

11

Adrenoceptor Antagonists

David P. Westfall



DRUG LIST

GENERIC NAME	PAGE	GENERIC NAME	PAGE
Acebutolol	114	Nadolol	114
Atenolol	114	Phenoxybenzamine	113
Betaxolol	114	Phentolamine	113
Bucindolol	117	Pindolol	114
Carteolol	114	Prazosin	112
Carvedilol	117	Propranolol	113
Doxazosin	111	Terazosin	112
Esmolol	112	Timolol	114
Labetalol	116	Tolazoline	112
Medroxalol	117	Trimazosin	112
Metoprolol	113		

ADRENOCEPTORS

Drugs that produce responses by interacting with adrenoceptors are referred to as *adrenoceptor agonists* or *adrenergic agonists*. Norepinephrine and isoproterenol are examples of such compounds. Agents that inhibit responses mediated by adrenoceptor activation are known as *adrenoceptor antagonists*, *adrenergic antagonists*, or *adrenergic blocking agents*. Prazosin and propranolol are examples of receptor-blocking drugs. The pharmacology of the adrenoceptor antagonists is described in this chapter.

Norepinephrine is released from the varicosities of the postganglionic sympathetic nerves during neural activity and interacts with the adrenoceptors of the effector organ, producing the characteristic response of the

effector. This occurs because norepinephrine has an *affinity* for the receptors and possesses *intrinsic activity*; that is, it has the capacity to activate the receptors. Circulating catecholamines and other directly acting adrenomimetic drugs also interact with these receptors.

The adrenergic blocking agents also have an affinity for the adrenoceptors. The antagonists, however, have only limited or no capacity to activate the receptors; that is, they have little or negligible intrinsic activity. The blocking drugs compete with adrenomimetic substances for access to the receptors. Thus, *these agents reduce the effects produced by both sympathetic nerve stimulation and by exogenously administered adrenomimetics*. This action forms the basis for their therapeutic and investigational use.

Competition for receptors, hence receptor antagonism, is governed by the *law of mass action*; that is, the interaction between drug and receptor depends on the concentration of drug in the vicinity of the receptor and the number of receptors present. Because agonist and antagonist have an affinity for the same receptors, the two substances compete for binding to the receptors.

For most adrenoceptor antagonists (and agonists), the attachment of the blocking agent to the adrenoceptor is by relatively weak forces, such as hydrophobic, hydrogen, or van der Waals bonding. Because the drug easily dissociates from the receptor, the antagonism exhibited by these compounds is readily reversible on removal of the antagonists from the biophase. This type of antagonism is referred to as *reversibly competitive* or *equilibrium competitive* (see Chapter 2). However, one group of antagonists, the haloalkylamines, is highly chemically reactive. These compounds are capable of forming covalent bonds with various chemical groupings on receptors. Removal of these antagonists from the biophase is not sufficient to restore the responsiveness of the effector to agonists. Full tissue responsiveness may not occur for several days. Because of the apparently irreversible nature of this drug antagonism, it is termed *irreversibly competitive* or *non-equilibrium competitive* (see Chapter 2).

Adrenoceptor-blocking agents do not prevent the release of transmitters from adrenergic nerves as do the neuron-blocking agents, such as guanethidine, and they are not catecholamine-depleting agents, such as reserpine (see Chapter 20). *They prevent the agonist from interacting with its receptor.*

CLASSIFICATION OF BLOCKING DRUGS

An α -receptor is one that mediates responses for which the adrenomimetic order of potency is epinephrine greater than or equal to norepinephrine greater than isoproterenol, and that is susceptible to blockade by phentolamine and phenoxybenzamine. It follows from this definition that phentolamine and phenoxybenzamine are called α -adrenoceptor antagonists or α -blocking agents. A β -receptor mediates responses for which the adrenomimetic order of potency is isoproterenol greater than epinephrine greater than or equal to norepinephrine, and this receptor is susceptible to blockade by propranolol. Propranolol is, therefore, called a β -adrenoceptor antagonist or β -blocking agent.

β -Receptor Subtypes

The two main types of β -receptors have been given the designations β_1 and β_2 . Among the responses mediated by β_1 -receptors is cardiac stimulation, whereas β_2 -receptor stimulation mediates bronchodilation and re-

laxation of vascular and uterine smooth muscle (see Chapters 9 and 62). These findings are significant, since a number of both agonists and antagonists have some degree of selectivity for either β_1 - or β_2 -receptors.

A comparison of the effects produced by propranolol, a nonselective β -receptor blocking agent, with those of metoprolol, a relatively selective β_1 -receptor blocker, illustrates the clinical utility of such drugs. For example, a patient who is a candidate for β -blocker therapy (angina, hypertension), but who also has obstructive airway disease probably should not receive a nonselective β -blocking agent such as propranolol because of the possibility of aggravating bronchospasm. In this instance, metoprolol would be advantageous, since β -receptors of the respiratory system are β_2 , hence less affected by metoprolol than by propranolol. However, metoprolol's selectivity is only relative, and at high concentrations the drug will also antagonize β_2 responses.

Absolute selectivity of drug action does not exist. Any given effector tissue probably contains more than one receptor subtype, and it is likely that the proportion of receptor subtypes varies within that effector. Nevertheless, the designation of a drug as a selective agent for either a β_1 -receptor or a β_2 -receptor seems both useful and justified if one keeps in mind that the designation represents a shorthand notation for what is only a predominance of activities.

Molecular genetic techniques have confirmed the existence of multiple subtypes of β -adrenoceptors. β_1 -Receptors and β_2 -receptors have been cloned, and recent molecular biological evidence indicates the existence of at least one additional β -receptor subtype, called the β_3 -receptor. It is suggested that the β_3 -receptor may mediate some of the metabolic effects of catecholamines, although no available β -blocker has been shown to rely on β_3 -receptor antagonism for its therapeutic effectiveness.

α -Receptor Subtypes

There are differences between the receptors on nerves (*presynaptic* receptors) and those on effector cells (*postsynaptic* receptors). Furthermore, some α -agonists and antagonists exhibit selectivity for one of these receptor types. Terminology classifies receptors as either α_1 or α_2 . α_1 -Receptors are those whose stimulation has traditionally been associated with the postsynaptic α -receptors of smooth muscle, while α_2 -receptors are those originally associated with the presynaptic α -receptors of peripheral nerves. However, the designation of receptors as either α_1 or α_2 cannot be categorized strictly by anatomical location (i.e., presynaptic or postsynaptic), since evidence now indicates that α_2 -receptors occupy, in addition to peripheral nerves, a variety of sites including smooth muscle, adrenal medullary cells, the brain, and melanocytes.

The existence of α -receptor subclasses and the receptor selectivity exhibited by certain α -blocking agents have therapeutic implications. Phentolamine is a disappointing antihypertensive drug because its administration results in a reflex increase in both heart rate and contractile force; these effects tend to negate the reduction in blood pressure that it produces. In contrast, prazosin is an effective antihypertensive drug because the reflex cardiac stimulation it induces is much less. The differing hemodynamic effects produced by phentolamine and prazosin appear to be related to their relative degree of selectivity for α_1 - and α_2 -receptors. Phentolamine is a relatively nonselective receptor blocking agent, since in addition to blocking postsynaptic α_1 -receptors, it will block presynaptic α_2 -receptors; the latter action enhances release of norepinephrine, hence augments cardiac rate and contractile force. Blockade of α_2 -receptors may actually potentiate the cardiac effects of sympathetic nerve stimulation. Prazosin, in contrast to phentolamine, is relatively selective for α_1 -receptors; that is, it preferentially blocks responses mediated by the postsynaptic α_1 -receptors in the blood vessels without having a substantial effect on presynaptic α_2 -receptors. Thus, prazosin stimulates the heart less than does phentolamine.

Absolute selectivity of action for α_1 - or α_2 -receptors does not exist for any available α -agonists and antagonists. Furthermore, as is the case with β -receptors, a given effector tissue may contain more than one α -receptor subtype. Recent evidence suggests that in addition to α_1 -receptors, vascular smooth muscle may possess α_2 -receptors. Although the functional importance of α_2 -receptors in blood vessels seems to be less than that of α_1 -receptors, this can account for certain clinical observations, as for example the pressor response that occurs upon initiation of treatment with the α_2 -agonist clonidine.

It is becoming increasingly clear that neither α_1 - nor α_2 -receptors are homogeneous. There seem to be at least three subtypes of both α_1 - and α_2 -receptors, that is, α_{1A} , α_{1B} , α_{1D} , α_{2A} , α_{2B} and α_{2C} . At this point, the pharmacology and therapeutic usefulness of the major α -antagonists can be reasonably well explained by considering their relative selectivity for the two main classes of α -receptors, α_1 and α_2 . This is beginning to change, however. For example, tamsulosin (*Flomax*), a recently introduced α -antagonist, reportedly exhibits some selectivity for α_{1A} -receptors, which are rich in the prostate, as compared to α_{1B} -receptors, which are more plentiful in vascular smooth muscle. This may provide some advantage to tamsulosin as an agent for treatment of patients with benign prostate hypertrophy (discussed later).

α -RECEPTOR BLOCKING AGENTS

The clinically important α -blockers fall primarily into three chemical groups: the *haloalkylamines* (e.g., phe-

noxybenzamine), the *imidazolines* (e.g., phentolamine), and the *quinazoline derivatives* (e.g., prazosin). Of these three classes of α -adrenoceptor antagonists, the quinazoline compounds are of greatest clinical utility and are emphasized in this chapter. The use of the haloalkylamines and imidazolines has diminished in recent years because they lack selectivity for α_1 - and α_2 -receptors. Comparative information concerning the three chemical classes of antagonists is presented in Table 11.1

Quinazoline Derivatives

The chief use of these drugs is in the management of primary hypertension. Examples of quinazoline α -blockers include prazosin (*Minipress*), trimazosin (*Cardovar*), terazosin (*Hytrin*), and doxazosin (*Cardura*).

Mechanism of Action

The α -antagonism produced by prazosin and the other quinazoline derivatives is of the *equilibrium-competitive* type. The drugs are selective for α_1 -adrenoceptors, so that at usual therapeutic concentrations there is little or negligible antagonism of α_2 -adrenoceptors. However, selectivity is only relative and can be lost with high drug concentrations. While most of the pharmacological effects of prazosin are directly attributable to α_1 -antagonism, at high doses the drug can cause vasodilation by a direct effect on smooth muscle independent of α -receptors. This action appears to be related to an inhibition of phosphodiesterases that results in an enhancement of intracellular levels of cyclic nucleotides.

Absorption, Metabolism, Excretion

Prazosin is readily absorbed after oral administration, peak serum levels occur approximately 2 hours after a single oral dose, and the antihypertensive effect of prazosin persists for up to 10 hours. Its half-life in plasma ranges from 2.5 to 4 hours, and elimination from plasma appears to follow first-order kinetics. The drug is extensively (perhaps as high as 97%) bound to plasma proteins; this observation partially explains the lack of correlation between plasma drug levels and persistence of antihypertensive effect.

Hepatic *O*-dealkylation and glucuronide formation appear to be major pathways of biotransformation. Only about 10% of orally administered prazosin is excreted in the urine. Plasma levels of prazosin are increased in patients with renal failure; the nature of this interaction is unknown.

Pharmacological Actions

The most important pharmacological effect of prazosin is its ability to antagonize vascular smooth muscle contraction that is caused by either sympathetic nervous activity

TABLE 11.1 Comparative Information About the Three Classes of α -Adrenoceptor Antagonists

	Haloalkylamines	Imidazolines	Quinazolines
Prototype	Phenoxybenzamine (<i>Dibenzyline</i>)	Phentolamine (<i>Regitine</i>)	Prazosin (<i>Minipress</i>)
Others		Tolazoline (<i>Priscoline</i>)	Terazosin (<i>Hytrin</i>) Doxazosin (<i>Cardura</i>) Trimazosin (<i>Cardovar</i>)
Antagonism	Irreversible (non-equilibrium) competitive	Equilibrium competitive	Equilibrium competitive
Selectivity	Somewhat selective for α_1	Nonselective	Selective for α_1
Hemodynamic effects	Decreased peripheral vascular resistance and blood pressure Venodilation is prominent Cardiac stimulation occurs because of cardiovascular reflexes and enhanced release of norepinephrine	Similar to phenoxybenzamine	Decreased peripheral vascular resistance and blood pressure Veins seem to be less susceptible to antagonism than arteries; thus, postural hypotension is less of a problem Cardiac stimulation is less because release of norepinephrine is not enhanced
Actions other than α -blockade	Some antagonism of responses to ACh, 5-HT, and histamine Blockade of neuronal and extraneuronal uptake	Cholinomimetic, adrenomimetic, and histaminelike actions Antagonism of responses to 5-HT	At high doses some direct vasodilator action, probably due to phosphodiesterase inhibition
Routes	Intravenous and oral Oral absorption incomplete and erratic	Similar to phenoxybenzamine	Oral
Adverse reactions	Postural hypotension, tachycardia, miosis, nasal stuffiness, failure of ejaculation	Same as phenoxybenzamine and in addition gastrointestinal disturbances	Some postural hypotension, especially with the first dose; less of a problem overall than with phenoxybenzamine or phentolamine
Therapeutic uses	Conditions of catecholamine excess such as pheochromocytoma Peripheral vascular disease Benign prostatic hypertrophy	Same as phenoxybenzamine	Primary hypertension Benign prostatic hypertrophy

ACh, acetylcholine; 5-HT, 5-hydroxytryptamine.

or the action of adrenomimetics. Hemodynamically, the effects of prazosin differ from those of phenoxybenzamine and phentolamine in that venous smooth muscle is not as much affected by prazosin. Postural hypotension during chronic treatment is also less of a problem. Also, increases in heart rate, contractile force, and plasma renin activity, which normally occur after the use of vasodilators and α -blockers, are much less prominent following chronic treatment with prazosin.

Phenoxybenzamine and phentolamine, in addition to blocking postsynaptic α -receptors, also block α_2 -receptors on nerves and therefore can enhance the release of norepinephrine. When norepinephrine exerts a postsynaptic action by means of β -adrenoceptors (e.g., cardiac stimulation, renin release), blockade of presynaptic α_2 -receptors by phenoxybenzamine and phentolamine may actually potentiate the responses. *Prazosin blocks responses mediated by postsynaptic α_1 -receptors but has no effect on the presynaptic α_2 -receptors.* Thus,

stimulation of the heart and renin release is less prominent with this drug.

Clinical Uses

Prazosin is effective in reducing all grades of hypertension. The drug can be administered alone in mild and (in some instances) moderate hypertension. When the hypertension is moderate or severe, prazosin generally is given in combination with a thiazide diuretic and a β -blocker. The antihypertensive actions of prazosin are considerably potentiated by coadministration of thiazides or other types of antihypertensive drugs.

Prazosin may be particularly useful when patients cannot tolerate other classes of antihypertensive drugs or when blood pressure is not well controlled by other drugs. Since prazosin does not significantly influence blood uric acid or glucose levels, it can be used in hy-

pertensive patients whose condition is complicated by diabetes mellitus or gout.

Prazosin and other α -antagonists find use in the management of benign prostatic obstruction, especially in patients who are not candidates for surgery. Blockade of α -adrenoceptors in the base of the bladder and in the prostate apparently reduces the symptoms of obstruction and the urinary urgency that occurs at night.

Adverse Effects

Although less of a problem than with phenoxybenzamine or phentolamine, symptoms of postural hypotension, such as dizziness and light-headedness, are the most commonly reported side effects associated with prazosin therapy. These effects occur most frequently during initial treatment and when the dosage is sharply increased. Postural hypotension seems to be more pronounced during Na^+ deficiency, as may occur in patients on a low-salt diet or being treated with diuretics, β -blockers, or both.

β -ADRENOCEPTOR BLOCKING AGENTS

A large number of β -blockers are on the market in the United States. Of these, propranolol, a nonselective β -antagonist, was the first to be introduced and is the prototypical drug with which the others are compared. Metoprolol was the first β_1 -selective drug and timolol the first β -blocker approved for ophthalmic use.

As a class, β -blocking agents have greater structural similarity to their corresponding agonists than do the α -blockers. This structural similarity also accounts for the greater specificity of action exhibited by the β -receptor blocking drugs than by the α -adrenoceptor blocking drugs.

The similarity in structure to β -agonists is most certainly responsible for the finding that some β -blockers activate β -receptors; that is, they have some intrinsic sympathomimetic activity. The intrinsic activity of these compounds is generally modest in comparison with an agonist, such as isoproterenol, and they are generally referred to as *partial agonists* (see Chapter 2).

Mechanism of Action

All of the β -blockers exert equilibrium-competitive antagonism of the actions of catecholamines and other adrenomimetics at β -receptors. Probably the best-recognized action of these compounds that is not mediated by a β -receptor is depression of cellular membrane excitability. This effect has been described as a membrane-stabilizing action, a quinidinelike effect, or a local anesthetic effect. This action is not too surprising in view of the structural similarities between β -blockers and local anesthetics. However, with the usual therapeutic

doses, the actions of the β -receptor blocking agents appear to be almost entirely accounted for by their β -receptor antagonism.

Because the β -receptors of the heart are primarily of the β_1 type and those in the pulmonary and vascular smooth muscle are β_2 receptors, β_1 -selective antagonists are frequently referred to as *cardioselective blockers*. The intrinsic activity, cardioselectivity, and membrane-stabilizing actions of a number of β -blockers are summarized in Table 11.2

Absorption, Metabolism, and Excretion

Propranolol (*Inderal*) is suitable for both parental and oral administration. Absorption from the gastrointestinal tract is extensive. The peak therapeutic effect after oral administration occurs in 1 to 1.5 hours. The plasma half-life of propranolol is approximately 3 hours. The drug is concentrated in the lungs and to a lesser extent in the liver, brain, kidneys, and heart. Binding to plasma proteins is extensive (90%). The liver is the chief organ involved in the metabolism of propranolol, and the drug is subject to a significant degree of first-pass metabolism. At least eight metabolites have been recovered from the urine, the major excretory route.

The pharmacokinetic profile of metoprolol (*Lopresor*) is similar to that of propranolol. Metoprolol is readily and rapidly absorbed after oral administration and is subject to a significant amount of first-pass metabolism by the liver. Curiously, the duration of metoprolol's action is longer than one would predict from its plasma half-life, which ranges from 0.5 to 2.5 hours. The degree of binding of metoprolol to plasma proteins is modest (10%). The extensive distribution of metoprolol to the lungs and kidney is typical of a moderately lipophilic drug. Metoprolol undergoes considerable metabolism;

TABLE 11.2 Characteristics and Preparations of β -Blockers

β -Blocker	Cardio-selective	Partial Agonist Activity	Membrane Stabilizing Activity
Propranolol	No	None	Yes
Acebutolol	Yes	Slight	None
Atenolol	Yes	None	None
Betaxolol	Yes	None	Slight
Carteolol	No	Slight	None
Esmolol	Yes	None	None
Levobunolol	No	None	None
Metoprolol	Yes	None	Slight
Nadolol	No	None	None
Penbutolol	No	Slight	None
Pindolol	No	Yes	Slight
Timolol	No	Slight	None

only 3 to 10% of an administered dose is recovered as unchanged drug. The metabolites are essentially inactive as β -receptor blocking agents and are eliminated primarily by renal excretion. Small amounts of the drug are present in the feces.

Timolol (*Timoptic*) is almost completely absorbed from the gastrointestinal tract. Peak plasma levels occur 2 to 4 hours after oral administration; the plasma half-life of timolol is approximately 5.5 hours. The extensive tissue distribution of timolol into lung, liver, and kidney is similar to that of other β -blockers. Approximately 70% of the drug is excreted in the urine within 24 hours, mostly as highly polar unconjugated metabolites. Only 6% of an administered dose is recovered in the feces. Although timolol is approved for the *topical* treatment of elevated intraocular pressure, there is limited information about its pharmacokinetics following administration by this route. The drug apparently can reach the systemic circulation after intraocular instillation, but plasma levels are only about 7% of those achieved in the aqueous humor.

About half of an orally administered dose of acebutolol (*Sectral*) is absorbed. Approximately 25% of the drug is bound to plasma proteins, and its plasma half-life is about 4 hours. Metabolism of acebutolol produces a metabolite with β -blocking activity whose half-life is 10 hours.

Roughly half of an orally administered dose of atenolol (*Tenormin*) is absorbed. The drug is eliminated primarily by the kidney and unlike propranolol, undergoes little hepatic metabolism. Its plasma half-life is approximately 6 hours, although if it is administered to a patient with impaired renal function, its half-life can be considerably prolonged.

Absorption of an oral dose of betaxolol (*Kerlone*, *Betoptic*) is almost complete. The drug is subject to a slight first-pass effect such that the absolute bioavailability of the drug is about 90%. Approximately 50% of administered betaxolol binds to plasma proteins, and its plasma half-life is about 20 hours; it is suitable for dosing once per day. The primary route of elimination is by liver metabolism, with only 15% of unchanged drug being excreted.

Carteolol (*Cartrol*) is a long-acting β -blocker that is suitable for dosing once per day. It is almost completely absorbed and exhibits about 30% binding to plasma proteins. Unlike many β -blockers, carteolol is not extensively metabolized. Up to 70% of an administered dose is excreted unchanged.

The β -blocker esmolol (*Brevibloc*) is unusual in that it is very rapidly metabolized; its plasma half-life is only 9 minutes. It is subject to hydrolysis by cytosolic esterases in red blood cells to yield methanol and an acid metabolite, the latter having an elimination half-life of about 4 hours. Only 2% of the administered esmolol is excreted unchanged. Because of its rapid onset and

short duration of action, esmolol is used by the intravenous route for the control of ventricular arrhythmias in emergencies.

Nadolol (*Corgard*) is slowly and incompletely absorbed from the gastrointestinal tract, and only 30% of an orally administered dose is absorbed. Appreciable metabolism does not seem to occur; nadolol is excreted primarily unchanged in the urine and feces. The plasma half-life is quite long, approaching 24 hours, which permits dosing once per day.

Pindolol (*Visken*) is extensively absorbed from the gastrointestinal tract. First-pass metabolism is estimated at about 15%, and its plasma half-life is on the order of 3 to 4 hours. The binding of pindolol to plasma proteins is approximately 50%. The metabolic fate of pindolol is not completely understood, although 50% of an administered dose is recovered, primarily in the urine, as unchanged drug.

Pharmacological Actions

The most important actions of the β -blocking drugs are on the cardiovascular system. *β -Blockers decrease heart rate, myocardial contractility, cardiac output, and conduction velocity within the heart.* These effects are most pronounced when sympathetic activity is high or when the heart is stimulated by circulating agonists.

The actions of β -blockers on blood pressure are complex. After acute administration, blood pressure is only slightly altered. This is because of the compensatory reflex increase in peripheral vascular resistance that results from a β -blocker-induced decrease in cardiac output. Vasoconstriction is mediated by α -receptors, and α -receptors are not antagonized by β -receptor blocking agents. Chronic administration of β -blockers, however, results in a reduction of blood pressure, and this is the reason for their use in primary hypertension (see Chapter 20). The mechanism of this effect is not well understood, but it may include such actions as a reduction in renin release, antagonism of β -receptors in the central nervous system, or antagonism of presynaptic facilitatory β -receptors on sympathetic nerves.

Total coronary blood flow is reduced by the β -blockers. This effect may be due in part to the unopposed α -receptor-mediated vasoconstriction that follows β -receptor blockade in the coronary arteries. Additional contributing factors to the decrease in coronary blood flow are the negative chronotropic and inotropic effects produced by the β -blockers; these actions result in a decrease in the amount of blood available for the coronary system. The decrease in mean blood pressure may also contribute to the reduced coronary blood flow.

In view of the effects of the β -receptor blocking agents on coronary blood flow, it seems paradoxical that these drugs are useful for the prophylactic treatment of

angina pectoris, a condition characterized by inadequate myocardial perfusion. The chief benefit of the β -blockers in this condition derives from their ability to decrease cardiac work and oxygen demand. The use of the β -blockers in angina is considered in Chapter 17. The ability of β -blockers to decrease cardiac work and oxygen demand may also be responsible for the favorable effects of these agents in the long-term management of congestive heart failure.

The release of renin from the juxtaglomerular cells of the kidney is believed to be regulated in part by β -receptors; most β -blockers decrease renin release. While the drug-induced decrease in renin release may contribute to their hypotensive actions, it is probably not the only factor (see Chapter 20). Nevertheless, β -blockers are useful and logical agents to use when treating hypertension that is accompanied by high plasma renin activity, although angiotensin converting enzyme inhibitors are also widely used in this situation.

The glycogenolytic and lipolytic actions of endogenous catecholamines are mediated by β -receptors and are subject to blockade by β -blockers. This metabolic antagonism exerted by the β -blockers is particularly pronounced if the levels of circulating catecholamines have been increased reflexively in response to hypoglycemia. Other physiological changes induced by hypoglycemia, such as tachycardia, may be blunted by β -blockers. These agents therefore must be used with caution in patients susceptible to hypoglycemia (e.g., diabetics treated with insulin). Because the metabolic responses to catecholamines are mediated by β_2 -receptors and possibly by β_3 -receptors, β_1 -selective antagonists such as metoprolol and atenolol may be better choices whenever β -blocker therapy is indicated for a patient who has hypoglycemia.

Propranolol increases airway resistance by antagonizing β_2 -receptor-mediated bronchodilation. Although the resulting bronchoconstriction is not a great concern in patients with normal lung function, it can be quite serious in the asthmatic. *The cardioselective β -blockers produce less bronchoconstriction than do the nonselective antagonists.*

β -Blockers can reduce intraocular pressure in glaucoma and ocular hypertension. The mechanism is believed to be related to a decreased production of aqueous humor.

Clinical Uses

The β -receptor blocking agents have widespread and important uses in the management of cardiac arrhythmias, angina pectoris, and hypertension. Their uses in these conditions are reviewed in Chapters 16, 17, and 20, respectively. Even though acute administration of β -blockers can precipitate congestive heart failure in patients who are largely dependent on enhanced sym-

pathetic nerve activity to maintain sufficient cardiac output, the β -blockers have been shown to be quite useful in the long-term management of patients with mild to moderate heart failure. The β -blockers also offer proven benefit in preventing the recurrence of a myocardial infarction (MI). For this purpose, it is best if β -blocker therapy is instituted soon after the MI and continued for the long term. Other therapeutic applications of the β -blockers are discussed later in the chapter.

Hyperthyroidism

The β -blockers significantly reduce the peripheral manifestations of hyperthyroidism, particularly elevated heart rate, increased cardiac output, and muscle tremors. Although the β -blockers can improve the clinical status of the hyperthyroid patient, the patient remains biochemically hyperthyroid. The β -blockers should not be used as the sole form of therapy in hyperthyroidism. They are most logically employed in the management of hyperthyroid crisis, in the preoperative preparation for thyroidectomy, and during the initial period of administration of specific antithyroid drugs (see Chapter 65).

Glaucoma

β -Blockers can be used topically to reduce intraocular pressure in patients with chronic open-angle glaucoma and ocular hypertension. The mechanism by which ocular pressure is reduced appears to depend on decreased production of aqueous humor. Timolol has a somewhat greater ocular hypotensive effect than do the available cholinomimetic or adrenomimetic drugs. The β -blockers also are beneficial in the treatment of acute angle-closure glaucoma.

Anxiety States

Patients with anxiety have a variety of psychic and somatic symptoms. The peripheral manifestations of anxiety may include a number of symptoms (e.g., palpitations) that are due in part to overactivity of the sympathetic nervous system. The β -blocking agents may offer some benefit in the treatment of anxiety.

Migraine

The β -blockers may offer some value in the prophylaxis of migraine headache, possibly because a blockade of craniovascular β -receptors results in reduced vasodilation. The painful phase of a migraine attack is believed to be produced by vasodilation.

Adverse Effects and Contraindications

The most prominent side effects associated with the administration of the β -blockers are those directly attributable to their ability to block β -receptors. Although

β -blockers prevent an increase in heart rate and cardiac output resulting from an activation of the autonomic nervous system, these effects may not be troublesome in patients with adequate or marginal cardiac reserve. However, they can be life threatening for a patient with congestive heart failure. Also, because conduction of impulses in the heart may be slowed by β -blockers, patients with conduction disturbances, particularly through the atrioventricular node, should not be treated with β -blockers.

Caution must be exercised in the use of β -blockers in obstructive airway disease, since these drugs promote further bronchoconstriction. Cardioselective β -blockers have less propensity to aggravate bronchoconstriction than do nonselective β -blockers.

β -Blockers potentiate hypoglycemia by antagonizing the catecholamine-induced mobilization of glycogen. The use of β -blockers in hypoglycemic patients is therefore dangerous and must be undertaken with caution. If β -blocker therapy is required, a cardioselective β -blocker is preferred.

Whenever β -blocker therapy is employed, the period of greatest danger for asthmatics or insulin-dependent diabetics is during the initial period of drug administration, since the greatest disruption of the autonomic balance will occur at this time. If marked toxicity does not occur during this period, further doses are less likely to cause problems.

Although the β -blockers produce a number of central effects, it is not clear whether these effects are due to blockade of central β -receptors. After high doses, patients may have hallucinations, nightmares, insomnia, and depression.

Topical application of timolol to the eye is well tolerated, and the incidence of side effects, which consist of burning or dryness of the eyes, is reported to be 5 to 10%.

In spite of the potential seriousness of some of their side effects, β -blockers as a class are well tolerated and patient compliance is good.

DRUGS WITH COMBINED β - AND α -BLOCKING ACTIVITY

Labetalol

Labetalol (*Normodyne*, *Trandate*) possesses both β -blocking and α -blocking activity and is approximately one-third as potent as propranolol as a β -blocker and one-tenth as potent as phentolamine as an α -blocker. The ratio of β - to α -activity is about 3:1 when labetalol is administered orally and about 7:1 when it is administered intravenously. Thus the drug can be most conveniently thought of as a β -blocker with some α -blocking properties.

Mechanism of Action

Labetalol produces *equilibrium-competitive antagonism* at β -receptors but does not exhibit selectivity for β_1 - or β_2 -receptors. Like certain other β -blockers (e.g., pindolol and timolol), labetalol possesses some degree of intrinsic activity. This intrinsic activity, or partial agonism, especially at β_2 -receptors in the vasculature, has been suggested to contribute to the vasodilator effect of the drug. The membrane-stabilizing effect, or local anesthetic action, of propranolol and several other β -blockers, is also possessed by labetalol, and in fact the drug is a reasonably potent local anesthetic.

The α -blockade produced by labetalol is also of the equilibrium-competitive type. In a manner similar to prazosin, labetalol exhibits selectivity for α_1 -receptors. Presynaptic α -receptors, which are of the α_2 subclass, are not antagonized by labetalol. The drug also has some intrinsic activity at α -receptors, although this action is less than its intrinsic β -receptor-stimulating effects.

Labetalol appears to produce relaxation of vascular smooth muscle not only by α -blockade but also by a partial agonist effect at β_2 -receptors. In addition, labetalol may produce vascular relaxation by a direct non-receptor-mediated effect.

Labetalol can block the neuronal uptake of norepinephrine and other catecholamines. This action, plus its slight intrinsic activity at α -receptors, may account for the seemingly paradoxical, although infrequent, increase in blood pressure seen on its initial administration.

Absorption, Metabolism, and Excretion

Labetalol is almost completely absorbed from the gastrointestinal tract. However, it is subject to considerable first-pass metabolism, which occurs in both the gastrointestinal tract and the liver, so that only about 25% of an administered dose reaches the systemic circulation. While traces of unchanged labetalol are recovered in the urine, most of the drug is metabolized to inactive glucuronide conjugates. The plasma half-life of labetalol is 6 to 8 hours, and the elimination kinetics are essentially unchanged in patients with impaired renal failure.

Pharmacological Actions

Although capable of antagonizing a variety of responses in a number of effectors that are mediated by both β - and α -receptors, *the most important actions of labetalol are on the cardiovascular system*. These effects vary from individual to individual and depend on the sympathetic and parasympathetic tone at the time of drug administration.

The most common hemodynamic effect of acutely administered labetalol in humans is a *decrease in peripheral vascular resistance and blood pressure without an appreciable alteration in heart rate or cardiac output*.

This pattern differs from that seen following administration with either a conventional β - or α -blocker. Acute administration of a β -blocker produces a decrease in heart rate and cardiac output with little effect on blood pressure, while acute administration of an α -blocker leads to a decrease in peripheral vascular resistance and a reflexively initiated increase in cardiac rate and output. Thus, the pattern of cardiovascular responses observed after labetalol administration combines the features of β - and α -blockade, that is, a decrease in peripheral vascular resistance (due to α -blockade and direct vascular effects) without an increase in cardiac rate and output (due to β -blockade).

Prolonged oral therapy with labetalol results in cardiovascular responses similar to those obtained following conventional β -blocker administration, that is, decreases in peripheral vascular resistance, blood pressure, and heart rate. Generally, however, the decrease in heart rate is less pronounced than after administration of propranolol or other β -blockers.

Clinical Uses

Labetalol is useful for the chronic treatment of primary hypertension. It can be used alone but is more often employed in combination with other antihypertensive agents. Labetalol also has been used intravenously for the treatment of hypertensive emergencies. Like conventional β -blockers, labetalol may be useful for patients with coexisting hypertension and anginal pain due to ischemia. It is also being investigated as a possible therapeutic modality for ischemic heart disease, even in the absence of hypertension. The benefit derives from its β -blocking activity, which decreases cardiac work, and from its ability to decrease afterload by virtue of its α -blocking activity.

Labetalol, because it possesses both α - and β -blocking activity, is useful for the preoperative management of patients with a pheochromocytoma.

Adverse Effects

There have been reports of excessive hypotension and paradoxical pressor effects following intravenous administration of labetalol. These latter effects may be due to a labetalol-induced blockade of neuronal amine uptake, which increases the concentrations of norepinephrine in the vicinity of its receptors.

Approximately 5% of the patients who receive labetalol complain of side effects typical of noradrenergic nervous system suppression. These include postural hypotension, gastrointestinal distress, tiredness, sexual dysfunction, and tingling of the scalp. Most of these effects are related to α -blockade, although the tingling of the scalp may be due to the drug's intrinsic activity at α -receptors. Side effects associated with β -blockade, such as induction of bronchospasm and congestive heart failure, may also occur, but generally at a lower frequency than α -receptor-associated effects.

Skin rashes have been reported, as has an increase in the titer of antinuclear antibodies. Despite the latter observation, the appearance of a systemic lupus syndrome is rare. Labetalol also has been reported to interfere with chemical measurements of catecholamines and metabolites.

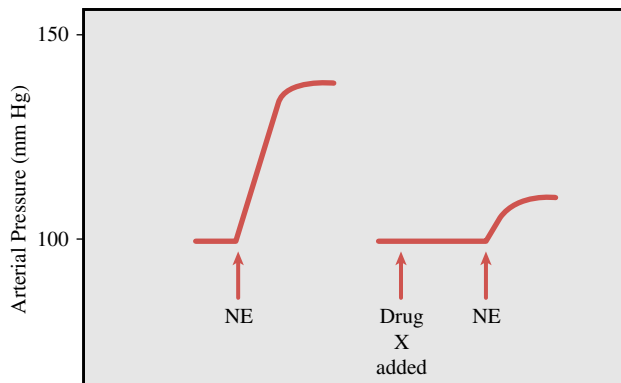
Other Compounds

Several other β -adrenoceptor antagonists, similar to labetalol, exhibit some degree of α -receptor antagonism. These include bucindolol, carvedilol, and medroxalol.

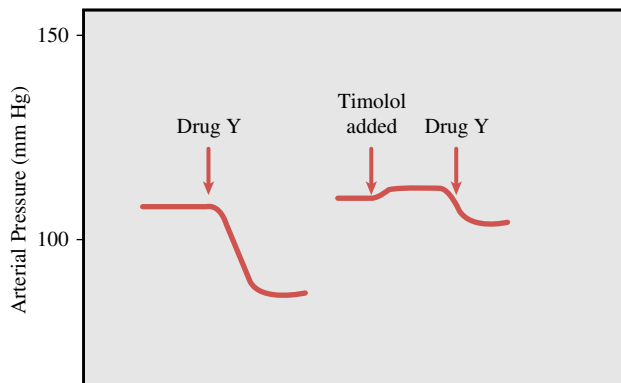
Study Questions

- Which of the following actions of epinephrine would be antagonized by prazosin but not by propranolol?
 - Increase in heart rate
 - Mydriasis
 - Release of renin
 - Bronchiolar dilation
 - Glycogenolysis
- Which of the following adrenoceptor antagonists will reduce responses mediated by both α - and β -receptors?
 - Propranolol
 - Prazosin
 - Phenoxybenzamine
 - Labetalol
 - Metoprolol

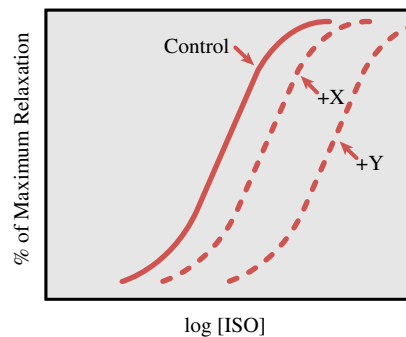
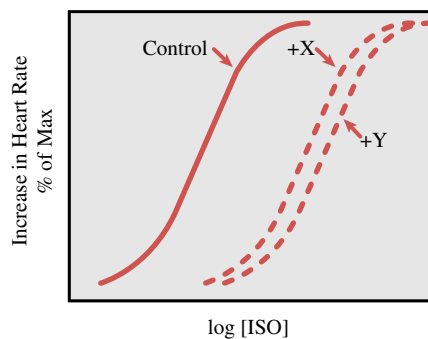
3. This question is based on the information provided in the accompanying diagram. Shown is the effect of applying norepinephrine on the arterial pressure of an isolated (in vitro) segment of artery from an experimental animal before and after adding drug X to the tissue. Drug X is present during the second application of norepinephrine. Drug X is most likely:
- Guanethidine
 - Propranolol
 - Cocaine
 - Prazosin
 - Atropine



4. This question is based on the information provided in the accompanying diagram. The experimental set up is the same as in the previous question. Drug Y is administered before and after timolol. Drug Y is most likely:
- Bradykinin
 - Histamine
 - Isoproterenol
 - Acetylcholine
 - Phenylephrine



5. This question refers to the accompanying graphs. Shown are dose-response curves for isoproterenol (control) both alone and in the presence of one or the other of two β -receptor antagonists, drugs X and Y. The responses being measured are an increase in heart rate of a human subject and relaxation of an in vitro strip of human bronchiolar smooth muscle. Drug X is most likely:
- Metoprolol
 - Propranolol
 - Pindolol
 - Timolol
 - Nadolol



ANSWERS

- B.** The adrenoceptors that epinephrine acts on to affect heart rate, renin release, bronchiolar tone, and glycogenolysis are β -receptors. Prazosin is an α -antagonist so would not antagonize epinephrine at those receptors. The radial smooth muscle in the iris has α -receptors that when activated, contract the radial muscle which dilates the pupil. This action is antagonized by prazosin.
- D.** Propranolol and metoprolol are selective for β -receptors, whereas prazosin and phenoxybenzamine are selective for α -receptors. Labetalol is the only antagonist in this list that has the ability to reduce responses mediated by both α - and β -receptors.
- D.** What is shown is an increase in pressure caused by norepinephrine and the reduction of the effect by drug X. Therefore, drug X is an antagonist of norepinephrine. Two of the choices are adrenoceptor antagonists, prazosin and propranolol, which are α - and β -receptor antagonists, respectively. The adrenoceptors that mediate vasoconstriction are α -receptors. Therefore, prazosin, the α -blocker, is the correct choice. Cocaine, because it blocks neuronal uptake of norepinephrine, would actually enhance the response to this catecholamine, as would guanethidine, because it also blocks neuronal uptake of norepinephrine. Atropine is a muscarinic receptor antagonist and would not affect responses to norepinephrine.
- C.** The vasodilation produced by drug Y is antagonized by timolol, a β -receptor antagonist. Although bradykinin, histamine, acetylcholine, and isoproterenol will all cause vasodilation, only isoproterenol does so by activating β -receptors. Phenylephrine is a sympathomimetic that is selec-

tive for α -receptors and would be expected to increase, rather than decrease, perfusion pressure.

- A.** Both sets of responses to isoproterenol are mediated by β -adrenoceptors, and all the choices are β -antagonists. However, drug X is more effective in antagonizing cardiac responses to isoproterenol than it is the bronchiolar responses. Drug X is therefore a cardioselective β -blocker, that is, selective for β_1 over β_2 receptors. Metoprolol is the only β_1 -selective antagonist among the choices.

SUPPLEMENTAL READING

- Brodde O-E. β_1 - and β_2 -adrenoceptors in the human heart: Properties, function, and alterations in chronic heart failure. *Pharmacol Rev* 1991;43:203–242.
- Brooks AM and Gillies WE. Ocular beta blockers in glaucoma management: Clinical pharmacology aspects. *Drugs Aging* 1992;2:208–221.
- Bylund DB et al. Nomenclature of adrenoceptors. *Pharmacol Rev* 1994;46:1211–1236.
- Cruickshank JM and Prichard BNC. *Beta-Blockers in Clinical Practice* (2nd ed). London: Churchill Livingstone, 1994.
- Harrison JK et al. Molecular characterization of α_1 - and α_2 - adrenoceptors. *Trends Pharmacol Sci* 1991;12:62–67.
- Lonnqvist F et al. Evidence for a functional β_3 -adrenoceptor in man. *Br J Pharmacol* 1993;110:929–936.
- Piasecki MT and Perez DM. Alpha 1-adrenergic receptors: New insights and directions. *J Pharmacol Exp Ther* 2001;298:403–410.
- Ruffolo RR Jr. et al. Structure and function of α -adrenoceptors. *Pharmacol Rev* 1991;43:475–505.

CASE Study Cardiopulmonary Complications of Eyedrops

A 61-year-old man with congenital heart disease and a history of chronic congestive heart failure was seen by an ophthalmologist for a routine eye examination. In general, the patient's health was reasonable and cardiac output was well compensated. During the examination, the physician found that the patient had open-angle glaucoma that required treatment to reduce the pressure in the eye. The ophthalmologist prescribed one eyedrop twice daily in each eye. Several months later the patient began to gain weight, became dyspneic and complained of "asthmatic attacks." An examination showed bronchospasm and severe congestive heart failure with a slow ventricular rate. Gastrointestinal function was normal. The eyedrops were stopped and the patient's condition stabilized. Is it possible that the eyedrops were responsible for the development of cardiopulmonary complications, and if so, what is a likely offending drug?

ANSWER: The finding that the patient's symptoms subsided after terminating the treatment certainly implicates the eyedrops in precipitating the congestive heart failure. Although it is unusual to absorb enough drug through the eye to produce systemic effects, it does happen and physicians should be aware of it. The usual classes of drugs used to treat open-angle glaucoma include the carbonic anhydrase inhibitors (e.g., acetazolamide), cholinergic

miotic agents (e.g., pilocarpine), β -adrenoceptor antagonists (e.g., timolol), and epinephrinelike drugs. Acetazolamide is unlikely to be the offending agent because it is usually administered orally. The clinical symptoms in this patient, including the bronchoconstriction and slow heart rate, are not consistent with the actions of epinephrine, which would be expected to cause bronchodilation and an increase in heart rate.

Pilocarpine, a naturally occurring cholinomimetic, and timolol, a β -blocking agent, both should be considered. Pilocarpine, because of its agonistic effect at muscarinic receptors, can cause bronchoconstriction and precipitate an asthmatic attack; β -blockers, such as timolol, should always be used with caution in an asthmatic patient and are known to worsen symptoms in some individuals with congestive heart failure. The weight gain in this patient, due to edema, and the dyspnea, due to pulmonary congestion, are classic signs of congestive heart failure and can be caused in a susceptible individual by a β -blocker. The slow heart rate is also consistent with either a β -blocker or use of pilocarpine. One might have expected gastrointestinal disturbances if the reaction to the glaucoma medication was due to the systemic accumulation of pilocarpine. All in all, the most likely choice is a β -blocker, and a different class of drug should be used to treat the glaucoma in this patient.