Selection And Uses Of Beta Blockers In Clinical Practice. A Synopsis

By

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Based on the relative potency of a series of sympathomimetic amines Ahlquist in 1948 concluded that there were two distinct types of adrenergic receptors. He classified them as alpha and beta receptors. The latter have subsequently been further divided into beta 1 and beta 2. The distribution of these receptors and their activities is shown in table 1.

Table I

Adrenergic receptors and their responses to stimulation in some organs and tissues

Organ or tissue	*On stimulation of beta-receptor*
Heart—$beta_1$	
sinus node	Acceleration of heart rate
AV node	Acceleration of conduction
atria and ventricles	Increase of contraction force
Vessels—$beta_2$	Dilatation
Bronchi—$beta_2$	Dilatation
Uterus—$beta_2$	Relaxation
Renal juxtaglomerular cells—$beta_1$	Increased renin release
Pancreatic beta cells—$beta_2$	Increase in insulin secretion
Muscular glycogen—$beta_2$	Glycogenolysis
Adipose tissue—$beta_1$	Lipolysis

Pharmacologic Properties:

Beta adrenoreceptor blocking agents or beta blockers, are synthetic drugs which antagonize the beta adreno receptor-mediated activity of the sympathetic nervous system. A multitude of beta blocking preparations are now available on the market, and each has its own characteristic, pharmacodynamic properties. These are summarized in table 2.

The beta blocking activity of each preparation on weight basis, is judged by inhibition of isoprenaline tachycardia. These differences have not been shown to be of any practical significance.

Besides abolishing the effects of endogenous transmittor substances, certain beta blockers such as alprenolol, oxprenolol and pindolol are also able to cause minimal beta receptor-mediated activity by themselves. This property of intrinsic sympathomimetic activity (ISA) is of clinical significance when selecting a beta blocker for a patient with a slow resting heart rate.

Beta 1 selectivity refers to the greater affinity of certain beta blockers, such as atenolol,

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Table 2:

Beta-blocker	*Beta-blocking activity (propranolol =1)*	*Intrinsic sympathomimetic activity (ISA)*	*Beta-selectivity*	*Membrane stabilizing activity (MSA)*	*Bioavail-ability (% of dose)*	*Elimination halflife after oral administration (h)*	*Variations in plasma levels*
Alprenolol	0.3	+	0	+	10	2-3	10-20-fold
Atenolol	1	0	+	0	≥40	3-4	3-fold
Metoprolol	1	0	+	0	50	3-4	7-fold
Oxprenolol	0.5-1	+	0	+	24-60	1-2	5-fold
Pindolol	6	+	0	+	100	3-4	4-fold
Practolol	0.3	+	+	0	100	5-13	2-fold
Propranolol	1	0	0	+	30	2-3	20-fold
Sotalol	0.3	0	0	0	≥60	5-6	4-fold
Timolol	6	0	0	0	50	4-5	20-fold

metoprolol for beta 1 receptor sites than beta 2 receptor sites. This property is useful in certain clinical situations, although its significance is reduced with increase in dosage.

The membrane stabilizing activity (MSA) or quinidine-like action seems to be of importance only under experimental conditions or in vitro.

GI absorption of beta blockers is generally good. In spite of this the bioavailability of several preparations remains low. The low bioavailability is due to theirb iotransformation in the liver, especially with the first pass metabolism. This leads to a great individual variation in plasma levels.

Other reasons besides the bioavailability, for individual variations are not very clear. The binding to plasma proteins, formation of active metabolites, elimination of beta blockers or receptor sensitivities have been suggested. In general, precise pathways of metabolism of the beta blockers have yet to be determined.

The elimination half life of beta blockers in plasma is generally short, but the duration of beta blockade seems to be longer than the time required for the elimination of the drug from the plasma. Thus, for example, plasma half life of propranolol is three hours, whereas the inhibition of exercise tachycardia persists for nine hours. This may explain the effectiveness of long dosage intervals in certain conditions although the information available on the therapeutic plasma concentration of several beta blockers—in several diseases—is still scarce.

Clinical Uses:

1. *Hypertension:* All beta blockers, whatever their ancillary properties, are effective in reducing blood pressure in hypertension. No significant differences have yet been demonstrated in the antihypertensive effects of different beta blockers in individually adjusted optimal doses. The choice of beta blocker therefore should be based on its known or anticipated side effects, which vary from one preparation to another.

As for subjective side effects, it is usually possible to find a suitable beta blocker for each individual. In terms of patient compliance, a single daily dose in the morning is advisable and also possible with any beta blocker with maintaining the antihypertensive effect for 24 hours. Two daily doses are recommended for certain beta blockers, when the required daily dose is high.

The antihypertensive mechanism is generally thought to be mediated by the combined responses of the circulatory system (decreased heart rate, decreased contractility and thus decreased cardiac output), the central nervous system and the renin-angiotensin system.

2. *Angina pectoris:* In the imbalance of myocardial oxygen consumption and supply responsible for the ischemic pain the beta blockers work either by reducing the oxygen consumption or by increasing the oxygen supply or both. This is achieved by reducing the heart rate, the myocardial contractility and the blood pressure. The resultant cardiomegaly however is an adverse effect and increases the oxygen consumption to certain extent.

All beta blockers when compared to propranolol have been shown in many studies to be equally effective in treatment of angina provided the therapeutic potency has been ascertained. The ISA and MSA appear to have no significance. The beta selectivity theoretically offers some advantages, but no superiority in the relief of angina has been demonstrated in clinical practice.

Some features of the patient with angina pectoris influencing the choice of a preparation are (a) if heart rate below 60/min, ISA blocker is preferable. (b) in patients with bronchoconstriction, insulin-dependent diabetes and Reynauds phenomena a beta 1 selective compound is preferable.

Calculation of "complete beta blockade' is best ascertained by considering both the resting and exercise-induced tachycardia; plasma levels have not been demonstrated to provide a helpful guide. The practical target for a resting heart rate should be approximately 50-60 beats/min.

In cases of needs of beta blockade withdrawal it is recommended that it not be stopped suddenly but withdrawn gradually over a period of days.

Vasodilators can be used simultaneously with the beta blockers for relief of angina and do not pose a serious problem in management. Beta blockers also suggest an improved survival in patients who have undergone bypass surgery.

Beta blockers along with vasodilators have been shown to be extremely useful in the management of *unstable angina*. This therapeutic modality has not only been able to provide significant relief but has been shown to decrease both the incidence of infarction and that during the acute phases.

In patients with *variant angina* where coronary spasm has been demonstrated to be responsible for both the clinical and electrocardiographic pictures, beta blocker drug should not be used except in special circumstances where coronary arteriography has demonstrated in addition to spasm, fixed lesions as well. The most logical therapeutic rationale however in such patients is the newer calcium antagonist either alone or in combination with beta blockers.

3. *Myocardial infarction:* Beta blocking drugs have previously been considered absolutely contraindicated in myocardial infarction but at the present time these are used to (a) treat rapid arrhythmias and (b) limit the size of the infarct.

As the tachyarrhythmias, especially those of the supraventricular and sinus origin will make the heart more prone to progressive ischemia, beta blockade therefore appears particularly suitable for decreasing these fast rates. Many studies in recent times using various forms of beta blockers have shown a reduction of infarct size, relief of chest pain and reduction of sudden death and reinfarction with long term use. No single beta blocker appears to be the drug of choice, few axioms from recent symposium which may be helpful are:

(a) differences among the various blockers—i.e. cardioselectivity, ISA and MSA—are clinically inconsequential with regard to the selection of an agent for use in the post MI patient. It is the beta blocking ability of these drugs that appears to confer the beneficial effect. (b) in choosing the most situable beta blocking agent the physician should use the agent with which he has had the most clinical experience. (c) dosage and duration should be determined by the lowest dose which produces beta blockade regardless of the number of milligrams necessary to achieve the desired effect. (d) once it has been decided that the beta blocker therapy is indicated in the patient who has experienced myocardial infarction, such treatment should be continued indefinitely.

There are certain contraindications for beta blockers during myocardial infarction and they should be kept in mind. Therse are cardiogenic shock, severe pump failure, hypotension (systolic pressure less than 100 mmHg), bradycardia of 50 beats/min, second and third degree AV block and broncho-constriction.

4. *Arrhythmias:* The antiarrhythmic effects of beta blocking drugs is based on a direct antiadrenergic effect. The arrhythmias which respond to beta blockade in most cases are sinus tachycardia, supraventricular tachycardias, especially atrial fibrillation (the arrhythmia may not be converted but the ventricular rate is easily controlled with or without antiarrhythmic drugs such as digitalis), tachycardias in cases of hyperthyroidism and WPW are special indications for beta blocker therapy. Beta blockers are also very efficacious in the control of arrhythmias in any setting with special emphasis in patients with prolonged QT interval, mitral valve prolapse syndrome and IHSS. In the latter situation the beta blockers also help in decreasing the outflow gradient.

Beta blockers are certainly contraindicated in cases of heart block, in sick sinus node syndrome and in accelerated idioventricular rhythm.

5. *Special circumstances:* (a) hyperthyroidism; beta blockers provide an efficacious mechanism to control the tachycardia or hyperthyroidism prior to and also in conjunction with antithyroid drugs. (b) IHSS as indicated earlier, these beta blockers not only by decreasing the contractility lower the outflow gradient but also help control the ventricular tachyarrhythmias.

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