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A PHARMACODYNAMIC AND PHARMACOKINETIC ASSESSMENT OF A NEW α-ADRENOCEPTOR ANTAGONIST, DOXAZOSIN (UK33274) IN NORMOTENSIVE SUBJECTS

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1 Doxazosin is a quinazoline derivative, related to prazosin, recently developed for the treatment of hypertension.

2 The intravenous administration of doxazosin (12 μg/kg) to six healthy normotensive subjects resulted in a significant fall in erect blood pressure, with a corresponding increase in heart rate, but there were no significant changes in supine blood pressure or heart rate.

3 The changes in blood pressure and heart rate were maximal at 6 h after intravenous dosing. With prazosin the maximum effects occurred within the first hour.

4 Pressor response studies with phenylephrine confirmed that doxazosin is a relatively selective postsynaptic α-adrenoceptor antagonist.

5 The mean elimination half-life of doxazosin was 11 h. This compared with a $T_{½}$ of 2.5 h for prazosin.

Introduction

Doxazosin (UK33274-Pfizer U.K. Ltd) is a quinazoline derivative closely related to prazosin (Figure 1) with similar activity (Singleton *et al.*, 1980; Timmermans *et al.*, 1980) as a peripherally-acting, selective postsynaptic α-adrenoceptor antagonist (Cambridge *et al.*, 1977).

Therapy with α-adrenoceptor blocking drugs is being increasingly used in the treatment of hypertension and cardiac failure but prazosin, although it is well established, has two relative disadvantages: it requires more than once daily administration and it occasionally causes postural hypotension and syncope as a 'first dose effect' (Graham *et al.*, 1976). Preliminary studies with doxazosin have shown that it has a slower rate of elimination, with the possibility of satisfactory once daily administration, and it has a shallower dose-response curve which might render it less likely to cause a first dose response with acute postural hypotension.

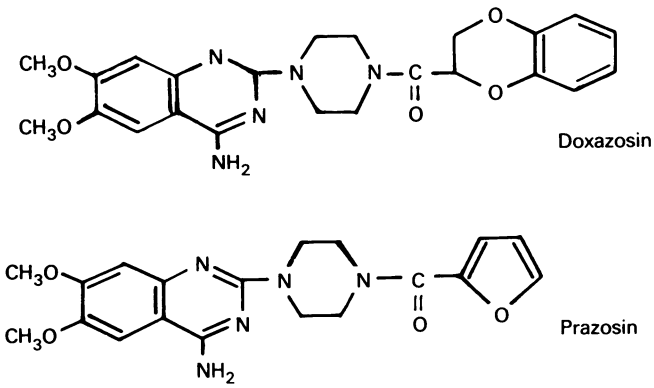

Figure 1 Chemical structures of prazosin and doxazosin.

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Methods

In a randomised single-blind study, six healthy male volunteers, aged 21–38 years, gave written, informed consent to the intravenous administration of doxazosin or saline vehicle as placebo on two separate study days, 1 week apart. On a third study day, at least 1 week later, a comparable evaluation was undertaken using 1 mg prazosin i.v. The study was approved by the local Research and Ethical Committee.

In a preliminary dose-ranging study in two individual subjects, the responses to 4 μg/kg and 8 μg/kg doxazosin were measured. No significant changes occurred in blood pressure or heart rate at these doses, either supine or erect. With 12 μg/kg there were consistent changes in erect blood pressure and heart rate and accordingly this dose was used throughout the main study.

Blood pressure was measured automatically by Roche Arteriosonde (model 1225) and heart rate was measured on a continuous ECG recording from standard anterior chest leads. Blood pressure and heart rate were repeatedly measured supine, after 10 min recumbency, and after 1 and 2 min standing throughout the study period of 24 h. Blood samples were withdrawn from an indwelling intravenous cannula at intervals up to 24 h after drug administration.

At 2.25 and 3.25 h after drug administration, subjects received, in randomised sequence, intravenous infusions of both phenylephrine (dose range 0.5–10.0 $\mu g\ kg^{-1}\ min^{-1}$) and noradrenaline (dose range 0.02–1.0 $\mu g\ kg^{-1}\ min^{-1}$).

The infusion dose rate was increased at 5 min intervals until a maximum steady state increase in blood pressure of not more than 45 mmHg systolic or 30 mmHg diastolic was achieved. Pressor response curves were then derived by plotting the rise in mean arterial pressure against the log dose of pressor amine and the dose required to raise mean arterial pressure by 20 mmHg (PD_{20}) was derived.

Whole blood drug concentration was measured by h.p.l.c. assay incorporating fluorescence detection (Rubin *et al.*, 1980) with a limit of detection of 1 ng/ml and an average coefficient of variation of 5.1%.

Statistical evaluation was by repeated measures analysis of variance for the heart rate and blood pressure profiles and by paired *t*-test elsewhere.

Results

(i) *Blood pressure and heart rate*

Following intravenous doxazosin there were no significant changes in supine blood pressure or heart rate compared to placebo. Throughout the 8 h of the study day, the average blood pressure was 115 ± 7/69 ± 5 mmHg after doxazosin compared to 116 ± 7/71 ± 6 mmHg after placebo. The mean heart rates similarly were not significantly different at 64 ± 7 beats/min and 63 ± 7 beats/min respectively. On standing there were significant changes in both blood pressure and heart rate (Figure 2). Significant reductions in both

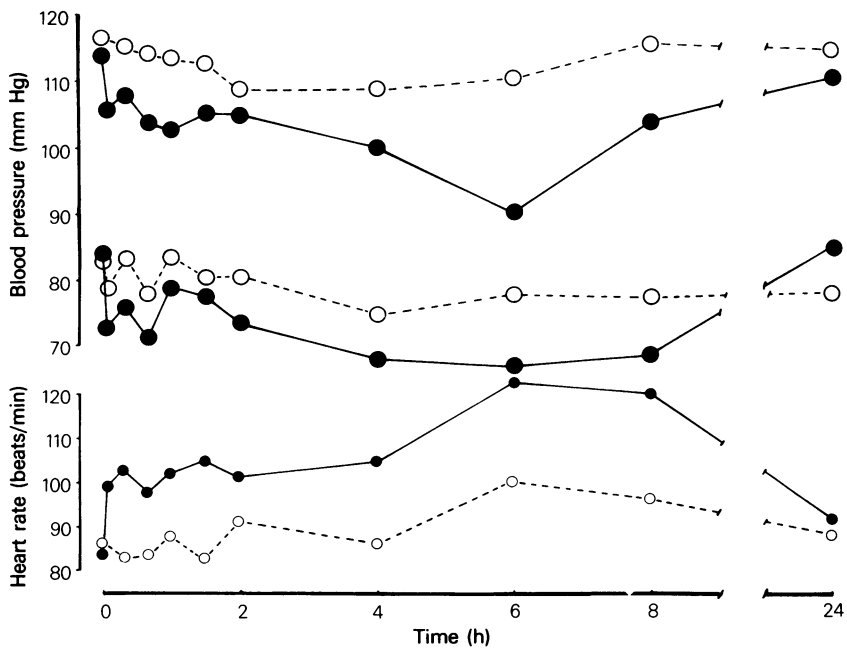

Figure 2 Average blood pressure (systolic and diastolic) and heart rate (after 2 min standing) comparing doxazosin (●) with placebo (○) (n = 6).

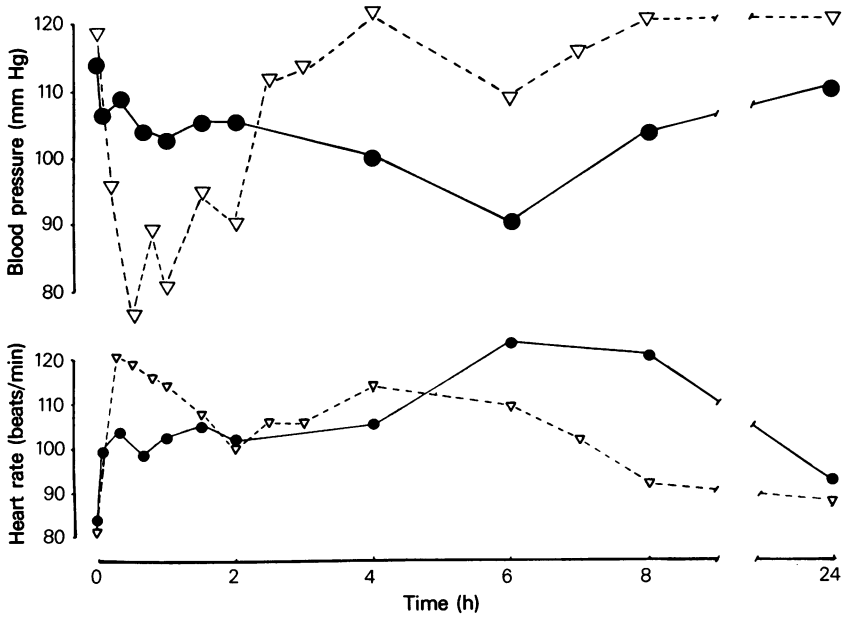

Figure 3 Profiles of erect systolic blood pressure and heart rate after intravenous doxazosin (●, 12 μg/kg) and intravenous prazosin (▽, 1 mg).

systolic and diastolic pressure ($P < 0.05$) and a significant increase in heart rate ($P < 0.01$) occurred after doxazosin, with the maximum changes occurring at 6 h after drug administration when average blood pressure (at 2 min erect) was 90 ± 15/66 ± 11 mmHg (compared to 110 ± 9/77 ± 8 after placebo) and heart rate 123 ± 9 beats/min (compared to 100 ± 15 after placebo). In Figure 3 the profile of standing systolic blood pressure following intravenous doxazosin is compared with the profile following 1 mg prazosin intravenously. The most significant differences occurred at times 0.5 and 6 h after drug administration: at 0.5 h prazosin had maximal hypotensive effect and at 6 h doxazosin had maximal effect.

(ii) *Pharmacokinetics*

The individual doses of doxazosin (12 μg/kg) ranged from 0.67 to 1.06 mg (mean 0.95 mg). Pharmacokinetic parameters were determined by non linear least squares fitting regression analysis whereby the whole blood drug concentration-time profile was best described by the following equation:

$$Y = Ae^{-\alpha t} + Be^{-\beta t}$$

where α represents the distribution phase rate constant and β represents the terminal elimination constant. The individual derived parameters are shown in Table 1 and a representative drug concentration-time

Table 1 Individual pharmacokinetic parameters after intravenous doxazosin (12 μg/kg).

Parameter values from analysis of drug concentration time curves on the basis of the equation:

$$Y = Ae^{-\alpha t} + Be^{-\beta t}$$

Subject	*A*	*α*	*B*	*β*	*AUC* (*ng ml⁻¹ h*)	*Clearance* (*ml/min*)	$T_{½}$ (*h*)
1	2.0 ± 0.6	3.0 ± 2.5	9.4 ± 0.4	0.085 ± 0.011	111.3	127.2	8.2
2	4.1 ± 0.7	1.1 ± 0.4	5.8 ± 0.7	0.059 ± 0.015	102.0	109.5	11.7
3	2.7 ± 0.5	4.2 ± 1.5	8.0 ± 0.2	0.066 ± 0.005	121.9	145.0	10.5
4	4.1 ± 0.3	0.83 ± 0.17	7.7 ± 0.3	0.048 ± 0.005	174.1	84.2	14.4
5	10.2 ± 2.1	7.9 ± 2.5	8.1 ± 0.4	0.091 ± 0.014	90.3	175.3	7.6
6	5.0 ± 0.4	2.8 ± 0.5	8.3 ± 0.2	0.047 ± 0.004	176.7	96.2	14.7
				Mean ± s.d.	129.3 ± 37.2	122.9 ± 33.5	11.2 ± 3

profile is shown in Figure 4. The mean AUC was 129 ng ml^{-1} h, the mean clearance was 123 ml/min and the mean elimination half-life was 11.2 h.

(iii) *Pressor responses*

The log dose-response curves for noradrenaline and phenylephrine are shown in Figure 5 (a, b). With each pressor amine there is a parallel shift of the curve to the right following doxazosin compared to placebo. The shifts associated with doxazosin were significant ($P < 0.05$) for both amines but the magnitude of shift was significantly greater for the selective α_1-adrenoceptor agonist, phenylephrine ($P < 0.05$). With phenylephrine the dose required to raise mean arterial pressure by 20 mmHg (PD_{20}) was increased three-fold by the administration of doxazosin from a mean of 1.50 μg kg^{-1} min^{-1} to a mean of 4.70 μg kg^{-1} min^{-1}. With noradrenaline, the PD_{20} was increased two-fold after doxazosin, from a mean of 0.19 μg kg^{-1} min^{-1} to a mean of 0.38 μg kg^{-1} min^{-1}. The results obtained using systolic and diastolic pressures separately showed comparable changes in pressor responsiveness.

Subjective effects

No side effects were volunteered by any subject on any of the study days, apart from orthostatic symptoms at times of severe postural hypotension.

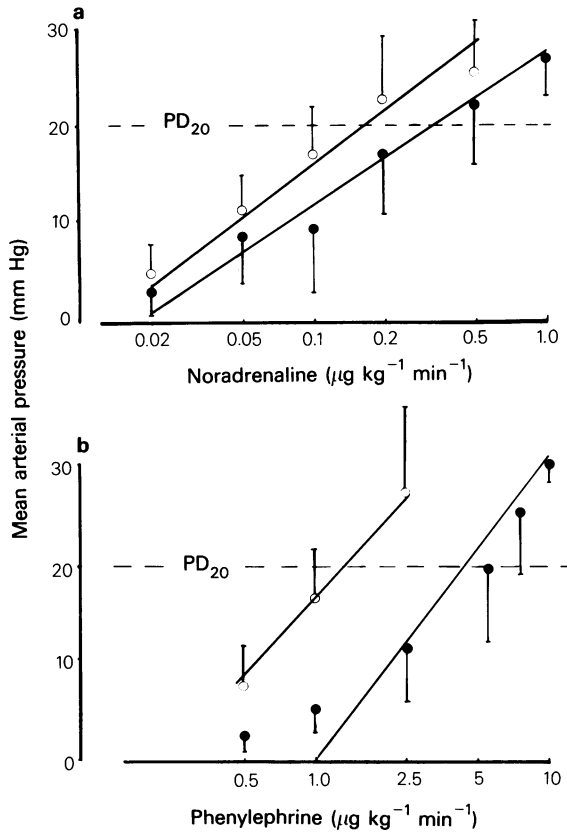

Figure 5 (a) Noradrenaline log dose-pressor response curves for doxazosin (●) and placebo (○) (mean ± s.d.)
(b) Phenylephrine log dose-pressor response curves for doxazosin (●) and placebo (○) (mean ± s.d.).

Discussion

The intravenous administration of 12 μg/kg doxazosin was associated with significant changes in blood

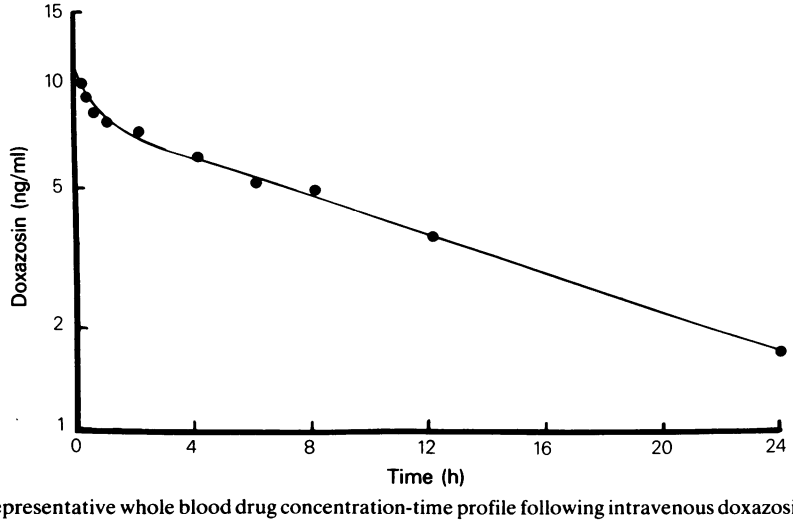

Figure 4 Representative whole blood drug concentration-time profile following intravenous doxazosin (12 μg/kg).

pressure and heart rate in the erect posture. As with prazosin (Elliott *et al.*, 1981) there were no significant changes in supine blood pressure or heart rate. The time profile of the postural blood pressure and heart rate effects of doxazosin, however, contrasts with that of prazosin. With doxazosin there is a slight initial fall in blood pressure within the first hour but the main hypotensive effect is only apparent from 2 h onwards and is maximal at 6 h after drug administration. There is an associated increase in heart rate which also is maximal at 6 h.

The responses to pressor infusions, although not specifically designed to evaluate doxazosin's mode of action, show significant α-adrenoceptor blockade. The greater degree of blockade against phenylephrine is consistent with relatively selective antagonism of α_1-adrenoceptors, comparable to that of prazosin (Singleton *et al.*, 1980; Timmermans *et al.*, 1980).

The major pharmacokinetic difference between doxazosin and prazosin lies in the elimination half-life which for doxazosin is significantly longer at 11 h, compared to the 2.5 h of prazosin (Elliott *et al.*, 1981).

In summary, doxazosin exerts a hypotensive effect apparently as a result of relatively selective postsynaptic α-adrenoceptor blockade and is thus comparable to prazosin as a vasodilator/antihypertensive agent. Its pharmacodynamic and pharmacokinetic profiles, however, indicate that there are significant differences from prazosin which may be of clinical importance. Further clinical studies in hypertensive patients should reveal whether these differences result in a more prolonged hypotensive effect, a reduced likelihood of acute postural hypotension (i.e. the 'first dose phenomenon') and the feasibility of single daily dosing.

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