral and i.v. doxazosin compared with placebo. α-adrenoceptor blockade (Figure 4) was present at both early (2.5 h) and late (6.5 h) times studied. The doses of phenylephrine required to raise mean arterial pressure by 20 mm Hg were significantly increased at both times studied after both routes of administration (Tables 4 and 5).

There was no significant difference between the mean i.v. and oral doxazosin pressor dose–response curves compared against each other at each infusion time. For the group therefore, there was no significant difference in the mean PD_{20} between the early and late infusions suggesting that α_1-adrenoceptor antagonism was comparable at both infusion times.

Drug concentration and blood pressure responses

There was no linear relationship between drug levels in blood and the blood pressure lowering effect of doxazosin, for either individuals or for the group as a whole. However, a more complex concentration–effect analysis described a significant correlation between the fall in systolic blood pressure (after five minutes standing) and the concentration of doxazosin in the 'effect compartment'. Estimates of the derived parameters are shown in Table 3: these parameters are *k*eq which characterises the drug concentration–effect disequilibrium, m which characterises the sensitivity for effect *vs* drug concentration, and i which is the intercept term. In each case, a satisfactory fit was obtained in terms of the high values for correlation coefficients.

The values of the model parameters Keq and m, which are indices of the duration of action and responsiveness to the drug, do not show wide variation

Table 2 Comparison of pharmacokinetic parameters of doxazosin in whole blood and plasma

	i.v. doxazosin				*Oral doxazosin*			
	$t_{½,z}$ (*min*)		*Clearance* (*ml/min*)		$t_{½,z}$ (*min*)		*Bioavailability* (%)	
Subject	*Whole blood*	*Plasma*	*Whole blood*	*Plasma*	*Whole blood*	*Plasma*	*Whole blood*	*Plasma*
1	460	483	185	119	608	481	76	81
2	504	565	132	90	437	486	69	74
3	572	583	141	89	527	631	60	60
4	571	620	129	76	448	638	55	52
5	535	532	151	91	485	517	73	74
6	729	665	94	62	697	670	43	46
Mean ± s.d.	562 ± 92	574 ± 64	139 ± 30	88 ± 19	534 ± 101	571 ± 85	62.8 ± 12.5	64.5 ± 13.9

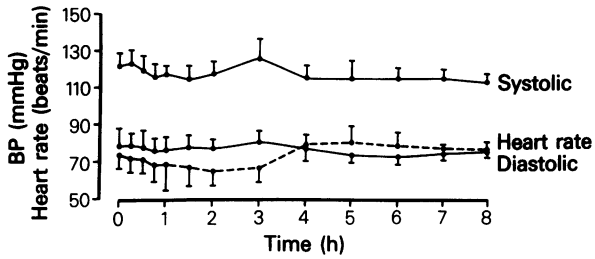

Figure 2 Supine blood pressure and heart rate (mean ± s.d.) after oral doxazosin 2 mg in six normotensive subjects.

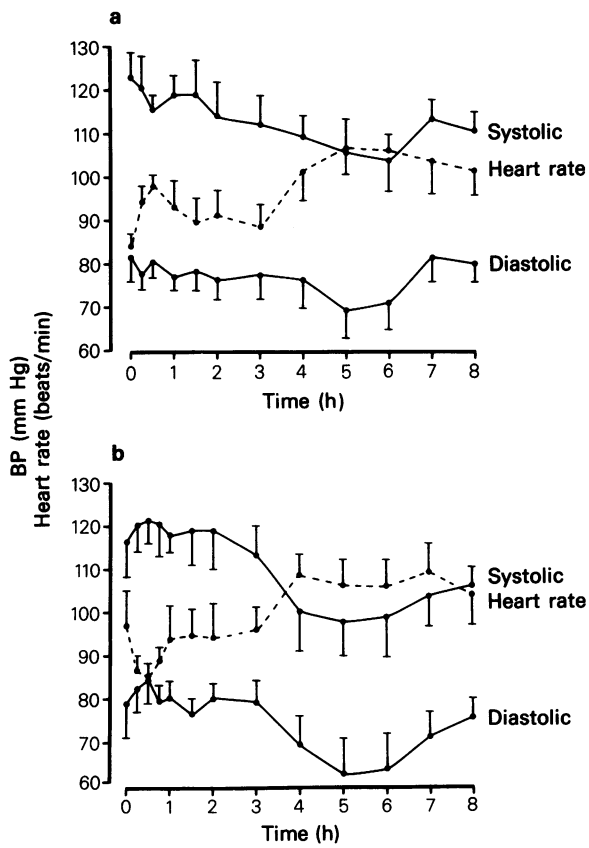

Figure 3 Blood pressure (●——●) and heart rate (●- - -●) after 5 min standing (mean ± s.d.) after i.v. doxazosin 1 mg (a) and oral doxazosin 2 mg (b).

suggesting that inter-individual variability in hypotensive response to doxazosin is not great. A representative 'modelled' systolic pressure is shown in Figure 5, comparing the profile of observed hypotensive effect with the profile fitted by effect 'modelling'.

Drug concentration and pressor responses

For the whole group there was no simple relationship between drug concentration and antagonism of the pressor response to phenylephrine. However, in each individual the relationship between the change in doxazosin concentration in the effect compartment and the change in pressor responsiveness was examined using the Kendall rank correlation test

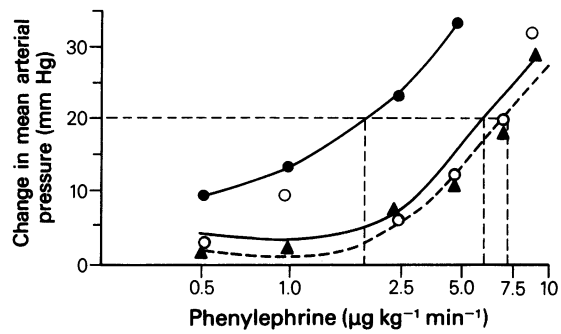

Figure 4 Representative pressor dose response relationship (subject 1) to intravenous phenylephrine in control untreated day (●——●) and 6.5 h after i.v. doxazosin (▲——▲) or oral doxazosin (○- - -○). The dose required to raise mean arterial pressure 20 mm Hg (PD_{20}) was derived.

(Figure 6). A significant ($P < 0.01$) correlation was observed between the change in drug concentration in the effect compartment and the difference in phenylephrine dose ratios at the times 2.5 and 6.5 h after drug administration.

Discussion

Following both i.v. and oral doxazosin, the terminal elimination half-life was found to average 9.5 h, not significantly different from the previously reported mean of 11 h (Elliott *et al.*, 1982). The maximum hypotensive effect of both oral and i.v. doxazosin occurred between 5–6 h also similar to previous observations. Previous studies suggest that doxazosin selectively blocks α_1-adrenoceptors in man (Singleton *et al.*, 1980; Elliott *et al.*, 1980), and in animals (Timmermans *et al.*, 1980), and the results of the pressor responses to phenylephrine in this study are consistent with this view. As there was no sig-

Table 3 Modelling of concentration: hypotensive effect relationship for doxazosin in six normotensive subjects

Subject	r	k *eq* (min^{-1})	*Slope* (*mm Hg [ng/ml]*)	*i* (*mm Hg*)
1	0.89	0.0089	−2.34	−1.1
2	0.81	0.0112	−2.40	1.8
3	0.84	0.0138	−1.89	2.9
4	0.91	0.0095	−1.95	−1.6
5	0.87	0.0083	−2.80	1.4
6	0.81	0.0132	−2.52	2.6
Mean ± s.d.		0.0108 ± 0.0023	−2.53 ± 0.35	1.0 ± 1.9

Table 4 Dose of i.v. phenylephrine ($\mu g\ kg^{-1}\ min^{-1}$) to raise mean arterial pressure 20 mm Hg. PD_{20} and dose ratios 2.5 h after i.v. doxazosin 1 mg and oral doxazosin 2 mg in six normotensive subjects

Subject	*Control*	*i.v. doxazosin*	*Dose ratio i.v. doxazosin/control*	*Oral doxazosin*	*Dose ratio oral doxazosin/control*
1	2.92	6.83	2.34	14.26	4.88
2	2.80	6.20	2.21	9.67	3.45
3	1.32	2.81	2.16	4.53	3.43
4	0.81	3.35	4.14	5.20	6.42
5	4.36	7.51	1.72	8.41	1.93
6	2.12	11.28	5.32	7.30	3.44
Mean PD_{20} ± s.d.	2.4 ± 1.3	6.3* ± 3.1		8.2* ± 3.5	
Mean dose ratio ± s.d.			2.98 ± 1.42		3.93 ± 1.54

*$P < 0.02$ when PD_{20} after treatment is compared with control untreated day

Table 5 Dose of i.v. phenylephrine ($\mu g\ kg^{-1}\ min^{-1}$) to raise mean arterial pressure 20 mm Hg. (PD_{20}) and dose ratios 6.5 h after i.v. doxazosin 1 mg and oral doxazosin 2 mg in six normotensive subjects

Subject	*Control*	*i.v. doxazosin*	*Dose ratio i.v. doxazosin/control*	*Oral doxazosin*	*Dose ratio oral doxazosin/control*
1	2.92	8.25	2.83	9.73	3.33
2	2.80	5.94	2.12	10.34	3.69
3	1.32	1.97	1.49	4.54	3.44
4	0.81	4.97	6.14	4.79	5.91
5	4.36	7.60	1.74	6.64	1.52
6	2.12	2.82	1.33	5.08	2.40
Mean PD_{20} ± s.d.	2.4 ± 1.3	5.3 ± 2.5*		7.0 ± 2.5*	
Mean dose ratio ± s.d.			2.61 ± 1.81		3.38 ± 1.48

*$P < 0.05$ when PD_{20} after treatment is compared to control untreated day

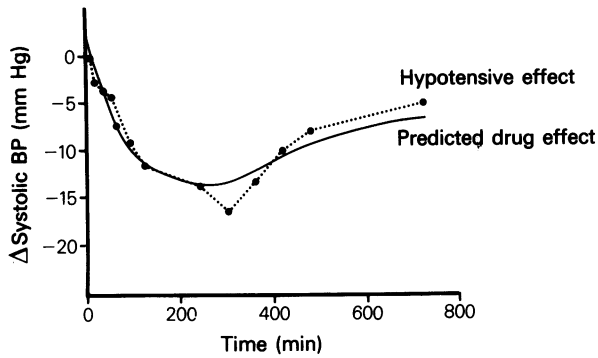

Figure 5 Fall in standing systolic blood pressure in a representative subject (subject 4) after i.v. doxazosin 1 mg. The actual observations are shown by the black stops and joined by the dotted line. The solid line is derived from the 'effect modelling' analysis and describes the observed data well.

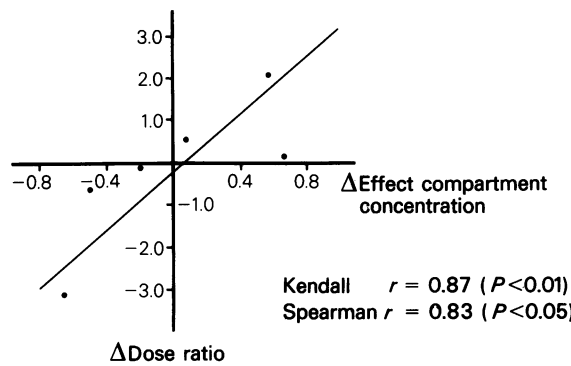

Figure 6 The relationship between changes in phenylephrine dose ratio and changes in calculated doxazosin concentrations in the effect compartment.

nificant difference between the mean shift to the right of the phenylephrine pressor dose–response curves following either i.v. or oral administration it is clear that, at the doses used, the route of administration does not influence the α-adrenoceptor blocking properties of the drug.

There was no immediately obvious relationship between the whole blood doxazosin concentrations and the reduction in blood pressure, with the maximum hypotensive effect at 4–6 h out of phase with maximum blood levels which were achieved within the first hour. While one or more active metabolites might explain this finding, we have no evidence at present that such metabolites are formed in man.

An alternative explanation is that the delay in achieving maximum hypotensive effect may depend on the time taken for doxazosin to reach a maximum concentration at receptor sites.

Thus, the significant kinetic parameter is not the drug concentration in blood but the drug concentration at the receptor (or in the 'effect' compartment). It is not uncommon for the time-course of drug effect to be out of phase with calculated drug levels in either the 'central' or 'peripheral' pharmacokinetic compartments (Galeazzi *et al.*, 1976; Sheiner *et al.*, 1978; Whiting & Kelman, 1980) and application of the technique of concentration-effect analysis confirmed that the delayed hypotensive effect of doxazosin correlated most closely with the calculated drug concentration in the 'effect' compartment in each individual subject. This close correlation makes it unlikely that there is a further significant contribution from an active metabolite.

Extending the 'modelling' technique to examine the α-adrenoceptor blocking effect revealed that, although there was no significant difference in the degree of α-adrenoceptor blockade for the group overall, there was a significant correlation between the change in pressor responsiveness and the change in doxazosin concentration in the 'effect' compartment. Thus, both the hypotensive effect and the α_1-adrenoceptor blockade can be correlated in individuals with the concentration of doxazosin in the 'effect' compartment. These results suggest that the hypotensive action of doxazosin in this study of normal volunteers was mediated via antagonism of α-adrenoceptors by doxazosin or putative active metabolites.

The prolonged terminal elimination half-life of doxazosin and the gradual onset and prolonged duration of its hypotensive effect justifies its further evaluation as an antihypertensive agent suitable for once or twice daily dosing.

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