Beta-Blockers in the Treatment of Cardiovascular Diseases

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INTRODUCTION

The past several years have witnessed a increase throughout the world in the use of beta-blocking drugs for the management of hypertension and angina.

The enthusiasm that has accompanied the use of beta-blocking agents has led to a proliferation of many new agents in this class over the years since their introduction into clinical use, with an accompanying increase in the use of these agents as first-step therapy in many clinical centers.

Several important reasons account for the growing acceptance of these agents in the management of hypertension: first, beta-receptor blocking agents are highly effective for eliciting meaningful reduction of elevated blood pressure in most patients and beta-blockers by diminishing myocardial oxygen demand improve exercise tolerance in patients of angina. Moreover, postural or exercise hypotension, as occurs with sympatholytic agents, does not commonly occur during treatment with beta-blockers, and finally, bea-blockers are generally well tolerated, if use in patients with known contraindications, such as, obstructive pulmonary disease or heart failure, is avoided.

This paper discusses the concept of beta-blockers, their properties with reference to their uses in clinical medicine.

With the undertstanding of the concept of neurohormonal transmission, it was realised that some of the responses to sympathetic or adrenergic stimulation were excitatory in nature, while others tend to be inhibitory. Effector cells contained either excitatory or inhibitory "receptive substances"[1].

In 1948 Ahlquist[2] suggested that instead of two different transmitters being released at sympathetic nerve endings, there was one transmitter but two different types of receptors, which he labelled alpha-receptor and beta-receptor. In general, alpha-receptor stimulation was associated with excitatory responses and beta-receptor stimulation with inhibitory responses. Ahlquist noted two important exceptions:

(i) Cardiac excitability was classified as a beta-receptor response, and

(ii) Inhibition of gut activity appeared to be an alpha response. However, subsequent studies have shown this to be a mixed response involving both alpha and beta receptors.

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Distribution of Receptors and Classification of Responses to Adrenergic Stimulation

BETA RECEPTORS

Tissue	*Response*
Heart.	Increased heart rate; increased myocaridal contractility.
Blood vessels of skeletal muscles.	Dilatation.
Bronchial muscle	Relaxation.
Stomach:	
Mobility and tone.	Decrease.
Urinary bladder:	
Detrusor.	Relaxation.
Eye:	
Ciliary muscle.	Relaxation for far vision.
Intestine:	
Mobility and tone.	Decrease.

Distribution of Receptors and Classification of Responses to Adrenergic Stimulation

ALPHA RECEPTORS

Tissue	*Response*
Blood vessels:	
Skin and mucusa.	Constriction.
Intestine:	
Sphincters.	Contraction.
Urinary bladder:	
Trigone and sphincter.	Contration.
Eye:	
Radial muscle of iris.	Mydriasis.
Skin:	
Pilomotor muscles	Contraction
Sweat glands.	Secretion

Lands, et al.[3] further defined Ahlquist's concept, and in 1967 proposed the existence of at least two types of beta-receptors. They were able to demonstrate that myocardial receptors differed from those associated with smooth muscle.[4] Terminology differentiating one type from the other was adopted, namely "beta-1" receptor sites affecting the myocardium, and "beta-2" for smooth muscle affecting the bronchial muscles.

Pharmacological Properties of Beta-Blockers

Apart from the basic pharmacodynamic properties of Bea-Blockers which are discussed under the various indications for use of Beta-Blockers in the following pages of this paper, there are three important pharmacological properties possessed by Beta-Blockers, i.e., (i) Cardioselectivity, (ii) Intrinsic Sympathomimetic Activity, and (iii) Local Anesthetic Activity. These three properties vary from one compound to another. The following table summarises these properties of various commonly used Beta-Blocking agents:

Drug	*Cardio-selectivity*	*Intrinsic Sympatho-mimetic Activity*	*Local Anesthetic Activity*
Acebutolol	+	+	+
Alprenolol	0	+	+
Atenolol	+	0	0
Metoprolol	+	0	0
Oxprenolol	0	+	+
Pindolol	0	+	0
Practolol	+	+	0
Propranolol	0	0	+
Sotalol	0	0	0
Timolol	0	0	0

(Adapted from Prichard, B.N.C.)[5]

(i) Cardioselectivity:

Beta-Blockers have been classified as "cardioselective" or non selective according to their relative abilities to inhibit stimulation of Beta-1 or Beta-2 receptors[6]. So-called cardioselective beta-blockers (acebutolol, atenolol, metoprolol, and practolol) have 50 to 100 times the ability to inhibit the effects of isoprenaline stimulation on myocardial performance (B-1). Their relative freedom from effect on Beta-2 receptors is highly dependent on drug concentration, so that in a given dose the drug may remain cardioselective but at higher dose may block both Beta-1 and Beta-2. So that the Beta-Blockers are best avoided in patients with bronchial spasm, however, if they have to be used, cardioselective beta-blockers are naturally better choice.

(ii) Intrinsic Sympathomimetic Activity (ISA):

Intrinsic Sympathomimetic Activity or ISA means that agents having Intrinsic Sympathomimetic Activity have some ability to stimulate the beta-receptor sites in addition to their ability to produce beta-receptor blockade. Thus those beta-blockers which have ISA act as partial antagonists by virtue of this dual activity; others which have little or no intrinsic activity act solely as antagonists.

Because of their stimulant activity they may exert some sympathetic stimulation on the heart, but the effect is not easy to predict and varies under different circumstances.

Whether this dual activity is real advantage is difficult to say. However, some physicians feel that agents with intrinsic sympathomimetic activity are "safer" somehow because the ISA partially offsets the effect of the beta-blockade.

Others feel that intrinsic sympathomimetic activity is not desirable from therapeutic standpoint becuase it counteracts the principal effect of the beta-blocker and may therefore make it less effective and less predictable.

Although theoretically beta-blocking compounds that posses ISA should be less likely to precipitate heart failure due to partial antagonist activity or stimulant activity, such has not been demonstrated clinically in all cases. Certain compounds with ISA have precipitated heart failure in patients with compromised cardiac function.[5—6] It is much of a choice of individual physical as to which compound he uses and what experience he has gained from it.

(iii) Local Anesthetic Activity ("Quinidine-Like Effect"):

Some, but not all, beta-adrenergic receptor blocking agents possess local anesthetic (or membrane-stabilizing) activity. This property is associated with effects on cardiac action potential and nonspecific depression of cardiac function which is not very desirable, especially in cases where this function is already affected due to coronary artery disease or disease of myocardial muscle. The term "quinidine-like effect" is often used interchangeably in the literature to describe this property of certain beta-blocking agents. There is no direct relationship between beta-blocking activity and local anesthetic effect. Among currently employed beta-adrenergic blockers, alprenolol, oxprenolol and propranolol possess moderate local anesthetic activity, while timolol, atenolol, pindolol alongwith certain other currently available beta-blockers have little or no such activity. Some authors feel that local anesthetic activity may

be an important factor in control of arrhythmias, although others feel that beta-blockers without this action also work as equally good anti-arrhythmic agents. Many users of propranolol find that this effect is not much of problem for their patients. Again it is a matter of confidence in use of a drug and individual physician's experience.

Renin Profiling:

The renin-angiotensin-aldosterone system is proposed as one mechanism of regulating blood pressure[7—8] (Figure 1). When renin, an enzyme secreted by the kidney, reacts with a circulating alpha2-globulin substrate, angiotensin I is formed. Angiotensin I is biologically inactive, but when hydrolyzed by pulmonary enzymes, it is converted to antiotensin II, by weight the most potent pressor agent known. Angiotensin II exerts its effect by constricting the arteriovasculature, thereby tending to elevate blood pressure. At the same time, but within a slower and more prolonged time frame, angiotensin II promotes release of aldosterone, a hormone that stimulates renal sodium and fluid retention. This increase in fluid content also tends to raise blood pressure.

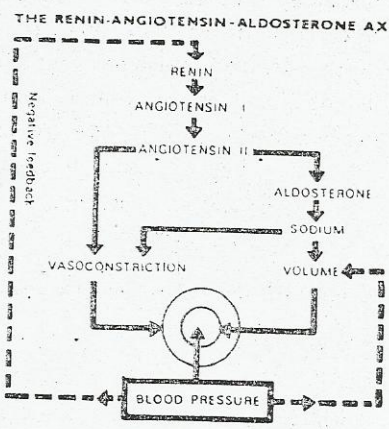

Fig. 1: The vasoconstriction volume hypothesis for blood pressure proposes that although many inputs may be involved, the two ultimate determinants of blood pressure are the degree of vasoconstriction of the arterial bed between the aortic valves and the capillaries and the volume of fluid filling this bed. Adapted from Laragh. JH.[7]

With this understanding of role of renin the mediation of blood pressure, plasma renin profiling, as a selection process for appropriate anti-hypertensive therapy, has become a subject of considerable interest and controversy, for example, beta-blockers are advocated for patients with high plasma renin concentrations as they tend to reduce renin levels and diuretics are advocated for patients with low plasma renin concentrations as diuretics have no effect or cause some increase in plasma renin levels. However, todate this classification has not helped in selection and treatment of hypertensive patients as both types may rspond to either treatment.

Blocking Potency of Various Beta-Blockers

Daily dosages of beta-blocking drugs vary according to their relative potency. Milligram for milligram, timolol and pindolol are the most potent beta-blocking agents available[6]. Some authorities reckon that one benefit of the relative potency is its narrow effective dosage which can assist the clinician to achieve a therapeutic end-point with relative speed and ease. Following table gives relative potencies of various commonly known beta blockers:

Beta-Blockade Potency Ratios
(*Propranolol*=1)

Drug	*Potency Ratio*
Acebutolol	0.3
Alprenolol	0.3
Atenolol	1.0
Timolol	6.0—8.0
Metoprolol	1.0
Oxprenolol	0.5—1.0
Pindolol	6.0
Practolol	0.3
Propranolol	1.0
Sotalol	0.3

Adapted from Waal-Manning, H.J.[6]

In the opnion of Meier[9] one advantage of high potency beta-blocking compounds is their 'ecological' considerations (clearance, saturation of enzymes and elimination systems, drug interaction and competitive bindings). A small amount of a potent drug is advantageous for a patient especially in chronic treatment and when many other drugs have to be administered simultaneously.

However, it is the choice and experience of the clinician that which drug he finds best in his practice.

Beta-Blocking Agents in Hypertension:

General Considerations: The past several years witnessed a striking increase throughout the world in the use of beta-blocking drugs for the management of hypertension.

Several important reasons account for the growing acceptance of these agents in the management of hypertension: first, beta-receptor blocking agents are highly effective for eliciting meaningful reductions of elevated blood pressure in most patients; second, postural or exercise hypotension, as occurs with sympatholytic agents, does not commonly occur during treatment with beta-blockers, and finally, beta-blockers are generally well tolerated, if use in patients with known contraindications, such as obstructive pulmonary disease or heart failure, is avoided.

There is also an advantage to adding a beta-blocking drug to already instituted diuretic therapy[10]. In this way, control is often improved, and the doses of both agents can be kept low, thereby minimizing dose-related side effects.

In Frohlich's view[11], clinical experience to-date suggests that while the hypertensive action of beta-blockers is most evident when used to treat the types of hypertension that are adrenergically mediated, however, beta blockade should not be reserved only for those types of hypertension with obvious adrenergic components. Administered alone or in combination they have demonstrated efficacy in hypertensive patients with or without hyperdynamic circulation[11], which is commonly seen in hypertensive patients that are adrenergically overactive.

How Do Beta-Blocker Lower Blood Pressure?

It has been suggested that beta-blockade may lower blood pressure (a) by reducing both the cardiac output at rest and the increases in output induced by exercise and catecholamine activity, this adjustment leading to the resetting of cardiovascular reflexes (baroreceptors); (b) by suppressing plasma renin activity; (c) by a central action in the brain. There are objections to accepting any of these three alone as explaining the mode of action.

Not only is initial heart rate a poor guide to resonse to treatment, but in addition there is little relation between the fall in heart rate that occurs with the drug and the fall in blood pressure. If a fall in cardiac output is invariable with beta blockade, a fall in pressure is not.

Most beta-blocking drugs have been shown to depress levels of plasma renin activity (Buhler, et al., 1972)[12] Thomas and co-workers (1976)[13] also measured plasma renin activity and divided their hypertensive patients into three groups (according to their renin levels, i.e., low, normal or high plasma renin levels). All patients received oxprenolol and the falls in blood pressure were equal in each group. It seems clear, therefore, that the renin status of the patient is a poor predictor of the response to beta blockade.

A hypotensive effect mediated via the sympathetic neurones in the central nervous system has been suggested. The blood pressure in rabbits can be lowered by injecting the laevo-isomer of propranolol into the cerebral ventricle, an effect not produced by dextropropranolol which lacks beta-blocking activity (Lewist et al., 1973)[14]. This possible mechanism of action needs to be further investigated in man. The fact that beta-blocking drugs which freely pass the blood brain barrier are no more potent than other which do not, gives no support to this concept.

Rationale for use and Mode of action of Beta-Blocking drugs in angina pectoris

Angina pectoris has along been assumed to occur when the demand for oxygen exceeds the supply, usually because coronary blood flow is restricted by coronary atherosclerosis under conditions requiring increased oxygen supply (Keefer and Resnick, 1978)[15].

As an increase in cardiac sympathetic activity is a feature of the conditions which precipitate attacks of angina, namely exercise, emotion, cold environment, and food, then blockade of cardiac B-adrenoceptors with drugs, such as propranolol might be expected to reduce the frequency of these attacks. This was the basis on which the development for clinical use of B-adrenergic blocking (B-blocking) drugs in Angina Pectoris was initially undertaken (Black and Stephenson, 1926)[16].

Four main factors—heart trate, ventricular systolic pressure, rate of rise of left ventricular pressure, i.e., the speed of left ventricular contraction, and the size of the left ventricle—influence oxygen demand by the left ventricle (Robinson, 1971)[17]. Heart rate and systolic pressure seem the most important.

B-adrenergic receptor inhibitory drugs reduce heart rate, thus reducing work done and allowing longer for diastolic filling. B-Blockade also reduces the rise of blood pressure on exercise, the velocity of cardiac contraction (Sonnenblick et al., 1965[18], Furnival et al., 1970[19], Thadani et al., 1973[20]) and oxygen consumption at any given work load (Wolfson and Gorlin, 1969)[21], they would be expected to improve the symptoms of angina pectoris in patients with coronary heart disease. However, in patients with borderline cardiac decompensation, heart failure may result with an increase in ventricular dimensions and in myocardial wall tension necessary to produce a given pressure.

A group of patients who have derived considerable benefit from treatment with beta-blocking drugs are those with angina pectoris associated with hypertension[22].

To sum-up one may quote Kay[22] who comments, "B-blockers have been under review for the last 12 years and there appears to be no doubt these drugs are effective in reducing the frequency and severity of angina pectoris..."

Whether the action of B-receptor blocking drugs is simply a matter of producing the haemodynamic changes or is more complicated, B-receptor blocking drugs, irrespective of whether or not they possess partial agonist properties or local anaesthetic activity (membrane stabilising action), or whether they produce general or selective blockade of B-receptors, have all produced some increase in acute working capacity without pain. Therefore, such benefit appears to result from their common property, blockade of cardiac B-adrenoceptors (Wilson et al., 1969[23], Prichard et al., 1970[24], Boakes and Prichard, 1973[25]).

Beta-Blocking Agents in Cardiac Arrythmias

Both the local anaesthetic or membrane stabilising properties of Beta-Blocking drugs and their beta-blocking action are important in defining the activity of these agents in cardiac arrythmias. Most appropriately, the drugs act effectively to block catecholamine-stimulated arrhythmias. These occur in phaeochromocytoma during induction of anaesthesia and certain conditions of stress. When digitalis is not effective in increasing the degree of A-V block in patients with atrial fibrillation and atrial flutter, especially during exercise, the addition of a Beta Blocking drug frequently results in adequate control of the ventricular heart rate. Propranolol has been shown to be effective in treating both atrial and ventricular arrthmias induced by digitalis glycosides excess, and in those paroxysmal arrythmias which prove resistant to digitialis and and quindine. However, more recently Beta-Blockers devoid of local anaesthetic activity have also proved effective in control of arrythmias which indicates that these drugs act mainly because of their inherent beta-blocking property in cases of arrythmias.

Beta-Blocking Agents in Hyperthyroidism

Symptomatic relief of the circulatory actions of excess thyroid hormone is obtained by Beta-Blocking drugs (Turner)[26]. Its use is especially useful while awaiting definitive therapy.

Beta-Blocking Agents in Obstructive Cardiomyopathy

The role of the adrenergic nervous system in influencing the outflow tract obstruction from the left and right ventricles in obstructive cardiomyopathy is well established. In man, stimulation of the sympathetic nervous system produces significant outflow tract obstruction in obstructive cardiomyopathy, and leads to further ventricular hypertrophy and then to more out flow tract obstruction (Flamm et al., 1968)[27]. This vicious cycle may be interrupted by treatment with Beta-Blocking drugs: producing favourable alteration in the gradient between the left ventricle and aorta.

CONCLUSION

In conclusion it may be said that many pharmacological aspects of Beta-Blockers have been uncovered, but its exact mode of action, especially in hypertension, is not fully understood. There are many advantages in the use of Beta Blockers in various fields of cardiovascular diseases, however, Beta-Blockers are active pharmacological agents and their use should be

made judiciously and carefully. Proper selection of patients for treatment with Beta-Blockers is necessary and this would not be possible unless the doctor knows about the properties of Beta-Blockers clearly and he understands about the indications and limitations of these agents. The two contra-indications, i.e., congestive heart failure and bronchial spasm should always be kept in mind. Diabetic patients, treated with Beta-Blockers, may need adjustment in their dosage regimen of antidiabetic agents. There is one more caution that when Beta-Blockers are used in a patient for long time, they should not be withdrawn suddenly because withdrawal means resetting of cardiovascular reflexes, especially in cases of angina pectoris, which can only be achieved without any harmful effect on the body by gradual reduction in dosage over a period of time. Needless to say that like all new drugs about which we start with a lot of enthusiasm, we should keep a watch as to the complications whtat may arise with these agents over prolonger period of treatment and this should be done by all doctors who are maintaining their patients on long-term therapy with Beta-Blockers.

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