*Br. J. clin. Pharmac.* (1987), **24**, 21S–28S

# Is the ISA of pindolol $\beta_2$-adrenoceptor selective?

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**1** Pindolol is a β-adrenoceptor blocking drug with ISA (also called partial agonist activity). This means that in addition to blocking the effects of β-adrenoceptor agonists, it produces some stimulation of β-adrenoceptors.
**2** *In vitro* studies with pindolol show that its maximum stimulant action is similar to that of isoprenaline in tissues possessing mainly $\beta_2$-adrenoceptors, but is negligible in tissues possessing mainly $\beta_1$-adrenoceptors. This suggests selective stimulation of $\beta_2$-adrenoceptors.
**3** In man the arteriodilator effects observed after intra-arterially infused pindolol at concentrations within the same range as those producing an antihypertensive effect also suggest a stimulant action on vascular $\beta_2$-adrenoceptors.
**4** The fact that pindolol prevents the reduction of resting heart rate and cardiac output observed after drugs lacking ISA at first sight suggests stimulation of cardiac $\beta_1$-adrenoceptors. However, human atria possess not only $\beta_1$- but also $\beta_2$-adrenoceptors, stimulation of which would produce the same effect.
**5** Although all β-adrenoceptor antagonists lower blood pressure, recent experiments have shown that those agents with combined $\beta_1$-adrenoceptor blocking activity and ISA at those receptors are less effective. This observation lends weight to the thesis that pindolol does not stimulate $\beta_1$-adrenoceptors since it lowers blood pressure as effectively as drugs lacking ISA.
**6** The evidence available therefore suggests that although pindolol blocks both $\beta_1$- and $\beta_2$-subtypes, it selectively stimulates $\beta_2$-adrenoceptors.

**Keywords** pindolol intrinsic sympathomimetic activity $\beta_2$-adrenoceptor

## Introduction

Twenty years ago, when Prichard (1964) discovered the antihypertensive effects of β-adrenoceptor blocking drugs, little attention was paid to other properties of these compounds, although the first compound found to lower blood pressure in man (pronethalol), actually possessed ISA. β-adrenoceptor blocking drugs have now gained an important place in the therapeutic armamentarium for the treatment of hypertension. In parallel with their widening therapeutic use, interest in the potential advantages conferred by ancillary properties has increased. Since our previous review of the evidence for the clinical advantages provided by intrinsic sympathomimetic activity (ISA) (Aellig, 1984) new data have become available, which help to clarify some of the questions relating to the haemodynamic effects of these agents, and which suggest the possibility of selectively stimulating only one sub-type of β-adrenoceptor.

The pharmacological actions of β-adrenoceptor blocking drugs with intrinsic sympathomimetic activity (ISA) have been reviewed in detail by Clark *et al.* (1982). Such drugs are partial agonists, which means that even at full saturation of the receptor system, their stimulant

effect on β-adrenoceptors is less than that obtainable with full agonists such as the naturally-occurring catecholamines, noradrenaline and adrenaline. The concept of a compound producing two apparently opposite effects, i.e. stimulation and blockade, may seem at first paradoxical, but in fact is not so. A compound must combine chemically with a receptor in order to evoke a stimulant effect, and so long as this combination exists, access of other stimulants to the receptor is prevented. Thus blockade is simply the passive result of receptor occupation. Because of the low level of agonist activity on the heart in the β-adrenoceptor blocking drugs in clinical use, the only evidence for the stimulatory effect is the partial or total compensation of the reduction in resting heart rate observed after pure β-adrenoceptor blockade.

*Effects on peripheral resistance*

Experimental and clinical studies (e.g. Svendsen *et al.*, 1979; Man in't Veld & Schalekamp, 1982) have shown that the acute administration of a β-adrenoceptor blocking drug without ISA reduces cardiac output, and this leads to a reflex rise in peripheral resistance. Drugs with ISA produce such changes to a smaller extent or not at all. In a plethysmographic study in healthy volunteers propranolol reduced calf blood flow, whereas the effect of pindolol did not differ from that of placebo (Aellig, 1982). During chronic therapy of essential hypertension, however, drugs without ISA still increase peripheral resistance, whereas pindolol produces a reduction below pre-treatment values. Drugs with less ISA show intermediate effects (Man in't Veld & Schalekamp, 1982).

Svensson *et al.* (1981) observed that vascular resistance in the calf decreased in hypertensive patients treated for 6 months with pindolol but increased in those on metoprolol, despite the fact that both compounds produced the same reduction of blood pressure. They postulated that the vasodilator effect of pindolol was due to stimulation of vascular $\beta_2$-adrenoceptors. We tried to find evidence to prove or disprove this hypothesis.

Comparison of the haemodynamic effects of different β-adrenoceptor blocking drugs in the anaesthetized dog showed that heart rate and cardiac output were markedly reduced by propranolol and atenolol but were not influenced by pindolol (Clark, 1982). Vascular resistance in the hind limb increased markedly after propranolol and atenolol but not after pindolol (Figure 1). This was in agreement with results obtained in studies in man (Svendsen *et al.*, 1979). In order to show that the increase in femoral vascular resistance observed after drugs without ISA was due to reflex vasoconstriction in response to the reduction in cardiac output, one limb of the dog was denervated. Under these experimental conditions, no differences between the three drugs were expected, because in the denervated limb a reflex increase in vascular resistance would no longer occur. As shown in Figure 1, no significant change in resistance occurred after the drugs without ISA. Surprisingly, however, pindolol produced a marked reduction in resistance, supporting the thesis that the drug is capable of exerting a direct dilator effect.

*Direct effects on arteries and other tissues*

The vasodilator effect of pindolol was investigated further in isolated perfused canine mesenteric arteries. Isoprenaline (a full β-adrenoceptor agonist) produced the expected marked and dose-dependent reduction in vascular resistance (Figure 2). With pindolol, surprisingly, about the same dilator effect was obtained as with isoprenaline. In these experiments therefore, pindolol behaved like a full agonist at $\beta_2$-adrenoceptors (Clark & Bertholet, 1983).

The actions of pindolol on other isolated tissues were therefore analysed. Figure 3 shows a comparison of the stimulant effects of pindolol and isoprenaline in a series of isolated tissues, selected to include those in which responses are mediated either by $\beta_1$- or by $\beta_2$- or by both adrenoceptor subtypes. The effects of pindolol are expressed as a percentage of the maximum effects obtained with isoprenaline. In a tissue such as the guinea pig atrium, in which rate increases are mediated principally by $\beta_1$-adrenoceptors, pindolol exerts a negligible stimulant action compared with that observed after isoprenaline (Kaumann & Blinks, 1980). The relaxant effects on canine mesenteric arteries (discussed above) and on the rat uterus (Clark & Bertholet, 1984), however, approach those of the full agonist isoprenaline. These tissues possess a pure population of $\beta_2$-adrenoceptors. On guinea pig trachea and on kitten atria, which possess both β-adrenoceptor subtypes, pindolol exerts about 40–50% of the maximum isoprenaline effect (Waite, 1978; Kaumann & Blinks, 1980). These findings in isolated tissues therefore suggested that, although pindolol blocks both $\beta_1$- and $\beta_2$-adrenoceptors non-selectively (Bertholet *et al.*, 1981) its stimulant effects are mainly confined to the $\beta_2$-subtype. The question of course arose as to whether these *in vitro* findings could be extrapolated to man.

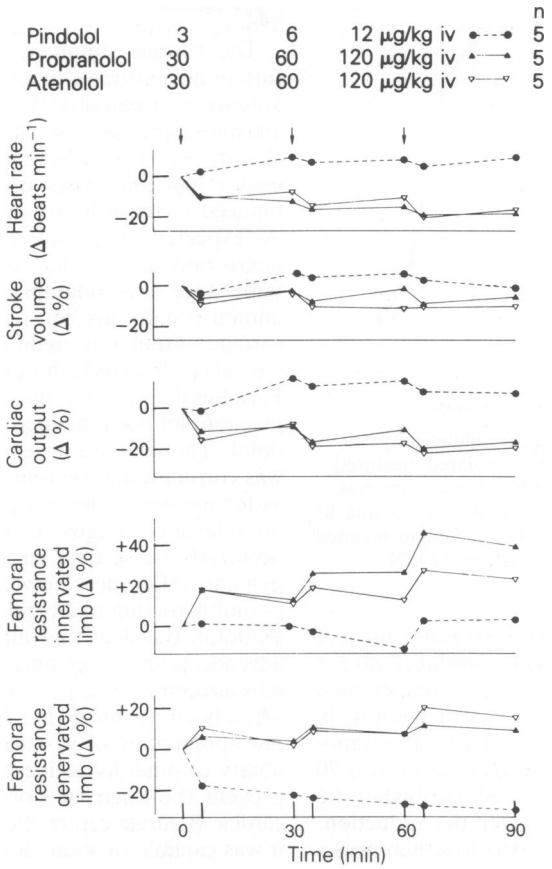


**Figure 1** Haemodynamic effects of β-adrenoceptor blocking agents in chloralose-urethane anaesthetized dogs; mean changes in groups of five animals. Doses indicated are cumulative. Cardiac output determined by dye dilution. One hind limb denervated by cutting femoral and sciatic nerves. Femoral blood flow measured with electromagnetic flow meters. (Data from Clark, 1982).

*Intraarterial administration* in vivo

Chang *et al.* (1983) infused pindolol directly into the brachial artery of healthy subjects. Arterial blood flow was measured by venous occlusion plethysmography. Figure 4 shows that pindolol increased blood flow dose-dependently. This effect was inhibited by concomitant infusion of propranolol. The results suggested that, in this acute experiment, pindolol produced vasodilation due to direct stimulation of vascular $\beta_2$-adrenoceptors. An important question, however, was whether the plasma concentrations of pindolol in the arteries of these subjects bore any relation to those present in the normal clinical situation. In a further study (Chang *et al.*, 1985), plasma levels of pindolol were measured in the venous outflow of the arm investigated and correlated with the increase in arterial flow. Figure 5 shows that there was a good correlation between the logarithm of plasma concentrations of pindolol and the vasodilator response. The arteriodilator effect of pindolol occurred at plasma concentrations within the same range as those producing an antihypertensive effect. Similar experiments with practolol show that this $\beta_1$-selective partial agonist does not dilate arteries, confirming its lack of stimulant activity on $\beta_2$-adrenoceptors (Chang *et al.*, 1983).

*Is the ISA $\beta_2$-adrenoceptor selective?*

The results obtained with pindolol on human arteries *in vivo* therefore support the *in vitro* data suggesting $\beta_2$-adrenoceptor stimulation. But does this also apply to the actions of pindolol on the heart? Rosenthal *et al.* (1979) treated 7000 hypertensive patients with pindolol and

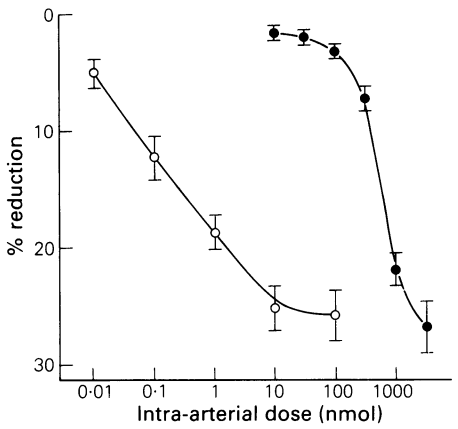


**Figure 2** Reductions in resistance induced by isoprenaline (○) and pindolol (●) in isolated, perfused mesenteric vessels of the dog. The preparation was perfused with Krebs-Henseleit solution containing 30 mM KCl at a constant rate of 6 ml $min^{-1}$ and maintained at 37° C. Data from Clark & Bertholet (1983).

found that at initial resting heart rate values of about 70 beats $min^{-1}$ the drug produced no net changes. The ISA therefore exactly compensated for the loss of sympathetic drive which normally results from blockade of cardiac β-adrenoceptors. At pre-treatment heart rates of over 70 beats $min^{-1}$, heart rate declined; the higher the pre-treatment rate, the greater the reduction. When initial heart rate was very low there was a slight increase. This latter effect has been reported to be of benefit in patients with bradyarrhythmias resulting from sinus node dysfunction (Viersma *et al.*, 1986; Cristal & Lazarowitz, 1986).

The cardiac stimulant effect of pindolol is further demonstrated in an experiment in healthy volunteers treated with single oral doses of 160 mg propranolol, 15 mg of pindolol or placebo (Figure 6). The doses of the two β-adrenoceptor blocking drugs used reduced exercise-induced tachycardia to about the same extent. As expected, propranolol also reduced resting heart rate and cardiac output (measured by impedance cardiography). After pindolol administration neither resting heart rate nor cardiac output was significantly different from the values observed after placebo administration. Peripheral resistance increased markedly after propranolol but remained unchanged after pindolol. The increase observed after propranolol was considered to be reflex in nature, compensating for the reduction in cardiac output, since no relevant changes in mean blood pressure occurred. These data suggest that the haemodynamic differences between pindolol and propranolol are due to a cardiac stimulant effect of pindolol. But does this imply stimulation of $\beta_1$-adrenoceptors? Ever since the subdivision of β-adrenoceptors into $\beta_1$- and $\beta_2$-subtypes, it has often been assumed that the heart possesses a pure population of $\beta_1$-adrenoceptors. Thus the ability of pindolol to increase heart rate, or to prevent the decrease normally resulting from cardiac β-adrenoceptor blockade suggested that it was capable of stimulating $\beta_1$-adrenoceptors, which is at variance with the conclusions drawn from the *in vitro* investigations discussed above. Radioligand binding experiments, and functional

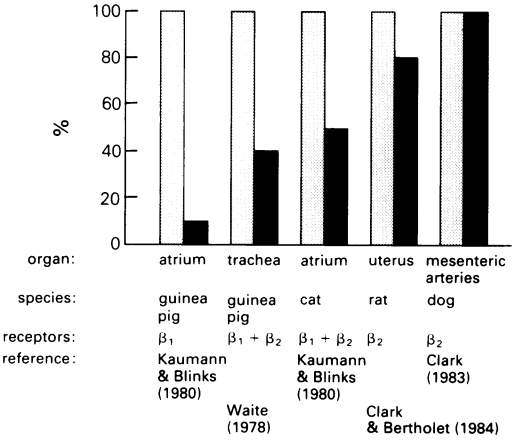


**Figure 3** Stimulant effects of pindolol (■) and isoprenaline (⊡) in tissues in which responses are mediated either by $\beta_1$- or by $\beta_2$- or by both β-adrenoceptor subtypes. The effects of pindolol are expressed as a percentage of the maximum effects obtained with the full agonist isoprenaline.

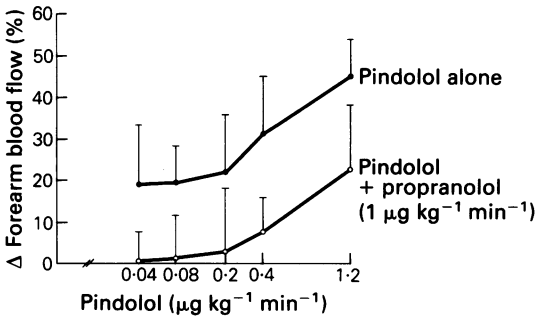


**Figure 4** Increase in forearm blood flow during intraarterial infusion of pindolol alone (•) and together with 1 μg $kg^{-1}$ $min^{-1}$ of propranolol (○) in 11 healthy volunteers (mean ± s.e. mean). Data from Chang *et al.* (1983).

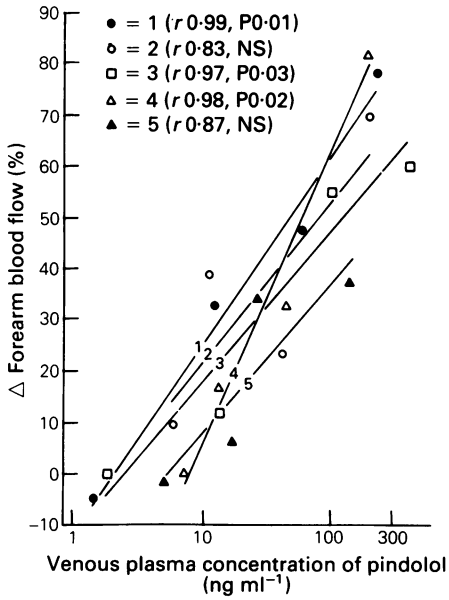


**Figure 5** Correlation between changes of forearm blood flow during intraarterial infusion of pindolol and the plasma concentration of pindolol in the venous outflow of the same arm in five healthy volunteers. From Chang *et al.* (1985), with kind permission of *Hypertension*.

studies using human cardiac tissue, however, have shown that, like many other tissues, the human myocardium possesses both β-adrenoceptor subtypes (Stiles *et al.*, 1983; Brown *et al.*, 1983; Wilson & Lincoln, 1984; Hedberg *et al.*, 1985; Vanhees *et al.*, 1986). It has been suggested that the $\beta_1$-subtype is stimulated mainly by noradrenaline released from nerve endings, and the $\beta_2$-subtype by circulating catecholamines; stimulation of either adrenoceptor subtype, however, leads to an increase in heart rate. Our findings regarding the lack of a reduction in resting heart rate and cardiac output by pindolol would therefore be compatible with the hypothesis that pindolol blocks the β-stimulant effects on the heart resulting from both neuronally released and circulating catecholamines and in addition, stimulates $\beta_2$-adrenoceptors on human atria.

There is good evidence from many comparative studies (e.g. Louis & McNeil, 1982) that the therapeutic efficacy of all β-adrenoceptor blocking drugs used for the treatment of hypertension is similar with respect to the magnitude of the reduction of elevated blood pressure. This is true irrespective of whether the drugs are $\beta_1$-selective or not and whether they possess partial agonist activity or not. Recent evidence, however, suggests that there are exceptions to this rule. Dahlöf *et al.* (1984) and Leonetti *et al.* (1985) reported that $\beta_1$-selective drugs with $\beta_1$-selective partial agonist activity are less effective in the treatment of hypertension. In the study by Leonetti *et al.* (1985), two groups of patients with essential hypertension were treated with either xamoterolol or epanolol ($\beta_1$-selective compounds with $\beta_1$-ISA), and one group also with atenolol. All three drugs reduced exercise-induced tachycardia to about the same extent, confirming that the doses used were equi-active in blocking $\beta_1$-adrenoceptors. The reduction of diastolic blood pressure, however, was much greater during treatment with atenolol than with epanolol; xamoterol had only a very modest effect. This finding is not altogether surprising, however, since the mechanism responsible for the antihypertensive activity of β-adrenoceptor blocking agents is believed to be dependent on $\beta_1$-adrenoceptor blockade. If $\beta_1$-adrenoceptor blockade is opposed by $\beta_1$-adrenoceptor stimulation, then blood pressure would not be expected to fall. The fact that compounds with $\beta_1$-

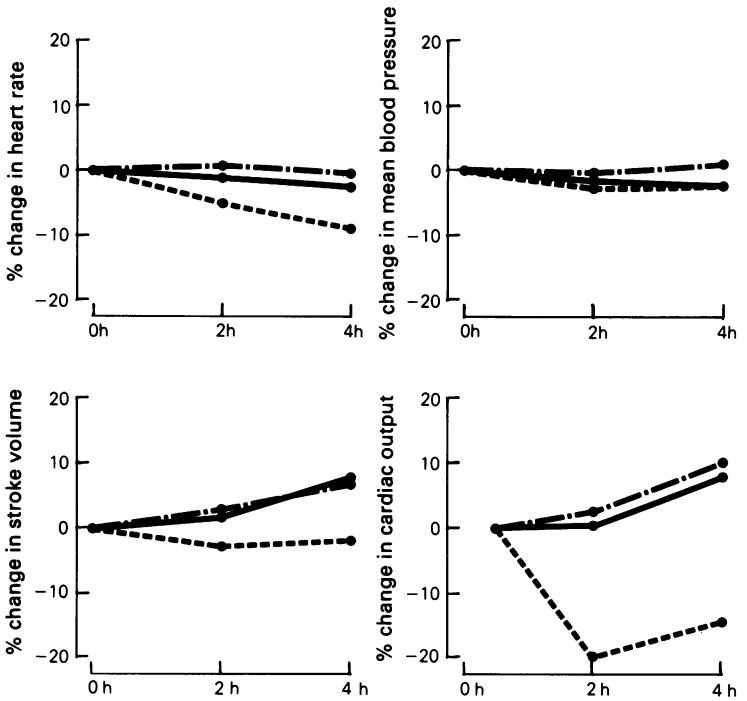


**Figure 6** Change in heart rate (from the ECG), mean blood pressure (Riva-Rocci-Method), stroke volume and cardiac output determined by impedance cardiography in six healthy volunteers after 15 mg pindolol (●—●), 160 mg propranolol (●---●) and placebo (●-·-●).

selective ISA are less effective antihypertensive drugs than the other β-adrenoceptor blocking drugs adds weight to the thesis that pindolol does not stimulate $\beta_1$-adrenoceptors to a relevant degree since it lowers blood pressure as effectively as drugs lacking ISA.

The results available therefore suggest that, in accordance with the data from isolated organs, pindolol combines with both $\beta_1$- and $\beta_2$-adrenoceptors, but appears to stimulate the $\beta_2$-adrenoceptor subtype selectively. The stimulant activity of a drug on a given receptor type is a function of not only affinity, efficacy and receptor reserve, but also the efficiency of the mechanisms which translate receptor stimulation into a measurable response (Kenakin & Beek, 1980). In tissues in which $\beta_2$-adrenoceptors are relatively abundant, and the stimulus-response mechanism efficient, e.g. blood vessels and the uterus, a drug with a relatively low ISA could produce a marked effect. The rather modest effect on heart rate produced by pindolol could reflect a relatively low density of $\beta_2$-adrenoceptors in this tissue, and/or an inefficient stimulus-response mechanism.

*Implications and conclusions*

It is clear from the foregoing that the haemodynamic response to β-adrenoceptor blockade can be altered by intrinsic sympathomimetic activity. These alterations are fundamentally different if this activity is exerted selectively on one β-adrenoceptor subtype only. If ISA is selective for the $\beta_1$-adrenoceptor, antihypertensive activity is markedly attenuated or lost, whereas if exerted predominantly on the $\beta_2$ adrenoceptor, therapeutic activity is maintained and some of the unfavourable acute haemodynamic changes observed after β-adrenoceptor blocking drugs without ISA are prevented. Drugs without ISA, whether $\beta_1$-selective or not, reduce cardiac output and increase peripheral resistance acutely. The selective $\beta_2$-adrenoceptor stimulant effect of pindolol combined with its main pharmacological action—blockade of $\beta_1$- and $\beta_2$-adrenoceptors—explains the favourable haemodynamic profile of this drug for the treatment of hypertension. Peripheral $\beta_2$-adrenoceptor stimulation leads to vasodilatation, and atrial $\beta_2$-adrenoceptor stimulation

prevents excessive reductions in heart rate. Therefore cardiac output is not reduced and peripheral resistance not elevated. A stimulant action of pindolol on $\beta_2$-adrenoceptors therefore not only explains the direct vasodilator effect of the drug but also the lack of reduction of normal resting heart rate and cardiac output caused by blockade of $\beta_1$-adrenoceptors. During chronic therapy β-adrenoceptor blockade gradually reduces peripheral resistance. According to van den Meiracker *et al.* (1987) this effect begins within a few hours following administration. After drugs without ISA, resistance values usually still remain above baseline; with pindolol, however, resistance falls to below pre-treatment values since it was not elevated acutely.

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