PHARMACOLOGY OF GUANFACINE

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- 1 The pharmacological effects of the centrally acting antihypertensive drug guanfacine are reviewed.
- 2 The drug lowers systemic blood pressure in hypertensive rats dose-dependently after oral application of 0.3–5 mg/kg.
- 3 Evidence is presented that guanfacine produces its antihypertensive action by a specific stimulation of central α -adrenoceptors.
- 4 Certain pharmacological differences between clonidine and guanfacine are discussed.

Introduction

MOST of the pharmacological effects of guanfacine (Estulic®, *N*-amidino-2-(2,6-dichlorophenyl) acetamide HCl) have been previously published in detail (Scholtysik, Lauener, Eichenberger, Bürki, Salzmänn, Müller-Schweinitzer & Waite, 1975; Saameli, Scholtysik & Waite, 1975; Scholtysik & Jerie, 1976; Scholtysik, 1979; Scholtysik, Jerie & Picard, 1980). Based on these articles the present paper provides a brief general survey on pharmacological effects which characterize guanfacine as an antihypertensive agent.

Antihypertensive effects

Guanfacine has been found to lower the blood pressure of rats made hypertensive by unilateral nephrectomy and chronic treatment with desoxycorticosterone acetate (DOCA) and sodium chloride, of Grollman rats and of genetically hypertensive rats (Scholtysik *et al.*, 1980). The antihypertensive effect was dose-dependent after oral doses between 0.3 and 5 mg/kg. In DOCA-rats the maximum effect was attained 2–4 h after administration of single oral doses and the blood pressure usually returned to its original level after 24 hours.

Central cardiovascular effects

Evidence for a central site of action of guanfacine has been obtained by Waite (1975) from experiments in anaesthetized cats in which the drug reduces the central sympathetic outflow. The effect of guanfacine has been studied by quantifying the spontaneous

preganglionic sympathetic nerve activity recorded from a left splanchnic nerve. At a cumulative intravenous dose of 83 $\mu\text{g/kg}$, guanfacine reduces sympathetic nerve activity by 50%. The dose necessary to produce 50% inhibition after intracerebroventricular injection is 44.6 $\mu\text{g/kg}$. Reduction in spontaneous preganglionic sympathetic nerve activity has been attributed to central inhibition of the sympathetic tone (Schmitt, Schmitt, Boissier & Guidicelli, 1967). The results with guanfacine strongly suggest a similar action.

Further evidence for a central site of action has been obtained from experiments in anaesthetized dogs (Scholtysik *et al.*, 1975). Guanfacine was infused at a rate of 1 $\mu\text{g kg}^{-1} \text{ min}^{-1}$ either by the intravenous route or into the left vertebral artery. A reduction in the mean blood pressure was observed only during intravertebral-arterial infusion, but not during intravenous infusion. Van Zwieten (1975) has shown that a typical feature of centrally acting antihypertensives is a depressor action following their administration in minute amounts into the vertebral artery. The intravertebral action of guanfacine can thus be interpreted as being central. Additional support has been obtained by studying changes in blood pressure and heart rate following intravenous and intracerebroventricular (i.c.v.) injections in anaesthetized cats (Scholtysik *et al.*, 1975). Guanfacine decreases both blood pressure and heart rate progressively following i.c.v. injection of a single dose of 3 $\mu\text{g/kg}$. The same dose given intravenously was without significant effect. The intraventricular action of guanfacine was largely abolished by pretreatment with the α -adrenoceptor-blocking drug phentolamine injected i.c.v. These findings show that the effects of guanfacine on blood pressure and heart

rate are evoked by stimulating α -adrenoceptors within the central nervous system.

Facilitation of vagally-mediated reflex bradycardia has been attributed to central α -adrenoceptor stimulation (Antonaccio & Robson, 1973; Walland, Kobinger & Csongrady, 1974). The influence of guanfacine on reflex bradycardia elicited by transient occlusion of the aorta has therefore been investigated in anaesthetized dogs (Scholtysik, 1979). Guanfacine facilitated reflex bradycardia in a dose-dependent manner. This effect was completely antagonized by injecting the α -adrenoceptor-blocking agent phentolamine into the cisterna magna.

The central α -adrenoceptor agonist activity of guanfacine has been confirmed by biochemical findings (Scholtysik *et al.*, 1975, 1980). The effect of the drug on central noradrenaline turnover has been investigated in rats in which the synthesis of noradrenaline was blocked by diethyl-dithiocarbamate (DDC). DDC reduces the noradrenaline content in the brain stem and spinal cord, reflecting a normal rate of noradrenaline turnover. Guanfacine, which has no effect on the normal noradrenaline content, inhibits the DDC-induced disappearance of noradrenaline, suggesting that the drug reduces noradrenaline turnover. These results have been confirmed by Velly (1977).

Reduction in the turnover of noradrenaline in the central nervous system has been described as a characteristic biochemical consequence of central α -adrenoceptor stimulation (Andén, Grabowska & Strömbom, 1976).

The view that central α -adrenoceptor activation is involved in the sympathoinhibitory and cardiovascular depressor actions of guanfacine agrees with a number of other findings concerning the central regulation of the general sympathetic tone. Direct application of noradrenaline to vasomotor centres in the rat induces cardiovascular depression, and the effect can be prevented by phentolamine (de Jong, 1974). Other α -adrenoceptor stimulants, like phenylephrine and α -methylnoradrenaline, also induce a decreased blood pressure in response to i.c.v. application in cats, and the effect can be antagonized by α -adrenoceptor blockade (Day & Roach, 1974).

The pharmacological results with guanfacine presented so far demonstrate that the drug, like noradrenaline and clonidine, activates central α -adrenoceptors and hence decreases the central sympathetic tone. As clonidine belongs to the class of centrally acting antihypertensives, it will be of particular interest to consider pharmacological differences in the central actions of guanfacine and clonidine.

One point of difference concerns the site of central action of the two drugs. Topical application of clonidine 2 μ g/kg to the exposed ventral surface of the

medulla oblongata in the cat induces a marked fall in the mean arterial blood pressure by more than 50 mm Hg and in the heart rate by more than 30 beats/min (Bousquet & Guertzenstein, 1973; Scholtysik *et al.*, 1975). Guanfacine (up to 20 μ g/kg) was ineffective in this test model (Scholtysik *et al.*, 1975), suggesting that the sites of action within the central nervous system may be different for the two drugs.

The drugs differ also in their effects on dopamine (DA) turnover in the rat brain (Scholtysik, Lindt & Eichenberger, 1972; Scholtysik *et al.*, 1980). For this investigation the principle of blocking DA synthesis was applied, using the methyl ester of α -methyltyrosine (H 44/68) to inhibit tyrosine hydroxylase activity. Clonidine 0.5 mg/kg orally inhibits the H 44/68-induced disappearance of DA in the rat corpus striatum by nearly 20% ($P < 0.01$), whereas guanfacine has no significant effect up to 10 mg/kg orally.

Recently, stimulation of central histamine₂ receptors has been described for clonidine, based on antagonistic effects by metiamide (Karppanen, Paakkari, Paakkari, Huotari & Orma, 1976; Finch, Harvey, Hicks & Owen, 1978). In contrast to clonidine the cardiovascular effects of guanfacine could not be antagonized by metiamide (Salzmann, unpublished results).

Another point of difference concerns a central side-effect. In conscious dogs the lowest dose for a detectable sedative action was 3 mg/kg subcutaneously (s.c.) for guanfacine and 0.03 mg/kg s.c. for clonidine (Scholtysik *et al.*, 1975). Thus, guanfacine was observed to produce relatively less sedation than clonidine (Scholtysik *et al.*, 1975). A comparison of the effects of the two drugs on the EEG was therefore carried out using rats with chronically implanted electrodes. After the administration of equipotent antihypertensive doses, in contrast to guanfacine, clonidine reduced the total duration of wakefulness by 60%; and the increase in the total duration of drowsiness produced by guanfacine was much less pronounced than after clonidine (Kleinlogel, Scholtysik & Sayers, 1975).

Peripheral cardiovascular effects

Peripheral α -adrenoceptor stimulation has been demonstrated in different pharmacological models (Kleinlogel *et al.*, 1975; Scholtysik *et al.*, 1975). Intravenous injection in the anaesthetized normotensive cat produces an initial transient pressor phase which is promptly followed by a small but prolonged fall in blood pressure. In the pithed-rat preparation, transient pressor effects occur after intravenous administration. These dose-dependent pressor effects can be prevented by α -adrenoceptor blockade with phentolamine but are not influenced

by pretreatment with reserpine. The results demonstrate a direct vascular α -adrenoceptor-stimulant activity for guanfacine. *In vitro* experiments on spiral strips of canine veins and arteries have led to the same conclusion (Scholtysik *et al.*, 1975). Guanfacine caused contraction of both preparations in about the same concentration ranges. In the presence of phentolamine the dose-response curves are shifted to the right, indicating competitive antagonism.

Further evidence of peripheral presynaptic α -adrenoceptor stimulation by guanfacine has been obtained from experiments in which the neurotransmission of adrenergic heart nerves has been investigated (Pacha, Salzmann & Scholtysik, 1975). In pithed cats and rabbit isolated hearts guanfacine produces a dose-dependent inhibition of accelerator nerve stimulation effects. Both phentolamine and phenoxybenzamine abolish this inhibition. Doxey (1979) has used the anococcygeus muscle of the pithed rat to investigate pre- and postsynaptic α -adrenoceptor agonist activity simultaneously in the same tissue. Guanfacine activates presynaptic α -adrenoceptors ten times more selectively than does clonidine.

It has been established that postganglionic peripheral sympathetic nerves are endowed with α -adrenoceptors, stimulation of which causes a decrease in transmitter release (Kirpekar, Furchgott, Wakade & Prat, 1973; Starke & Altmann, 1973).

There is strong evidence that guanfacine stimulates these peripheral presynaptic receptors which inhibit sympathetic nerve function. This peripheral sympathetic neurone inhibition may contribute to the antihypertensive effect of the drug.

Conclusions

Guanfacine is an effective antihypertensive drug. In hypertensive rats a dose-dependent lowering of blood pressure was observed within the range 0.3–5 mg/kg orally. There is considerable pharmacological evidence in support of the view that guanfacine produces its antihypertensive effect by an action mediated within the central nervous system. α -adrenoceptor activation seems to be involved in the central mechanism of action. In addition, peripheral presynaptic α -adrenoceptor stimulation, which inhibits sympathetic neurotransmission, may contribute to some extent to the antihypertensive effect.

Clonidine has a similar mechanism of action. However, guanfacine differs from clonidine in so far as it does not act on the ventral medullary surface of cats (different site of action), is devoid of dopamine or histamine₂ receptor-stimulant properties (higher specificity of central action), and shows less sedative EEG effects in rats.

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