Clinical Pharmacology of Beta-Adrenergic Blockers

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The beta (β)-adrenoceptor blockers were introduced to clinical medicine in the early 1960's as drugs specifically designed to reduce the adrenergic influences on the heart and thereby be protective against angina pectoris. The developers of propranolol, the prototype for the β-adrenoceptor blockers, would have been amazed at the numbers of syndromes that are currently benefited by the use of the drug. In fact, the success of propranolol has spawned a number of other β-adrenoceptor blocking drugs so that now eight are on the market in the United States, and a number of others are available outside this country. This review briefly discusses the clinical pharmacology of these drugs, the differences between them, the mechanism of action for their use in the major cardiovascular illnesses and other syndromes for which they have been shown to be of benefit, and their side effects. A more complete review has been published recently.[1]

Clinical Pharmacology

All of the β-adrenoceptor blocking drugs act as competitive inhibitors of β-adrenoceptors present throughout the body, and most of their actions are mediated through the blockade of these receptors. There are two subtypes of β-adrenoceptors. The β_1-adrenoceptors are predominant in the heart and kidney and mediate the inotropic and chronotropic responses to catecholamines as well as the release of renin. These receptors are present at the junction of the adrenergic neuron with the effector organ, and thus β_1-adrenoceptors are said to be innervated. They respond both to norepinephrine released from adrenergic neurons and circulating epinephrine. β_2-Adrenoceptors are present in the lung, skeletal muscle, vascular smooth muscle, and liver and mediate bronchodilation, tremor, vasodilation, and certain metabolic effects. These adrenoceptors exist in areas outside the junction of the adrenergic neuron with the effector organ, and thus β_2-adrenoceptors are not thought to be innervated. They respond preferentially to circulating epinephrine rather than to norepinephrine. None of the organs has only one β-adrenoceptor subtype. For instance, the heart, which has predominantly β_1-adrenoceptors, may have as many as a third of the receptors of the β_2 subtype. The practical consequence of this overlap in receptors is that no matter how specific the agonist or antagonist is for one subtype, it is impossible to confine the effects of the agonist or antagonist to any given organ. For example, even if one were using a very specific β_2-adrenoceptor agonist to produce bronchodilation, there would still be some cardiac effect because of the β_2-adrenoceptors in the heart. In fact, currently available agonists and antagonists are not entirely specific for any one subtype of β-adrenoceptor, and at higher concentrations, both receptor subtypes will be affected to some extent.

β-Adrenoceptor blockade can be determined pharmacologically or physiologically. Pharmacologically, the degree of shift of the dose response curve of an agonist has been a useful way of assessing the degree of β-adrenoceptor blockade. Since the blockade is competitive, it can be overcome with a sufficient amount of the agonist, a fact that can be exploited in the treatment of overdoses or unwanted effects of β-adrenoceptor blockade.

A physiological way to determine the degree of β-adrenoceptor blockade is to determine the response to a sympathetic stress such as exercise. At rest, sympathetic tone is minimal, and heart rate is largely controlled by parasympathetic tone; thus a small amount of β-adrenoceptor blockade is all that is required to reduce maximally the sympathetic component of resting heart rate. As the amount of exercise is increased, more β-adrenoceptor blockade will be required to reduce maximally the sympathetic portion of exercise-induced tachycardia. However, there is a finite limit to the degree of sympathetic stimulation produced by any stress, and it is possible to give enough of a β-adrenoceptor antagonist to block nearly all of the effects of any physiological sympathetic stress.[2] It must be remembered that part of exercise-induced tachycardia is due to a reduction of parasympathetic tone rather than activation of sympathetic tone. Thus, one can achieve a heart rate up to 110 beats/minute from parasympathetic withdrawal without any sympathetic activation, and this degree of exercise-induced tachycardia cannot be blocked by β-adrenoceptor inhibiting drugs.

The β-adrenoceptor blocking drugs currently available differ in several ways (Tables 1 and 2). Propranolol and acebutolol have a property called "membrane-stabilizing effect." This effect is unrelated to β-adrenoceptor blockade and is related to blockade of sodium entry through channels in excitable tissues. This property has also been called "quinidine-like" or "local anesthetic." In usual doses, this effect is probably not of clinical consequence. However, at very high doses that are sometimes used clinically, this effect may have some importance, particularly in controlling cardiac arrhythmias.

β_1-Adrenoceptor selectivity is possessed by metoprolol, atenolol, and acebutolol. This property indicates that the drug has a higher affinity for the β_1-adrenoceptors than for the β_2-adrenoceptors. Thus, drugs with β_1-adrenoceptor selectivity will have more

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Table 1. Properties of Beta-Adrenoceptor Blocking Drugs

1. Membrane stabilizing activity (MSA): acebutolol, propranolol
2. β_1-Adrenoceptor selectivity (cardioselectivity): acebutolol, atenolol, metoprolol
3. Intrinsic sympathomimetic activity (ISA): acebutolol, pindolol
4. Lipid solubility: see Table 2
5. α-Adrenoceptor blockade: labetalol

effect on those organs that have predominantly β_1-adrenoceptors, such as the heart, than on other organs that have predominantly β_2-adrenoceptors, such as the lung or the peripheral vasculature. For this reason, β_1-adrenoceptor selectivity has been called "cardioselectivity." As noted above, however, the selectivity is only relative and β_2-adrenoceptors are affected by these drugs, particularly at higher doses.

Intrinsic sympathomimetic activity (ISA) is possessed by pindolol and acebutolol. This property has also been called "partial agonist" activity. The drugs possessing this property not only occupy the β-adrenoceptor with high affinity and thereby block the effects of epinephrine and norepinephrine, but they also stimulate the receptor a small amount on their own. Thus, drugs with ISA do not decrease resting heart rate as much as other β-adrenoceptor blocking drugs, and in individuals with extremely low sympathetic activity, such as those with autonomic insufficiency, these drugs may actually increase heart rate. However, when the adrenergic nervous system is stimulated, these drugs block the effects of the endogenous catecholamines so that stress-induced tachycardia is effectively blocked by drugs with ISA.

The β-adrenoceptors differ in lipid solubility. Propranolol has the highest lipid solubility and atenolol and nadolol the lowest. The importance of this effect is uncertain. The commonly accepted belief that drugs with low lipid solubility will not cross the blood brain barrier is not entirely correct. All of the β-adrenoceptor blocking drugs achieve levels in the cerebral spinal fluid. However, the more lipid soluble drugs cross the blood brain barrier more rapidly and more completely.[3] In addition, the lipid soluble drugs will concentrate in the lipid of the brain. This may account for the apparently higher incidence of central nervous system (CNS) side effects with drugs that have high lipid solubility. Lipid solubility also has another effect that is important to the use of β-adrenoceptor blocking drugs. Drugs with high lipid solubility must be metabolized by the liver before they can be excreted. Since the liver is the first organ that is encountered after drugs are absorbed into the portal circulation, a considerable amount (>50%) of orally administered drug may be removed by the liver before it ever reaches the systemic circulation. This "first-pass" or "presystemic" elimination of drug is important for several of the β-adrenoceptor blockers (see Table 2) and accounts for the large difference in oral versus intravenous dose for equivalent effects. The "first pass" elimination also accounts for large interindividual differences in blood levels and effects achieved after any given oral dose. If the liver is bypassed due to portal-systemic shunting, then oral administration of β-adrenoceptor blockers that have high "first-pass" elimination will produce much greater effects than in a normal individual. On the other hand, drugs with low lipid solubility are excreted unchanged by the kidney; renal disease, not liver disease, will alter the elimination of these drugs.

Table 2. Beta-Adrenergic Blockers

Drug	*Oral Bioav.*	*First Pass Metab.*	*Elim t½*	*Route of Elimin*	*Lipid Solubility*	*Usual Daily Dose*
Propranolol (Inderal)	10–30%	Yes	3–6 hrs.	Hepatic metab.	High	80–320 mg (q.i.d., b.i.d. except q.d. in hypertensives)
Metoprolol (Lopressor)	40–50%	Yes	3–6 hrs.	Hepatic metab.	Intermediate	100–400 mg (q.i.d., b.i.d. except q.d. in hypertensives)
Nadolol (Corgard)	24–35%	No	20 hrs.	Renal excretion	Low	80–240 mg (q.d.)
Atenolol (Tenormin)	60%	No	6–9 hrs	Renal excretion mainly	Low	50–100 mg (b.i.d., q.d.)
Timolol (Blocadren)	75%	Not significant	4–5 hrs	Hepatic metab. mainly (20% renal)	Intermediate	20 mg (b.i.d.)
Pindolol (Visken)	87%	small %	3–5 hrs	Hepatic metab. renal excretion 35%	Intermediate	10–30 mg (b.i.d.)
Labetalol (Trandate, Normodyne)	30%	Yes	4–6 hrs	Hepatic metab.	High	400–1200 mg (b.i.d.)
Acebutolol (Sectral)	35–50%	Yes (to active metabolite)	3–4 hrs (8–13 hrs metabolite)	Hepatic (parent) renal (metabolite)	Intermediate	400–1200 mg (b.i.d. except q.d. in hypertensives)

The final difference between these drugs is the other receptor blocking activities that they may possess. Labetalol has α_1-adrenoceptor blocking activity as well as β-adrenoceptor blocking activity. Although it has been claimed that the α_1-adrenoceptor blocking activity and the β-adrenoceptor blocking activity of labetalol are two properties in a single molecule, this is not true. Labetalol exists as four stereoisomers. One of these isomers contains the predominant β-adrenoceptor blocking activity whereas another isomer possesses the predominant α_1-adrenoceptor blocking activity.[4] Two of the isomers in the commercially available preparation are relatively inactive. Therefore, labetalol is actually a mixture of compounds, each with different properties.

Therapeutic Indications

Therapeutic indications for β-adrenoceptor blockade are listed in Table 3.

Angina pectoris. All of the β-adrenoceptor blockers tested have been useful in the treatment of angina pectoris, the syndrome for which these drugs were developed. The β-adrenoceptor blockers are effective in this syndrome by reducing cardiac oxygen demands, particularly during sympathetic stresses. The major action accounting for this effect is the reduction in heart rate, but a negative inotropic effect and a reduced arterial pressure may also be beneficial. If vasospasm of the coronary arteries is the cause of the angina pectoris, then β-adrenoceptor blockers often are of no benefit and may actually worsen the patient's symptoms.[5] Severe angina with pain at rest that is not due to vasospasm may be improved by β-adrenoceptor blockers, but in this situation, drugs that have intrinsic sympathomimetic activity may not be as beneficial as drugs without this property.[6]

Arrhythmias. Supraventricular tachyarrhythmias are another indication for β-adrenoceptor blockers. Propranolol has had the longest track record in this area. The drug will restore sinus rhythm in most patients who have paroxysmal supraventricular tachycardia and will slow the ventricular response in patients with atrial fibrillation and atrial flutter. The β-adrenoceptor blockers have also been used for ventricular arrhythmias. The drugs are extremely effective in abolishing arrhythmias that are caused by enhanced catecholamine secretion or enhanced sensitivity to catecholamines, as produced by some general anesthetics. The β-adrenoceptor blockers can also be used in other patients with ventricular arrhythmias with suppression of ectopic ventricular beats in 40 to 50% of such patients. One study found an increased response rate when propranolol was given at doses higher than those required to maximally block exercise tachycardia. This may be evidence that some antiarrhythmic effects of propranolol at high doses are related to a property other than β-blockade, such as the membrane stabilizing property of that drug.[7]

Table 3. **Therapeutic Indications for β-Adrenoceptor Blocking Drugs***

Major
Ischemic Cardiac Disease
angina pectoris
after a myocardial infarction
Arrhythmias
supraventricular
ventricular
Hypertension
Other
Cardiomyopathies
Thyrotoxicosis
Dissecting Aortic Aneurysm
Migraine Headaches
Essential Tremor
Anxiety, Particularly Performance Anxiety

*Not all indications have been approved for all drugs by the Food and Drug Administration.

Post myocardial infraction. One important use for β-adrenoceptor blocking drugs is to reduce mortality (primarily sudden death) and reinfarction when given to patients who have had myocardial infarction.[8] Much of the benefit appears to occur within the first 6 months of the infarction, and the duration of therapy is unknown at this time, but benefit persists for at least 2½ to 3 years. There are probably several mechanisms for this beneficial action including antiarrhythmic effects and anti-ischemic effects. Whether all of the β-adrenoceptor blockers can be used for this indication is unknown, but positive studies have been reported for timolol, propranolol, and metoprolol. The benefit to patients appears to be related to their risk of dying after a myocardial infarction. Those patients who have the best prognosis because they have good ventricular function, no angina or ventricular ectopy, and a negative stress test after myocardial infarction will have very little benefit from the β-adrenoceptor blocking drugs. Those patients with complications during myocardial infarction and ventricular ectopy or evidence of continuing ischemia after myocardial infarction derive greater benefit from the β-adrenoceptor block drugs.[9]

Hypertension. The other major use of β-adrenoceptor blocking drugs is hypertension. β-Adrenoceptor blocking drugs have been useful to block sympathetically mediated increases in cardiac output, heart rate, and renin activity which are produced by the other antihypertensive drugs. β-Adrenoceptor blockers can also be used as sole drugs in hypertension, but their mechanism of action is unclear, although there is no lack of theories.[10] It is clear that there are population differences in responses to β-adrenoceptor blockers, with young patients and white patients generally being more responsive than old patients or black patients.

Headaches. Of the other indications for β-adrenoceptor blockers (Table 3), their use for migraine headaches and performance anxiety probably affects the largest number of otherwise normal individuals. Propranolol, nadolol, timolol, atenolol, and metoprolol have been shown to be useful in prophylaxis for migraine headaches. Drugs that have intrinsic sympathomimetic activity have not been useful. What property of these drugs accounts for the efficacy in migraine is not clear.[11] To date, no theory has satisfactorily explained all of the data. Since so many of the β-adrenoceptor blocking drugs have been beneficial, it is hard to escape the possibility that a property related to β-adrenoceptor blockade is the important quality. However, one study reported that the d isomer of propranolol, which does not produce significant β-adrenoceptor blockade, was also effective in this syndrome.[12]

Performance anxiety. Performance anxiety is a universal phenomenon that usually does not require therapy; in fact, some anxiety seems to be beneficial for peak performance. However, if performance suffers because of the manifestations of anxiety, then one may consider using a β-adrenoceptor blocking drug.[13] These drugs act to block the peripheral or somatic man-

ifestations of anxiety but do not have major effects to alter the anxiety *per se*.[14–17] The β-adrenoceptor blocking drugs available in the United States that have been studied for performance anxiety include propranolol, pindolol, atenolol, and nadolol. The theory is that "anxiety feeds upon itself."[15] If a person feels anxious, the peripheral manifestations of sympathetic stimulation, i.e., a tremor, hyperventilation, and tachycardia, may cause the performance to deteriorate, thus triggering an increase in anxiety and further decrements in performance. By blocking the tachycardia, tremor, and hyperventilation with β-adrenoceptor blockers, one can break the positive feedback cycle and may therefore improve performance. It is of interest that the improvement in performance is most readily demonstrable with tasks in which tremor, either in the arms, hands, or voice is an important determinant of performance. For a purely mental task, such as taking an examination, the benefit from β-adrenoceptor blocking drugs is less certain.[18,19] In contrast, in areas in which performance depends upon physical strength or endurance rather than fine motor movements, β-adrenoceptor blockers may be detrimental. Thus, for athletes, who may also experience performance anxiety, β-adrenoceptor blocking drugs can interfere with the athlete's performance because these drugs may reduce the ability to condition as well as to perform to the same degree or duration of exercise.[20,21] The beneficial effect of β-adrenoceptor blocking drugs on performance anxiety is in contrast to the detrimental effects on performance of the drugs usually used for anxiety, such as the benzodiazepines.[16] These drugs may make the individual feel calmer but performance deteriorates because of the mental effects of these drugs. In some individuals, this deterioration of performance can be detected and anxiety may paradoxically increase.

Which β-adrenoceptor blocking drug is best for performance anxiety has not been determined. Since catecholamine-induced tremor is thought to be largely a β_2-adrenoceptor mediated event,[22] drugs that produce nonselective β-adrenoceptor blockade should in theory be preferable to β_1 selective blockers. Other factors to consider when choosing a drug for this indication are the onset and duration of action and potential side effects. One would prefer a drug with a short duration of action that could be taken about an hour before a performance and not have any persisting effects after the performance. Since the beneficial effects appear to be peripheral, one would also prefer a drug that would not give side effects in the central nervous system. Finally, one would like to preserve blood flow to the extremities since cold hands and feet may cause some problems with performance requiring fine motor control of the fingers, particularly in the winter. None of the drugs currently available is perfect for this indication. Propranolol is effective and widely used but may cause some CNS side effects, although this is not usually a problem with short-term use, and it can reduce peripheral blood flow resulting in cold hands.[23,24] Nadolol, although it may not produce as many CNS side effects as propranolol, has a long duration of action, perhaps too long for this indication. Pindolol may preserve peripheral blood flow better than propranolol and nadolol,[23,25] but its ISA may not allow as great a benefit for the tremor as compared to other nonselective β-adrenoceptor blockers.[26] Pindolol has, however, been shown to be effective for performance anxiety, and comparative studies would be required to indicate whether the benefits of ISA outweigh the potential detrimental effects. Atenolol has also been shown to be effective. However, this drug is selective for β_1-adrenoceptors, and therefore may not be as effective against the tremor as the other drugs that have been studied.[22]

Adverse Effects

The adverse effects of the β-adrenoceptor blockers can be severe, but usually these drugs are extremely well tolerated.[24] Patients who are prone to develop life-threatening toxicity from β-adrenoceptor blockade are those with barely compensated heart failure, asthma or other bronchospastic diseases, or disease of the cardiac conducting system. With β-adrenoceptor blockade, these patients may develop severe heart failure, bronchospasm, or heart block, respectively.

Central nervous system adverse effects of β-adrenoceptor blockers include sleep disturbances as well as hallucinations or depression. Although well-controlled comparative studies have not been done, it appears that the more water-soluble β-adrenoceptor blocking drugs have fewer CNS side effects.[3] However, these side effects should rarely pose a problem with single dose use of these drugs as for performance anxiety. If the drugs are taken the night before a performance, however, sleep disturbances may occur. Fatigue is a common side effect that may be related to CNS effects of these drugs as well as to the effects on the cardiovascular system.

Side effects related to the peripheral vasculature include the cold hands and feet already mentioned and the potential of worsening claudication in patients with atherosclerotic peripheral vascular disease. However, in patients with mild to moderate peripheral vascular disease or Raynaud's phenomenon, well-controlled studies do not indicate that symptoms are worsened by the selective or nonselective β-adrenoceptor blocking drugs.[27,28]

Some of the β-adrenoceptor blockers have been shown to increase triglyceride and decrease high density lipoprotein (HDL) cholesterol levels. There is a possibility that over many years this could have a detrimental effect on cardiovascular risk. However, the effect appears to be small and the beneficial effects of β-adrenoceptor blocking drugs in patients with cardiovascular disease seem to outweigh the increased risk that these risk factor changes may cause.

In patients with diabetes, β-adrenoceptor blocking drugs can produce potential problems. The major effect is on the response of patients to hypoglycemia. Patients who develop hypoglycemia in response to their antidiabetic drugs, may have some delay in recovery if they are receiving nonselective β-adrenoceptor blocking drugs.[29] This effect is less with the selective β_1-adrenoceptor blocking drugs. In addition to this metabolic effect, the catecholamine-mediated hemodynamic effects that occur with hypoglycemia differ if patients are on β-adrenoceptor blocking drugs.[29,30] Normally, there is a release of epinephrine from the adrenal gland in response to hypoglycemia, and this increase in circulating epinephrine causes an increase in heart rate and cardiac output, a decrease in peripheral vascular resistance, and no change in mean arterial pressure with diastolic pressure falling and systolic pressure rising. If the patient is on a nonselective β-adrenoceptor blocking drug and develops hypoglycemia, there will be a different hemodynamic response. The β-adrenoceptor mediated vasodilation pro-

duced by epinephrine in the peripheral vasculature is blocked, leaving the α-adrenoceptor mediated vasoconstriction unopposed resulting in an increase in systolic, diastolic, and mean arterial pressure. Because of the increase in pressure, there is a reflex increase in parasympathetic output to the heart that produces a bradycardia, which may be marked. If the patient is on a β_1-selective adrenoceptor blocker, epinephrine can still act on the vascular β_2-adrenoceptors to reduce peripheral vascular resistance, and thus diastolic pressure will not rise, and a reflex bradycardia will not occur. Because of these effects, both on the recovery from hypoglycemia and the hemodynamics, the cardioselective (β_1 selective) adrenoceptor blocking drugs are preferable to the nonselective drugs in patients with diabetes.

In a manner similar to their effects during hypoglycemia, nonselective β-adrenoceptor blockers can produce hypertension and bradycardia in other circumstances in which circulating epinephrine levels are increased, such as after withdrawal of clonidine, in patients with pheochromocytoma, and in patients who have received epinephrine for other indications.

Patients who have received propranolol chronically for angina pectoris have, on occasion, experienced adverse effects when the β-adrenoceptor blocker was abruptly discontinued. This withdrawal effect does not occur commonly but is associated with worsening angina, arrhythmias, myocardial infarction, or even sudden death.[31] Experimental data indicate that after withdrawal of continuous propranolol therapy, there is a period of time during which patients may be more sensitive to the effects of adrenergic stimulation.[32] The mechanism of this is unknown, but one possibility is the fact that β-adrenoceptors increase in density during the continuous administration of propranolol. When the β-adrenoceptor blocker is abruptly withdrawn, there is a short period of time where the β-adrenoceptors may continue to be elevated in density and mediate the enhanced response to adrenergic stimulation.[33] Although this withdrawal syndrome has not been described with all β-adrenoceptor blocking drugs, it is wise to discontinue these drugs gradually after prolonged use in patients with coronary artery disease.

In spite of the potential side effects, the β-adrenoceptor blocking drugs have been extremely well tolerated as long as the patients prone to heart failure, heart block, and bronchospasm do not receive them. Even in high doses, these drugs usually do not cause any problem.[34] Certainly for short-term or single-dose occasional use for performance anxiety in normal individuals, they are very safe. Nonetheless, it is important that these drugs be given under the direction of a physician and that patients take them only when potential benefits outweigh the risks.

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