20 Antihypertensive Drugs

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Hypertension is one of the most serious concerns of modern medical practice. It is estimated that in the United States, as many as 60 million people are hypertensive or are being treated with antihypertensive drugs. Among the growing population of elderly Americans, some 15 million have high blood pressure. The level of blood pressure in itself is not a chief concern, since individuals with high blood pressure may be asymptomatic for many years. What is of prime significance is that *hypertension has been shown convincingly to be the single most important contributing factor to cardiovascular disease*, the leading cause of morbidity and untimely death in the United States.

The actual level of pressure that can be considered hypertensive is difficult to define; it depends on a number of factors, including the patient's age, sex, race, and lifestyle. As a working definition, many cardiovascular treatment centers consider that a diastolic pressure of 90 mm Hg or higher or a systolic pressure of 140 mm Hg or higher represents hypertension. In this chapter, reference is made to the stages of hypertension according to the recommendations of the Sixth Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension is considered to be *stage I, or mild*, if diastolic pressure is 90 to 99 mm Hg and/or systolic pressure is 140 to 159 mm Hg. *Stage II*, or *moderate*, hypertension is diastolic pressure of l00 to 109 mm Hg and/or systolic pressure of 160 to 179 mm Hg. *Stage III*, or *severe*, hypertension exists when diastolic pressure is 110 mm Hg or greater and/or systolic pressure is 180 mm Hg or greater.

These values should not be considered as absolutes but rather as indicators for facilitating discussion, particularly in relation to the indications for use of specific drugs. Since in general terms *hypertension* can be defined as the level of blood pressure at which there is risk, the ultimate judgment concerning the severity of hypertension in any given individual must also include a consideration of factors other than diastolic or systolic pressure.

The aim of therapy is straightforward: *reduction of blood pressure to within the normal range*. When hypertension is secondary to a known organic disease, such as renovascular disease or pheochromocytoma, therapy is directed toward correction of the underlying malady. Unfortunately, about 90% of cases of hypertension are of unknown etiology. The therapy of *primary,* or *essential hypertension,* as these cases are generally called, is often empirical.

There are three general approaches to the pharmacological treatment of primary hypertension. The first involves the use of diuretics to reduce blood volume. The second employs drugs that interfere with the renin–angiotensin system, and the third is aimed at a drug-induced reduction in peripheral vascular resistance, cardiac output, or both. A reduction in peripheral vascular resistance can be achieved directly by relaxing vascular smooth muscle with drugs known as vasodilators or indirectly by modifying the activity of the sympathetic nervous system.

The directly acting vasodilators, with the exception of calcium channel antagonists and sympathetic nervous system depressants, receive the bulk of attention in this chapter. Other chapters offer additional information on diuretics (see Chapter 21), the renin–angiotensin system (see Chapter 18), adrenergic receptor antagonists (see Chapter 11), and the calcium channel antagonists (Chapter 19).

DIURETICS

The exact mechanisms by which diuretics lower blood pressure are not entirely understood. Initially, diuretics produce a mild degree of Na^+ depletion, which leads to a decrease in extracellular fluid volume and cardiac output. The effectiveness of diuretic therapy in mild hypertension may also involve either interference with or blunting of cardiovascular reflexes. Regardless of the details, there is general agreement that the blood pressure–lowering effects of diuretics do ultimately depend on the production of diuresis. *High salt intake or low rates or glomerular filtration will eliminate the antihypertensive effects of the drugs.*

The value of diuretics lies in their ability to reverse the Na^+ retention commonly associated with many antihypertensive drugs that probably induce Na^+ retention and fluid volume expansion as a compensatory response to blood pressure reduction.

When diuretic therapy is indicated for the treatment of primary hypertension, the thiazide-type compounds (e.g., chlorothiazide, hydrochlorothiazide) are generally the drugs of choice. *They can be used alone or in combination with other antihypertensive agents.* Approximately 30% of patients with mild hypertension may be treated effectively with thiazide therapy alone.

Thiazide diuretics are not the drugs of choice in patients with renal insufficiency. In this situation, the loop diuretics furosemide and bumetanide are recommended; they have greater intrinsic natriuretic potency than do the thiazides and do not depress renal blood flow.

In situations of known renin–angiotensin–aldosterone involvement, such as in hypertension secondary to renal disease (i.e., renovascular hypertension), diuretics probably should not be used because they further elevate plasma renin.

The K^+-sparing action of spironolactone, triamterene, and amiloride serves as the basis for their occasional use in the therapy of primary hypertension. The drugs can be employed in conjunction with other types of diuretics to help alleviate the K^+ loss caused by them. Under these conditions, K^+ balance is improved while natriuresis is maintained.

Additional information concerning details of diuretic pharmacology is found in Chapter 21.

VASODILATORS

The drugs discussed in this section produce a direct relaxation of vascular smooth muscle and thereby their actions result in vasodilation. This effect is called *direct* because it does not depend on the innervation of vascular smooth muscle and is not mediated by receptors, such as adrenoceptors, cholinoreceptors, or receptors for histamine, that are acted on by classical transmitters and mediators.

The vasodilators decrease total peripheral resistance and thus correct the hemodynamic abnormality that is responsible for the elevated blood pressure in primary hypertension. In addition, because they act directly on vascular smooth muscle, the vasodilators are *effective in lowering blood pressure, regardless of the etiology of the hypertension.* Unlike many other antihypertensive agents, the vasodilators do not inhibit the activity of the sympathetic nervous system; therefore, orthostatic hypotension and impotence are not problems. Additionally, most vasodilators relax arterial smooth muscle to a greater extent than venous smooth muscle, thereby further minimizing postural hypotension.

Although vasodilators would appear to be ideal drugs for the treatment of hypertension, their effectiveness, particularly when they are used chronically, is severely limited by neuroendocrine and autonomic reflexes that tend to counteract the fall in blood pressure. How these reflexes compromise the fall in blood pressure produced by the vasodilators is shown in Fig. 20.1. The diagram does not show all of the possible interrelationships but rather is meant to draw attention to the most prominent reflex changes. These reflexes include an augmentation of sympathetic nervous activity that leads

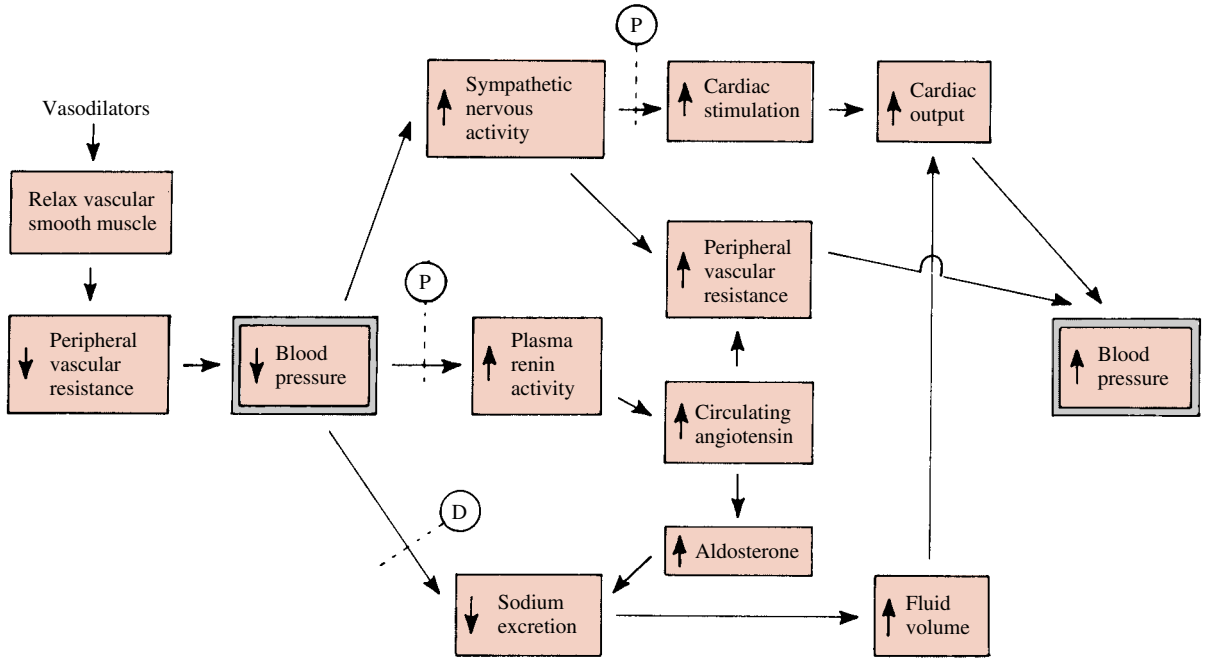

FIGURE 20.1
Neuroendocrine pathways that are activated when vasodilators decrease blood pressure. These pathways lead ultimately to an increase in blood pressure and thus compromise the effectiveness of the vasodilators. The effectiveness can be preserved by coadminstration of propranolol (P) and a diuretic (D).

to an increase in heart rate and cardiac output. Large increases in cardiac output occurring as a result of vasodilator therapy will substantially counter the drug-induced reduction of blood pressure. Increased reflex sympathetic input to the heart also augments myocardial oxygen demand; this is especially serious in patients with coronary insufficiency and little cardiac reserve.

Plasma renin activity is elevated after treatment with vasodilators. The hyperreninemia appears to be due in part to enhanced sympathetic nervous activity. Elevated renin levels lead to an increase in the concentration of circulating angiotensin, a potent vasoconstrictor (see Chapter 18) and thus an increase in peripheral vascular resistance.

Thus, it seems that the lack of sympathetic nervous system inhibition produced by the vasodilators, which is advantageous in some ways, can also be a disadvantage in that reflex increases in sympathetic nerve activity will lead to hemodynamic changes that reduce the effectiveness of the drugs. *Therefore, the vasodilators are generally inadequate as the sole therapy for hypertension.* However, many of the factors that limit the usefulness of the vasodilators can be obviated when they are administered in combination with a β-*adrenoceptor antagonist,* such as propranolol, and a *diuretic.* Propranolol reduces the cardiac stimulation that occurs in response to increases in sympathetic nervous activity, and the large increase in cardiac output caused by the vasodilators will be reduced. Propranolol also reduces plasma renin levels, and that is an additional benefit. The reduction in Na^+ excretion and the increase in plasma volume that occurs with vasodilator therapy can be reduced by concomitant treatment with a diuretic. These relationships are shown in Fig. 20.1.

Mechanism of Action

Available evidence suggests that a single unifying mechanism does not exist but rather that various vasodilators may act at different places in the series of processes that couple excitation of vascular smooth muscle cells with contraction. For example, the vasodilators known as calcium channel antagonists block or limit the entry of calcium through voltage-dependent channels in the membrane of vascular smooth muscle cells. In this way, the calcium channel blockers limit the amount of free intracellular calcium available to interact with smooth muscle contractile proteins (see Chapter 14).

Other vasodilators, such as diazoxide and minoxidil, cause dilation of blood vessels by activating potassium channels in vascular smooth muscle. An increase in potassium conductance results in hyperpolarization of the cell membrane, which will cause relaxation of vascular smooth muscle.

Another group of drugs, the so-called nitrovasodilators, of which nitroprusside is an example, activate soluble guanylate cyclase in vascular smooth muscle, which brings about an increase in the intracellular levels of cyclic guanosine monophosphate (cGMP). Increases in cGMP are associated with vascular smooth muscle relaxation. The action of the nitrovasodilators appears to be quite similar to that of the endogenous vasodilator released by a variety of stimuli from endothelial cells of blood vessels. This substance, originally named endothelial-derived relaxing factor, or EDRF, is nitric oxide or a closely related nitrosothiol compound. *The knowledge that the nitrovasodilators generate nitric oxide in vivo suggests that this substance may be the final common mediator of a number of vascular smooth muscle relaxants.*

This chapter describes four vasodilators in detail. Two of these agents, *hydralazine* and *minoxidil,* are effective orally and are used for the chronic treatment of primary hypertension. The other two drugs, *diazoxide* and *sodium nitroprusside,* are effective only when administered intravenously. They are generally used in the treatment of hypertensive emergencies or during surgery.

Hydralazine

The vasodilation produced by hydralazine (*Apresoline*) depends in part on the presence of an intact blood vessel endothelium. This implies that hydralazine causes the release of nitric oxide, which acts on the vascular smooth muscle to cause relaxation. In addition, hydralazine may produce vasodilation by activating K^+ channels.

Absorption, Metabolism, and Excretion

Hydralazine is well absorbed (65–90%) after oral administration. Its peak antihypertensive effect occurs in about 1 hour, and its duration of action is about 6 hours.

The major pathways for its metabolism include ring hydroxylation, with subsequent glucuronide conjugation and *N*-acetylation. Hydralazine exhibits a first-pass effect in that a large part of an orally administered dose is metabolized before the drug reaches the systemic circulation. The first-pass metabolism occurs in the intestinal mucosa (mostly *N*-acetylation) and the liver. The primary excretory route is through renal elimination, and about 80% of an oral dose appears in the urine within 48 hours. About 10% is excreted unchanged in the feces.

Approximately 85% of the hydralazine in plasma is bound to plasma proteins. Although this does not appear to be a major therapeutic concern, the potential for interactions with other drugs that also bind to plasma proteins does exist. The plasma half-life of hydralazine in patients with normal renal function is 1.5 to 3 hours. Interestingly, the half-life of the antihypertensive effect is somewhat longer than the plasma half-life. This may occur because hydralazine is specifically accumulated in artery walls, where it may continue to exert a vasodilator action even though plasma concentrations are low.

The plasma half-life of hydralazine may be increased fourfold or fivefold in patients with renal failure. If renal failure is present, therefore, both the antihypertensive and toxic effects of hydralazine may be enhanced. Since *N*-acetylation of hydralazine is an important metabolic pathway and depends on the activity of the enzyme *N*-acetyltransferase, genetically determined differences in the activity of this enzyme in certain individuals (known as slow acetylators) will result in higher plasma levels of hydralazine; therefore, the drug's therapeutic or toxic effects may be increased.

Pharmacological Actions

Hydralazine produces widespread but apparently not uniform vasodilation; that is, vascular resistance is decreased more in cerebral, coronary, renal, and splanchnic beds than in skeletal muscle and skin. Renal blood flow and ultimately glomerular filtration rate may be slightly increased after acute treatment with hydralazine. However, after several days of therapy, the renal blood flow is usually no different from that before drug use.

In therapeutic doses, hydralazine produces little effect on nonvascular smooth muscle or on the heart. Its pharmacological actions are largely confined to vascular smooth muscle and occur predominantly on the arterial side of the circulation; venous capacitance is much less affected. Because cardiovascular reflexes and venous capacitance are not affected by hydralazine, postural hypotension is not a clinical concern. Hydralazine treatment does, however, result in an increase in cardiac output. This action is brought about by the combined effects of a reflex increase in sympathetic stimulation of the heart, an increase in plasma renin, and salt and water retention. These effects limit the hypotensive usefulness of hydralazine to such an extent that *it is rarely used alone.*

Clinical Uses

Hydralazine is generally reserved for moderately hypertensive ambulatory patients whose blood pressure is not well controlled either by diuretics or by drugs that interfere with the sympathetic nervous system. It is almost always administered in combination with a diuretic (to prevent Na^+ retention) and a β-blocker, such as propranolol (to attenuate the effects of reflex cardiac stimulation and hyperreninemia). *The triple combination of a diuretic, β-blocker, and hydralazine constitutes a unique hemodynamic approach to the treatment of hypertension,* since three of the chief determinants of blood pressure are affected: cardiac output (β-blocker),

plasma volume (diuretic), and peripheral vascular resistance (hydralazine).

Although hydralazine is available for intravenous administration and has been used in the past for hypertensive emergencies, it is not generally employed for this purpose. The onset of action after intravenous injection is relatively slow, and its actions are somewhat unpredictable in comparison with those of several other vasodilators.

Adverse Effects

Most side effects associated with hydralazine administration are due to vasodilation and the reflex hemodynamic changes that occur in response to vasodilation. These side effects include headache, flushing, nasal congestion, tachycardia, and palpitations. More serious manifestations include myocardial ischemia and heart failure. These untoward effects of hydralazine are greatly attenuated when the drug is administered in conjunction with a β-blocker.

When administered chronically in high doses, hydralazine may produce a rheumatoidlike state that when fully developed, resembles disseminated lupus erythematosus.

Minoxidil

Minoxidil (*Loniten*) is an orally effective vasodilator. It is more potent and longer acting than hydralazine and does not accumulate significantly in patients with renal insufficiency. It depends on in vivo metabolism by hepatic enzymes to produce an active metabolite, minoxidil sulfate. Minoxidil sulfate activates potassium channels, resulting in hyperpolarization of vascular smooth muscle and relaxation of the blood vessel.

Absorption, Metabolism, and Excretion

Peak concentrations of minoxidil in the blood occur 1 hour after oral administration, although the therapeutic effect may take 2 or more hours to manifest. This is probably related to the time it takes to convert minoxidil to minoxidil sulfate. The antihypertensive action after an oral dose of minoxidil lasts 12 to 24 hours. The long duration of action allows the drug to be administered only once or twice a day, a regimen that may be beneficial for compliance. Interestingly, the therapeutic half-life is considerably longer than the plasma half-life. This may be, as has been suggested for hydralazine, a result either of accumulation of the drug and its active metabolite in arterial walls or a longer plasma half-life of the sulfated metabolite, or both.

The ultimate disposition of minoxidil depends primarily on hepatic metabolism and only slightly on renal excretion of unchanged drug. Because of this, pharmacological activity is not cumulative in patients with renal failure.

Pharmacological Actions

The hemodynamic effects of minoxidil are generally similar to those of hydralazine, with the noteworthy exception that a greater decrease in peripheral vascular resistance and consequently a larger reduction in blood pressure can be achieved with minoxidil. Minoxidil produces no important changes in either renal blood flow or glomerular filtration rate. It has little or no effect on venous capacitance and does not inhibit the reflex activation of the sympathetic nervous system. Orthostasis and other side effects of sympathetic blockade are therefore not a problem. As with hydralazine, there is a significant increase in cardiac output that is secondary to reflex increases in sympathetic activity, hyperreninemia, and salt and water retention. These effects can substantially reduce the effectiveness of minoxidil when it is used alone. The addition of a β-blocker and a diuretic to the therapeutic regimen will preserve minoxidil's antihypertensive action while attenuating some of the undesirable side effects.

Clinical Uses

The major indications for the use of minoxidil are (1) severe hypertension that may be life threatening and (2) hypertension that is resistant to milder forms of therapy. Compromises in renal function do not prolong either the plasma or the therapeutic half-life of minoxidil, and therefore, it seems to be particularly important for hypertensive patients with chronic renal failure.

Adverse Effects

Signs of toxicity common to vasodilator therapy in general also occur with minoxidil; they are attributable to vasodilation and reflex increases in sympathetic nerve activity. These include headache, nasal congestion, tachycardia, and palpitations. These effects do not have great clinical importance, since minoxidil is almost always administered in combination with a β-blocker, which antagonizes the indirect cardiac effects. A more troublesome side effect, particularly in women, is the growth of body hair, possibly due to a direct stimulation of the growth and maturation of cells that form hair shafts. Apparently, minoxidil activates a specific gene that regulates hair shaft protein. In any case, this particular side effect has been capitalized upon, and minoxidil is now marketed as *Rogaine* for the treatment of male pattern baldness.

Diazoxide

Diazoxide (*Hyperstat*) is chemically similar to the thiazide diuretics. It is devoid of diuretic activity and causes Na^+ and water retention. Diazoxide is a very potent vasodilator and is available only for intravenous

use in the treatment of hypertensive emergencies. The mechanism by which diazoxide relaxes vascular smooth muscle is related to its ability to activate potassium channels and produce a hyperpolarization of the cell membrane.

Absorption, Metabolism, and Excretion

Diazoxide lowers blood pressure within 3 to 5 minutes after rapid intravenous injection, and its duration of action may be 4 to 12 hours. Interestingly, if diazoxide is either injected slowly or infused its hypotensive action is quite modest. This is believed to be due to a rapid and extensive binding of the drug to plasma proteins. Both the liver and kidney contribute to its metabolism and excretion. The plasma half-life is therefore prolonged in patients with chronic renal failure.

Pharmacological Actions

The hemodynamic effects of diazoxide are similar to those of hydralazine and minoxidil. It produces direct relaxation of arteriolar smooth muscle with little effect on capacitance beds. Since it does not impair cardiovascular reflexes, orthostasis is not a problem. Its administration is, however, associated with a reflex increase in cardiac output that partially counters its antihypertensive effects. Propranolol and other β-blockers potentiate the vasodilating properties of the drug. Diazoxide has no direct action on the heart. Although renal blood flow and glomerular filtration may fall transiently, they generally return to predrug levels within an hour.

Clinical Uses

Diazoxide is administered intravenously for the treatment of *hypertensive emergencies,* particularly malignant hypertension, hypertensive encephalopathy, and eclampsia. It is effective in 75 to 85% of the patients to whom it is administered and rarely reduces blood pressure below the normotensive range.

In patients with coronary insufficiency, a β-blocker can be given in conjunction with diazoxide to decrease the cardiac work associated with reflex increases in sympathetic stimulation of the heart. However, β-blockers potentiate the hypotensive effect of diazoxide, and therefore, the dose of the vasodilator should be lowered. The dose of diazoxide should also be lowered if the patient has recently been treated with guanethidine or another drug that depresses the action of the sympathetic nervous system. Such drugs permit a greater hypotensive effect because they reduce the increase in cardiac output that normally partially counteracts the fall in pressure.

Diazoxide appears to have a direct antinatriuretic action. This direct action, coupled with the neuroendocrine reflexes that are activated by a decrease in peripheral vascular resistance, leads to severe retention of Na^+ and water. Since tolerance to diazoxide can develop rapidly, it is frequently administered in conjunction with a diuretic.

Adverse Effects

Since diazoxide is not often used for long-term treatment, toxicities associated with chronic use are rare. The chief concern is the side effects associated with the increased workload on the heart, which may precipitate myocardial ischemia and Na^+ and water retention. These undesirable effects can be controlled by concurrent therapy with a β-blocker and a diuretic.

Diazoxide may cause hyperglycemia, especially in diabetics, so if the drug is used for several days, blood glucose levels should be measured.

When used in the treatment of toxemia, diazoxide may stop labor, because it relaxes uterine smooth muscle.

Sodium Nitroprusside

Sodium nitroprusside (*Nipride*) is a potent directly acting vasodilator capable of reducing blood pressure in all patients, regardless of the cause of hypertension. It is used only by the intravenous route for the treatment of *hypertensive emergencies.* The pharmacological activity is caused by the nitroso moiety. The actions of the drug are similar to those of the nitrites and nitrates that are used as antianginal agents (see Chapter 17). The action of the nitrovasodilators depends on the intracellular production of cGMP.

Absorption, Metabolism, and Excretion

The onset of the hypotensive action of sodium nitroprusside is rapid, within 30 seconds after intravenous administration. If a single dose is given, the action lasts for only a couple of minutes. Therefore, sodium nitroprusside must be administered by continuous intravenous infusion. After the infusion is stopped, blood pressure returns to predrug levels within 2 to 3 minutes.

Nitroprusside is metabolically degraded by the liver, yielding thiocyanate. Because thiocyanate is excreted by the kidney, toxicities due to this compound are most likely in patients with impaired renal function.

Pharmacological Actions

In contrast to hydralazine, minoxidil, and diazoxide, sodium nitroprusside relaxes venules as well as arterioles. Thus, it decreases both peripheral vascular resistance and venous return to the heart. This action limits the increase in cardiac output that normally follows vasodilator therapy. Sodium nitroprusside does not inhibit sympathetic reflexes, so heart rate may increase following its administration even though cardiac output is not

increased. Renal blood flow remains largely unaffected by sodium nitroprusside, because the decrease in renal vascular resistance is proportional to the decrease in mean arterial pressure. As with all vasodilators, plasma renin activity increases.

Clinical Uses

Sodium nitroprusside is used in the management of hypertensive crisis. Although it is effective in every form of hypertension because of its relatively favorable effect on cardiac performance, sodium nitroprusside has special importance in the treatment of severe hypertension with acute myocardial infarction or left ventricular failure. Because the drug reduces preload (by venodilation) and afterload (by arteriolar dilation), it improves ventricular performance and in fact is sometimes used in patients with refractory heart failure, even in the absence of hypertension.

Adverse Effects

The most commonly encountered side effects of sodium nitroprusside administration are nausea, vomiting, and headache, which quickly dissipate when the infusion is terminated. When sodium nitroprusside treatment extends for several days, there is some danger of toxicity owing to the accumulation of its thiocyanate metabolite. Thiocyanate intoxication includes signs of delirium and psychosis; hypothyroidism also may occur. If nitroprusside is administered for several days, thiocyanate levels should be monitored.

Close supervision is required when nitroprusside is used because of the drug's potency and short duration of action.

DRUGS THAT IMPAIR SYMPATHETIC NERVOUS SYSTEM FUNCTIONING

The drugs discussed in this section reduce blood pressure by depressing the activity of the sympathetic nervous system. This is accomplished in four ways: (1) by reducing the number of impulses traveling in the sympathetic nerves, (2) by inhibiting neurotransmitter release, (3) by depleting the stores of norepinephrine, and (4) by antagonizing the actions of norepinephrine on effector cells. The sites of action of these drugs are diverse and may best be appreciated by considering the sympathetic arc concerned with blood pressure regulation (Fig. 20.2).

While there may be some involvement of the adrenergic nervous system in primary hypertension, there is no clear evidence that a malfunction of this system is causally involved in primary hypertension. Therefore, *even though drugs may depress the sympathetic system and thus lower blood pressure, it should not be assumed that this therapeutic approach corrects the cause of the elevated pressure.* Only in a few specific cases, such as pheochromocytoma, can hypertension be directly related to abnormalities in the functioning of the sympathetic system.

ADRENOCEPTOR ANTAGONISTS

The adrenoceptor-blocking agents are described in detail in Chapter 11, although their use in the treatment of hypertension is briefly described here. Drugs of this group are subdivided into α-adrenoceptor antagonists (α-blockers) and β-adrenoceptor antagonists (β- blockers).

α-Blocking Drugs

Phenoxybenzamine and phentolamine have been available for a number of years and are sometimes referred to as classical α-blockers. The frequency of their use for the treatment of primary hypertension has greatly diminished in recent years because of the development of drugs such as prazosin that are relatively selective for α_1-receptors. α_1-Receptor–selective antagonists will not potentiate the release of norepinephrine from sympathetic nerves. Thus, the stimulation of the heart and renin release, actions that limit the usefulness of classical α-blockers, are less with α_1-selective antagonists.

Unlike the vasodilators, which have a more prominent effect on arterial beds than on venous beds, the α-blockers prevent vasoconstriction in both vascular beds. Because of the venous dilation, postural hypotension is a feature of α-blockade, although less so with prazosin than with the classical α-blockers.

Prazosin and its derivatives that are selective for α_1-adrenoceptors are quite useful for the management of primary hypertension. The α_1-receptor–selective antagonists can be used alone in mild hypertension. When hypertension is moderate or severe, prazosin is generally administered in combination with a thiazide 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 types of antihypertensive agents 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 hypertensive patients whose condition is complicated by gout or diabetes mellitus. Prazosin treatment is associated with favorable effects on plasma lipids. Thus, it may be of particular importance in managing patients with hyperlipidemia.

Further information about the pharmacokinetics, adverse reactions, and preparations of α-blockers is given in Chapter 11.

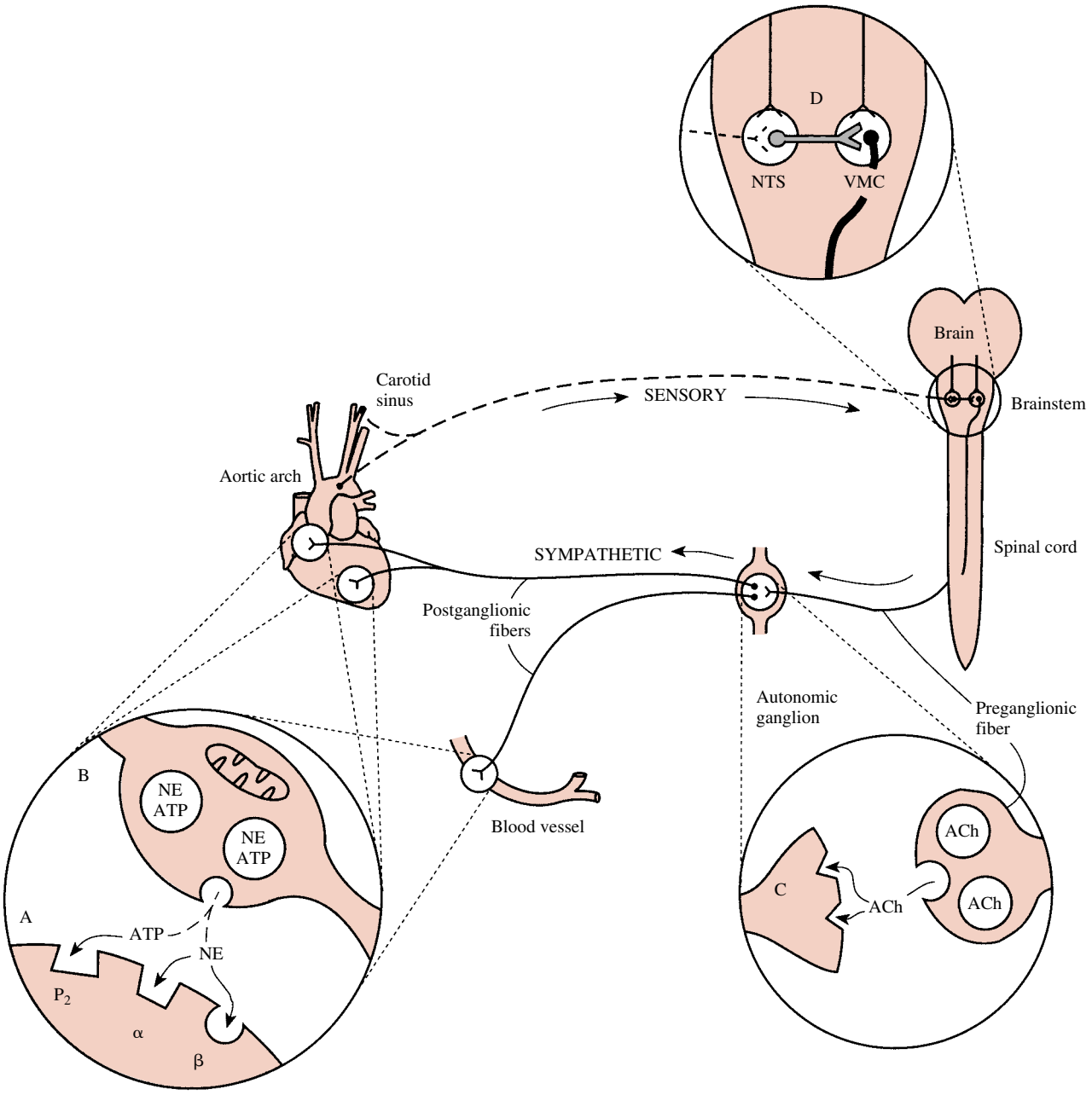

FIGURE 20.2
Sympathetic arc involved in blood pressure regulation and sites where drugs may act to influence the system. *A.* Receptors on effector cell. *B.* Adrenergic varicosity. *C.* Nicotinic receptors (postganglionic fibers). *D.* Brainstem nuclei. NTS, nucleus of the tractus solitarii; VMC, vasomotor center; ACh, acetylcholine; NE, norepinephrine; α, α-adrenoceptors; β, β-adrenoceptors; P_2, P_2-purinoceptors; ATP, adenosine triphosphate.

β-*Blocking Drugs*

β-Blockers competitively antagonize the responses to catecholamines that are mediated by β-receptors (see Chapter 11). These drugs have a number of clinical uses, including treatment of cardiac arrhythmias (see Chapter 10) and angina pectoris (see Chapter 17), for which their therapeutic benefit is directly related to the blockade of β-receptors in the myocardium.

β-Blockers are also used in the treatment of hypertension, although this seems to be somewhat paradoxical in that blockade of vascular smooth muscle β-receptors might be expected to unmask or leave unopposed re-

sponses to catecholamines that occur through vascular α-receptors. Unopposed α-mediated responses would be expected to increase, rather than decrease, blood pressure. Nevertheless, β-*blockers have proved to be quite effective antihypertensive agents*, and they have an important place in the treatment of primary hypertension.

The mechanism by which β-blockers produce a sustained reduction in blood pressure in patients with primary hypertension is not completely understood, but it may include such actions as reduction in renin release, antagonism of central nervous system (CNS) β-receptors, or antagonism of presynaptic facilitatory β-receptors on sympathetic nerves.

Decreases in heart rate and cardiac output are the most obvious results of administration of β-blockers. Initially, blood pressure is not much affected, since peripheral vascular resistance will be reflexly elevated as a result of the drug-induced decrease in cardiac output. The reduction of blood pressure that occurs in chronic treatment correlates best with changes in peripheral vascular resistance rather than with a drug-induced variation in heart rate or cardiac output.

The reduction in plasma volume produced by β-blockers contrasts with the increased volume seen with other types of antihypertensives. Tolerance to the antihypertensive actions of β-blockers therefore is less of a problem than with the vasodilating drugs. An additional difference from the vasodilators is that *plasma renin activity is reduced, rather than increased, by propranolol (Inderal*). Orthostatic hypotension does not occur with β-blockers.

The β-blockers are quite popular antihypertensive drugs. They are well tolerated, and serious side effects are seldom observed. When used alone over several weeks, β-blockers produce a significant reduction in blood pressure in approximately 30% of patients with mild to moderate hypertension. Thus, β-*blockers can be employed as a first step in the management of high blood pressure. However, they are often used in conjunction with a diuretic when therapy with a single agent is not satisfactory*. The combination of a β-blocker, thiazide diuretic, and vasodilator provides significant control of moderate to severe hypertension in approximately 80% of patients.

From a hemodynamic viewpoint, there are several obvious advantages to using a β-blocker in combination with a vasodilator. Reflex-mediated cardiac stimulation is a common feature of vasodilator treatment and can severely limit its antihypertensive effectiveness. A β-blocker will reduce the cardiac stimulation and thus preserve the effectiveness of the vasodilator. Conversely, the vasodilator will prevent the increase in peripheral vascular resistance that occurs on initiation of treatment with a β-blocker. Furthermore, vasodilator treatment initiates reflexes that lead to an increase in plasma renin activity. Thus, β-blockers, such as propranolol, that reduce plasma renin activity are of obvious value.

Although the β-blockers are well-tolerated drugs and patient compliance is good, there may be problems with their administration, particularly in patients with decompensated hearts and cardiac conductance disturbances. These potential problems and the adverse effect of β-blockers are described in detail in Chapter 11.

ADRENERGIC NEURON-BLOCKING DRUGS

The adrenergic neuron-blocking drugs are antihypertensive because *they prevent the release of transmitters from peripheral postganglionic sympathetic nerves*. The contraction of vascular smooth muscle due to sympathetic nerve stimulation is thereby reduced, and blood pressure decreases. Guanethidine is the prototypical member of this class.

Guanethidine

Guanethidine (*Ismelin*) is a powerful antihypertensive agent that is quite effective in the treatment of moderate to severe hypertension. It is most frequently used in the treatment of severe hypertension that is resistant to other agents.

Guanethidine exerts its effects at peripheral sympathetic nerve endings following its active transport into the nerve varicosities by the neuronal amine transport system. This is the same uptake system that transports norepinephrine into the varicosity (see Chapter 9). The accumulation of guanethidine in adrenergic neurons, through an as yet unexplained mechanism, disrupts the process by which action potentials trigger the release of stored norepinephrine and other cotransmitters from nerve terminals. It is this action of guanethidine that is primarily responsible for its antihypertensive properties. Parasympathetic function is not altered, a fact that distinguishes guanethidine from the ganglionic blocking agents (see Chapter 14).

Guanethidine is suitable for oral use, and this is its usual route of administration. However, absorption from the gastrointestinal tract is variable. The half-life of guanethidine is 5 days, with about one-seventh of the total administered dose eliminated per day. The slow elimination contributes to the cumulative and prolonged effects of the drug.

Guanethidine reduces blood pressure by its ability to diminish vascular tone; both the arterial and venous sides of the circulatory system are involved. The resulting venous pooling contributes to orthostatic hypotension, a prominent feature of guanethidine treatment. The reduction in blood pressure is more prominent when the patient is standing than recumbent.

A reduction in cardiac output attributable to a decreased venous return and the inability of sympathetic nerve impulses to release enough transmitters to stimulate the heart occur during the early stages of guanethidine therapy.

With the possible exception of minoxidil, guanethidine is the most potent orally effective antihypertensive drug. Because guanethidine produces a number of side effects that are due primarily to the imbalance between sympathetic and parasympathetic function it produces, it is generally reserved for the treatment of severe hypertension.

A common and troublesome side effect is postural hypotension. Sexual impotence does occur, and male patients may have difficulty ejaculating. Symptoms of unopposed parasympathetic activity include such gastrointestinal disturbances as diarrhea and increased gastric secretion.

Guanethidine may aggravate congestive heart failure or actually precipitate failure in patients with marginal cardiac reserve, owing to its ability to produce vascular volume expansion, edema, and a reduced effectiveness of sympathetic cardiac stimulation.

Guanethidine is contraindicated in patients with pheochromocytoma because the drug may release catecholamines from the tumor. The concomitant use of monoamine oxidase (*MAO*) inhibitors and guanethidine is also to be avoided, since this combined drug treatment eliminates two of the principal mechanisms for terminating the actions of the catecholamines and certain other adrenomimetic drugs, that is, biotransformation and neuronal uptake. Dangerously high concentrations of catecholamines at receptor sites are possible.

The tricyclic antidepressants (e.g., desipramine and amitriptyline) and some phenothiazines block the sympathetic neuronal amine uptake system; they thereby would also block the uptake of guanethidine and thus reduce its hypotensive effectiveness. Conversely, guanethidine competitively inhibits the uptake of drugs that are substrates for neuronal uptake, such as the indirectly acting adrenomimetics, or sympathomimetics (see Chapter 10).

DRUGS THAT INTERFERE WITH NOREPINEPHRINE STORAGE

Reserpine (*Serpasil*) is the prototypical drug interfering with norepinephrine storage. Reserpine lowers blood pressure by reducing norepinephrine concentrations in the noradrenergic nerves in such a way that less norepinephrine is released during neuron activation. Reserpine does not interfere with the release process per se as does guanethidine.

Under normal circumstances, when an action potential invades the sympathetic nerve terminal, a portion of the released norepinephrine is recycled. This event requires two successive steps: (1) transfer of norepinephrine across the neuronal membrane into the cytosol by an energy-dependent carrier-mediated active process, and (2) transfer of the recaptured amine from the cytosol into the noradrenergic storage vesicles, where it is stored until needed. *Reserpine inhibits only the second uptake process.* As a consequence of this inhibition of vesicular uptake, norepinephrine cannot be stored intraneuronally, and much of the cytosolic amine is metabolized by MAO.

In addition to impairing norepinephrine storage and thereby enhancing its catabolism, reserpine impairs the vesicular uptake of dopamine, the immediate precursor of norepinephrine. Since dopamine must be taken up into the adrenergic vesicles to undergo hydroxylation and form norepinephrine, reserpine administration impairs norepinephrine synthesis. *The combined effects of the blockade of dopamine and norepinephrine vesicular uptake lead to transmitter depletion.*

Reserpine also interferes with the neuronal storage of a variety of central transmitter amines such that significant depletion of norepinephrine, dopamine, and 5-hydroxytryptamine (serotonin) occurs. This central transmitter depletion is responsible for the sedation and other CNS side effects associated with reserpine therapy. The depletion of brain amines also may contribute to the antihypertensive effects of reserpine.

The chief use of reserpine is in the treatment of mild to moderate hypertension. As with other sympathetic depressant drugs, tolerance to the antihypertensive effects of reserpine can occur, owing to a compensatory increase in blood volume that frequently accompanies decreased peripheral vascular resistance. Reserpine, therefore, should be used in conjunction with a diuretic.

Because of its sedative properties, reserpine offers special benefit to hypertensive patients who exhibit symptoms of agitated psychotic states and who may be unable to tolerate therapy with phenothiazine derivatives.

The most troublesome untoward effects of treatment with reserpine involve the CNS. Sedation and depression are the most common, although nightmares and thoughts of suicide also occur. Reserpine treatment, therefore, is contraindicated in patients with a history of severe depression. The occasional report of reserpine-induced extrapyramidal symptoms, which are similar to those seen in patients with Parkinson' s disease, is believed to be a result of dopamine depletion from neurons in the CNS.

Peripheral nervous system side effects are the result of a reserpine-induced reduction of sympathetic function and unopposed parasympathetic activity; symptoms include nasal congestion, postural hypotension, diarrhea, bradycardia, increased gastric secretion, and occasionally impotence. Because of the increased gastric secretion, reserpine is contraindicated for patients

with peptic ulcer. In patients with little cardiac reserve, reserpine must be administered with caution because of its ability to interfere with sympathetic stimulation of the heart.

DRUGS THAT INTERFERE WITH NOREPINEPHRINE SYNTHESIS

Metyrosine (*Demser*) is an example of this class of drugs. Chemically, metyrosine is α-methyl tyrosine. The drug blocks the action of tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of catecholamines. Unlike α-methyldopa, metyrosine is not itself incorporated into the catecholamine synthetic pathway. The ultimate action of the drug is to decrease the production of catecholamines.

Metyrosine is well absorbed from the gastrointestinal tract and is excreted in the urine largely as unchanged drug.

Metyrosine is not employed for the treatment of essential hypertension but rather is used for the management of pheochromocytoma. It is useful for preoperative treatment and for long-term therapy when surgery is not feasible.

Sedation is the most common adverse effect of metyrosine. Other CNS disturbances, such as anxiety, confusion, and disorientation, have also been reported. Symptoms of sympathetic nervous system depression in general, such as nasal congestion and dryness of mouth, can also occur.

GANGLIONIC BLOCKING AGENTS

The basis for the antihypertensive activity of the ganglionic blockers lies in their ability to block transmission through autonomic ganglia (Fig. 20.2*C*). This action, which results in a decrease in the number of impulses passing down the *postganglionic* sympathetic (and parasympathetic) nerves, decreases vascular tone, cardiac output, and blood pressure. *These drugs prevent the interaction of acetylcholine (the transmitter of the preganglionic autonomic nerves) with the nicotinic receptors on postsynaptic neuronal membranes of both the sympathetic and parasympathetic nervous systems.*

The ganglionic blocking agents are extremely potent antihypertensive agents and can reduce blood pressure regardless of the extent of hypertension. Unfortunately, blockade of transmission in both the sympathetic and parasympathetic systems produces numerous untoward responses, including marked postural hypotension, blurred vision, and dryness of mouth, constipation, paralytic ileus, urinary retention, and impotence. Owing to the frequency and severity of these side effects and to the development of other powerful antihypertensive agents, the ganglionic blocking agents are rarely used. The orally effective ganglionic blocking agents in fact are not recommended for the treatment of primary hypertension. However, certain intravenous preparations, such as the short-acting agent trimethaphan camsylate (*Arfonad*), are used occasionally for hypertensive emergencies and in surgical procedures in which hypotension is desirable to reduce the possibility of hemorrhage.

A more complete description of trimethaphan and other ganglionic blocking agents can be found in Chapter 14.

CENTRALLY ACTING HYPOTENSIVE DRUGS

Two important antihypertensive agents, α-methyldopa and clonidine, act predominantly in the *brain* (Fig. 20.2*D*). Although the details of their actions may differ in some respects, *their antihypertensive activity is ultimately due to their ability to decrease the sympathetic outflow from the brain to the cardiovascular system*.

α-Methyldopa

The spectrum of activity of α-methyldopa (*Aldomet*) lies between those of the more potent agents, such as guanethidine, and the milder antihypertensives, such as reserpine. α-Methyldopa is a structural analogue of dihydroxyphenylalanine (dopa) and differs from dopa only by the presence of a methyl group on the α-carbon of the side chain.

Mechanism of Action

A number of theories have been put forward to account for the hypotensive action of α-methyldopa. Current evidence suggests that for α-methyldopa to be an antihypertensive agent, it must be converted to α-methylnorepinephrine; however, *its site of action appears to be in the brain rather than in the periphery.* Systemically administered α-methyldopa rapidly enters the brain, where it accumulates in noradrenergic nerves, is converted to α-methylnorepinephrine, and is released. *Released α-methylnorepinephrine activates CNS α-adrenoceptors whose function is to decrease sympathetic outflow.* Why α-methylnorepinephrine decreases sympathetic outflow more effectively than does the naturally occurring transmitter is not entirely clear.

Absorption, Metabolism, and Excretion

Approximately 50% of an orally administered dose of α-methyldopa is absorbed from the gastrointestinal tract. Both peak plasma drug levels and maximal blood pressure–lowering effects are observed 2 to 6 hours after oral administration. A considerable amount of unchanged α-methyldopa and several conjugated and decarboxylated metabolites can be found in the urine.

Pharmacological Actions

The primary hemodynamic alteration responsible for the hypotensive effects of α-methyldopa remains in dispute. When the patient is supine, the reduction in blood pressure produced by α-methyldopa correlates best with a decrease in peripheral vascular resistance, cardiac output being only slightly reduced. When the patient is upright, the fall in blood pressure corresponds more closely with a reduced cardiac output.

An important aspect of α-methyldopa's hemodynamic effects is that renal blood flow and glomerular filtration rate are not reduced. As occurs with most sympathetic depressant drugs and vasodilators, long-term therapy with α-methyldopa leads to fluid retention, edema formation, and plasma volume expansion. While data conflict somewhat, it is generally thought that α-methyldopa suppresses plasma renin activity.

Clinical Uses

α-Methyldopa is not generally believed to be suitable for monotherapy of primary hypertension. Because plasma volume increases as the duration of α-methyldopa therapy is extended, the drug should be used in conjunction with a diuretic; this will produce a significantly greater fall in blood pressure than would occur with either drug used alone. Because α-methyldopa lowers blood pressure without compromising either renal blood flow or the glomerular filtration rate, *it is particularly valuable in hypertension complicated by renal disease.* However, if end-stage renal failure accompanies severe hypertension, α-methyldopa may not be effective.

The presence of α-methyldopa and its metabolites in the urine reduces the diagnostic value of urinary catecholamine measurements as an indicator of pheochromocytoma, since these substances interfere with the fluorescence assay for catecholamines.

Adverse Effects

The most commonly encountered side effects of α-methyldopa are sedation and drowsiness. These CNS effects are probably the result of reductions in brain catecholamine levels. Other side effects, also typical of sympathetic depression, are dry mouth, nasal congestion, orthostatic hypertension, and impotence.

Autoimmune reactions associated with α-methyldopa treatment include thrombocytopenia and leukopenia. Since a few cases of an α-methyldopa–induced hepatitis have occurred, the drug is contraindicated in patients with active hepatic disease. Flulike symptoms also are known to occur.

Clonidine and Related Drugs

Clonidine (*Catapres*) is effective orally and is used primarily for the treatment of moderate hypertension. It is structurally related to the α-adrenoceptor antagonists phentolamine and tolazoline. *Clonidine, however, is not an α-blocker, but is actually an α-agonist.* Its antihypertensive effectiveness appeared paradoxical until it was recognized that clonidine activated central α_2-receptors, thus reducing sympathetic outflow to the periphery.

Guanabenz (*Wytensin*) and guanfacine (*Tenex*) are two drugs with considerable structural similarity to clonidine. These agents also are central α_2-agonists and exhibit an antihypertensive profile similar to that of clonidine.

Mechanism of Action

The antihypertensive activity of clonidine can be ascribed solely to a decrease in the sympathetic activity transmitted from the brain to the peripheral vasculature. After clonidine administration, direct measurements of sympathetic nerve activity show that electrical discharge is reduced in a number of sympathetic nerves, including the cardiac, splanchnic, and cervical nerves.

It is generally agreed that clonidine acts in the same general area in the brain as does α-methyldopa, that is, somewhere in the medulla oblongata. The principal difference between clonidine and α-methyldopa is that clonidine acts *directly* on α_2-receptors, whereas α-methyldopa first must be converted by synthetic enzymes to α-methylnorepinephrine.

Absorption, Metabolism, and Excretion

Clonidine is well absorbed after oral administration. Peak plasma levels occur between 2 and 4 hours after drug administration and correlate well with pharmacological activity. The plasma half-life in patients with normal renal function is 12 hours. Urinary excretion of clonidine and its metabolites accounts for almost 90% of the administered dose, and fecal excretion accounts for the rest. Approximately 50% of an administered dose is excreted unchanged; the remainder is oxidatively metabolized in the liver.

Pharmacological Actions

An acute intravenous injection of clonidine may produce a transient pressor response that apparently is due to stimulation of peripheral vascular α-receptors. The pressor response does not occur after oral administration, because the drug's centrally mediated depressor action overrides it.

The decrease in blood pressure produced by clonidine correlates better with a decreased cardiac output than with a reduction in peripheral vascular resistance. The reduction in cardiac output is the result of both a decreased heart rate and reduced stroke work; the latter effect is probably caused by a diminished venous return.

Renal blood flow and glomerular filtration are not decreased, although renal resistance is diminished. Like α-methyldopa, it is a useful agent for hypertension complicated by renal disease. Plasma renin activity is reduced by clonidine, presumably as a result of a centrally mediated decrease in sympathetic stimulation of the juxtaglomerular cells of the kidney.

Clinical Uses

The primary indication for clonidine use is in mild and moderate hypertension that has not responded adequately to treatment with a diuretic or a β-blocker. Since clonidine causes sodium and water retention and plasma volume expansion, it generally is administered in combination with a diuretic. A vasodilator can be added to the clonidine–diuretic regimen in the treatment of resistant forms of hypertension. Such drug combinations can be quite effective, since the reflex increases in heart rate and cardiac output that result from vasodilator administration are reduced or negated by clonidine-induced decreases in heart rate and cardiac output.

For severely hypertensive patients, clonidine has been used in combination with a diuretic, a vasodilator, and a β-blocker. Some care must be taken, however, because the coadministration of clonidine and a β-blocker may cause excessive sedation. Clonidine is especially useful in patients with renal failure, since its duration of action is not appreciably altered by renal disease and it does not compromise renal blood flow.

Adverse Effects

It is estimated that about 7% of patients receiving clonidine discontinue the drug because of side effects. Although the symptoms are generally mild and tend to subside if therapy is continued for several weeks, as many as 50% of the patients complain of drowsiness and dryness of mouth. Other untoward effects include constipation, nausea or gastric upset, and impotence. These effects are characteristic of interference with the functioning of the sympathetic nervous system.

A potentially dangerous effect is *rebound hypertension*, which follows abrupt withdrawal of clonidine therapy. This posttreatment hypertension appears to be the result of excessive sympathetic activity. The genesis of the syndrome is not well understood. A contributing factor may be development of supersensitivity in either the sympathetic nerves or the effector organs of the cardiovascular system due to the clonidine-caused chronic reduction in sympathetic activity. Thus, when the drug is abruptly withdrawn, an exaggerated response to "normal" levels of activity may occur. If treatment with clonidine is terminated gradually, rebound hypertension is unlikely. Patients should be warned of the danger of abruptly discontinuing clonidine treatment.

Study Questions

1. A 55-year-old patient has been referred to you. She complains about a skin rash and a cough. In the course of history taking, she tells you that she takes high blood pressure medication but she doesn't remember the name. You suspect a drug toxicity. Which of the following antihypertensive agents is the patient most likely taking?
(A) Captopril
(B) Nifedipine
(C) Prazosin
(D) Propanolol
(E) Clonidine

2. Which of the following compounds depends least upon the release of EDRF (nitric oxide) from endothelial cells to cause vasodilation?
(A) Bradykinin
(B) Histamine
(C) Minoxidil
(D) Hydralazine
(E) Acetylcholine

3. Which of the following antihypertensive drugs is contraindicated in a hypertensive patient with a pheochromocytoma?
(A) Metyrosine
(B) Labetalol
(C) Prazosin
(D) Phenoxybenzamine
(E) Guanethidine

4. Which of the following antihypertensive agents would decrease renin release?
(A) Prazosin
(B) Clonidine
(C) Captopril
(D) Nitroprusside
(E) Diazoxide

ANSWERS

1. A. Although many drugs can evoke a reaction such as a rash, a rash and a dry cough are well-recognized side effects of angiotensin converting enzyme

(ACE) inhibitors, such as captopril. Up to 20% of these patients may develop a cough with ACE inhibitors. The cause is not known for certain, but it may be related to the accumulation in the lungs of bradykinin or other inflammatory mediators. Inhibiting ACE leads to an increase in bradykinin, which is normally broken down by this enzyme. The rash was originally attributed to a sulfhydryl group in captopril but is known to occur with other non–sulfhydryl-containing ACE-inhibitors.

2. **C.** The vasodilation caused by bradykinin, histamine, hydralazine, and acetylcholine depends in part upon nitric oxide release from the endothelium. Minoxidil activates K^+ channels, which results in vascular smooth muscle hyperpolarization and thereby relaxation.
3. **E.** Guanethidine does not normally cause release of catecholamines from the adrenal medulla. However, it may provoke the release of catecholamines from pheochromocytoma. This action plus its ability to antagonize neuronal uptake of catecholamines could trigger a hypertensive crisis. The other drugs are good choices to lower blood pressure in a patient with pheochromocytoma: metyrosine, by decreasing synthesis; labetalol, by blocking both the α- and β-effects of the catecholamines; prazosin and especially phenoxybenzamine, by introducing a fairly long α-blockade.
4. **B.** Clonidine is an antihypertensive because it decreases sympathetic outflow from the CNS to the periphery and therefore reduces the sympathetically induced stimulation of renin release. The sympathetic effect on renin release is mediated by β-receptors, so prazosin, an α-blocker would not decrease release. Captopril is an ACE inhibitor and is likely to enhance renin release, although it would prevent the effects of renin by reducing the formation of angiotensin II. Nitroprusside and diazoxide are directly acting vasodilators and will promote renin release reflexively.

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Case Study Hypertensive Emergency

A 50-year-old woman is seen in the emergency department complaining of a severe headache, shortness of breath, and ankle edema. Her vision is blurry and her blood pressure is 200/140 mm Hg. A blood test reveals azotemia and proteinuria. A chest radiograph reveals an enlarged cardiac silhouette. Is this a hypertensive emergency, and if so what pharmacological treatment might be considered?

ANSWER: This patient appears to be have malignant hypertension and signs of congestive heart failure. The azotemia and proteinuria are signs of renal disease and often portend deteriorating renal function. The enlarged heart and ankle edema are signs of heart failure, as is the shortness of breath. The blood pressure is very high, and this should be treated as an emergency. With blood pressure this high and the ominous clinical signs, this patient needs to be hospitalized and receive drug therapy to lower the blood pressure. The physician in a case such as this would likely choose intravenous therapy to get control of the blood pressure quickly. Although there are a number of choices, sodium nitroprusside should be at the top of the list. Diazoxide is also a good choice. Nitroprusside has a rapid onset of action, within seconds of starting an infusion. It may benefit this patient to improve cardiac output by reducing afterload and preload. Other antihypertensives that could be considered in this situation are labetalol, a combined α- and β-blocker, and nicardipine, a calcium channel antagonist. An advantage of these agents is that they can be administered intravenously, and once the patient is stabilized, one can switch to an oral formulation.