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# Pharmacokinetic and pharmacodynamic studies with two α-adrenoceptor antagonists, doxazosin and prazosin in the rabbit

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**1** The cardiovascular effects of doxazosin, a quinazoline derivative related to prasozin were investigated and compared to prazosin in the rabbit.

**2** Radioligand binding studies using rabbit cerebral membranes showed that both doxazosin and prazosin were roughly equipotent at displacing [$^3$H]-prazosin from specific binding sites. However, the lower $pA_2$ value for doxazosin at $\alpha_1$-adrenoceptors in isolated thoracic aorta preparations suggests a lower potency compared to prazosin.

**3** The dose-related pressor effects of intravenous phenylephrine were used to assess vascular $\alpha_1$-adrenoceptor antagonism *in vivo*. There was a close agreement between $\alpha_1$-adrenoceptor antagonist potency and maximum hypotensive effects with both doxazosin and prazosin. The $\alpha_1$-adrenoceptor antagonist effects of doxazosin were more prolonged than those of prazosin.

**4** Studies using either radioligand binding or pressor responses to B-HT 920 showed that doxazosin did not show any significant affinity for the $\alpha_2$-adrenoceptor. Similarly, no direct vasodilator effects were observed either in animals administered angiotensin II or in isolated thoracic aorta spiral strip preparations contracted with potassium.

**5** Doxazosin has a longer terminal elimination half-life than prazosin. The pharmacokinetics of doxazosin were linear over the dose range examined.

**6** Following pharmacological 'autonomic blockade' and treatment with prazosin, doxazosin did not cause any further fall in blood pressure.

**7** These observations suggest that doxazosin, like prazosin, appears to exert its hypotensive action through $\alpha_1$-adrenoceptor antagonism. The prolonged fall in blood pressure and well sustained $\alpha_1$-adrenoceptor antagonism after doxazosin raise the possibility of an active metabolite which also has $\alpha_1$-adrenoceptor blocking properties.

## Introduction

Doxazosin is a quinazoline derivative related to prazosin. Like prazosin, it is a relatively selective peripheral postsynaptic $\alpha_1$-adrenoceptor antagonist in animals (Karamat Ali *et al.*, 1980; Timmermans *et al.*, 1980; Cambridge & Davey, 1980; Wilson *et al.*, 1981; Vincent *et al.*, 1983a; Downing *et al.*, 1983); in human vascular preparations *in vitro* (Stevens & Moulds, 1981); and in man *in vivo* (Singleton *et al.*, 1980; 1982; Elliott *et al.*, 1982; Vincent *et al.*, 1983b).

This paper describes further *in vitro* and *in vivo* studies in the rabbit using doxazosin and prazosin. The affinity and specificity of these agents for the $\alpha_1$-adrenoceptor is compared as is their potency and duration as $\alpha_1$-adrenoceptor antagonists. In addition, the relationship between pharmacokinetic and pharmacodynamic profiles and $\alpha_1$-adrenoceptor antagonism is investigated together with other possible receptor and non-receptor mediated mechanisms of blood pressure reduction.

Part of this work was presented to the British Pharmacological Society, Cambridge, April 1983.

## Methods

Male New Zealand white rabbits weighing 2.2–3.3 kg (Hyline Commercial Rabbits, Northwich, Cheshire) were housed individually in cages and fed a diet of

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rabbit pellet and water *ad libitum*. An arterial cannula was inserted into the central artery of the ear under local anaesthesia (Korner, 1965; Reid, 1979) for the measurement of mean arterial pressure using a Statham P23 ID pressure transducer and a Grass polygraph model 7B. Heart rate was measured directly from the arterial pressure trace. A venous cannula placed in a marginal ear vein under local anaesthesia was used for drug administration. The animals were allowed to recover from this minor surgical procedure unrestrained in individual cages for at least one hour before any measurements were made.

In preliminary experiments, 0.3 mg $kg^{-1}$ doxazosin and 0.1 mg $kg^{-1}$ prazosin gave comparable $\alpha_1$-adrenoceptor antagonism as assessed by the shift of the dose-response curve for the pressor effects of phenylephrine. For subsequent experiments, except where indicated, doxazosin 0.3 mg $kg^{-1}$ and prazosin 0.1 mg $kg^{-1}$ were used. Six to eight rabbits were studied in each experimental group. In all experiments, active treatment was compared with parallel control groups treated with 0.9% w/v NaCl solution (saline).

*Pharmacokinetics and pharmacodynamics*

Doxazosin 0.3 mg $kg^{-1}$ or prazosin 0.1 mg $kg^{-1}$ or an equivalent volume of saline vehicle (control) was given by intravenous bolus injection through a cannula in a marginal vein of the ear. Arterial blood samples were collected and mean arterial pressure and heart rate measured at corresponding intervals all through the day of the experiment. The total volume of blood removed did not exceed 16 ml over 8 h. The volume of blood removed was replaced by an equivalent volume of saline.

Doxazosin and prazosin were assayed in whole blood using h.p.l.c. with fluorescence detection (Yee *et al.*, 1979; Rubin *et al.*, 1980). The drug concentrations were appropriately fitted to a two compartment model, using computer assisted least squares non-linear regression with inverse weighting for drug concentrations, and the pharmacokinetic parameters subsequently derived.

*Pressor responses and duration of $\alpha_1$-adrenoceptor antagonism*

Pressor response curves were constructed using bolus intravenous doses of phenylephrine (0.001–0.3 mg $kg^{-1}$), a selective $\alpha_1$-adrenoceptor agonist, (Wikberg, 1978) before and after the administration of 0.3 mg $kg^{-1}$ doxazosin, 0.1 mg $kg^{-1}$ prazosin or saline vehicle. To determine the duration of $\alpha_1$-adrenoceptor antagonism, pressor responses to intravenous phenylephrine were repeated 15, 60, 120, 180, 240, 300 and 360 min following drug or vehicle administration. At least 4 doses of phenylephrine were studied on each occasion.

In a separate series of experiments, pressor responses to B-HT 920 (0.01–0.2 mg $kg^{-1}$) a selective $\alpha_2$-adrenoceptor agonist (Kobinger & Pichler, 1980; Hammer *et al.*, 1980) or angiotensin II (1–10 $\mu$g $kg^{-1}$), a direct vasoconstrictor, were evaluated before and at 15 and 240 min after doxazosin 0.3 mg $kg^{-1}$ or prazosin 0.1 mg $kg^{-1}$. Again, at least 4 doses of agonist were studied at each time. The pressor dose-responses were analysed by the method described by Sumner *et al.* (1982) and all data points fitted to a quadratic function. The dose of phenylephrine required to cause a rise of 40 mmHg mean arterial pressure ($PD_{40}$) was derived. Similarly, the $PD_{20}$ and $PD_{60}$ were derived for B-HT 920 and angiotensin II respectively.

*Non-receptor-mediated responses*

Non-receptor-mediated responses were evaluated *in vivo* in animals following pharmacological 'total' autonomic blockade (TAB). Each animal received propranolol 2 mg $kg^{-1}$ and this dose was repeated hourly (Reid, 1979). In addition, each animal received atropine 2 mg $kg^{-1}$ followed by an infusion of 0.1 mg $kg^{-1}$ $min^{-1}$ (Korner *et al.*, 1968) and phenoxybenzamine 5 mg $kg^{-1}$ (Hamilton *et al.*, 1983). This drug regime was adequate to prevent any chronotropic and depressor responses to isoprenaline 2.5 $\mu$g $kg^{-1}$ occurring, to markedly attenuate the pressor response to B-HT 920 0.2 mg $kg^{-1}$ and to shift the dose-response curve for the pressors effects of phenylephrine by more than 1000 fold. Thirty minutes after phenoxybenzamine, each animal received intravenous bolus injections of doxazosin (3 mg $kg^{-1}$) or prazosin (1 mg $kg^{-1}$) or saline vehicle.

In a separate experiment, with a similar protocol, after phenoxybenzamine treatment each animal received 0.5 mg $kg^{-1}$ prazosin followed 20 min later by 3 mg $kg^{-1}$ doxazosin or saline.

In vitro *experiments: rabbit isolated aortic strips*

Rabbits were killed with intravenous pentobarbitone sodium (60 mg $kg^{-1}$) and the descending thoracic aorta removed. Helical strips were prepared in the manner described by Furchgott & Bhadrakom (1953). Strips measuring 1.5 × 0.3 cm were suspended in 5 ml organ baths containing Krebs bicarbonate solution gassed with a mixture of 95% $O_2$ and 5% $CO_2$. Cocaine ($10^{-5}$M) was added to block neuronal uptake, 17-$\beta$-oestradiol ($10^{-5}$M) to block extra-neuronal uptake and propranolol ($10^{-6}$M) to block $\beta$-adrenoceptor-mediated vasodilatation.

The pH of the bathing medium was 7.4. The temperature was maintained at 37°C by means of a Churchill thermostatic flow pump. An initial tension of 2 g was placed on the aortic strip and the tissue allowed to equilibrate over 90 min while the bathing medium was changed frequently. Isometric tension

was recorded via a Lectromed 4151 force transducer displayed on a Lectromed MX 412 type recorder. Cumulative dose-response curves were constructed (Van Rossum, 1963) using phenylephrine ($10^{-9}$ to $10^{-2}$M) before and after incubating the tissue with doxazosin $10^{-9}$ to $10^{-7}$M or prazosin $10^{-10}$ to $10^{-8}$M for 15 min. $pA_2$ values were calculated by the method of Arunlakshana & Schild (1959).

In a separate experiment tissues were contracted with 40 mM KCl. The effects of doxazosin $10^{-4}$ to $10^{-2}$M and prazosin $3 \times 10^{-4}$ to $10^{-2}$M were evaluated on the potassium-induced contractile response. In the Krebs medium for this experiment, propranolol, cocaine and 17-β-oestradiol were omitted.

*Radioligand binding studies*

Rabbit brain membranes were prepared as described by Karliner *et al.* (1979). Aliquots of the membrane suspension (0.8 ml) were incubated for 25 min at 25°C with doxazosin $10^{-9}$ to $10^{-4}$M and prazosin $10^{-9}$ to $10^{-4}$M in the presence of either 3 nM [$^3$H]-prazosin (Greengrass & Bremner, 1979) or 7.5 nM [$^3$H]-clonidine (U'Pritchard & Snyder, 1979). The reaction was terminated by rapid vacuum filtration through GF/B glass fibre filters. The filters were washed twice with ice cold 0.05 M Tris buffer, pH 7.5, and left to dry at room temperature overnight. Eight ml of fisofluor containing 0.1% Triton X100 was then added to the dry filters and the bound tritium label counted in a liquid scintillation counter.

Total binding of the radiolabelled compound was determined in the absence of any displacing agent. Non-specific binding was defined as the amount of [$^3$H]-prazosin or [$^3$H]-clonidine bound in the presence of $10^{-5}$M phentolamine.

Using these assay conditions, the stereo-specificity, pharmacological specificity and kinetics of the ligands [$^3$H]-prazosin and [$^3$H]-clonidine were consistent with binding to $\alpha_1$- and $\alpha_2$-adrenoceptors respectively.

*Statistics*

Results are presented as the mean ± standard deviation (s.d.). Statistical analysis was by repeated measures analysis of variance for mean arterial pressure and heart rate responses and Student's *t* test for paired data, with Bonferroni correction elsewhere.

*Drugs*

Radiolabelled and unlabelled prazosin and doxazosin were obtained from Pfizer Ltd, Sandwich; B-HT 920 (6-allyl-2-amino-5,6,7,8-tetrahydro-4H-Thiazolo-[4,5-d]-azepine dihydrochloride) from Boehringer Ingleheim Ltd; angiotensin II from Ciba; phenoxybenzamine from Smith, Kline and French Ltd; phenylephrine and 17-β-oestradiol from Sigma; propranolol from the Imperial Chemical Industries Ltd; and atropine sulphate from Antigen Limited, Roscrea, Ireland. Radiolabelled clonidine was obtained from the Radiochemical Centre, Amersham. All drugs were made up fresh in saline or in distilled water before being added to the Krebs solution.

## Results

*Blood pressure and heart rate*

Blood pressure fell significantly ($P < 0.05$) after both doxazosin and prazosin at the doses used. The maximum fall in mean arterial pressure occurred between 5–7 h with doxazosin. Within the first 30 min, mean arterial pressure fell more with prazosin than doxazosin but between 4–8 h the mean fall with doxazosin was greater than in either the prazosin-treated or control animals. There was no significant increase in heart rate with either drug at the doses used compared to that in control animals (Figure 1).

*Pharmacokinetics*

In the rabbit, the mean terminal elimination half-life for doxazosin was 171 ± 56 min compared to 112 ± 38 min for prazosin. Doxazosin also had a

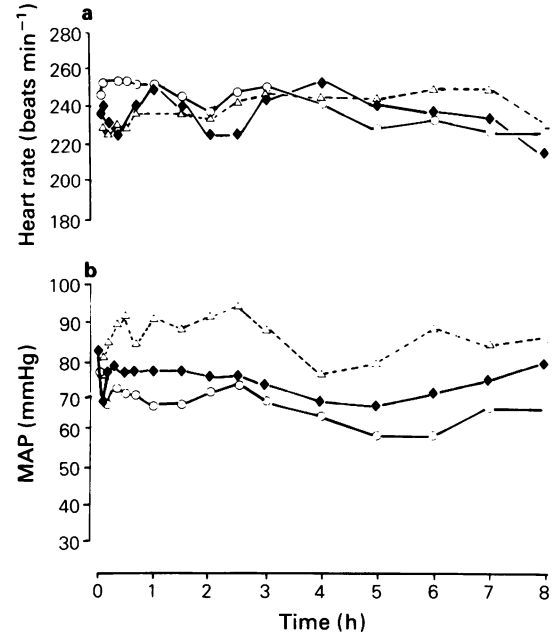


**Figure 1** Mean arterial pressure (MAP; b) and heart rate (a) following the intravenous administration of doxazosin (○), prazosin (◆) and saline control (△) to 8 conscious rabbits.

**Table 1** Derived pharmacokinetic parameters after intravenous administration of doxazosin and prazosin to the rabbit

| | *Doxazosin* ($0.3\,mg\,kg^{-1}$) | *Doxazosin* ($1\,mg\,kg^{-1}$) | *Prazosin* ($0.1\,mg\,kg^{-1}$) |
|---|---|---|---|
| AUC ($ng\,ml^{-1}\,min$) | 4641.6 ± 1120 | 23336 ± 2325.7* | 4124.9 ± 834.6 |
| $\beta t_{\frac{1}{2}}$ (min) | 171.9 ± 55.9 | 178.3 ± 83.8* | 112.8 ± 38.1 |
| Cl ($ml\,min^{-1}$) | 191.5 ± 33.9 | 185.8 ± 24.3* | 92.7 ± 22.6 |
| $Vd_{ss}$ (l) | 45.1 ± 13.5 | 40.1 ± 9.6* | 14.0 ± 4.8 |

Data shown are mean ± s.d.; $n = 8$, *n = 4.
AUC = area under the concentration-time curve; $\beta t_{\frac{1}{2}}$ = terminal elimination half-life; Cl = clearance; $Vd_{ss}$ = apparent volume of distribution at steady state.

larger volume of distribution and more rapid clearance than prazosin in the rabbit (Table 1). At the higher dose of doxazosin ($1\,mg\,kg^{-1}$) the half-life, clearance and volume of distribution were unchanged suggesting linear kinetics at these doses (Table 1). No metabolites were identified on the chromatogram of the whole blood samples assayed for either prazosin or doxazosin.

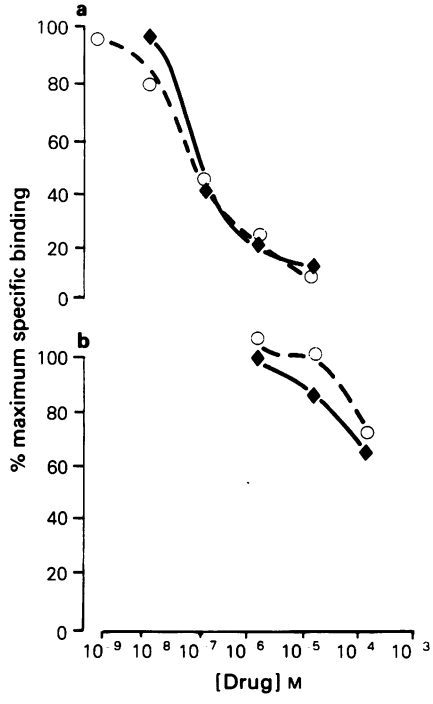


**Figure 2** Radioligand displacement of [$^3$H]-prazosin (a) and [$^3$H]-clonidine (b) by doxazosin (○) and prazosin (◆) in isolated cerebral membranes of the rabbit.

*Radioligand binding to rabbit cerebral membranes*

*In vitro* ligand binding to membranes from rabbit cerebral cortex with [$^3$H]-prazosin ($\alpha_1$ specific ligand) and [$^3$H]-clonidine ($\alpha_2$ specific ligand) showed that both doxazosin and prazosin were roughly equipotent at displacing the radioligand [$^3$H]-prazosin. The $IC_{50}$ value (the molar concentration of drug required to displace 50% of the bound ligand) was $5.2 \times 10^{-8}$M for doxazosin and $8.9 \times 10^{-8}$M for prazosin (Figure 2). For both drugs, the $IC_{50}$ for the displacement of [$^3$H]-clonidine was greater than $10^{-5}$M suggesting that both drugs have relatively little affinity for the $\alpha_2$-adrenoceptor in this preparation.

*Isolated thoracic aorta preparation*

Doxazosin caused a concentration-dependent shift of the contractile responses to cumulative doses of phenylephrine. The $pA_2$ value obtained from Schild regression analysis was 7.6 ± 1.5 with a slope of 0.94 ± 1.0 for doxazosin (Figure 3). This value contrasts with the $pA_2$ of 8.99 ± 0.8 and a slope of 0.98 ± 0.3 for prazosin. Incubation for up to 45 min did not alter the $pA_2$ for either prazosin or doxazosin.

Both doxazosin and prazosin in concentrations up to $10^{-2}$M failed to relax contractile responses induced by potassium chloride.

*Pressor responses to intravenous phenylephrine and duration of $\alpha_1$-adrenoceptor antagonism.*

There was a parallel rightward shift of the dose-response curve to intravenous phenylephrine after

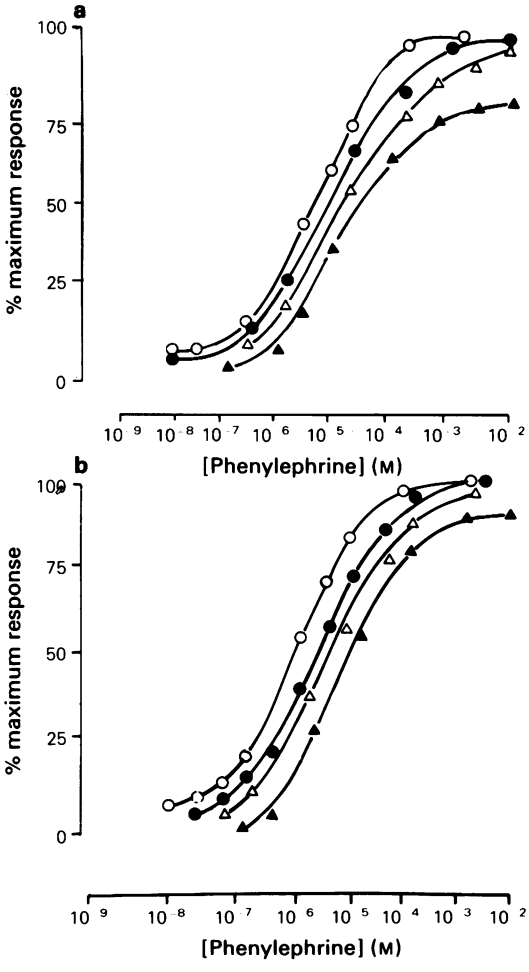


**Figure 3** Contractile responses of rabbit isolated thoracic aorta to phenylephrine. (a) Shows responses to control (○); prazosin $10^{-10}$M (●), $10^{-9}$M (△) and $10^{-8}$M (▲); while (b) shows responses in the presence of saline control (○), doxazosin $10^{-9}$M (●), $10^{-8}$M (△) and $10^{-7}$M (▲). Each point is the mean of 6 observations.

either doxazosin or prazosin administration. The maximum shift of the dose-response curve occurred after 15 min with prazosin, with a dose-ratio of 3.8 ± 1.4 compared to 3.0 ± 0.6 at this time after doxazosin (Figure 4). $\alpha_1$-Adrenoceptor antagonism was more prolonged after doxazosin. A progressive increase to a maximum shift at 4 h (dose-ratio 4.3 ± 2.7) was observed in contrast to prazosin which showed a gradual recovery with a dose-ratio of 2.3 ± 0.7 at 4 h (Table 2).

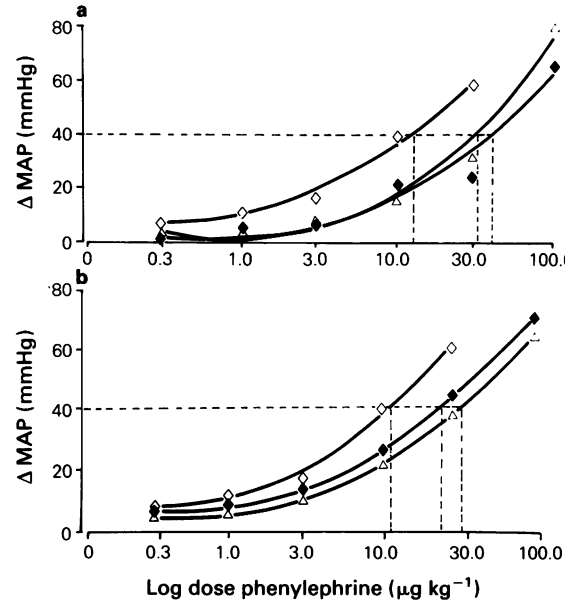


**Figure 4** The pressor responses (change in mean arterial pressure (MAP)) to phenylephrine in animals given either saline (◇), doxazosin 0.3 mg kg$^{-1}$ (△), or prazosin 0.1 mg kg$^{-1}$ (◆), either 15 min (a) or 4 h (b) previously.

*Pressor responses to B-HT 920 and angiotensin II*

There was considerable inter animal variability in responses to B-HT 920 and neither doxazosin nor prazosin caused a significant shift of the pressor responses to intravenous B-HT 920 in the rabbit (Table 3).

Doxazosin and prazosin also failed to cause a significant shift of the pressor responses to the direct vasoconstrictor agent, angiotensin II, in the rabbit (Table 3).

*Total autonomic blockade*

In conscious rabbits following pharmacological 'total' autonomic blockade, doxazosin 3 mg kg$^{-1}$ caused a rise in mean pressure of 16 ± 5.2 mmHg lasting 2–3 min. Using a similar protocol, prazosin 1 mg kg$^{-1}$ caused a fall in pressure of 44.2 ± 8.2 mmHg lasting for 1.5–2 min followed by a pressor response of 19.0 ± 7.4 mmHg lasting 2–3 min. With both treatments, there was no change in heart rate confirming the adequacy of autonomic blockade (Figure 5). The animals treated with prazosin were subsequently given a further 1 mg prazosin after 30 min which resulted in a mean depressor response of 26.5 ± 13.4 mmHg lasting 1.5–2 min followed by a mean pressor effect of

**Table 2** Dose of phenylephrine (mg kg$^{-1}$, i.v.) needed to raise mean arterial pressure 40 mmHg ($PD_{40}$) before and after 300 μg kg doxazosin$^{-1}$ or 100 μg kg$^{-1}$ prazosin or saline vehicle

| *Time* | $PD_{40}$ | *Saline vehicle* (dose-ratio) | $Pd_{40}$ | *Doxazosin* (dose-ratio) | $PD_{40}$ | *Prazosin* (dose-ratio) |
|---|---|---|---|---|---|---|
| Control | 12.0 ± 2.2 | 1.0 | 11.3 ± 4.3 | 1.0 | 12.0 ± 2.0 | 1.0 |
| 15 mins | 12.5 ± 3.3 | 1.0 ± 0.2 | 32.8 ± 9.6* | 3.0 ± 0.6 | 44.1 ± 10.9* | 3.8 ± 1.4 |
| 60 mins | 10.7 ± 3.0 | 0.9 ± 0.2 | 30.3 ± 5.2* | 2.9 ± 0.9 | 33.2 ± 5.1* | 2.8 ± 0.6 |
| 120 mins | 13.7 ± 2.9 | 1.2 ± 0.2 | 32.0 ± 9.5* | 2.9 ± 0.4 | 28.0 ± 4.7* | 2.3 ± 0.5 |
| 180 mins | 13.7 ± 4.1 | 1.2 ± 0.3 | 33.1 ± 8.6* | 3.1 ± 0.9 | 26.9 ± 6.4* | 2.3 ± 0.5 |
| 240 mins | 13.7 ± 3.7 | 1.1 ± 0.3 | 41.8 ± 19.8* | 4.3 ± 2.7 | 26.3 ± 6.5* | 2.3 ± 0.7 |

Data shown are mean ± s.d.; $n = 8$ rabbits.
*$P < 0.05$ compared with control values.

**Table 3** Doses of (a) angiotensin II and (b) B-HT 920 (μg kg$^{-1}$, i.v.) needed to raise mean arterial pressure 60 mmHg ($PD_{60}$) (a) and 20 mmHg ($PD_{20}$) (b) 15 min and 4 h after 300 μg kg$^{-1}$ doxazosin or 100 μ kg$^{-1}$ prazosin

| a | $PD_{60}$ *Doxazosin* | *Prazosin* |
|---|---|---|
| Control | 2.9 ± 0.9 | 3.3 ± 1.8 |
| 15 min | 3.3 ± 1.2 | 4.7 ± 5.2 |
| 4 h | 2.8 ± 1.6 | 3.5 ± 1.6 |

| b | $PD_{20}$ *Doxazosin* | *Prazosin* |
|---|---|---|
| Control | 42.0 ± 9.1 | 52.3 ± 9.9 |
| 15 min | 52.3 ± 18.9 | 132.0 ± 69.4 |
| 4 h | 49.1 ± 25.4 | 95.1 ± 55.9 |

Data shown are mean ± s.d.; $n = 6$ rabbits.

8.1 ± 3.8 mmHg lasting 2–3 min; and no associated change in heart rate was observed.

In a separate group of animals, following 'total' autonomic blockade, prazosin 0.5 mg kg$^{-1}$ caused a mean depressor response of 29.2 ± 13.9 mmHg followed by a pressor effect of 30.0 ± 12 mmHg. Subsequent administration of doxazosin 3 mg kg$^{-1}$ caused only a pressor effect of 12.0 ± 5.7 mmHg with no change in heart rate (Figure 5).

## Discussion

Following intravenous administration of doxazosin and prazosin, there was a fall in mean arterial pressure compared to that in control animals. After prazosin there was a rapid fall which was maximal within 30 min with recovery over 2 h. With doxazosin, the response was more gradual in onset and was maximal

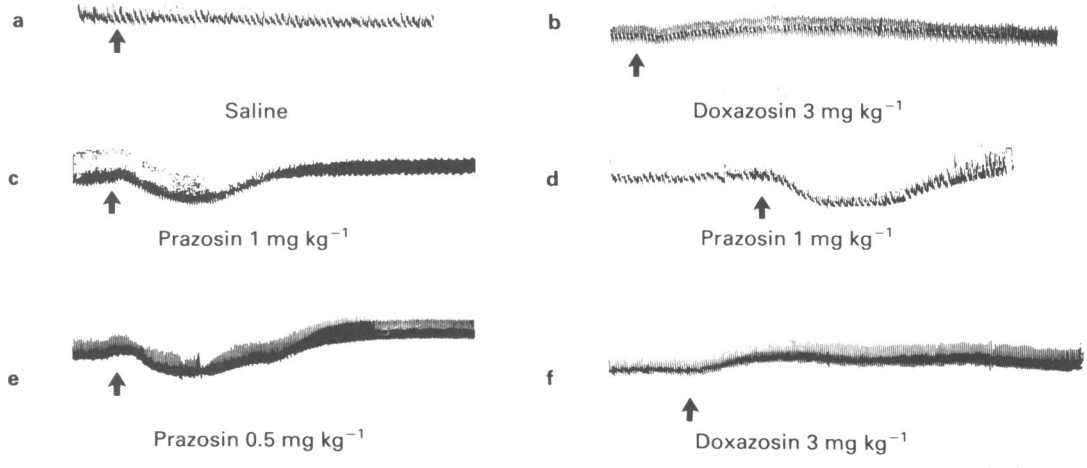


**Figure 5** The effect of treatment with doxazosin and prazosin after pharmacological autonomic blockade; (a) response to saline; (b) response to doxazosin 3 mg kg$^{-1}$; (c) response to prazosin 1 mg kg$^{-1}$; (d) response to prazosin 1 mg kg$^{-1}$ given 30 min after pretreatment with prazosin 1 mg kg$^{-1}$; (e) response to prazosin 0.5 mg kg$^{-1}$; (f) response to doxazosin 3 mg kg$^{-1}$ after pretreatment with prazosin 0.5 mg kg$^{-1}$.

about 4–7 h later. With both treatments, there was no significant increase in heart rate at the doses used.

Doxazosin has a somewhat longer terminal elimination half-life than prazosin. It is more extensively distributed and also cleared faster than prazosin. However, these pharmacokinetic observations are not consistent with its apparent sustained $\alpha_1$-adrenoceptor antagonist effect. The observation that its maximum hypotensive effect occurs about 6 h later, by which time drug levels are low, would suggest either the involvement of an active metabolite or that doxazosin exerts its haemodynamic action in a different manner from prazosin or at a different site from that at which drug concentration was measured.

For both doxazosin and prazosin, maximum $\alpha_1$-adrenoceptor antagonism corresponded with maximum hypotensive response. At the doses used, the extent of $\alpha_1$-adrenoceptor antagonism was similar 15 min after treatment. Whereas there was a gradual recovery with prazosin, there was a paradoxical late increase and more prolonged $\alpha_1$-adrenoceptor antagonism with doxazosin. These observations can only in part be accounted for by the longer terminal elimination half-life of doxazosin and it is difficult to explain the delayed hypotensive response and paradoxical increase in $\alpha_1$-adrenoceptor antagonism considering the pharmacokinetic parameters. However, the results do suggest the involvement of an active metabolite with substantial $\alpha_1$-adrenoceptor antagonist properties, although no metabolite was detected by our assay technique under the conditions used. Alternatively, doxazosin could bind to the receptor in a partially covalent manner, but there is no evidence to support this hypothesis at present.

Doxazosin, like prazosin, failed to antagonize the pressor responses to B-HT 920 or antiotensin II. The pressor response to B-HT 920 results from activation of postsynaptic vascular $\alpha_2$-adrenoceptors (Kobinger & Pichler, 1980). The existence of postsynaptic $\alpha_2$-adrenoceptors has been demonstrated *in vivo* in animals (Drew & Whiting, 1979; Timmermans *et al.*, 1979; Reid & Hamilton, 1980; Docherty & McGrath, 1980; Starke & Docherty, 1980, McGrath, 1982) and in man (Elliott & Reid, 1983). The lack of effect of prazosin and doxazosin on pressor responses to B-HT 920 suggests that these drugs at the doses used have no effect on $\alpha_2$-adrenoceptors. This is consistent with previous observations of the lack of effect of prazosin and doxazosin on clonidine-induced responses and the failure of both drugs to increase transmitter release in rabbit pulmonary artery preparations (Cambridge & Davey, 1980). Similarly, the absence of any significant effect on the pressor responses to angiotensin II or potassium chloride suggests the lack of a direct smooth muscle relaxant action with both drugs at the doses used and under the conditions of the study.

The radioligand displacement studies further confirmed the $\alpha_1$-adrenoceptor selectivity of the drugs. Both doxazosin and prazosin were equipotent at displacing [$^3$H]-prazosin suggesting that they have a similar affinity for the $\alpha_1$-adrenoceptor. Neither doxazosin nor prazosin have any appreciable affinity or specificity for the $\alpha_2$-adrenoceptor, as suggested by the high molar concentration required to displace 50% of bound [$^3$H]-clonidine. However, the $pA_2$ values for doxazosin and prazosin were $7.6 \pm 1.5$ and $8.89 \pm 0.8$, respectively. A high $pA_2$ value suggests a greater specificity and potency of an antagonist for a particular receptor. The explanation for the disparity between the affinity obtained from ligand binding and the $pA_2$ values derived from the Schild regression analysis is not clear. Alternatively, there may be differences between the $\alpha_1$-receptor population in cerebral membranes compared to the peripheral vasculature. The fact that the slopes of the Schild plots were not significantly different from unity suggests that both drugs are competitive $\alpha_1$-adrenoceptor antagonists. However, the observation that at high concentration, both doxazosin and prazosin tended to depress the maximum response ($E_{max}$) suggests that specificity for the $\alpha_1$-adrenoceptor may be dose-related. A similar observation has been made by Stevens & Moulds (1981) who described significant depression of $E_{max}$ when using human vascular preparations. This may also be related to the ability of doxazosin and prazosin to block non-competitively the 'fast' but not the 'slow' component of the contractile responses (Downing *et al.*, 1983).

Pharmacological 'total' autonomic blockade allows the study of mechanisms not involving sympathetic and parasympathetic activity (Korner *et al.*, 1973; West *et al.*, 1975) and in particular $\alpha_1$-adrenoceptor-independent responses. In this preparation, doxazosin caused a pressor effect. Administration of doxazosin to animals pretreated with prazosin also did not lead to any further fall in mean arterial pressure. This suggests that doxazosin, prazosin and phenoxybenzamine act on a common receptor to mediate a depressor response. Pressor effects have been described with other $\alpha_1$-adrenoceptor antagonists when used in high doses in animals where the autonomic nervous system has been interrupted (Benfey & Varma, 1962; Hilliard *et al.*, 1972; Erker & Chan, 1977); and with prazosin (Drew & Whiting 1979). Recently, Angus & Lew (1984) observed an agonist effect of phentolamine in the rabbit, and attributed it to activation of vascular receptors that mediate vasodepressor responses which are sensitive to benextramine and yohimbine. It is possible that doxazosin in high doses also activates these receptors. Further investigations of the mechanism of this pressor effect are indicated.

Prazosin caused a depressor response followed by a pressor effect in this preparation. Constantine & Lebel

(1980) described pressor responses to noradrenaline mediated by vascular $\alpha_2$-adrenoceptors in phenoxybenzamine- and propranolol-treated dogs. Whether the depressor response to prazosin involves these vascular $\alpha_2$-adrenoceptors or is related to another mechanism of action is not clear. The depressor responses were followed by a pressor effect, similar to those observed with other α-adrenoceptor antagonists. Neither doxazosin nor prazosin had a sustained depressor effect in this preparation, suggesting that they do not exert a direct vasodilator effect of any importance. However, prazosin but not doxazosin caused a depressor response in this preparation by an $\alpha_1$-adrenoceptor independent mechanism.

In conclusion, doxazosin, like prazosin, appears to exert its hypotensive action through $\alpha_1$-adrenoceptor antagonism. There is at present no good evidence for an $\alpha_1$-adrenoceptor-independent mechanism contributing to drug effect. The prolonged fall in blood pressure and $\alpha_1$-adrenoceptor antagonism after doxazosin raises the possibility of an active metabolite which also has $\alpha_1$-adrenoceptor blocking properties.

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