Beta adrenergic blockers: Pharmacological and anesthetic considerations

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Because anesthesia providers will be called upon to manage patients who are receiving beta blockers, they must be familiar with this classification of drugs. This article features a brief review of the physiology of the adrenergic nervous system and its beta receptor, followed by the pharmacodynamic properties and clinical applications of beta blockers. The selective beta antagonists are emphasized. The author concludes with a discussion of anesthetic considerations for the patient who has received these drugs preoperatively, and precautions for the intraoperative administration of beta-adrenergic receptor blocking drugs.

The perioperative management of patients with cardiovascular disorders is dependent upon an understanding of the disease process and the impact of an uncontrolled autonomic nervous system on the underlying pathology. It has long been recognized that cardiovascular depression can be reversed by drugs that augment the autonomic nervous system. In recent years, however, the hazards of an overactive sympathetic nervous system on cardiovascular function have been identified. Drugs that antagonize these deleterious effects soon appeared.

The introduction of beta adrenergic blocking drugs into clinical medicine has provided one of the major pharmacotherapeutic advances of the past several decades. Although the non-selective beta blocking drug propranolol is still widely used, recent attention has been focused on newer beta blockers.

The beta adrenergic blocking drugs play a major role in the medical management of patients with hypertension, angina pectoris, and dysrhythmias. Optimal care of these patients requires an in-depth understanding of the non-selective as well as the newer selective beta receptor blocking drugs.

The sympathetic nervous system

The autonomic nervous system plays a major role in maintaining homeostasis. Two major divisions of this system, the sympathetic and the parasympathetic, consist of neurons and ganglia which innervate glands, the heart, blood vessels, and visceral smooth muscle. In general, the two divisions have antagonistic effects. The parasympathetic segment functions to conserve or restore the organism, while the sympathetic segment prepares the organism for "fight or flight."1

Pharmacologically, these systems are classified as cholinergic or adrenergic systems. Cholinergic is a term that describes those fibers that release acetylcholine as their neurotransmitter. Acetylcholine evokes a physiological response by interacting with nicotinic or muscarinic cholinergic receptors. Adrenergic is a term describing those fibers that release norepinephrine as their neurotransmitter. Norepinephrine evokes a response by interacting with alpha or beta adrenergic receptors. The com-
ponents of the peripheral autonomic nervous system, their receptors, and the general effects of receptor stimulation are summarized in Table I.²

The sympathetic division of the autonomic nervous system originates from cells located in the lateral horns of the spinal cord from T₁ to L₂-₃. These preganglionic fibers leave the cord and synapse with postganglionic nerve cells located in the ganglia on each side of the vertebral column or in the abdominal cavity. Once a synapse has occurred, the impulse is carried by postganglionic fibers to the adrenergic neuroeffector junction. The adrenergic neuroeffector junction consists of a postganglionic nerve terminal, a synaptic gap, and an adjacent effector cell. The nerve terminal contains the machinery for the synthesis, storage, release and metabolism of the adrenergic neurotransmitter. The adjacent effector cell contains the adrenergic receptors, which are specific cellular structures capable of the selective binding of neurotransmitters or synthetic compounds.

In 1948, Ahlquist postulated the existence of two types of adrenergic receptors. He called these receptors alpha and beta.³ Approximately 30 years later, Lands identified the existence of two types of beta receptors, which he called beta₁ (cardiac) and beta₂ (noncardiac). More recently, presynaptic alpha receptors have been identified. This

Table I
Autonomic nervous system

<table>
<thead>
<tr>
<th>Sympathetic</th>
<th>Parasympathetic</th>
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<tbody>
<tr>
<td>ACh</td>
<td>ACh</td>
</tr>
<tr>
<td>Nicotinic</td>
<td>Nicotinic</td>
</tr>
<tr>
<td>1. Stimulation of autonomic ganglia</td>
<td>1. Stimulation of inhibition of smooth muscle</td>
</tr>
<tr>
<td>2. Stimulation of adrenal medulla to release catecholamines</td>
<td>2. Stimulation of exocrine glands</td>
</tr>
<tr>
<td>NE</td>
<td>ACh</td>
</tr>
<tr>
<td>Adrenergic receptors</td>
<td>Muscarinic receptor</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Alpha</strong></td>
<td><strong>Beta₁</strong></td>
</tr>
<tr>
<td>1. Vasoconstriction</td>
<td>1. Increased heart rate</td>
</tr>
<tr>
<td>2. Increased contractility</td>
<td>2. Stimulation of exocrine glands</td>
</tr>
<tr>
<td>3. Increased conduction velocity</td>
<td>3. Decreased cardiac conduction</td>
</tr>
<tr>
<td>4. Increased myocardial demand</td>
<td>4. Decreased myocardial contractility</td>
</tr>
<tr>
<td><strong>Beta₂</strong></td>
<td></td>
</tr>
<tr>
<td>1. Dilatation of bronchioles</td>
<td></td>
</tr>
<tr>
<td>2. Dilatation of arterioles</td>
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</tr>
</tbody>
</table>

preganglionic fibers
postganglionic fibers
has led to the division of alpha receptors into alpha, (postsynaptic) and alpha\(_2\) (presynaptic).\(^4\)

As can be seen in Table II, stimulation of noncardiac beta receptors results in an inhibitory physiological response.\(^5\) In contrast, stimulation of cardiac beta receptors leads to an excitatory response with increased heart rate and contractility. There is some question today as to whether the beta\(_1\) receptors should be further subdivided into groups of those responsible for heart rate changes and those affecting contractility.\(^6\)

The specific effects of postsynaptic alpha\(_1\) stimulation include vasoconstriction in all blood vessels. The presynaptic alpha\(_2\) receptor seems to be autoregulatory in nature. Stimulation of this receptor by norepinephrine inhibits the further release of this neurotransmitter from the nerve terminal. In other words, once liberated, norepinephrine inhibits its own release.

**The second messenger**

Although their function and location are described, adrenergic receptors have not been isolated chemically. However, the concept of a postsynaptic alpha or beta receptor is used to explain the biologic response initiated following drug or hormone interaction with the plasma membrane of the target cell. Conceptually, the receptor is located on the outer surface of the target cell. The combination of a drug or hormone with its specific receptor leads to the stimulation of adenylate cyclase, which is bound to the plasma membrane.

The increased activity of adenylate cyclase increases the amount of cyclic adenosine mono-phosphate (cyclic AMP or cAMP) inside the cell. Cyclic AMP, also known as the second messenger, acts inside the cell to alter the rate of one or more intracellular processes. The result is a physiological or pharmacological response. Inhibition of the intracellular enzyme phosphodiesterase, which is responsible for inactivation of cyclic AMP, leads to an accumulation of the "second messenger" and production of a biologic response indistinguishable from that provoked by a neurotransmitter. Aminophylline produces a beta effect by inhibition of the phosphodiesterase enzyme.\(^7\)

**Pharmacologic aspects of beta receptor blockade**

In order to understand the pharmacological characteristics of nonselective or selective beta blocking drugs, some basic pharmacological terms should be defined. A competitive antagonist can be defined as a drug that combines reversibly with the same receptor site as the agonist. In other words the antagonist, or inhibitor, will occupy the same receptor sites as the agonist, or stimulator, but no biological response will occur. The antagonistic response can be overcome by increasing the concentration of the agonist. In contrast, noncompetitive or irreversible antagonism is characterized by no reversal of block. In the latter case, increasing agonist concentration will not restore the original response. To date, all clinically useful beta blocking agents are competitive agents.

Other terms that relate to beta blockade include affinity and intrinsic activity. Affinity is a measure of the ability of an agonist or antagonist

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**Table II**

Classification of responses of various organs to adrenergic stimulation

<table>
<thead>
<tr>
<th>Organ</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td></td>
</tr>
<tr>
<td>SA node</td>
<td>B(_1) Tachycardia</td>
</tr>
<tr>
<td>Atria</td>
<td>B(_1) Increased automaticity</td>
</tr>
<tr>
<td>AV node</td>
<td>B(_1) Increased conduction velocity</td>
</tr>
<tr>
<td>Ventricle</td>
<td>B(_1) Increased contractility and conduction velocity</td>
</tr>
<tr>
<td>Blood vessels</td>
<td></td>
</tr>
<tr>
<td>Skeletal muscle, heart, brain</td>
<td>B(_2), a Vasodilatation, constriction</td>
</tr>
<tr>
<td>Skin, gut, liver, kidney</td>
<td>a Vasoconstriction</td>
</tr>
<tr>
<td>Bronchi</td>
<td>B(_2) Relaxation</td>
</tr>
<tr>
<td>Eye</td>
<td>B Relaxation for far vision</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>a, B(_2) Reduction of motility</td>
</tr>
<tr>
<td>Metabolic</td>
<td>a, B(_2) Glycogenolysis, gluconeogenesis</td>
</tr>
</tbody>
</table>

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to form a complex with a receptor. Intrinsic ac-
tivity describes the biologic effectiveness of the
drug-receptor complex.

In recent years, it has been recognized that
some beta blockers retain a degree of agonist
activity with respect to the same receptor. This
property is known as *intrinsic-sympathomimetic
activity*. Drugs that are commonly used clinically,
such as propranolol and metoprolol, lack this
property. The non-selective beta blocker pindolol
has this property. To date, it is not clear whether
drugs with intrinsic sympathomimetic activity are

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**Figure 1**
Currently available beta blocking drugs

<table>
<thead>
<tr>
<th>Adrenergic agonist</th>
<th>Nonselective beta antagonist</th>
<th>Selective beta antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>I soproterenol</td>
<td>Propranolol (Inderal®)</td>
<td>Atenolol (Tenormin®)</td>
</tr>
<tr>
<td>HO-CHCHNH-OH-CH(CH3)2</td>
<td>OCH2CHCH-NA-OH-CH(CH3)2</td>
<td>OCH2CHCH2-N-CH(CH3)2-CH200NH2</td>
</tr>
<tr>
<td>Timolol (Blocadren®)</td>
<td>Nadolol (Corgard®)</td>
<td>Metoprolol (Lopressor®)</td>
</tr>
<tr>
<td>OCH2CHCH2NHCH-CH(CH3)2</td>
<td>OCH2CHCH2NHCH(CH3)2</td>
<td>OCH2CHCH2NHCH(CH3)2</td>
</tr>
<tr>
<td>Pindolol (Visken®)</td>
<td></td>
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</tbody>
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safer in patients at risk from beta-blockade, but it seems that this might be the case.\textsuperscript{8}

The structure of the beta blocking agents appears to affect their activity. In reviewing the structural formula of currently available beta blocking drugs, it is apparent that the chemical structures of the beta antagonist have several features in common with isoproterenol. (Figure 1.) The 2-C side chain with an alkyl substituted secondary or tertiary amine seems to determine the affinity for the beta receptor. The larger the alkyl group, the greater the affinity for the beta receptor. The nature of the substituents on the aromatic ring determines whether the effect will be predominantly activation or blockade.

**Beta antagonism: The prototype**

For many years, propranolol was the only beta adrenergic blocking drug available for clinical use in the United States. Propranolol is a nonselective beta adrenergic blocking agent that is used widely for the treatment of hypertension, the prophylaxis of angina pectoris, and the control of certain types of cardiac dysrhythmias. It blocks both $B_1$ and $B_2$ receptors competitively and does not exhibit any intrinsic agonistic properties.

Several mechanisms contribute to propranolol's usefulness as an antihypertensive. A decrease in heart rate and myocardial contractility leads to a decrease in cardiac output and thus arterial blood pressure. In addition, propranolol blocks the release of norepinephrine from adrenergic nerve terminals. This effect might contribute to its antihypertensive effect. The release of renin from the juxtaglomerular apparatus is stimulated by $B_2$ adrenergic agonist. Renin leads to formation of angiotensin II, which enhances sodium and water reabsorption in the distal segment of the nephron by increasing the release of aldosterone. In addition, angiotensin II leads to vasoconstriction. The release of renin is blocked by drugs such as propranolol.

Propranolol is second only to nitroglycerin in its effectiveness in the management of angina. The administration of this drug results in decreased heart rate, systolic blood pressure, and force and rate of myocardial oxygen consumption, and improved myocardial oxygen supply and demand ratio.\textsuperscript{9}

The beta adrenergic blockers have pronounced effects on cardiac rhythm and automaticity. Propranolol reduces sinus rate, decreases the spontaneous rate of depolarization of ectopic pacemakers, and slows conduction in the atria and in the atrioventricular node. Large doses of the drug exert a quinidine-like effect on the myocardium, which might also contribute to its antiarrhythmic effect.

A number of other conditions respond to treatment with propranolol. With hypertrophic obstructive cardiomyopathies, forceful myocardial contraction can increase outflow resistance. Beta blocking drugs have been shown to improve hemodynamic parameters in these patients. In patients with pheochromocytoma, propranolol is useful in the management of tachycardia and arrhythmias. However, because beta blockade leaves alpha receptors unopposed, propranolol should not be administered to a patient with a pheochromocytoma unless alpha adrenergic blockade is also present. Hyperthyroidism and anxiety states are improved by beta blockade. In addition, the drug is useful in the prophylaxis of migraine headache. As the pathophysiology of migraine is poorly understood, it is not surprising that the mechanism of action of propranolol also is unknown. It is useful in preventing migraine attacks in some patients, however.

Although the beta blocking drugs are useful in certain cardiovascular disorders, troublesome side effects can occur. Propranolol consistently increases airway resistance. Although this effect is small and of no clinical significance in normal individuals, it can be marked and potentially dangerous in asthmatics. Since this drug prolongs atrioventricular conduction, it should be avoided in patients with greater than first degree heart block. Patients with congestive heart failure depend on their intrinsic sympathetic tone to augment a failing circulation. Because of this, beta blockers should generally be avoided in patients with congestive heart failure. A possible exception to this rule, however, is the patient who has cardiac failure secondary to a serious tachyarrhythmia.

The pharmacokinetics of the beta blocking drugs have been studied extensively. Current information is summarized in Table III. Although propranolol is almost completely absorbed following oral administration, much of the administered drug is metabolized by the liver during its first passage through the portal circulation. Only about one-third of the drug reaches the systemic circulation. Propranolol is completely metabolized before excretion in the urine. One of the products of hepatic metabolism, 4-hydroxypropranolol, possesses beta-blocking activity comparable to the parent compound. The half-life of the metabolite is short, however, and it probably contributes little to the therapeutic effect of the drug.

In the management of hypertension, propra-
nolol is administered orally. An initial dose of 40 mg twice daily is gradually increased to 160 to 480 mg per day. In the treatment of angina pectoris or for the control of dysrhythmias, doses of 40 to 320 mg per day are usually given. Propranolol may be administered intravenously for the management of ST changes of ischemia associated with tachycardia, recurrent ventricular arrhythmias, or significant atrial tachyarrhythmias. Under these circumstances the usual dose is 0.25-0.5 mg, administered slowly over 1 to 2 minutes. The total dose rarely exceeds 2-3 mg and during intravenous administration, one should carefully observe blood pressure, ECG, and cardiac function.

**New nonselective beta blockers**

Timolol (Timoptic®, Blocadren®) is a nonselective beta adrenergic antagonist that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic activity. It is five to 10 times more potent than propranolol as a beta blocking agent, and its duration of action after oral administration is approximately four hours.

Although clinical studies suggest that timolol may be effective as an antihypertensive agent, its primary use is as an ophthalmic preparation for the treatment of chronic wide angle glaucoma. The precise mechanism of the ocular hypotensive action has not been clearly established. Studies in man suggest, however, that its predominant action may be related to reduced aqueous formation and a slight increase in outflow.

Timolol is administered as eyedrops in solutions of 0.25 or 0.5%. The recommended dosage is one drop of 0.25% timolol solution in each eye twice a day. The duration of beneficial effect is in excess of seven hours. For hypertension, the initial dose is 10 mg twice a day. The usual total maintenance is 20 to 40 mg per day. As with propranolol, timolol ophthalmic solution must be used with caution in patients with known contraindications to the systemic use of beta-adrenergic receptor blocking agents. Patients receiving timolol ophthalmic solution should be carefully screened preoperatively for possible effects of timolol on the cardiac conduction system. In the presence of severe bradycardia or heart block, timolol should be discontinued before elective surgery until a normal heart rate is restored. If the clinical situation does not permit discontinuation, atropine, isoproterenol, and a temporary pacemaker should be available perioperatively.

Nadolol (Corgard®) is a synthetic nonselective beta-adrenergic receptor blocking agent. Like propranolol, it inhibits both the beta₁ receptors located chiefly in cardiac muscle and the beta₂ receptors located in the bronchial and vascular musculature. Nadolol has no intrinsic sympathomimetic activity and, unlike some other beta blockers, it has little direct myocardial depressant activity.

Nadolol is indicated in the management of hypertension and in the long-term management of patients with angina pectoris. Although the mechanism of its antihypertensive effect has not been clearly established, factors that may be involved include competitive antagonism of catecholamines at peripheral adrenergic neuron sites, leading to a decreased cardiac output, and a central effect leading to a reduced sympathetic outflow to the periphery. Also playing a role is suppression of

<table>
<thead>
<tr>
<th>Table III</th>
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<tbody>
<tr>
<td>Pharmacokinetics and elimination kinetics of beta blockers</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Absorption</th>
<th>Bioavailability</th>
<th>Elimination half-life</th>
<th>Metabolism</th>
<th>Elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-selective Blockers:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>&gt; 90%</td>
<td>30%</td>
<td>3.5-6 hrs.</td>
<td>Hepatic</td>
<td>Kidney</td>
</tr>
<tr>
<td>Timolol</td>
<td>&gt; 90%</td>
<td>50%</td>
<td>4-5 hrs.</td>
<td>Hepatic</td>
<td>Kidney &amp; Liver</td>
</tr>
<tr>
<td>Nadolol</td>
<td>30%</td>
<td>30%</td>
<td>20-24 hrs.</td>
<td>—</td>
<td>Kidney</td>
</tr>
<tr>
<td>Pindolol</td>
<td>&gt; 90%</td>
<td>10%</td>
<td>3-4 hrs.</td>
<td>Hepatic</td>
<td>Kidney &amp; Liver</td>
</tr>
<tr>
<td>Selective Blockers:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>&gt; 95%</td>
<td>50%</td>
<td>3-4 hrs.</td>
<td>Hepatic</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Atenolol</td>
<td>50%</td>
<td>40%</td>
<td>6-9 hrs.</td>
<td>—</td>
<td>Kidney</td>
</tr>
</tbody>
</table>
renin secretion by blockade of the beta adrenergic receptors responsible for renin release.

By blocking catecholamine-induced increases in heart rate, velocity and extent of myocardial contraction, and blood pressure, nadolol reduces the oxygen requirements of the heart. This effect makes it useful in the long-term management of patients with ischemic heart disease.

As can be seen in Table III, absorption of nadolol after oral administration is approximately 30%. Peak serum concentrations usually occur in three to four hours. Approximately 30% of the nadolol present in the serum is reversibly bound to plasma proteins. The half-life of therapeutic doses of this agent is approximately 20 to 24 hours. This permits once daily dosage. Unlike many other beta blocking drugs, nadolol is not metabolized, and thus it is excreted unchanged by the kidney. As expected, the elimination half-life is increased in patients with renal failure.

In patients with ischemic heart disease, the initial dose of 40 mg of nadolol is gradually increased until there is pronounced slowing of the heart rate. The usual maintenance dose is 80 to 240 mg administered once daily. Most patients respond to 160 mg or less daily. In hypertensive patients, the usual maintenance dose is 80 to 320 mg. Like other nonselective beta blocking agents, nadolol is contraindicated in patients with cardiac failure, bronchospastic disease, and greater than first degree heart block.

Pindolol (Visken®) is a synthetic beta adrenergic receptor blocking agent which possesses intrinsic sympathomimetic activity but does not possess quinidine membrane stabilizing activity. It is currently being used in the management of hypertension. Like other nonselective beta blockers, it is contraindicated in patients with bronchial asthma, overt cardiac failure, second or third degree heart block, or severe bradycardia.

Due to its beta receptor antagonism, pindolol attenuates increases in heart rate, systolic blood pressure, and cardiac output. The intrinsic sympathomimetic activity or partial agonist activity is mediated directly at the adrenergic receptor. Such activity is characterized by smaller reductions in the resting heart rate than what is seen with drugs that lack the intrinsic sympathomimetic activity. It appears that the property of intrinsic sympathomimetic activity is capable of reducing bronchospasm. Some patients with hyperactive airways that have not tolerated other beta blockers have improved with pindolol.11

Pindolol is rapidly absorbed from the gastrointestinal tract and has no significant first pass hepatic metabolism. It undergoes extensive metabolism, however. Approximately 60% is metabolized to an inactive metabolite and 40% is excreted unchanged in the urine. The half-life of this drug in healthy subjects or hypertensive patients with normal renal function is three to four hours.

Selective beta blockers

Metoprolol (Lopressor®) is a relatively selective beta1 adrenergic antagonist that is devoid of agonistic activity. Its preferential selectivity for beta1 receptors makes this an attractive drug for the patient with cardiovascular pathology and co-existing increased airway resistance. It should be remembered, however, that the preferential selectivity is not absolute. It is cardioselective but not cardiospecific. At higher doses, metoprolol inhibits beta2 adrenergic receptors of the bronchial and vascular musculature.

Metoprolol is efficiently and rapidly absorbed from the gastrointestinal tract. However, metoprolol, like propranolol, is subject to first-pass metabolism in the liver. In man, only 40% of the drug reaches the systemic circulation. The half-life of this drug is approximately three hours. It is extensively metabolized in the body but the metabolites appear to lack significant pharmacological activity. Less than 10% of this drug is excreted unchanged.

Metoprolol is primarily used in the treatment of hypertension. Although it is generally well tolerated, patients with bronchospastic disorders have developed bronchospasm after using it. Like other agents with beta1 blocking activity, metoprolol is contraindicated in sinus bradycardia and overt cardiac failure.

Atenolol (Tenormin®) is a beta1 cardioselective adrenergic blocking agent which does not possess membrane stabilizing or intrinsic sympathomimetic activity. It is indicated in the management of hypertension and is contraindicated when bradycardia or cardiac failure are present.

Absorption of an oral dose of atenolol is rapid but incomplete. Approximately 50% of an oral dose is absorbed from the gastrointestinal tract, and the remainder is excreted unchanged in the feces. It undergoes very little hepatic metabolism and the absorbed portion is eliminated primarily by renal excretion. The elimination half-life of atenolol is approximately six to seven hours. Following doses of 50 to 100 mg, beta-blocking and antihypertensive effects persist for approximately 24 hours.

Selective beta blockers theoretically have two advantages. Beta1 selective agents are safer than
nonselective agents in patients with acute or chronic obstructive pulmonary disease because beta2 receptors remain available to influence adrenergic bronchodilation. More importantly, the use of these drugs preserves responsiveness to therapy with beta2 stimulants even at high doses. Diminished beta2 blockade also reduces side effects in patients with other diseases that are sensitive to these pharmacological effects. Patients who might fall into this category include those having peripheral vascular disease with intermittent claudication and those having diabetes mellitus.

Combined alpha and beta blockers

Until 1972, only alpha or beta adrenergic antagonists were available. Labetalol, which was introduced in 1972, is a unique adrenergic antagonist that is effective at both alpha and beta receptors. It is approved for treatment of hypertension in Great Britain and is also being investigated for the therapy of angina pectoris and dysrhythmias. It is available for both intravenous and oral use. Clinical trials with this drug are just beginning in the United States.12

Labetalol is a competitive antagonist that is six to 10 times less potent than phentolamine at alpha receptors, and 1.5 to four times less potent than propranolol at beta receptors. It is four to 16 times less potent at alpha than at beta receptors. Like propranolol, labetalol is a nonselective beta antagonist. It is, however, four times less potent than propranolol to the heart and 11 times less potent than propranolol to the lungs. It produces less bronchoconstriction than propranolol at similar degrees of cardiac beta blockade.

By efficiently blocking both the alpha receptors of the resistance vessels and the beta receptors of the heart, labetalol can be expected to lower blood pressure by decreasing the systemic vascular resistance. The reduction in blood pressure occurs without a reflex increase in heart rate. In addition to its antihypertensive effect, labetalol increases exercise tolerance in patients with ischemic heart disease. At equipotent doses, the latter effect is more pronounced with labetalol than propranolol. Because of its combined alpha and beta antagonism, labetalol should lower the heart rate and blood pressure more than propranolol. In addition, alpha receptors are present in the coronary arteries. Labetalol increases coronary blood flow and may prove to be useful in the management of coronary spasm.

Labetalol is well absorbed when administered orally. Like propranolol, a considerable fraction of the drug is metabolized in the first circulation through the liver. Its half-life in plasma is approximately five hours, and about 5% of the drug is excreted unchanged in the urine. It is a potent hypotensive agent.

Beta blockers and the surgical patient

It has been estimated that more than 60 million prescriptions for beta blockers were written in the United States in 1980. Increasingly, anesthesia providers will be confronted with patients who are receiving these drugs. Proper management of patients on chronic beta blocker therapy in the preoperative period can significantly reduce the risks associated with anesthesia and surgery.

In 1972, Viljoen and associates recommended that propranolol be discontinued two weeks before surgery because of its known cardiac depressant action.13 Their recommendation was based on a study of five patients with advanced coronary artery disease who received propranolol to within 24 hours of surgery; four of the patients died, and the fifth had a stormy course. Although it appeared that propranolol was the culprit, subsequent exploration of these five cases revealed that they were not routine coronary artery bypass cases. All five patients had undergone operations carrying a higher mortality rate than routine coronary artery bypass operations. In addition, all were anesthetized with methoxyflurane, a known myocardial depressant.

Routine withholding of propranolol in the surgical patient was short lived. By 1975, reports indicating that this practice was hazardous began to appear. In one study, severe complications, which included two deaths, were observed in six out of 20 patients. Increased severity of angina pectoris was observed in an additional four patients.14 There is evidence today that the chronic occupation of beta receptors by beta antagonists can increase the number of beta receptors.15 Prolonged administration of a beta blocker can induce catecholamine hypersensitivity, which can lead to problems when the drug is suddenly withdrawn. Cessation of beta blockade leaves an increased number of active, unbound receptors. Interaction of adrenergic agonists with these receptors leads to an exaggerated response.16

The beta adrenergic withdrawal syndrome, a hyperadrenergic state that is apparently caused by supersensitivity to catecholamines, can occur anywhere between 24 hours and two weeks, although it is usually manifest between three and six days. The syndrome is characterized by hypertension, tachycardia, anxiety, and sweating. There is a dramatic increase in cardiac symptomatology. The
mechanisms responsible for the withdrawal syndrome are probably common to all beta blockers, not just propranolol.

Because of the hazards associated with the withdrawal syndrome, most authorities today recommend continuing propranolol up until the time of surgery. If surgery is scheduled for 8:00 am, the last dose of propranolol is often given at 10:00 pm the night prior to surgery. For operations later in the day, the last dose of propranolol may be given at 8:00 am. Some authors feel that the new long acting beta blockers, nadolol and atenolol, should be withheld the morning of surgery because of the prolonged duration of their pharmacological effects, and until more information is available regarding their interactions with anesthesia.

The continued administration of beta blockers through the perioperative period will minimize the occurrence of complications associated with the patient's preoperative disease. The lower heart rate is beneficial in reducing myocardial oxygen demand. Also, the incidence and severity of episodes of tachycardia, dysrhythmias, hypertension, and ischemia are probably decreased in patients maintained on beta blockers up to the day of surgery. Clinically, the resting heart rate is the best guide to receptor blockade. Effective beta block produced by propranolol is probably present when the resting heart rate is 50 to 60 beats per minute. Routine physical activity should be expected to increase the heart rate 10 to 20%. A patient on an optimal dose of propranolol has no evidence of congestive heart failure or atrioventricular heart block on the electrocardiogram.  

The rate of hepatic extraction of propranolol is very sensitive to changes in hepatic blood flow. Conceivably, reductions in hepatic blood flow produced by anesthetic drugs and surgical stimulation could accentuate the degree of existing beta block or exaggerate the pharmacologic effects produced by the intravenous injection of propranolol during the intraoperative period. A single oral dose of cimetidine has been shown to reduce hepatic blood flow. Chronic treatment with cimetidine reduces hepatic blood flow and accentuates the decreased heart rate. This effect is probably related to decreased hepatic clearance of the drug. This observation is important, because many patients receive cimetidine as part of their preoperative medication in an attempt to increase the pH of gastric fluid prior to the induction of anesthesia.

Interactions between beta antagonist drugs and drugs likely to be used during anesthesia are predictable. Knowledge of these interactions makes the management of patients being treated with beta antagonist drugs safer. Anesthetic agents can be divided into those that depend on the release of endogenous catecholamines to counteract their depressive effects and those that do not. Ether, cyclopropane, and ketamine depend on endogenous catecholamines for circulatory integrity. Those anesthetic agents that do not depend on catecholamine release for circulatory stability include halothane, narcotics, enflurane, and isoflurane.

If ether and cyclopropane were used today, it would appear prudent to avoid beta blockade with these anesthetics. Since ketamine appears to be similar to ether in regard to its dependence on endogenous catecholamines for circulatory stability, it may be wise to avoid it in combination with beta blockers. In dogs, the cardiac depressant effects of halothane and propranolol are additive. Cardiac depression in the presence of propranolol and 1% inspired halothane is similar to that depression produced by 1.5% inspired halothane in the absence of propranolol. This additive myocardial depression produced by propranolol is not considered to be excessive or dangerous, however.

Similar studies suggest that isoflurane is more compatible with beta blockade than halothane. Cardiac depression produced by enflurane in combination with propranolol is greater than that observed during therapy with beta block and halothane. Despite these differences, there is no clinical experience to support the preferential selection of one of these agents over another in a patient receiving beta blockers. In contrast, the appearance that beta antagonist drugs do not increase the operative risk, and they should not be discontinued preoperatively. In the author's experience, patients with high degrees of beta blockade tolerate narcotic or halothane anesthesia well. Enflurane anesthesia, however, may be poorly tolerated by these patients.

The choice of muscle relaxants may be influenced by pre-existing beta blockade. Pancuronium would be a good choice because it does not decrease blood pressure and the beta blockade would tend to attenuate any increase in heart rate produced by the drug. Because propranolol results in a parasympathetic dominance, it would appear that the muscarinic effects of succinylcholine could be exaggerated in the presence of beta blockade. In reality, however, the heart rate generally increases following administration of succinylcholine in patients receiving propranolol.

In some institutions, it is common practice to administer small amounts of intravenous propranolol 10 minutes prior to induction of anesthesia in borderline hypertensive patients. This effectively obviates the hypertensive response to laryngoscopy.
and surgical stimulation. Occasionally, patients will become weak and acutely dyspneic following a defasciculating dose of pancuronium or d-Tubocurarine that is given five minutes after the propranolol. The most reasonable explanation for this occurrence is the potentiation of nondepolarizing neuromuscular block by propranolol. In patients receiving high doses of beta blockers, this potentiation can be clinically significant. It is advisable to use a nerve stimulator to determine doses of nondepolarizing relaxants in these patients.

In patients who have received large doses of propranolol, profound bradycardia has been observed following the administration of neostigmine for reversal of the nondepolarizing block. In contrast, other investigators have not observed bradycardia when neostigmine or pyridostigmine are administered in the presence of beta blockade. It would appear, therefore, that it is acceptable to reverse nondepolarizing muscle relaxants with an anticholinesterase drug combined with an anticholinergic drug.

Intravenous injection of propranolol in the perioperative period is indicated for the control of supraventricular tachycardia, dysrhythmias, and occasionally for the treatment of systolic hypotension. The suggested dose rates at which propranolol is administered intravenously vary greatly. In most hospitals, it is administered in increments of 0.25 to 0.5 mg IV until the desired effect is achieved. In children, the increments are smaller.

On rare occasions, reversal of propranolol-associated circulatory depression during the perioperative period is necessary. In most instances, circulatory depression associated with beta adrenergic blockade consists of the combination of bradycardia and hypotension. Most hypotensive episodes during anesthesia will respond to the usual measures of decreasing the depth of general anesthesia and administering intravenous fluids. Bradycardia will usually respond to atropine or cardiac pacing.

In the unlikely event that these measures do not reverse the situation, adrenergic agonists such as isoproterenol or dopamine can be used to directly compete for the beta receptor. Large doses may be required. In the presence of normal doses of propranolol, the standard dose of isoproterenol may need to be increased 25 to 50 times. Because it works intracellularly at the level of the contractile proteins to improve myocardial contractility, calcium should be effective in reversing cardiac depression. A dose of 250 to 1000 mg of calcium chloride or calcium gluconate administered intravenously over 10 to 20 minutes will effectively bypass beta blockade and provide isotropic support. Aminophylline, 4 to 6 mg/kg, is effective in reversing bronchospastic problems related to beta blockade.

Finally, glucagon at a dose of 5 to 10 mg followed by a continuous infusion of 1 mg per minute may be effective in reversing beta blockade.

Summary

Beta adrenergic blocking drugs are being used for a multitude of cardiovascular and noncardiovascular conditions. Many patients receiving these drugs will be presenting for anesthesia and surgical procedures. Optimal management of these patients is dependent upon an understanding of the clinical pharmacology of these agents and knowledge of potential interactions between beta blockers and anesthetic drugs.

At the present time, this field of pharmacology is explosive. In recent months, numerous new selective and nonselective beta antagonists have been introduced. The anesthetist must be familiar with these drugs because side effects and drug interactions are expected to be similar to those seen with the prototype, propranolol.

REFERENCES


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