Regular Review

Which beta blocker?

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Nine beta adrenoceptor blocking drugs are currently marketed in Britain with one further compound possessing both alpha and beta adrenoceptor blocking activity. Several of these drugs are constituents of fixed dose combinations with diuretics; slow release formulations of several beta blockers are also marketed. The aim of this review is to discuss whether the differences between beta blockers are clinically important or merely represent marketing ploys used for advertising purposes by the pharmaceutical industry.

A therapeutic agent is judged on two scores—efficacy and toxicity. Beta blockers pose problems because of their diverse clinical indications and the heterogeneity of their side effects. Assessment of risk versus benefit has to take account not only of the nature of the primary disease for which beta blockers are prescribed but also of any other disorders from which the patient may suffer. For example, a patient with angina may also have asthma, a patient with hypertension may have associated peripheral vascular disease, and a patient with a cardiac arrhythmia may also be on the verge of heart failure.

Lipid solubility

Relative lipid solubility is one of the most important properties of beta blockers, and this can be measured by the extent to which the drug partitions between an organic solvent and water. Propranolol, oxprenolol, metoprolol, and timolol are the most lipid soluble beta blockers, and the least lipid soluble (and hence the most water soluble) are atenolol, nadolol, and sotalol, with acebutolol and pindolol occupying intermediary positions.¹ The more lipophilic the beta blocker the more rapid and complete its absorption from the gastrointestinal tract is likely to be²—and the more likely it is to be extensively metabolised in the gut wall and liver (the so called “first pass effect”)³ and to be eliminated rapidly. Variations between patients in rates of metabolism as a determinant of differences in response are thus more likely to occur with the relatively lipid soluble members of the group,⁴ as are drug interactions due to inhibition of hepatic drug metabolism—for example, with cimetidine.⁵ Lipophilic beta blockers will also gain access to the brain, and, with it, bring the likelihood of producing central nervous system side effects such as bad dreams. Muscle fatigue produced by beta blockers is an extremely common but complex adverse effect; there is no good evidence that it is related to their degree of lipid solubility.

Water soluble beta blockers tend to be eliminated un-

changed by the kidney and to have longer half lives in plasma, and will thus tend to accumulate in renal failure with the attendant risks of exaggerated effects. With respect to drug efficacy there is no evidence that high lipid solubility increases the ability of the beta blocker to control blood pressure, prevent angina, or stop cardiac arrhythmias. Currently the most convincing evidence for the secondary prevention of ischaemic heart disease has been shown with propranolol, timolol, and metoprolol,⁶ all of which are relatively lipid soluble, but this assessment may change as newer studies are reported. The emergency management of thyrotoxicosis can be achieved with beta blockers irrespective of their lipid solubility.

Cardioselectivity

A second pharmacological property on which extensive therapeutic claims are based is cardioselectivity. Beta adrenoceptors do not constitute a homogeneous population.⁷ Tissues such as the heart, parts of the eye responsible for production of aqueous humour, and the renin secreting tissues of the kidney contain a preponderance of beta₁ adrenoceptors, whereas bronchial tissue, peripheral blood vessels, the uterus, and the insulin secreting tissue of the pancreas contain beta receptors principally of the beta₂ subgroup.⁸ None of these tissues contains exclusively one subgroup of receptors, and all tissues contain blood vessels supplied with beta₂ adrenoceptors. Furthermore, the beta receptor population is not static and can be modified dramatically by drugs—beta blockers themselves cause an increase in the number of receptors,⁹ and beta stimulants decrease them.¹⁰ The number decreases with age.¹¹ The effect of various diseases on numbers of beta adrenoceptors is not clearly understood.

Since all currently available beta blockers antagonise beta₁ adrenoceptors competitively all can be used to block cardiac beta adrenoceptors and thus be used to prevent angina or cardiac arrhythmias (though there are minor differences in the electrophysiological effects of different drugs). All beta blockers can be used to decrease the formation of aqueous humour and therefore be used to lower intraocular pressure. Though the basis on which beta blockers lower blood pressure is not fully understood and there are complex pharmacological arguments that cardioselective beta blockers might be more effective antihypertensive agents,¹² practical clinical experience is against this. Both cardioselective and non-selective beta blockers appear to lower blood pressure equally.

Where controversy abounds—and facts and fallacies become

intermixed—is in the relevance of cardioselectivity to the adverse effects produced by beta blockers. The basis of this confusion merits discussion. Firstly, cardioselectivity is a concept based on in vitro pharmacological testing; to extrapolate it widely to intact man—especially with disease—is not possible. Secondly, as mentioned above, no tissue possesses exclusively one type of beta adrenoceptor, merely a preponderance of one subgroup. Thirdly, cardioselectivity is not only a relative but also a dose dependent phenomenon; this can best be illustrated with respect to the bronchi.

Healthy volunteers and even asthmatics in remission, whose bronchial calibre is independent of sympathetic drive, tolerate blockade of beta₂ adrenoceptors with little or no change in ventilatory function.¹³ Any safety assessment of a beta blocker based on studies in these people may be quite misleading. When the bronchial calibre is highly dependent on sympathetic tone, as happens in the asthmatic during an attack, even a cardioselective beta blocker may possess enough beta₂ adrenoceptor blocking activity to precipitate severe bronchospasm, and this attribute becomes more evident as the dose of the beta blocker is increased.¹³ The one saving grace of having precipitated asthma with a cardioselective beta blocker is that a selective beta₂ agonist such as salbutamol or terbutaline is more likely to reverse the bronchospasm quickly than when a non-selective blocker has been used. Clinicians need to remember that at high doses (or high plasma concentrations) of cardioselective beta blockers beta₁ selectivity is less than at low doses (or low plasma concentrations). To obtain the maximum benefit of cardioselectivity in patients at risk the clinician should keep the dose of the cardioselective beta blocker as low as possible.

Muscular fatigue and intermittent claudication are common side effects in patients given beta blockers. The effect of beta blockers on the peripheral circulation is due both to a direct effect on beta₂ adrenoceptors in the vessel wall and to an indirect reflex constriction mediated by alpha adrenoceptors in response to the diminution in cardiac output which all beta blockers produce.¹⁴ Cardioselectivity is thus not the only determinant of which beta blocker will diminish muscle blood flow resulting in intermittent claudication and also cold extremities. The symptom of cold peripheries is difficult to evaluate, and its incidence depends greatly on the methods used to elicit adverse effects. A well designed comparative study has, however, shown that propranolol (non-cardioselective) reduced skin temperature, skin blood flow, and resting muscle blood flow while metoprolol (cardioselective) did not.¹⁵ In theory, a drug such as labetalol which possesses both alpha blocking and beta blocking activity might be expected to produce less peripheral circulatory disturbance than conventional beta blockers, but unfortunately there are no good comparative clinical data.

The problem of impaired exercise performance produced by beta blockers has recently been reviewed in the *BMJ*.¹⁶ Since skeletal muscle fibres are mainly supplied by beta₂ adrenoceptors it might be predicted that cardioselective blockers would be less likely to cause such problems. Though some reports would support this¹⁸ it has not been the universal experience,¹⁸⁻¹⁹ possibly because exercise performance depends not only on the efficiency of muscle contraction itself but also on cardiac output, limb blood flow, and accumulation of products of oxidative metabolism. Hypoglycaemia induced by exercise is, however, more likely to occur with a non-selective blocker such as propranolol than a cardioselective agent such as atenolol²⁰ for reasons which are discussed below.

Nadolol, a non-cardioselective beta blocker has been claimed to increase renal blood flow.²¹ This renal vasodilator effect (for this is the assumed basis) is presumably unrelated to its beta blocking action, for nadolol lowers cardiac output like any other beta blocker. Nadolol has a structural similarity to dopamine, a renal vasodilator,²² and this may be the basis for its renal vasodilator action.²³ Recent comparative studies of nadolol and atenolol on renal function have cast doubt on the uniqueness of this finding and even its occurrence in patients with impairment of kidney function.²⁴⁻²⁵

Apart from the side effects related to bronchial calibre, peripheral blood flow, and exercise capacity, the main relevance of cardioselectivity is its effect on carbohydrate metabolism. Beta₂ adrenoceptors mediate secretion of insulin after a glucose load.²⁶ This raises several interesting questions about beta blockade. Firstly, does prolonged administration of beta blockers increase the risk of developing diabetes? The answer appears to be no, irrespective of the selectivity of the drug.²⁷ Secondly, will long term beta blockade in an established diabetic cause deterioration in control? There is little evidence to suggest this, but it is a matter of continuing study. What is clear, however, is that the response to hypoglycaemia can be greatly influenced by beta blockers, and beta₁ selectivity may confer advantages when beta blockers are given to the labile diabetic. The recovery of blood sugar from insulin induced hypoglycaemia is produced by both glycogen breakdown, which is mediated through alpha adrenoceptors, and gluconeogenesis, which is mediated through beta₂ adrenoceptors in the liver.²⁸⁻²⁹ Thus a beta blocker which does not block beta₂ adrenoceptors, would have an advantage. Furthermore, the diabetic on beta blockers will be less able to recognise the autonomic responses associated with hypoglycaemia—sweating, tachycardia, pallor, and tremor. The haemodynamic disturbances accompanying hypoglycaemia may be profound, and selective beta blockers do not impair the warning tachycardia induced by low blood sugar or cause the rise in blood pressure to the extent that a non-selective blocker may do.³⁰⁻³¹

In summary, cardioselectivity is a property of limited clinical relevance with respect to efficacy but perhaps of slightly more importance with respect to toxicity. Atenolol, metoprolol, and acebutolol possess beta₁ selectivity (and the selectivity of acebutolol with respect to the peripheral blood vessels is not clear).³²

Partial agonist activity

The term partial agonist activity (formerly called intrinsic sympathomimetic activity) may itself seem paradoxical. How can a molecule such as a beta blocker both stimulate and block a receptor at the same time? The beta adrenoceptor is a small region of the cell surface membrane which combines with a drug. Three major parts of the molecule of the beta stimulant isoprenaline are important for its combination with the receptor.³³ When present in sufficient concentration isoprenaline will evoke a maximum response since it stimulates all the receptors with which it combines. Modification of one of these sites of attachment on the drug results in a structure which is not optimal for occupation of the receptor, and thus activation of the receptor is slow and inefficient; even when all receptors are occupied the maximum response will be less than that produced by the full agonist isoprenaline, though this does depend on the level of sympathetic activity at the

time of drug administration. Since this modified compound with partial agonist activity must combine with the receptor to produce its albeit smaller pharmacological effect, the access of other molecules to the receptor will be prevented, and thus the pharmacological effect of a partial agonist is not only that of stimulation but of receptor occupation—that is, blockade. The blocking activity of partial agonists such as salbutamol is of minor importance since their stimulatory activity predominates and is sufficiently pronounced to exert beneficial therapeutic effects—for example, in asthma. On the other hand, the intrinsic activity of pindolol is too weak to be of use in obstructive lung disease, but it is sufficient to modify the frequency and severity of side effects which may occur as a result of beta adrenoceptor blockade. Novel beta blockers with very large partial agonist activity are currently under trial, and these may even be of value in treating heart failure in man.³⁴ Currently available beta blockers which do possess partial agonist activity are (in descending order of potency) pindolol, oxprenolol, and acebutolol.

Partial agonist activity has usually been demonstrated by showing an increase in heart rate in animals which have both had a vagotomy and been depleted of catecholamines,³⁵ and not in man, especially one with cardiovascular disease. How far, therefore, does partial agonist activity matter in clinical practice? Firstly, let us consider beta₁ mediated effects. Most studies show that beta blockers possessing partial agonist activity tend to have less effect on resting heart rate and cardiac output than beta blockers without this property.³⁶ In conditions of increased sympathetic drive, such as exercise, the effects of partial agonist activity are overwhelmed, and beta blockers possessing partial agonist activity act as full antagonists. Much the same applies with beta₂ mediated effects. Since there is relatively little sympathetic tone in bronchial muscle at rest beta blockers have relatively little effect on bronchial tone, irrespective of whether they possess partial agonist activity (or cardioselectivity, as we have seen above). If beta blockers are administered when bronchi are under the effect of beta₂ stimulation—that is, in the asthmatic during an attack—there is no evidence that partial agonist activity confers any benefit.³⁷ In blood vessels partial agonist activity is of no importance in modifying beta blocking effects on muscle blood flow during exercise, though at rest a beta blocker with partial agonist activity may have less effect on decreasing forearm blood flow than a beta blocker without this property.³⁸

Published clinical reports can be culled to produce many interpretations of the importance of partial agonist activity. In hypertension two comparative studies using maximal doses showed that propranolol (which does not possess partial agonist activity) produced a 3–4 mm Hg greater fall in supine and standing blood pressure than oxprenolol (which does possess partial agonist activity).^{39–40} Furthermore, a paradoxical increase in blood pressure may occur with the use of larger doses of beta blockers with more marked partial agonist activity—for example, pindolol.⁴¹ One might predict that partial agonist activity might detract from the antianginal properties of a beta blocker. Classical angina, however, is invariably associated with increased sympathetic drive, and again, in these conditions, partial agonist activity is swamped, rendering the agent a full antagonist. Thus beta blockers with partial agonist activity are effective antianginal agents.⁴² Beta blockers have been shown to exert a beneficial effect after myocardial infarction, and, as already discussed, the most convincing current evidence exists for the drugs propranolol, timolol, and metoprolol,⁶ none of which has

appreciable partial agonist activity (and which are relatively lipid soluble). These beta blockers are also effective in reducing the peripheral manifestations of thyrotoxicosis,⁴³ probably more effectively than those with partial agonist activity.

In terms of adverse effects beta blockers possessing partial agonist activity will cause less resting bradycardia than other beta blockers, but there are very few instances when the bradycardia induced by beta blockers is harmful, being far more likely to cause concern to the doctor than to the patient. The incidence of heart failure has been shown to be similar and small in two large studies in patients with hypertension treated with either propranolol or oxprenolol.^{44–45} There is evidence that beta blockers possessing partial agonist activity are less likely to cause cold hands and feet and worsen Raynaud's phenomenon, and this property appears to be more important than cardioselectivity in determining skin blood flow.³⁸ The effects on exercise capacity are less clear, and good comparative data are needed on the long term effects of various beta blockers on blood flow in the limbs. Beta blockers have recently been shown to increase plasma triglycerides, decrease concentrations of high density lipoproteins and increase concentrations of low density lipoproteins.⁴⁶ These changes may constitute a coronary risk factor. Pindolol, with high partial agonist activity, does not produce this detrimental pattern,⁴² and non-selective blockers such as propranolol and oxprenolol increase serum triglycerides more than cardioselective agents.⁴⁸ Assessment of the importance of the lipid abnormalities induced by beta blockers is difficult when their overall effect may be to decrease the incidence of ischaemic heart disease by other mechanisms.

Membrane stabilising activity

The fourth and final property is membrane stabilising activity. Drugs showing this activity reduce the rate of rise in cardiac action potential and produce other electrophysiological changes. Any therapeutic importance of this activity has been largely discounted since effective membrane stabilising activity is seen with beta blockers only at doses 100 times the accepted therapeutic range.⁸

Conclusions

It is easy to dismiss the differences between beta blockers. Their most important attribute is to block beta adrenoceptors competitively. Whereas there may be no great differences in therapeutic efficacy the profiles of adverse effects do differ between different blockers, and these differences can be used to the individual patient's benefit. The medicinal chemist can now manipulate the beta blocker molecule to exaggerate specific properties, and one awaits keenly the imminent arrival of a new generation of beta blockers whose therapeutic profiles may be quite different from those of today's agents.

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