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β-adrenoceptor partial agonists: a renaissance in cardiovascular therapy?

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Introduction

β-adrenoceptors were first identified more than 40 years ago by Ahlquist (1948), and were subsequently shown to consist of two subtypes, known as β_1 and β_2 (Lands *et al.*, 1967). Both subtypes are widely distributed in the body where they mediate a variety of physiological responses to sympathetic nervous stimulation or circulating catecholamines. More recently, evidence for additional subtypes has been presented; of these a receptor mediating the metabolic effects of β-adrenoceptor stimulation has been the most thoroughly characterised and has been provisionally classified as a β_3-adrenoceptor (Emorine *et al.*, 1989) (Table 1). Antagonist drugs acting at the β-adrenoceptor have become established in the management of a wide variety of cardiovascular diseases, most notably arterial hypertension, ischaemic heart disease and cardiac arrhythmias (Kumana, 1987). The effectiveness of β-adrenoceptor blockers in these clinical conditions has been attributed to their ability to block the β_1-adrenoceptor subtype. This results in effects particularly on cardiac function, leading to a reduction of heart rate at rest with attenuation of the rise on exercise, reduced force of cardiac contraction, and a stabilising effect on the depolarisation of cardiac conducting tissue. Many of the established β-adrenoceptor blockers have additional effects which modify their pharmacological profile, although these properties do not necessarily enhance their clinical usefulness.

Most β-adrenoceptor blockers have a greater or lesser antagonist effect at the β_2-adrenoceptor. Non-selective compounds such as propranolol have considerable antagonist potency at the two receptor subtypes. 'Cardioselective' compounds such as atenolol have far greater specificity for β_1-adrenoceptors, although the term is slightly misleading. The selectivity is relative and not absolute, and as doses are increased, β_2-adrenoceptor blockade assumes a greater importance. It is also now recognised that some 25% of cardiac adrenoceptors are of the β_2-subtype. Blockade of β_2-adrenoceptors has little relevance to the major cardiovascular therapeutic effects of β-adrenoceptor blockers, and is implicated in the genesis of unwanted effects such as bronchospasm and worsening of tissue perfusion in peripheral vascular disease. For this reason 'cardioselective' antagonist drugs are frequently preferred by clinicians for treating cardiovascular disease.

There is *in vitro* evidence that β-adrenoceptor antagonists show different affinities for the β_3-adrenoceptor, but the clinical implications of this observation are uncertain.

A further property of some β-adrenoceptor blockers is their ability to stimulate submaximally the β-adrenoceptor, a property once referred to as intrinsic sympathomimetic activity (ISA), but more correctly termed partial agonist activity (PAA). Until recently PAA has not been widely perceived to offer many clinical advantages. The advent of newer agents with more selective PAA should encourage re-appraisal of this image.

The pharmacological basis of β-adrenoceptor partial agonist activity

Whether a molecule leads to stimulation or blockade when it occupies a β-adrenoceptor depends on how it affects events in the cell linked to that receptor. To elicit a response, an agonist must initiate receptor coupling. Thus, after binding to the receptor via disulphide bonds, the agonist triggers a regulatory G protein (the Gs protein) which couples the receptor to a membrane-bound enzyme,

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Table 1 Examples of responses mediated by postsynaptic adrenoceptors

Site of action	*Adrenoceptor*	*Effect*
Heart	$\beta_1>\beta_2$	Increased heart rate
	$\beta_1>\alpha_1$	Increased contractility
	β_1	Increased excitability and conduction velocity
Arteries	$\alpha_1>\alpha_2$	Constriction
	β_1	Dilatation of coronary arteries
	β_2	Dilatation
Veins	α_1	Constriction
Lung	α	Bronchoconstriction
	$\beta_2>\beta_1$	Bronchodilatation
Uterus	β_2	Relaxation
Gut	β_1	Relaxation
Bladder	β	Detrussor relaxation
Eye	α	Mydriasis
	β_1	Increased intraocular pressure
Skeletal muscle	β_2	Tremor, enhanced potassium uptake
Mast cells	α_2	Increased mediator release
	β_2	Inhibition of mediator release
Platelets	α_2,β	Increased aggregation
Gluconeogenesis	α	Increased
Glycogenolysis	α	Increased in liver
	β_1	Increased in heart
	$\beta_3>\beta_2$	Increased in skeletal muscle and liver
Lipolysis	$?\beta_3>\beta_1>\beta_2$	Increased
Insulin secretion	α_2	Inhibited
	$?\beta_3>\beta_2$	Increased
Glucagon	$?\beta_3>\beta_2$	Increased
Renin	$\beta_1>\beta_2$	Increased

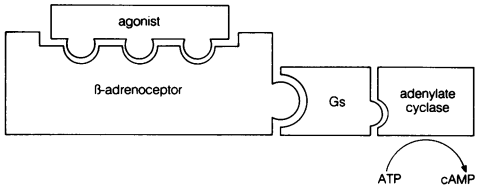

Figure 1 Diagrammatic representation of the major components of the β-adrenoceptor.

adenylate cyclase. Activation of this enzyme generates the 'second messenger' substance, cyclic 3′5′adenosine monophosphate (cAMP), which leads to a complex modulation of intracellular enzymes (Figure 1). In the heart this results in positive inotropic and chronotropic effects. When a full antagonist binds to the receptor, coupling does not occur and since access is denied to any potential agonist, the receptor is 'blocked'. If a molecule occupies the receptor but only initiates coupling with a low efficiency, then a submaximal or 'partial' response is generated, and such compounds are said to have partial agonist activity (PAA) (Figure 2). All agonists, partial agonists and antagonists of the β-adrenoceptor in clinical use can compete for reversible receptor binding. Their effectiveness will also depend on the affinity of the molecule for receptor binding. The natural agonists noradrenaline and adrenaline show high receptor binding affinity. Therapeutic molecules with high affinity for the receptor which mediates their effect will successfully compete for binding with the natural ligand. Compounds with PAA and low receptor affinity will stimulate the receptor submaximally but are readily displaced by the natural agonist when sympathetic tone increases. Therefore, to act as an antagonist at the receptor, the compound must have a high binding affinity.

If sympathetic tone (and therefore the con-

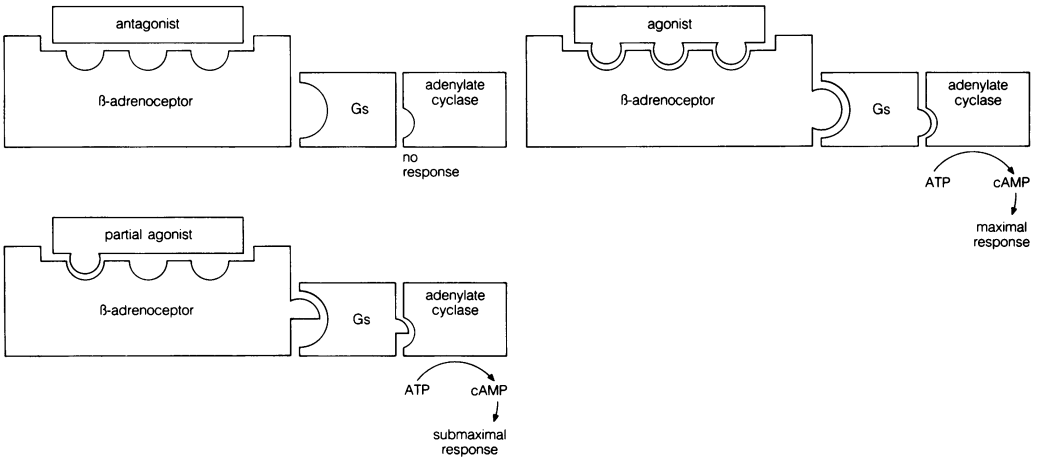

Figure 2 Diagrammatic representation of the responses to a β-adrenoceptor agonist, antagonist and partial agonist.

centrations of the endogenous agonists, noradrenaline and adrenaline) are low, e.g. at rest, then a partial agonist can occupy receptors with little competition from the endogenous agonist and lead to submaximal receptor stimulation. However, if noradrenaline concentrations are high, e.g. during sympathetic stimulation as in response to strenuous exercise, then there will be considerable competition for receptor occupancy. The weak receptor stimulation by the partial agonist will reduce the overall response of the tissue compared with that triggered by noradrenaline alone and the drug will act as a receptor blocker (Figure 3).

Potency and selectivity of partial agonist activity

It is possible to design a range of molecules which initiate various degrees of receptor coupling and thus possess different amounts of PAA. With increasing levels of PAA (i.e. the percentage of maximum tissue response that can be achieved if the drug occupies all available receptors), there will be more stimulation at low levels of endogenous sympathetic tone and a greater sympathetic drive can be mounted before the drug begins to show its receptor blocking activity.

A further consideration with β-adrenoceptor partial agonists is receptor selectivity. The concept of 'cardioselective' and non-selective β-adrenoceptor blockers has already been discussed. In addition, both non-selective β-adrenoceptor agonists (e.g. isoprenaline) and those relatively selective for either the β_1- (e.g. dobutamine) or β_2- (e.g. salbutamol) adrenoceptor are established in clinical practice. It is theoretically possible to design partial agonist drugs with any combination of these properties, and the choice will influence the pharmacological effects and thus clinical indications for the drug. Many newer β-adrenoceptor partial agonists show greater selectivity than established drugs and it is this property that demands reappraisal of the potential for this class of drug in clinical practice.

The drugs considered here fall into three broad categories:

1. β_1-selective antagonist, β_1-selective partial agonist: e.g. epanolol, xamoterol
2. Non-selective β-antagonist, β_2-selective partial agonists, e.g. dilevalol
3. Non-selective β-antagonist, non-selective β-partial agonist, e.g. pindolol, oxprenolol, carteolol.

Several other molecules under investigation also possess β-adrenoceptor blocking activity and PAA, e.g. celiprolol, medroxalol. However, the contribution of PAA to their clinical actions is uncertain, since they also possess vasodilator properties that are independent of the PAA. These compounds are not discussed. The agonist and antagonist profiles of several β-adrenoceptor blockers are shown in Table 2.

Pharmacodynamics of β-adrenoceptor blockade

Before addressing the pharmacological consequences of PAA it will be helpful to summarise the actions of β-adrenoceptor blockers which can be modified by PAA. Five main areas are considered.

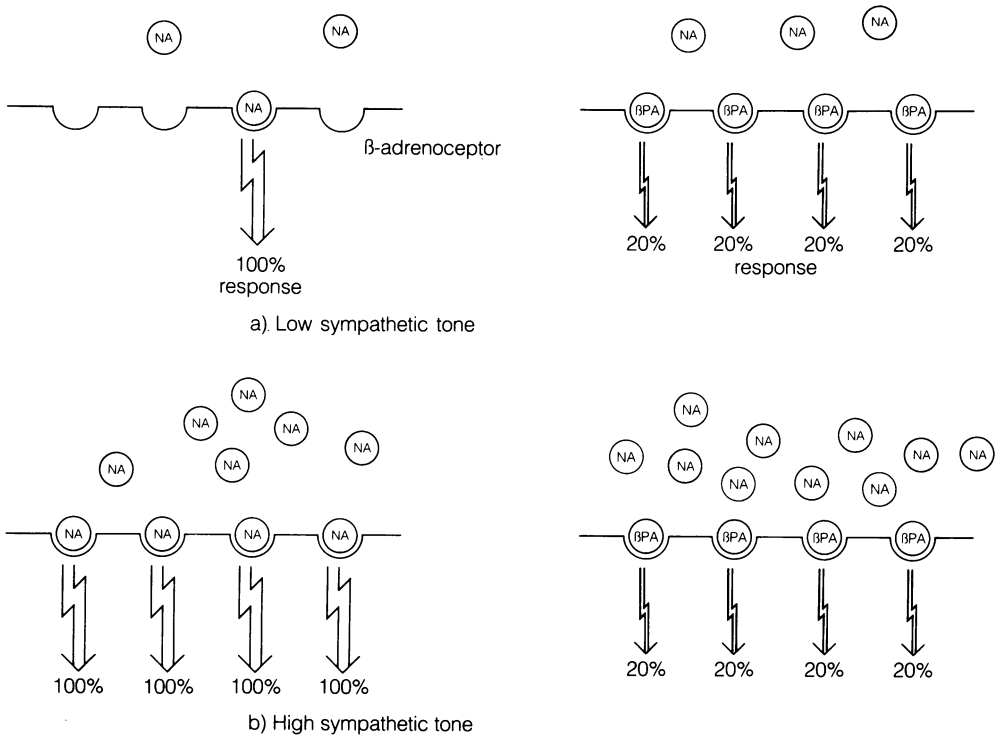

Figure 3 Effects of a β-adrenoceptor partial agonist in the presence of low and high endogenous sympathetic tone.

Table 2 Characteristics of β-adrenoceptor antagonists with partial agonist activity

Drug	*Antagonist activity*		*Partial agonist activity*	
	β_1	β_2	β_1	β_2
Carteolol	+	+	35%	35%
Pindolol	+	+	25%	25%
Oxprenolol	+	+	18%	18%
Alprenolol	+	+	10%	10%
Penbutolol	+	+	5%	5%
Dilevalol	+	+	—	50%
Xamoterol	+	−	45%	—
Cicloprolol	+	−	30%	—
Epanolol	+	−	20%	—
Acebutolol	+	±	10%	?

Cardiac haemodynamics

Acute administration of both cardioselective and non-selective β-adrenoceptor blockers leads to a fall in resting heart rate of about 15–20% and in cardiac output of approximately 20–25%. Myocardial contractility is also depressed by β-adrenoceptor blockade, leading to a reduction in stroke volume. These changes are maintained during chronic administration (Man in't Veld & Schalekamp, 1983). On exercise, cardiac output rises less than during treatment with placebo, mainly due to inhibition of the increase in heart rate since stroke volume is unchanged (Frishman & Silverman, 1979; Port *et al.*, 1980). A major consequence of these actions is reduced myocardial oxygen consumption and lengthened time for diastolic perfusion

of the coronary vascular bed. Diastolic relaxation after β-adrenoceptor blockade has not been extensively studied but atenolol has been reported to improve diastolic relaxation in patients with hypertension and impaired left ventricular function, while worsening this in patients with normal initial filling rates (Cuocolo *et al.*, 1986).

Peripheral haemodynamics

The acute reduction in cardiac output after β-adrenoceptor blockade leads to a reflex increase in peripheral vascular resistance of about 20–30% mediated by sympathetic stimulation of α-adrenoceptors in arterioles. As a consequence, blood pressure does not usually change after intravenous β-adrenoceptor blockade, even in hypertensive patients. However, over the next few hours peripheral resistance decreases to only 5–15% above pre-treatment levels, and blood pressure falls as a result of the persistant reduction in cardiac output (Man in't Veld & Schalekamp, 1988). Peripheral resistance on exercise shows the expected fall even after β-adrenoceptor blockade, but still remains above pre-treatment values (Lund-Johansen, 1983). The lower systolic blood pressure during exercise is a further factor contributing to reduced myocardial oxygen demand. The resting haemodynamic profile of pure β-adrenoceptor blockers is compared with that of the main groups of drugs with PAA in Table 3.

Airway function

β_2-adrenoceptor blockade may increase airways resistance in subjects with reversible airways obstruction, leading to wheeze. Patients with hyperreactive bronchi, e.g. unstable asthmatics or those recovering from acute exacerbations are at greatest risk. While this effect is most clearly recognised with non-selective β-adrenoceptor blockers, the β_1-adrenoceptor selectivity of compounds such as atenolol is a relative, dose-related phenomenon (Tattersfield & Harrison, 1983). However, the increase in bronchial tone tends to be less with cardioselective than non-selective drugs and, importantly, the airways retain their ability to dilate in response to β_2-adrenoceptor stimulation (Decalmer *et al.*, 1978).

Effects on plasma lipids

Several epidemiological studies have demonstrated a relationship between total serum cholesterol and the risk of subsequent coronary artery disease. It has been suggested that the high density lipoprotein (HDL) carrier of serum cholesterol (and particularly the subfraction HDL_2) may have a protective role, enhancing cholesterol clearance from arterial walls. Elevated serum triglycerides may also increase the risk of atheroma, although a role independent of cholesterol has been disputed (Northcote, 1988).

Non-selective β-adrenoceptor blockers cause a substantial increase in serum triglycerides, by an average of 32% (Weidmann *et al.*, 1985). The total plasma cholesterol concentration is unaffected but HDL, and in particular HDL_2 (Durrington *et al.*, 1985), is reduced by an average of 16%. Cardioselective drugs tend to cause smaller changes in lipids, with an average increase in triglycerides of 20% and a decrease in HDL-cholesterol of 7% (Weidmann *et al.*, 1985). The mechanisms underlying these

Table 3 Resting haemodynamic profiles of β-adrenoceptor antagonists with or without partial agonist activity

Properties	*Drug*	*Heart rate*	*Cardiac output*	*Peripheral resistance*
Non-selective blocker	Propranolol	↓ ↓	↓ ↓	↑
β_1-selective blocker	Atenolol	↓ ↓	↓ ↓	↑
Non-selective blocker + non-selective PAA	Carteolol	→/↑	→	↓
	Pindolol	→/↓	→/↑	↓
Non-selective blocker + β_2-selective PAA	Dilevalol	↓	↓	↓
β_1-selective blocker + β_1-selective PAA	Xamoterol	↓/↑	↑ ↑	→/↓
	Epanolol	↓	↓	→

Key ↓ decreased ↑ increased → unchanged

Table 4 Comparative clinical efficacy of β-adrenoceptor blockers with and without partial agonist activity

		Angina	*Hypertension*	*Arrhythmias*	*Heart failure*
Non-selective blocker	Propranolol	++	++	++	+/−
β_1-selective blocker	Atenolol	++	++	++	+/−
Non-selective blocker + non-selective PAA	Pindolol	+	++	+	?
Non-selective blocker + β_2-selective PAA	Dilevalol	?	++	?	?
β_1-selective blocker	Xamoterol	?+	0	?+	++/−*
+	Epanolol	++	0	?	?0/−
β_1-selective PAA					

++ highly effective
\+ effective
0 ineffective
− potentially deleterious
* potentially deleterious in severe heart failure
? few or no comparative data with pure β-adrenoceptor blockers

changes are complex and poorly understood (Elliott, 1988) but may be related to unopposed α-adrenoceptor stimulation which inhibits lipoprotein lipase.

Despite these lipid effects, β-adrenoceptor blockers reduce atheroma formation in experimental animal models, which raises doubts about the clinical importance of the lipids (Northcote, 1988).

Effects on the β-adrenoceptor population

During chronic administration, β-adrenoceptor blockers increase the number and/or sensitivity of β_1-adrenoceptors in the heart (Aarons & Molinoff, 1982), a process known as 'up-regulation'. Non-selective β-adrenoceptor blockers also up-regulate β_2-adrenoceptors in human lymphocytes (Aarons *et al.*, 1980), which is believed to reflect the response in solid tissues. Cardioselective drugs such as atenolol do not appear to alter β_2-adrenoceptor responses. Up-regulation of β-adrenoceptors has been implicated in the rebound phenomenon reported in some patients when β-adrenoceptor blockers are suddenly withdrawn (Prichard *et al.*, 1983). Symptoms of tachycardia, headache, chest discomfort and anxiety are most commonly reported, although patients with ischaemic heart disease may develop unstable angina, and possibly even myocardial infarction (George & Robertson, 1987).

Pharmacodynamic consequences of partial agonist activity

β_1-selective partial agonists

The two agents considered in this category exemplify the potential importance of the degree of PAA in determining the profile of the drug. Epanolol possesses about 20% PAA (Smith *et al.*, 1983) while xamoterol has approximately 45% PAA (Nuttall & Snow, 1982). Prenalterol has PAA at about 55% and in most clinical situations behaves as an agonist. It will not, therefore, be discussed here.

Cardiac haemodynamics Resting heart rate is attenuated to a lesser extent by epanolol than by atenolol (Harry *et al.*, 1989). Xamoterol, with its greater PAA increases resting heart rate (Sasayama *et al.*, 1986; Sato *et al.*, 1987) although the rate may fall during treatment of patients with left ventricular dysfunction (probably due to improved cardiac output). On exercise, both epanolol and xamoterol blunt the rate of rise of heart rate (Pringle *et al.*, 1986; Sato *et al.*, 1987), consistent with β_1-adrenoceptor blockade.

Despite its PAA, epanolol reduces resting cardiac output by 5–10% (Bonde *et al.*, 1987; Lund-Johansen *et al.*, 1985) although this fall is less than occurs with a pure β-adrenoceptor blocker. The greater PAA of xamoterol leads to

a 20–30% rise in resting cardiac output (Hashimoto *et al.*, 1986; Tango *et al.*, 1985), reflecting increased systolic contractility in patients with either normal or impaired left ventricular function (Ikaheimo & Takkunen, 1984; Molajo & Bennett, 1985; Pouleur *et al.*, 1982). The effects of xamoterol on resting ventricular function therefore mimic the positive inotropism of sympathetic stimulation. In patients with impaired left ventricular function, this enhanced ventricular performance is apparent at low or moderate levels of exercise and even at maximal exercise when the β-adrenoceptor blockade is most apparent, xamoterol does not reduce cardiac performance compared with placebo (de Feyter & Serruys, 1990). However, when left ventricular dysfunction is severe, resting sympathetic tone is high and xamoterol may demonstrate similar properties to a full antagonist at rest with consequent haemodynamic deterioration.

Peripheral haemodynamics Epanolol behaves as a β-adrenoceptor blocker in its effects on peripheral resistance; when given to hypertensives there is an initial transient rise in total peripheral resistance but a rapid return to basal values (Lund-Johansen *et al.*, 1985). However, since there is little depression of resting cardiac output, epanolol only reduces modestly resting blood pressure when compared with atenolol (Leonetti *et al.*, 1985; Wilcox *et al.*, 1985). Systolic blood pressure is reduced on exercise by higher doses of epanolol while the rise in exercise heart rate is blunted by lower doses (Erikssen *et al.*, 1988).

Xamoterol causes little change or small reductions in peripheral resistance in volunteers, or patients with ventricular dysfunction (Bhatia *et al.*, 1986; Jennings *et al.*, 1984; Tango *et al.*, 1985; Trap-Jensen *et al.*, 1982), probably as a reflex response to an increase in systolic blood pressure (Tango *et al.*, 1985; Trap-Jensen *et al.*, 1982). During exercise there is a reduction in the rate of rise of systolic blood pressure (Jennings *et al.*, 1984; Tango *et al.*, 1985) reflecting the onset of effective β-adrenoceptor blockade.

Airway function Xamoterol causes less bronchoconstriction in asthmatics than atenolol. Nevertheless, substantial reductions in FEV_1 have been reported which respond rapidly to a β_2-adrenoceptor agonist (Lammers *et al.*, 1986; Lofdahl & Svedmyr, 1984). By contrast, epanolol reduced mid-expiratory flow rates in asthmatics to a similar extent to atenolol (Groth *et al.*, 1986).

Effects on plasma lipids Limited data on the effects of epanolol on plasma lipids suggest that there is little change after 1 year of treatment (ICI, data on file). Xamoterol has no effect on plasma triglycerides during short-term treatment (Kullmer *et al.*, 1988) but long-term effects on cholesterol or triglycerides have not been reported.

Effects on the β-adrenoceptor population There are no reports of the effects of epanolol on β-adrenoceptor regulation. In the rat ventricle, xamoterol did not alter β-adrenoceptor numbers or sensitivity after 6 days of subcutaneous injection, in contrast to the down-regulation induced by the full agonist, isoprenaline (Kowalski *et al.*, 1990). Neither xamoterol nor epanolol reduced lymphocyte β_2-adrenoceptor numbers in volunteers, compared with a decrease after pindolol (Schlieper *et al.*, 1987).

Non-selective antagonists with β_2-selective PAA

Dilevalol is the R,R stereoisomer of labetalol, which is a mixture of several isomers possessing various degrees of antagonist activity at the α- or β-adrenoceptor as well as PAA. Unlike labetalol, dilevalol does not possess α-adrenoceptor blocking activity. The PAA of dilevalol is β_2-selective at about 50% of the activity of a full agonist (Sybertz *et al.*, 1982) and, therefore, twice that of pindolol.

Cardiac haemodynamics After both acute and chronic administration to hypertensive subjects, dilevalol reduced heart rate to a lesser extent than atenolol or metoprolol (Strom *et al.*, 1989). However, the blunted rise in heart rate in response to exercise is reminiscent of a typical β-adrenoceptor blocker (Tsukiyama *et al.*, 1987). Cardiac output and stroke volume are little changed at rest, but on exercise cardiac output rises less quickly than with placebo, while stroke volume increases (Bugni, 1987; Tsukiyama *et al.*, 1987).

Peripheral haemodynamics Dilevalol lowers blood pressure to a similar degree to metoprolol and propranolol (Materson *et al.*, 1989; Schoenberger *et al.*, 1989). This is achieved by an average 20% fall in systemic vascular resistance which correlates well with the hypotensive effect (Strom *et al.*, 1989). There is no change in vascular resistance during exercise compared with pre-treatment values (Vidt, 1988), which contrasts with the rise after atenolol. Unlike many compounds with substantial vaso-

dilator activity, postural hypotension with dilevalol is unusual (Given *et al.*, 1989).

Airway function β_2-adrenoceptor PAA might be expected to offer a degree of protection to the airways of asthmatic patients. Indeed, dilevalol causes less bronchoconstriction than metoprolol, but like metoprolol it blunts the bronchodilator response to β_2-adrenoceptor stimulation (Chodosh & Tuck, 1987). Although there are few data available, it seems likely that caution will be necessary in prescribing for patients with asthma.

Effect on plasma lipids Dilevalol has been reported to cause a small increase in HDL cholesterol in patients with a low pre-treatment level while total cholesterol was unchanged. Triglycerides in this study increased by about 12%, which was about half the change seen with metoprolol (Materson *et al.*, 1989). Other investigators have found little change in lipids with dilevalol (Lacourciere *et al.*, 1988).

Effects on the β-adrenoceptor population Dilevalol has been reported to down-regulate lymphocyte β_2-adrenoceptors in healthy volunteers (Sbirrazzuoli *et al.*, 1989). No data are available for β_1-adrenoceptor regulation.

Non-selective antagonists with non-selective PAA

Pindolol is probably the most widely employed drug in this category, and possesses about 25% PAA (Nyberg *et al.*, 1981). Carteolol is a more recent addition with slightly more PAA at about 35% (Yabuuchi & Kinoshita, 1974). Compounds such as penbutolol and oxprenolol have about half as much PAA as pindolol. Pindolol is used here to illustrate the properties of this group.

Cardiac haemodynamics Pindolol produces less reduction in resting heart rate than propranolol at equipotent doses (Hill & Turner, 1969), with an average fall of about 5% after acute administration and slightly less during chronic use (Man In't Veld & Schalekamp, 1983). The compounds with less PAA show an intermediate reduction. As a result, resting cardiac output is unchanged acutely and may even rise by about 5% during chronic use. During exercise, pindolol acts as a β-adrenoceptor blocker. The exercise level/heart rate curve is flattened to the same degree by pindolol as by metoprolol and timolol (Jennings *et al.*, 1981), although at high exercise levels the heart rate with pindolol is higher than with the other drugs. Thus, the PAA of pindolol is similar to basal sympathetic tone at rest, but the β-adrenoceptor blocking effect rapidly becomes dominant as sympathetic tone rises. During exercise, cardiac output also rises less rapidly than on placebo, but to a greater extent than after a full antagonist (Lund-Johansen, 1983). Although systolic contractility is probably little influenced by pindolol, diastolic relaxation is reduced in patients with left ventricular dysfunction (Rousseau *et al.*, 1984).

Peripheral haemodynamics In common with full antagonists, pindolol has little acute effect on blood pressure, but by contrast there is no increase in peripheral vascular resistance (Man In't Veld & Schalekamp, 1983). During chronic administration, peripheral resistance falls by about 20% which is accompanied by a reduction in blood pressure in hypertensive subjects similar to that seen with full antagonists. The hypotensive response is significantly greater than with epanolol, which possesses a similar degree of PAA at β_1-adrenoceptors (Simon & Wittig, 1987). This supports a major role for β_2-adrenoceptor stimulation in the hypotensive action of pindolol. The reduction in peripheral resistance with pindolol is maintained, but attenuated during exercise (Lund-Johansen, 1983).

Airway function Most observations suggest that patients with hyper-reactive bronchi show similar falls in FEV_1 with pindolol and propranolol. The therapeutic response to β-adrenoceptor agonists may also be inhibited by pindolol (Benson *et al.*, 1977; Lammers *et al.*, 1985). Pindolol cannot, therefore, be considered safe in the asthmatic patient.

Effects on plasma lipids Pindolol shows little adverse effect on plasma lipid profiles. The average increase in triglycerides is less than 10%, and unlike full antagonists, pindolol increases HDL by about 10% (Weidmann *et al.*, 1985). Compounds with less PAA have an intermediate effect.

Effects on the β-adrenoceptor population In contrast to pure β-adrenoceptor blockers, pindolol down-regulates β_2-adrenoceptors in both atrial muscle and in lymphocytes, although atrial β_1-adrenoceptors show up-regulation expected from β_1-adrenoceptor blockade (Brodde *et al.*, 1988). These conflicting results are difficult to explain from the evidence that pindolol stimulates cardiac β_1-adrenoceptors in the resting state (McCaffrey *et al.*, 1987). The diver-

gent changes in receptor populations during therapy with pindolol could contribute to the reduced risk of withdrawal reactions compared with propranolol (Prichard & Walden, 1982).

The clinical implications of PAA

The different haemodynamic profiles of the various types of β-adrenoceptor partial agonist have consequences for clinical practice. Some important therapeutic indications for β-adrenoceptor blockers and potential unwanted effects which may be influenced by PAA are considered further here. Comparative efficacy of these drugs is summarised in Table 4.

Systemic hypertension

β-adrenoceptor blockers are established in the management of all forms of hypertension, although the mechanism of their antihypertensive action is still not fully understood (Oliver & Waller, 1988). PAA clearly influences the mechanism by which β-adrenoceptor blockers lower blood pressure. In particular, β_2-adrenoceptor PAA leads to reduction of resting peripheral resistance without lowering cardiac output which is a more physiological approach to treating hypertension than that offered by a pure β-adrenoceptor blocker. Whether this confers any advantage in clinical practice is unknown. Although pindolol and dilevalol have very different haemodynamic profiles compared with a full β-adrenoceptor blocker, they lower day-time blood pressure to a similar degree (Mann *et al.*, 1981; Schoenberger *et al.*, 1989). At night, however, when blood pressure normally reaches the nadir of its circadian variation, there is a less marked reduction with pindolol (Mann *et al.*, 1981), an observation of uncertain clinical significance.

A further potential benefit of PAA in hypertension is the lesser disturbance of the plasma lipid profile. It has been suggested that the lipid changes produced by β-adrenoceptor blockers may contribute to the failure of hypotensive therapy to reduce the incidence of coronary heart disease. Compounds with PAA might, therefore, have an impact on coronary risk.

The β_1-selective partial agonists show a very different profile; neither epanolol nor xamoterol have significant hypotensive properties (Leonetti *et al.*, 1985; Wilcox *et al.*, 1985).

Angina

Several mechanisms contribute to the anti-anginal actions of β-adrenoceptor blockers in exercise-induced ischaemia (Challenor *et al.*, 1989), but the most important of these is believed to be the reduction of exercise heart rate. Cardiac stimulation by a partial agonist may, therefore, reduce the anti-anginal efficacy of the agent. Despite a high level of PAA both pindolol (Dwyer *et al.*, 1982; Golightly, 1982) and xamoterol (Barrios *et al.*, 1986; Detry *et al.*, 1984) have anti-ischaemic actions. Comparative data with pure β-adrenoceptor blockers are not available for xamoterol, but pindolol is reported to be less effective in angina than atenolol (Magnani *et al.*, 1983; Quyyumi *et al.*, 1984). In particular nocturnal ischaemia with pindolol is more prolonged, possibly associated with the higher resting heart rate. However, epanolol possesses a similar degree of PAA to pindolol yet is probably as effective as propranolol or atenolol (Berkenboom *et al.*, 1987; Chambers *et al.*, 1987). β_2-adrenoceptor stimulation in the heart and peripheral vessels by pindolol could explain the different responses, but, arterial vasodilatation may be desirable in angina to reduce myocardial work (Challenor *et al.*, 1989). If stimulation of both β_1- and β_2-adrenoceptors in the heart is undesirable, the β_2-adrenoceptor selectivity of dilevalol may be advantageous. At present, there are no comparative data for dilevalol to test this hypothesis.

Reduced coronary perfusion pressure may be detrimental in patients with fixed coronary artery stenosis, leading to significant impairment of diastolic myocardial perfusion (Boden *et al.*, 1985). Most antagonist drugs reduce diastolic blood pressure, and this may be undesirable in normotensive patients with angina and in those with mild hypertension who require more than one drug to control ischaemic pain. Several studies have also suggested a J-shaped relationship between blood pressure and cardiovascular mortality in patients with treated mild hypertension. Impaired coronary perfusion at the lowest treated diastolic blood pressures could account for these observations (Cruickshank, 1988). Epanolol does not cause significant hypotension and may reduce the risk of coronary underperfusion in this situation. Studies are required to confirm whether there are real benefits in clinical practice.

Heart failure

In patients with marked impairment of left ventricular function the reduced cardiac output leads to a reflex increase in sympathetic drive. The consequent β-adrenoceptor down-regulation (Bristow *et al.*, 1986) blunts the cardiac response to catecholamines. Conven-

tional doses of β-adrenoceptor blockers in these patients will occupy the remaining receptors and frequently precipitate or worsen heart failure. However, small doses of β-adrenoceptor blocker have been successfully used to treat heart failure. Initiating treatment with as little as 5 mg of metoprolol daily followed by very gradual dose titration to modest levels under close clinical supervision leads to up-regulation of β-adrenoceptors which may improve the response to sympathetic stimulation during exercise (Engelmeier *et al.*, 1986; Swedberg *et al.*, 1979). Nevertheless, even minimal doses of a β-adrenoceptor blocker occasionally produce a low output clinical state, and this approach to treatment is not without its hazards (Anderson *et al.*, 1985; Jacob & Hafer, 1983).

By contrast, compounds with predominant β-adrenoceptor agonist activity such as prenalterol or full agonists like dobutamine are useful in the short-term management of heart failure (Rude, 1983). Unfortunately, the rapid development of tolerance limits their value for chronic use (Colucci *et al.*, 1981; Lambertz *et al.*, 1984) and probably reflects further receptor down-regulation (Colucci *et al.*, 1981). Arrhythmias and metabolic exhaustion of the myocardium also remain a major concern with this form of treatment (Katz, 1986).

Xamoterol has sufficient β_1-adrenoceptor stimulant activity to give useful, if moderate, haemodynamic improvements at rest and during submaximal exercise (Virk *et al.*, 1989). This is translated into significant improvements in symptoms and exercise tolerance in patients with mild or moderate degrees of heart failure (The German and Austrian Xamoterol Study Group, 1988; Waller *et al.*, 1989). Nevertheless, caution is necessary in patients with severe left ventricular impairment who rely on sympathetic drive to maintain cardiac output. In these patients, the β-adrenoceptor blocking action of the drug may cause marked deterioration (Ikaheimo & Takkunen, 1984).

Epanolol has not been studied in heart failure, but probably has too little PAA to be clinically useful. Similarly there are no data for dilevalol, but the vasodilatory action may partially offset cardiac depression.

Bradycardias and arrhythmias

Compounds with β_1-adrenoceptor PAA tend to cause less bradycardia than full antagonists and pindolol has been successfully substituted for atenolol when profound bradycardia was troublesome (James *et al.*, 1986). However, it is unusual for bradycardia at rest to require a change in treatment and compounds with β_1-adrenoceptor PAA should still be avoided in patients with a high degree of atrio-ventricular block.

Sympathetic stimulation can be arrhythmogenic, particularly in the ischaemic myocardium and β-adrenoceptor antagonists have been used successfully for the management of several supraventricular and ventricular arrhythmias (Upward *et al.*, 1988). It is possible, therefore, that compounds with PAA may be arrhythmogenic in some situations. Nevertheless, pindolol has been shown to suppress many forms of arrhythmia, although the few comparative studies indicate that pindolol may be less effective than propranolol (Arbab & Turner, 1971; Chiche *et al.*, 1972).

Xamoterol has not been widely studied as an antiarrhythmic but in combination with amiodarone it was more effective than metoprolol in suppressing sustained ventricular tachycardia (Paul *et al.*, 1989).

When added to digoxin for treatment of chronic atrial fibrillation, xamoterol reduces resting bradycardia but also limits the increase in heart rate during exercise (Molajo *et al.*, 1984; Sasayama *et al.*, 1986). This is a more favourable profile of heart rate control than is achieved with a combination of digoxin and a pure β-adrenoceptor blocker, which may cause marked nocturnal bradycardia.

There are few data on the antiarrhythmic activity of drugs with β_2-adrenoceptor selective PAA, such as dilevalol.

Peripheral vascular disease

In some patients, β-adrenoceptor blockers have adverse effects on the peripheral circulation leading to cold peripheries (Marshall *et al.*, 1976) or exacerbation of intermittent claudication (Rodger *et al.*, 1976; Smith & Warren, 1982). Both a fall in cardiac output which leads to a reflex peripheral vasoconstriction, and a loss of β_2-adrenoceptor mediated vasodilatation in skeletal muscle in the case of non-selective drugs may contribute to these problems.

Compounds with PAA may be less likely to cause cold peripheries (Marshall *et al.*, 1976) but data for pindolol are conflicting with reports of a lesser (Morgan *et al.*, 1974; Ohlsson & Lindell, 1981) or similar (Feleke *et al.*, 1983; Greminger *et al.*, 1983) incidence compared with pure β-adrenoceptor blockers. Cold extremities may be rather less frequent with dilevalol (Materson *et al.*, 1989) or epanolol (Chambers *et al.*, 1987).

One study reported that pindolol improved walking distance in hypertensive patients with

intermittent claudication; in these patients atenolol had no effect (Roberts *et al.*, 1987). There are no published data for newer agents.

Conclusions

β-adrenoceptor partial agonist activity, the ability to stimulate the receptor submaximally, has not conferred sufficient clinical advantages to non-selective partial agonists such as pindolol to encourage wide clinical acceptance. Indeed, pindolol may be less effective in angina and arrhythmia control than full antagonists. Recently, several compounds have been developed with greater selectivity in their agonist or antagonist potencies for either the β_1- or β_2-adrenoceptor subtypes.

Compounds with a high degree of β_1-adrenoceptor PAA, such as xamoterol and epanolol, but little β_2-adrenoceptor activity cause less reduction in resting cardiac output than pure β-adrenoceptor blockers. The high level of PAA possessed by xamoterol leads to improvement in left ventricular performance at rest and during exercise which may be of benefit in patients with left ventricular dysfunction and mild to moderate degrees of heart failure. Tolerance due to receptor down-regulation is less likely with a partial agonist than with a full agonist, although in severe heart failure the β-adrenoceptor blocking activity of xamoterol may be detrimental. Both epanolol and xamoterol have anti-ischaemic actions, and despite PAA epanolol appears to be as effective as full β-adrenoceptor blockers. The lack of a hypotensive effect may also reduce the risk of coronary hyperperfusion in normotensive patients with angina.

Dilevalol with β_2-selective PAA and compounds with non-selective PAA such as pindolol are effective hypotensive agents comparable with pure β-adrenoceptor blockers, but achieve this goal in a more physiological manner by maintaining resting cardiac output and reducing peripheral resistance. They also cause less disturbance of the plasma lipid profile which may contribute to lowering the risk of coronary disease in hypertensive patients. The consequences of the selective β_2-adrenoceptor PAA of dilevalol in angina are unknown, but may be more favourable than non-selective PAA.

There are few data on the use of these newer agents in treating arrhythmias, and little evidence of important clinical differences from pure β-adrenoceptor blockers in patients with asthma or peripheral vascular disease.

The presence of selective PAA clearly modifies the haemodynamic consequences of β-adrenoceptor blockade and the potential advantages of the individual profiles of the newer drugs deserve further study.

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