The cardiovascular pharmacology of xamoterol, cicloprolol, prenalterol and pindolol in the anaesthetised dog

S. E. HADFIELD, S-J. SLEE & H. M. SNOW

ICI Pharmaceuticals, Alderley Park, Macclesfield, Cheshire

An anaesthetised dog preparation was used to examine the pharmacological profiles of xamoterol, cicloprolol, prenalterol and pindolol. The effects of these agents on heart rate and hind limb perfusion pressure revealed that xamoterol is highly cardioselective and has no significant agonist activity at β_2 -receptors and no membrane stabilising effect. These pharmacological properties are not complicated by the formation of active metabolites and may explain the clinical benefits in the long-term treatment of heart failure.

Keywords xamoterol cicloprolol prenalterol pindolol

Introduction

The two β -adrenoceptor partial agonists xamoterol and prenalterol have been used in the treatment of heart failure. These were compared with cicloprolol and pindolol which have been classified as β -adrenoceptor blockers with intrinsic sympathomimetic activity (ISA). Previous measurements of affinity and intrinsic activity have been made in different species both *in vitro* and *in vivo* making comparison of results difficult. The aim of this study was to quantify the direct actions of the compounds on the heart, primarily β_1 -adrenoceptors, and peripheral circulation, β_2 -adrenoceptors (Bilski *et al.*, 1983), in a standard anaesthetised dog preparation, depleted of catecholamines, in which cardiovascular reflexes had been prevented from occurring.

Methods

The effects of the compounds on heart rate and pressure in a hind limb perfused at constant blood flow were assessed in an anaesthetised dog (pentobarbitone 30 mg kg⁻¹). Cardiovascular reflexes were prevented from occurring by pre-treatment with syrosingopine (to deplete catecholamines) and by cutting the vagi in the neck.

Partial agonist activity and affinity (ED₅₀) were calculated from agonist dose-response curves. An estimate of the apparent dissociation constant K_B was obtained by using each compound as an antagonist of the actions of

isoprenaline on heart rate and hind limb perfusion pressure. Dose-response curves to isoprenaline were obtained in the absence and presence of increasing doses of a compound. The curves were normalised and from the resulting set of parallel curves, dose-ratios (DR) were calculated. Log (DR–1) was plotted against the log of the corresponding dose of compound. The value of the dose of compound when the DR is 2 is an index of the antagonist potency and has been named the apparent dissociation constant (K_B , mol kg⁻¹).

Results

Values for the partial agonist activity, ED₅₀ and K_B on heart rate and hind limb perfusion pressure are shown in Table 1. Selectivity was calculated as the ratio of the affinity constant (K_B) for the β_2 -adrenoceptors divided by the ED₅₀ for heart rate (β_1).

All of the compounds studied are partial agonists at the β_1 -adrenoceptor; however, only xamoterol is a selective agonist, having no agonist activity at the β_2 -adrenoceptor (Figure 1).

With respect to affinity, both xamoterol and cicloprolol are cardioselective, i.e. have a greater affinity for β_1 -adrenoceptors than for β_2 -adrenoceptors; prenalterol is much less selective and pindolol has greater affinity for β_2 -adrenoceptors (Figure 2).

The dose-response curve for pindolol is biphasic, probably because of the formation of

Table 1 Effect of partial agonist activity (PAA) and ED_{50} on heart rate (HR) and hind limb perfusion pressure (HLPP). Selectivity was calculated as the ratio of the affinity constant (K_B) for the β_2 -adrenoceptors divided by the ED_{50} for heart rate (β_1)

Drug	Effect on HR (β_1)		Effect on HLPP (β_2)		Affinity constant K_B ($nmol\ kg^{-1}$)		Selectivity for β_1 -adrenoceptors $K_B(\beta_2)/ED_{50}(\beta_1)$
	PAA (%)	ED_{50} ($nmol\ kg^{-1}$)	PAA (%)	ED_{50} ($nmol\ kg^{-1}$)	β_1	β_2	
Xamoterol	49.7 ± 2.5	6.8 ± 1.5	0	—	25.5 ± 1.5	208.9 ± 59.9	30.7
Cicloprolol	27.2 ± 1.5	65.9 ± 4.7	5.7* ± 2.7	—	120.3 ± 22.8	2117*	32.0
Prenalterol	64.2 ± 2.1	52.8 ± 4.9	53.0 ± 8.0	159.8 ± 29.9	54.6 ± 4.9	291.6 ± 53.6	5.5
Pindolol	13.6 ± 1.2	21.7 ± 6.0	19.8 ± 4.4	22.5 ± 10.1	43.5 ± 13.3	5.2 ± 0.8	0.2
Pindolol + metabolites	29.5 ± 2.2	—	41.7 ± 4.8	—	11.7 ± 1.2	5.2 ± 0.8	—

* $n = 2$

Figure 1 Partial agonist activity of xamoterol, ciclopriolol, prenalterol and pindolol in β_1 - (heart rate response, ■) and β_2 -adrenoceptors (hind limb perfusion pressure response, ▨).

Figure 2 Dose-response curves (heart rate) to isoprenaline ($n = 4$), xamoterol ($n = 4$), prenalterol ($n = 5$), ciclopriolol ($n = 5$) and pindolol ($n = 4$). Each response represents mean $\pm$ s.e. mean.

active metabolites (Figure 2). The active metabolites of pindolol appear to have greater intrinsic sympathomimetic activity and greater affinity for both β_1 - and β_2 -adrenoceptors than pindolol itself.

The dose-response curve to ciclopriolol on heart rate shows that at high doses the heart rate decreases, a possible membrane stabilising effect of the drug (Figure 2).

Discussion

Xamoterol is a β_1 -adrenoceptor partial agonist (Nuttall & Snow, 1982) which has been shown to be of benefit in the chronic treatment of heart failure (The German and Austrian Xamoterol Study Group, 1988). Prenalterol and pindolol, also having agonist activity at the β_1 -adreno-

ceptor, are of limited use. Prenalterol, though of benefit in acute studies, was unsuccessful on chronic dosing (Currie *et al.*, 1984; Lambertz *et al.*, 1984), and pindolol has been shown to have deleterious effects on cardiac contraction in patients with ischaemic heart failure (Rousseau *et al.*, 1984; Binkley *et al.*, 1986).

The reasons for these clinically observed differences may be due to the differences in pharmacological profile between the compounds. For example, of the four compounds studied, xamoterol has high cardioselectivity, no partial agonist activity at β_2 -adrenoceptors, no membrane stabilising effects and the actions of the drug are not complicated by the formation of active metabolites. This unique pharmacological profile may explain the clinical benefits of xamoterol in the treatment of chronic heart failure.

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