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Health-related Aspects of the Use and Abuse of Beta-Adrenoceptor Blocking Drugs

M. Orme

Department of Pharmacology and Therapeutics, New Medical School,
Ashton Street, Liverpool, L69 3BX, United Kingdom.

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1. INTRODUCTION AND HISTORY

It was Langley [1] who first suggested that adrenergic receptors contained inhibitory and excitatory elements but it was really Ahlquist [2] who developed the topic and at whose door the development of modern drugs can be laid. Ahlquist proposed from his various studies that excitatory effects should be termed alpha-effects and that inhibitory effects should be called beta-effects. At that time inhibitors of the alpha-effects were known but beta-blocking drugs were yet to be thought of. It was Black and Stephenson [3] who predicted that, because angina pectoris was made worse by situations that caused increased sympathetic activity, beta-adrenergic blocking drugs should be of benefit to patients with this condition. The development of these drugs since that time has been very rapid and they are one of the most widely used group of drugs in clinical practice. It is not surprising therefore that they may occasionally be abused.

2. PHARMACOLOGICAL PROPERTIES OF BETA-BLOCKING DRUGS

In 1967 Lands *et al.* [4] described a differentiation of beta receptors into beta-1 and beta-2 receptors. Essentially beta-1 receptors mediated the cardiac effects and beta-2 receptors mediated the peripheral vascular and metabolic effects.

The first clinically useful beta blocking drug, propranolol, had effects at both receptors and is now known as a non-selective beta blocker. Subsequent drugs were developed to have more inhibitory actions on the cardiac or beta-1 receptors and these are known as cardio-selective drugs. It is important to realise that these drugs are not cardiospecific and will have some effects on beta-2 receptors.

The first clinically useful cardio-selective beta blocker was practolol but this has now been superseded by atenolol. Practolol was withdrawn from clinical use because of adverse effects. Recent clinical experience has shown that it is important to try to separate the beta effects that increase the force of cardiac contraction (positive inotropic effect) from those that stimulate the rate of cardiac contraction (positive chronotropic effect), although there are no beta-

receptor blockers as yet that are this selective. However, we now recognise beta-3 receptors and it is likely that modern molecular biology techniques will identify even more sub-types.

Beta-receptor blocking drugs have a number of other pharmacological actions which may or may not be clinically relevant to their use and abuse. Some drugs have both agonist (stimulatory) actions as well as antagonist effects on the beta receptors. This property is known as partial agonist activity or intrinsic sympathomimetic activity (ISA) and is largely irrelevant in clinical use. Table 1 lists some commonly used beta-blocking drugs and their additional properties. Some beta blockers have a membrane stabilising activity (MSA) which has been claimed to be the way they are useful as anti-arrhythmic drugs. This is unlikely to be true in clinical practice since the concentrations needed to achieve this effect are very much higher than those found in clinical use. Some beta blockers are marketed that have vasodilator properties and these effects may be mediated by an alpha-blocking effect (e.g. labetalol) or sometimes by a direct effect on vascular smooth muscle or via a stimulation of beta-2 receptors (e.g. celiprolol).

Table 1
Properties of some Beta Adrenoceptor Blocking Drugs

Drug	Beta - 1 Selective	Lipid/Water Solubility	ISA	MSA
Acebutol	Yes	Lipid	Yes	No
Alprenol		Lipid	Yes	Yes
Atenolol	Yes	Water	No	No
Betaxolol	Yes	Lipid	No	No
Carvedilol*		Lipid	No	No
Celiprolol+	Yes	Water	No	No
Labetalol*		Water	No	No
Metoprolol	Yes	Lipid	No	No
Nadolol		Water	No	No
Oxprenolol		Lipid	Yes	Yes
Pindolol		Lipid	Yes	No
Propranolol		Lipid	No	Yes
Sotalol		Water	No	No@
Timolol		Lipid	No	

* Also has vasodilator action via alpha blockade
\+ Also has vasodilator action via beta-2 stimulation
@ Is also antiarrhythmic via effect on action potential

The original beta blockers were lipid soluble drugs that easily crossed the blood brain barrier and were extensively metabolised in the liver prior to excretion from the body. In some eyes the adverse CNS effects seen in some patients (e.g. tiredness, vivid dreams [5]) were related to this property and recently more drugs have been produced that are water soluble and which are therefore excreted unchanged by the kidney (e.g. atenolol, nadolol). It is now clear that water soluble beta blocking drugs can cause CNS effects [6] and that such drugs do have

other pharmacological effects such as actions on a variety of interleukins and an effect on atrial natriuretic peptide [7]

3. PHARMACOKINETICS OF BETA BLOCKING DRUGS

3.1. Healthy Resting Volunteers

Many beta blocking drugs are extensively metabolised in the liver, particularly those that are lipid soluble. In some cases, (e.g. propranolol) there may be a very considerable first pass effect such that the bioavailability of the drug may be very low [8]. In a few cases, such as propranolol, the metabolites may also have pharmacological activity which may or may not be the same as the parent drug [8]. In most cases the plasma half-life of the drug is fairly short (between 2 and 8 hours) and this has led to the development of sustained release preparations. There are a few drugs with longer half-lives such as betaxolol, nadolol, and sotalolol, (10-20 hours) and one drug has been released recently with a very short half-life. Esmolol is given intravenously, usually by the anaesthetist, and has a half-life of about 10 minutes.

In most cases the beta-blocking drugs are given by mouth but a number of other routes have been investigated. In particular they may be given as eye-drops (e.g. timolol) for the treatment of glaucoma and there is significant absorption of the drug into the systemic circulation when given by this route [9].

3.2. Effect of Exercise on Pharmacokinetics

There are few data on this subject but Frank and his colleagues [10] looked at the kinetics of 1 mg of propranolol given intravenously in 14 healthy subjects before and after sub-maximal exercise. There was no overall significant difference between the two situations except in the derived peak concentrations. However, there were wide inter-individual variations and in more than half of the subjects there was a striking reduction in the clearance of propranolol on exercise. This was attributed to diversion of blood flow to skeletal muscle and away from the liver which is the main site of metabolism. Further work is needed in this field since there may be significant clinical effects in some subjects.

4. USE OF BETA BLOCKING DRUGS

4.1. Use in Patients with Disease.

It has already been noted that beta blocking drugs were developed for the treatment of patients with angina pectoris [3] and in this condition the drugs have been very beneficial. The drugs have also come to be used in a wide range of clinical conditions which are listed in Table 2. The benefit in patients with hypertension came as a surprise and the mechanism of this beneficial effect is still debated. In most of the conditions it is the beta receptor blockade which is important rather than any ancillary property the drug may possess and in spite of what might be expected cardioselective drugs are no more effective in patients with angina, hypertension or cardiac arrhythmias than the non-selective drugs.

It was recognised fairly early that propranolol had a beneficial effect in patients with hyperthyroidism, in particular, relieving the anxiety and the tremor that are part of this disease [11]. This led to the use of propranolol for the treatment of anxiety in general where the drug

Table 2

Clinical Uses of Beta-Adrenergic Blocking Drugs

Major Indications	Minor Indications
Hypertenstion	Anxiety
Angina pectoris	Tremors
Cardiac arrhythmias	Migraine
Thyrotoxicosis	Hypertrophic obstructive cardiomyopathy
Following myocardial infarction	Portal hypertension

was shown to be effective. Interestingly propranolol was shown to be ineffective in relieving the central manifestations of anxiety [12] and the benefits were related to peripheral beta blockade. It was not surprising that the beta blockers should be used for the treatment of tremors, particularly action tremors of the upper limbs [13]. The many clinical uses of beta-blocking drugs have led to the production of a very large number of these drugs. In the United Kingdom some 15 separate chemical entities are available in over 70 different preparations and this number is likely to continue to rise.

4.2. Use in Healthy Subjects

Once clinical benefit had been shown in patients with tremor and anxiety it was not long before beta blocking drugs were prescribed for normal individuals who were placed in stressful situations. Thus these drugs have been used by students undergoing oral examinations and they have been of benefit to musicians suffering from stage fright [14] and in reducing the anxiety associated with public speaking [15]. Inevitably these drugs have been used by sportsmen to reduce tremor. This applies to rifle shooters particularly in the biathlon, where intense physical activity in skiing is interposed with the need to shoot rapidly and accurately. It had been reported that Russian sportsmen have, in the past, used large doses of benzodiazepines such as diazepam which had a detrimental effect on their physical performance. Imhof and Brunner [16] have shown that beta blockers such as oxprenolol reduce the heart rate of ski jumpers and more recently metoprolol was shown to improve the performance of pistol shooters [17]. The performance of a group of 33 expert pistol shooters improved significantly ($p < 0.002$) after 150 mg metoprolol compared to placebo treatment and the improvement appeared to be correlated with the reduction in the heart rate.

As a result of these observations the Medical Commission of the International Olympic Committee has placed beta blocking drugs on the prohibited list. Sports where these drugs are prohibited include archery, shooting, bowls, ski jumping, free style skiing, bobsleigh, luge, diving, synchronised swimming and modern pentathlon [18]. The debate over whether these drugs affect the physical aspects of performance in sports is addressed later. In the 1988

Winter Games in Calgary 15 samples of urine provided by 428 athletes tested positive for banned substances but no abuse of a beta blocking drug was detected [19].

5. ADVERSE EFFECTS OF BETA BLOCKING DRUGS

All beta receptor blocking drugs produce adverse effects and their importance has been debated over the years. In many cases the prevalence of adverse effects has not been properly tested and in any placebo controlled trial it is expected that 30% of patients will develop a placebo-induced adverse effect. Nevertheless a long list of adverse effects have been reported with the use of beta-blockers and most of these are listed in Table 3.

Table 3

Adverse Effects of Beta Adrenergic Blocking Drugs

Life Threatening	Symptomatic	Metabolic effects
Heart failure	Cold hands and feet	Hypoglycaemia
Asthma	CNS effects	Reduced HDL lipoprotein
Heart Block	Vivid dreams	Increase in plasma urate and potassium
	Tiredness	
	Sleep disturbance	
	Mood alteration	
	Impotence	
	Nausea and diarrhoea	

The life threatening adverse effects are largely predictable from a knowledge of the pharmacology of the beta blocking drugs. Thus asthma or any form of bronchospasm may occur due to an effect on bronchial smooth muscle. Heart failure follows inhibition of the positive inotropic effects of adrenergic stimulation when beta blockers are used and heart block may occur if the heart rate falls too low.

The metabolic effects are, in general, fairly minor although severe hypoglycaemia can occur spontaneously and the non-selective beta blockers particularly prolong the hypoglycaemia induced by insulin in diabetic patients. There is a further problem in that the awareness of hypoglycaemia is reduced since the beta blocker reduces the tachycardia and palpitations that often warn a patient of an impending hypoglycaemic episode.

5.1. Effects on Exercise-Induced Metabolic Changes

Beta-blocking drugs interfere with many of the exercise-induced metabolic changes seen in humans since many of them are caused by sympathetic stimulation via beta adrenergic receptors. Thus the cyclic AMP content of skeletal muscle at rest is significantly reduced by propranolol and there is no increase after exercise as would normally be the case [20]. In addition ATP levels in skeletal muscle following exercise are reduced by beta blocking drugs. There is also a decrease in the blood and muscle lactate during beta blocker therapy compared

to that seen in control individuals during sub-maximal exercise. There is, however, no effect on breakdown of muscle glycogen [21]. There is also evidence of an inhibition of lipolysis during exercise when propranolol is taken compared to controls [22].

5.2. Quality of Life

Although side affects may occur during therapy with beta blocking drugs, the long term effects on morbidity need to be considered compared to the effects of no treatment or with the effects of other comparable drugs. It is very difficult to measure the quality of life in this way but several attempts have now been made to do this. A large multicentre study has shown that, in patients with hypertension, the general quality of life was better in patients on propranolol than in patients on methyldopa but not as good as in patients taking captopril [23].

6. BETA BLOCKING DRUGS AND EXERCISE PERFORMANCE

This field is one of the areas that is most contentious in terms of the adverse effects of beta blocking drugs. The early literature had many anecdotal reports on the adverse effects of beta blockers on exercise performance and it was very difficult to dissect out the various elements which include central and peripheral effects, the effect of disease, the nature of the beta blocking drug and its dose and outside conditions such as cold weather. There is little doubt that when beta blockers are used to treat patients with angina, exercise tolerance increases significantly. There is also general agreement now that when beta blockers are given to physically fit healthy individuals there is a small but significant reduction in their exercise capacity [24]. There is a suggestion that exercise performance in such people is less affected by cardio-selective beta blockers than by non-selective drugs. There are some suggestions that the nature of the test performed will affect the result. Thus McLenachan and his colleagues [25] showed that maximal exercise capacity was reduced by beta blockers, even selective ones and increased fatigue was apparent. However, when sub-maximal exercise capacity was examined, clear differences were observed between beta blockers, with atenolol still impairing exercise performance and celiprolol being no different from placebo.

In patients with hypertension it has been harder to demonstrate a convincing reduction in exercise performance when beta blocking drugs are given. In some studies there has been no effect shown [26] while in other studies there has been an increased exercise capacity during therapy with beta blockers [27]. The standard view is that there is some reduction in exercise capacity and increased fatigue during beta blocker therapy but that the effect, when quantifiable, may be as little as 2% [28]. There is little evidence of an effect on peripheral muscle fatigue mechanisms and little evidence, too, that fatigue or poor exercise capacity is due to reduced muscle blood flow [29].

This, suggests that central mechanisms may after all be responsible. Much work still needs to be done to elucidate the actual processes involved.

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Discussion: Health-Related Aspects of the Use and Abuse of Beta-Adrenoceptor Blocking Drugs

D.R. Mottram:

Could I ask you about the so called third generation of beta-blockers as exemplified by celiprolol which, as you say, has got beta-1 blocking activity and beta-2 agonist activity. It is probably too early to assess them clinically against the older generation of beta-blockers, however, what do you feel about the potential advantages associated with these drugs, in terms of fewer side effects in asthma patients and in relation to cold extremities?

M. Orme:

In terms of their clinical efficacy on measurements such as blood pressure, there is no real difference compared to the older beta blocking drugs. As far as side effects are concerned, the cold extremities that may be caused by beta blockers are now thought to be due to a reduction of cardiac output rather than to the peripheral effects of the drugs. The vasodilatation with celiprolol may be of benefit here and the reduced likelihood of precipitating asthma is also an advantage of such newer beta blockers. Any beta blocker however can precipitate asthma in a sensitive individual and so, in my view, the overall benefit is marginal.

P.M. Clarkson:

I find it interesting that the use of beta-blockers by athletes seems to be on the down swing. A few months ago I spoke at a conference on medical aspects of performing artists and beta-blockers appear to be on the increase in the performing arts world. In fact, there were children, young teenagers at the performing arts school, who are being prescribed beta-blockers for important competitions or auditions. I am concerned about the health-related aspects of using beta-blockers. The health-related problems seem to be more prevalent with long-term use. Are we to be as concerned with young people (or anyone) who take beta-blockers on occasion?

M. Orme:

The problem is that there are very few data on healthy individuals who take beta-blockers in the long term. All the quality -of-life data is in patients with a disease process, usually hypertension. The long term data here strongly suggests that they are doing more good than harm. The occasional user of beta blockers is most unlikely to come to harm apart from the obvious case of asthmatic individuals etc. I share your concern over the long term use in healthy individuals.

D.P.M. MacLaren:

What is the mode of action of beta-blockers in terms of bringing about hypoglycaemia?.

M. Orme:

The main effect of beta blockers in terms of causing hypoglycaemia is to antagonise the effect of adrenaline. Adrenaline causes the conversion of glycogen to glucose in a 'fight or flight' type of response and this will perpetuate the hypoglycaemia. It is more likely with a non-selective beta blocker than with a cardioselective drug. In addition beta blockers reduce

the ability of an individual to recognise a hypoglycaemic episode by reducing the tachycardia and tremor that often warns of an impending problem.

T. Reilly:

With regard to the use of beta-blockers in sports like archery, for example, one effect that probably is usually ignored is the effect of a longer R-R interval. So in the case of these drugs one should consider not only the decrease in tremor, but also the opportunity for whole-body relaxation.

It has been shown that the loose in archery is timed precisely with a particular part of the cardiac cycle. In elite archers the loose systematically and repeatedly occurs coincident with a stage of the cardiac cycle. I wonder if you had any observations on that and I would like to bring in anybody else with observations as well as on the influence of skilled and high-level performers who know their activities so well that they can do these things.

M. Orme:

I was not aware of what you said about lead archers, but it does not surprise me. We are all aware of the effect of cardiac contraction on human movement, If you stand on an ordinary (non-digital) weighing machine, you can see the needle flicking in time with your heart beat. Thus an arrow let loose just as the heart was contracting would be more likely to go off target when the room for error is so small. If the heart rate is slowed by taking beta blockers then the longer time for diastolic filling of the heart gives a longer time for letting the arrow loose when the body is relatively relaxed.

K.A. Perkins:

Interestingly, there are rather old data showing that psychomotor performance, measured as reaction time, is improved if the stimulus is presented between beats as opposed to during beats.