Beta Blockers in the Treatment of Cardiovascular Disease

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Raven Press ■ New York

Raven Press, 1140 Avenue of the Americas, New York, New York 10036

Made in the United States of America

Library of Congress Cataloging in Publication Data
Main entry under title:

Beta blockers in the treatment of cardiovascular disease.

Includes index.
1. Adrenergic beta receptor blockaders. 2. Cardiovascular system—Diseases—Chemotherapy. I. Kostis, John B. II. De Felice, Eugene A. [DNLM: 1. Adrenergic beta receptor blockaders—Therapeutic use. 2. Cardiovascular diseases—Drug therapy. QV 132 B5618]
RC684.A35B48 1983 616.1'061 83-42985
ISBN 0-89004-290-X
0-88167-008-1 (pbk.)

The material contained in this volume was submitted as previously unpublished material, except in the instances in which credit has been given to the source from which some of the illustrative material was derived.

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Second Printing, June 1985

Preface

The introduction of beta-blocking drugs into clinical practice is regarded as one of the major therapeutic advances in this century. Beta-blocking drugs have been found to be efficacious in the treatment of angina pectoris, arrhythmias, hypertension, and myocardial infarction. This class of drugs also is considered to be useful in a number of other cardiovascular (e.g., psychocardiac disorders, mitral valve prolapse) and noncardiovascular (e.g., migraine prophylaxis, glaucoma, management of stress and anxiety) indications.

Since beta-blocking drugs were introduced in 1966, they have assumed an increasingly important place in the physician's armamentarium. Because of their excellent record of efficacy and safety, beta-blocking drugs have become one of the most commonly prescribed classes of drugs to be used in the treatment of cardiovascular diseases. For example, beta blockers were prescribed in over 40% of cases of hypertension according to an audit of new prescriptions in 1981. Also, many medical centers throughout the world now employ beta-blocking drugs as first-step therapy of essential hypertension.

Owing to their relative safety and broad clinical applications, the practicing physician needs to know as much as possible about beta-blocking drugs. The book focuses on our current understanding of beta blockade and the pharmacology and clinical utility in the major cardiovascular diseases in which beta-blocking drugs have been found to have their most significant applications.

The chapter on the clinical pharmacology of beta blockers is a comprehensive review of the subject and contains detailed descriptions of the relationship of the chemical structure to the pharmacological properties of these agents. The reader may refer to this section of the book to clarify specific questions and obtain pertinent references for further reading or may study the chapter in its entirety.

Beta blockers are usually prescribed for chronic or recurrent conditions, such as hypertension, angina, and arrhythmias. For this reason, patient acceptance, side effects profile, and safety during long-term use are important. The chapter on the effect of beta blockers on blood lipids on intrinsic sympathomimetic activity and on the hemodynamic effects of beta blockers are pertinent in this respect.

The chapters on hypertension, angina, and arrhythmias are state-of-the-art reviews of the common indications of beta blockers. They contain information on the differential effects of beta blockers of various pharmacological profiles in these disorders.

A special chapter on the mechanism of the antihypertensive effect of beta-blockers is included. Agents with different ancillary properties, especially with respect to the presence or absence of intrinsic sympathomimetic activity, lower the blood pressure through different hemodynamic effects—a point of importance to both the pharmacologist and the clinician.

The chapters on the secondary prevention of coronary artery disease in survivors of acute myocardial infarction, in the management of stress and anxiety, and on autonomic dysfunctions describe current knowledge on the use of beta blockers in these conditions.

This book is intended to serve the physician's need to better understand and utilize beta-blocking drugs more effectively and safely. Biomedical scientists interested primarily in a compilation and interpretation of the latest literature on the pharmacological and clinical aspects of beta-adrenergic blockade as it pertains to cardiovascular medicine also will find this book useful.

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Beta Blockers in the Treatment of Cardiovascular Disease, edited by J. B. Kostis and E. A. De Felice. Raven Press, New York © 1984.

Clinical Pharmacology of Beta-Adrenoceptor Blocking Drugs

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The concept of differing adrenergic receptors can be traced back to Langley (224) in 1905, who suggested that they contained inhibitory and excitatory receptor substances. The following year, Sir Henry Dale found that while the excitatory actions of epinephrine were blocked by ergot, the inhibitory ones were not, providing evidence for two types of adrenergic receptors. Then, in 1948, Ahlquist (8) published his now classical paper in the *American Journal of Physiology* on the effect of six sympathetic stimulating drugs on a variety of adrenergic responses. Their order of potency fell into two distinct sequences: the alpha effects, which included vasoconstriction, with epinephrine the most potent, followed by norepinephrine; and the beta effects, which included smooth muscle relaxation and cardiac stimulation. Isoproterenol was the most active of the latter group; epinephrine was third; norepinephrine was least effective. These receptors have subsequently been further divided into alpha-1, alpha-2, beta-1, and beta-2 receptors (14,230,231).

It occurred to Sir James Black that overactivity of the sympathetic nervous system was frequently deleterious to the heart, particularly in angina pectoris and arrhythmias, and thus he began the quest for therapeutically useful agents that would interfere with the effect of catecholamines on the heart; and the pharmacology of pronethalol (Nethalide) was reported by Black and Stephenson in 1962 (39). The use of beta-blocking drugs has been demonstrated in many diseases (329) and they represent one of the most important therapeutic advances of recent times.

CLASSIFICATION OF BETA-BLOCKING DRUGS

Beta-blocking drugs can be divided into those that are nonselective and those that have a selective action on one type of beta receptor—beta-1 or beta-2—and further, into drugs that in addition possess alpha-receptor blocking properties. They may be subdivided into various groups according to the presence or absence of intrinsic sympathomimetic activity (ISA) and membrane activity (120,317) (see Table 1).

At doses used in man, the blood concentrations produced are probably too low to have any significant membrane-stabilising effect. The *d*-isomer of propranolol, which has the same membrane-stabilising action (but not the beta-blocking effect)

TABLE 1. *Classification of beta-adrenoceptor blocking drugs*[a]

	Partial agonist effect (intrinsic sympathomimetic effect)	Membrane-stabilising effect (quinidine-like effect)
Division 1: nonselective (beta-1 and beta-2) block		
Group 1		
Oxprenolol	+	+
Alprenolol		
Penbutolol		
Group 2		
Propanolol	−	+
Group 3		
Pinidolol	+	−
Group 4		
Sotalol	−	−
Timolol		
Nadolol		
Division 2: cardioselective block (beta-1)		
Group 1		
Acebutolol	+	+
Group 3		
Practolol	+	−
Group 4		
Atenolol	−	−
Metoprolol		
Division 3: nonselective block + alpha block		
Group 2		
Labetalol	−	+
Division 4: cardioselective block + alpha block		
No example yet available		

[a]All these drugs have been shown to lower the blood pressure.

as the *d*-isomer responsible for the activity of racaemic (commercially available) propranolol, lacks antianginal or antihypertensive effect (320,428). Any "cardiodepressant" action (a term that is confusing and best avoided) in man is not a direct effect but results from the prevention of sympathetic stimulation. The other differing properties of beta-blocking drugs are discussed below.

CHEMISTRY

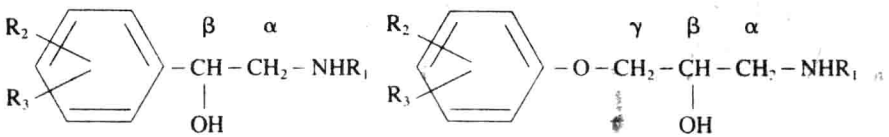
Beta adrenoceptors are specific structures located on or within cells that interact with epinephrine and norepinephrine or other beta agonists through the facility of a complementary structural relationship. The binding of the physiological agonist produces a conformational change at the receptor and initiates the movement of

ions or the activation of enzymes with the expenditure or production of energy. Antagonists, on the other hand, appear only to occupy the receptor (with quite different thermodynamic characteristics), while they prevent continuing function by competitively inhibiting access of agonist (268).

Isoproterenol, a synthetic catecholamine, is the most potent agonist of all. It is not surprising that many synthetic analogs of the catecholamines are effective antagonists for the beta receptor. They all have a ring structure to which is attached an aliphatic side chain. Whilst general observations may attempt to relate structure to function, it should be appreciated that no precise rules cover all the observed findings, as becomes apparent from reviews of the structure-function relationship (22,309). A number of features influence activity: substitution, lengthening, branching, and cyclizing the side chain, as well as substitution on the terminal nitrogen and in the ring structure, all have different effects.

General Considerations

According to the structure of the side chain, inhibitors are divided into two main classes, the aryl- or heteroaryl-ethanolamines (I), and the aryl- or hetero-aryl-oxypropanolamines (II).



I II

The oxygen bridge, which lengthens the side chain, increases the potency of the antagonism of the propanolamines (79).

It is not essential for beta-blocking activity that the side chain be attached directly to a benzene nucleus. Isopropyl-substituted ethanolamine maintains activity when attached to various heteroaryl structures such as naphthyl (182), benzodioxanyl (183), benzodioxinyl (220), benzofuranyl (123), and indole rings (pindolol) (146). With pindolol and timolol (362), considerable potency is associated with a heterocyclic ring. As discussed below, substitution of the aromatic nucleus helps determine potency, cardioselectivity, and partial agonism.

Bulky aliphatic groups such as the isopropyl moiety on the amine nitrogen (R_1) of the side chain seem to favour interaction with the receptor site, though their presence is not essential. The hydroxyl group in the side chain is essential for significant pharmacological activity, and the asymmetrically substituted carbon atom to which it is attached confers optical activity. It is therefore also relevant to consider isomerism.

Side Chain Substitution

Alkyl substitution of the α, β, (or γ) carbon atom usually results in a decrease in adrenoceptor-blocking activity (181), which has been documented for the etha-

nolamine series (76). There is, however, an exception in that methylation of the alpha carbon atom tends to preferentially decrease inhibition of the beta-1 receptor. This phenomenon has been observed with the methyl derivatives of dichloroisoprenaline (84,269), INPEA (382), and propranolol (239). Among the aryloxypropanolamines, methylation of the alpha carbon atom decreases beta-1 blocking potency by about 10- to 12-fold and also beta-2 blocking activity but to a lesser degree (121). In the case of practolol, alpha methylation effectively decreases the cardioselectivity (239). Butoxamine and *N*-isopropyl methoxamine are methylated on the alpha carbon and therefore relatively beta-2 selective, but alpha methylation among the aryloxy-amino-butan-2-ols does not enhance beta-2 selectivity.

Side Chain Branching

Branching at the beta carbon leads to decreased or abolished activity (79) and at the alpha carbon to reduced activity. Tucker (410) studied the effect of alpha carbon alkyl substitution in the *threo* (aryloxy) butanolamines and found the series to behave atypically. Normally, replacement of the isopropyl group with a tertiary butyl group on the terminal nitrogen increases potency, but in this butylamino series, it had the reverse effect with one or two exceptions. From three-dimensional models of this arrangement, it appears that the adjacent methyl and *t*-butyl groups form a large lipophilic envelope which totally encloses the N atom. This supports the view that the N atom is important for interaction with the receptor and that it should be exposed for maximal effect.

Side Chain Elongation

Lengthening of the aliphatic side chain of propranolol by one carbon atom between the ring and the hydroxyl-bearing carbon leads to complete loss of activity (79), and replacement of the ether oxygen (-O-) by a methylene bridge ($-CH_2-$) has virtually the same effect (182). Insertions of sulfur or nitrogen bridges have slightly more variable effects but in general decrease activity. An ether oxygen just distal to the nitrogen of a fluor-enylamine results in a 9-fluorenone oxime with a potency above that of propranolol. The oximino side-chain structure, like alpha methylation, seems to favour beta-2 inhibition (186,226). This compound tends to preferentially block the beta-2 receptor and inhibits isoproterenol-induced renin release. Despite the latter property, it did not lower the blood pressure of spontaneously hypertensive rats and actually produced a dose-related increase in the blood pressure of normotensive animals (226).

Side Chain Cyclization

Incorporation of the ether oxygen of the oxypropanolamine series into the heterocyclic ring does not appear to result in loss of activity. Benzodioxane derivatives (183) are, for example, about 10 times more potent than propranolol or benzofuran derivatives such as bufuralol (123). If the oxygen atom is removed from the cyclic

structure, as is the case with tetrahydronaphthalene compounds (309), then activity is very much reduced. To maintain any useful beta-adrenergic inhibitory powers, it does appear that the oxygen atom needs to be retained either within or directly attached to any cyclic formation in the side chain.

When the terminal nitrogen atom is attached to or in a five-, six-, or seven-member ring, there is a decrease in blocking potency (79,220) but not necessarily of antihypertensive activity in rats. Incorporation of the nitrogen into an N_4- (2-methoxyphenyl) piperazine ethanol structure increased cardioselectivity and hypotensive effect. In dogs, a dose of 2.5 mg/kg was sufficient to induce hypotension, but at least 5 mg/kg were needed to achieve a 50% reduction in the effect of isoproterenol on the resting heart rate, suggesting an additional mode of action to lower the blood pressure (220).

Amino N-Substitution

In general, alterations in potency by *N*-alkylation is parallel in the agonists and antagonists. Among the oxypropanolamines, maximal activity is seen with *N*-isopropyl, *N*-tertiary butyl, and *N*-secondary butyl groups (79,80,409). Tertiary amines have less potency than the secondary equivalents (79). Hydroxylation has relatively little effect, but alkoxy or further amine substitution results in loss of activity (80). Arylalkyl groups (particularly those with an alpha alkyl component) are very active, and this again implies some kind of specific receptor interaction at the N atom. For example, (±) hydroxy benzyl propanolol is twice as active as (−) propanolol in the inhibition of turkey erythrocyte adenyl cyclase activation (58). If both hydrogen atoms are replaced to produce a tertiary amine, activity is lost, at least in the case of the propranolol. Arylamino substitutions are inactive.

In vitro comparison using guinea pig left atria and trachea has been made in a series with various substitutions made on the nitrogen of an aminoethanol side chain affixed to position 2 of a 1:4 benzodioxinyl nucleus (220). The isopropyl and tertiary butyl derivatives had a beta-1 blocking potency similar to that of propranolol but with a beta-1:beta-2 ratio of about 10:1. A 3:4 dimethoxyphenyl-ethyl substitution further increased potency and cardioselectivity (beta-1:beta-2 = 90:1) to well above that of propranolol (see below).

Isomerisation

As with the agonists, it is the laevo or (R) isomers that are pharmacologically the most active (184). Active ethanolamines have R- absolute configuration; for example, DCI (180), INPEA, and sotalol (60). Among these compounds, the *erythro* isomer is therefore more active than the *threo* (181). As judged by indirect methodology, both the active oxypropanolamines and ethanolamines have the same absolute configuration; for example, propranolol (103) and alprenolol (60). There is some indication from studies with FM 24 (a beta-blocking agent with a duration of action five times that of propranolol) that *R* and *S* enantiomers behave differently not only in terms of activity but also of reversibility (232).

Ring Substitution

Ortho or meta placing of alkyl, halogen, alkoxy, or nitro groups is associated with activity. Shortened duration of action and decreased activity are seen if the substitution is in the para position (80,291,410). The positions of dialkyl substitution also seems to be important because the 2′, 3′ dimethyl amino phenoxy propanolamine blocks the beta-1 and beta-2 receptors, but the 2,4 dimethyl derivative blocks only the beta-2 receptor (378). Multiple ring substitution gives variable results, but in general 2,6 alkylation results in loss of activity (cf. 2′OH propranolol). This may well be due to steric inhibition. The same observation with reference to activity (ortho>meta>para) is apparent for electron-attracting groups such as CN (276) and NO_2 (24). Position appears, therefore, more important than the electrophilicity of the substituted group. Hydrogen bonding with the receptor would appear to be implicated, and this can be enhanced by further substituting electron-attracting groups in the ortho position. However, the larger the group, the less the activity—again, presumably due to steric interference.

Further observations on the importance of position for ring substituents is provided in a direct comparison of the 7 possible monohydroxy-ring-substituted propranolols (290). All displaced isoproterenol dose-response curves for heart rate, contractile force, and femoral arterial flow in dogs to the right. The 6′OH propranolol was the most potent and the 2′OH the least potent for all three parameters, and none appeared selective. The 4′OH and 5′OH derivatives were similar in potency to propranolol, and 4′OH propranolol is produced after oral doses in humans (300). Interestingly, the 2′ and 8′OH isomers were similar in their distributions between octanol and aqueous buffer and had similar potencies in reducing hind-limb perfusion pressure. Hydrogen bonding probably occurs in these two compounds between the phenolic hydroxyl groups and the side chain, with the direct vasodilator effect (372) being secondary to the resulting lipophilicity. Although the 3′, 4′, 5′, 6′, and 7′OH propranolols differed by no more than 15% in their liposolubility, the 6′OH compound was the least soluble but some 23 times more potent as a beta blocker. This again confirms that the position of ring substituents is important.

CARDIOSELECTIVITY

A number of proposals have been made to relate physical properties and molecular structure to cardioselectivity. It has been argued that liposolubility should favour access of drug to receptor site (218) and that structural features such as the -OCH2- moiety in the side chain, with an amidic or other hydrogen-binding group in the para- ring position (which lowers the logarithm of the partition coefficient), (81,380) are significant. Unfortunately, detailed qualitative comparisons and experimental observations do not confirm any simple relationship. If water solubility were to confer cardioselectivity, then the nonselective sotalol and nadolol would be expected to have this property. Furthermore, few conclusions take into account the fact that beta blockers are weak bases, and their dissociation into ionised forms with different tissue solubilities will be pH dependent. Lipophilic compounds such

as propranolol and oxprenolol show about a 13-fold greater change in free drug concentration with pH change than do, for example, hydrophilic drugs such as practolol and atenolol (172). Most comparisons from slightly differing experiments are therefore not strictly valid. Although critical review (192) of one set of carefully derived comparable data (450) confirmed a general relationship between the fractions of bound to free drug and the logarithms of their partition coefficients between *n*-octanol and aqueous buffer (pH 7.4), there was no obvious relationship to cardioselectivity that could embrace all drugs examined. Cardioselectivity does not appear to be related to any simple physical property.

Amino N-Substitution

The attachment of a $-CH_2CH_2OC_6H_4OCONH_2$ to the N of 2′-methyl propranolol resulted in tolamolol with a degree of cardioselectivity. The attachment of $-CH_2CH_2NHCONHR'$ (where R′ is aliphatic) also confers cardioselectivity, but so do dimethoxyphenylethyl radicals that do not contain the amide group (175,220,238). Insertion of the latter group increased the selectivity ratio of alprenolol from 1.3 to 12 and for practolol from 18 to 393. Results with propranolol were less impressive.

Ring Substitution

The cardioselective beta blockers (Table 1) are most potent when substituted in the *p*-position (276). Both *p*-amidic- and *p*-hydroxypropenyl ($-CH=CHCH_2OH$) substituted oxypropanolamines, while having overall reduced potency, have increased cardioselectivity (380,409). Ortho substitution usually results in an active but nonselective agent, although there are exceptions such as the *N*-substituted dimethoxyphenylethyl propanolamines discussed below. Amongst the ethanolamine series, for example, there is labetalol, with a *p*-OH group and an adjacent H_2NCO-. The drug and its methyl ester are nonselective. However, if the chain in the *p*-position is lengthened to form, for example, the $CH_3CH_2CH_2CH_2-O-$ ether, then cardioselectivity results. Para substitution amongst the oxypropanolamines with hydrogen-bonding groups such as acetamide enhances cardioselectivity (22,23,418).

A series of halogen-nitro ring substituted derivatives of *N*-isopropyl or *N*-tertiary butyl phenylethanolamine (238) have been used to determine the influence of number and position on the effect of polar substitution in the aromatic ring. A single nitro (INPEA) or halogen group in the para position of *N*-isopropylphenethanolamine resulted in a nonselective agent. Among the tertiary butyl compounds, a single nitro (or chloro) group in the para position favoured beta-2 selectivity. Among doubly substituted derivatives, 3′ nitro-4′bromo and 3′ nitro-4′chloro tended to be beta-2 selective but not so among the isopropanolamine series. Here only the *N*-substituted 3,4-dimethoxyphenyl derivative was cardioselective.

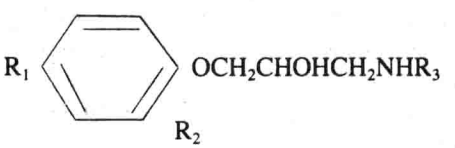
The effect of ring substitution in the (aryloxy) butanolamines is similar to that in the oxypropanolamines (80); that is, ortho or meta derivatives are more potent than the para compounds. However, in contrast to the oxypropanolamines, amide

substitution in 4′, rather than enhancing cardioselectivity, actually abolishes or greatly lessens it as determined by isoproterenol-induced tachycardia (410). An explanation could be that the methyl group on the side chain interferes with the binding of the terminal amide group to a necessary accessory receptor site (409). The fact that the ortho position is less sensitive to steric bulk than the para is confirmed in the isopropanolamines, since 2-$OCH_2CONHCH_3$ is cardioselective (more potent than practolol), but 4-$NHCOCH_2CH_3$ is not. 3,4-Dimethoxyphenylethyl substitution of the terminal N- also improves cardioselectivity (168), and this, with para substitution as already discussed, greatly enhances cardioselectivity (175). Cardioselectivity seems to be favoured by the presence of the homoveratrylamine (3,4-dimethoxyphenyl) moiety (175,220), whether in the nucleus or attached to the side chain nitrogen.

INTRINSIC SYMPATHOMIMETIC ACTIVITY (ISA)

Early work with dichloroisoprenaline revealed that it is possible for an adrenoceptor-blocking drug (as with other receptor inhibitors) to prevent access of receptor agonist but at the same time itself act as a weak agonist—ISA, or partial agonist activity (PAA). The property appears to be related in part to direct substitution of the ring system with polar or electron withdrawing (i.e., attracting) groups (e.g., chlorine in the case of dichloroisoprenaline or a methyl-amide group in practolol). Atenolol, which has no PAA, also contains a methyl-amide substitution, but the arrangement is such that the electronegative atoms are not conjugated directly with the ring system (Fig. 1). The interposition of a methylene or ethylene group between these substituents and the ring (e.g., atenolol or metoprolol) reduces greatly or eliminates PAA.

Polar substitution of the aromatic ring of the aryl oxypropanolamines has been shown to increase sympathomimetic activity (22,202). As expected, partial agonism is evident in phenylethanolamine structures with a *p*-chloro group (182), but it is destroyed if an adjacent nitro group is introduced. If the para position is occupied, (e.g., by bromine), then the *N*-*t*-butyl substituted compounds show the same effect,



	R_1	R_2	R_3
Practolol	CH_3CONH-	H	$CH(CH_3)_2$
Metoprolol	$CH_3OCH_2CH_2-$	H	$CH(CH_3)_2$
Atenolol	H_2NCOCH_2-	H	$CH(CH_3)_2$
Acebutolol	C_3H_7CONH-	$-COCH_3$	$CH(CH_3)_2$

FIG. 1. The structure of the cardioselective beta blockers.

but *N*-isopropyl compounds show the opposite effect; i.e., lone *p*-halogen groups do not confer partial agonist activity, but when the adjacent nitro group is introduced, then it appears (50 to 60% that of isoprenaline)—i.e., the converse of the case with *p*-substituted chlorine (238).

N-aryloxyethyl substitution of the terminal nitrogen in place of more usual groupings (e.g., isopropyl) also can abolish intrinsic activity, but other amine substituents (e.g., *p*-hydroxybenzyl substitution of propranolol or hydroxybenzyl pindolol) are more potent both as agonists and antagonists (453) than their parent substances. They have higher affinity for the beta receptor than either of the parent substances or isoproterenol. Compounds having this property to a significant extent include pindolol, oxprenolol, acebutolol, alprenolol, and practolol; the clinical relevance is discussed below.

BLOCKADE OF ADRENORECEPTORS

Blockade of Exogenous Stimulation

Beta-adrenoceptor blocking drugs are competitive inhibitors (antagonists) at the beta-adrenergic receptor. This means that an increase in concentration of the stimulating drug (agonist)—e.g., isoproterenol—will overcome the blockade. The net effect on the receptor is proportional to the local concentration of agonist and antagonist. There is, therefore, no such thing as complete beta blockade in terms of an exogenous stimulus (e.g., isoproterenol). Any increase in concentration of antagonist can be overcome by increasing the concentration of agonist, which in turn can be blocked again by an increasing concentration of antagonist. It is therefore possible to construct a series of dose-response curves to isoproterenol in the presence of increasing doses of beta-adrenoceptor antagonist. The dose-response curves show a parallel shift to the right, with the same maximum response being obtained after the various doses of antagonist by increasing the dose of the agonist, isoproterenol (341).

Single doses of isoproterenol are a less satisfactory way of assessing beta blockade (254). Responses to single doses vary widely between individuals (139), and the response to a previously adequate dose of isoproterenol is abolished completely for a prolonged period after an oral dose of a beta-blocking drug (300), thus no assessment of the changing degree of beta-receptor antagonism can be made as drug concentration alters. Multiple doses of isoproterenol should therefore be given and a dose-response curve obtained. This may be done by using bolus injections or continuous infusions of isoproterenol (254). Continuous infusions result in more exposure to the unpleasant effects of isoproterenol. There is also some suggestion that tolerance may occur (74), but although there may be a reduction in the increment of heart rate to a given dose of isoproterenol, there is no fall in the actual tachycardia reached (208).

Beta-blocking drugs vary greatly in their ability to inhibit isoproterenol. For equivalent inhibition of exercise tachycardia, far less antagonism of the cardiac