The interaction between prazosin and clonidine

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Summary
1. The interaction between prazosin and clonidine was studied in anaesthetized rats, pithed rats and in anaesthetized cats.
2. Prazosin diminished the clonidine-induced hypotensive effect in anaesthetized rats, probably via an antagonism at the level of central α-adrenoceptors.
3. In pithed rats, stimulation of the Nervi accelerantes caused tachycardia, which was diminished considerably by clonidine. The antagonism by clonidine was partly reversed by prazosin, suggesting that prazosin possesses a certain degree of presynaptic activity apart from its predominant effect at the postsynaptic α-receptor. Piperoxan was more active than prazosin.
4. The central hypotensive effect of clonidine, injected into the left vertebral artery of cats was significantly reduced by prazosin, administered before clonidine via the same route. Intravenously injected prazosin did not diminish the central hypotensive effect of clonidine. The antagonism is, therefore, caused by a central mechanism.
5. The combined application of clonidine and prazosin in antihypertensive treatment is probably not only irrational but ought to be discouraged in view of the interaction between the drugs, which leads to a reduced antihypertensive potency of clonidine.

Key words: blood pressure, clonidine, heart rate, interaction, prazosin, pre- and post-synaptic α-adrenoreceptors.

Introduction
The antihypertensive drug clonidine is known to exert its blood pressure-lowering influence via stimulation of α-adrenoreceptors in the brain stem (Schmitt, Schmitt & Fénard, 1971; reviews by Kobinger, 1973; van Zwieten, 1975). So far, it has not been established firmly whether this effect involves pre- or post-synaptic α-receptor stimulation. Prazosin, one of the newer antihypertensive agents is an α-sympatholytic drug, which lowers blood pressure by blockade of postsynaptic α-receptors (Cambridge, Davey & Massingham, 1977). This property contrasts with various other α-sympatholytic compounds (phentolamine, phenoxybenzamine, yohimbine, piperoxan) which are known to possess affinity for both pre- and post-synaptic α-adrenoreceptors (Cubeddu, Barnes, Langer & Weiner, 1974; Borowski, Ehrl & Starke, 1976). It was therefore thought to be of interest to study the interaction between clonidine and prazosin in animal models. Apart from the theoretical arguments discussed above it would seem worthwhile to know whether there was any interaction between clonidine and prazosin which might influence their antihypertensive effects in clinical practice.

Methods
Experiments were carried out in normotensive rats and cats. In rats, anaesthetized with 75 mg of pentobarbitone/kg (intraperitoneally) arterial blood pressure was taken from a cannulated carotid artery and recorded by means of a Hellige-HE 19 device. Drugs were injected into a femoral vein. In a second series of experiments the Nervi accelerantes of pithed rats were stimulated via the pithing rod as described by Drew (1976) in such a manner that heart rate was increased. Blood pressure and heart rate were recorded as in the anaesthetized rats. Changes in heart rate were used to measure the effects at presynaptic α-adrenoceptors.

In cats, anaesthetized with α-glucocorticosterone (60
mg/kg, intraperitoneally), drugs were injected either into the left vertebral artery or into a femoral vein as described previously (van Zwieten, 1975). Blood pressure and heart rate were recorded as described above.

**Results**

*Anaesthetized, normotensive rats*

Clonidine (7-50 or 22.5 nmol/kg) considerably reduced both arterial pressure and heart rate. The hypotensive effect was reduced by at least 50% by pretreatment with prazosin (2.38 μmol/kg), piperoxan (74.13 μmol/kg) or yohimbine (2.56 μmol/kg). The various α-sympatholytic drugs were administered intraperitoneally, 60 min before clonidine was given. Yohimbine and piperoxan were more potent blocking agents than prazosin, at least in the doses given. Prazosin did not influence the clonidine-induced bradycardia, but piperoxan and yohimbine significantly reduced this effect. Mean arterial pressure and heart rate of prazosin-pretreated animals were lowered by about 20 and 10%, respectively, towards control rats. These cardiovascular parameters differed not significantly from control values after pretreatment with piperoxan and yohimbine. However, this hypotensive effect of prazosin itself cannot explain the antagonism with clonidine, since the depressor effect of hydralazine was not influenced by this pretreatment.

*Stimulated heart preparation (pithed rats)*

The basal heart rate (approx. 350 beats/min) was increased by about 120 beats/min on stimulation and remained stable at this higher level as long as stimulation was continued. Clonidine (375 nmol/kg, intravenously) diminished this increment in heart rate by about 50%. When a new steady state was reached at a lower level, prazosin (7.14 μmol/kg, intravenously) was injected. Thereupon heart rate increased by about 30 beats/min. Accordingly, prazosin can block to some extent the bradycardia produced by clonidine via an action on presynaptic α-receptors. The inhibitory effect of prazosin was dose-dependent and a dose–response curve could be made. A similar dose–response curve for piperoxan lies to the left of that for prazosin, suggesting that the inhibitory effect of piperoxan in this model is more pronounced than that of prazosin.

*Anaesthetized cats*

Clonidine (3.75 nmol/kg) was always injected into the left vertebral artery. Without pretreatment clonidine thus applied diminished arterial pressure promptly by 39.2 ± 4.7% of the initial value (mean ± SEM; n = 9; see Fig. 1).

This *centrally* induced hypotensive effect of clonidine (compare Sattler & van Zwieten, 1967) was significantly diminished (P < 0.001) by pretreatment with prazosin (7.14 nmol/kg) when the latter drug had been injected into the vertebral artery, but not after an intravenous administration of the same dose of prazosin (Fig. 1). A lower dose of 2.38 nmol of prazosin/kg via the vertebral artery hardly influenced the depressor effect of clonidine.

Similarly, pretreatment with an intraperitoneal dose of 71.4 nmol of prazosin/kg did not significantly impair the central hypotensive activity of clonidine. Prazosin (7.14 nmol/kg, intravenously or vertebrally and 71.4 nmol/kg, intraperitoneally) decreased arterial pressure by about 15–20% of the initial value. Thereafter, blood pressure nearly regained its original level within about 10 min. Consequently, subsequent injections of clonidine were performed at a level of arterial pressure virtually the same as in animals which had received the vehicle instead of prazosin.

Higher doses of prazosin administered intravenously or via the vertebral artery and the intraperitoneal routes, also diminished the central hypotensive effect of clonidine, but these higher doses alone caused a considerable fall in blood pressure, so that the hypotensive activity of clonidine could not be properly assessed.
The present experiments also threw some light on the hypotensive properties of prazosin itself. Prazosin when injected into the vertebral artery caused considerable hypotension even in low doses. However, the hypotensive effect after injection via the vertebral artery was virtually the same as that after intravenous administration of the same dose.

A small tachycardia was caused by prazosin (<10%) at all doses tested, irrespective of the route of administration.

Discussion

The present experiments suggest that prazosin can block the effects of clonidine in various models. In the anaesthetized rat the hypotensive effect of clonidine was diminished by prazosin but also by yohimbine and piperoxan. This antagonism probably occurs at the level of central α-adrenoceptors and is presumably a specific interaction between the two drugs, since prazosin, although it reduced arterial pressure, did not interfere with the hypotensive effect of hydralazine. The bradycardic action of clonidine was not influenced by prazosin. This finding contrasts with recent results of Cavero & Roach (1978) in which oral prazosin antagonized the clonidine (37.5 nmol, intracerebroventricularly)-induced hypotension and bradycardia in urethane-anaesthetized rats.

In the pithed rat, the increase in heart rate brought about by stimulation according to Drew (1976) was diminished by clonidine. This finding reflects the presynaptic activity of clonidine. The fact that prazosin partially reversed this inhibitory influence of clonidine shows that prazosin possesses a measurable degree of presynaptic α-sympatholytic activity, apart from its predominant postsynaptic blocking potency. Our experimental findings are, with this respect at variance with those described by Cavero, Lefèvre & Roach (1977) who could not demonstrate any interference of prazosin with the clonidine-induced reduction of the stimulated heart rate in pithed rats.

Our findings suggest that prazosin is a less perfect postsynaptic α-sympatholytic agent than has been presumed so far, although the postsynaptic activity is certainly dominant. In cats, prazosin has been demonstrated to antagonize the central hypotensive properties of clonidine at very low doses. Most likely, the antagonism occurs at the level of central α-adrenoceptors. Prazosin probably inhibits receptors at central sites which possess similar features to peripheral postsynaptic α-adrenoceptors.

The present experiments also suggest that prazosin as such displays no important central hypotensive properties. The hypotensive effect of this drug was shown to be the same after its administration either intravenously or to the vertebral artery.

In conclusion, the present studies would suggest that a combined application of clonidine and prazosin in antihypertensive therapy should be avoided because the antihypertensive effect of clonidine might be blocked by prazosin. It has to be admitted that such a combination would be irrational. Nevertheless, the interaction of both drugs has given rise to interesting theoretical considerations.

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References