Chapter 84

# Vasodilators

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**Key Findings**

- Vasodilators reduce blood pressure primarily by actions on vascular smooth muscle.
- Vasodilators can be classified as adrenergic inhibitors (ganglion-blocking drugs and post-ganglionic adrenergic inhibitors) and direct-acting vascular smooth muscle relaxants (hydralazine/endralazine, minoxidil, diazoxide, sodium nitroprusside, and potassium channel agonists).
- Vasodilators are effective antihypertensive agents but are associated with severe side effects.
- Vasodilators now have a very restricted clinical role, mainly in hypertensive emergencies and in patients with severe hypertension refractory to other agents.

## INTRODUCTION

Over the past three decades, antihypertensive drug therapy has made a tremendous impact on morbidity and mortality from cardiovascular disease. Because rigorous control of blood pressure is needed to maximally improve outcome and few patients achieve this with first-choice therapy, a wide selection of antihypertensive agents is desirable.

The lower blood pressure that occurs with most antihypertensive drugs is associated with decreased peripheral vascular resistance. In some cases, this effect is indirect as a result of actions upon neural or humoral control systems or through an autoregulatory response to lower blood pressure. Other drugs have direct actions upon vascular smooth muscle.

Among the most effective antihypertensive drugs are those that inhibit sympathetic activity. This may be achieved at practically any anatomic level of adrenergic function. The term *vasodilator* was originally reserved for direct-acting vascular smooth muscle relaxants. Individual vasodilators may act upon resistance vessels, large arteries, or venous capacitance vessels.

Differential actions at these sites play a major role in the hemodynamic profile of the drugs[1] (Table 84–1). A predominant action upon the resistance vessels causes an immediate fall in blood pressure, activation of baroreceptor reflexes, and increased cardiac output.[2] Orthostatic hypotension is not seen. By contrast, relaxation of the venous capacitance vessels causes a reduction of venous return to the heart and a fall in cardiac output associated with a fall in blood pressure.[3] Cardiovascular baroreceptors are again activated.

Changes in the patterns of the large arterial waveform resulting from large arterial relaxation and dilatation of resistance vessels may have important consequences for the development of atheroma. These changes may not be reflected in blood pressure measured conventionally in the brachial artery.[4] Therefore, it seems possible that different types of vasodilators may have differential consequences for cardiovascular morbidity, although there are no endpoint data to define a particularly favorable pattern.

There are other consequences of vasodilator therapy apart from activation of the sympathetic nervous system. Parasympathetic withdrawal contributes to the cardiac response.[5] Renin and aldosterone levels are usually increased, partly as a result of increased sympathetic activity and partly as a result of decreased renal arterial perfusion pressure.[6] Agents that have a predominant action upon resistance vessels produce edema by increased capillary hydrostatic pressure resulting in disturbance of the Starling equilibrium. This is not seen with venodilator drugs.

Every direct-acting smooth muscle vasodilator and most adrenergic inhibitors induce compensatory sodium and water retention and extracellular fluid volume expansion following reduction of arterial pressure.[7,8] To maintain persistent and steady contraction of fluid volume, concomitant diuretic therapy is needed. A thiazide is generally the best choice for patients with relatively normal renal function because duration of action is greater than that of a loop diuretic. The diuretic enhances antihypertensive action by maintaining constriction of the extracellular and intracellular compartments.

## ROLE OF VASODILATORS IN HYPERTENSION

The heterogeneous action of vasodilators is reflected in the different indications for usage. Because of the availability of newer better-tolerated drugs, in most developed countries use is restricted to management of patients with severe hypertension not readily controlled with other agents, parenteral treatment of hypertensive emergencies, and control of hypertension in pregnancy.

Whereas use of vasodilators has decreased drastically in favor of newer agents with different mechanisms of action, these agents continue to be used widely around the world. This is undoubtedly related to the availability of generic formulations and lower cost.

| CORRELATION OF RELATIVE ACTIVITY OF VASODILATOR DRUGS IN RESISTANCE AND CAPACITANCE VESSELS WITH CIRCULATORY EFFECTS | | | |
|---|---|---|---|
| | **Arterioselective** | **Nonselective** | **Vesoselective** |
| Cardiac output | ↓↑ | ↑ | ↓ (upright) |
| Arterial pressure | ↓ | ↓ | ↓ (greater upright) |
| Central venous pressure | No change | No change | ↓ |
| Pulmonary artery pressure | ↑ | | ↓ |

**Table 84–1.** Correlation of Relative Activity of Vasodilator Drugs in Resistance and Capacitance Vessels with Circulatory Effects

## MECHANISM OF ACTION AND PHARMACOKINETICS

### Adrenergic inhibitors

Central adrenergic efferent impulses pass through major cardiovascular centers in the hypothalamus, medulla, and other subcortical areas of the spinal cord to synapse with second neurons located in the sympathetic ganglia at the thoracolumbar level of the spinal column. These most distal neurons are stimulated at the ganglion level by the release of acetylcholine from the terminals of the central neurons, thereby propagating the peripheral outflow of adrenergic impulses. Neural impulses (passing distally via the adrenergic neurons) reach the heart or blood vessels, where norepinephrine is released from nerve terminals. Norepinephrine stimulates the effector organ (heart, venule, or arteriole) by attachment to specific binding sites, alpha- or beta-adrenergic receptors. Norepinephrine is metabolized within the nerve terminal by monoamine oxidase in the mitochondria.

Binding of norepinephrine at the effector receptor may result in several possible processes. Stimulation of the beta-adrenergic receptor will produce vasoconstriction of the arteriole and venule. Stimulation of the alpha-adrenergic receptor will promote peripheral vasodilatation and increase heart rate, myocardial contractility, and myocardial metabolism.

There are many loci at which antihypertensive agents may inhibit the adrenergic nerve stimulus, including efferent sensory pathways from the heart, vessels, and mechanoreceptors; centrally at the ganglion level; or at the nerve terminal. Certain antihypertensive agents may also inhibit norepinephrine biosynthesis or block its action at the adrenergic receptor.

#### *Ganglion-blocking drugs*

Ganglion blockers act by occupying receptor sites on the post-ganglionic axon to stabilize the membrane against acetylcholine stimulation. These drugs have no effect on pre-ganglionic acetylcholine release, cholinesterase activity, post-ganglionic neuronal catecholamine release, or vascular smooth muscle contractility.[9]

Adrenergic transmission to the heart and vessels is impaired, with the result that heart rate, myocardial contractility, and total peripheral resistance are reduced. The fall in arterial pressure and vascular resistance is not as great in the supine as in the upright position because the adrenergic venomotor effect is enhanced by the gravitational effect of pooling blood when the patient is upright. Examples include hexamethonium, pentolinium, mecamylamine, pempidine, chlorisondamine, and trimetaphan. The only widely used agent in this class, trimetaphan, is excreted by glomerular filtration and active secretion (30% is unchanged in urine).

#### *Post-ganglionic adrenergic inhibitors*

When acetylcholine stimulates the post-ganglionic axon at the ganglionic levels, the impulse is propagated and cumulates in the release of norepinephrine at the nerve terminal with stimulation of adrenergic receptors in the vascular smooth muscle membrane. The impulse can be interrupted pharmacologically by a variety of mechanisms, including depletion of neurohumoral stores at the nerve terminal, prevention of norepinephrine uptake by the nerve terminal, inhibition of catecholamine biosynthesis, and therapeutic introduction of false neurotransmitters that block the adrenergic receptors on vascular smooth muscle.

##### Rawolfia alkaloids

Reserpine and more than 20 related compounds deplete the myocardium, blood vessels, adrenergic nerve terminals, adrenal medulla, and brain of catecholamines and serotonin.[10] By depleting the nerve terminal of norepinephrine stores and inhibiting norepinephrine re-uptake, adrenergic transmission is altered so that vascular resistance falls. With prolonged treatment, the persistent arterial hypotension is associated with slight decreases in renal blood flow and glomerular filtration rate. This may be related to the reduction in cardiac output or a venodilator effect similar to that of ganglion-blocking drugs.[10] Reserpine has oral bioavailability of 30%. Plasma half-life is prolonged (one to two weeks). Plasma protein binding is 96%.

##### Adrenergic neuron-blocking agents

These agents interfere with adrenergic neurotransmission at the post-ganglionic nerve terminals. Like reserpine there is depletion of catecholamine stores in nerve terminals, blood vessels, and the myocardium, but unlike reserpine there is little effect on catecholamine stores in the adrenal glands or brain.

After ingestion, there is a transient pressor phase associated with increased heart rate and cardiac output related

to catecholamine release. A prolonged period of cardiac, vascular, and nerve terminal catecholamine depletion follows, associated with progressive reduction in systemic arterial pressure (explained by reduction in vascular resistance). Hypotension is less marked in the supine posture or with agents that simultaneously contract or prevent reexpansion of plasma volume.[7,8]

Guanethidine has oral absorption of 50 to 60% despite undergoing quite extensive pre-systemic metabolism (30 to 40%). Plasma half-life is two to eight days, and protein binding is less than 10%. Metabolism is in the liver. Bethanidine has complete oral absorption and undergoes no significant pre-systemic metabolism. Plasma half-life is 8 to 15 hours. Plasma protein binding is less than 10%. Bethanidine is excreted unchanged in the urine.

Debrisoquine has oral absorption of less than 85%. There is no pre-systemic metabolism and half-life is 10 to 26 hours. Protein binding is 25%. Metabolism is subject to genetic polymorphism via the P450 isoenzyme P450 II DI. Some 92% of Caucasians are extensive metabolizers, and 8% have poor metabolizer phenotypes. Plasma concentrations are several-fold higher in poor metabolizers. Bretylium was withdrawn as an antihypertensive agent because of incomplete and variable absorption after oral administration, rapid occurrence of tolerance, and a high rate of side effects. This drug is unsuitable for long-term use.

### Monoamine oxidase inhibitors

Examples include pargyline, transcylypramine, phenylzine, and iproniazid. Pargyline was introduced primarily as an antihypertensive agent. Only a relatively few hypertensive individuals were studied and results were not striking.

### Veratrium alkaloids

These agents alter the responsiveness of vagal efferent nerve fibers in the coronary sinus, left ventricle, and carotid sinus so that any pressure will result in altered nerve traffic. The stimulus is interpreted in the medullary vasomotor center as reflecting a higher pressure than actually exists, as a result of an induced delay in the vagal repolarization process.

The altered input in the cerebral vasomotor centers results in a reflexive fall in blood pressure and heart rate. The latter response may be abolished by atropine. Because adrenergic function is not blocked but only reset at a different pressure level, the usual postural and adrenergic reflexive responses are not altered. The result is a significant fall in peripheral resistance with little change in cardiac output despite marked bradycardia. Cerebral and renal blood flow and glomerular filtration rate remain normal unless the hypotensive response is excessive.

## Direct-acting vascular smooth muscle relaxants

Agents in this class act by decreasing arteriolar resistance. Mechanisms of action are variable, although the final common pathway is vascular smooth muscle relaxation (Figure 84–1).

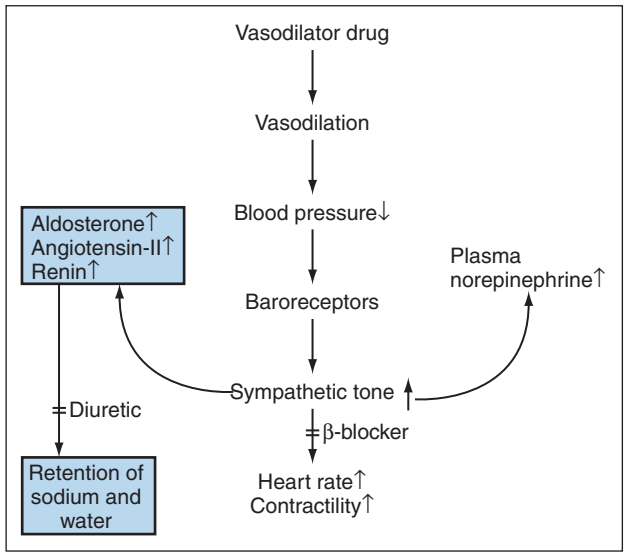


**Figure 84–1.** Reflex mechanisms triggered by vasodilation induced by vasodilator drugs.

### *Hydralazine*

Hydralazine is a dilator of resistance vessels and has little action on venous beds.[11] After intravenous administration, hydralazine has slow onset of action of 15 to 20 minutes. Blood pressure fall is accompanied by baroreceptor-mediated sympathetic activation with tachycardia and sweating. After oral administration, onset of action is gradual and the duration of action is prolonged. The peak effect is seen 30 to 120 minutes after dosing. Higher doses do not increase the peak blood pressure reduction but prolong the duration of action.

The precise mode of action is unknown, but hydralazine causes activation of guanylate cyclase and accumulation of cyclic guanosine monophosphate (GMP).[12] By altering cellular calcium metabolism, hydralazine interferes with the movement of calcium that is responsible for initiating or maintaining the contractile state of vascular smooth muscle. Accumulation of cyclic GMP stimulates cyclic GMP-dependent protein kinase. This eventually leads to dephosphorylation of the light chain of myosin, which is thought to be involved in the contractile process in the phosphorylated form. Preferential dilation of arterioles (versus veins) minimizes postural hypotension, promotes increased cardiac output, and tends to lower diastolic more than systolic blood pressure. Blood flow increases in coronary, cerebral, and renal vascular beds.

In addition, a component of action is dependent on the presence of intact endothelium. Hydralazine may cause release of nitric oxide from the vascular endothelium. Hydralazine also stimulates the renin-angiotensin aldosterone (RAAS) system. This, together with a compensatory increase in heart rate and contractility, tends to counteract the antihypertensive effect.

Hydralazine is rapidly and completely (100%) absorbed from the gastrointestinal tract after oral administration.[11] The time to maximum serum concentration is one to two hours. Biotransformation commences in the gut wall and during first-pass through the liver (pre-systemic metabolism

of 65 to 90%).[11] The liver is the major site of metabolism of hydralazine. Of the administered dose, 80% is excreted in the urine almost entirely as metabolites. The major metabolic pathways are N-acetylation and hydroxylation, with subsequent glucuronidation. Plasma half-life is two to four hours.[11] Plasma protein binding is 87%.

The acetylation pathway is subject to genetic polymorphism. Elimination is more rapid in "fast acetylators" than in "slow acetylators." "Slow acetylators" have almost twice the plasma concentration of "fast acetylators." This leads to greater antihypertensive effect and greater risk of side effects in "slow acetylators."

### *Endralazine*

Endralazine is a vasodilator chemically similar to hydralazine. Acetylation is not a major route of metabolism and therefore response is not related to acetylator phenotype.[13]

### *Minoxidil*

Treatment is associated with dilatation of resistance vessels.[14] There is little or no action on the venous bed. Minoxidil acts by activation of adenosine triphosphate (ATP)-sensitive potassium channels in arterial smooth muscle.[15] As a result, the smooth muscle membrane is hyperpolarized and calcium influx though voltage-gated calcium channels is inhibited. Cytosolic calcium concentration is reduced.

Oral absorption is 100%. Plasma half-life is 2.8 to 4.2 hours and plasma protein binding is negligible. Minoxidil is extensively metabolized in the liver. A sulphated metabolite is pharmacologically active and probably accounts for much of the activity of the parent drug.

### *Diazoxide*

Diazoxide is a non-natriuretic thiazide congener that is an extremely potent vasodilator,[16] acting on resistance vessels and without effect on the venous bed.[17] The mode of action is opening of ATP-sensitive potassium channels in vascular smooth muscle cells.

Oral absorption is 85 to 95%. Plasma half-life is 28 hours. More than 90% of diazoxide is protein blood. Elimination is primarily by glomerular filtration. About 20% is metabolized in the liver to inactive metabolites.

### *Sodium nitroprusside*

Sodium nitroprusside is administered as a slow intravenous infusion to produce rapidly reversible decrease in blood pressure.[18] The mode of action is to increase GMP within vascular smooth muscle activating vasorelaxation. This effect is probably mediated by non-enzymatic degradation of nitric oxide. The result is activation of vascular smooth muscle soluble guanylate cyclase with generation of cyclic adenosine monophosphate (AMP).[19]

Sodium nitroprusside is mainly excreted through the kidney. Clearance is extremely rapid. Half-life for blood pressure lowering is 32 to 40 seconds. The antihypertensive effect is potentiated in renal failure, although because a dose-titration regimen is employed adjustment of dose is unnecessary. The drug is metabolized non-enzymatically to cyanide, which reacts with thiosulphates to form thiocyanate (which is also excreted through the kidney).[20] The metabolic products of sodium nitroprusside are not active in the cardiovascular system.

### *Other potassium channel agonists*

The recognition that minoxidil and diazoxide act through smooth muscle potassium channels increased interest in other agents with a similar mode of action and that may not give rise to the same serious side effects.[15,21] Hyperpolarization of the vascular smooth muscle membrane inhibits the opening of voltage-operated calcium channels and increases excretion of calcium by sodium-calcium exchange, inhibiting intracellular calcium release and increasing uptake of norepinephrine by the extraneuronal catecholamine transporter. In addition, potassium channel activators cause vasodilatation of small and large arteries but have little effect on the venous circulation.

Pinacidil has high oral absorption. Its half-life is 1.6 to 2.9 hours. Plasma protein binding is 40%. Metabolism and elimination is by biotransformation in the liver via cytochrome P-450, followed by renal elimination. Nicorandil has a nitrate moiety incorporated in the molecule. This significantly modifies the pharmacologic vasodilator profile.[22] Thus, nicorandil increases smooth muscle cyclic GMP.[23] Tachycardia is transient and cardiac output is not usually increased.

## INDICATIONS/CONTRAINDICATIONS AND OBJECTIVES

### Adrenergic inhibition

#### *Ganglion-blocking drugs*

Because interference with transmission of the autonomic impulse at the ganglia level impairs adrenergic and parasympathetic impulse transmission, the clinical use of ganglion blockers is associated with severe side effects and unwanted parasympathetic inhibition. With the advent of newer agents, ganglion blockers have become mostly of academic interest.

The exception is trimetaphan, which is still useful as an antihypertensive agent. Trimetaphan is delivered by slow intravenous infusion.[24] The starting dose is 0.5 to 2 mg/min and the adequate dose is usually 0.5 to 6 mg/min. Reduction of arterial pressure is immediate. Marked interindividual variability necessitates direct arterial blood pressure monitoring. When the infusion is discontinued, return of arterial pressure to pre-infusion levels is prompt. Thus, when administered in severe hypertension long-acting antihypertensive therapy must be initiated before discontinuing the infusion.

Trimetaphan can be used in hypertension with dissecting aortic aneurysm where the drug reduces velocity of ventricular ejection and hence sheering force. In controlling hypertension in acute aortic dissection, during surgery, and in arteriography, trimetaphan may be more manageable than agents with more prolonged action. Under these circumstances, ganglion blockade will not be associated with the secondary reflexive stimulation of the heart that is found with other vasodilators.

There are several contraindications to trimetaphan, including atheromatous vascular disease because of reduced

blood supply, pyloric stenosis because of compromised gastric outflow via ganglionic blockade and in pregnancy because of the risk of paralytic or meconium ileus in the newborn. The duration of action of suxamethonum is prolonged by inhibition of pseudocholinesterase. The neuromuscular blocking action of trimetaphan enhances nondepolarizing muscle relaxants.

### *Rawolfia alkaloids*

Reserpine and similar alkaloids are efficacious in reducing arterial pressure when used with a diuretic.[25,26] Reserpine is generally added to the treatment regimen if response to a thiazide (or thiazide-like) diuretic is inadequate. Reserpine is also useful in treating hypertensive emergencies.[27] The maintenance dose of reserpine is up to 0.1 mg daily. Because reserpine has a long half-life, a loading dose is employed to obtain a reasonably rapid steady-state concentration.

Reserpine is contraindicated absolutely in depression and in those with a history of depression. The drug is also contraindicated in severe renal failure and is best avoided in peptic ulceration, ulcerative colitis, or asthma. Reserpine may cause complications in the neonate if used in pregnancy. These include nasal obstruction (anosmia), bradycardia, and hypothermia. Thus, reserpine is no longer a drug of choice in hypertensive emergencies in pregnancy. A reduced dose is recommended in the elderly.

Several drug interactions have been reported. There is enhanced peripheral vasodilatation and hypotension with alcohol. Enhanced falls in blood pressure are also seen with glyceryl trinitrate, L-dopa, fenfluramine, and phenothiazines. The pressor effects of phenylephrine and catecholamines are enhanced, whereas the effect of direct-acting amines (such as ephedrine) is diminished. There is excessive central nervous system excitation with monomine oxidase inhibitors. Reserpine lowers the convulsive threshold in epilepsy. The bradycardic effect of digoxin and the negative isotropic effects of antiarrhythmic agents, such as disopyramide and quinidine, are enhanced. There is increased myocardial depression with halothane and increased prolactin/breast enlargement with the oral contraceptive steroids.

### *Adrenergic neuron-blocking agents*

#### Guanethidine

Because of prolonged action and because sympathetic inhibition is usually maximal at night, guanethidine needs to be administered only once daily. The starting dose of 10 mg is titrated to the required dose, which is usually 25 to 75 mg daily although up to 200 to 300 mg daily may be needed. Antihypertensive effect can be hastened by initiation with a loading dose.

Because fluid retention and expanded intravascular and extracellular fluid volumes are prominent, a diuretic is indicated, with the caveat that patients should be monitored carefully for hypokalemia and impaired renal excretory function. The phenomenon is due to fluid expansion because impairment of drug absorption over time seems unlikely. However, the common adverse effect of diarrhea may reduce absorption. Abrupt withdrawal is not associated with rebound hypertension because of the prolonged half-life. The mechanism of action leads to postural hypotension, particularly after exercise or circumstances favoring vasodilatation (such as heat, alcohol, or pyrexia). This is a particular risk in the elderly and when a diuretic is added.

When urgent reduction of blood pressure is indicated, guanethidine can be given parenterally (intramuscular or intravenous). A slow intravenous infusion or intramuscular injection avoids the initial pressor response due to catecholamine release. The maximum effect after intramuscular use is seen in one to two hours. Guanethidine is safe in pregnancy. Loss of blood pressure control may be due to drug interactions. Uptake into adrenergic nerve endings is reduced by concomitant tricyclic antidepressant therapy.

#### Bethanidine

The initial dose of 5 to 10 mg three times daily is titrated as necessary to a maximum dose of 200 mg daily. Bethanidine was widely used as third drug in combination with a thiazide and a beta blocker. The drug accumulates in renal failure, whereby antihypertensive effects may be enhanced.

#### Debrisoquine

The dose range is 20 to 400 mg daily, administered by twice- or thrice-daily dosing regimens. Debrisoquine is used with a beta blocker and diuretic to avoid fluid retention. Poor metabolizers respond to 10 mg twice daily, which is therefore the usual starting dose unless the metabolic phenotype is known. The starting dose is 40 mg twice daily in extensive metabolizers.

Adrenergic neuron-blocking agents are contraindicated in pheochromocytoma. Withdrawal of neurally released norepinephrine induces extreme sensitivity to circulating catecholamines. These drugs may exaggerate hypertension consequent on sudden release of catecholamines from the tumor.

### *Monoamine oxidase inhibitors*

Monamine oxidase inhibitors may aggravate hypertension by inhibition of norepinephrine metabolism. Because monoamine oxidase is inhibited in the post-ganglionic nerve terminal, several weak pressor amines accumulate at this site. These substances are believed to act as false neurohumoral transmitters, tending to elevate blood pressure. Because of the potentially severe hypertensive crisis that may be associated with use, these drugs should be considered primarily of academic interest in the treatment of hypertension.

### *Veratrium alkaloids*

Clinical use has been severely restricted by side effects.

## Direct-acting smooth muscle relaxants

With the fall in total peripheral resistance and arterial pressure, reflex stimulation of the heart occurs so that tachycardia and palpitation results frequently unless the cardiac reflex responses are offset by an adrenergic inhibitor (usually a beta blocker). These agents should not be administered to hypertensive patients with heart failure, myocardial infarction, angina, or aortic dissection because the reflexive cardiac effects will aggravate the underlying cardiac condition.

### Hydralazine

Hydralazine entered the therapeutic armamentarium shortly after the ganglian-blocking agents and was one of the most effective drugs in the 1950s.[28] Usage declined rapidly in the 1960s but hydralazine returned to regular usage in stepped-care regimens of the late 1960s, in combination with a beta blocker and diuretic. Hydralazine has largely been replaced by other peripherally acting drugs and is now not widely used, although the drug remains effective and safe in specialist hands.

Hydralazine is usually administered three or four times daily, preferably starting with an individual dose of 12.5 to 25 mg. A lower dose (10 mg) may be used if there are side effects. The dose is then increased as necessary to a maximum of 200 to 300 mg daily. Slow acetylators show greater lowering of blood pressure.[11] The daily dose should not exceed 200 mg. High doses are more likely to be associated with development of anti-nuclear antibodies (ANA) and a lupus-like syndrome.[11] The acetylator phenotype can be determined readily by a simple urinary test of sulphonamide acetylation.[29] Periodic full blood count and ANA titers are recommended during chronic hydralazine therapy. Because hydralazine undergoes hepatic metabolism, dose adjustment is unnecessary in renal impairment.

Pretreatment with a beta blocker prevents sympathetic activation, reduces side effects, and potentiates the antihypertensive action.[30] Hydralazine is used with a beta blocker and diuretic to control moderate to severe hypertension. Where renal function is seriously impaired, a loop diuretic rather than a thiazide is needed to avoid edema. A multicenter trial[31] evaluated hydralazine, labetalol, methyldopa, prazosin, and placebo for value as a third drug when added to ongoing beta-blocker and diuretic treatment. Overall, hydralazine was the most generally suitable third drug.

Much of the early information demonstrating that antihypertensive therapy can diminish morbidity and mortality involved hydralazine-treated patients.[25,26,32,33] A combination of reserprine, hydrochlorothiazide, and hydralazine was used in the landmark Veterans Administration Cooporative Study Group Trials,[25] which demonstrated unequivocally the merits of antihypertensive therapy not only in severe but in moderate hypertension.

For urgent control of blood pressure, hydralazine can be given parenterally. Onset of action is in 15 minutes,[2] but the dose and frequency of administration required for blood pressure control are highly variable, the long duration of action makes dose titration difficult, and many patients do not respond adequately to any dose of hydralazine. Therefore, hydralazine is not an ideal drug for hypertensive emergencies. Sodium nitroprusside is more effective if continuous monitoring in an intensive therapy unit is available.

Although there have been no formal studies in pregnancy, and although the drug is teratogenic in some animals, hydralazine is widely used in pregnant women.[34] The main contraindication is coronary artery disease because increased cardiac output increases cardiac work and may provoke angina and myocardial ischemia or infarction. However, if hypertension is severe reduction in blood pressure and cardiac work will more than compensate. In mitral valve disease, hydralazine may increase pulmonary artery pressure and induce congestive heart failure. Endralazine lowers blood pressure over 24 hours with once-daily dosing.[35]

### Minoxidil

Because of the severity of adverse effects, usage is limited to severe hypertension unresponsive to other treatments.[36] Minoxidil is usually administered twice daily with an initial dose of 2.5 to 5 mg. Once-daily dosing is sometimes employed. The maximum daily dose is usually 50 mg, although doses up to 100 mg have been used.

Pretreatment with a beta blocker limits sympathetic activation.[37] Sodium retention requires concomitant diuretic therapy in most. A loop diuretic is often necessary. Minoxidil is excreted into breast milk and therefore is best avoided in breast-feeding mothers. Safety in pregnancy has not been established.

### Diazoxide

Oral diazoxide can be used in resistant hypertension as a twice-daily regimen, although the long half-life suggests that once-daily treatment may be sufficient. A graded sustained fall in blood pressure usually results. The initial dose is 50 to 100 mg twice daily, increasing as necessary to a total daily dose of 1 g.[38] The severity of side effects has rendered this usage largely obsolete.

Intravenous diazoxide is still occasionally used in the treatment of hypertensive emergencies. Diazoxide has been useful for the patient with hypertensive encephalopathy, and in those with severe, malignant, or accelerated hypertension (without heart failure) for whom rapid and immediate reduction in arterial pressure is mandatory. Blood pressure is lowered rapidly and consistently but rarely below normal. The first dose is usually effective and the action persists for several hours. The maximal daily dose is 150 mg. Higher doses previously used were associated with unacceptable hypotension and exacerbation of ischemic heart disease. For the same reason, rapid infusion is no longer recommended and the bolus should be administered over about 10 minutes.[39] Repeated doses can be administered every 5 to 15 minutes until target blood pressure is achieved. After each dose, the patient should remain recumbent and should be closely monitored for 30 minutes.

Diazoxide has been successful in severe hypertension in children. The usual effective dose is 5 mg/kg. Hypertensive crises induced by pheochromocytoma or due to monoamine oxidase inhibitor therapy should not be treated with diazoxide because blood pressure responds more specifically to alpha blockers. Safety in pregnancy has not been demonstrated conclusively.

Contraindications include subarachnoid hemorrhage, intracerebral hemorrhage, postoperative bleeding, functional hypoglycemia, and hypersensitivity to thiazides. In the case of dissection of aortic aneurysms, the increase in stroke volume and left ventricular ejection rate reflexively induced by diazoxide augment stresses in the aortic wall. The antidiuretic properties of diazoxide can lead to significant fluid retention which may precipitate congestive heart failure in patients with impaired cardiac reserve.

### *Sodium nitroprusside*

Sodium nitroprusside is used for the short-term treatment of severely hypertensive patients at high risk, to normalize blood pressure before and during surgery for renal artery stenosis or pheochromocytoma, in hypotensive anesthesia, and in dissecting aortic aneurysm. Sodium nitroprusside is useful in hypertensive emergencies because of rapid onset of action, titratability, and rapid reversibility of excess blood pressure reduction.

The absence of tachycardia in most patients means that sodium nitroprusside is free of the cardiac symptoms produced by some other vasodilators. The drug is administered dissolved in 5% dextrose in water as an intravenous infusion using an infusion pump or drip regulator. The infusion should be protected from light using aluminum foil.

The drip rate is titrated against blood pressure. The average dose is 0.5 to 8.0 μg/kg/min. The rate should be increased slowly to prevent or reduce compensatory reactions (sharp rises in catecholamines and renin, tachycardia, and tachyphylaxis). The infusion should not be terminated abruptly to prevent excessive rebound in blood pressure. The starting dose is 0.3 to 1.0 μg/kg/min and is increased gradually until the desired blood pressure reduction is achieved, preferably while monitoring intra-arterial blood pressure. To avoid excessive levels of cyanide and to lessen the possibility of precipitous blood pressure reduction, the maximum recommended dose is 8 μg/kg/min. If this is insufficient, another approach should be tried.

Prolonged infusions are undesirable because of the risk of thiocyanate intoxication, but if continuous therapy over several days is required acid/base balance should be assessed by measurement of plasma bicarbonate, lactate, and the lactate/pyruvate ratio. This is a more sensitive measure of intoxication than plasma concentration of thiocyanate or cyanide under these conditions because toxicity is associated with the development of acidosis.

Sodium nitroprusside is contraindicated in severe liver impairment, Leber's optic atrophy, and tobacco amblyopia. Precaution is needed in disturbed cerebral blood flow because of the risk of too rapid lowering of blood pressure. Caution is also required in hypothyroidism because thiocyanate inhibits iodine uptake and binding by the thyroid. Care should be taken in renal failure because excretion of thiocyanate is decreased.

### *Other potassium channel agonists*

#### Pinacidil

Greatest experience in hypertension is with this agent.[40] Pinacidil is usually administered as a sustained-release preparation. In doses ranging from 12.5 to 37.5 mg twice daily, pinacidil has a useful blood-pressure-lowering action. Dose-dependent edema offsets the antihypertensive effect. This can be overcome by concomitant diuretic. Pinacidil is contraindicated in congestive heart failure and should be used with caution in coronary or cerebrovascular disease and tachyarrhythmias because of the tendency to tachycardia.

Because pinacidil undergoes hepatic metabolism, dose reduction is advised in severe hepatic dysfunction and in the elderly because renal clearance of the metabolite is reduced. Nevertheless, pinacidil has been used with success in renal hypertension. Intravenous pinacidil can be used in emergencies. Because of tachycardia, pinacidil has no advantage over other drugs.

#### Nicarandil

Intravenous use produces a fall in blood pressure, but oral treatment (20 to 40 mg daily) in normotensive subjects during exercise produces little effect on blood pressure.

#### Chromakalim

This agent has been much less extensively investigated, but chromakalim lowers blood pressure in both hypertensive and normotensive subjects following oral doses of 0.75 to 1.5 mg.[41]

## COMPLICATIONS

Major complications are listed in Tables 84–2 through 84–5.

## Adrenergic inhibitors

### *Ganglion-blocking drugs*

As a result of reduction in vasomotor tone, treated patients will pool blood in dependent capacitance vessels. This effect explains the phenomenon of orthostatic hypotension that can be associated with syncope.[42] To enhance the antihypertensive effect in the supine posture, it is necessary to reduce intravascular (and extracellular) fluid volume and prevent the expansion of blood volume.[7,8] Prolonged therapy with trimetaphan for 48 to 72 hours is associated with refractory responses (tachyphylaxis).[43]

Reduction in cardiac output results in at least proportionate reduction of renal blood flow, sometimes associated with reduced creatinine clearance.[44] Because parasympathetic inhibition also results from ganglionic blockade, tonic activity leads to risk of paralytic ileus and acute urinary retention. Thus, abdominal pain with reduced bowel sounds, constipation, or reduced urinary output in a patient with aortic dissection may not reflect extension of the dissection into the mesenteric or renal arteries but instead may be a side effect of treatment. Other adverse drug reactions with trimetaphan include asthma attacks because of histamine release. Large doses may provoke muscle relaxation leading to cardiac arrest.

### *Rawolfia alkaloids*

Parasympathetic activity remains unopposed, explaining many common side effects (including bradycardia, prolonged atrioventricular conduction, increased gastric acid excretion with possible secondary peptic ulceration, and frequency of bowel movements). These adverse effects may be counteracted by parasympathetic inhibitors.

Although arterial dilatation with increased blood flow has been considered greatest in the skin, other vascular beds are also involved. The frequent complaint of nasal mucosal congestion and suffiness is ameliorated by nasally administered vasoconstrictors.[45] However, prolonged use may result in chemical rhinitis.

As a result of depletion of brain catecholamines and serotonin, there may be behavioral alterations and subtle

| ADVERSE REACTIONS DUE TO ADRENERGIC INHIBITORS: GANGLION BLOCKERS AND RAWOLFIA ALKALOIDS | | |
|---|---|---|
| **Drug** | **Common Side Effects** | **Other Side Effects** |
| Ganglion blockers | ■ Orthostatic hypotension<br>■ Tachyphylaxis<br>■ Reduced creatinine clearance | ■ Paralytic ileus<br>■ Urinary retention<br>■ Asthma<br>■ Respiratory arrest |
| Rawolfia alkaloids | ■ Bradycardia<br>■ Prolonged AV conduction<br>■ Nasal stuffiness<br>■ Depression | ■ Peptic ulceration<br>■ Diarrhea<br>■ Bronchospasm<br>■ Increased appetite<br>■ Fluid retention, weight gain<br>■ Loss of libido, impotence<br>■ Menstrual irregularities<br>■ Amenorrhea<br>■ Galactorrhea<br>■ Ocular palsies<br>■ Extrapyramidal symptoms |

**Table 84–2.** Adverse Reactions Due to Adrenergic Inhibitors: Ganglion Blockers and Rawolfia Alkaloids

| ADVERSE REACTIONS DUE TO ADRENERGIC INHIBITORS: ADRENERGIC NEURON-BLOCKING AGENTS, MONOAMINE OXIDASE INHIBITORS, AND VERATRIUM ALKALOIDS | | |
|---|---|---|
| **Drug** | **Common Side Effects** | **Other Side Effects** |
| Adrenergic neuron blockers | ■ Orthostatic hypotension<br>■ Muscle weakness<br>■ Bradycardia<br>■ Diarrhea<br>■ Retrograde ejaculation<br>■ Fluid retention<br>■ Dizziness<br>■ Nasal stuffiness<br>■ Lethargy | ■ Nausea and vomiting<br>■ Thrombocytopenia<br>■ Loss of scalp hair<br>■ Dry mouth<br>■ Blurred vision<br>■ Anorexia<br>■ Epigastric discomfort<br>■ Itch, rashes, and urticaria |
| Monoamine oxidase inhibitors | ■ Euphoria<br>■ Insomnia<br>■ Acute psychosis<br>■ Severe hypertension with certain foods | ■ Hepatocellular necrosis<br>■ Blood dyscrasias |
| Veratrium alkaloids | ■ Nausea and vomiting<br>■ Excessive salivation<br>■ Diaphoresis<br>■ Blurred vision<br>■ Mental confusion | |

**Table 84–3.** Adverse Reactions Due to Adrenergic Inhibitors: Adrenergic Neuron-blocking Agents, Monoamine Oxidase Inhibitors, and Veratrium Alkaloids

or overt depression (sometimes leading to suicide).[46] Less severe central complications include drowsiness and nightmares. Parkinsonism, dyskinesia, and dystonia can result from dopamine depletion in the basal ganglia. Congestive heart failure may be precipitated or worsened.

### *Adrenergic neuron-blocking drugs*

Because of coincidental inhibition of venous tone,[45] venous return to the heart is reduced by peripheral pooling of blood in dependent areas of the body with upright posture. As a result, orthostatic hypertension is prominent.[47]

Associated with the resulting fall in cardiac output, there is a proportionate reduction in organ blood flow. Severe hypotension may aggravate angina and lead to myocardial infarction, cerebrovascular insufficiency with syncope, or even stroke. The renal and splanchnic territories may receive a smaller proportion of total cardiac output, but glomerular filtration rate and renal function appear to return to normal with time.[48] With reducing skeletal muscle blood flow and adrenergic innervation of skeletal muscle, weakness may result. This can be exacerbated by diuretic treatment.[49] Muscle weakness may be aggravated still further during and immediately after exercise.[50]

| ADVERSE REACTIONS DUE TO DIRECT-ACTING VASCULAR SMOOTH MUSCLE RELAXANTS: HYDRALAZINE AND MINOXIDIL | | |
|---|---|---|
| **Drugs** | **Common Side Effects** | **Other Side Effects** |
| Hydralalzine | ■ Headache<br>■ Nasal stuffiness<br>■ Tachycardia<br>■ Palpitation<br>■ Flushing<br>■ Sweating<br>■ Peripheral neuropathy<br>■ Lupus reaction | ■ Fluid retention, edema<br>■ Drug fever<br>■ Skin eruptions<br>■ Blood dyscrasias<br>■ Purpura |
| Minoxidil | ■ ECG changes<br>■ Fluid retention, edema<br>■ Hirsutism<br>■ Flushing<br>■ Palpitation<br>■ Headache | ■ Nasal stuffiness<br>■ Nausea<br>■ Breast tenderness<br>■ Skin reactions |

**Table 84–4.** Adverse Reactions Due to Direct-acting Vascular Smooth Muscle Relaxants: Hydralazine and Minoxidil

| ADVERSE REACTIONS DUE TO DIRECT-ACTING VASCULAR SMOOTH MUSCLE RELAXANTS: DIAZOXIDE, SODIUM NITROPRUSSIDE, AND OTHER POTASSIUM CHANNEL AGONISTS | | |
|---|---|---|
| **Drug** | **Common Side Effects** | **Other Side Effects** |
| Diazoxide | ■ Hyperglycemia<br>■ Tachycardia<br>■ Palpitation<br>■ Fluid retention, edema<br>■ Hypertrichosis<br>■ Headache | ■ Chest pain<br>■ Extrapyrimidal reactions<br>■ Skin rashes<br>■ Hypotension<br>■ Acute pancreatitis<br>■ Fever<br>■ Lymphadenopathy<br>■ Gout<br>■ Blood dyscrasias/purpura<br>■ Nausea and vomiting<br>■ Abdominal pain, ileus, and diarrhea |
| Sodium nitroprusside | ■ Hypothyroidism<br>■ Methemoglobinemia<br>■ Nausea and vomiting<br>■ Headache | ■ Restlessness<br>■ Muscle twitching<br>■ Cyanide intoxication |
| Other potassium channel agonists | ■ Headache<br>■ Dizziness<br>■ Palpitation<br>■ Tachycardia<br>■ Edema | ■ Hypertrichosis<br>■ Nausea dyspepsia<br>■ Rashes<br>■ Increased ANA titers |

**Table 84–5.** Adverse Reactions Due to Direct-acting Vascular Smooth Muscle Relaxants: Diazoxide, Sodium Nitroprusside, and Other Potassium Channel Agonists

Some side effects (orthostatic hypotension, excessive hypotension, bradycardia, increased gastric excretion) result from unopposed parasympathetic activity and impaired adrenergic function. Similarly, diarrhea, retrograde ejaculation, and fluid retention may be explained by reduced adrenergic transmission. Many of these side effects may be counteracted by reduction in dosage or the addition of a parasympatholytic agent or diuretic.

Because these agents act by entering the nerve terminal, any agent that prevents this will block the action. This is the means by which tricyclic antidepressants act,[51] and therefore these classes of drugs should not be prescribed concomitantly. Drugs that reduce efferent sympathetic output enhance postural hypotension and bradycardia. Examples include alpha blockers, beta blockers, and ganglion blockers. Cardiac glycosides may also enhance bradycardia.

### *Monoamine oxidase inhibitors*

The major side effects are centrally mediated mental and emotional reactions, including euphoria, insomnia, and

acute psychosis. More important is the severe hypertensive crisis following the ingestion of foods containing tyramine, such as aged cheeses, beer, sherry, Chianti, and herring.[52]

### *Veratrium alkaloids*

Because of the narrow therapeutic index, the effective control of arterial pressure is not infrequently associated with side effects.

## Direct-acting vascular smooth muscle relaxants

Side effects common to these agents include headache and nasal stuffiness attributable to local vasodilatation, fluid retention, and edema. The latter effects can result in pseudotolerance.

### *Hydralazine*

Peripheral neuropathy is dose dependent and is rare at doses up to 200 mg daily.[53] This complication is more common in slow acetylators. Neuropathy is first manifest by paraesthesia, numbness, and tingling of the extremities. Pyridoxine deficiency is the likely cause and correction can be achieved by administration of pyridoxine.[11]

The lupus reaction gives rise to malaise, myalgia, and arthralgia/arthritis, and is associated with raised ANA titers.[54] Raised titers are often encountered in asymptomatic patients and are not a contraindication to continuation, although the lupus syndrome is. Hydralazine does not worsen idiopathic systemic lupus erythematosis.

There may be more severe signs of systemic illness such as weight loss, splenomegaly, and effusion in serous cavities. Rashes may also occur. If not diagnosed promptly, the degree of temporary disability may be severe. Renal and cerebral involvement is rare. The hydralazine lupus reaction usually occurs after six months of therapy at doses over 400 mg daily and is almost always seen in slow acetylators. Patients with HLA DR4 phenotype are particularly susceptible.[55] The syndrome resolves when the drug is withdrawn, although months or years may be required for complete clearing.[11] After withdrawal of hydralazine, positive tests for ANA may persist for years.

Although the lupus reaction is reduced substantially at daily doses of 200 mg or less, there is still a significant incidence. In one study,[56] the incidence was 6.7% over three years. No cases were seen at 50 mg daily, 5.4% with 100 mg daily, and 10.4% with 200 mg daily. The incidence was higher in women (11.6%) than in men (2.8%). In women taking 200 mg daily, the three-year incidence was 19.4%. Thus, the true incidence of lupus syndrome is unacceptably high.

Decrease in white cell count is more common in blacks. Mild gastrointestinal side effects sometimes occur but present no clinical problems at conventional doses. Endralazine is not associated with the lupus syndrome.

### *Minoxidil*

Increase in cardiac work may account for electrocardiograph (ECG) changes, which are often observed during the first few days of therapy. ECG changes include ST depression and T-wave inversion[57] but are not associated with cardiac enzyme elevation. However, reflex tachycardia may provoke angina in those with ischemic heart disease. Pulmonary edema may be the consequence of increased cardiac output.

An uncommon cardiac adverse event is pericardial effusion, which is rarely associated with tamponade.[58] Deaths have been reported. Dependent edema and ascites are extremely common.

A very common side effect of minoxidil is hirsutism, which is particularly bothersome in women. Hypertrichosis mainly affects the forehead and face and is most apparent in dark-haired individuals. There is no pharmacologic treatment for excess hair growth, and the only remedy is removal of hair or discontinuation of the drug. After discontinuation, hair growth reverses in a few months.

### *Diazoxide*

Diazoxide shares the adverse effects of minoxidil. In addition, diazoxide causes impairment of glucose tolerance in the majority of patients. Hyperglycemia is due to inhibition of insulin secretion. The effect is probably mediated by action upon pancreatic islet cell potassium channels and can be reversed by sulphanylurea drugs.[38] Diabetic betoacidosis and hyperosmolar non-ketonic coma are infrequent but can develop very rapidly. Conventional therapy with insulin and restoration of fluid and electrolyte balance is usually effective.

Increased hepatic enzymes, uremia, reduced creatinine clearance, reversible nephrotic syndrome, decreased urine output, hematuria, and albuminuria occur very occasionally. Thrombocytopenia with or without purpura may require discontinuation. Drug interactions include bleeding with anticoagulants and hypotension with beta blockers. Diuretics potentiate hyperuricemia by inhibition of tubular secretion of uric acid.

### *Sodium nitroprusside*

Retrosternal discomfort, palpitation, dizziness, and abdominal discomfort can occur if blood pressure reduction is too rapid. Cyanide intoxication is rare unless the recommended dose is exceeded. Metabolic acidosis may be followed by hypoxia and tetanic spasms.

### *Other potassium channel agonists*

When used as monotherapy, side effects of pinacidil are dose related. ECG T-wave changes have been reported in the initial phase of treatment.[40] Hypertrichosis is seen occasionally.[59]

## SUMMARY

Vasodilators are highly effective antihypertensive agents that dominated the management of hypertension in the 1950s and 1960s. However, treatment with these agents is associated with an unacceptable level of adverse reactions. With the advent of newer and better-tolerated antihypertensive agents, their use has declined dramatically. Many vasodilators can now be considered only of historical interest.

In developed countries, vasodilators have a limited clinical role. Some direct-acting vascular smooth muscle relaxants continue to have utility in the management of hypertensive emergencies (notably sodium nitroprusside) and in severe hypertension refractory to other antihypertensive agents (notably minoxidil). In developing countries, however (where the cost of newer agents may be prohibitive), vasodilators continue to be prescribed more widely. The safe and effective long-term use of these drugs requires careful attention to adverse reactions with concomitant administration of beta blockers and diuretics to avoid the consequences of reflex cardiac stimulation and salt and water retention.

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