Cardiovascular effects of prazosin in dogs

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Summary

1. In pentobarbitone-anaesthetized dogs, prazosin (2 x 1.3 μmol day⁻¹ kg⁻¹; 2 x 0.5 mg day⁻¹ kg⁻¹) administered orally for 3 days reduced resting aortic blood pressure as well as the pressor response to bilateral carotid occlusion. Prazosin neither affected resting heart rate nor the tachycardia induced by intravenous isoprenaline, noradrenaline and electrical stimulation of preganglionic and post-ganglionic sympathetic nerve fibres. Prazosin significantly attenuated the fall in perfusion pressure in a perfused hind leg resulting from the section of the ipsilateral sympathetic lumbar chain. Furthermore, the drug inhibited by about 50% the hind-leg pressor responses elicited by intra-arterial administration of α-adrenoreceptor agonists and by stimulation of the lumbar sympathetic chain, without altering the effects of angiotensin II.

2. Acute administration of prazosin into the innervated hind leg provoked a dose-related reduction in vascular resistance. However, after spinal anaesthesia no such an effect was observed even when vascular tone was increased by infusion of vasopressin. Under the same experimental conditions administration of papaverine induced a vasodilatation.

3. This study confirms that prazosin impairs the function of vascular α-adrenoreceptors, and strongly challenges the claim that this compound produces a directly mediated vasodilatation of the leg vascular bed.

Key words: α-adrenoreceptor blockade, hind-leg perfusion, prazosin, vascular myorelaxant action.

Introduction

Prazosin (2-[4-(2-furoyl)-piperazine-1-yl]-4-amino-6,7-dimethoxyquinazoline hydrochloride) exerts hypotensive effects in normotensive and/or hypertensive dogs, cats and rats (Constantine, McShane, Scriabine & Hess, 1973; Massingham & Hayden, 1975; Wood, Phelan & Simpson, 1975; Cavero & Lefèvre, 1976). Its effectiveness in human hypertension has been assessed in several clinical trials (Cohen, 1970; Fernandes, Sanford, Smith, Weder, Kim, Gould, Busby, Swartz & Onesti, 1975; Mroczek, Fotiu, Davidov & Finnerty, 1974; Pitts, 1974).

Constantine et al. (1973) have suggested that in the dog the hypotensive effect of prazosin involves a direct smooth muscle relaxation and a functional blockade of vascular adrenoreceptor sites. However, Wood et al. (1975) could not confirm the direct vasodilatory action of prazosin in the rat denervated leg. This study was undertaken to investigate further the cardiovascular properties of prazosin.

Methods

The experiments were carried out in mongrel dogs of either sex anaesthetized with intravenous pentobarbitone sodium (141 μmol/kg (35 mg/kg) for induction, and then 20-1-40-3 μmol h⁻¹ kg⁻¹ (5-10 mg h⁻¹ kg⁻¹) for maintenance). The effects of 7.8-780 nmol of prazosin (3-300 μg) injected intra-arterially into the blood-perfused hind leg were assessed in dogs untreated or pretreated with hexamethonium (7.3 μmol/kg; 2 mg/kg) or cinchocaine (7.9 μmol; 3 mg) given into the cisterna magna to induce spinal anaesthesia. In the latter experiment, prazosin was injected intra-arterially into the hind leg after raising perfusion
either by stimulating the lumbar sympathetic chain or infusing vasopressin, noradrenaline or LD 3098 [2-(2'-cyclopropylphenoxy)methyl]-imidazoline hydrochloride], a specific α-adreno-receptor agonist.

Dogs receiving placebo or prazosin (1·3 μmol/kg) (0·5 mg/kg) twice daily for a 3 days period were anaesthetized 16 h after the last dose.

In all dogs blood pressure was recorded via a catheter introduced into the aortic arch via the branchial artery. The heart rate was measured with an ECG-triggered ratemeter. Pressor and cardiac chronotropic responses to 30 s occlusion of carotid arteries were obtained before and after section of the vagi. After thoracotomy pre- and post-ganglionic sympathetic fibres at the level of the right stellate ganglion were electrically stimulated for 610 s

Cardiac chronotropic responses to intravenous noradrenaline and isoprenaline and electrical stimulation of pre- and post-ganglionic sympathetic fibres at the level of the right stellate ganglion were not affected by the treatment.

Pressor responses elicited by intra-arterial administration of noradrenaline, phenylephrine and a new specific α-adrenoreceptor stimulant, LD 3098 (Le-fèvre, Najer, Cavero & Giudicelli, 1975), as well as by electrical stimulation of the sympathetic lumbar chain, were all decreased by about 50% in dogs dosed for 3 days with prazosin. No modification of angiotensin II response was observed.

In spinally anaesthetized dogs, doses of prazosin up to 780 nmol (300 μg) injected in the perfused hind leg were almost completely inactive, whereas papaverine (295 nmol; 100 μg) still induced a significant vasodilatation. In this preparation, the vasodilator property of prazosin was re-established when vascular tone was increased by lumbar sympathetic chain stimulation or by intra-arterial perfusion of α-adrenoreceptor agonists but not vasopressin.

Discussion

Oral administration of prazosin to normotensive dogs significantly reduced resting blood pressure. The concomitant inhibition of the pressor response to occlusion of the common carotid arteries may result from interactions at many sites along this reflex arc. However, in the hind-leg vasculature a clear-cut diminution of the neural tone was detected when the sympathetic supply of this vasculature was interrupted by severing the lumbar sympathetic chain. Furthermore, vasopressor responses to

Results

In acute experiments, injection of prazosin into the innervated hind leg provoked a dose-related vasodilatation. For instance, the changes in perfusion pressure after prazosin (7·8 nmol and 78 nmol; 3 and 30 μg) were −26·2 mmHg (SEM 5·6; n = 5) and −58·2 mmHg (SEM 5·6; n = 5). In contrast after hexamethonium (7·3 μmol/kg) (2 mg/kg) the same doses of prazosin gave −6·5 mmHg (SEM 2·8; n = 6) and −20·3 (SEM 9·3; n = 6). This variability of response was probably related to the degree of ganglionic blockade. In fact, satisfactory vasodilatory responses to intra-arterial prazosin were observed only in two dogs, in which mean aortic blood pressure was not decreased below 115 mmHg by hexamethonium.

In dogs treated for 3 days with oral prazosin mean aortic blood pressure and heart rate were 121·6 mmHg (SEM 5·9; n = 8) and 153·4 beats/min (SEM 7·6; n = 8) respectively, whereas in placebo-treated animals the values of these variables were 143·0 mmHg (SEM 6·6; n = 8; P < 0·05, t-test vs. prazosin treatment) and 151·1 beats/min (SEM 7·7; n = 8). Prazosin significantly inhibited by 40%; the maximal increases in aortic blood pressure and heart rate after 30 s bilateral carotid occlusion.
electrical stimulation of the caudal trunk of this chain were reduced by 50%. Since a similar degree of inhibition in hind-leg vascular responses after intra-arterially administered \(\alpha\)-adrenoreceptor agonists was observed it is likely that prazosin affects the normal functions of vascular \(\alpha\)-adrenoreceptors located post-synaptically. Therefore, the present findings are consistent with the conclusion of Constantine et al. (1973) for the dog and Wood et al. (1975) for the rat that prazosin interferes with the vasoconstrictor responses mediated by \(\alpha\)-adrenoreceptors at the end-organ level. Furthermore, a significant degree of adrenergic neuron blockade by prazosin can be excluded in view of the results obtained on the hind-leg vasculature and on the heart.

The present studies also show that oral prazosin does not alter ganglionic transmission, at least through the right stellate ganglion.

Constantine et al. (1973) reported that in the dog hind leg, intra-arterially-administered prazosin produced vasodilatation before and after ganglionic blockade with hexamethonium (2 mg/kg) although in the latter instance larger doses of prazosin were required to obtain responses similar to those obtained in presence of full neural sympathetic tone. We confirmed these results: however, prazosin was active only in those dogs in which hexamethonium did not sufficiently reduce aortic blood pressure. Prazosin did not produce significant vasodilatation in the hind leg of dogs pretreated with cinchocaine intracisternally to abolish sympathetic tone of neural or humoral origin. Furthermore, the lack of effect of prazosin was not related to maximal leg vasodilatation, since perfusion of a vasoconstrictor, vasopressin, failed to re-establish the vasomotor effects of prazosin. In addition, papaverine exhibited a significant myorelaxant activity under similar experimental conditions. However, prazosin caused vasodilatation when a sufficient degree of adrenergic constriction was elicited by electrical stimulation of the lumbar sympathetic chain or infusion of \(\alpha\)-adrenoreceptor agonists. It may be concluded that prazosin is effective as a vasodilating compound in the dog leg only when a certain level of sympathetic tone of neural or humoral origin is present.

These findings confirm and extend the observations of Wood et al. (1975), who also failed to detect any direct myorelaxant properties of prazosin by using the rat denervated hind leg and perfused mesenteric artery preparations. Furthermore, Constantine et al. (1973), who described prazosin as a direct vasodilator, reported that this compound did not affect blood pressure in pithed cats even when resting blood pressure was elevated by a continuous infusion of angiotensin, which is considered to be a directly acting vasoconstrictor. Prazosin also failed to decrease the raised blood pressure in pithed, spontaneously hypertensive rats infused with vasopressin (Cavero & Lefèvre, 1976).

In conclusion, it appears that prazosin is devoid of measurable direct myorelaxant properties in the leg vasculature of the dog. Its effectiveness in reducing vascular resistance in this vascular bed appears to result from an interference with \(\alpha\)-adrenoreceptor function at post-synaptic level. Even though it is somewhat hazardous to extend the results obtained in the skeletal muscle vascular bed of dogs to the whole vasculature, it may be that the anti-hypertensive properties of prazosin are specifically related to a functional impairment of \(\alpha\)-adrenoreceptors mediating vasoconstriction.

Acknowledgments

The author thanks Ms G. Charpy, J. Lechaire and S. Fénard for their technical collaboration. Thanks are extended to Dr P. Manoury, Chemistry Department, Synthélabo for the synthesis of prazosin.

References


