Are Selective Beta-Adrenoceptor Blocking Drugs an Advantage?

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Beta-adrenoceptor blocking drugs (beta-blockers) are widely used in the treatment of hypertension, angina pectoris and a variety of other disorders. When given in equipotent doses, determined by their ability to reduce exercise- or isoprenaline-induced tachycardia, the members of this group of drugs achieve comparable reduction of blood pressure and anginal pain. Some are relatively cardioselective (β1-selective), some possess partial agonist activity, and they also differ in terms of cost, duration of effect and route of elimination. Since many of the adverse reactions to beta-blockers are produced by their effects on receptors other than those in the heart, the possession of relative cardioselectivity may be considered a particularly important property.

The aim of this review is to determine the basis of selectivity and its relevance. Initially, the nature of the receptors and the methods of determining their site and function will be described. Thereafter, the potential and demonstrable advantages of relatively selective beta-blocking drugs will be considered in terms of their tendency to cause less unwanted effects on respiratory function, carbohydrate metabolism, the peripheral arteries and at other sites.

The Basis of Selectivity

Ahlquist in 1948[1] first divided the adrenergic receptors into alpha and beta. Alpha receptors show a typical potency order for the agonists of adrenaline>noradrenaline>isoprenaline, and beta receptors a potency order—isoprenaline>adrenaline>noradrenaline. Subsequently, Lands and his colleagues[2] subdivided the beta receptors. Beta 1 receptors show an equal affinity for adrenaline and noradrenaline and are found in the heart and adipose tissue. Beta 2 receptors show a greater affinity for adrenaline and are found, for example, in skeletal and smooth muscle and liver. It is easy to derive from this an over-simplified concept which suggests that in a particular tissue there will be either β1 or β2 receptors and that a selective agonist or antagonist will only act on a tissue with the appropriate receptors, i.e. a selective β1 antagonist will only act on the heart which contains β1 receptors. This is not correct.

Over the last decade advances in the investigation of beta-adrenergic receptors have been made possible by studying the pharmacological effects of selective and non-selective agents on single tissues[3] and their capacity to produce cyclic AMP, the mediator of the response to beta receptor stimulation[4]. Of particular value has been the use of radiolabelled beta receptor agonists and antagonists[5]. Our understanding based on the use of these techniques can be summarised as follows—

1. There are only two types of beta receptors[6], although the possibility of more than two has been suggested.
2. The tissues that have been studied contain predominantly, but not solely, one type of receptor[3,4].
3. Non-selective agonists and antagonists bind with equal affinity to either receptor. Selective agents will also bind to both receptors but have a much greater affinity to one receptor and a much lesser affinity to the other[6]. Thus, in the cat, the non-selective propranolol will block isoprenaline-induced tachycardia, vasodilation and bronchial relaxation at about the same concentration. The selective blockers atenolol and metoprolol require 14 and 32 times greater concentrations respectively to block the vasodilation and 20 and 50 times to prevent bronchial relaxation[3].
4. Beta-receptor density in any tissue is not static[5]; beta-blockade[7] increases and age decreases it[8].

Some beta-blockers may therefore be considered relatively but not completely β1-selective. These are atenolol, metoprolol and perhaps acebutolol[9]. *In vitro* and animal studies suggest that these selective drugs, when given to man, should have much less effect on those tissues which contain mainly β2 receptors unless the dose is very large.

Clinical Relevance of Selectivity

Respiratory Function

The stimulation of both adrenergic and cholinergic receptors influences airway resistance. The adrenergic system is probably more important, beta stimulation causing bronchial dilation and alpha stimulation causing bronchoconstriction[10]. Beta-blockers might therefore be expected to oppose sympathetically-induced bronchodilation and be harmful to asthmatics. Early experience with propranolol indicated that this was so[11,12]. The observation that beta receptors in the bronchi are mainly,

but not solely, $\beta 2$, stimulated the search for a $\beta 1$-selective blocker. Practolol was produced and seemed able to inhibit the effects of isoprenaline on the heart, with little effect on sympathetically-induced bronchodilation[13]. Since then the oral form of practolol has been withdrawn because it caused adverse reactions involving the eye, skin, peritoneum and other sites[14]. However, newer relatively selective beta-blockers are available and should theoretically reduce the risk of airways obstruction due to blockade of $\beta 2$-mediated bronchodilation. Alternatively, it may be possible to reduce this risk either by administering beta-blockers with some partial agonist activity (PAA) that might have some intrinsic bronchodilating effect, or by blocking alpha-mediated bronchoconstriction by giving a combined alpha + beta-blocker.

Investigations into the relative merits of cardioselectivity, partial agonist activity and alpha-blocking potential present problems to the investigator. Since beta-blockers are known to be potentially harmful to asthmatic subjects, their deliberate administration may be ethically unacceptable. Moreover, patients with asthma do not behave as a homogeneous group; many will tolerate beta antagonists without difficulty, a few develop severe bronchoconstriction[15,16]. Because of these problems, studies have been carried out on normal volunteers using exercise- or isoprenaline-induced bronchodilation as the action to be opposed[17]. Such studies do provide information, but they need to be performed with care and their results interpreted with caution[18].

Selective Antagonists and Respiratory Function. Most studies in healthy volunteers have failed to show a convincing difference between the effects of selective and non-selective beta-blockers on airway conduction during exercise[9,17]. On the other hand, some studies in hypertensive patients with no respiratory symptoms have demonstrated that, when taking metoprolol as opposed to propranolol, there is a less marked effect on FEV_1[19], maximal mid-expiratory flow rate[20] and peak flow at rest and on exercise[21].

Studies on patients with obstructive airways disease have compared metoprolol, atenolol, propranolol and practolol and have shown that the selective drugs are less likely to affect lung function adversely. Metoprolol was first evaluated in Scandinavia and compared with propranolol after intravenous dosing[22], and with both propranolol and practolol after oral dosing[23,24] to asthmatic subjects. Whilst the intravenously administered drugs achieved a comparable reduction in heart rate, metoprolol had less effect on FEV_1 (mean absolute reductions in FEV_1 being: placebo 0.04, metoprolol 0.12 and propranolol 0.20 litres) and did not appear to modify the increasing FEV_1 in response to increasing doses of isoprenaline, whereas propranolol did. These results were confirmed in the oral study and metoprolol was shown to be as selective as practolol, and neither impaired isoprenaline-induced bronchodilation. This advantage over propranolol has been confirmed in patients with chronic airways obstruction[25,26].

The intravenous type of 'provocation test' has been used to assess selectivity in two Scottish studies. In one group of 12 asthmatic subjects[27] and another group of 10 cigarette smoking bronchitics[28], intravenous doses of placebo, metoprolol and propranolol were given. The active drugs had similar effects on heart rate but the mean reduction in FEV_1 on metoprolol was significantly less (placebo 0.06, metoprolol 0.28 and propranolol 0.44 litres[27]).

Evidence from a number of different centres using double blind techniques shows that in terms of potential respiratory dysfunction, metoprolol is preferable to propranolol and gives results similar to those of practolol. In each case, metoprolol caused some deterioration in lung function, which one would have predicted, but less than that caused by a non-selective agent. Furthermore, and of clinical importance, any airways obstruction could be overcome by the use of a $\beta 2$-agonist.

Data on atenolol may be obtained from a series of studies published by two groups from Southampton and Wythenshawe[16,29-31]. In these, atenolol was compared with a variety of other beta-blockers, including selective and non-selective antagonists and two with partial agonist activity. In each case, atenolol was shown to cause least disturbance to respiratory function and, taken together, these papers present a formidable demonstration of the selectivity of atenolol. However, the extremely 'good' results are in part explained by two factors. First, the patients were subdivided into responders, who showed more than a 20 per cent fall in FEV_1 in response to one of the beta-blockers, and non-responders. When this technique was used in one study, both groups showed a comparable response to isoprenaline, and the results for the whole group were not so impressive as those of the responder group alone[16]. Secondly, in another study[30], the reduction in FEV_1 after atenolol was less than that after placebo and the response to isoprenaline was greater. This is difficult to understand, since we know that there are some $\beta 1$ receptors in the lung[6]. These anomalous results appear to be the result of a low pre-treatment FEV_1 attained by the patients before atenolol was given, as noted by Johnson and Clarke[32], who found in their own study that atenolol and metoprolol gave similar results. As the same group received all drugs in random order[30], it might have been fairer to note that the mean FEV_1 values two hours after dosing were: metoprolol 1.78, propranolol 1.70, atenolol 1.75 and placebo 2.15 litres. This indicates that all beta-blockers may adversely affect pulmonary function, but the selective drugs do so less. Other studies confirm these results and have shown that atenolol causes less pulmonary disturbance than propranolol[33], is comparable or even preferable to practolol[34] and comparable to metoprolol[35]. Atenolol can therefore be regarded as a selective agent with sparing of the bronchi to an extent that is statistically significant and probably clinically relevant. Data on long-term administration to a large group of bronchitic patients are not available.

Acebutolol is also a selective beta-blocker, but theoretically has the added advantage of possessing partial agonist activity[9]. There is, however, less data on this drug. When given intravenously to healthy individuals in

a dose producing a comparable reduction in exercise-induced tachycardia, it caused less reduction in FEV_1 than propranolol[36]. In asthmatic subjects, oral acebutolol (100-200 mg) has been shown not to differ from placebo in terms of its effects on respiratory function[37], and to cause the same slight reductions in FEV_1, FVC and peak flow rates as practolol[38].

The reduction in FEV_1 is less after acebutolol than after propranolol and there appears to be an unimpaired response to isoprenaline[39]. Furthermore, the FEV_1 two hours after beta-blockade and following isoprenaline administration is only slightly less than that after placebo.

It would seem that if a bronchitic patient requires a beta-blocker, a selective agent is preferable on theoretical grounds, on the evidence of short-term studies and also because these agents do not materially impair the response to $\beta 2$-stimulants that can and should be used if wheezing develops.

Partial Agonist Activity (PAA or ISA). Some beta-blockers such as oxprenolol and pindolol possess partial agonist activity and it has been suggested that this may be as important as cardioselectivity in reducing the risk of beta-blocker-induced airways obstruction. In healthy volunteers propranolol significantly reduces exercise-induced bronchodilation, whereas oxprenolol and pindolol, in doses which produce a comparable reduction in exercise heart rate, do not[40]. However, the effects are relatively small. Studies in patients have not convincingly demonstrated that drugs with partial agonist activity are safer in people with obstructive airways disease. After intravenous doses, oxprenolol[41], and pindolol[42], caused a deterioration in respiratory function tests and in another study pindolol was found to cause more bronchoconstriction than practolol[43].

In the clinical situation the value of PAA remains unproven as far as respiratory function is concerned and it would seem that non-selective beta-blockers, with or without PAA, will impair the response to bronchodilators[42,44].

Alpha Blockade. There are also alpha receptors in the bronchial tree[45]. Their role in healthy individuals and in patients with bronchial asthma is not fully understood. However, stimulation of these receptors causes bronchoconstriction in exercise-induced asthma[46] and histamine sensitivity[47]. In these situations, alpha blockade may reduce the amount of airways obstruction[47], although alpha-blockers have not found a place in the routine treatment of asthma. Nevertheless, there is a possibility that a drug which blocked both alpha and beta receptors might have less effect than a 'pure' beta-blocker on respiratory function. Labetalol does block alpha and both $\beta 1$ and $\beta 2$ receptors[48,49] and has been suggested as an alternative for patients with respiratory problems. An early study in asthmatic subjects using intravenous dosing showed that propranolol reduced FEV_1 and labetalol did not[50]. Data on clinical studies in patients with respiratory disorders and information on responses to bronchodilators whilst on labetalol are still awaited.

Carbohydrate Metabolism

The role of catecholamines and the autonomic nervous system in maintaining carbohydrate homeostasis is complicated. The possible effects of beta-blockers include the release of insulin in response to a rise in blood sugar levels, the metabolic response to a fall in blood sugar, and the haemodynamic and other responses to hypoglycaemia that make the patient aware of his predicament.

Hyperglycaemia. It has been known for many years that adrenaline increases blood sugar levels by its action on the liver and peripheral tissues. When insulin assays became available, the effects of catecholamines on insulin secretion could be investigated, and it was shown that the beta-stimulant, isoprenaline, increased insulin secretion[51]. It was subsequently shown[52] that the increase in insulin secretion could be prevented by propranolol but not by the $\beta 1$ selective antagonist, practolol. This suggested that a $\beta 2$ receptor was involved, which was confirmed in animal studies by demonstrating that salbutamol, a selective $\beta 2$-stimulant, also enhanced insulin release[52,53]. More recently, terbutaline, another selective $\beta 2$-stimulant, has been shown to enhance insulin secretion in man[54].

The evidence suggests that a $\beta 2$ adrenoceptor mechanism may mediate enhanced insulin secretion in response to a glucose load. This possibility poses two questions with respect to beta-blocker therapy. First, will these drugs increase the risk of patients developing diabetes? The answer appears to be no[55]. Secondly, will their administration to known diabetics cause a significant deterioration? There is relatively little to suggest that they seriously disturb diabetic control, though they may cause a deterioration in some patients[56,57].

The potential advantages of using a selective drug are still being investigated. Waal-Manning[58] has shown that some diabetics improve when changed from a non-selective to a selective beta-blocker. This was particularly well shown in one patient who had four glucose tolerance tests, two on metoprolol and two on oxprenolol. Subsequently, Wright and colleagues[57] studied a group of maturity onset diabetics on diet and oral therapy. Metoprolol and propranolol both caused a small rise in mean blood sugar levels and those on propranolol were slightly higher.

The effect of beta-blocker therapy on glucose tolerance is not yet clear. Although there is evidence to suggest that a $\beta 2$ receptor mechanism is involved in the enhancement of insulin secretion, clinical data showing a convincing advantage for the selective beta-blockers have not yet been produced.

Metabolic Response to Hypoglycaemia. When hypoglycaemia is induced by insulin administration, the blood sugar concentration falls to a nadir after 25 minutes and then starts to rise, initially fairly rapidly and then more slowly. Garber and colleagues[59] showed that the initial recovery phase is produced by glycogenolysis and the second by gluconeogenesis. Both processes are stimulated by the release of adrenaline, which occurs when the blood

sugar falls, and which stimulates cyclic AMP in the liver. The adrenergic mechanism may not be the only factor in restoring the blood sugar to normal[60], and adrenoceptor blocking drugs might therefore be expected to modify rather than prevent the response to hypoglycaemia.

Investigations into the nature of adrenoceptors in the liver suggest that glycogenolysis is mediated by an alpha receptor and gluconeogenesis by a beta receptor[61]. Data on the beta receptor in man are largely based on the blood sugar responses to selective agents. Non-selective antagonists tend to impair the recovery from hypoglycaemia, whilst selective β2-stimulants such as salbutamol[62] and terbutaline[54] cause a rise in the blood sugar. A β2 receptor, therefore, appears to play some part in glucose production from the liver and perhaps other sites. A β2-blocking drug might be expected to impair the response to insulin-induced hypoglycaemia and reduce the ability to mobilise glucose during exercise and periods of starvation.

In 1966, Abramson and his colleagues[63] showed that propranolol delayed the recovery from intravenously administered insulin. More recent studies in healthy volunteers have confirmed this effect of propranolol but have also shown that if atenolol, acebutolol or metoprolol are given, the delay in recovery from insulin-induced hypoglycaemia is either less marked or undetectable[64-67].

Similar studies have been performed in diabetic patients. The differences between the various beta-blockers and placebo were relatively small in those on oral agents[68], whereas in insulin treated diabetics recovery was not significantly impaired by metoprolol but it was by propranolol[61]. Although these observations suggest that some diabetic patients on insulin therapy might be at greater risk of suffering from hypoglycaemic attacks, there is no evidence of this happening in practice. It remains a theoretical possibility requiring further observation.

The release and production of glucose is also part of the response to periods of starvation. This may be important to any patient on beta-blockers, but it is particularly relevant to any who may be starved for a surgical procedure. There are several reports of patients who have had severe hypoglycaemic reactions during periods of starvation whilst on propranolol. This is a difficult subject to study and quantitate. Gold *et al.*[69] reviewed the literature and appeared to show an effect of propranolol on alanine utilisation during starvation. The possibility that selective beta-blockers are less likely to be associated with hypoglycaemia during periods of starvation remains to be investigated.

During exercise, glucose is utilised to provide energy, and hypoglycaemia may therefore occur. There is some evidence, in patients on propranolol, of a tendency for the blood sugar to fall lower than in those not receiving beta-blockers[70]. Linton *et al.*[71] and Franz and Lohmann[72] found that selective beta-blockers are also associated with a greater degree of hypoglycaemia than occurs with placebo, but their effect is slower and less marked than that of a non-selective drug.

Autonomic Responses to Hypoglycaemia. The development of hypoglycaemia causes a feeling of hunger, tremor, pallor and sweating, and there are haemodynamic changes, including a tachycardia, a rise in systolic pressure and a fall in diastolic pressure. The haemodynamic effects are significantly modified by propranolol in volunteers[73]. Since these effects are produced by adrenaline, selective drugs would be expected to have less effect on sympathetically-induced vasodilatation. Smith *et al.*[61] showed that in diabetic patients who were hypoglycaemic during selective blockade, the increase in heart rate and systolic pressure was less marked and, instead of falling, the diastolic pressure tended to rise a little. On the other hand, propranolol caused a fall in heart rate and a marked rise in diastolic pressure (mean 17, maximum 40 mm Hg). In addition, one of the seven patients on propranolol suffered from severe bradycardia (less than 30 beats per minute) and had to be resuscitated. The relevance of these responses to intravenous insulin to the routine management of diabetics receiving subcutaneous insulin is still being evaluated. Some feel that the potential hazards of beta-blockade have been over-estimated, particularly as the sweating may be even more marked than when not on beta-blockers, making the hypoglycaemic attack easily recognisable[74], whereas others feel that there is already a case for preferring a selective agent when treating diabetics[75,76].

Peripheral Arteries

The haemodynamic response to stimulation of the beta receptors by adrenaline or isoprenaline includes tachycardia, a rise in systolic and a fall in diastolic pressure, and an increase in limb blood flow[77,78]. According to the Lands classification[2], the first two effects are mediated by β1 receptors, the latter two by β2 receptors. The validity of this classification has been confirmed by studies in which the actions of catecholamines have been counteracted by treatment with selective and non-selective beta antagonists. Whilst all beta-blockers will attenuate the rise in pulse rate and systolic pressure, non-selective drugs may prevent or reduce both the fall in diastolic pressure and the increase in peripheral blood flow in response to adrenaline[77,79], and isoprenaline[78]. In these studies metoprolol, and in another study atenolol[80], have been shown to have less effect on diastolic pressure and muscle blood flow. In this context acebutolol may behave as a selective antagonist at low doses[80], although some[81], have suggested that acebutolol does not spare the peripheral vascular β2 receptors. The response of these β2 receptors and the differences in the haemodynamic actions of non-selective and selective beta receptor antagonists are thus fairly well established. The next step is to consider the potential relevance of these observations.

Role of β2 receptors in Peripheral Arteries. Many factors influence the flow of blood through the limbs. Although changes in tone in the peripheral vessels may appear to be important, peripheral perfusion is probably more depen-

dent on the cardiac output and the extent and severity of arteriosclerosis in the larger vessels. The changes in tone which do occur will depend partly on the amount of alpha-mediated vasoconstriction and β2-mediated vasodilation. In addition, there are often locally released mediators that may be very potent vasodilators, particularly when the tissues are ischaemic. Therefore, drugs that oppose the β2-mediated vasodilation can only modify, rather than control, the blood flow. Furthermore, beta-blocking drugs may exert a greater effect by reducing cardiac output and also by an alpha-blocking potential that some of them possess.

Selective and Non-selective Agents in Blood Pressure Control. There is some evidence to suggest that selective beta-blocking drugs are more effective at reducing diastolic blood pressure at rest than non-selective agents given in comparable doses[82]. There is, however, more evidence to suggest that selective and non-selective agents are equally effective. Data on blood pressure control during stress and exercise are limited and not easy to interpret. Studies on individuals subjected to the stress of doing mental arithmetic, which caused a rise in heart rate and systolic and diastolic blood pressure, demonstrated a comparable response to pre-treatment with a selective and a non-selective beta-blocker[83]. However, in a simulated driving test, propranolol was associated with a significant rise in diastolic pressure, whereas the small rise on metoprolol was comparable to that on placebo[84].

Hypoglycaemia is another form of stress that releases adrenaline. Smoking also provokes an increase in the plasma concentrations of adrenaline; the cardiac output increases, the blood pressure rises and the systemic peripheral resistance falls. Propranolol pre-treatment causes predictable effects, namely a fall in cardiac output, a rise in mean blood pressure and an increase in peripheral resistance[85]. Trap-Jensen and his colleagues[86] confirmed these observations and showed that pre-treatment with atenolol tended to reduce the tachycardia and rise in systolic pressure whilst having little effect on diastolic pressure and forearm blood flow. Perhaps more important, this study showed that myocardial oxygen consumption rose less after atenolol than after propranolol pre-treatment or after smoking alone.

Studies during exercise can be divided into those using static and those using dynamic exercise and some have looked at both[87]. In an investigation of 13 hypertensive patients, handgrip studies produced rises in systolic pressure and pulse rate that were reduced to the same extent by both metoprolol and propranolol[83]. However, on the highest dose of metoprolol (400 mg/day), diastolic pressure increased by 10 mmHg less than on the highest dose of propranolol (320 mg/day). A second study on 23 mild to moderate hypertensive subjects involved exposure to alprenolol, metoprolol and propranolol during isometric and dynamic exercise studies[88]. The drugs had similar effects on the pulse and blood pressure during dynamic exercise but, during isometric exercise, the mean blood pressure on propranolol was significantly higher than on metoprolol.

These studies suggest that the differences in the effects of selective and non-selective agents on the autonomic responses to adrenaline may have some relevance to clinical practice. The rise in mean blood pressure and the increase in peripheral resistance that occurs during some forms of mental stress, with smoking and in response to certain types of exercise when patients are on a non-selective beta-blocker appear less likely to occur when a selective drug is being taken.

Selectivity and Muscle Pains and Fatigue. Muscle fatigue is a relatively common complaint of patients taking beta-blocking drugs. The mechanisms involved in the production of the symptoms are not fully understood. Reduction in blood flow, changes in the balance of energy sources and other mechanisms may play a part[89]. β2 receptor blockade may influence both the mobilisation of glucose from muscle[72,90] and the arterial blood supply. A selective agent may therefore be less likely to cause this symptom. One study has shown less shortening of the time to exhaustion during exercise[91], although two studies have failed to show any difference between metoprolol and propranolol, except that propranolol reduced endurance rather more[89,92].

Cold Hands and Feet. Many patients who receive beta-blockers are also suffering from generalised arteriosclerosis. The blockade of β2 vasodilator receptors and, perhaps more important, any cause of a reduction in cardiac output will impair peripheral perfusion. This may present as a complaint of cold hands and feet, which is relatively common[93], as intermittent claudication[94] or, rarely, as peripheral gangrene[95,96]. Both selective and non-selective agents can cause these complications and, in the case of the latter two symptoms, where there is presumably extensive atheromatous disease of the peripheral arteries, we have no evidence to suggest that drugs which are less likely to influence the β2 vasodilator receptors are any safer. The symptom of cold peripheries is difficult to evaluate and its incidence is very dependent on the methods used to elicit adverse effects. However, McSorley and Warren[97] have shown that whereas propranolol reduced skin temperature, skin blood flow and resting muscle blood flow, metoprolol did not. In addition, White and Udwadia[98] have shown that beta-blockers enhance the vasoconstrictor effects of noradrenaline on the dorsal hand vein and found that the effect of propranolol was much greater than practolol. Only propranolol caused a reduction in skin temperature. It appears that selective beta-blockers are less likely to reduce blood flow and it would seem reasonable to expect that, when they are used, symptoms caused by impaired perfusion should occur less often.

Other Sites

In addition to the major sites where the actions of selective and non-selective beta-blockers exert the effects already described, there are some other functions that may be of interest, but in which the role of selectivity is still being investigated.

Beta-blockers and Lipids. The possible interactions between beta-blockers and serum lipids have been studied fairly extensively but it is difficult to obtain a clear picture of their effects. Although it is known that catecholamines stimulate lipolysis, there is still doubt about whether the receptor involved is $\beta 1$, $\beta 2$ or a combination of the two[80]. The situation is made difficult because different techniques are used, including random blood samples, careful studies in metabolic wards and *in vitro* studies on human, rat and other animals' fat cells. In addition, the term serum lipids covers a number of different entities.

Faced with this potential complexity, it is necessary to attempt to produce some simple conclusions based on the consensus of results. Most studies have demonstrated that treatment with beta-blockers produces a rise in the plasma triglycerides[58,99,100]. There does not appear to be a clear difference between the effects of selective and non-selective agents and the extent of the increase is usually small so that the final concentrations remain within the normal range. Some studies have shown that treatment with metoprolol did not modify the triglyceride levels[101,102], or increased them less than did propranolol[100].

Most studies have shown that beta-blockers do not alter the total serum cholesterol[58,99,101,102]. Data on individual lipoproteins are limited. Tanaka and his colleagues[103] found that propranolol treatment reduced HDL and England and his co-workers[104] showed that the two selective agents, metoprolol and atenolol, also reduced HDL. Beta-blockers appear to cause relatively minor changes in the plasma lipids and there is little to suggest that the effects of the selective agents differ from the others.

Renin Release. Although it has been suggested that renin release may be mediated by a $\beta 2$ receptor, most authors consider that both $\beta 1$ and $\beta 2$ receptors are involved [80,105]. There is no evidence to suggest that there is a clinically relevant difference in renin response to selective and non-selective drugs.

Cellular Transfer of Potassium. The role of sodium and potassium in the aetiology of hypertension has been a subject of debate and confusion for many years. Recently, several groups of investigators have demonstrated differences in the rates of transfer of sodium and potassium across cell membranes between hypertensive and normotensive individuals[106]. These transfer processes may be modified by beta-blocker therapy so that plasma potassium tends to rise during propranolol therapy although the total exchangeable potassium is not affected[107]. $\beta 2$ stimulant drugs have the opposite effect, causing a reduction in the plasma potassium concentration[62]. Though the rise in plasma potassium occurring during exercise may be mediated by a $\beta 1$ receptor[108], one of the processes by which potassium is taken up by cells appears to be mediated by a $\beta 2$ receptor. The relevance of these observations to the use of beta-blockers in the treatment of hypertension and angina has yet to be determined. Since the individual responses differ markedly[108], the risk of developing hyperkalaemia when non-selective beta-blockers are used to treat arrhythmias has to be seriously considered. In addition, high serum potassium levels have been noted in cardiopulmonary by-pass patients treated with non-selective drugs, whereas selective beta-blockers seem less likely to produce this complication[109].

Conclusions

The evidence presented in this review suggests that there are some definite advantages, some possible advantages and no disadvantages associated with the use of selective as opposed to non-selective beta-blockers. The potential advantages apply to a significant number of patients likely to be given beta-blockers, including those with respiratory problems, those who smoke, diabetics and any with peripheral vascular disease.

Although the administration of any beta-blocker to an asthmatic or bronchitic is potentially dangerous, the use of a selective drug in those with respiratory problems reduces the risk of impairing lung function and does not appear to interfere with the response to a $\beta 2$-stimulant bronchodilator. For the diabetic patient, there are good theoretical reasons for preferring a cardioselective drug, and the normal metabolic and haemodynamic responses to hypoglycaemia have been shown to be affected less than when propranolol is used. There is, however, inadequate evidence to suggest that diabetic control will be better on a selective beta-blocker. Finally, the effects of beta-blockers on the peripheral arteries have been considered. There is some evidence to suggest that mean arterial pressure rises and peripheral perfusion falls when a person on a non-selective beta-blocker is subjected to various stresses including smoking. These are not seen or are less marked when a selective drug is used. The possibility that cold hands and feet will occur less often on a selective drug remains to be proved.

The three beta-blockers that are relatively cardioselective are acebutolol, atenolol and metoprolol. There is much more data on atenolol and metoprolol, particularly in patients, and the evidence available suggests that these two are equally cardioselective. They differ in terms of cost, plasma half-life and route of elimination.

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