SECTION III CARDIOVASCULAR-RENAL DRUGS

CHAPTER 11

Antihypertensive Agents

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CASE STUDY

A 35-year-old man presents with a blood pressure of 150/95 mm Hg. He has been generally healthy, is sedentary, drinks several cocktails per day, and does not smoke cigarettes. He has a family history of hypertension, and his father died of a myocardial infarction at age 55. Physical examination is remarkable only for moderate obesity. Total cholesterol is 220, and high-density lipoprotein (HDL) cholesterol level is 40 mg/dL. Fasting glucose is 105 mg/dL. Chest x-ray is normal. Electrocardiogram shows left ventricular enlargement. How would you treat this patient?

Hypertension is the most common cardiovascular disease. In a survey carried out in 2007/2008, hypertension was found in 29% of American adults. The prevalence varies with age, race, education, and many other variables. According to some studies, 60–80% of both men and women will develop hypertension by age 80. Sustained arterial hypertension damages blood vessels in kidney, heart, and brain and leads to an increased incidence of renal failure, coronary disease, heart failure, stroke, and dementia. Effective pharmacologic lowering of blood pressure has been shown to prevent damage to blood vessels and to substantially reduce morbidity and mortality rates. Unfortunately, several surveys indicate that only one third to one half of Americans with hypertension have adequate blood pressure control. Many effective drugs are available. Knowledge of their antihypertensive mechanisms and sites of action allows accurate prediction of efficacy and toxicity. As a result, rational use of these agents, alone or in combination, can lower blood pressure with minimal risk of serious toxicity in most patients.

HYPERTENSION & REGULATION OF BLOOD PRESSURE

Diagnosis

The diagnosis of hypertension is based on repeated, reproducible measurements of elevated blood pressure (Table 11–1). The diagnosis serves primarily as a prediction of consequences for the patient; it seldom includes a statement about the cause of hypertension.

Epidemiologic studies indicate that the risks of damage to kidney, heart, and brain are directly related to the extent of blood pressure elevation. Even mild hypertension (blood pressure

TABLE 11–1 Classification of hypertension on the basis of blood pressure.

Systolic/Diastolic Pressure (mm Hg)	Category
< 120/80	Normal
120–135/80–89	Prehypertension
≥ 140/90	Hypertension
140–159/90–99	Stage 1
≥ 160/100	Stage 2

From the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. JAMA 2003;289:2560.

140/90 mm Hg) increases the risk of eventual end-organ damage. Starting at 115/75 mm Hg, cardiovascular disease risk doubles with each increment of 20/10 mm Hg throughout the blood pressure range. Both systolic hypertension and diastolic hypertension are associated with end-organ damage; so-called isolated systolic hypertension is not benign. The risks—and therefore the urgency of instituting therapy—increase in proportion to the magnitude of blood pressure elevation. The risk of end-organ damage at any level of blood pressure or age is greater in African Americans and relatively less in premenopausal women than in men. Other positive risk factors include smoking; metabolic syndrome, including obesity, dyslipidemia, and diabetes; manifestations of end-organ damage at the time of diagnosis; and a family history of cardiovascular disease.

It should be noted that the diagnosis of hypertension depends on measurement of blood pressure and not on symptoms reported by the patient. In fact, hypertension is usually asymptomatic until overt end-organ damage is imminent or has already occurred.

Etiology of Hypertension

A specific cause of hypertension can be established in only 10–15% of patients. Patients in whom no specific cause of hypertension can be found are said to have *essential* or *primary hypertension.* Patients with a specific etiology are said to have *secondary hypertension.* It is important to consider specific causes in each case, however, because some of them are amenable to definitive surgical treatment: renal artery constriction, coarctation of the aorta, pheochromocytoma, Cushing's disease, and primary aldosteronism.

In most cases, elevated blood pressure is associated with an overall increase in resistance to flow of blood through arterioles, whereas cardiac output is usually normal. Meticulous investigation of autonomic nervous system function, baroreceptor reflexes, the renin-angiotensin-aldosterone system, and the kidney has failed to identify a single abnormality as the cause of increased peripheral vascular resistance in essential hypertension. It appears, therefore, that elevated blood pressure is usually caused by a combination of several (multifactorial) abnormalities. Epidemiologic evidence points to genetic factors, psychological stress, and environmental and dietary factors (increased salt and decreased potassium or calcium intake) as contributing to the development of hypertension. Increase in blood pressure with aging does not occur in populations with low daily sodium intake. Patients with labile hypertension appear more likely than normal controls to have blood pressure elevations after salt loading.

The heritability of essential hypertension is estimated to be about 30%. Mutations in several genes have been linked to various rare causes of hypertension. Functional variations of the genes for angiotensinogen, angiotensin-converting enzyme (ACE), the β_2 adrenoceptor, and α adducin (a cytoskeletal protein) appear to contribute to some cases of essential hypertension.

Normal Regulation of Blood Pressure

According to the hydraulic equation, arterial blood pressure (BP) is directly proportionate to the product of the blood flow (cardiac output, CO) and the resistance to passage of blood through precapillary arterioles (peripheral vascular resistance, PVR):

$$BP = CO \times PVR$$

Physiologically, in both normal and hypertensive individuals, blood pressure is maintained by moment-to-moment regulation of cardiac output and peripheral vascular resistance, exerted at three anatomic sites (Figure 11–1): arterioles, postcapillary venules (capacitance vessels), and heart. A fourth anatomic control site, the kidney, contributes to maintenance of blood pressure by regulating the volume of intravascular fluid. Baroreflexes, mediated by autonomic nerves, act in combination with humoral mechanisms, including the renin-angiotensin-aldosterone system, to coordinate function at these four control sites and to maintain normal blood pressure. Finally, local release of vasoactive substances from vascular endothelium may also be involved in the regulation of vascular

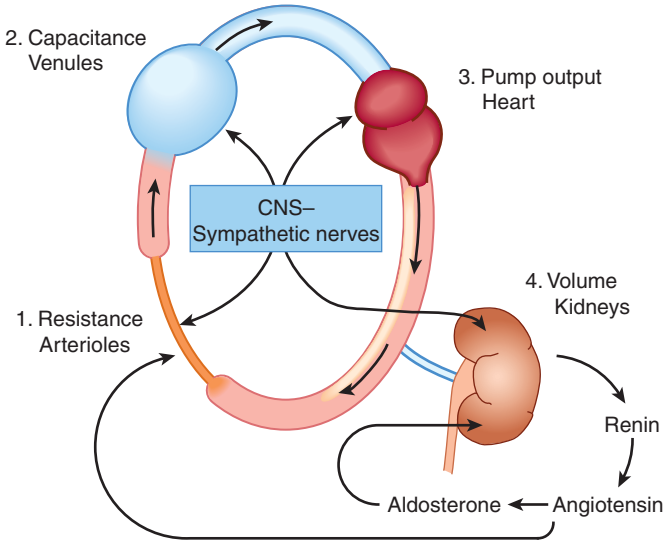


FIGURE 11–1 Anatomic sites of blood pressure control.

resistance. For example, endothelin-1 (see Chapter 17) constricts and nitric oxide (see Chapter 19) dilates blood vessels.

Blood pressure in a hypertensive patient is controlled by the same mechanisms that are operative in normotensive subjects. Regulation of blood pressure in hypertensive patients differs from healthy patients in that the baroreceptors and the renal blood volume-pressure control systems appear to be "set" at a higher level of blood pressure. All antihypertensive drugs act by interfering with these normal mechanisms, which are reviewed below.

A. Postural Baroreflex

Baroreflexes are responsible for rapid, moment-to-moment adjustments in blood pressure, such as in transition from a reclining to an upright posture (Figure 11–2). Central sympathetic neurons arising from the vasomotor area of the medulla are tonically active. Carotid baroreceptors are stimulated by the stretch of the vessel walls brought about by the internal pressure (arterial blood pressure). Baroreceptor activation inhibits central sympathetic discharge. Conversely, reduction in stretch results in a reduction in baroreceptor activity. Thus, in the case of a transition to upright posture, baroreceptors sense the reduction in arterial pressure that results from pooling of blood in the veins below the level of the heart as reduced wall stretch, and sympathetic discharge is disinhibited. The reflex increase in sympathetic outflow acts through nerve endings to increase peripheral vascular resistance (constriction of arterioles) and cardiac output (direct stimulation of the heart and constriction of capacitance vessels, which increases venous return to the heart), thereby restoring normal blood pressure. The same baroreflex acts in response to any event that lowers arterial pressure, including a primary reduction in peripheral vascular resistance (eg, caused by a vasodilating agent) or a reduction in intravascular volume (eg, due to hemorrhage or to loss of salt and water via the kidney).

B. Renal Response to Decreased Blood Pressure

By controlling blood volume, the kidney is primarily responsible for long-term blood pressure control. A reduction in renal perfusion pressure causes intrarenal redistribution of blood flow and increased reabsorption of salt and water. In addition, decreased pressure in renal arterioles as well as sympathetic neural activity (via β adrenoceptors) stimulates production of renin, which increases production of angiotensin II (see Figure 11–1 and Chapter 17). Angiotensin II causes (1) direct constriction of resistance vessels and (2) stimulation of aldosterone synthesis in the adrenal cortex, which increases renal sodium absorption and intravascular blood volume. Vasopressin released from the posterior pituitary gland also plays a role in maintenance of blood pressure through its ability to regulate water reabsorption by the kidney (see Chapters 15 and 17).

BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

All antihypertensive agents act at one or more of the four anatomic control sites depicted in Figure 11–1 and produce their effects by interfering with normal mechanisms of blood pressure regulation. A useful classification of these agents categorizes them according to the principal regulatory site or mechanism on which they act (Figure 11–3). Because of their common mechanisms of action, drugs within each category tend to produce a similar spectrum of toxicities. The categories include the following:

1. **Diuretics,** which lower blood pressure by depleting the body of sodium and reducing blood volume and perhaps by other mechanisms.

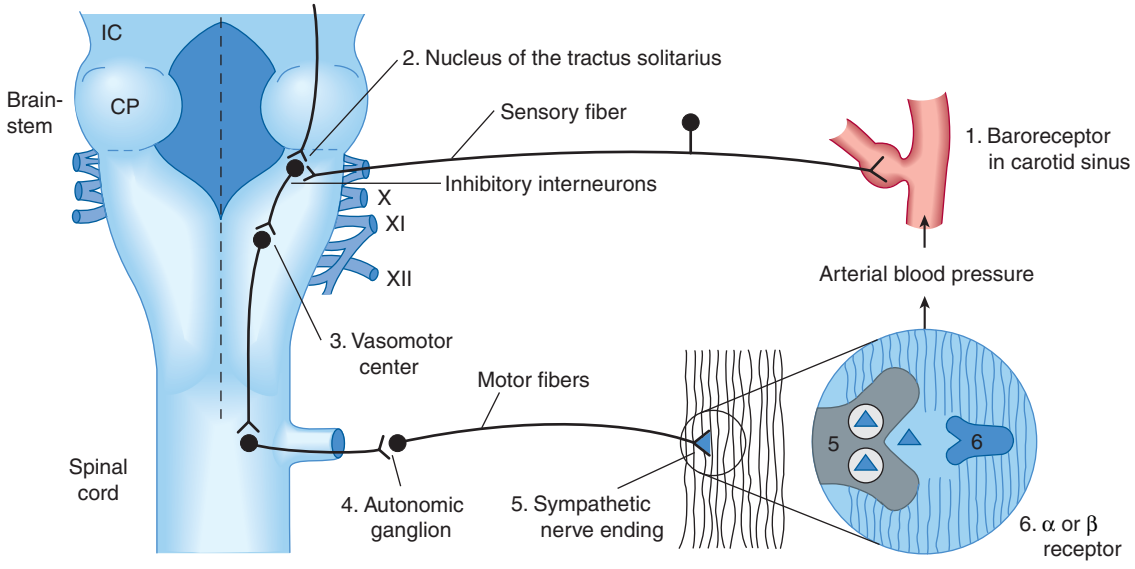


FIGURE 11–2 Baroreceptor reflex arc.

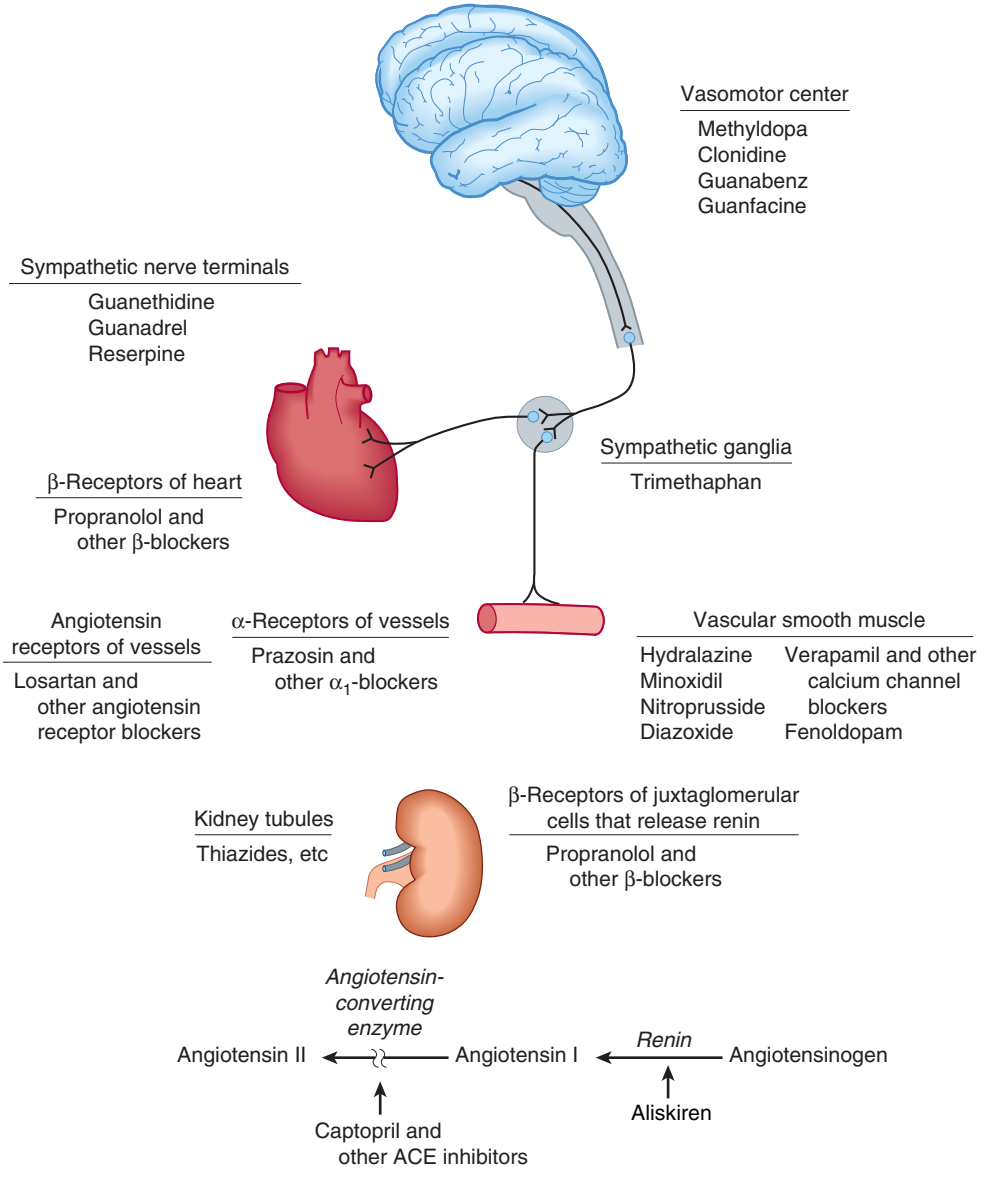


FIGURE 11–3 Sites of action of the major classes of antihypertensive drugs.

2. **Sympathoplegic agents,** which lower blood pressure by reducing peripheral vascular resistance, inhibiting cardiac function, and increasing venous pooling in capacitance vessels. (The latter two effects reduce cardiac output.) These agents are further subdivided according to their putative sites of action in the sympathetic reflex arc (see below).
3. **Direct vasodilators,** which reduce pressure by relaxing vascular smooth muscle, thus dilating resistance vessels and—to varying degrees—increasing capacitance as well.
4. **Agents that block production or action of angiotensin** and thereby reduce peripheral vascular resistance and (potentially) blood volume.

The fact that these drug groups act by different mechanisms permits the combination of drugs from two or more groups with increased efficacy and, in some cases, decreased toxicity. (See Box: Resistant Hypertension & Polypharmacy.)

DRUGS THAT ALTER SODIUM & WATER BALANCE

Dietary sodium restriction has been known for many years to decrease blood pressure in hypertensive patients. With the advent of diuretics, sodium restriction was thought to be less important. However, there is now general agreement that dietary control of blood pressure is a relatively nontoxic therapeutic measure and may even be preventive. Even modest dietary sodium restriction lowers blood pressure (though to varying extents) in many hypertensive persons.

Resistant Hypertension & Polypharmacy

Monotherapy of hypertension (treatment with a single drug) is desirable because compliance is likely to be better and cost is lower, and because in some cases adverse effects are fewer. However, most patients with hypertension require two or more drugs, preferably acting by different mechanisms (polypharmacy). According to some estimates, up to 40% of patients may respond inadequately even to two agents and are considered to have "resistant hypertension." Some of these patients have treatable secondary hypertension that has been missed, but most do not and three or more drugs are required.

One rationale for polypharmacy in hypertension is that most drugs evoke compensatory regulatory mechanisms for maintaining blood pressure (see Figures 6–7 and 11–1), which may markedly limit their effect. For example, vasodilators such as hydralazine cause a significant decrease in peripheral vascular resistance, but evoke a strong compensatory tachycardia and salt and water retention (Figure 11–4) that is capable of almost completely reversing their effect. The addition of a β blocker prevents the tachycardia; addition of a diuretic (eg, hydrochlorothiazide) prevents the salt and water retention. In effect, all three drugs increase the sensitivity of the cardiovascular system to each other's actions.

A second reason is that some drugs have only modest maximum efficacy but reduction of long-term morbidity mandates their use. Many studies of angiotensin-converting enzyme (ACE) inhibitors report a maximal lowering of blood pressure of less than 10 mm Hg. In patients with stage 2 hypertension (pressure > 160/100 mm Hg), this is inadequate to prevent all the sequelae of hypertension, but ACE inhibitors have important long-term benefits in preventing or reducing renal disease in diabetic persons, and reduction of heart failure.

Finally, the toxicity of some effective drugs prevents their use at maximally effective dosage. The widespread indiscriminate use of β blockers has been criticized because several large clinical trials indicate that some members of the group, eg, metoprolol and carvedilol, have a greater benefit than others, eg, atenolol. However, all β blockers appear to have similar benefits in reducing mortality after myocardial infarction, so these drugs are particularly indicated in patients with an infarct and hypertension.

In practice, when hypertension does not respond adequately to a regimen of one drug, a second drug from a different class with a different mechanism of action and different pattern of toxicity is added. If the response is still inadequate and compliance is known to be good, a third drug should be added. If three drugs (usually including a diuretic) are inadequate, dietary sodium restriction and an additional drug may be necessary.

Mechanisms of Action & Hemodynamic Effects of Diuretics

Diuretics lower blood pressure primarily by depleting body sodium stores. Initially, diuretics reduce blood pressure by reducing blood volume and cardiac output; peripheral vascular resistance may increase. After 6–8 weeks, cardiac output returns toward normal while peripheral vascular resistance declines. Sodium is believed to contribute to vascular resistance by increasing vessel stiffness and neural reactivity, possibly related to altered sodium-calcium exchange with a resultant increase in intracellular calcium. These effects are reversed by diuretics or sodium restriction.

Diuretics are effective in lowering blood pressure by 10–15 mm Hg in most patients, and diuretics alone often provide adequate treatment for mild or moderate essential hypertension. In more severe hypertension, diuretics are used in combination with sympathoplegic and vasodilator drugs to control the tendency toward sodium retention caused by these agents. Vascular responsiveness—ie, the ability to either constrict or dilate—is diminished by sympathoplegic and vasodilator drugs, so that the vasculature behaves like an inflexible tube. As a consequence, blood pressure becomes exquisitely sensitive to blood volume. Thus, in severe hypertension, when multiple drugs are used, blood pressure may be well controlled when blood volume is 95% of normal but much too high when blood volume is 105% of normal.

Use of Diuretics

The sites of action within the kidney and the pharmacokinetics of various diuretic drugs are discussed in Chapter 15. Thiazide diuretics are appropriate for most patients with mild or moderate hypertension and normal renal and cardiac function. More powerful diuretics (eg, those acting on the loop of Henle) such as furosemide are necessary in severe hypertension, when multiple drugs with sodium-retaining properties are used; in renal insufficiency, when glomerular filtration rate is less than 30 or 40 mL/min; and in cardiac failure or cirrhosis, in which sodium retention is marked.

Potassium-sparing diuretics are useful both to avoid excessive potassium depletion and to enhance the natriuretic effects of other diuretics. Aldosterone receptor antagonists in particular also have a favorable effect on cardiac function in people with heart failure.

Some pharmacokinetic characteristics and the initial and usual maintenance dosages of hydrochlorothiazide are listed in Table 11–2. Although thiazide diuretics are more natriuretic at higher

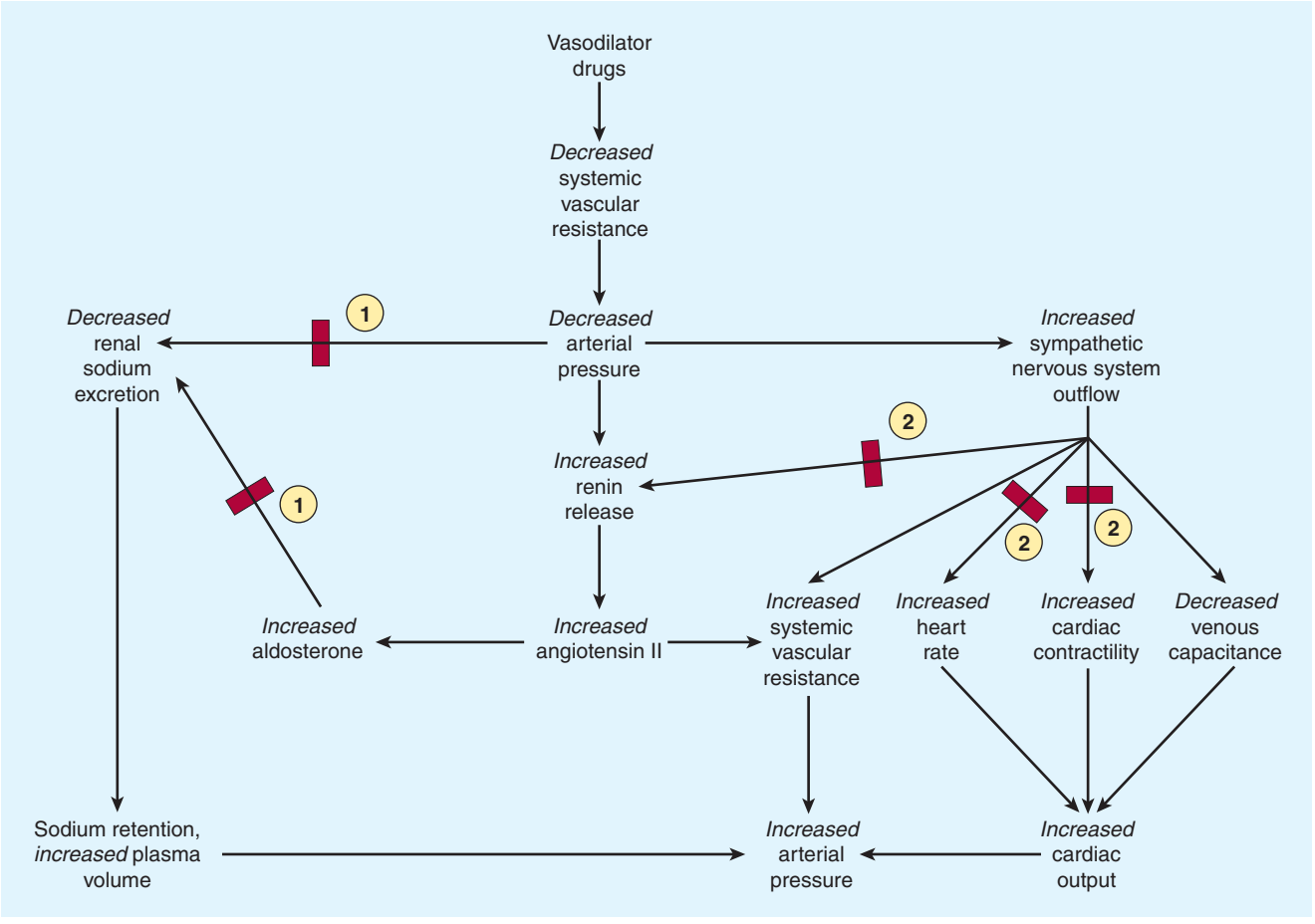


FIGURE 11–4 Compensatory responses to vasodilators; basis for combination therapy with β blockers and diuretics. ① Effect blocked by diuretics. ② Effect blocked by β blockers.

doses (up to 100–200 mg of hydrochlorothiazide), when used as a single agent, lower doses (25–50 mg) exert as much antihypertensive effect as do higher doses. In contrast to thiazides, the blood pressure response to loop diuretics continues to increase at doses many times greater than the usual therapeutic dose.

Toxicity of Diuretics

In the treatment of hypertension, the most common adverse effect of diuretics (except for potassium-sparing diuretics) is potassium depletion. Although mild degrees of hypokalemia are tolerated well by many patients, hypokalemia may be hazardous in persons taking digitalis, those who have chronic arrhythmias, or those with acute myocardial infarction or left ventricular dysfunction. Potassium loss is coupled to reabsorption of sodium, and restriction of dietary sodium intake therefore minimizes potassium loss. Diuretics may also cause magnesium depletion, impair glucose tolerance, and increase serum lipid concentrations. Diuretics increase uric acid concentrations and may precipitate gout. The use of low doses minimizes these adverse metabolic effects without impairing the antihypertensive action. Potassium-sparing diuretics may produce hyperkalemia, particularly in patients with renal insufficiency and those taking ACE inhibitors or angiotensin receptor blockers; spironolactone (a steroid) is associated with gynecomastia.

DRUGS THAT ALTER SYMPATHETIC NERVOUS SYSTEM FUNCTION

In many patients, hypertension is initiated and sustained at least in part by sympathetic neural activation. In patients with moderate to severe hypertension, most effective drug regimens include an agent that inhibits function of the sympathetic nervous system. Drugs in this group are classified according to the site at which they impair the sympathetic reflex arc (Figure 11–2). This neuroanatomic classification explains prominent differences in cardiovascular effects of drugs and allows the clinician to predict interactions of these drugs with one another and with other drugs.

The subclasses of sympathoplegic drugs exhibit different patterns of potential toxicity. Drugs that lower blood pressure by actions on the central nervous system tend to cause sedation and mental depression and may produce disturbances of sleep, including nightmares. Drugs that act by inhibiting transmission through

TABLE 11–2 Pharmacokinetic characteristics and dosage of selected oral antihypertensive drugs.

Drug	Half-life (h)	Bioavailability (percent)	Suggested Initial Dose	Usual Maintenance Dose Range	Reduction of Dosage Required in Moderate Renal Insufficiency[1]
Amlodipine	35	65	2.5 mg/d	5–10 mg/d	No
Atenolol	6	60	50 mg/d	50–100 mg/d	Yes
Benazepril	0.6[2]	35	5–10 mg/d	20–40 mg/d	Yes
Captopril	2.2	65	50–75 mg/d	75–150 mg/d	Yes
Clonidine	8–12	95	0.2 mg/d	0.2–1.2 mg/d	Yes
Diltiazem	3.5	40	120–140 mg/d	240–360 mg/d	No
Guanethidine	120	3–50	10 mg/d	25–50 mg/d	Possible
Hydralazine	1.5–3	25	40 mg/d	40–200 mg/d	No
Hydrochlorothiazide	12	70	25 mg/d	25–50 mg/d	No
Lisinopril	12	25	10 mg/d	10–80 mg/d	Yes
Losartan	1–2[3]	36	50 mg/d	25–100 mg/d	No
Methyldopa	2	25	1 g/d	1–2 g/d	No
Metoprolol	3–7	40	50–100 mg/d	200–400 mg/d	No
Minoxidil	4	90	5–10 mg/d	40 mg/d	No
Nebivolol	12	Nd[4]	5 mg/d	10–40 mg/d	No
Nifedipine	2	50	30 mg/d	30–60 mg/d	No
Prazosin	3–4	70	3 mg/d	10–30 mg/d	No
Propranolol	3–5	25	80 mg/d	80–480 mg/d	No
Reserpine	24–48	50	0.25 mg/d	0.25 mg/d	No
Verapamil	4–6	22	180 mg/d	240–480 mg/d	No

[1]Creatinine clearance ≥ 30 mL/min. Many of these drugs do require dosage adjustment if creatinine clearance falls below 30 mL/min.

[2]The active metabolite of benazepril has a half-life of 10 hours.

[3]The active metabolite of losartan has a half-life of 3–4 hours.

[4]Nd, not determined.

autonomic ganglia (ganglion blockers) produce toxicity from inhibition of parasympathetic regulation, in addition to profound sympathetic blockade and are no longer used. Drugs that act chiefly by reducing release of norepinephrine from sympathetic nerve endings cause effects that are similar to those of surgical sympathectomy, including inhibition of ejaculation, and hypotension that is increased by upright posture and after exercise. Drugs that block postsynaptic adrenoceptors produce a more selective spectrum of effects depending on the class of receptor to which they bind. Although not discussed in this chapter, it should be noted that renal sympathetic denervation is effective in lowering blood pressure in patients with hypertension resistant to antihypertensive drugs.

Finally, one should note that *all* of the agents that lower blood pressure by altering sympathetic function can elicit compensatory effects through mechanisms that are not dependent on adrenergic nerves. Thus, the antihypertensive effect of any of these agents used alone may be limited by retention of sodium by the kidney and expansion of blood volume. For this reason, sympathoplegic antihypertensive drugs are most effective when used concomitantly with a diuretic.

CENTRALLY ACTING SYMPATHOPLEGIC DRUGS

Centrally acting sympathoplegic drugs were once widely used in the treatment of hypertension. With the exception of clonidine, these drugs are rarely used today.

Mechanisms & Sites of Action

These agents reduce sympathetic outflow from vasomotor centers in the brainstem but allow these centers to retain or even increase their sensitivity to baroreceptor control. Accordingly, the antihypertensive and toxic actions of these drugs are generally less dependent on posture than are the effects of drugs that act directly on peripheral sympathetic neurons.

Methyldopa (L-α-methyl-3,4-dihydroxyphenylalanine) is an analog of L-dopa and is converted to α-methyldopamine and α-methylnorepinephrine; this pathway directly parallels the synthesis of norepinephrine from dopa illustrated in Figure 6–5. Alpha-methylnorepinephrine is stored in adrenergic nerve vesicles, where it stoichiometrically replaces norepinephrine, and is released by nerve

stimulation to interact with postsynaptic adrenoceptors. However, this replacement of norepinephrine by a false transmitter in peripheral neurons is *not* responsible for methyldopa's antihypertensive effect, because the α-methylnorepinephrine released is an effective agonist at the α adrenoceptors that mediate peripheral sympathetic constriction of arterioles and venules. In fact, methyldopa's antihypertensive action appears to be due to stimulation of *central* α adrenoceptors by α-methylnorepinephrine or α-methyldopamine.

The antihypertensive action of **clonidine,** a 2-imidazoline derivative, was discovered in the course of testing the drug for use as a nasal decongestant.

After intravenous injection, clonidine produces a brief rise in blood pressure followed by more prolonged hypotension. The pressor response is due to direct stimulation of α adrenoceptors in arterioles. The drug is classified as a partial agonist at α receptors because it also inhibits pressor effects of other α agonists.

Considerable evidence indicates that the hypotensive effect of clonidine is exerted at α adrenoceptors in the medulla of the brain. In animals, the hypotensive effect of clonidine is prevented by central administration of α antagonists. Clonidine reduces sympathetic and increases parasympathetic tone, resulting in blood pressure lowering and bradycardia. The reduction in pressure is accompanied by a decrease in circulating catecholamine levels. These observations suggest that clonidine sensitizes brainstem vasomotor centers to inhibition by baroreflexes.

Thus, studies of clonidine and methyldopa suggest that normal regulation of blood pressure involves central adrenergic neurons that modulate baroreceptor reflexes. Clonidine and α-methylnorepinephrine bind more tightly to α_2 than to α_1 adrenoceptors. As noted in Chapter 6, α_2 receptors are located on presynaptic adrenergic neurons as well as some postsynaptic sites. It is possible that clonidine and α-methylnorepinephrine act in the brain to reduce norepinephrine release onto relevant receptor sites. Alternatively, these drugs may act on postsynaptic α_2 adrenoceptors to inhibit activity of appropriate neurons. Finally, clonidine also binds to a nonadrenoceptor site, the **imidazoline receptor,** which may also mediate antihypertensive effects.

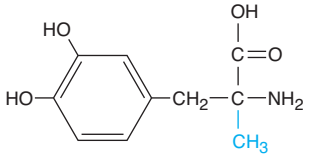
Methyldopa and clonidine produce slightly different hemodynamic effects: clonidine lowers heart rate and cardiac output more than does methyldopa. This difference suggests that these two drugs do not have identical sites of action. They may act primarily on different populations of neurons in the vasomotor centers of the brainstem.

Guanabenz and **guanfacine** are centrally active antihypertensive drugs that share the central α-adrenoceptor–stimulating effects of clonidine. They do not appear to offer any advantages over clonidine and are rarely used.

METHYLDOPA

Methyldopa was widely used in the past but is now used primarily for hypertension during pregnancy. It lowers blood pressure chiefly by reducing peripheral vascular resistance, with a variable reduction in heart rate and cardiac output.

Most cardiovascular reflexes remain intact after administration of methyldopa, and blood pressure reduction is not markedly dependent on posture. Postural (orthostatic) hypotension sometimes occurs, particularly in volume-depleted patients. One potential advantage of methyldopa is that it causes reduction in renal vascular resistance.



α-Methyldopa
(α-methyl group in color)

Pharmacokinetics & Dosage

Pharmacokinetic characteristics of methyldopa are listed in Table 11–2. Methyldopa enters the brain via an aromatic amino acid transporter. The usual oral dose of methyldopa produces its maximal antihypertensive effect in 4–6 hours, and the effect can persist for up to 24 hours. Because the effect depends on accumulation and storage of a metabolite (α-methylnorepinephrine) in the vesicles of nerve endings, the action persists after the parent drug has disappeared from the circulation.

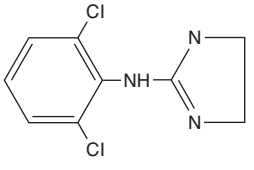
Toxicity

The most common undesirable effect of methyldopa is sedation, particularly at the onset of treatment. With long-term therapy, patients may complain of persistent mental lassitude and impaired mental concentration. Nightmares, mental depression, vertigo, and extrapyramidal signs may occur but are relatively infrequent. Lactation, associated with increased prolactin secretion, can occur both in men and in women treated with methyldopa. This toxicity is probably mediated by inhibition of dopaminergic mechanisms in the hypothalamus.

Other important adverse effects of methyldopa are development of a positive Coombs test (occurring in 10–20% of patients undergoing therapy for longer than 12 months), which sometimes makes cross-matching blood for transfusion difficult and rarely is associated with hemolytic anemia, as well as hepatitis and drug fever. Discontinuation of the drug usually results in prompt reversal of these abnormalities.

CLONIDINE

Blood pressure lowering by clonidine results from reduction of cardiac output due to decreased heart rate and relaxation of capacitance vessels, as well as a reduction in peripheral vascular resistance.



Clonidine

Reduction in arterial blood pressure by clonidine is accompanied by decreased renal vascular resistance and maintenance of renal blood flow. As with methyldopa, clonidine reduces blood pressure in the supine position and only rarely causes postural hypotension. Pressor effects of clonidine are not observed after ingestion of therapeutic doses of clonidine, but severe hypertension can complicate a massive overdose.

Pharmacokinetics & Dosage

Typical pharmacokinetic characteristics are listed in Table 11–2.

Clonidine is lipid-soluble and rapidly enters the brain from the circulation. Because of its relatively short half-life and the fact that its antihypertensive effect is directly related to blood concentration, oral clonidine must be given twice a day (or as a patch, below) to maintain smooth blood pressure control. However, as is not the case with methyldopa, the dose-response curve of clonidine is such that increasing doses are more effective (but also more toxic).

A transdermal preparation of clonidine that reduces blood pressure for 7 days after a single application is also available. This preparation appears to produce less sedation than clonidine tablets but is often associated with local skin reactions.

Toxicity

Dry mouth and sedation are common. Both effects are centrally mediated and dose-dependent and coincide temporally with the drug's antihypertensive effect.

Clonidine should not be given to patients who are at risk for mental depression and should be withdrawn if depression occurs during therapy. Concomitant treatment with tricyclic antidepressants may block the antihypertensive effect of clonidine. The interaction is believed to be due to α-adrenoceptor–blocking actions of the tricyclics.

Withdrawal of clonidine after protracted use, particularly with high dosages (more than 1 mg/d), can result in life-threatening hypertensive crisis mediated by increased sympathetic nervous activity. Patients exhibit nervousness, tachycardia, headache, and sweating after omitting one or two doses of the drug. Because of the risk of severe hypertensive crisis when clonidine is suddenly withdrawn, all patients who take clonidine should be warned of the possibility. If the drug must be stopped, it should be done gradually while other antihypertensive agents are being substituted. Treatment of the hypertensive crisis consists of reinstitution of clonidine therapy or administration of α- and β-adrenoceptor–blocking agents.

GANGLION-BLOCKING AGENTS

Historically, drugs that block activation of postganglionic autonomic neurons by acetylcholine were among the first agents used in the treatment of hypertension. Most such drugs are no longer available clinically because of intolerable toxicities related to their primary action (see below).

Ganglion blockers competitively block nicotinic cholinoceptors on postganglionic neurons in both sympathetic and parasympathetic ganglia. In addition, these drugs may directly block the nicotinic acetylcholine channel, in the same fashion as neuromuscular nicotinic blockers (see Figure 27–6).

The adverse effects of ganglion blockers are direct extensions of their pharmacologic effects. These effects include both sympathoplegia (excessive orthostatic hypotension and sexual dysfunction) and parasympathoplegia (constipation, urinary retention, precipitation of glaucoma, blurred vision, dry mouth, etc). These severe toxicities are the major reason for the abandonment of ganglion blockers for the therapy of hypertension.

ADRENERGIC NEURON-BLOCKING AGENTS

These drugs lower blood pressure by preventing normal physiologic release of norepinephrine from postganglionic sympathetic neurons.

Guanethidine

In high enough doses, guanethidine can produce profound sympathoplegia. The resulting high maximal efficacy of this agent made it the mainstay of outpatient therapy of severe hypertension for many years. For the same reason, guanethidine can produce all of the toxicities expected from "pharmacologic sympathectomy," including marked postural hypotension, diarrhea, and impaired ejaculation. Because of these adverse effects, guanethidine is now rarely used.

Guanethidine is too polar to enter the central nervous system. As a result, this drug has none of the central effects seen with many of the other antihypertensive agents described in this chapter.

Guanadrel is a guanethidine-like drug that is available in the USA. **Bethanidine** and **debrisoquin**, antihypertensive agents not available for clinical use in the USA, are similar.

A. Mechanism and Sites of Action

Guanethidine inhibits the release of norepinephrine from sympathetic nerve endings (see Figure 6–4). This effect is probably responsible for most of the sympathoplegia that occurs in patients. Guanethidine is transported across the sympathetic nerve membrane by the same mechanism that transports norepinephrine itself (NET, uptake 1), and uptake is essential for the drug's action. Once guanethidine has entered the nerve, it is concentrated in transmitter vesicles, where it replaces norepinephrine. Because it replaces norepinephrine, the drug causes a gradual depletion of norepinephrine stores in the nerve ending.

Because neuronal uptake is necessary for the hypotensive activity of guanethidine, drugs that block the catecholamine uptake process or displace amines from the nerve terminal (see Chapter 6) block its effects. These include cocaine, amphetamine, tricyclic antidepressants, phenothiazines, and phenoxybenzamine.

B. Pharmacokinetics and Dosage

Because of guanethidine's long half-life (5 days), the onset of sympathoplegia is gradual (maximal effect in 1–2 weeks), and sympathoplegia persists for a comparable period after cessation of

therapy. The dose should not ordinarily be increased at intervals shorter than 2 weeks.

C. Toxicity

Therapeutic use of guanethidine is often associated with symptomatic postural hypotension and hypotension following exercise, particularly when the drug is given in high doses. Guanethidine-induced sympathoplegia in men may be associated with delayed or retrograde ejaculation (into the bladder). Guanethidine commonly causes diarrhea, which results from increased gastrointestinal motility due to parasympathetic predominance in controlling the activity of intestinal smooth muscle.

Interactions with other drugs may complicate guanethidine therapy. Sympathomimetic agents, at doses available in over-the-counter cold preparations, can produce hypertension in patients taking guanethidine. Similarly, guanethidine can produce hypertensive crisis by releasing catecholamines in patients with pheochromocytoma. When tricyclic antidepressants are administered to patients taking guanethidine, the drug's antihypertensive effect is attenuated, and severe hypertension may follow.

Reserpine

Reserpine, an alkaloid extracted from the roots of an Indian plant, *Rauwolfia serpentina,* was one of the first effective drugs used on a large scale in the treatment of hypertension. At present, it is rarely used owing to its adverse effects.

A. Mechanism and Sites of Action

Reserpine blocks the ability of aminergic transmitter vesicles to take up and store biogenic amines, probably by interfering with the vesicular membrane-associated transporter (VMAT, see Figure 6–4). This effect occurs throughout the body, resulting in depletion of norepinephrine, dopamine, and serotonin in both central and peripheral neurons. Chromaffin granules of the adrenal medulla are also depleted of catecholamines, although to a lesser extent than are the vesicles of neurons. Reserpine's effects on adrenergic vesicles appear irreversible; trace amounts of the drug remain bound to vesicular membranes for many days.

Depletion of peripheral amines probably accounts for much of the beneficial antihypertensive effect of reserpine, but a central component cannot be ruled out. Reserpine readily enters the brain, and depletion of cerebral amine stores causes sedation, mental depression, and parkinsonism symptoms.

At lower doses used for treatment of mild hypertension, reserpine lowers blood pressure by a combination of decreased cardiac output and decreased peripheral vascular resistance.

B. Pharmacokinetics and Dosage

See Table 11–2.

C. Toxicity

At the low doses usually administered, reserpine produces little postural hypotension. Most of the unwanted effects of reserpine result from actions on the brain or gastrointestinal tract.

High doses of reserpine characteristically produce sedation, lassitude, nightmares, and severe mental depression; occasionally, these occur even in patients receiving low doses (0.25 mg/d). Much less frequently, ordinary low doses of reserpine produce extrapyramidal effects resembling Parkinson's disease, probably as a result of dopamine depletion in the corpus striatum. Although these central effects are uncommon, it should be stressed that they may occur at any time, even after months of uneventful treatment. Patients with a history of mental depression should not receive reserpine, and the drug should be stopped if depression appears.

Reserpine rather often produces mild diarrhea and gastrointestinal cramps and increases gastric acid secretion. The drug should not be given to patients with a history of peptic ulcer.

ADRENOCEPTOR ANTAGONISTS

The detailed pharmacology of α- and β-adrenoceptor blockers is presented in Chapter 10.

BETA-ADRENOCEPTOR–BLOCKING AGENTS

Of the large number of β blockers tested, most have been shown to be effective in lowering blood pressure. The pharmacologic properties of several of these agents differ in ways that may confer therapeutic benefits in certain clinical situations.

Propranolol

Propranolol was the first β blocker shown to be effective in hypertension and ischemic heart disease. Propranolol has now been largely replaced by cardioselective β blockers such as metoprolol and atenolol. All β-adrenoceptor–blocking agents are useful for lowering blood pressure in mild to moderate hypertension. In severe hypertension, β blockers are especially useful in preventing the reflex tachycardia that often results from treatment with direct vasodilators. Beta blockers have been shown to reduce mortality after a myocardial infarction and some also reduce mortality in patients with heart failure; they are particularly advantageous for treating hypertension in patients with these conditions (see Chapter 13).

A. Mechanism and Sites of Action

Propranolol's efficacy in treating hypertension as well as most of its toxic effects result from nonselective β blockade. Propranolol decreases blood pressure primarily as a result of a decrease in cardiac output. Other β blockers may decrease cardiac output or decrease peripheral vascular resistance to various degrees, depending on cardioselectivity and partial agonist activities.

Propranolol inhibits the stimulation of renin production by catecholamines (mediated by β_1 receptors). It is likely that propranolol's effect is due in part to depression of the renin-angiotensin-aldosterone system. Although most effective in patients with high

plasma renin activity, propranolol also reduces blood pressure in hypertensive patients with normal or even low renin activity. Beta blockers might also act on peripheral presynaptic β adrenoceptors to reduce sympathetic vasoconstrictor nerve activity.

In mild to moderate hypertension, propranolol produces a significant reduction in blood pressure without prominent postural hypotension.

B. Pharmacokinetics and Dosage

See Table 11–2. Resting bradycardia and a reduction in the heart rate during exercise are indicators of propranolol's β-blocking effect, and changes in these parameters may be used as guides for regulating dosage. Propranolol can be administered twice daily, and slow-release preparations are available.

C. Toxicity

The principal toxicities of propranolol result from blockade of cardiac, vascular, or bronchial β receptors and are described in more detail in Chapter 10. The most important of these predictable extensions of the β-blocking action occur in patients with bradycardia or cardiac conduction disease, asthma, peripheral vascular insufficiency, and diabetes.

When propranolol is discontinued after prolonged regular use, some patients experience a withdrawal syndrome, manifested by nervousness, tachycardia, increased intensity of angina, and increase of blood pressure. Myocardial infarction has been reported in a few patients. Although the incidence of these complications is probably low, propranolol should not be discontinued abruptly. The withdrawal syndrome may involve up-regulation or supersensitivity of β adrenoceptors.

Metoprolol & Atenolol

Metoprolol and atenolol, which are cardioselective, are the most widely used β blockers in the treatment of hypertension. Metoprolol is approximately equipotent to propranolol in inhibiting stimulation of β_1 adrenoceptors such as those in the heart but 50- to 100-fold less potent than propranolol in blocking β_2 receptors. Relative cardioselectivity may be advantageous in treating hypertensive patients who also suffer from asthma, diabetes, or peripheral vascular disease. Although cardioselectivity is not complete, metoprolol causes less bronchial constriction than propranolol at doses that produce equal inhibition of β_1-adrenoceptor responses. Metoprolol is extensively metabolized by CYP2D6 with high first-pass metabolism. The drug has a relatively short half-life of 4–6 hours, but the extended-release preparation can be dosed once daily (Table 11–2). Sustained-release metoprolol is effective in reducing mortality from heart failure and is particularly useful in patients with hypertension and heart failure.

Atenolol is not extensively metabolized and is excreted primarily in the urine with a half-life of 6 hours; it is usually dosed once daily. Recent studies have found atenolol less effective than metoprolol in preventing the complications of hypertension. A possible reason for this difference is that once-daily dosing does not maintain adequate blood levels of atenolol. The usual dosage is 50–100 mg/d. Patients with reduced renal function should receive lower doses.

Nadolol, Carteolol, Betaxolol, & Bisoprolol

Nadolol and carteolol, nonselective β-receptor antagonists, are not appreciably metabolized and are excreted to a considerable extent in the urine. Betaxolol and bisoprolol are β_1-selective blockers that are primarily metabolized in the liver but have long half-lives. Because of these relatively long half-lives, these drugs can be administered once daily. Nadolol is usually begun at a dosage of 40 mg/d, carteolol at 2.5 mg/d, betaxolol at 10 mg/d, and bisoprolol at 5 mg/d. Increases in dosage to obtain a satisfactory therapeutic effect should take place no more often than every 4 or 5 days. Patients with reduced renal function should receive correspondingly reduced doses of nadolol and carteolol.

Pindolol, Acebutolol, & Penbutolol

Pindolol, acebutolol, and penbutolol are partial agonists, ie, β blockers with some intrinsic sympathomimetic activity. They lower blood pressure by decreasing vascular resistance and appear to depress cardiac output or heart rate less than other β blockers, perhaps because of significantly greater agonist than antagonist effects at β_2 receptors. This may be particularly beneficial for patients with bradyarrhythmias or peripheral vascular disease. Daily doses of pindolol start at 10 mg; of acebutolol, at 400 mg; and of penbutolol, at 20 mg.

Labetalol, Carvedilol, & Nebivolol

These drugs have both β-blocking and vasodilating effects. Labetalol is formulated as a racemic mixture of four isomers (it has two centers of asymmetry). Two of these isomers—the *(S,S)-* and *(R,S)*-isomers—are relatively inactive, a third *(S,R)-* is a potent α blocker, and the last *(R,R)-* is a potent β blocker. Labetalol has a 3:1 ratio of β:α antagonism after oral dosing. Blood pressure is lowered by reduction of systemic vascular resistance (via α blockade) without significant alteration in heart rate or cardiac output. Because of its combined α- and β-blocking activity, labetalol is useful in treating the hypertension of pheochromocytoma and hypertensive emergencies. Oral daily doses of labetalol range from 200 to 2400 mg/d. Labetalol is given as repeated intravenous bolus injections of 20–80 mg to treat hypertensive emergencies.

Carvedilol, like labetalol, is administered as a racemic mixture. The *S*(–) isomer is a nonselective β-adrenoceptor blocker, but both *S*(–) and *R*(+) isomers have approximately equal α-blocking potency. The isomers are stereoselectively metabolized in the liver, which means that their elimination half-lives may differ. The average half-life is 7–10 hours. The usual starting dosage of carvedilol for ordinary hypertension is 6.25 mg twice daily. Carvedilol reduces mortality in patients with heart failure and is therefore particularly useful in patients with both heart failure and hypertension.

Nebivolol is a β_1-selective blocker with vasodilating properties that are *not* mediated by α blockade. D-Nebivolol has highly selective β_1 blocking effects, while the L-isomer causes vasodilation; the drug is marketed as a racemic mixture. The vasodilating effect may be due to an increase in endothelial release of nitric oxide via induction of endothelial nitric oxide synthase. The hemodynamic

effects of nebivolol therefore differ from those of pure β blockers in that peripheral vascular resistance is acutely lowered (by nebivolol) as opposed to increased acutely (by the older agents). Nebivolol is extensively metabolized and has active metabolites. The half-life is 10–12 hours, but the drug can be given once daily. Dosing is generally started at 5 mg/d, with dose escalation as high as 40 mg, if necessary. The efficacy of nebivolol is similar to that of other antihypertensive agents, but several studies report fewer adverse effects.

Esmolol

Esmolol is a β_1-selective blocker that is rapidly metabolized via hydrolysis by red blood cell esterases. It has a short half-life (9–10 minutes) and is administered by constant intravenous infusion. Esmolol is generally administered as a loading dose (0.5–1 mg/kg), followed by a constant infusion. The infusion is typically started at 50–150 mcg/kg/min, and the dose increased every 5 minutes, up to 300 mcg/kg/min, as needed to achieve the desired therapeutic effect. Esmolol is used for management of intraoperative and postoperative hypertension, and sometimes for hypertensive emergencies, particularly when hypertension is associated with tachycardia.

PRAZOSIN & OTHER ALPHA$_1$ BLOCKERS

Mechanism & Sites of Action

Prazosin, terazosin, and doxazosin produce most of their antihypertensive effects by selectively blocking α_1 receptors in arterioles and venules. These agents produce less reflex tachycardia when lowering blood pressure than do nonselective α antagonists such as phentolamine. Alpha$_1$-receptor selectivity allows norepinephrine to exert unopposed negative feedback (mediated by presynaptic α_2 receptors) on its own release (see Chapter 6); in contrast, phentolamine blocks both presynaptic and postsynaptic α receptors, with the result that reflex activation of sympathetic neurons by phentolamine's effects produces greater release of transmitter onto β receptors and correspondingly greater cardioacceleration.

Alpha blockers reduce arterial pressure by dilating both resistance and capacitance vessels. As expected, blood pressure is reduced more in the upright than in the supine position. Retention of salt and water occurs when these drugs are administered without a diuretic. The drugs are more effective when used in combination with other agents, such as a β blocker and a diuretic, than when used alone. Owing to their beneficial effects in men with prostatic hyperplasia and bladder obstruction symptoms, these drugs are used primarily in men with concurrent hypertension and benign prostatic hyperplasia.

Pharmacokinetics & Dosage

Pharmacokinetic characteristics of prazosin are listed in Table 11–2. Terazosin is also extensively metabolized but undergoes very little first-pass metabolism and has a half-life of 12 hours. Doxazosin has an intermediate bioavailability and a half-life of 22 hours.

Terazosin can often be given once daily, with doses of 5–20 mg/d. Doxazosin is usually given once daily starting at 1 mg/d and progressing to 4 mg/d or more as needed. Although long-term treatment with these α blockers causes relatively little postural hypotension, a precipitous drop in standing blood pressure develops in some patients shortly after the first dose is absorbed. For this reason, the first dose should be small and should be administered at bedtime. Although the mechanism of this first-dose phenomenon is not clear, it occurs more commonly in patients who are salt- and volume-depleted.

Aside from the first-dose phenomenon, the reported toxicities of the α_1 blockers are relatively infrequent and mild. These include dizziness, palpitations, headache, and lassitude. Some patients develop a positive test for antinuclear factor in serum while on prazosin therapy, but this has not been associated with rheumatic symptoms. The α_1 blockers do not adversely and may even beneficially affect plasma lipid profiles, but this action has not been shown to confer any benefit on clinical outcomes.

OTHER ALPHA-ADRENOCEPTOR–BLOCKING AGENTS

The nonselective agents, **phentolamin**e and **phenoxybenzamine,** are useful in diagnosis and treatment of pheochromocytoma and in other clinical situations associated with exaggerated release of catecholamines (eg, phentolamine may be combined with propranolol to treat the clonidine withdrawal syndrome, described previously). Their pharmacology is described in Chapter 10.

VASODILATORS

Mechanism & Sites of Action

This class of drugs includes the oral vasodilators, hydralazine and minoxidil, which are used for long-term outpatient therapy of hypertension; the parenteral vasodilators, nitroprusside, diazoxide, and fenoldopam, which are used to treat hypertensive emergencies; the calcium channel blockers, which are used in both circumstances; and the nitrates, which are used mainly in angina (Table 11–3).

Chapter 12 contains additional discussion of vasodilators. All the vasodilators that are useful in hypertension relax smooth muscle of arterioles, thereby decreasing systemic vascular resistance. Sodium nitroprusside and the nitrates also relax veins. Decreased arterial resistance and decreased mean arterial blood pressure elicit compensatory responses, mediated by baroreceptors and the sympathetic nervous system (Figure 11–4), as well as renin, angiotensin, and aldosterone. Because sympathetic reflexes are intact, vasodilator therapy does not cause orthostatic hypotension or sexual dysfunction.

Vasodilators work best in combination with other antihypertensive drugs that oppose the compensatory cardiovascular responses. (See Box: Resistant Hypertension & Polypharmacy.)

TABLE 11–3 Mechanisms of action of vasodilators.

Mechanism	Examples
Release of nitric oxide from drug or endothelium	Nitroprusside, hydralazine, nitrates,[1] histamine, acetylcholine
Reduction of calcium influx	Verapamil, diltiazem, nifedipine
Hyperpolarization of smooth muscle membrane through opening of potassium channels	Minoxidil, diazoxide
Activation of dopamine receptors	Fenoldopam

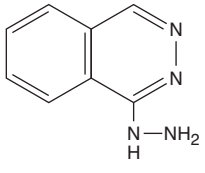
[1]See Chapter 12.

HYDRALAZINE

Hydralazine, a hydrazine derivative, dilates arterioles but not veins. It has been available for many years, although it was initially thought not to be particularly effective because tachyphylaxis to its antihypertensive effects developed rapidly. The benefits of combination therapy are now recognized, and hydralazine may be used more effectively, particularly in severe hypertension. The combination of hydralazine with nitrates is effective in heart failure and should be considered in patients with both hypertension and heart failure, especially in African-American patients.

Pharmacokinetics & Dosage

Hydralazine is well absorbed and rapidly metabolized by the liver during the first pass, so that bioavailability is low (averaging 25%) and variable among individuals. It is metabolized in part by acetylation at a rate that appears to be bimodally distributed in the population (see Chapter 4). As a consequence, rapid acetylators have greater first-pass metabolism, lower blood levels, and less antihypertensive benefit from a given dose than do slow acetylators. The half-life of hydralazine ranges from 1.5 to 3 hours, but vascular effects persist longer than do blood concentrations, possibly due to avid binding to vascular tissue.



Hydralazine

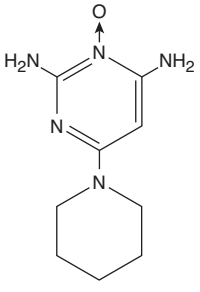
Usual dosage ranges from 40 mg/d to 200 mg/d. The higher dosage was selected as the dose at which there is a small possibility of developing the lupus erythematosus-like syndrome described in the next section. However, higher dosages result in greater vasodilation and may be used if necessary. Dosing two or three times daily provides smooth control of blood pressure.

Toxicity

The most common adverse effects of hydralazine are headache, nausea, anorexia, palpitations, sweating, and flushing. In patients with ischemic heart disease, reflex tachycardia and sympathetic stimulation may provoke angina or ischemic arrhythmias. With dosages of 400 mg/d or more, there is a 10–20% incidence—chiefly in persons who slowly acetylate the drug—of a syndrome characterized by arthralgia, myalgia, skin rashes, and fever that resembles lupus erythematosus. The syndrome is not associated with renal damage and is reversed by discontinuance of hydralazine. Peripheral neuropathy and drug fever are other serious but uncommon adverse effects.

MINOXIDIL

Minoxidil is a very efficacious orally active vasodilator. The effect results from the opening of potassium channels in smooth muscle membranes by minoxidil sulfate, the active metabolite. Increased potassium permeability stabilizes the membrane at its resting potential and makes contraction less likely. Like hydralazine, minoxidil dilates arterioles but not veins. Because of its greater potential antihypertensive effect, minoxidil should replace hydralazine when maximal doses of the latter are not effective or in patients with renal failure and severe hypertension, who do not respond well to hydralazine.



Minoxidil

Pharmacokinetics & Dosage

Pharmacokinetic parameters of minoxidil are listed in Table 11–2. Even more than with hydralazine, the use of minoxidil is associated with reflex sympathetic stimulation and sodium and fluid retention. Minoxidil must be used in combination with a β blocker and a loop diuretic.

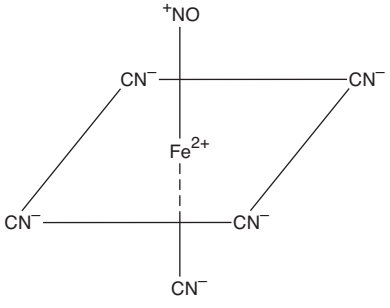
Toxicity

Tachycardia, palpitations, angina, and edema are observed when doses of β blockers and diuretics are inadequate. Headache, sweating, and hypertrichosis, which is particularly bothersome in women, are relatively common. Minoxidil illustrates how one person's toxicity may become another person's therapy. Topical minoxidil (as Rogaine) is used as a stimulant to hair growth for correction of baldness.

SODIUM NITROPRUSSIDE

Sodium nitroprusside is a powerful parenterally administered vasodilator that is used in treating hypertensive emergencies as well as severe heart failure. Nitroprusside dilates both arterial and venous vessels, resulting in reduced peripheral vascular resistance and venous return. The action occurs as a result of activation of guanylyl cyclase, either via release of nitric oxide or by direct stimulation of the enzyme. The result is increased intracellular cGMP, which relaxes vascular smooth muscle (Figure 12–2).

In the absence of heart failure, blood pressure decreases, owing to decreased vascular resistance, whereas cardiac output does not change or decreases slightly. In patients with heart failure and low cardiac output, output often increases owing to afterload reduction.



Nitroprusside

Pharmacokinetics & Dosage

Nitroprusside is a complex of iron, cyanide groups, and a nitroso moiety. It is rapidly metabolized by uptake into red blood cells with liberation of cyanide. Cyanide in turn is metabolized by the mitochondrial enzyme rhodanase, in the presence of a sulfur donor, to the less toxic thiocyanate. Thiocyanate is distributed in extracellular fluid and slowly eliminated by the kidney.

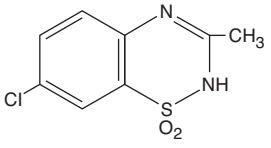
Nitroprusside rapidly lowers blood pressure, and its effects disappear within 1–10 minutes after discontinuation. The drug is given by intravenous infusion. Sodium nitroprusside in aqueous solution is sensitive to light and must therefore be made up fresh before each administration and covered with opaque foil. Infusion solutions should be changed after several hours. Dosage typically begins at 0.5 mcg/kg/min and may be increased up to 10 mcg/kg/min as necessary to control blood pressure. Higher rates of infusion, if continued for more than an hour, may result in toxicity. Because of its efficacy and rapid onset of effect, nitroprusside should be administered by infusion pump and arterial blood pressure continuously monitored via intra-arterial recording.

Toxicity

Other than excessive blood pressure lowering, the most serious toxicity is related to accumulation of cyanide; metabolic acidosis, arrhythmias, excessive hypotension, and death have resulted. In a few cases, toxicity after relatively low doses of nitroprusside suggested a defect in cyanide metabolism. Administration of sodium thiosulfate as a sulfur donor facilitates metabolism of cyanide. Hydroxocobalamin combines with cyanide to form the nontoxic cyanocobalamin. Both have been advocated for prophylaxis or treatment of cyanide poisoning during nitroprusside infusion. Thiocyanate may accumulate over the course of prolonged administration, usually several days or more, particularly in patients with renal insufficiency who do not excrete thiocyanate at a normal rate. Thiocyanate toxicity is manifested as weakness, disorientation, psychosis, muscle spasms, and convulsions, and the diagnosis is confirmed by finding serum concentrations greater than 10 mg/dL. Rarely, delayed hypothyroidism occurs, owing to thiocyanate inhibition of iodide uptake by the thyroid. Methemoglobinemia during infusion of nitroprusside has also been reported.

DIAZOXIDE

Diazoxide is an effective and relatively long-acting parenterally administered arteriolar dilator that is occasionally used to treat hypertensive emergencies. Diminishing usage suggests that it may be withdrawn. Injection of diazoxide results in a rapid fall in systemic vascular resistance and mean arterial blood pressure. Studies of its mechanism suggest that it prevents vascular smooth muscle contraction by opening potassium channels and stabilizing the membrane potential at the resting level.



Diazoxide

Pharmacokinetics & Dosage

Diazoxide is similar chemically to the thiazide diuretics but has no diuretic activity. It is bound extensively to serum albumin and to vascular tissue. Diazoxide is partially metabolized; its metabolic pathways are not well characterized. The remainder is excreted unchanged. Its half-life is approximately 24 hours, but the relationship between blood concentration and hypotensive action is not well established. The blood pressure-lowering effect after a rapid injection is established within 5 minutes and lasts for 4–12 hours.

When diazoxide was first marketed, a dose of 300 mg by rapid injection was recommended. It appears, however, that excessive hypotension can be avoided by beginning with smaller doses (50–150 mg). If necessary, doses of 150 mg may be repeated every 5 to 15 minutes until blood pressure is lowered satisfactorily. Nearly all patients respond to a maximum of three or four doses. Alternatively, diazoxide may be administered by intravenous infusion at rates of 15–30 mg/min. Because of reduced protein binding, hypotension occurs after smaller doses in persons with chronic renal failure, and smaller doses should be administered to these patients. The hypotensive effects of diazoxide are also greater

when patients are pretreated with β blockers to prevent the reflex tachycardia and associated increase in cardiac output.

Toxicity

The most significant toxicity from diazoxide has been excessive hypotension, resulting from the recommendation to use a fixed dose of 300 mg in all patients. Such hypotension has resulted in stroke and myocardial infarction. The reflex sympathetic response can provoke angina, electrocardiographic evidence of ischemia, and cardiac failure in patients with ischemic heart disease, and diazoxide should be avoided in this situation.

Diazoxide inhibits insulin release from the pancreas (probably by opening potassium channels in the beta cell membrane) and is used to treat hypoglycemia secondary to insulinoma. Occasionally, hyperglycemia complicates diazoxide use, particularly in persons with renal insufficiency.

In contrast to the structurally related thiazide diuretics, diazoxide causes renal salt and water *retention.* However, because the drug is used for short periods only, this is rarely a problem.

FENOLDOPAM

Fenoldopam is a peripheral arteriolar dilator used for hypertensive emergencies and postoperative hypertension. It acts primarily as an agonist of dopamine D_1 receptors, resulting in dilation of peripheral arteries and natriuresis. The commercial product is a racemic mixture with the (*R*)-isomer mediating the pharmacologic activity.

Fenoldopam is rapidly metabolized, primarily by conjugation. Its half-life is 10 minutes. The drug is administered by continuous intravenous infusion. Fenoldopam is initiated at a low dosage (0.1 mcg/kg/min), and the dose is then titrated upward every 15 or 20 minutes to a maximum dose of 1.6 mcg/kg/min or until the desired blood pressure reduction is achieved.

As with other direct vasodilators, the major toxicities are reflex tachycardia, headache, and flushing. Fenoldopam also increases intraocular pressure and should be avoided in patients with glaucoma.

CALCIUM CHANNEL BLOCKERS

In addition to their antianginal (see Chapter 12) and antiarrhythmic effects (see Chapter 14), calcium channel blockers also reduce peripheral resistance and blood pressure. The mechanism of action in hypertension (and, in part, in angina) is inhibition of calcium influx into arterial smooth muscle cells.

Verapamil, diltiazem, and the **dihydropyridine** family (**amlodipine, felodipine, isradipine, nicardipine, nifedipine,** and **nisoldipine**) are all equally effective in lowering blood pressure, and many formulations are currently approved for this use in the USA. **Clevidipine** is a newer member of this group that is formulated for intravenous use only.

Hemodynamic differences among calcium channel blockers may influence the choice of a particular agent. Nifedipine and the other dihydropyridine agents are more selective as vasodilators and have less cardiac depressant effect than verapamil and diltiazem. Reflex sympathetic activation with slight tachycardia maintains or increases cardiac output in most patients given dihydropyridines. Verapamil has the greatest depressant effect on the heart and may decrease heart rate and cardiac output. Diltiazem has intermediate actions. The pharmacology and toxicity of these drugs is discussed in more detail in Chapter 12. Doses of calcium channel blockers used in treating hypertension are similar to those used in treating angina. Some epidemiologic studies reported an increased risk of myocardial infarction or mortality in patients receiving short-acting nifedipine for hypertension. It is therefore recommended that short-acting oral dihydropyridines not be used for hypertension. Sustained-release calcium blockers or calcium blockers with long half-lives provide smoother blood pressure control and are more appropriate for treatment of chronic hypertension. Intravenous nicardipine and clevidipine are available for the treatment of hypertension when oral therapy is not feasible; parenteral verapamil and diltiazem can also be used for the same indication. Nicardipine is typically infused at rates of 2–15 mg/h. Clevidipine is infused starting at 1–2 mg/h and progressing to 4–6 mg/h. It has a rapid onset of action and has been used in acute hypertension occurring during surgery. Oral short-acting nifedipine has been used in emergency management of severe hypertension.

INHIBITORS OF ANGIOTENSIN

Renin, angiotensin, and aldosterone play important roles in at least some people with essential hypertension. Approximately 20% of patients with essential hypertension have inappropriately low and 20% have inappropriately high plasma renin activity. Blood pressure of patients with high-renin hypertension responds well to drugs that interfere with the system, supporting a role for excess renin and angiotensin in this population.

Mechanism & Sites of Action

Renin release from the kidney cortex is stimulated by reduced renal arterial pressure, sympathetic neural stimulation, and reduced sodium delivery or increased sodium concentration at the distal renal tubule (see Chapter 17). Renin acts upon angiotensinogen to split off the inactive precursor decapeptide angiotensin I. Angiotensin I is then converted, primarily by endothelial ACE, to the arterial vasoconstrictor octapeptide angiotensin II (Figure 11–5), which is in turn converted in the adrenal gland to angiotensin III. Angiotensin II has vasoconstrictor and sodium-retaining activity. Angiotensin II and III both stimulate aldosterone release. Angiotensin may contribute to maintaining high vascular resistance in hypertensive states associated with high plasma renin activity, such as renal arterial stenosis, some types of intrinsic renal disease, and malignant hypertension, as well as in essential hypertension after treatment with sodium restriction, diuretics, or vasodilators. However, even in low-renin hypertensive states, these drugs can lower blood pressure (see below).

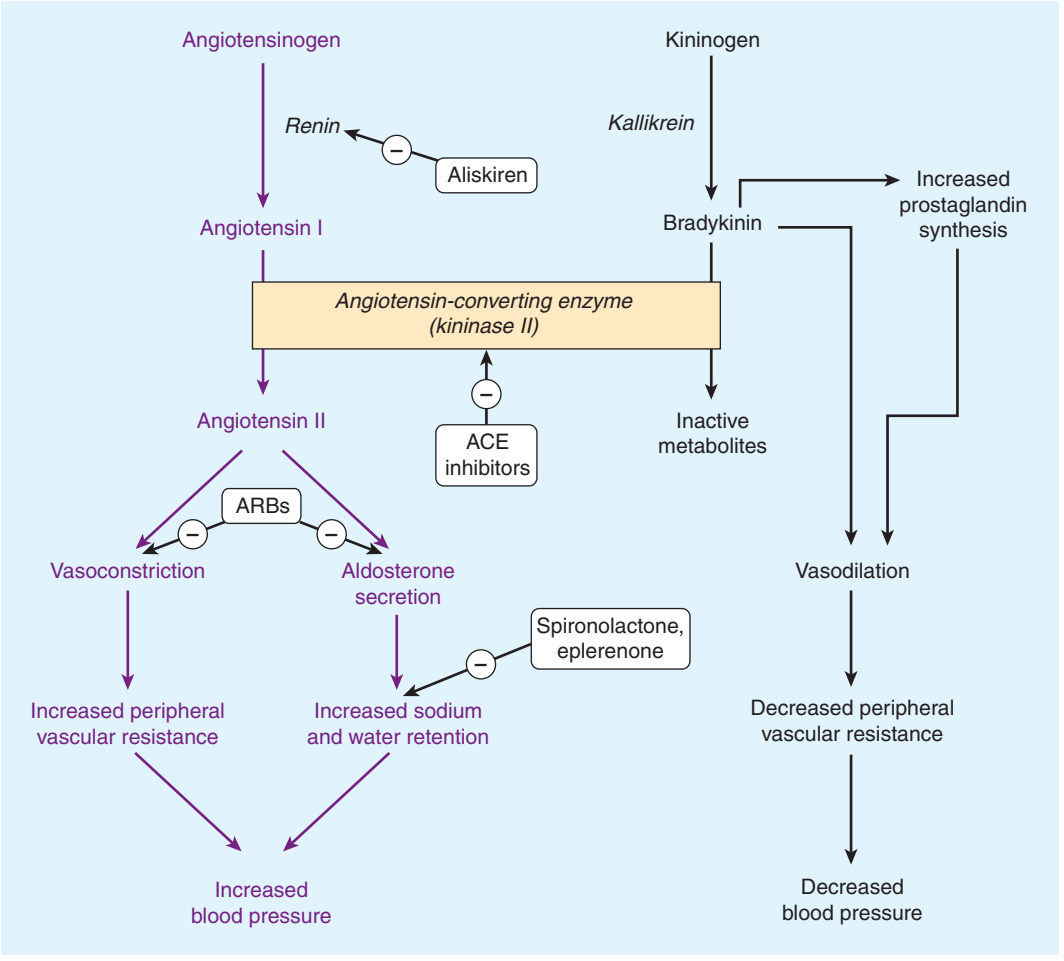


FIGURE 11–5 Sites of action of drugs that interfere with the renin-angiotensin-aldosterone system. ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers.

A parallel system for angiotensin generation exists in several other tissues (eg, heart) and may be responsible for trophic changes such as cardiac hypertrophy. The converting enzyme involved in tissue angiotensin II synthesis is also inhibited by ACE inhibitors.

Three classes of drugs act specifically on the renin-angiotensin system: ACE inhibitors; the competitive inhibitors of angiotensin at its receptors, including losartan and other nonpeptide antagonists; and aliskiren, an orally active renin antagonist (see Chapter 17). A fourth group of drugs, the aldosterone receptor inhibitors (eg, spironolactone, eplerenone) are discussed with the diuretics. In addition, β blockers, as noted earlier, can reduce renin secretion.

ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS

Captopril and other drugs in this class inhibit the converting enzyme peptidyl dipeptidase that hydrolyzes angiotensin I to angiotensin II and (under the name plasma kininase) inactivates bradykinin, a potent vasodilator, which works at least in part by stimulating release of nitric oxide and prostacyclin. The hypotensive activity of captopril results both from an inhibitory action on the renin-angiotensin system and a stimulating action on the kallikrein-kinin system (Figure 11–5). The latter mechanism has been demonstrated by showing that a bradykinin receptor antagonist, **icatibant** (see Chapter 17), blunts the blood pressure-lowering effect of captopril.

Enalapril is an oral prodrug that is converted by hydrolysis to a converting enzyme inhibitor, enalaprilat, with effects similar to those of captopril. Enalaprilat itself is available only for intravenous use, primarily for hypertensive emergencies. Lisinopril is a lysine derivative of enalaprilat. **Benazepril, fosinopril, moexipril, perindopril, quinapril, ramipril,** and **trandolapril** are other long-acting members of the class. All are prodrugs, like enalapril, and are converted to the active agents by hydrolysis, primarily in the liver.

Angiotensin II inhibitors lower blood pressure principally by decreasing peripheral vascular resistance. Cardiac output and heart rate are not significantly changed. Unlike direct vasodilators, these

agents do not result in reflex sympathetic activation and can be used safely in persons with ischemic heart disease. The absence of reflex tachycardia may be due to downward resetting of the baroreceptors or to enhanced parasympathetic activity.

Although converting enzyme inhibitors are most effective in conditions associated with high plasma renin activity, there is no good correlation among subjects between plasma renin activity and antihypertensive response. Accordingly, renin profiling is unnecessary.

ACE inhibitors have a particularly useful role in treating patients with chronic kidney disease because they diminish proteinuria and stabilize renal function (even in the absence of lowering of blood pressure). This effect is particularly valuable in diabetes, and these drugs are now recommended in diabetes even in the absence of hypertension. These benefits probably result from improved intrarenal hemodynamics, with decreased glomerular efferent arteriolar resistance and a resulting reduction of intraglomerular capillary pressure. ACE inhibitors have also proved to be extremely useful in the treatment of heart failure, and after myocardial infarction, and there is recent evidence that ACE inhibitors reduce the incidence of diabetes in patients with high cardiovascular risk (see Chapter 13).

Pharmacokinetics & Dosage

Captopril's pharmacokinetic parameters and dosing recommendations are set forth in Table 11–2. Peak concentrations of enalaprilat, the active metabolite of enalapril, occur 3–4 hours after dosing with enalapril. The half-life of enalaprilat is about 11 hours. Typical doses of enalapril are 10–20 mg once or twice daily. Lisinopril has a half-life of 12 hours. Doses of 10–80 mg once daily are effective in most patients. All of the ACE inhibitors except fosinopril and moexipril are eliminated primarily by the kidneys; doses of these drugs should be reduced in patients with renal insufficiency.

Toxicity

Severe hypotension can occur after initial doses of any ACE inhibitor in patients who are hypovolemic as a result of diuretics, salt restriction, or gastrointestinal fluid loss. Other adverse effects common to all ACE inhibitors include acute renal failure (particularly in patients with bilateral renal artery stenosis or stenosis of the renal artery of a solitary kidney), hyperkalemia, dry cough sometimes accompanied by wheezing, and angioedema. Hyperkalemia is more likely to occur in patients with renal insufficiency or diabetes. Bradykinin and substance P seem to be responsible for the cough and angioedema seen with ACE inhibition.

ACE inhibitors are contraindicated during the second and third trimesters of pregnancy because of the risk of fetal hypotension, anuria, and renal failure, sometimes associated with fetal malformations or death. Recent evidence also implicates first-trimester exposure to ACE inhibitors in increased teratogenic risk. Captopril, particularly when given in high doses to patients with renal insufficiency, may cause neutropenia or proteinuria. Minor toxic effects seen more typically include altered sense of taste, allergic skin rashes, and drug fever, which may occur in up to 10% of patients.

Important drug interactions include those with potassium supplements or potassium-sparing diuretics, which can result in hyperkalemia. Nonsteroidal anti-inflammatory drugs may impair the hypotensive effects of ACE inhibitors by blocking bradykinin-mediated vasodilation, which is at least in part, prostaglandin mediated.

ANGIOTENSIN RECEPTOR-BLOCKING AGENTS

Losartan and **valsartan** were the first marketed blockers of the angiotensin II type 1 (AT_1) receptor. **Candesartan, eprosartan, irbesartan, telmisartan,** and **olmesartan** are also available. They have no effect on bradykinin metabolism and are therefore more selective blockers of angiotensin effects than ACE inhibitors. They also have the potential for more complete inhibition of angiotensin action compared with ACE inhibitors because there are enzymes other than ACE that are capable of generating angiotensin II. Angiotensin receptor blockers provide benefits similar to those of ACE inhibitors in patients with heart failure and chronic kidney disease. Losartan's pharmacokinetic parameters are listed in Table 11–2. The adverse effects are similar to those described for ACE inhibitors, including the hazard of use during pregnancy. Cough and angioedema can occur but are less common with angiotensin receptor blockers than with ACE inhibitors.

CLINICAL PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

Hypertension presents a unique problem in therapeutics. It is usually a lifelong disease that causes few symptoms until the advanced stage. For effective treatment, medicines that may be expensive and sometimes produce adverse effects must be consumed daily. Thus, the physician must establish with certainty that hypertension is persistent and requires treatment and must exclude secondary causes of hypertension that might be treated by definitive surgical procedures. Persistence of hypertension, particularly in persons with mild elevation of blood pressure, should be established by finding an elevated blood pressure on at least three different office visits. Ambulatory blood pressure monitoring may be the best predictor of risk and therefore of need for therapy in mild hypertension. Isolated systolic hypertension and hypertension in the elderly also benefit from therapy.

Once the presence of hypertension is established, the question of whether to treat and which drugs to use must be considered. The level of blood pressure, the age of the patient, the severity of organ damage (if any) due to high blood pressure, and the presence of cardiovascular risk factors all must be considered. Assessment of renal function and the presence of proteinuria are useful in antihypertensive drug selection. At this stage, the patient

must be educated about the nature of hypertension and the importance of treatment so that he or she can make an informed decision regarding therapy.

Once the decision is made to treat, a therapeutic regimen must be developed. Selection of drugs is dictated by the level of blood pressure, the presence and severity of end organ damage, and the presence of other diseases. Severe high blood pressure with life-threatening complications requires more rapid treatment with more efficacious drugs. Most patients with essential hypertension, however, have had elevated blood pressure for months or years, and therapy is best initiated in a gradual fashion.

Education about the natural history of hypertension and the importance of treatment compliance as well as potential adverse effects of drugs is essential. Obesity should be treated and drugs that increase blood pressure (sympathomimetic decongestants, nonsteroidal anti-inflammatory drugs, oral contraceptives, and some herbal medications) should be eliminated if possible. Follow-up visits should be frequent enough to convince the patient that the physician thinks the illness is serious. With each follow-up visit, the importance of treatment should be reinforced and questions concerning dosing or side effects of medication encouraged. Other factors that may improve compliance are simplifying dosing regimens and having the patient monitor blood pressure at home.

OUTPATIENT THERAPY OF HYPERTENSION

The initial step in treating hypertension may be nonpharmacologic. As discussed previously, sodium restriction may be effective treatment for many patients with mild hypertension. The average American diet contains about 200 mEq of sodium per day. A reasonable dietary goal in treating hypertension is 70–100 mEq of sodium per day, which can be achieved by not salting food during or after cooking and by avoiding processed foods that contain large amounts of sodium. Eating a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat, and moderation of alcohol intake (no more than two drinks per day) also lower blood pressure.

Weight reduction even without sodium restriction has been shown to normalize blood pressure in up to 75% of overweight patients with mild to moderate hypertension. Regular exercise has been shown in some but not all studies to lower blood pressure in hypertensive patients.

For pharmacologic management of mild hypertension, blood pressure can be normalized in many patients with a single drug. However, most patients with hypertension require two or more antihypertensive medications (see Box: Resistant Hypertension & Polypharmacy). Thiazide diuretics, β blockers, ACE inhibitors, angiotensin receptor blockers, and calcium channel blockers have all been shown to reduce complications of hypertension and may be used for initial drug therapy. There has been concern that diuretics, by adversely affecting the serum lipid profile or impairing glucose tolerance, may add to the risk of coronary disease, thereby offsetting the benefit of blood pressure reduction. However, a recent large clinical trial comparing different classes of antihypertensive mediations for initial therapy found that chlorthalidone (a thiazide diuretic) was as effective as other agents in reducing coronary heart disease death and nonfatal myocardial infarction, and was superior to amlodipine in preventing heart failure and superior to lisinopril in preventing stroke.

The presence of concomitant disease should influence selection of antihypertensive drugs because two diseases may benefit from a single drug. For example, drugs that inhibit the renin-angiotensin system are particularly useful in patients with diabetes or evidence of chronic kidney disease with proteinuria. Beta blockers or calcium channel blockers are useful in patients who also have angina; diuretics, ACE inhibitors, angiotensin receptor blockers, β blockers or hydralazine combined with nitrates in patients who also have heart failure; and α_1 blockers in men who have benign prostatic hyperplasia. Race may also affect drug selection: African Americans respond better on average to diuretics and calcium channel blockers than to β blockers and ACE inhibitors. Ethnic Chinese patients are more sensitive to the effects of β blockers and may require lower doses.

If a single drug does not adequately control blood pressure, drugs with different sites of action can be combined to effectively lower blood pressure while minimizing toxicity ("stepped care"). If a diuretic is not used initially, it is often selected as the second drug. If three drugs are required, combining a diuretic, a sympathoplegic agent or an ACE inhibitor, and a direct vasodilator (eg, hydralazine or a calcium channel blocker) is often effective. In the USA, fixed-dose drug combinations containing a β blocker, an ACE inhibitor, or an angiotensin receptor blocker plus a thiazide, and a calcium channel blocker plus an ACE inhibitor are available. Fixed-dose combinations have the drawback of not allowing for titration of individual drug doses but have the advantage of allowing fewer pills to be taken, potentially enhancing compliance.

Assessment of blood pressure during office visits should include measurement of recumbent, sitting, and standing pressures. An attempt should be made to normalize blood pressure in the posture or activity level that is customary for the patient. The large Hypertension Optimal Treatment study suggests that the optimal blood pressure end point is 138/83 mm Hg. Lowering blood pressure below this level produces no further benefit. In diabetic patients, however, there is a continued reduction of event rates with progressively lower blood pressures. Systolic hypertension (> 140 mm Hg in the presence of normal diastolic blood pressure) is a strong cardiovascular risk factor in people older than 50 years of age and should be treated.

In addition to noncompliance with medication, causes of failure to respond to drug therapy include excessive sodium intake and inadequate diuretic therapy with excessive blood volume, and drugs such as tricyclic antidepressants, nonsteroidal anti-inflammatory drugs, over-the-counter sympathomimetics, abuse of stimulants (amphetamine or cocaine), or excessive doses of caffeine and oral contraceptives that can interfere with actions of some antihypertensive drugs or directly raise blood pressure.

MANAGEMENT OF HYPERTENSIVE EMERGENCIES

Despite the large number of patients with chronic hypertension, hypertensive emergencies are relatively rare. Marked or sudden elevation of blood pressure may be a serious threat to life, however, and prompt control of blood pressure is indicated. Most frequently, hypertensive emergencies occur in patients whose hypertension is severe and poorly controlled and in those who suddenly discontinue antihypertensive medications.

Clinical Presentation & Pathophysiology

Hypertensive emergencies include hypertension associated with vascular damage (termed malignant hypertension) and hypertension associated with hemodynamic complications such as heart failure, stroke, or dissecting aortic aneurysm. The underlying pathologic process in malignant hypertension is a progressive arteriopathy with inflammation and necrosis of arterioles. Vascular lesions occur in the kidney, which releases renin, which in turn stimulates production of angiotensin and aldosterone, which further increase blood pressure.

Hypertensive encephalopathy is a classic feature of malignant hypertension. Its clinical presentation consists of severe headache, mental confusion, and apprehension. Blurred vision, nausea and vomiting, and focal neurologic deficits are common. If untreated, the syndrome may progress over a period of 12–48 hours to convulsions, stupor, coma, and even death.

Treatment of Hypertensive Emergencies

The general management of hypertensive emergencies requires monitoring the patient in an intensive care unit with continuous recording of arterial blood pressure. Fluid intake and output must be monitored carefully and body weight measured daily as an indicator of total body fluid volume during the course of therapy.

Parenteral antihypertensive medications are used to lower blood pressure rapidly (within a few hours); as soon as reasonable blood pressure control is achieved, oral antihypertensive therapy should be substituted because this allows smoother long-term management of hypertension. The goal of treatment in the first few hours or days is not complete normalization of blood pressure because chronic hypertension is associated with autoregulatory changes in cerebral blood flow. Thus, rapid normalization of blood pressure may lead to cerebral hypoperfusion and brain injury. Rather, blood pressure should be lowered by about 25%, maintaining diastolic blood pressure at no less than 100–110 mm Hg. Subsequently, blood pressure can be reduced to normal levels using oral medications over several weeks. The drug most commonly used to treat hypertensive emergencies is the vasodilator sodium nitroprusside. Other parenteral drugs that may be effective include fenoldopam, nitroglycerin, labetalol, calcium channel blockers, diazoxide, and hydralazine. Esmolol is often used to manage intraoperative and postoperative hypertension. Diuretics such as furosemide are administered to prevent the volume expansion that typically occurs during administration of powerful vasodilators.

SUMMARY Drugs Used in Hypertension

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
DIURETICS				
• Thiazides: Hydrochlorothiazide	Block Na/Cl transporter in renal distal convoluted tubule	Reduce blood volume and poorly understood vascular effects	Hypertension, mild heart failure	
• Loop diuretics: Furosemide	Block Na/K/2Cl transporter in renal loop of Henle	Like thiazides • greater efficacy	Severe hypertension, heart failure	See Chapter 15
• Spironolactone • Eplerenone	Block aldosterone receptor in renal collecting tubule	Increase Na and decrease K excretion • poorly understood reduction in heart failure mortality	Aldosteronism, heart failure, hypertension	
SYMPATHOPLEGICS, CENTRALLY ACTING				
• Clonidine, methyl dopa	Activate α_2 adrenoceptors	Reduce central sympathetic outflow • reduce norepinephrine release from noradrenergic nerve endings	Hypertension • clonidine also used in withdrawal from abused drugs	Oral • clonidine also patch • *Toxicity:* sedation • methyldopa hemolytic anemia
SYMPATHETIC NERVE TERMINAL BLOCKERS				
• Reserpine	Blocks vesicular amine transporter in noradrenergic nerves and depletes transmitter stores	Reduce all sympathetic effects, especially cardiovascular, and reduce blood pressure	Hypertension but rarely used	Oral • long duration (days) • *Toxicity:* Reserpine: psychiatric depression, gastrointestinal disturbances
• Guanethidine	Interferes with amine release and replaces norepinephrine in vesicles	Same as reserpine	Same as reserpine	Guanethidine: Severe orthostatic hypotension • sexual dysfunction

(*continued*)

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
α BLOCKERS				
• Prazosin • Terazosin • Doxazosin	Selectively block α_1 adrenoceptors	Prevent sympathetic vasoconstriction • reduce prostatic smooth muscle tone	Hypertension • benign prostatic hyperplasia	Oral • *Toxicity:* Orthostatic hypotension
β BLOCKERS				
• Metoprolol, others • Carvedilol	Block β_1 receptors; carvedilol also blocks α receptors	Prevent sympathetic cardiac stimulation • reduce renin secretion	Hypertension • heart failure	See Chapter 10
• *Propranolol: Nonselective prototype β blocker* • *Atenolol: Very widely used β_1-selective blocker*				
VASODILATORS				
• Verapamil • Diltiazem	Nonselective block of L-type calcium channels	Reduce cardiac rate and output • reduce vascular resistance	Hypertension, angina, arrhythmias	See Chapter 12
• Nifedipine, amlodipine, other dihydropyridines	Block vascular calcium channels > cardiac calcium channels	Reduce vascular resistance	Hypertension, angina	See Chapter 12
• Hydralazine	Causes nitric oxide release	Vasodilation • reduce vascular resistance • arterioles more sensitive than veins • reflex tachycardia	Hypertension • minoxidil also used to treat hair loss	Oral • *Toxicity:* Angina, tachycardia • Hydralazine: Lupus-like syndrome
• Minoxidil	Metabolite opens K channels in vascular smooth muscle			Minoxidil: Hypertrichosis
PARENTERAL AGENTS				
• Nitroprusside • Fenoldopam • Diazoxide • Labetalol	Releases nitric oxide Activates D_1 receptors Opens K channels α, β blocker	Powerful vasodilation	Hypertensive emergencies	Parenteral • short duration • *Toxicity:* Excessive hypotension, shock
ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS				
• Captopril, many others	Inhibit angiotensin-converting enzyme	Reduce angiotensin II levels • reduce vasoconstriction and aldosterone secretion • increase bradykinin	Hypertension • heart failure, diabetes	Oral • *Toxicity:* Cough, angioedema • hyperkalemia • renal impairment • teratogenic
ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)				
• Losartan, many others	Block AT_1 angiotensin receptors	Same as ACE inhibitors but no increase in bradykinin	Hypertension • heart failure	Oral • *Toxicity:* Same as ACE inhibitors but less cough
RENIN INHIBITOR				
• Aliskiren	Inhibits enzyme activity of renin	Reduces angiotensin I and II and aldosterone	Hypertension	Oral • *Toxicity:* Hyperkalemia, renal impairment • potential teratogen

PREPARATIONS AVAILABLE

BETA-ADRENOCEPTOR BLOCKERS

Acebutolol (generic, Sectral)
Oral: 200, 400 mg capsules

Atenolol (generic, Tenormin)
Oral: 25, 50, 100 mg tablets
Parenteral: 0.5 mg/mL for injection

Betaxolol (Kerlone)
Oral: 10, 20 mg tablets

Bisoprolol (Zebeta)
Oral: 5, 10 mg tablets

Carteolol (Cartrol)
Oral: 2.5, 5 mg tablets

Carvedilol (Coreg)
Oral: 3.125, 6.25, 12.5, 25 mg tablets; 10, 20, 40, 80 mg extended-release capsules

Esmolol (BreviBloc)
Parenteral: 10, 250 mg/mL for injection

Labetalol (generic, Normodyne, Trandate)
Oral: 100, 200, 300 mg tablets
Parenteral: 5 mg/mL for injection

Metoprolol (generic, Lopressor)
Oral: 50, 100 mg tablets
Oral extended-release (Toprol-XL): 25, 50, 100, 200 mg tablets
Parenteral: 1 mg/mL for injection

Nadolol (generic, Corgard)
Oral: 20, 40, 80, 120, 160 mg tablets

Nebivolol (Bystolic)
Oral: 2.5, 5, 10 mg tablets

Penbutolol (Levatol)
Oral: 20 mg tablets

Pindolol (generic, Visken)
Oral: 5, 10 mg tablets

Propranolol (generic, Inderal)
Oral: 10, 20, 40, 60, 80, 90 mg tablets; 4, 8 mg/mL oral solution; Intensol, 80 mg/mL solution
Oral sustained-release (generic, Inderal LA): 60, 80, 120, 160 mg capsules
Parenteral: 1 mg/mL for injection

Timolol (generic, Blocadren)
Oral: 5, 10, 20 mg tablets

CENTRALLY ACTING SYMPATHOPLEGIC DRUGS

Clonidine (generic, Catapres)
Oral: 0.1, 0.2, 0.3 mg tablets
Transdermal (Catapres-TTS): patches that release 0.1, 0.2, 0.3 mg/24 h

Guanabenz (generic, Wytensin)
Oral: 4, 8 mg tablets

Guanfacine (Tenex)
Oral: 1, 2 mg tablets

Methyldopa (generic)
Oral: 250, 500 mg tablets
Parenteral (Methyldopate HCl): 50 mg/mL for injection

POSTGANGLIONIC SYMPATHETIC NERVE TERMINAL BLOCKERS

Guanadrel (Hylorel)
Oral: 10, 25 mg tablets

Guanethidine (Ismelin)
Oral: 10, 25 mg tablets

Reserpine (generic)
Oral: 0.1, 0.25 mg tablets

ALPHA$_1$–SELECTIVE ADRENOCEPTOR BLOCKERS

Doxazosin (generic, Cardura)
Oral: 1, 2, 4, 8 mg tablets

Prazosin (generic, Minipress)
Oral: 1, 2, 5 mg capsules

Terazosin (generic, Hytrin)
Oral: 1, 2, 5, 10 mg capsules and tablets

GANGLION-BLOCKING AGENTS

Mecamylamine (Inversine)
Oral: 2.5 mg tablets

VASODILATORS USED IN HYPERTENSION

Diazoxide (Hyperstat IV)
Parenteral: 15 mg/mL ampule
Oral (Proglycem): 50 mg capsule; 50 mg/mL oral suspension (for insulinoma)

Fenoldopam (generic, Corlopam)
Parenteral: 10 mg/mL for IV infusion

Hydralazine (generic, Apresoline)
Oral: 10, 25, 50, 100 mg tablets
Parenteral: 20 mg/mL for injection

Minoxidil (generic, Loniten)
Oral: 2.5, 10 mg tablets
Topical (generic, Rogaine): 2% lotion

Nitroprusside (generic, Nitropress)
Parenteral: 50 mg/vial

CALCIUM CHANNEL BLOCKERS

Amlodipine (generic, Norvasc)
Oral 2.5, 5, 10 mg tablets

Clevidipine (Cleviprex)
Parenteral: 0.5 mg/mL emulsion for injection

Diltiazem (generic, Cardizem)
Oral: 30, 60, 90, 120 mg tablets (unlabeled in hypertension)
Oral sustained-release (Cardizem CD, Cardizem SR, Dilacor XL): 60, 90, 120, 180, 240, 300, 360, 420 mg capsules
Parenteral: 5 mg/mL for injection

Felodipine (generic, Plendil)
Oral extended-release: 2.5, 5, 10 mg tablets

Isradipine (generic, DynaCirc)
Oral: 2.5, 5 mg capsules; 5, 10 mg controlled-release tablets

Nicardipine (generic, Cardene)
Oral: 20, 30 mg capsules
Oral sustained-release (Cardene SR): 30, 45, 60 mg capsules
Parenteral (Cardene I.V.): 0.1, 2.5 mg/mL for injection

Nifedipine (generic, Adalat, Procardia)
Oral: 10, 20 mg capsules (off-label use in hypertension)
Oral extended-release (Adalat CC, Procardia-XL): 30, 60, 90 mg tablets

Nisoldipine (Sular)
Oral extended-release: 8.5, 17, 25.5, 34 mg tablets

Verapamil (generic, Calan, Isoptin)
Oral: 40, 80, 120 mg tablets
Oral sustained-release (generic, Calan SR, Verelan): 120, 180, 240 mg tablets; 100, 120, 180, 200, 240, 300, 360 mg capsules
Parenteral: 2.5 mg/mL for injection

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Benazepril (generic, Lotensin)
Oral: 5, 10, 20, 40 mg tablets

Captopril (generic, Capoten)
Oral: 12.5, 25, 50, 100 mg tablets

Enalapril (generic, Vasotec)
Oral: 2.5, 5, 10, 20 mg tablets
Parenteral (Enalaprilat): 1.25 mg/mL for injection

Fosinopril (generic, Monopril)
Oral: 10, 20, 40 mg tablets

Lisinopril (generic, Prinivil, Zestril)
Oral: 2.5, 5, 10, 20, 40 mg tablets

Moexipril (generic, Univasc)
Oral: 7.5, 15 mg tablets

Perindopril (Aceon)
Oral: 2, 4, 8 mg tablets

Quinapril (Accupril)
Oral: 5, 10, 20, 40 mg tablets

Ramipril (Altace)
Oral: 1.25, 2.5, 5, 10 mg capsules

Trandolapril (Mavik)
Oral: 1, 2, 4 mg tablets

ANGIOTENSIN RECEPTOR BLOCKERS

Azilsartan (Edarbi)
Oral: 40, 80 mg tablets

Candesartan (Atacand)
Oral: 4, 8, 16, 32 mg tablets

Eprosartan (Teveten)
Oral: 600 mg tablets

Irbesartan (Avapro)
Oral: 75, 150, 300 mg tablets

Losartan (Cozaar)
Oral: 25, 50, 100 mg tablets

Olmesartan (Benicar)
Oral: 5, 20, 40 mg tablets

Telmisartan (Micardis)
Oral: 20, 40, 80 mg tablets

Valsartan (Diovan)
Oral: 40, 80, 160, 320 mg tablet

RENIN INHIBITOR

Aliskiren (Tekturna)
Oral: 150, 300 mg tablets

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CASE STUDY ANSWER

The patient has JNC stage 1 hypertension (see Table 11-1). The first question in management is how urgent is it to treat the hypertension. Cardiovascular risk factors in this man include family history of early coronary disease and elevated cholesterol. Evidence of end-organ impact includes left ventricular enlargement on EKG. The strong family history suggests that this patient has essential hypertension. However, the patient should undergo the usual screening tests including renal function, thyroid function, and serum electrolyte measurements. An echocardiogram should also be considered to determine whether the patient has left ventricular hypertrophy secondary to valvular or other structural heart disease as opposed to hypertension.

Initial management in this patient can be behavioral, including dietary changes and aerobic exercise. However, most patients like this will require medication. Thiazide diuretics in low doses are inexpensive, have relatively few side effects, and are effective in many patients with mild hypertension. Other first-line agents include angiotensin-converting enzyme inhibitors and calcium channel blockers. Beta blockers might be considered if the patient had coronary disease or had labile hypertension. A single agent should be prescribed and the patient reassessed in a month. If a second agent is needed, one of the two agents should be a thiazide diuretic. Once blood pressure is controlled, patients should be followed periodically to reinforce the need for compliance with both lifestyle changes and medications.

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CHAPTER

12

Vasodilators & the Treatment of Angina Pectoris

Bertram G. Katzung, MD, PhD*

CASE STUDY

A 74-year-old man presents with a history of anterior chest pressure whenever he walks more than one block. The chest discomfort is diffuse, and he cannot localize it; sometimes it radiates to his lower jaw. The discomfort is more severe when he walks after meals but is relieved within 5–10 minutes when he stops walking. Assuming that a diagnosis of stable effort angina is correct, what medical treatments should be implemented to reduce the acute pain of an attack and to prevent future attacks?

Ischemic heart disease is one of the most common cardiovascular disease in developed countries, and angina pectoris is the most common condition involving tissue ischemia in which vasodilator drugs are used. The name *angina pectoris* denotes chest pain caused by accumulation of metabolites resulting from myocardial ischemia. The organic nitrates, eg, **nitroglycerin,** are the mainstay of therapy for the immediate relief of angina. Another group of vasodilators, the **calcium channel blockers,** is also important, especially for prophylaxis, and β **blockers,** which are *not* vasodilators, are also useful in prophylaxis. Several newer groups of drugs are under investigation, including drugs that alter myocardial metabolism and selective cardiac rate inhibitors.

By far the most common cause of angina is atheromatous obstruction of the large coronary vessels (coronary artery disease, CAD). Inadequate blood flow in the presence of CAD results in **effort angina,** also known as **classic angina.** However, transient spasm of localized portions of these vessels, which is usually associated with underlying atheromas, can also cause significant myocardial ischemia and pain (**vasospastic** or **variant angina**). Variant angina is also called **Prinzmetal** angina.

The primary cause of angina pectoris is an imbalance between the oxygen requirement of the heart and the oxygen supplied to it via the coronary vessels. In effort angina, the imbalance occurs when the myocardial oxygen requirement increases, especially during exercise, and coronary blood flow does not increase proportionately. The resulting ischemia usually leads to pain. In fact, coronary flow reserve is frequently impaired in such patients because of endothelial dysfunction, which is associated with impaired vasodilation. As a result, ischemia may occur at a lower level of myocardial oxygen demand. In some individuals, the ischemia is not always accompanied by pain, resulting in "silent" or "ambulatory" ischemia. In variant angina, oxygen delivery decreases as a result of reversible coronary vasospasm.

Unstable angina, an **acute coronary syndrome,** is said to be present when episodes of angina occur at rest and when there is an increase in the severity, frequency, and duration of chest pain in patients with previously stable angina. Unstable angina is caused by episodes of increased epicardial coronary artery resistance or small platelet clots occurring in the vicinity of an atherosclerotic plaque. In most cases, formation of labile partially occlusive thrombi at the site of a fissured or ulcerated plaque is the mechanism for reduction in flow. The course and the prognosis of unstable angina are variable, but this subset of acute coronary syndrome is associated with a high risk of myocardial infarction and death and is considered a medical emergency.

*The author thanks Dr. Kanu Chatterjee, MB, FRCP, who was coauthor of this chapter in prior editions.

In theory, the imbalance between oxygen delivery and myocardial oxygen demand can be corrected by **decreasing oxygen demand** or by **increasing delivery** (by increasing coronary flow). In effort angina, oxygen demand can be reduced by decreasing cardiac work or, according to some studies, by shifting myocardial metabolism to substrates that require less oxygen per unit of adenosine triphosphate (ATP) produced. In variant angina, on the other hand, spasm of coronary vessels can be reversed by nitrate or calcium channel-blocking vasodilators. Lipid-lowering drugs, especially the "statins," have become extremely important in the long-term treatment of atherosclerotic disease (see Chapter 35). In unstable angina, vigorous measures are taken to achieve both—increase oxygen delivery and decrease oxygen demand.

PATHOPHYSIOLOGY OF ANGINA

Determinants of Myocardial Oxygen Demand

The major determinants of myocardial oxygen requirement are set forth in Table 12–1. The effect of arterial blood pressure is mediated through its effect on wall stress. As a consequence of its continuous activity, the heart's oxygen needs are relatively high, and it extracts approximately 75% of the available oxygen even in the absence of stress. The myocardial oxygen requirement increases when there is an increase in heart rate, contractility, arterial pressure, or ventricular volume. These hemodynamic alterations frequently occur during physical exercise and sympathetic discharge, which often precipitate angina in patients with obstructive coronary artery disease.

Drugs that reduce cardiac size, rate, or force reduce cardiac oxygen demand. Thus, vasodilators, β blockers, and calcium blockers have predictable benefits in angina. A small, late component of sodium current helps to maintain the long plateau and prolong the calcium current of myocardial action potentials. Drugs that block this late sodium current can indirectly reduce calcium influx and consequently reduce cardiac contractile force. The heart favors fatty acids as a substrate for energy production. However, oxidation of fatty acids requires more oxygen per unit of ATP generated than oxidation of carbohydrates. Therefore, drugs that shift myocardial metabolism toward greater use of glucose (fatty acid oxidation inhibitors) have the potential, at least in theory, to reduce the oxygen demand without altering hemodynamics.

TABLE 12–1 Determinants of myocardial oxygen consumption.

Wall stress
Intraventricular pressure
Ventricular radius (volume)
Wall thickness
Heart rate
Contractility

Determinants of Coronary Blood Flow & Myocardial Oxygen Supply

Increased demand for oxygen in the normal heart is met by augmenting coronary blood flow. Coronary blood flow is directly related to the perfusion pressure (aortic diastolic pressure) and the duration of diastole. Because coronary flow drops to negligible values during systole, the duration of diastole becomes a limiting factor for myocardial perfusion during tachycardia. Coronary blood flow is inversely proportional to coronary vascular resistance. Resistance is determined mainly by intrinsic factors—including metabolic products and autonomic activity—and by various pharmacologic agents. Damage to the endothelium of coronary vessels has been shown to alter their ability to dilate and to increase coronary vascular resistance.

Determinants of Vascular Tone

Peripheral arteriolar and venous tone (smooth muscle tension) both play a role in determining myocardial wall stress (Table 12–1). Arteriolar tone directly controls peripheral vascular resistance and thus arterial blood pressure. In systole, intraventricular pressure must exceed aortic pressure to eject blood; arterial blood pressure thus determines the *systolic* wall stress in an important way. Venous tone determines the capacity of the venous circulation and controls the amount of blood sequestered in the venous system versus the amount returned to the heart. Venous tone thereby determines the *diastolic* wall stress.

The regulation of smooth muscle contraction and relaxation is shown schematically in Figure 12–1. The mechanisms of action of the major types of vasodilators are listed in Table 11–2. As shown in Figures 12–1 and 12–2, drugs may relax vascular smooth muscle in several ways:

1. **Increasing cGMP:** As indicated in Figures 12–1 and 12–2, cGMP facilitates the dephosphorylation of myosin light chains, preventing the interaction of myosin with actin. **Nitric oxide** is an effective activator of soluble guanylyl cyclase and acts mainly through this mechanism. Important molecular donors of nitric oxide include **nitroprusside** (see Chapters 11 and 19) and the organic **nitrates** used in angina.
2. **Decreasing intracellular Ca^{2+}: Calcium channel blockers** predictably cause vasodilation because they reduce intracellular Ca^{2+}, a major modulator of the activation of myosin light chain kinase (Figure 12–1). **Beta blockers** and **calcium channel blockers** also reduce Ca^{2+} influx in cardiac muscle fibers, thereby reducing rate, contractility, and oxygen requirement under most circumstances.
3. **Stabilizing or preventing depolarization of the vascular smooth muscle cell membrane:** The membrane potential of excitable cells is stabilized near the resting potential by increasing potassium permeability. Potassium channel openers, such as minoxidil sulfate (see Chapter 11) increase the permeability of K^+ channels, probably ATP-dependent K^+ channels. Certain newer agents under investigation for use in angina (eg, **nicorandil**) may act, in part, by this mechanism.
4. **Increasing cAMP in vascular smooth muscle cells:** As shown in Figure 12–1, an increase in cAMP increases the rate of inactivation of myosin light chain kinase, the enzyme responsible

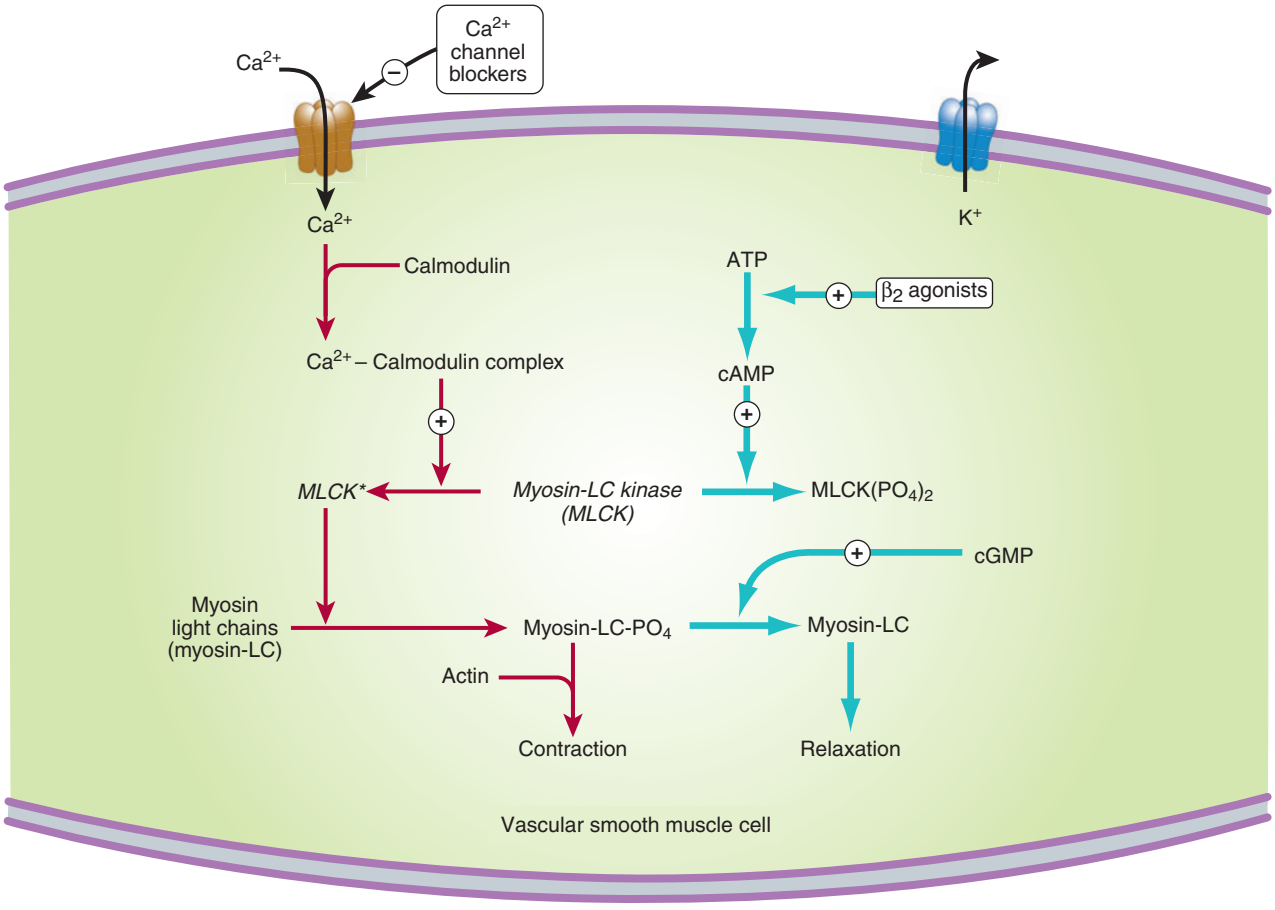


FIGURE 12–1 Control of smooth muscle contraction and site of action of calcium channel-blocking drugs. Contraction is triggered (red arrows) by influx of calcium (which can be blocked by calcium channel blockers) through transmembrane calcium channels. The calcium combines with calmodulin to form a complex that converts the enzyme myosin light-chain kinase to its active form (*MLCK**). The latter phosphorylates the myosin light chains, thereby initiating the interaction of myosin with actin. Other proteins, calponin and caldesmon (not shown), inhibit the ATPase activity of myosin during the relaxation of smooth muscle. Interaction with the Ca^{2+}-calmodulin complex reduces their interaction with myosin during the contraction cycle. Beta$_2$ agonists (and other substances that increase cAMP) may cause relaxation in smooth muscle (blue arrows) by accelerating the inactivation of MLCK and by facilitating the expulsion of calcium from the cell (not shown). cGMP facilitates relaxation by the mechanism shown in Figure 12–2.

for triggering the interaction of actin with myosin in these cells. This appears to be the mechanism of vasodilation caused by β_2 agonists, drugs that are *not* used in angina (because they cause too much cardiac stimulation), and by fenoldopam, a D_1 agonist used in hypertensive emergencies.

BASIC PHARMACOLOGY OF DRUGS USED TO TREAT ANGINA

Drug Action in Angina

The three drug groups traditionally used in angina (organic nitrates, calcium channel blockers, and β blockers) *decrease myocardial oxygen requirement* by decreasing the determinants of oxygen demand (heart rate, ventricular volume, blood pressure, and contractility). In some patients, the nitrates and the calcium channel blockers may cause a redistribution of coronary flow and *increase oxygen delivery* to ischemic tissue. In variant angina, these two drug groups also increase myocardial oxygen delivery by reversing coronary artery spasm. The newer drugs, represented by ranolazine and ivabradine, are discussed later.

NITRATES & NITRITES

Chemistry

These agents are simple nitric and nitrous acid esters of polyalcohols. **Nitroglycerin** may be considered the prototype of the group. Although nitroglycerin is used in the manufacture of dynamite, the systemic formulations used in medicine are not explosive. The conventional sublingual tablet form of nitroglycerin may lose potency when stored as a result of volatilization and adsorption to plastic surfaces. Therefore, it should be kept in tightly closed glass containers. Nitroglycerin is not sensitive to light.

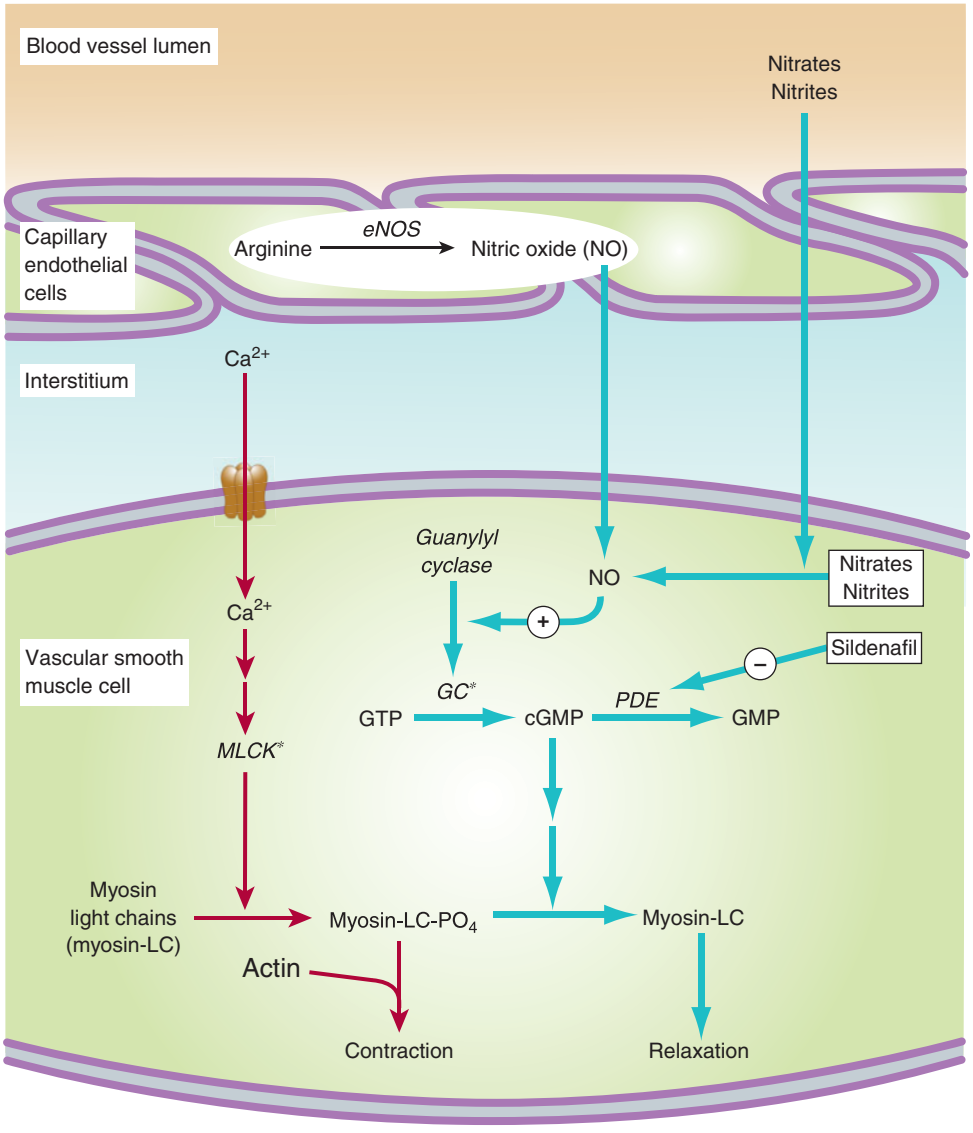
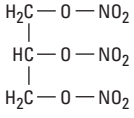


FIGURE 12–2 Mechanism of action of nitrates, nitrites, and other substances that increase the concentration of nitric oxide (NO) in vascular smooth muscle cells. Steps leading to relaxation are shown with blue arrows. MLCK*, activated myosin light-chain kinase (see Figure 12–1). GC*, activated guanylyl cyclase; PDE, phosphodiesterase; eNOS, endothelial nitric oxide synthase.

All therapeutically active agents in the nitrate group appear to have identical mechanisms of action and similar toxicities, although susceptibility to tolerance may vary. Therefore, pharmacokinetic factors govern the choice of agent and mode of therapy when using the nitrates.



Nitroglycerin (glyceryl trinitrate)

Pharmacokinetics

The liver contains a high-capacity organic nitrate reductase that removes nitrate groups in a stepwise fashion from the parent molecule and ultimately inactivates the drug. Therefore, oral bioavailability of the traditional organic nitrates (eg, nitroglycerin and **isosorbide dinitrate**) is low (typically < 10–20%). For this reason, the sublingual route, which avoids the first-pass effect, is preferred for achieving a therapeutic blood level rapidly. Nitroglycerin and isosorbide dinitrate both are absorbed efficiently by this route and reach therapeutic blood levels within a few minutes. However, the total dose administered by this route must be limited to avoid excessive effect; therefore, the total duration of effect is brief (15–30 minutes). When much longer duration of action is needed, oral preparations can be given that contain an amount of drug sufficient to result in sustained systemic blood levels of the parent drug plus active metabolites. Other routes of administration available for nitroglycerin include transdermal and buccal absorption from slow-release preparations (described below).

Amyl nitrite and related nitrites are highly volatile liquids. Amyl nitrite is available in fragile glass ampules packaged in a protective cloth covering. The ampule can be crushed with the fingers, resulting in rapid release of vapors inhalable through the cloth covering. The inhalation route provides very rapid absorption and, like the sublingual route, avoids the hepatic first-pass effect. Because of its unpleasant odor and short duration of action, amyl nitrite is now obsolete for angina.

Once absorbed, the unchanged nitrate compounds have half-lives of only 2–8 minutes. The partially denitrated metabolites have much longer half-lives (up to 3 hours). Of the nitroglycerin metabolites (two dinitroglycerins and two mononitro forms), the 1,2-dinitro derivative has significant vasodilator efficacy and probably provides most of the therapeutic effect of orally administered nitroglycerin. The 5-mononitrate metabolite of isosorbide dinitrate is an active metabolite of the latter drug and is available for oral use as **isosorbide mononitrate**. It has a bioavailability of 100%.

Excretion, primarily in the form of glucuronide derivatives of the denitrated metabolites, is largely by way of the kidney.

Pharmacodynamics

A. Mechanism of Action in Smooth Muscle

After more than a century of study, the mechanism of action of nitroglycerin is still not fully understood. There is general agreement that the drug must be bioactivated with the release of nitric oxide. Unlike nitroprusside and some other direct nitric oxide donors, nitroglycerin activation requires enzymatic action. Nitroglycerin can be denitrated by glutathione *S*-transferase in smooth muscle and other cells. A mitochondrial enzyme, aldehyde dehydrogenase isoform 2 (ALDH2) and possibly isoform 3, ALDH3, is also capable of activating nitroglycerin and releasing nitric oxide. The differential selectivity of glutathione *S*-transferase and ALDH2 for different organic nitrates suggests that the ALDH2 may be the more important enzyme for nitroglycerin bioactivation. Free nitrite ion is released, which is then converted to **nitric oxide** (see Chapter 19). Nitric oxide (probably complexed with cysteine) combines with the heme group of soluble guanylyl cyclase, activating that enzyme and causing an increase in cGMP. As shown in Figure 12–2, formation of cGMP represents a first step toward smooth muscle relaxation. The production of prostaglandin E or prostacyclin (PGI_2) and membrane hyperpolarization may also be involved. There is no evidence that autonomic receptors are involved in the primary nitrate response. However, autonomic *reflex* responses, evoked when hypotensive doses are given, are common.

As described in the following text, tolerance is an important consideration in the use of nitrates. Although tolerance may be caused in part by a decrease in tissue sulfhydryl groups, eg, on cysteine, it can be only partially prevented or reversed with a sulfhydryl-regenerating agent. Increased generation of oxygen free radicals during nitrate therapy may be another important mechanism of tolerance. Recent evidence suggests that diminished availability of calcitonin gene-related peptide (CGRP, a potent vasodilator) is also associated with nitrate tolerance.

Nicorandil and several other investigational antianginal agents appear to combine the activity of nitric oxide release with potassium channel-opening action, thus providing an additional mechanism for causing vasodilation. Nitroglycerin has not been reported to open potassium channels.

B. Organ System Effects

Nitroglycerin relaxes all types of smooth muscle regardless of the cause of the preexisting muscle tone (Figure 12–3). It has practically no direct effect on cardiac or skeletal muscle.

1. Vascular smooth muscle—All segments of the vascular system from large arteries through large veins relax in response to nitroglycerin. Most evidence suggests a gradient of response, with veins responding at the lowest concentrations, arteries at slightly higher ones. The epicardial coronary arteries are sensitive, but concentric atheromas can prevent significant dilation. On the other hand, eccentric lesions permit an increase in flow when nitrates relax the smooth muscle on the side away from the lesion. Arterioles and precapillary sphincters are dilated least, partly because of reflex responses and partly because different vessels vary in their ability to release nitric oxide from the drug.

A primary direct result of an effective dose of nitroglycerin is marked relaxation of veins with increased venous capacitance and decreased ventricular preload. Pulmonary vascular pressures and heart size are significantly reduced. In the absence of heart failure, cardiac output is reduced. Because venous capacitance is increased, orthostatic hypotension may be marked and syncope can result. Dilation of large epicardial coronary arteries may improve oxygen delivery in the presence of eccentric atheromas. Temporal artery pulsations and a throbbing headache associated with meningeal artery pulsations are common effects of nitroglycerin and amyl nitrite. In heart failure, preload is often abnormally high; the nitrates and other vasodilators, by reducing preload, may have a beneficial effect on cardiac output in this condition (see Chapter 13).

The indirect effects of nitroglycerin consist of those compensatory responses evoked by baroreceptors and hormonal mechanisms responding to decreased arterial pressure (see Figure 6–7); this often results in tachycardia and increased cardiac contractility. Retention of salt and water may also be significant, especially with intermediate- and long-acting nitrates. These compensatory responses contribute to the development of tolerance.

In normal subjects without coronary disease, nitroglycerin can induce a significant, if transient, increase in total coronary blood flow. In contrast, there is no evidence that total coronary flow is increased in patients with angina due to atherosclerotic obstructive coronary artery disease. However, some studies suggest that *redistribution* of coronary flow from normal to ischemic regions may play a role in nitroglycerin's therapeutic effect. Nitroglycerin also exerts a weak negative inotropic effect on the heart via nitric oxide.

2. Other smooth muscle organs—Relaxation of smooth muscle of the bronchi, gastrointestinal tract (including biliary system), and genitourinary tract has been demonstrated experimentally. Because of their brief duration, these actions of the

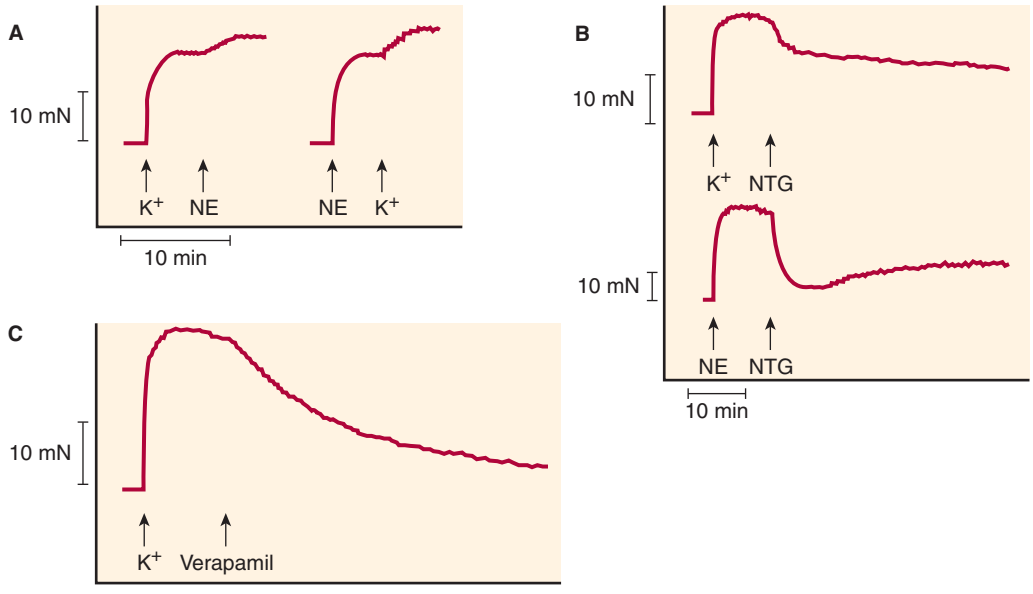


FIGURE 12–3 Effects of vasodilators on contractions of human vein segments studied in vitro. **A** shows contractions induced by two vasoconstrictor agents, norepinephrine (NE) and potassium (K^+). **B** shows the relaxation induced by nitroglycerin (NTG), 4 µmol/L. The relaxation is prompt. **C** shows the relaxation induced by verapamil, 2.2 µmol/L. The relaxation is slower but more sustained. (Modified and reproduced, with permission, from Mikkelsen E, Andersson KE, Bengtsson B: Effects of verapamil and nitroglycerin on contractile responses to potassium and noradrenaline in isolated human peripheral veins. Acta Pharmacol Toxicol 1978;42:14.)

nitrates are rarely of any clinical value. During recent decades, the use of amyl nitrite and isobutyl nitrite (not nitrates) by inhalation as recreational (sex-enhancing) drugs has become popular with some segments of the population. Nitrites readily release nitric oxide in erectile tissue as well as vascular smooth muscle and activate guanylyl cyclase. The resulting increase in cGMP causes dephosphorylation of myosin light chains and relaxation (Figure 12–2), which enhances erection. The pharmacologic approach to erectile dysfunction is are discussed in the Box: Drugs Used in the Treatment of Erectile Dysfunction.

3. Action on platelets—Nitric oxide released from nitroglycerin stimulates guanylyl cyclase in platelets as in smooth muscle. The increase in cGMP that results is responsible for a decrease in platelet aggregation. Unfortunately, recent prospective trials have established no survival benefit when nitroglycerin is used in acute myocardial infarction. In contrast, intravenous nitroglycerin may be of value in unstable angina, in part through its action on platelets.

4. Other effects—*Nitrite* ion reacts with hemoglobin (which contains ferrous iron) to produce methemoglobin (which contains ferric iron). Because methemoglobin has a very low affinity for oxygen, large doses of nitrites can result in pseudocyanosis, tissue hypoxia, and death. Fortunately, the plasma level of nitrite resulting from even large doses of organic and inorganic nitrates is too low to cause significant methemoglobinemia in adults. In nursing infants, the intestinal flora is capable of converting significant amounts of inorganic nitrate, eg, from well water, to nitrite ion. In addition, sodium nitrite is used as a curing agent for meats, eg, corned beef. Thus, inadvertent exposure to large amounts of nitrite ion can occur and may produce serious toxicity.

One therapeutic application of this otherwise toxic effect of nitrite has been discovered. Cyanide poisoning results from complexing of cytochrome iron by the CN^- ion. Methemoglobin iron has a very high affinity for CN^-; thus, administration of sodium nitrite ($NaNO_2$) soon after cyanide exposure regenerates active cytochrome. The cyanmethemoglobin produced can be further detoxified by the intravenous administration of sodium thiosulfate ($Na_2S_2O_3$); this results in formation of thiocyanate ion (SCN^-), a less toxic ion that is readily excreted. Methemoglobinemia, if excessive, can be treated by giving methylene blue intravenously. This antidotal procedure is now being replaced by hydroxocobalamin, a form of vitamin B_{12}, which also has a very high affinity for cyanide and converts it to another form of vitamin B_{12}.

Toxicity & Tolerance

A. Acute Adverse Effects

The major acute toxicities of organic nitrates are direct extensions of therapeutic vasodilation: orthostatic hypotension, tachycardia, and throbbing headache. Glaucoma, once thought to be a contraindication, does not worsen, and nitrates can be used safely in the presence of increased intraocular pressure. Nitrates are contraindicated, however, if intracranial pressure is elevated. Rarely, transdermal nitroglycerin patches have ignited when external defibrillator electroshock was applied to the chest of patients in ventricular fibrillation. Such patches should be removed before use of external defibrillators to prevent superficial burns.

Drugs Used in the Treatment of Erectile Dysfunction

Erectile dysfunction in men has long been the subject of research (by both amateur and professional scientists). Among the substances used in the past and generally discredited are "Spanish Fly" (a bladder and urethral irritant), yohimbine (an α_2 antagonist; see Chapter 10), nutmeg, and mixtures containing lead, arsenic, or strychnine. Substances currently favored by practitioners of herbal medicine but of dubious value include ginseng and kava.

Scientific studies of the process have shown that erection requires *relaxation* of the nonvascular smooth muscle of the corpora cavernosa. This relaxation permits inflow of blood at nearly arterial pressure into the sinuses of the cavernosa, and it is the pressure of the blood that causes erection. (With regard to other aspects of male sexual function, ejaculation requires intact sympathetic motor function, while orgasm involves independent superficial and deep sensory nerves.) Physiologic erection occurs in response to the release of nitric oxide from nonadrenergic-noncholinergic nerves (see Chapter 6) associated with parasympathetic discharge. Thus, parasympathetic motor innervation must be intact and nitric oxide synthesis must be active. (It appears that a similar process occurs in female erectile tissues.) Certain other smooth muscle relaxants—eg, PGE_1 analogs or α antagonists—if present in high enough concentration, can independently cause sufficient cavernosal relaxation to result in erection. As noted in the text, nitric oxide activates guanylyl cyclase, which increases the concentration of cGMP, and the latter second messenger stimulates the dephosphorylation of myosin light chains (Figure 12–2) and relaxation of the smooth muscle. Thus, any drug that increases cGMP might be of value in erectile dysfunction if normal innervation is present. **Sildenafil** (Viagra) acts to increase cGMP by inhibiting its breakdown by phosphodiesterase isoform 5 (PDE-5). The drug has been very successful in the marketplace because it can be taken orally. However, sildenafil is of little or no value in men with loss of potency due to cord injury or other damage to innervation and in men lacking libido. Furthermore, sildenafil potentiates the action of nitrates used for angina, and severe hypotension and a few myocardial infarctions have been reported in men taking both drugs. It is recommended that at least 6 hours pass between use of a nitrate and the ingestion of sildenafil. Sildenafil also has effects on color vision, causing difficulty in blue-green discrimination. Two similar PDE-5 inhibitors, **tadalafil** and **vardenafil**, are available. It is important to be aware that numerous nonprescription mail-order products that contain sildenafil analogs such as hydroxythiohomosildenafil and sulfoaildenafil have been marketed as "male enhancement" agents. These products are not approved by the FDA and incur the same risk of dangerous interactions with nitrates as the approved agents.

PDE-5 inhibitors have also been studied for possible use in other conditions. Clinical studies show distinct benefit in some patients with pulmonary arterial hypertension but not in patients with advanced idiopathic pulmonary fibrosis. The drugs have possible benefit in systemic hypertension, cystic fibrosis, and benign prostatic hyperplasia. Both sildenafil and tadalafil are currently approved for pulmonary hypertension. Preclinical studies suggest that sildenafil may be useful in preventing apoptosis and cardiac remodeling after ischemia and reperfusion.

The drug most commonly used in patients who do not respond to sildenafil is **alprostadil,** a PGE_1 analog (see Chapter 18) that can be injected directly into the cavernosa or placed in the urethra as a minisuppository, from which it diffuses into the cavernosal tissue. Phentolamine can be used by injection into the cavernosa. These drugs will cause erection in most men who do not respond to sildenafil.

B. Tolerance

With continuous exposure to nitrates, isolated smooth muscle may develop complete tolerance (tachyphylaxis), and the intact human becomes progressively more tolerant when long-acting preparations (oral, transdermal) or continuous intravenous infusions are used for more than a few hours without interruption. The mechanisms by which tolerance develops are not completely understood. As previously noted, diminished release of nitric oxide resulting from reduced bioactivation may be partly responsible for tolerance to nitroglycerin. Systemic compensation also plays a role in tolerance in the intact human. Initially, significant sympathetic discharge occurs, and after one or more days of therapy with long-acting nitrates, retention of salt and water may reverse the favorable hemodynamic changes normally caused by nitroglycerin.

Tolerance does not occur equally with all nitric oxide donors. Nitroprusside, for example, retains activity over long periods. Other organic nitrates appear to be less susceptible than nitroglycerin to the development of tolerance. In cell-free systems, soluble guanylate cyclase is inhibited, possibly by nitrosylation of the enzyme, only after prolonged exposure to exceedingly high nitroglycerin concentrations. In contrast, treatment with antioxidants that protect ALDH2 and similar enzymes appears to prevent or reduce tolerance. This suggests that tolerance is a function of diminished bioactivation of organic nitrates and to a lesser degree, a loss of soluble guanylate cyclase responsiveness to nitric oxide.

Continuous exposure to high levels of nitrates can occur in the chemical industry, especially where explosives are manufactured. When contamination of the workplace with volatile organic nitrate compounds is severe, workers find that upon starting their work

week (Monday), they suffer headache and transient dizziness ("Monday disease"). After a day or so, these symptoms disappear owing to the development of tolerance. Over the weekend, when exposure to the chemicals is reduced, tolerance disappears, so symptoms recur each Monday. Other hazards of industrial exposure, including dependence, have been reported. There is no evidence that physical dependence develops as a result of the *therapeutic* use of short-acting nitrates for angina, even in large doses.

C. Carcinogenicity of Nitrate and Nitrite Derivatives

Nitrosamines are small molecules with the structure R_2–N–NO formed from the combination of nitrates and nitrites with amines. Some nitrosamines are powerful carcinogens in animals, apparently through conversion to reactive derivatives. Although there is no direct proof that these agents cause cancer in humans, there is a strong epidemiologic correlation between the incidence of esophageal and gastric carcinoma and the nitrate content of food in certain cultures. Nitrosamines are also found in tobacco and in cigarette smoke. There is no evidence that the small doses of nitrates used in the treatment of angina result in significant body levels of nitrosamines.

Mechanisms of Clinical Effect

The beneficial and deleterious effects of nitrate-induced vasodilation are summarized in Table 12–2.

A. Nitrate Effects in Angina of Effort

Decreased venous return to the heart and the resulting reduction of intracardiac volume are important beneficial hemodynamic effects of nitrates. Arterial pressure also decreases. Decreased intraventricular pressure and left ventricular volume are associated with decreased wall tension (Laplace relation) and decreased myocardial oxygen requirement. In rare instances, a paradoxical *increase* in myocardial oxygen demand may occur as a result of excessive reflex tachycardia and increased contractility.

Intracoronary, intravenous, or sublingual nitrate administration consistently increases the caliber of the large epicardial coronary arteries except where blocked by concentric atheromas. Coronary arteriolar resistance tends to decrease, though to a lesser extent. However, nitrates administered by the usual systemic routes may *decrease* overall coronary blood flow (and myocardial oxygen consumption) if cardiac output is reduced due to decreased venous return. The reduction in oxygen consumption is the major mechanism for the relief of effort angina.

TABLE 12–2 Beneficial and deleterious effects of nitrates in the treatment of angina.

Effect	Result
Potential beneficial effects	
Decreased ventricular volume Decreased arterial pressure Decreased ejection time	Decreased myocardial oxygen requirement
Vasodilation of epicardial coronary arteries	Relief of coronary artery spasm
Increased collateral flow	Improved perfusion to ischemic myocardium
Decreased left ventricular diastolic pressure	Improved subendocardial perfusion
Potential deleterious effects	
Reflex tachycardia	Increased myocardial oxygen requirement
Reflex increase in contractility	Increased myocardial oxygen requirement
Decreased diastolic perfusion time due to tachycardia	Decreased coronary perfusion

B. Nitrate Effects in Variant Angina

Nitrates benefit patients with variant angina by relaxing the smooth muscle of the epicardial coronary arteries and relieving coronary artery spasm.

C. Nitrate Effects in Unstable Angina

Nitrates are also useful in the treatment of the acute coronary syndrome of unstable angina, but the precise mechanism for their beneficial effects is not clear. Because both increased coronary vascular tone and increased myocardial oxygen demand can precipitate rest angina in these patients, nitrates may exert their beneficial effects both by dilating the epicardial coronary arteries and by simultaneously reducing myocardial oxygen demand. As previously noted, nitroglycerin also decreases platelet aggregation, and this effect may be of importance in unstable angina.

Clinical Use of Nitrates

Some of the forms of nitroglycerin and its congeners are listed in Table 12–3. Because of its rapid onset of action (1–3 minutes), sublingual nitroglycerin is the most frequently used agent for the immediate treatment of angina. Because its duration of action is short (not exceeding 20–30 minutes), it is not suitable for maintenance therapy. The onset of action of intravenous nitroglycerin is also rapid (minutes), but its hemodynamic effects are quickly reversed when the infusion is stopped. Clinical use of intravenous nitroglycerin is therefore restricted to the treatment of severe, recurrent rest angina. Slowly absorbed preparations of nitroglycerin include a buccal form, oral preparations, and several transdermal forms. These formulations have been shown to provide blood concentrations for long periods but, as noted above, this leads to the development of tolerance.

The hemodynamic effects of sublingual or chewable isosorbide dinitrate and the oral organic nitrates are similar to those of nitroglycerin given by the same route. The recommended dosage schedules for commonly used long-acting nitrate preparations, along with their durations of action, are listed in Table 12–3. Although transdermal administration may provide blood levels of nitroglycerin for 24 hours or longer, the full hemodynamic effects usually do not persist for more than 6–8 hours. The clinical efficacy of

TABLE 12–3 Nitrate and nitrite drugs used in the treatment of angina.

Drug	Dose	Duration of Action
Short-acting		
Nitroglycerin, sublingual	0.15–1.2 mg	10–30 minutes
Isosorbide dinitrate, sublingual	2.5–5 mg	10–60 minutes
Amyl nitrite, inhalant	0.18–0.3 mL	3–5 minutes
Long-acting		
Nitroglycerin, oral sustained-action	6.5–13 mg per 6–8 hours	6–8 hours
Nitroglycerin, 2% ointment, transdermal	1–1.5 inches per 4 hours	3–6 hours
Nitroglycerin, slow-release, buccal	1–2 mg per 4 hours	3–6 hours
Nitroglycerin, slow-release patch, transdermal	10–25 mg per 24 hours (one patch per day)	8–10 hours
Isosorbide dinitrate, sublingual	2.5–10 mg per 2 hours	1.5–2 hours
Isosorbide dinitrate, oral	10–60 mg per 4–6 hours	4–6 hours
Isosorbide dinitrate, chewable oral	5–10 mg per 2–4 hours	2–3 hours
Isosorbide mononitrate, oral	20 mg per 12 hours	6–10 hours

slow-release forms of nitroglycerin in maintenance therapy of angina is thus limited by the development of significant tolerance. Therefore, a nitrate-free period of at least 8 hours between doses should be observed to reduce or prevent tolerance.

OTHER NITRO-VASODILATORS

Nicorandil is a nicotinamide nitrate ester that has vasodilating properties in normal coronary arteries but more complex effects in patients with angina. Clinical studies suggest that it reduces both preload and afterload. It also provides some myocardial protection via preconditioning by activation of cardiac K_{ATP} channels. One large trial showed a significant reduction in relative risk of fatal and nonfatal coronary events in patients receiving the drug. Nicorandil is currently approved for use in the treatment of angina in Europe and Japan and has been submitted for approval in the USA.

CALCIUM CHANNEL-BLOCKING DRUGS

It has been known since the late 1800s that transmembrane calcium influx is necessary for the contraction of smooth and cardiac muscle. The discovery of a calcium channel in cardiac muscle was followed by the finding of several different types of calcium channels in different tissues (Table 12–4). The discovery of these channels made possible the measurement of the calcium current, I_{Ca}, and subsequently, the development of clinically useful blocking

TABLE 12–4 Properties of several recognized voltage-activated calcium channels.

Type	Channel Name	Where Found	Properties of the Calcium Current	Blocked By
L	$Ca_V1.1$–$Ca_V1.4$	Cardiac, skeletal, smooth muscle, neurons ($Ca_V1.4$ is found in retina), endocrine cells, bone	Long, large, high threshold	Verapamil, DHPs, Cd^{2+}, ω-aga-IIIA
T	$Ca_V3.1$–$Ca_V3.3$	Heart, neurons	Short, small, low threshold	sFTX, flunarizine, Ni^{2+} ($Ca_V3.2$ only), mibefradil[1]
N	$Ca_V2.2$	Neurons, sperm[2]	Short, high threshold	Ziconotide,[3] gabapentin,[4] ω-CTXGVIA, ω-aga-IIIA, Cd^{2+}
P/Q	$Ca_V2.1$	Neurons	Long, high threshold	ω-CTX-MVIIC, ω-aga-IVA
R	$Ca_V2.3$	Neurons, sperm[2]	Pacemaking	SNX-482, ω-aga-IIIA

[1]Antianginal drug withdrawn from market.

[2]Channel types associated with sperm flagellar activity may be of the Catsper1–4 variety.

[3]Synthetic snail peptide analgesic (see Chapter 31).

[4]Antiseizure agent (see Chapter 24).

DHPs, dihydropyridines (eg, nifedipine); sFTX, synthetic funnel web spider toxin; ω-CTX, conotoxins extracted from several marine snails of the genus *Conus;* ω-aga-IIIA and ω-aga-IVA, toxins of the funnel web spider, *Agelenopsis aperta;* SNX-482, a toxin of the African tarantula, *Hysterocrates gigas.*

TABLE 12–5 Clinical pharmacology of some calcium channel-blocking drugs.

Drug	Oral Bioavailability (%)	Half-life (hours)	Indication	Dosage
Dihydropyridines				
Amlodipine	65–90	30–50	Angina, hypertension	5–10 mg orally once daily
Felodipine	15–20	11–16	Hypertension, Raynaud's phenomenon	5–10 mg orally once daily
Isradipine	15–25	8	Hypertension	2.5–10 mg orally twice daily
Nicardipine	35	2–4	Angina, hypertension	20–40 mg orally every 8 hours
Nifedipine	45–70	4	Angina, hypertension, Raynaud's phenomenon	3–10 mcg/kg IV; 20–40 mg orally every 8 hours
Nisoldipine	< 10	6–12	Hypertension	20–40 mg orally once daily
Nitrendipine	10–30	5–12	Investigational	20 mg orally once or twice daily
Miscellaneous				
Diltiazem	40–65	3–4	Angina, hypertension, Raynaud's phenomenon	75–150 mcg/kg IV; 30–80 mg orally every 6 hours
Verapamil	20–35	6	Angina, hypertension, arrhythmias, migraine	75–150 mcg/kg IV; 80–160 mg orally every 8 hours

drugs. Although the blockers currently available for clinical use in cardiovascular conditions are exclusively L-type calcium channel blockers, selective blockers of other types of calcium channels are under intensive investigation. Certain antiseizure drugs are thought to act, at least in part, through calcium channel (especially T-type) blockade in neurons (see Chapter 24).

Chemistry & Pharmacokinetics

Verapamil, the first clinically useful member of this group, was the result of attempts to synthesize more active analogs of papaverine, a vasodilator alkaloid found in the opium poppy. Since then, dozens of agents of varying structure have been found to have the same fundamental pharmacologic action (Table 12–5). Three chemically dissimilar calcium channel blockers are shown in Figure 12–4. Nifedipine is the prototype of the dihydropyridine family of calcium channel blockers; dozens of molecules in this family have been investigated, and several are currently approved in the USA for angina and other indications. Nifedipine is the most extensively studied of this group, but the properties of the other dihydropyridines can be assumed to be similar to it unless otherwise noted.

The calcium channel blockers are orally active agents and are characterized by high first-pass effect, high plasma protein binding, and extensive metabolism. Verapamil and diltiazem are also used by the intravenous route.

Pharmacodynamics

A. Mechanism of Action

The voltage-gated L-type calcium channel is the dominant type in cardiac and smooth muscle and is known to contain several drug receptors. It consists of $\alpha 1$ (the larger, pore-forming subunit), $\alpha 2$, β, γ, and δ subunits. Four variant $\alpha 1$ subunits have been recognized. Nifedipine and other dihydropyridines have been demonstrated to bind to one site on the $\alpha 1$ subunit, whereas verapamil and diltiazem appear to bind to closely related but not identical receptors in another region of the same subunit. Binding of a drug to the verapamil or diltiazem receptors allosterically affects dihydropyridine binding. These receptor regions are stereoselective, since marked differences in both stereoisomer-binding affinity and pharmacologic potency are observed for enantiomers of verapamil, diltiazem, and optically active nifedipine congeners.

Blockade of calcium channels by these drugs resembles that of sodium channel blockade by local anesthetics (see Chapters 14 and 26). The drugs act from the inner side of the membrane and bind more effectively to open channels and inactivated channels. Binding of the drug reduces the frequency of opening in response to depolarization. The result is a marked decrease in transmembrane calcium current, which in smooth muscle results in long-lasting relaxation (Figure 12–3) and in cardiac muscle results in reduction in contractility throughout the heart and decreases in sinus node pacemaker rate and atrioventricular node conduction velocity.* Although some neuronal cells harbor L-type calcium channels, their sensitivity to these drugs is lower because the channels in these cells spend less time in the open and inactivated states.

Smooth muscle responses to calcium influx through *ligand-gated* calcium channels are also reduced by these drugs but not as markedly. The block can be partially reversed by elevating the concentration of calcium, although the levels of calcium required are not easily attainable in patients. Block can also be partially

*At very low doses and under certain circumstances, some dihydropyridines increase calcium influx. Some special dihydropyridines, eg, Bay K 8644, actually increase calcium influx over most of their dose range.

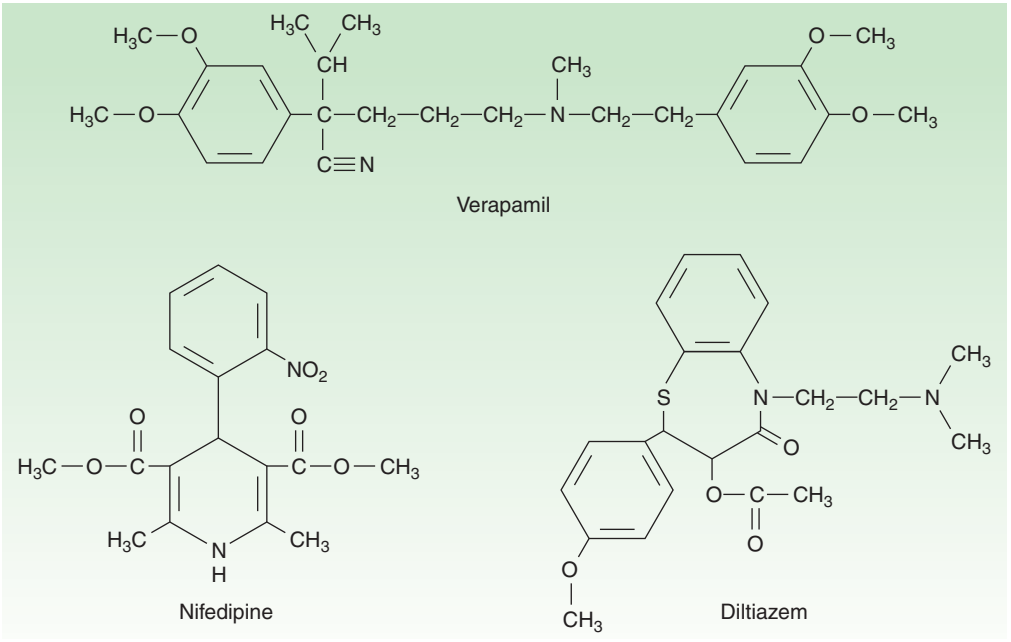


FIGURE 12–4 Chemical structures of several calcium channel-blocking drugs.

reversed by the use of drugs that increase the transmembrane flux of calcium, such as sympathomimetics.

Other types of calcium channels are less sensitive to blockade by these calcium channel blockers (Table 12–4). Therefore, tissues in which these other channel types play a major role—neurons and most secretory glands—are much less affected by these drugs than are cardiac and smooth muscle. **Mibefradil** is a selective T-type calcium channel blocker that was introduced for antiarrhythmic use but has been withdrawn. Ion channels other than calcium channels are much less sensitive to these drugs. Potassium channels in vascular smooth muscle are inhibited by verapamil, thus limiting the vasodilation produced by this drug. Sodium channels as well as calcium channels are blocked by **bepridil,** an obsolete antiarrhythmic drug.

B. Organ System Effects

1. Smooth muscle—Most types of smooth muscle are dependent on transmembrane calcium influx for normal resting tone and contractile responses. These cells are relaxed by the calcium channel blockers (Figure 12–3). Vascular smooth muscle appears to be the most sensitive, but similar relaxation can be shown for bronchiolar, gastrointestinal, and uterine smooth muscle. In the vascular system, arterioles appear to be more sensitive than veins; orthostatic hypotension is not a common adverse effect. Blood pressure is reduced with all calcium channel blockers (see Chapter 11). Women may be more sensitive than men to the hypotensive action of diltiazem. The reduction in peripheral vascular resistance is one mechanism by which these agents may benefit the patient with angina of effort. Reduction of coronary artery spasm has been demonstrated in patients with variant angina.

Important differences in vascular selectivity exist among the calcium channel blockers. In general, the dihydropyridines have a greater ratio of vascular smooth muscle effects relative to cardiac effects than do diltiazem and verapamil. The relatively smaller effect of verapamil on vasodilation may be the result of simultaneous blockade of vascular smooth muscle potassium channels described earlier. Furthermore, the dihydropyridines may differ in their potency in different vascular beds. For example, **nimodipine** is claimed to be particularly selective for cerebral blood vessels. Splice variants in the structure of the $\alpha 1$ channel subunit appear to account for these differences.

2. Cardiac muscle—Cardiac muscle is highly dependent on calcium influx during each action potential for normal function. Impulse generation in the sinoatrial node and conduction in the atrioventricular node—so-called slow-response, or calcium-dependent, action potentials—may be reduced or blocked by all of the calcium channel blockers. Excitation-contraction coupling in all cardiac cells requires calcium influx, so these drugs reduce cardiac contractility in a dose-dependent fashion. In some cases, cardiac output may also decrease. This reduction in cardiac mechanical function is another mechanism by which the calcium channel blockers can reduce the oxygen requirement in patients with angina.

Important differences between the available calcium channel blockers arise from the details of their interactions with cardiac ion channels and, as noted above, differences in their relative smooth muscle versus cardiac effects. Sodium channel block is modest with verapamil, and still less marked with diltiazem. It is negligible with nifedipine and other dihydropyridines. Verapamil and diltiazem interact kinetically with the calcium channel receptor in a different manner than the dihydropyridines; they block tachycardias in

calcium-dependent cells, eg, the atrioventricular node, more selectively than do the dihydropyridines. (See Chapter 14 for additional details.) On the other hand, the dihydropyridines appear to block smooth muscle calcium channels at concentrations below those required for significant cardiac effects; they are therefore less depressant on the heart than verapamil or diltiazem.

3. Skeletal muscle—Skeletal muscle is not depressed by the calcium channel blockers because it uses intracellular pools of calcium to support excitation-contraction coupling and does not require as much transmembrane calcium influx.

4. Cerebral vasospasm and infarct following subarachnoid hemorrhage—Nimodipine, a member of the dihydropyridine group of calcium channel blockers, has a high affinity for cerebral blood vessels and appears to reduce morbidity after a subarachnoid hemorrhage. Nimodipine was approved for use in patients who have had a hemorrhagic stroke, but it has recently been withdrawn. **Nicardipine** has similar effects and is used by intravenous and intracerebral arterial infusion to prevent cerebral vasospasm associated with stroke. Verapamil as well, despite its lack of vasoselectivity, is used by the intra-arterial route in stroke. Some evidence suggests that calcium channel blockers may also reduce cerebral damage after thromboembolic stroke.

5. Other effects—Calcium channel blockers minimally interfere with stimulus-secretion coupling in glands and nerve endings because of differences between calcium channel type and sensitivity in different tissues. Verapamil has been shown to inhibit insulin release in humans, but the dosages required are greater than those used in management of angina and other cardiovascular conditions.

A significant body of evidence suggests that the calcium channel blockers may interfere with platelet aggregation in vitro and prevent or attenuate the development of atheromatous lesions in animals. However, clinical studies have not established their role in human blood clotting and atherosclerosis.

Verapamil has been shown to block the P-glycoprotein responsible for the transport of many foreign drugs out of cancer (and other) cells (see Chapter 1); other calcium channel blockers appear to have a similar effect. This action is not stereospecific. Verapamil has been shown to partially reverse the resistance of cancer cells to many chemotherapeutic drugs in vitro. Some clinical results suggest similar effects in patients (see Chapter 54). Animal research suggests possible future roles of calcium blockers in the treatment of osteoporosis, fertility disorders and male contraception, immune modulation, and even schistosomiasis. Verapamil does not appear to block transmembrane divalent metal ion transporters such as DMT1.

Toxicity

The most important toxic effects reported for calcium channel blockers are direct extensions of their therapeutic action. Excessive inhibition of calcium influx can cause serious cardiac depression, including bradycardia, atrioventricular block, cardiac arrest, and heart failure. These effects have been rare in clinical use.

Retrospective case-control studies reported that immediate-acting nifedipine increased the risk of myocardial infarction in patients with hypertension. Slow-release and long-acting dihydropyridine calcium channel blockers are usually well tolerated. However, dihydropyridines, compared with angiotensin-converting enzyme (ACE) inhibitors, have been reported to increase the risk of adverse cardiac events in patients with hypertension with or without diabetes. These results suggest that relatively short-acting calcium channel blockers such as prompt-release nifedipine have the potential to enhance the risk of adverse cardiac events and should be avoided. Patients receiving β-blocking drugs are more sensitive to the cardiodepressant effects of calcium channel blockers. Minor toxicities (troublesome but not usually requiring discontinuance of therapy) include flushing, dizziness, nausea, constipation, and peripheral edema. Constipation is particularly common with verapamil.

Mechanisms of Clinical Effects

Calcium channel blockers decrease myocardial contractile force, which reduces myocardial oxygen requirements. Calcium channel block in arterial smooth muscle decreases arterial and intraventricular pressure. Some of these drugs (eg, verapamil, diltiazem) also possess a nonspecific antiadrenergic effect, which may contribute to peripheral vasodilation. As a result of all of these effects, left ventricular wall stress declines, which reduces myocardial oxygen requirements. Decreased heart rate with the use of verapamil or diltiazem causes a further decrease in myocardial oxygen demand. Calcium channel-blocking agents also relieve and prevent focal coronary artery spasm in variant angina. Use of these agents has thus emerged as the most effective prophylactic treatment for this form of angina pectoris.

Sinoatrial and atrioventricular nodal tissues, which are mainly composed of calcium-dependent, slow-response cells, are affected markedly by verapamil, moderately by diltiazem, and much less by dihydropyridines. Thus, verapamil and diltiazem decrease atrioventricular nodal conduction and are often effective in the management of supraventricular reentry tachycardia and in decreasing ventricular responses in atrial fibrillation or flutter. Nifedipine does not affect atrioventricular conduction. Nonspecific sympathetic antagonism is most marked with diltiazem and much less with verapamil. Nifedipine does not appear to have this effect. Significant reflex tachycardia in response to hypotension occurs most frequently with nifedipine and less so with diltiazem and verapamil. These differences in pharmacologic effects should be considered in selecting calcium channel-blocking agents for the management of angina.

Clinical Uses of Calcium Channel-Blocking Drugs

In addition to angina, calcium channel blockers have well-documented efficacy in hypertension (see Chapter 11) and supraventricular tachyarrhythmias (see Chapter 14). They also show moderate efficacy in a variety of other conditions, including hypertrophic

cardiomyopathy, migraine, and Raynaud's phenomenon. Nifedipine has some efficacy in preterm labor but is more toxic and not as effective as **atosiban,** an investigational oxytocin antagonist (see Chapter 17).

The pharmacokinetic properties of these drugs are set forth in Table 12–5. The choice of a particular calcium channel-blocking agent should be made with knowledge of its specific potential adverse effects as well as its pharmacologic properties. Nifedipine does not decrease atrioventricular conduction and therefore can be used more safely than verapamil or diltiazem in the presence of atrioventricular conduction abnormalities. A combination of verapamil or diltiazem with β blockers may produce atrioventricular block and depression of ventricular function. In the presence of overt heart failure, all calcium channel blockers can cause further worsening of failure as a result of their negative inotropic effect. **Amlodipine,** however, does not increase mortality in patients with heart failure due to nonischemic left ventricular systolic dysfunction and can be used safely in these patients.

In patients with relatively low blood pressure, dihydropyridines can cause further deleterious lowering of pressure. Verapamil and diltiazem appear to produce less hypotension and may be better tolerated in these circumstances. In patients with a history of atrial tachycardia, flutter, and fibrillation, verapamil and diltiazem provide a distinct advantage because of their antiarrhythmic effects. In the patient receiving digitalis, verapamil should be used with caution, because it may increase digoxin blood levels through a pharmacokinetic interaction. Although increases in digoxin blood level have also been demonstrated with diltiazem and nifedipine, such interactions are less consistent than with verapamil.

In patients with unstable angina, immediate-release short-acting calcium channel blockers can increase the risk of adverse cardiac events and therefore are contraindicated (see Toxicity, above). However, in patients with non–Q-wave myocardial infarction, diltiazem can decrease the frequency of postinfarction angina and may be used.

BETA-BLOCKING DRUGS

Although they are not vasodilators (with the exception of carvedilol and nebivolol), β-blocking drugs (see Chapter 10) are extremely useful in the management of effort angina. The beneficial effects of β-blocking agents are related to their hemodynamic effects—decreased heart rate, blood pressure, and contractility—which decrease myocardial oxygen requirements at rest and during exercise. Lower heart rate is also associated with an increase in diastolic perfusion time that may increase coronary perfusion. However, reduction of heart rate and blood pressure, and consequently decreased myocardial oxygen consumption, appear to be the most important mechanisms for relief of angina and improved exercise tolerance. Beta blockers may also be valuable in treating silent or ambulatory ischemia. Because this condition causes no pain, it is usually detected by the appearance of typical electrocardiographic signs of ischemia. The total amount of "ischemic time" per day is reduced by long-term therapy with a β blocker. Beta-blocking agents decrease mortality of patients with recent myocardial infarction and improve survival and prevent stroke in patients with hypertension. Randomized trials in patients with stable angina have shown better outcome and symptomatic improvement with β blockers compared with calcium channel blockers.

Undesirable effects of β-blocking agents in angina include an increase in end-diastolic volume and an increase in ejection time, both of which tend to increase myocardial oxygen requirement. These deleterious effects of β-blocking agents can be balanced by the concomitant use of nitrates as described below.

Contraindications to the use of β blockers are asthma and other bronchospastic conditions, severe bradycardia, atrioventricular blockade, bradycardia-tachycardia syndrome, and severe unstable left ventricular failure. Potential complications include fatigue, impaired exercise tolerance, insomnia, unpleasant dreams, worsening of claudication, and erectile dysfunction.

NEWER ANTIANGINAL DRUGS

Because of the high prevalence of angina, new drugs are actively sought for its treatment. Some of the drugs or drug groups currently under investigation are listed in Table 12–6.

Ranolazine is a newer antianginal drug that appears to act by reducing a late sodium current (I_{Na}) that facilitates calcium entry via the sodium-calcium exchanger (see Chapter 13). The resulting reduction in intracellular calcium concentration reduces cardiac contractility and work. Ranolazine is approved for use in angina in the USA.

Certain metabolic modulators (eg, **trimetazidine**) are known as **pFOX inhibitors** because they partially inhibit the fatty acid oxidation pathway in myocardium. Because metabolism shifts to oxidation of fatty acids in ischemic myocardium, the oxygen requirement per unit of ATP produced increases. Partial inhibition of the enzyme

TABLE 12–6 New drugs or drug groups under investigation for use in angina.

Drugs
Amiloride
Capsaicin
Direct bradycardic agents, eg, ivabradine
Inhibitors of slowly inactivating sodium current, eg, ranolazine
Metabolic modulators, eg, trimetazidine
Nitric oxide donors, eg, L-arginine
Potassium channel activators, eg, nicorandil
Protein kinase G facilitators, eg, detanonoate
Rho-kinase inhibitors, eg, fasudil
Sulfonylureas, eg, glibenclamide
Thiazolidinediones
Vasopeptidase inhibitors
Xanthine oxidase inhibitors, eg, allopurinol

required for fatty acid oxidation (long-chain 3-ketoacyl thiolase, LC-3KAT) appears to improve the metabolic status of ischemic tissue. (Ranolazine was initially assigned to this group of agents.). Trimetazidine is not approved for use in angina in the USA. A much older drug, **allopurinol,** represents another type of metabolic modifier. Allopurinol inhibits xanthine oxidase (see Chapter 36), an enzyme that contributes to oxidative stress and endothelial dysfunction. A recent study suggests that high-dose allopurinol prolongs exercise time in patients with atherosclerotic angina.

So-called *bradycardic* drugs, relatively selective I_f sodium channel blockers (eg, **ivabradine**), reduce cardiac rate by inhibiting the hyperpolarization-activated sodium channel in the sinoatrial node. No other significant hemodynamic effects have been reported. Ivabradine appears to reduce anginal attacks with an efficacy similar to that of calcium channel blockers and β blockers. The lack of effect on gastrointestinal and bronchial smooth muscle is an advantage of ivabradine, and Food and Drug Administration approval is expected.

The Rho kinases comprise a family of enzymes that inhibit vascular relaxation and diverse functions of several other cell types. Excessive activity of these enzymes has been implicated in coronary spasm, pulmonary hypertension, apoptosis, and other conditions. Drugs targeting the enzyme have therefore been sought for possible clinical applications. **Fasudil** is an inhibitor of smooth muscle Rho kinase and reduces coronary vasospasm in experimental animals. In clinical trials in patients with CAD, it has improved performance in stress tests.

CLINICAL PHARMACOLOGY OF DRUGS USED TO TREAT ANGINA

Because the most common cause of angina is atherosclerotic disease of the coronaries (CAD), therapy must address the underlying causes of CAD as well as the immediate symptoms of angina. In addition to reducing the need for antianginal therapy, such primary management has been shown to reduce major cardiac events such as myocardial infarction.

First-line therapy of CAD depends on modification of risk factors such as smoking, hypertension (see Chapter 11), hyperlipidemia (see Chapter 35), obesity, and clinical depression. In addition, antiplatelet drugs (see Chapter 34) are very important.

Specific pharmacologic therapy to prevent myocardial infarction and death consists of antiplatelet agents (aspirin, ADP receptor blockers, Chapter 34) and lipid-lowering agents, especially statins (Chapter 35). Aggressive therapy with statins has been shown to reduce the incidence and severity of ischemia in patients during exercise testing and the incidence of cardiac events (including infarction and death) in clinical trials. ACE inhibitors also reduce the risk of adverse cardiac events in patients at high risk for CAD, although they have not been consistently shown to exert antianginal effects. In patients with unstable angina and non-ST-segment elevation myocardial infarction, aggressive therapy consisting of coronary stenting, antilipid drugs, heparin, and antiplatelet agents is recommended.

The treatment of established angina and other manifestations of myocardial ischemia includes the corrective measures previously described as well as treatment to prevent or relieve symptoms. Treatment of symptoms is based on reduction of myocardial oxygen demand and increase of coronary blood flow to the potentially ischemic myocardium to restore the balance between myocardial oxygen supply and demand.

Angina of Effort

Many studies have demonstrated that nitrates, calcium channel blockers, and β blockers increase time to onset of angina and ST depression during treadmill tests in patients with angina of effort (Figure 12–5). Although exercise tolerance increases, there is usually no change in the angina threshold, ie, the rate-pressure product at which symptoms occur.

For maintenance therapy of chronic stable angina, long-acting nitrates, calcium channel-blocking agents, or β blockers may be chosen; the drug of choice depends on the individual patient's response. In hypertensive patients, monotherapy with either slow-release or long-acting calcium channel blockers or β blockers may be adequate. In normotensive patients, long-acting nitrates may be suitable. The combination of a β blocker with a calcium channel blocker (eg, propranolol with nifedipine) or two different calcium channel blockers (eg, nifedipine and verapamil) has been shown to be more effective than individual drugs used alone. If response to a single drug is inadequate, a drug from a different class should be added to maximize the beneficial reduction of cardiac work while minimizing undesirable effects (Table 12–7). Some patients may require therapy with all three drug groups.

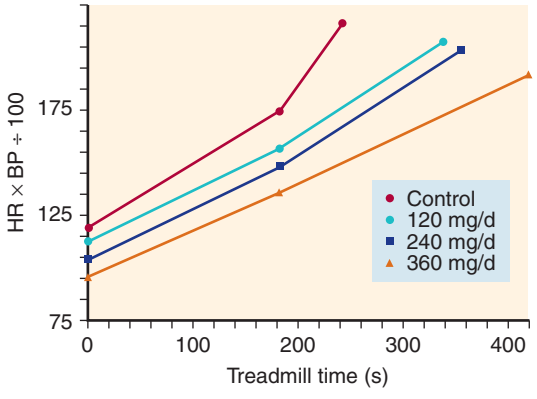


FIGURE 12–5 Effects of diltiazem on the double product (heart rate × systolic blood pressure) in a group of 20 patients with angina of effort. In a double-blind study using a standard protocol, patients were tested on a treadmill during treatment with placebo and three doses of the drug. Heart rate (HR) and systolic blood pressure (BP) were recorded at 180 seconds of exercise (midpoints of lines) and at the time of onset of anginal symptoms (rightmost points). Note that the drug treatment decreased the double product at all times during exercise and prolonged the time to appearance of symptoms. (Data from Lindenberg BS et al: Efficacy and safety of incremental doses of diltiazem for the treatment of angina. J Am Coll Cardiol 1983;2:1129. Used with permission of the American College of Cardiology.)

TABLE 12–7 Effects of nitrates alone and with β blockers or calcium channel blockers in angina pectoris.

	Nitrates Alone	Beta Blockers or Calcium Channel Blockers	Combined Nitrates with Beta Blockers or Calcium Channel Blockers
Heart rate	*Reflex[1] increase*	Decrease	Decrease
Arterial pressure	Decrease	Decrease	Decrease
End-diastolic volume	Decrease	*Increase*	None or decrease
Contractility	*Reflex[1] increase*	Decrease	None
Ejection time	Decrease[1]	*Increase*	None

[1]Baroreceptor reflex.

Note: Undesirable effects are shown in italics.

Surgical revascularization (ie, coronary artery bypass grafting [CABG]) and catheter-based revascularization (ie, percutaneous coronary intervention [PCI]) are the primary methods for promptly restoring coronary blood flow and increasing oxygen supply in unstable or medically refractory angina.

Vasospastic Angina

Nitrates and the calcium channel blockers are effective drugs for relieving and preventing ischemic episodes in patients with variant angina. In approximately 70% of patients treated with nitrates plus calcium channel blockers, angina attacks are completely abolished; in another 20%, marked reduction of frequency of anginal episodes is observed. Prevention of coronary artery spasm (with or without fixed atherosclerotic coronary artery lesions) is the principal mechanism for this beneficial response. All presently available calcium channel blockers appear to be equally effective, and the choice of a particular drug should depend on the patient. Surgical revascularization and angioplasty are not indicated in patients with variant angina.

Unstable Angina & Acute Coronary Syndromes

In patients with unstable angina with recurrent ischemic episodes at rest, recurrent platelet-rich nonocclusive thrombus formation is the principal mechanism. Aggressive antiplatelet therapy with a combination of aspirin and clopidogrel is indicated. Intravenous heparin or subcutaneous low-molecular-weight heparin is also indicated in most patients. If percutaneous coronary intervention with stenting is required, glycoprotein IIb/IIIa inhibitors such as abciximab should be added. In addition, therapy with nitroglycerin and β blockers should be considered; calcium channel blockers should be added in refractory cases for relief of myocardial ischemia. Primary lipid-lowering and ACE-inhibitor therapy should also be initiated.

TREATMENT OF PERIPHERAL ARTERY DISEASE (PAD) & INTERMITTENT CLAUDICATION

Atherosclerosis can result in ischemia of peripheral muscles just as coronary artery disease causes cardiac ischemia. Pain (claudication) occurs in skeletal muscles, especially in the legs, during exercise and disappears with rest. Although claudication is not immediately life-threatening, peripheral artery disease is associated with increased mortality, can severely limit exercise tolerance, and may be associated with chronic ischemic ulcers and susceptibility to infection.

Intermittent claudication results from obstruction of blood flow by atheromas in large and medium arteries. Treatment is primarily directed at reversal or control of atherosclerosis and requires measurement and control of hyperlipidemia (see Chapter 35), hypertension (see Chapter 11), and obesity; cessation of smoking; and control of diabetes, if present. Physical therapy and exercise training is of proven benefit. Conventional vasodilators are of no benefit because vessels distal to the obstructive lesions are usually already dilated at rest. Antiplatelet drugs such as aspirin or clopidogrel are often used to prevent clotting in the region of plaques. Two drugs are used almost exclusively for peripheral artery disease. **Pentoxifylline**, a xanthine derivative, is thought to act by reducing the viscosity of blood, allowing it to flow more easily through partially obstructed areas. **Cilostazol,** a phosphodiesterase type 3 (PDE3) inhibitor, is poorly understood, but may have selective antiplatelet and vasodilating effects. Both drugs have been shown to increase exercise tolerance in patients with severe claudication. Percutaneous angioplasty with stenting is often effective in patients with medically intractable signs and symptoms of ischemia.

SUMMARY Drugs Used in Angina Pectoris

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
NITRATES				
• Nitroglycerin	Releases nitric oxide in smooth muscle, which activates guanylyl cyclase and increases cGMP	Smooth muscle relaxation, especially in vessels • other smooth muscle is relaxed but not as markedly • vasodilation decreases venous return and heart size • may increase coronary flow in some areas and in variant angina	Angina: Sublingual form for acute episodes • oral and transdermal forms for prophylaxis • IV form for acute coronary syndrome	High first-pass effect, so sublingual dose is much smaller than oral • high lipid solubility ensures rapid absorption • *Toxicity:* Orthostatic hypotension, tachycardia, headache • *Interactions:* Synergistic hypotension with phosphodiesterase type 5 inhibitors (sildenafil, etc)
• *Isosorbide dinitrate: Very similar to nitroglycerin, slightly longer duration of action*				
• *Isosorbide mononitrate: Active metabolite of the dinitrate; used orally for prophylaxis*				
BETA BLOCKERS				
• Propranolol	Nonselective competitive antagonist at β adrenoceptors	Decreased heart rate, cardiac output, and blood pressure • decreases myocardial oxygen demand	Prophylaxis of angina • for other applications, see Chapters 10, 11, and 13	Oral and parenteral, 4–6 h duration of action • *Toxicity:* Asthma, atrioventricular block, acute heart failure, sedation • *Interactions:* Additive with all cardiac depressants
• *Atenolol, metoprolol, others: β_1-Selective blockers, less risk of bronchospasm, but still significant*				
• *See Chapters 10 and 11 for other β blockers and their applications*				
CALCIUM CHANNEL BLOCKERS				
• Verapamil, diltiazem	Nonselective block of L-type calcium channels in vessels and heart	Reduced vascular resistance, cardiac rate, and cardiac force results in decreased oxygen demand	Prophylaxis of angina, hypertension, others	Oral, IV, duration 4–8 h • *Toxicity:* Atrioventricular block, acute heart failure; constipation, edema • *Interactions:* Additive with other cardiac depressants and hypotensive drugs
• Nifedipine (a dihydropyridine)	Block of vascular L-type calcium channels > cardiac channels	Like verapamil and diltiazem; less cardiac effect	Prophylaxis of angina, hypertension	Oral, duration 4–6 h • *Toxicity:* Excessive hypotension, baroreceptor reflex tachycardia • *Interactions:* Additive with other vasodilators
• *Other dihydropyridines: Like nifedipine but slower onset and longer duration (up to 12 h or longer)*				
MISCELLANEOUS				
• Ranolazine	Inhibits late sodium current in heart • also may modify fatty acid oxidation	Reduces cardiac oxygen demand • fatty acid oxidation modification may improve efficiency of cardiac oxygen utilization	Prophylaxis of angina	Oral, duration 6–8 h • *Toxicity:* QT interval prolongation, nausea, constipation, dizziness • *Interactions:* Inhibitors of CYP3A increase ranolazine concentration and duration of action
• *Ivabradine: Investigational inhibitor of sinoatrial pacemaker; reduction of heart rate reduces oxygen demand*				

PREPARATIONS AVAILABLE

NITRATES & NITRITES

Amyl nitrite (generic)
Inhalant: 0.3 mL capsules

Isosorbide dinitrate (generic, Isordil)
Oral: 5, 10, 20, 30, 40 mg tablets; 5, 10 mg chewable tablets
Oral sustained-release (Isochron, Dilatrate SR): 40 mg tablets and capsules
Sublingual: 2.5, 5 mg sublingual tablets

Isosorbide mononitrate (Ismo, others)
Oral: 10, 20 mg tablets; extended-release: 30, 60, 120 mg tablets

Nitroglycerin
Sublingual or buccal: 0.3, 0.4, 0.6 mg tablets; 0.4 mg/metered dose aerosol spray
Oral sustained-release (generic, Nitro-Time): 2.5, 6.5, 9 mg capsules
Parenteral (generic): 5 mg/mL for IV administration; 100, 200, 400 mcg/mL in dextrose for IV infusion
Transdermal patches (generic, Nitrek, Nitro-Dur, Transderm-Nitro): to release at rates of 0.1, 0.2, 0.3, 0.4, 0.6, or 0.8 mg/h
Topical ointment (generic, Nitro-Bid): 20 mg/mL ointment (1 inch, or 25 mm, of ointment contains about 15 mg nitroglycerin)

CALCIUM CHANNEL BLOCKERS

Amlodipine (generic, Norvasc, AmVaz)
Oral: 2.5, 5, 10 mg tablets

Clevidipine (Cleviprex) (approved only for use in hypertensive emergencies)
Parenteral: 0.5 mg/mL for IV infusion

Diltiazem (Cardizem, generic)
Oral: 30, 60, 90, 120 mg tablets
Oral sustained-release (Cardizem SR, Dilacor XL, others): 60, 90, 120, 180, 240, 300, 360, 420 mg capsules, tablets
Parenteral: 5 mg/mL for injection

Felodipine (generic, Plendil)
Oral extended-release: 2.5, 5, 10 mg tablets

Isradipine (DynaCirc)
Oral: 2.5, 5 mg capsules
Oral controlled-release: 5, 10 mg tablets

Nicardipine (Cardene, others)
Oral: 20, 30 mg capsules
Oral sustained-release (Cardene SR): 30, 45, 60 mg capsules
Parenteral (Cardene I.V.): 2.5 mg/mL

Nifedipine (Adalat, Procardia, others)
Oral: 10, 20 mg capsules
Oral extended-release (Procardia XL, Adalat CC): 30, 60, 90 mg tablets

Nisoldipine (Sular)
Oral extended-release: 8.5, 17, 25.5, 34 mg tablets

Verapamil (generic, Calan, Isoptin)
Oral: 40, 80, 120 mg tablets
Oral sustained-release: 100, 120, 180, 240 mg tablets or capsules
Parenteral: 2.5 mg/mL for injection

BETA BLOCKERS

See Chapter 10.

SODIUM CHANNEL BLOCKERS

Ranolazine (Ranexa)
Oral: 500, 1000 mg extended-release tablets

DRUGS FOR ERECTILE DYSFUNCTION

Sildenafil (Viagra, Revatio)
Oral: 20 (approved for use in pulmonary arterial hypertension), 25, 50, 100 mg tablets

Tadalafil (Cialis, Adcirca)
Oral: 2.5, 5, 10, 20 mg tablets (20 mg approved for use in pulmonary hypertension)

Vardenafil (Levitra)
Oral: 2.5, 5, 10, 20 mg tablets

DRUGS FOR PERIPHERAL ARTERY DISEASE

Cilostazol (generic, Pletal)
Oral: 50, 100 mg tablets

Pentoxifylline (generic, Trental)
Oral: 400 mg controlled-release, extended-release tablets

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CASE STUDY ANSWER

The case described is typical of stable atherosclerotic angina. Treatment of acute episodes should include sublingual tablets or sprayed nitroglycerin, 0.4–0.6 mg. Relief of discomfort within 2–4 minutes can be expected. If anginal episodes are frequent, or to prevent episodes of angina, a β blocker such as metoprolol should be tried first. If contraindications to the use of a β blocker are present, a medium- to long-acting calcium channel blocker such as verapamil, diltiazem, or amlodipine is likely to be effective.

CHAPTER 13

Drugs Used in Heart Failure

Bertram G. Katzung, MD, PhD*

CASE STUDY

A 65-year-old man has developed shortness of breath with exertion several weeks after experiencing a viral illness. This is accompanied by swelling of the feet and ankles and increasing fatigue. On physical examination he is found to be mildly short of breath lying down, but feels better sitting upright. Pulse is 105 and regular, and blood pressure is 90/60 mm Hg. His lungs show crackles at both bases, and his jugular venous pressure is elevated. The liver is enlarged, and there is 3+ edema of the ankles and feet. An echocardiogram shows a dilated, poorly contracting heart with a left ventricular ejection fraction of about 20% (normal: 60%). The presumptive diagnosis is dilated cardiomyopathy secondary to a viral infection with stage C, class III heart failure. What treatment is indicated?

Heart failure occurs when cardiac output is inadequate to provide the oxygen needed by the body. It is a highly lethal condition, with a 5-year mortality rate conventionally said to be about 50%. The most common cause of heart failure in the USA is coronary artery disease, with hypertension also an important factor. Two major types of failure may be distinguished. Approximately 50% of younger patients have **systolic failure,** with reduced mechanical pumping action (contractility) and reduced ejection fraction. The remaining group has **diastolic failure,** with stiffening and loss of adequate relaxation playing a major role in reducing filling and cardiac output; ejection fraction may be normal even though stroke volume is significantly reduced. The proportion of patients with diastolic failure increases with age. Because other cardiovascular conditions (especially myocardial infarction) are now being treated more effectively, more patients are surviving long enough for heart failure to develop, making heart failure one of the cardiovascular conditions that is actually increasing in prevalence.

Heart failure is a progressive disease that is characterized by a gradual reduction in cardiac performance, punctuated in many cases by episodes of acute decompensation, often requiring hospitalization. Treatment is therefore directed at two somewhat different goals: (1) reducing symptoms and slowing progression as much as possible during relatively stable periods and (2) managing acute episodes of decompensated failure. These factors are discussed in Clinical Pharmacology of Drugs Used in Heart Failure.

Although it is believed that the primary defect in early systolic heart failure resides in the excitation-contraction coupling machinery of the heart, the clinical condition also involves many other processes and organs, including the baroreceptor reflex, the sympathetic nervous system, the kidneys, angiotensin II and other peptides, aldosterone, and apoptosis of cardiac cells. Recognition of these factors has resulted in evolution of a variety of drug treatment strategies (Table 13–1).

Large clinical trials have shown that therapy directed at noncardiac targets is more valuable in the long-term treatment of heart failure than traditional positive inotropic agents (cardiac glycosides [digitalis]). Extensive trials have shown that ACE inhibitors, angiotensin receptor blockers, certain β blockers, aldosterone receptor antagonists, and combined hydralazine-nitrate therapy are the only agents in current use that actually prolong life in patients with chronic heart failure. These strategies are useful in both systolic and diastolic failure. Positive inotropic drugs, on the other hand, are helpful mainly in acute systolic failure. Cardiac glycosides also reduce symptoms in chronic systolic

*The author thanks Dr. William W. Parmley, MD, who was coauthor of this chapter in prior editions.

TABLE 13–1 Drug groups used in heart failure.

Chronic heart failure	Acute heart failure
Diuretics	Diuretics
Aldosterone receptor antagonists	Vasodilators
Angiotensin-converting enzyme inhibitors	Beta agonists
Angiotensin receptor blockers	Bipyridines
Beta blockers	Natriuretic peptide
Cardiac glycosides	
Vasodilators	

heart failure. Other positive inotropic drugs have consistently *reduced* survival in chronic failure, and their use is discouraged.

Control of Normal Cardiac Contractility

The vigor of contraction of heart muscle is determined by several processes that lead to the movement of actin and myosin filaments in the cardiac sarcomere (Figure 13–1). Ultimately, contraction results from the interaction of *activator* calcium (during systole) with the actin-troponin-tropomyosin system, thereby releasing the actin-myosin interaction. This activator calcium is released from the sarcoplasmic reticulum (SR). The amount released depends on the amount stored in the SR and on the amount of *trigger* calcium that enters the cell during the plateau of the action potential.

A. Sensitivity of the Contractile Proteins to Calcium and Other Contractile Protein Modifications

The determinants of calcium sensitivity, ie, the curve relating the shortening of cardiac myofibrils to the cytoplasmic calcium concentration, are incompletely understood, but several types of drugs can be shown to affect calcium sensitivity in vitro. **Levosimendan** is the most recent example of a drug that increases calcium sensitivity (it may also inhibit phosphodiesterase) and reduces symptoms in models of heart failure.

A recent report suggests that an experimental drug, **omecantiv mecarbil** (CK-1827452), alters the rate of transition of myosin from a low-actin-binding state to a strongly actin-bound force-generating state. Preliminary studies in experimental animal models of heart failure indicate that this agent may provide a new approach to the treatment of heart failure in humans. Clinical trials are underway.

B. Amount of Calcium Released from the Sarcoplasmic Reticulum

A small rise in free cytoplasmic calcium, brought about by calcium influx during the action potential, triggers the opening of calcium-gated, ryanodine-sensitive calcium channels (RyR2) in the membrane of the cardiac SR and the rapid release of a large amount of the ion into the cytoplasm in the vicinity of the actin-troponin-tropomyosin complex. The amount released is proportional to the amount stored in the SR and the amount of trigger calcium that enters the cell through the cell membrane. (Ryanodine is a potent negative inotropic plant alkaloid that interferes with the release of calcium through cardiac SR channels.)

C. Amount of Calcium Stored in the Sarcoplasmic Reticulum

The SR membrane contains a very efficient calcium uptake transporter known as the sarcoplasmic endoplasmic reticulum Ca^{2+}-ATPase (SERCA). This pump maintains free cytoplasmic calcium at very low levels during diastole by pumping calcium into the SR. SERCA is normally inhibited by phospholamban; phosphorylation of phospholamban by protein kinase A (eg, by β agonists) removes this inhibition. The amount of calcium sequestered in the SR is thus determined, in part, by the amount accessible to this transporter and the activity of the sympathetic nervous system. This in turn is dependent on the balance of calcium influx (primarily through the voltage-gated membrane L-type calcium channels) and calcium efflux, the amount removed from the cell (primarily via the sodium-calcium exchanger, a transporter in the cell membrane). The amount of Ca^{2+} released from the SR depends on the response of the RyR channels to trigger Ca^{2+}.

D. Amount of Trigger Calcium

The amount of trigger calcium that enters the cell depends on the availability of membrane calcium channels and the duration of their opening. As described in Chapters 6 and 9, sympathomimetics cause an increase in calcium influx through an action on these channels. Conversely, the calcium channel blockers (see Chapter 12) reduce this influx and depress contractility.

E. Activity of the Sodium-Calcium Exchanger

This antiporter (NCX) uses the sodium gradient to move calcium against its concentration gradient from the cytoplasm to the extracellular space. Extracellular concentrations of these ions are much less labile than intracellular concentrations under physiologic conditions. The sodium-calcium exchanger's ability to carry out this transport is thus strongly dependent on the intracellular concentrations of both ions, especially sodium.

F. Intracellular Sodium Concentration and Activity of Na^+/K^+-ATPase

Na^+/K^+-ATPase, by removing intracellular sodium, is the major determinant of sodium concentration in the cell. The sodium influx through voltage-gated channels, which occurs as a normal part of almost all cardiac action potentials, is another determinant, although the amount of sodium that enters with each action potential is much less than 1% of the total intracellular sodium. Na^+/K^+-ATPase appears to be the primary target of **digoxin** and other cardiac glycosides.

Pathophysiology of Heart Failure

Heart failure is a syndrome with many causes that may involve one or both ventricles. Cardiac output is usually below the normal range ("low-output" failure). Systolic dysfunction, with reduced

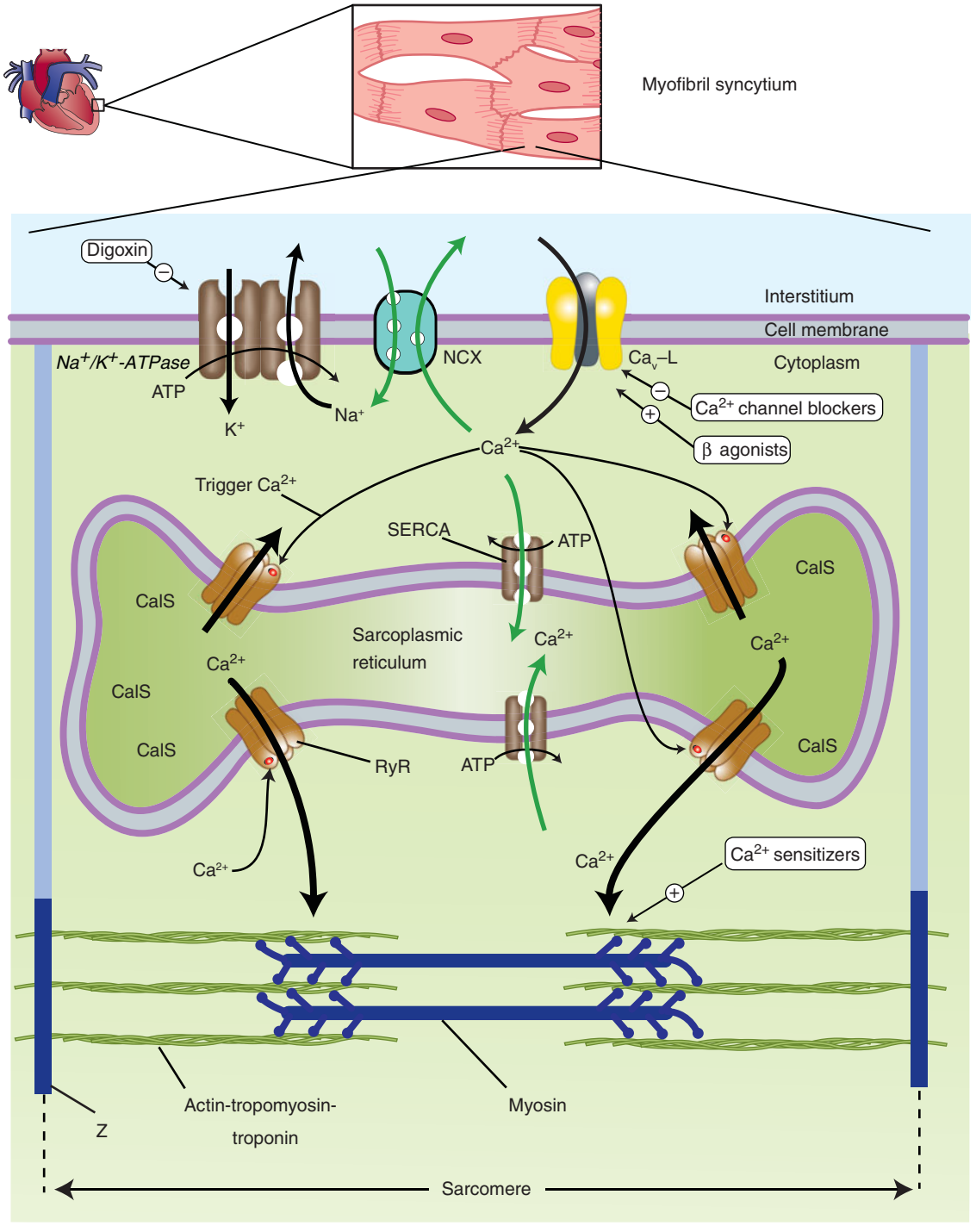


FIGURE 13–1 Schematic diagram of a cardiac muscle sarcomere, with sites of action of several drugs that alter contractility. Na^+/K^+-ATPase, the sodium pump, is the site of action of cardiac glycosides. NCX is the sodium-calcium exchanger. Ca_v-L is the voltage-gated, L-type calcium channel. SERCA (sarcoplasmic endoplasmic reticulum Ca^{2+}-ATPase) is a calcium transporter ATPase that pumps calcium into the sarcoplasmic reticulum (SR). CaIS is calcium bound to calsequestrin, a high-capacity Ca^{2+}-binding protein. RyR (ryanodine RyR2 receptor) is a calcium-activated calcium channel in the membrane of the SR that is triggered to release stored calcium. Calcium sensitizers act at the actin-troponin-tropomyosin complex where activator calcium brings about the contractile interaction of actin and myosin. Black arrows represent processes that initiate contraction or support basal tone. Green arrows represent processes that promote relaxation.

cardiac output and significantly reduced ejection fraction (< 45%; normal > 60%), is typical of acute failure, especially that resulting from myocardial infarction. Diastolic dysfunction often occurs as a result of hypertrophy and stiffening of the myocardium, and although cardiac output is reduced, ejection fraction may be normal. Heart failure due to diastolic dysfunction does not usually respond optimally to positive inotropic drugs.

"High-output" failure is a rare form of heart failure. In this condition, the demands of the body are so great that even increased cardiac output is insufficient. High-output failure can result from hyperthyroidism, beriberi, anemia, and arteriovenous shunts. This form of failure responds poorly to the drugs discussed in this chapter and should be treated by correcting the underlying cause.

The primary signs and symptoms of all types of heart failure include tachycardia, decreased exercise tolerance, shortness of breath, and cardiomegaly. Peripheral and pulmonary edema (the congestion of congestive heart failure) are often but not always present. Decreased exercise tolerance with rapid muscular fatigue is the major direct consequence of diminished cardiac output. The other manifestations result from the attempts by the body to compensate for the intrinsic cardiac defect.

Neurohumoral (extrinsic) compensation involves two major mechanisms (previously presented in Figure 6–7)—the sympathetic nervous system and the renin-angiotensin-aldosterone hormonal response—plus several others. Some of the detrimental as well as beneficial features of these compensatory responses are illustrated in Figure 13–2. The baroreceptor reflex appears to be reset, with a lower sensitivity to arterial pressure, in patients with heart failure. As a result, baroreceptor sensory input to the vasomotor center is reduced even at normal pressures; sympathetic outflow is increased, and parasympathetic outflow is decreased. Increased sympathetic outflow causes tachycardia, increased cardiac contractility, and increased vascular tone. Vascular tone is further increased by angiotensin II and endothelin, a potent vasoconstrictor released by vascular endothelial cells. Vasoconstriction increases afterload, which further reduces ejection fraction and cardiac output. The result is a vicious cycle that is characteristic of heart failure (Figure 13–3). Neurohumoral antagonists and vasodilators reduce heart failure mortality by interrupting the cycle and slowing the downward spiral.

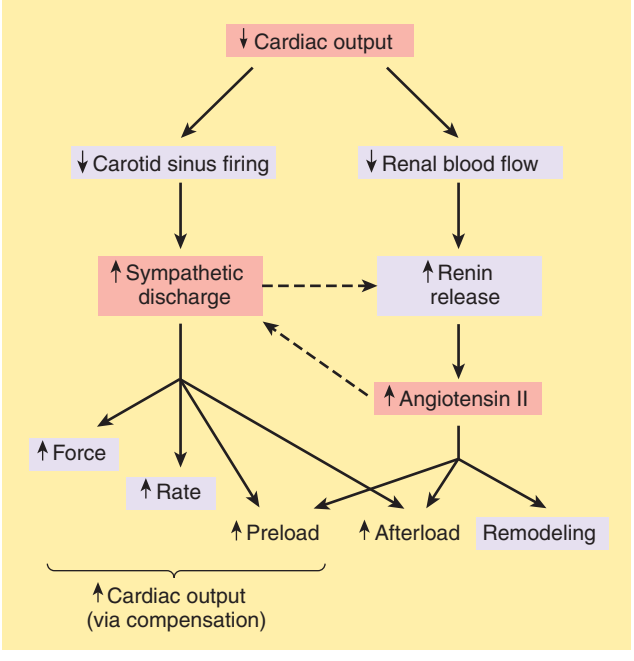


FIGURE 13–2 Some compensatory responses that occur during congestive heart failure. In addition to the effects shown, sympathetic discharge facilitates renin release, and angiotensin II increases norepinephrine release by sympathetic nerve endings (*dashed arrows*).

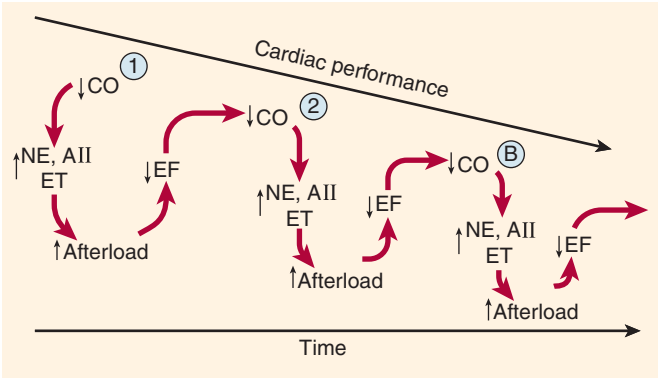


FIGURE 13–3 Vicious spiral of progression of heart failure. Decreased cardiac output (CO) activates production of neurohormones (NE, norepinephrine; AII, angiotensin II; ET, endothelin), which cause vasoconstriction and increased afterload. This further reduces ejection fraction (EF) and CO, and the cycle repeats. The downward spiral is continued until a new steady state is reached in which CO is lower and afterload is higher than is optimal for normal activity. Circled points 1, 2, and B represent points on the ventricular function curves depicted in Figure 13–4.

After a relatively short exposure to increased sympathetic drive, complex down-regulatory changes in the cardiac β_1-adrenoceptor–G protein-effector system take place that result in diminished stimulatory effects. $Beta_2$ receptors are *not* down-regulated and may develop increased coupling to the IP_3-DAG cascade. It has also been suggested that cardiac β_3 receptors (which do not appear to be down-regulated in failure) may mediate *negative* inotropic effects. Excessive β activation can lead to leakage of calcium from the SR via RyR channels and contributes to stiffening of the ventricles and arrhythmias. Prolonged β activation also increases caspases, the enzymes responsible for apoptosis. Increased angiotensin II production leads to increased aldosterone secretion (with sodium and water retention), to increased afterload, and to remodeling of both heart and vessels (discussed below). Other hormones are released, including natriuretic peptide, endothelin, and vasopressin (see Chapter 17). Within the heart, failure-induced changes have been documented in calcium handling in the SR by SERCA and phospholamban; in transcription factors that lead to hypertrophy and fibrosis; in mitochondrial function, which is critical for energy production in the overworked heart;

and in ion channels, especially potassium channels, which facilitate arrhythmogenesis, a primary cause of death in heart failure. Phosphorylation of RyR channels in the sarcoplasmic reticulum enhances and dephosphorylation reduces Ca^{2+} release; studies in animal models indicate that the enzyme primarily responsible for RyR dephosphorylation, protein phosphatase 1 (PP1), is upregulated in heart failure. These cellular changes provide many potential targets for future drugs.

The most important intrinsic compensatory mechanism is **myocardial hypertrophy.** This increase in muscle mass helps maintain cardiac performance. However, after an initial beneficial effect, hypertrophy can lead to ischemic changes, impairment of diastolic filling, and alterations in ventricular geometry. **Remodeling** is the term applied to dilation (other than that due to passive stretch) and other slow structural changes that occur in the stressed myocardium. It may include proliferation of connective tissue cells as well as abnormal myocardial cells with some biochemical characteristics of fetal myocytes. Ultimately, myocytes in the failing heart die at an accelerated rate through apoptosis, leaving the remaining myocytes subject to even greater stress.

Pathophysiology of Cardiac Performance

Cardiac performance is a function of four primary factors:

1. **Preload:** When some measure of left ventricular performance such as stroke volume or stroke work is plotted as a function of left ventricular filling pressure or end-diastolic fiber length, the resulting curve is termed the left ventricular function curve (Figure 13–4). The ascending limb (< 15 mm Hg filling pressure) represents the classic Frank-Starling relation described in physiology texts. Beyond approximately 15 mm Hg, there is a plateau of performance. Preloads greater than 20–25 mm Hg result in pulmonary congestion. As noted above, preload is usually increased in heart failure because of increased blood volume and venous tone. Because the function curve of the failing heart is lower, the plateau is reached at much lower values of stroke work or output. Increased fiber length or filling pressure increases oxygen demand in the myocardium, as described in Chapter 12. Reduction of high filling pressure is the goal of salt restriction and diuretic therapy in heart failure. Venodilator drugs (eg, nitroglycerin) also reduce preload by redistributing blood away from the chest into peripheral veins.
2. **Afterload:** Afterload is the resistance against which the heart must pump blood and is represented by aortic impedance and systemic vascular resistance. As noted in Figure 13–2, as cardiac output falls in chronic failure, a reflex increase in systemic vascular resistance occurs, mediated in part by increased sympathetic outflow and circulating catecholamines and in part by activation of the renin-angiotensin system. Endothelin, a potent vasoconstrictor peptide, is also involved. This sets the stage for the use of drugs that reduce arteriolar tone in heart failure.
3. **Contractility:** Heart muscle obtained by biopsy from patients with chronic low-output failure demonstrates a reduction in intrinsic contractility. As contractility decreases in the patient, there is a reduction in the velocity of muscle shortening, the rate of intraventricular pressure development (dP/dt), and the stroke output achieved (Figure 13–4). However, the heart is usually still capable of some increase in all of these measures of contractility in response to inotropic drugs.

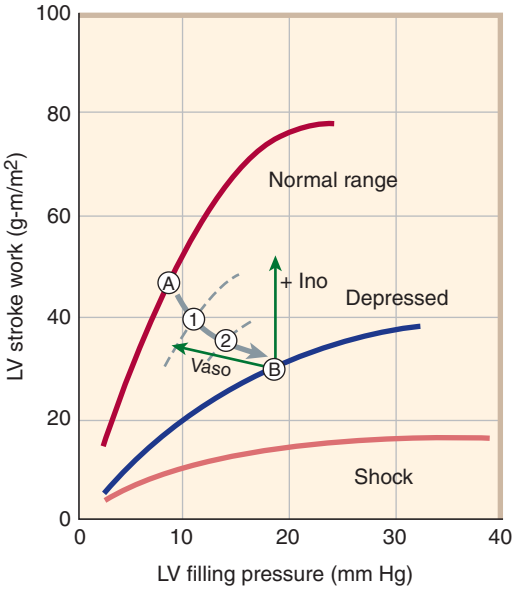


FIGURE 13–4 Relation of left ventricular (LV) performance to filling pressure in patients with acute myocardial infarction, an important cause of heart failure. The upper line indicates the range for normal, healthy individuals. At a given level of exercise, the heart operates at a stable point, eg, point A. In heart failure, function is shifted down and to the right, through points 1 and 2, finally reaching point B. A "pure" positive inotropic drug (+ Ino) would move the operating point upward by increasing cardiac stroke work. A vasodilator (Vaso) would move the point leftward by reducing filling pressure. Successful therapy usually results in both effects. (Modified and reproduced with permission, from Swan HJC, Parmley WW: Congestive heart failure. In: Sodeman WA Jr, Sodeman TM [editors]: *Pathologic Physiology.* Saunders, 1979.)

4. **Heart rate:** The heart rate is a major determinant of cardiac output. As the intrinsic function of the heart decreases in failure and stroke volume diminishes, an increase in heart rate—through sympathetic activation of β adrenoceptors—is the first compensatory mechanism that comes into play to maintain cardiac output.

BASIC PHARMACOLOGY OF DRUGS USED IN HEART FAILURE

Although digitalis is not the first drug and never the only drug used in heart failure, we begin our discussion with this group because other drugs are discussed in more detail in other chapters.

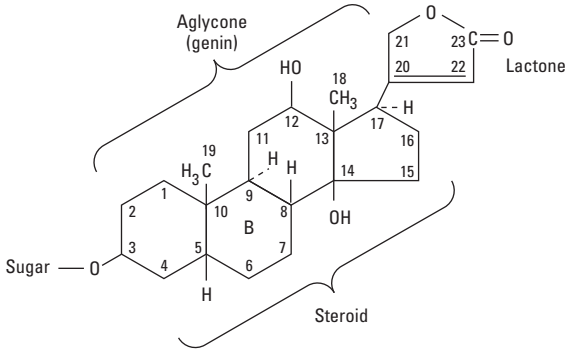
DIGITALIS

Digitalis is the genus name for the family of plants that provide most of the medically useful **cardiac glycosides,** eg, digoxin. Such plants have been known for thousands of years but were used erratically and with variable success until 1785, when William

Withering, an English physician and botanist, published a monograph describing the clinical effects of an extract of the purple foxglove plant (*Digitalis purpurea*, a major source of these agents).

Chemistry

All of the cardiac glycosides, or cardenolides—of which **digoxin** is the prototype—combine a steroid nucleus linked to a lactone ring at the 17 position and a series of sugars at carbon 3 of the nucleus. Because they lack an easily ionizable group, their solubility is not pH-dependent. Digoxin is obtained from *Digitalis lanata,* the white foxglove, but many common plants (eg, oleander, lily of the valley, and milkweed) contain cardiac glycosides with similar properties.



Pharmacokinetics

Digoxin, the only cardiac glycoside used in the USA, is 65–80% absorbed after oral administration. Absorption of other glycosides varies from zero to nearly 100%. Once present in the blood, all cardiac glycosides are widely distributed to tissues, including the central nervous system.

Digoxin is not extensively metabolized in humans; almost two thirds is excreted unchanged by the kidneys. Its renal clearance is proportional to creatinine clearance, and the half-life is 36–40 hours in patients with normal renal function. Equations and nomograms are available for adjusting digoxin dosage in patients with renal impairment.

Pharmacodynamics

Digoxin has multiple direct and indirect cardiovascular effects, with both therapeutic and toxic consequences. In addition, it has undesirable effects on the central nervous system and gut.

At the molecular level, all therapeutically useful cardiac glycosides **inhibit Na^+/K^+-ATPase,** the membrane-bound transporter often called the **sodium pump** (Figure 13–1). Although several isoforms of this ATPase occur and have varying sensitivity to cardiac glycosides, they are highly conserved in evolution. Inhibition of this transporter over most of the dose range has been extensively documented in all tissues studied. It is probable that this inhibitory action is largely responsible for the therapeutic effect (positive inotropy) as well as a major portion of the toxicity of digitalis. Other molecular-level effects of digitalis have been studied in the heart and are discussed below. The fact that a receptor for cardiac glycosides exists on the sodium pump has prompted some investigators to propose that an endogenous digitalis-like steroid, possibly **ouabain** or **marinobufagenin,** must exist. Furthermore, additional functions of Na^+/K^+-ATPase have been postulated, involving apoptosis, cell growth and differentiation, immunity, and carbohydrate metabolism.

A. Cardiac Effects

1. Mechanical effects—Cardiac glycosides increase contraction of the cardiac sarcomere by increasing the free calcium concentration in the vicinity of the contractile proteins during systole. The increase in calcium concentration is the result of a two-step process: first, an **increase of intracellular sodium** concentration because of Na^+/K^+-ATPase inhibition; and second, a relative **reduction of calcium expulsion** from the cell by the sodium-calcium exchanger (NCX in Figure 13–1) caused by the increase in intracellular sodium. The increased cytoplasmic calcium is sequestered by SERCA in the SR for later release. Other mechanisms have been proposed but are not well supported.

The net result of the action of therapeutic concentrations of a cardiac glycoside is a distinctive increase in cardiac contractility (Figure 13–5, bottom trace, panels A and B). In isolated myocardial preparations, the rate of development of tension and of relaxation are both increased, with little or no change in time to peak tension. This effect occurs in both normal and failing myocardium, but in the intact patient the responses are modified by cardiovascular reflexes and the pathophysiology of heart failure.

2. Electrical effects—The effects of digitalis on the electrical properties of the heart are a mixture of direct and autonomic actions. Direct actions on the membranes of cardiac cells follow a well-defined progression: an early, brief prolongation of the action potential, followed by shortening (especially the plateau phase). The decrease in action potential duration is probably the result of increased potassium conductance that is caused by increased intracellular calcium (see Chapter 14). All these effects can be observed at therapeutic concentrations in the absence of overt toxicity (Table 13–2).

At higher concentrations, resting membrane potential is reduced (made less negative) as a result of inhibition of the sodium pump and reduced intracellular potassium. As toxicity progresses, oscillatory depolarizing afterpotentials appear following normally evoked action potentials (Figure 13–5, panel C). The afterpotentials (also known as **delayed after-depolarizations,** DADs) are associated with overloading of the intracellular calcium stores and oscillations in the free intracellular calcium ion concentration. When afterpotentials reach threshold, they elicit action potentials (**premature depolarizations,** ectopic "beats") that are coupled to the preceding normal action potentials. If afterpotentials in the Purkinje conducting system regularly reach threshold in this way, bigeminy will be recorded on the electrocardiogram (Figure 13–6). With further intoxication, each afterpotential-evoked action potential will itself elicit a suprathreshold after-potential, and a self-sustaining tachycardia will

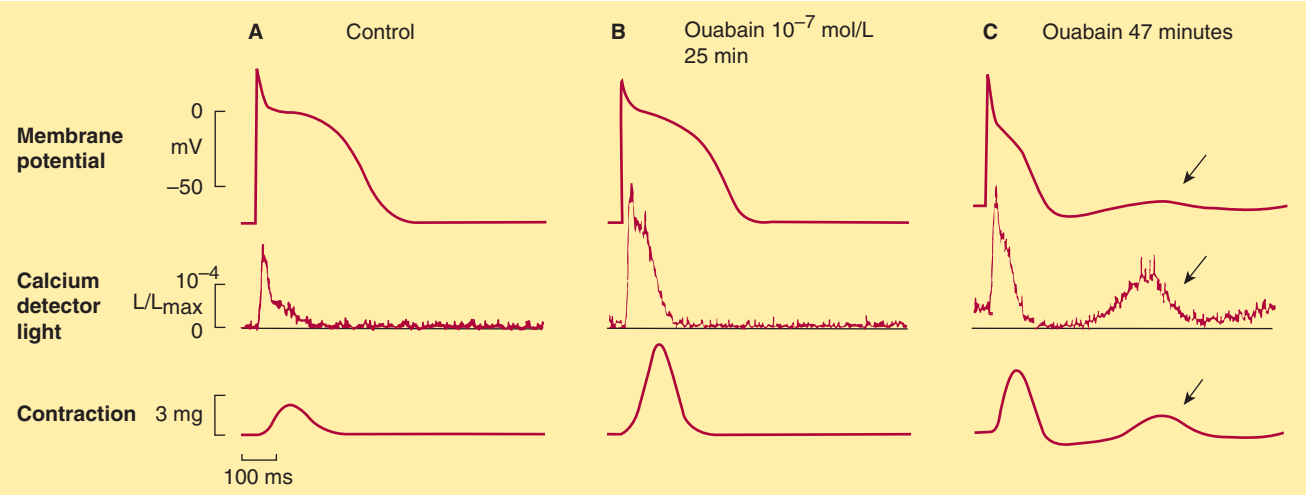


FIGURE 13–5 Effects of a cardiac glycoside, ouabain, on isolated cardiac tissue. The top tracing shows action potentials evoked during the control period (panel **A**), early in the "therapeutic" phase (**B**), and later, when toxicity is present (**C**). The middle tracing shows the light (L) emitted by the calcium-detecting protein aequorin (relative to the maximum possible, L_{max}) and is roughly proportional to the free intracellular calcium concentration. The bottom tracing records the tension elicited by the action potentials. The early phase of ouabain action (panel **B**) shows a slight shortening of action potential and a marked increase in free intracellular calcium concentration and contractile tension. The toxic phase (panel **C**) is associated with depolarization of the resting potential, a marked shortening of the action potential, and the appearance of an oscillatory depolarization, calcium increment, and contraction (*arrows*). (Unpublished data kindly provided by P Hess and H Gil Wier.)

be established. If allowed to progress, such a tachycardia may deteriorate into fibrillation; in the case of ventricular fibrillation, the arrhythmia will be rapidly fatal unless corrected.

Autonomic actions of cardiac glycosides on the heart involve both the parasympathetic and the sympathetic systems. In the lower portion of the dose range, cardioselective parasympathomimetic effects predominate. In fact, these atropine-blockable effects account for a significant portion of the early electrical effects of digitalis (Table 13–2). This action involves sensitization of the baroreceptors, central vagal stimulation, and facilitation of muscarinic transmission at the cardiac muscle cell. Because cholinergic innervation is much richer in the atria, these actions affect atrial and atrioventricular nodal function more than Purkinje or ventricular function. Some of the cholinomimetic effects are useful in the treatment of certain arrhythmias. At toxic levels, sympathetic outflow is increased by digitalis. This effect is not essential for typical digitalis toxicity but sensitizes the myocardium and exaggerates all the toxic effects of the drug.

The most common cardiac manifestations of digitalis toxicity include atrioventricular junctional rhythm, premature ventricular depolarizations, bigeminal rhythm, and second-degree atrioventricular blockade. However, it is claimed that digitalis can cause virtually any arrhythmia.

B. Effects on Other Organs

Cardiac glycosides affect all excitable tissues, including smooth muscle and the central nervous system. The gastrointestinal tract is the most common site of digitalis toxicity outside the heart. The effects include anorexia, nausea, vomiting, and diarrhea. This toxicity is caused in part by direct effects on the gastrointestinal tract and in part by central nervous system actions.

Central nervous system effects include vagal and chemoreceptor trigger zone stimulation. Less often, disorientation and hallucinations—especially in the elderly—and visual disturbances are noted. The latter effect may include aberrations of color perception. Gynecomastia is a rare effect reported in men taking digitalis.

TABLE 13–2 Effects of digoxin on electrical properties of cardiac tissues.

Tissue or Variable	Effects at Therapeutic Dosage	Effects at Toxic Dosage
Sinus node	↓ Rate	↓ Rate
Atrial muscle	↓ Refractory period	↓ Refractory period, arrhythmias
Atrioventricular node	↓ Conduction velocity, ↑ refractory period	↓ Refractory period, arrhythmias
Purkinje system, ventricular muscle	Slight ↓ refractory period	Extrasystoles, tachycardia, fibrillation
Electrocardiogram	↑ PR interval, ↓ QT interval	Tachycardia, fibrillation, arrest at extremely high dosage

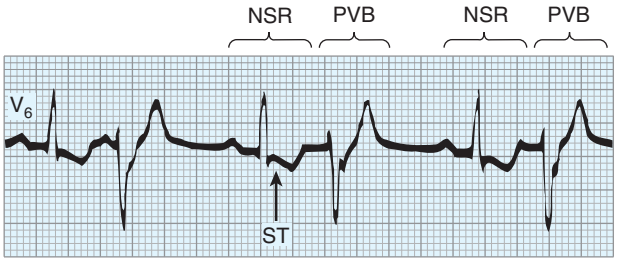


FIGURE 13–6 Electrocardiographic record showing digitalis-induced bigeminy. The complexes marked NSR are normal sinus rhythm beats; an inverted T wave and depressed ST segment are present. The complexes marked PVB are premature ventricular beats and are the electrocardiographic manifestations of depolarizations evoked by delayed oscillatory afterpotentials as shown in Figure 13–5. (Modified and reproduced, with permission, from Goldman MJ: *Principles of Clinical Electrocardiography,* 12th ed. Lange, 1986.)

C. Interactions with Potassium, Calcium, and Magnesium

Potassium and digitalis interact in two ways. First, they inhibit each other's binding to Na^+/K^+-ATPase; therefore, hyperkalemia reduces the enzyme-inhibiting actions of cardiac glycosides, whereas hypokalemia facilitates these actions. Second, abnormal cardiac automaticity is inhibited by hyperkalemia (see Chapter 14). Moderately increased extracellular K^+ therefore reduces the effects of digitalis, especially the toxic effects.

Calcium ion facilitates the toxic actions of cardiac glycosides by accelerating the overloading of intracellular calcium stores that appears to be responsible for digitalis-induced abnormal automaticity. Hypercalcemia therefore increases the risk of a digitalis-induced arrhythmia. The effects of magnesium ion are opposite to those of calcium. These interactions mandate careful evaluation of serum electrolytes in patients with digitalis-induced arrhythmias.

OTHER POSITIVE INOTROPIC DRUGS USED IN HEART FAILURE

Istaroxime is an investigational steroid derivative that increases contractility by inhibiting Na^+/K^+-ATPase (like cardiac glycosides) but in addition facilitates sequestration of Ca^{2+} by the SR. The latter action may render the drug less arrhythmogenic than digoxin. Istaroxime is in phase 2 clinical trials.

Drugs that inhibit **phosphodiesterases,** the family of enzymes that inactivate cAMP and cGMP, have long been used in therapy of heart failure. Although they have positive inotropic effects, most of their benefits appear to derive from vasodilation, as discussed below. The bipyridines **inamrinone** and **milrinone** are the most successful of these agents found to date, but their usefulness is limited. **Levosimendan,** a drug that sensitizes the troponin system to calcium, also appears to inhibit phosphodiesterase and to cause some vasodilation in addition to its inotropic effects. Some clinical trials suggest that this drug may be useful in patients with heart failure, and the drug has been approved in some countries (not the USA). A group of β-adrenoceptor stimulants has also been used as digitalis substitutes, but they may increase mortality (see below).

BIPYRIDINES

Inamrinone (previously called amrinone) and **milrinone** are bipyridine compounds that inhibit phosphodiesterase isozyme 3 (PDE-3). They are active orally as well as parenterally but are available only in parenteral forms. They have elimination half-lives of 3–6 hours, with 10–40% being excreted in the urine.

Pharmacodynamics

The bipyridines increase myocardial contractility by increasing inward calcium flux in the heart during the action potential; they may also alter the intracellular movements of calcium by influencing the sarcoplasmic reticulum. They also have an important vasodilating effect. Inhibition of phosphodiesterase results in an increase in cAMP and the increase in contractility and vasodilation.

The toxicity of inamrinone includes nausea and vomiting; arrhythmias, thrombocytopenia, and liver enzyme changes have also been reported in a significant number of patients. This drug has been withdrawn in some countries. Milrinone appears less likely to cause bone marrow and liver toxicity than inamrinone, but it does cause arrhythmias. Inamrinone and milrinone are now used only intravenously and only for acute heart failure or severe exacerbation of chronic heart failure.

BETA-ADRENOCEPTOR AGONISTS

The general pharmacology of these agents is discussed in Chapter 9. The selective β_1 agonist that has been most widely used in patients with heart failure is **dobutamine.** This parenteral drug produces an increase in cardiac output together with a decrease in ventricular filling pressure. Some tachycardia and an increase in myocardial oxygen consumption have been reported. Therefore, the potential for producing angina or arrhythmias in patients with coronary artery disease is significant, as is the tachyphylaxis that accompanies the use of any β stimulant. Intermittent dobutamine infusion may benefit some patients with chronic heart failure.

Dopamine has also been used in acute heart failure and may be particularly helpful if there is a need to raise blood pressure.

DRUGS WITHOUT POSITIVE INOTROPIC EFFECTS USED IN HEART FAILURE

These agents—not positive inotropic drugs—are the first-line therapies for chronic heart failure. The drugs most commonly used are diuretics, ACE inhibitors, angiotensin receptor antagonists, aldosterone antagonists, and β blockers (Table 13–1). In acute failure, diuretics and vasodilators play important roles.

DIURETICS

Diuretics, especially furosemide, are drugs of choice in heart failure and are discussed in detail in Chapter 15. They have no direct effect on cardiac contractility; their major mechanism of action in heart failure is to reduce venous pressure and ventricular preload. This results in reduction of salt and water retention and edema and its symptoms. The reduction of cardiac size, which leads to improved pump efficiency, is of major importance in systolic failure. **Spironolactone** and **eplerenone,** the aldosterone antagonist diuretics (see Chapter 15), have the additional benefit of decreasing morbidity and mortality in patients with severe heart failure who are also receiving ACE inhibitors and other standard therapy. One possible mechanism for this benefit lies in accumulating evidence that aldosterone may also cause myocardial and vascular fibrosis and baroreceptor dysfunction in addition to its renal effects.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS, ANGIOTENSIN RECEPTOR BLOCKERS, & RELATED AGENTS

ACE inhibitors such as **captopril** are introduced in Chapter 11 and discussed again in Chapter 17. These versatile drugs reduce peripheral resistance and thereby reduce afterload; they also reduce salt and water retention (by reducing aldosterone secretion) and in that way reduce preload. The reduction in tissue angiotensin levels also reduces sympathetic activity through diminution of angiotensin's presynaptic effects on norepinephrine release. Finally, these drugs reduce the long-term remodeling of the heart and vessels, an effect that may be responsible for the observed reduction in mortality and morbidity (see Clinical Pharmacology).

Angiotensin AT_1 receptor blockers such as **losartan** (see Chapters 11 and 17) appear to have similar but more limited beneficial effects. Angiotensin receptor blockers should be considered in patients intolerant of ACE inhibitors because of incessant cough. In some trials, **candesartan** was beneficial when *added* to an ACE inhibitor.

Aliskiren, a renin inhibitor recently approved for hypertension, is in clinical trials for heart failure. Preliminary results suggest an efficacy similar to that of ACE inhibitors.

VASODILATORS

Vasodilators are effective in acute heart failure because they provide a reduction in preload (through venodilation), or reduction in afterload (through arteriolar dilation), or both. Some evidence suggests that long-term use of hydralazine and isosorbide dinitrate can also reduce damaging remodeling of the heart.

A synthetic form of the endogenous peptide brain natriuretic peptide (BNP) is approved for use in acute (not chronic) cardiac failure as **nesiritide.** This recombinant product increases cGMP in smooth muscle cells and reduces venous and arteriolar tone in experimental preparations. It also causes diuresis. The peptide has a short half-life of about 18 minutes and is administered as a bolus intravenous dose followed by continuous infusion. Excessive hypotension is the most common adverse effect. Reports of significant renal damage and deaths have resulted in extra warnings regarding this agent, and it should be used with great caution.

Plasma concentrations of *endogenous* BNP rise in most patients with heart failure and are correlated with severity. Measurement of plasma BNP has become a useful diagnostic or prognostic test in some centers.

Related peptides include atrial natriuretic peptide (ANP) and urodilatin, a similar peptide produced in the kidney. **Carperitide** and **ularitide,** respectively, are investigational synthetic analogs of these endogenous peptides and are in clinical trials (see Chapter 15).

Bosentan and **tezosentan,** orally active competitive inhibitors of endothelin (see Chapter 17), have been shown to have some benefits in experimental animal models with heart failure, but results in human trials have been disappointing. Bosentan is approved for use in pulmonary hypertension (see Chapter 11). It has significant teratogenic and hepatotoxic effects.

BETA-ADRENOCEPTOR BLOCKERS

Most patients with chronic heart failure respond favorably to certain β blockers in spite of the fact that these drugs can precipitate acute decompensation of cardiac function (see Chapter 10). Studies with **bisoprolol, carvedilol, metoprolol,** and **nebivolol** showed a reduction in mortality in patients with stable severe heart failure, but this effect was not observed with another β blocker, bucindolol. A full understanding of the beneficial action of β blockade is lacking, but suggested mechanisms include attenuation of the adverse effects of high concentrations of catecholamines (including apoptosis), up-regulation of β receptors, decreased heart rate, and reduced remodeling through inhibition of the mitogenic activity of catecholamines.

CLINICAL PHARMACOLOGY OF DRUGS USED IN HEART FAILURE

The American College of Cardiology/American Heart Association (ACC/AHA) guidelines for management of chronic heart failure specify four stages in the development of heart failure (Table 13–3). Patients in stage A are at high risk because of other disease but have no signs or symptoms of heart failure. Stage B patients have evidence of structural heart disease but no symptoms of heart failure. Stage C patients have structural heart disease and symptoms of failure, and symptoms are responsive to ordinary therapy. Stage D patients have heart failure refractory to ordinary therapy, and special interventions (resynchronization therapy, transplant) are required.

Once stage C is reached, the severity of heart failure is usually described according to a scale devised by the New York Heart Association. Class I failure is associated with no limitations on ordinary activities, and symptoms that occur only with greater than ordinary exercise. Class II is characterized by slight limitation of activities, and results in fatigue and palpitations with ordinary

TABLE 13–3 Classification and treatment of chronic heart failure.

ACC/AHA Stage[1]	NYHA Class[2]	Description	Management
A	Prefailure	No symptoms but risk factors present[3]	Treat obesity, hypertension, diabetes, hyperlipidemia, etc
B	I	Symptoms with severe exercise	ACEI/ARB, β blocker, diuretic
C	II/III	Symptoms with marked (class II) or mild (class III) exercise	Add aldosterone antagonist, digoxin; CRT, hydralazine/nitrate[4]
D	IV	Severe symptoms at rest	Transplant, LVAD

[1]American College of Cardiology/American Heart Association classification.

[2]New York Heart Association classification.

[3]Risk factors include hypertension, myocardial infarct, diabetes.

[4]For selected populations, eg, African American.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; LVAD, left ventricular assist device.

physical activity. Class III failure results in no symptoms at rest, but fatigue, shortness of breath, and tachycardia occur with less than ordinary physical activity. Class IV is associated with symptoms even when the patient is at rest.

MANAGEMENT OF CHRONIC HEART FAILURE

The major steps in the management of patients with chronic heart failure are outlined in Table 13–3. The 2009 update to the ACC/AHA 2005 guidelines suggests that treatment of patients at high risk (stages A and B) should be focused on control of hypertension, hyperlipidemia, and diabetes, if present. Once symptoms and signs of failure are present, stage C has been entered, and active treatment of failure must be initiated.

SODIUM REMOVAL

Sodium removal—by dietary salt restriction and a diuretic—is the mainstay in management of symptomatic heart failure, especially if edema is present. In very mild failure a **thiazide** diuretic may be tried, but a loop agent such as **furosemide** is usually required. Sodium loss causes secondary loss of potassium, which is particularly hazardous if the patient is to be given digitalis. Hypokalemia can be treated with potassium supplementation or through the addition of an ACE inhibitor or a potassium-sparing diuretic such as spironolactone. Spironolactone or eplerenone should probably be considered in all patients with moderate or severe heart failure, since both appear to reduce both morbidity and mortality.

ACE INHIBITORS & ANGIOTENSIN RECEPTOR BLOCKERS

In patients with left ventricular dysfunction but no edema, an ACE inhibitor should be the first drug used. Several large studies have showed clearly that ACE inhibitors are superior to both placebo and to vasodilators and must be considered, along with diuretics, as first-line therapy for chronic heart failure. However, ACE inhibitors cannot replace digoxin in patients already receiving the glycoside because patients withdrawn from digoxin deteriorate while on ACE inhibitor therapy.

By reducing preload and afterload in asymptomatic patients, ACE inhibitors (eg, **enalapril**) slow the progress of ventricular dilation and thus slow the downward spiral of heart failure. Consequently, ACE inhibitors are beneficial in all subsets of patients—from those who are asymptomatic to those in severe chronic failure. This benefit appears to be a class effect; that is, all ACE inhibitors appear to be effective.

The angiotensin II AT_1 receptor blockers (ARBs, eg, **losartan**) produce beneficial hemodynamic effects similar to those of ACE inhibitors. However, large clinical trials suggest that angiotensin receptor blockers are best reserved for patients who cannot tolerate ACE inhibitors (usually because of cough).

VASODILATORS

Vasodilator drugs can be divided into selective arteriolar dilators, venous dilators, and drugs with nonselective vasodilating effects. The choice of agent should be based on the patient's signs and symptoms and hemodynamic measurements. Thus, in patients with high filling pressures in whom the principal symptom is dyspnea, venous dilators such as long-acting **nitrates** will be most helpful in reducing filling pressures and the symptoms of pulmonary congestion. In patients in whom fatigue due to low left ventricular output is a primary symptom, an arteriolar dilator such as **hydralazine** may be helpful in increasing forward cardiac output. In most patients with severe chronic failure that responds poorly to other therapy, the problem usually involves both elevated filling pressures and reduced cardiac output. In these circumstances, dilation of both arterioles and veins is required. In a trial in African-American patients already receiving ACE inhibitors, addition of hydralazine and isosorbide dinitrate reduced mortality. As a result, a fixed combination of these two agents has been made available as isosorbide dinitrate/hydralazine **(BiDil),** and this is currently approved for use only in African Americans.

BETA BLOCKERS & ION CHANNEL BLOCKERS

Trials of β-blocker therapy in patients with heart failure are based on the hypothesis that excessive tachycardia and adverse effects of high catecholamine levels on the heart contribute to the downward course of heart failure. The results clearly indicate that such therapy is beneficial if initiated cautiously at low doses, even though acutely blocking the supportive effects of catecholamines can worsen heart failure. Several months of therapy may be required before improvement is noted; this usually consists of a slight rise in ejection fraction, slower heart rate, and reduction in symptoms. As noted above, not all β blockers have proved useful, but **bisoprolol, carvedilol, metoprolol,** and **nebivolol** have been shown to reduce mortality.

In contrast, the calcium-blocking drugs appear to have no role in the treatment of patients with heart failure. Their depressant effects on the heart may worsen heart failure. On the other hand, slowing of heart rate with **ivabradine** (an I_f blocker, see Chapter 12) appears to be of benefit.

Digitalis

Digoxin is indicated in patients with heart failure and atrial fibrillation. It is usually given only when diuretics and ACE inhibitors have failed to control symptoms. Only about 50% of patients with normal sinus rhythm (usually those with documented systolic dysfunction) will have relief of heart failure from digitalis. Better results are obtained in patients with atrial fibrillation. If the decision is made to use a cardiac glycoside, digoxin is the one chosen in most cases (and the only one available in the USA). When symptoms are mild, slow loading (digitalization) with 0.125–0.25 mg per day is safer and just as effective as the rapid method (0.5–0.75 mg every 8 hours for three doses, followed by 0.125–0.25 mg per day).

Determining the optimal level of digitalis effect may be difficult. Unfortunately, toxic effects may occur before the therapeutic end point is detected. Measurement of plasma digoxin levels is useful in patients who appear unusually resistant or sensitive; a level of 1 ng/mL or less is appropriate.

Because it has a moderate but persistent positive inotropic effect, digitalis can, in theory, reverse all the signs and symptoms of heart failure. Although the net effect of the drug on mortality is mixed, it reduces hospitalization and deaths from progressive heart failure at the expense of an increase in sudden death. It is important to note that the mortality rate is reduced in patients with serum digoxin concentrations of less than 0.9 ng/mL but increased in those with digoxin levels greater than 1.5 ng/mL.

Other Clinical Uses of Digitalis

Digitalis is useful in the management of atrial arrhythmias because of its cardioselective parasympathomimetic effects. In atrial flutter and fibrillation, the depressant effect of the drug on atrioventricular conduction helps control an excessively high ventricular rate. Digitalis has also been used in the control of paroxysmal atrial and atrioventricular nodal tachycardia. At present, calcium channel blockers and adenosine are preferred for this application. Digoxin is explicitly contraindicated in patients with Wolff-Parkinson-White syndrome and atrial fibrillation (see Chapter 14).

Toxicity

In spite of its limited benefits and recognized hazards, digitalis is still heavily used and toxicity is common. Therapy for toxicity manifested as visual changes or gastrointestinal disturbances generally requires no more than reducing the dose of the drug. If cardiac arrhythmia is present and can be ascribed to digitalis, more vigorous therapy may be necessary. Serum digitalis and potassium levels and the electrocardiogram should always be monitored during therapy of significant digitalis toxicity. Electrolyte status should be corrected if abnormal (see above). Monitoring of potassium levels is particularly important in patients on renal dialysis.

In severe digitalis intoxication, serum potassium will already be elevated at the time of diagnosis (because of potassium loss from the intracellular compartment of skeletal muscle and other tissues). Furthermore, automaticity is usually depressed, and antiarrhythmic agents administered in this setting may lead to cardiac arrest. Such patients are best treated with prompt insertion of a temporary cardiac pacemaker catheter and administration of digitalis antibodies **(digoxin immune fab).** These antibodies recognize digitoxin and cardiac glycosides from many other plants in addition to digoxin. They are extremely useful in reversing severe intoxication with most glycosides.

Digitalis-induced arrhythmias are frequently made worse by cardioversion; this therapy should be reserved for ventricular fibrillation if the arrhythmia is glycoside-induced.

CARDIAC RESYNCHRONIZATION THERAPY

Patients with normal sinus rhythm and a wide QRS interval, eg, greater than 120 ms, have impaired synchronization of right and left ventricular contraction. Poor synchronization of ventricular contraction results in diminished cardiac output. Resynchronization, with left ventricular or biventricular pacing, has been shown to reduce mortality in patients with chronic heart failure who were already receiving optimal medical therapy.

MANAGEMENT OF DIASTOLIC HEART FAILURE

Most clinical trials have been carried out in patients with systolic dysfunction, so the evidence regarding the superiority or inferiority of drugs in heart failure with preserved ejection fraction is meager. Most authorities support the use of the drug groups described above, and the SENIORS 2009 study suggests that nebivolol is effective in both systolic and diastolic failure. Control of hypertension is particularly important, and revascularization should be considered if coronary artery disease is present.

Tachycardia limits filling time; therefore, bradycardic drugs may be particularly useful, at least in theory.

MANAGEMENT OF ACUTE HEART FAILURE

Acute heart failure occurs frequently in patients with chronic failure. Such episodes are usually associated with increased exertion, emotion, excess salt intake, nonadherence to medical therapy, or increased metabolic demand occasioned by fever, anemia, etc. A particularly common and important cause of acute failure—with or without chronic failure—is acute myocardial infarction.

Patients with acute myocardial infarction are best treated with emergency revascularization using either coronary angioplasty and a stent, or a thrombolytic agent. Even with revascularization, acute failure may develop in such patients. Many of the signs and symptoms of acute and chronic failure are identical, but their therapies diverge because of the need for more rapid response and the relatively greater frequency and severity of pulmonary vascular congestion in the acute form.

Measurements of arterial pressure, cardiac output, stroke work index, and pulmonary capillary wedge pressure are particularly useful in patients with acute myocardial infarction and acute heart failure. Such patients can be usefully characterized on the basis of three hemodynamic measurements: arterial pressure, left ventricular filling pressure, and cardiac index. When filling pressure is greater than 15 mm Hg and stroke work index is less than 20 g-m/m^2, the mortality rate is high. Intermediate levels of these two variables imply a much better prognosis.

Intravenous treatment is the rule in acute heart failure. Among diuretics, **furosemide** is the most commonly used. **Dopamine** or **dobutamine** are positive inotropic drugs with prompt onset and short durations of action; they are most useful in patients with severe hypotension. **Levosimendan** has been approved for use in acute failure in Europe, and noninferiority has been demonstrated against dobutamine. Vasodilators in use in patients with acute decompensation include **nitroprusside, nitroglycerine,** and nesiritide. Reduction in afterload often improves ejection fraction, but improved survival has not been documented. A small subset of patients in acute heart failure will have hyponatremia, presumably due to increased vasopressin activity. A V_{1a} and V_2 receptor antagonist, **conivaptan,** is approved for parenteral treatment of euvolemic hyponatremia. Several clinical trials have indicated that this drug and related V_2 antagonists **(tolvaptan)** may have a beneficial effect in some patients with acute heart failure and hyponatremia. Thus far, vasopressin antagonists do not seem to reduce mortality.

SUMMARY Drugs Used in Heart Failure

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
DIURETICS				
• Furosemide	Loop diuretic: Decreases NaCl and KCl reabsorption in thick ascending limb of the loop of Henle in the nephron (see Chapter 15)	Increased excretion of salt and water • reduces cardiac preload and afterload • reduces pulmonary and peripheral edema	Acute and chronic heart failure • severe hypertension • edematous conditions	Oral and IV • duration 2–4 h • *Toxicity:* Hypovolemia, hypokalemia, orthostatic hypotension, ototoxicity, sulfonamide allergy
• Hydrochlorothiazide	Decreases NaCl reabsorption in the distal convoluted tubule	Same as furosemide, but less efficacious	Mild chronic failure • mild-moderate hypertension • hypercalciuria • has not been shown to reduce mortality	Oral only • duration 10–12 h • *Toxicity:* Hyponatremia, hypokalemia, hyperglycemia, hyperuricemia, hyperlipidemia, sulfonamide allergy
• *Three other loop diuretics: Bumetanide and torsemide similar to furosemide; ethacrynic acid not a sulfonamide*				
• *Many other thiazides: All basically similar to hydrochlorothiazide, differing only in pharmacokinetics*				
ALDOSTERONE ANTAGONISTS				
• Spironolactone	Blocks cytoplasmic aldosterone receptors in collecting tubules of nephron • possible membrane effect	Increased salt and water excretion • reduces remodeling • reduces mortality	Chronic heart failure • aldosteronism (cirrhosis, adrenal tumor) • hypertension • has been shown to reduce mortality	Oral • duration 24–72 h (slow onset and offset) • *Toxicity:* Hyperkalemia, antiandrogen actions
• *Eplerenone: Similar to spironolactone; more selective antialdosterone effect; no significant antiandrogen action; has been shown to reduce mortality*				

(*continued*)

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
ANGIOTENSIN ANTAGONISTS				
Angiotensin-converting enzyme (ACE) inhibitors: • Captopril	Inhibits ACE • reduces AII formation by inhibiting conversion of AI to AII	Arteriolar and venous dilation • reduces aldosterone secretion • reduces cardiac remodeling	Chronic heart failure • hypertension • diabetic renal disease • has been shown to reduce mortality	Oral • half-life 2–4 h but given in large doses so duration 12–24 h • *Toxicity:* Cough, hyperkalemia, angioneurotic edema • *Interactions:* Additive with other angiotensin antagonists
Angiotensin receptor blockers (ARBs): • Losartan	Antagonize AII effects at AT_1 receptors	Like ACE inhibitors	Like ACE inhibitors • used in patients intolerant to ACE inhibitors • has been shown to reduce mortality	Oral • duration 6–8 h • *Toxicity:* Hyperkalemia; angioneurotic edema • *Interactions:* Additive with other angiotensin antagonists
• *Enalapril, many other ACE inhibitors: Like captopril*				
• *Candesartan, many other ARBs: Like losartan*				
BETA BLOCKERS				
• Carvedilol	Competitively blocks β_1 receptors (see Chapter 10)	Slows heart rate • reduces blood pressure • poorly understood effects • reduces heart failure mortality	Chronic heart failure: To slow progression • reduce mortality in moderate and severe heart failure • many other indications in Chapter 10	Oral • duration 10–12 h • *Toxicity:* Bronchospasm, bradycardia, atrioventricular block, acute cardiac decompensation • see Chapter 10 for other toxicities and interactions
• *Metoprolol, bisoprolol, nebivolol: Select group of β blockers that have been shown to reduce heart failure mortality*				
CARDIAC GLYCOSIDE				
• Digoxin	Na^+/K^+-ATPase inhibition results in reduced Ca^{2+} expulsion and increased Ca^{2+} stored in sarcoplasmic reticulum	Increases cardiac contractility • cardiac parasympathomimetic effect (slowed sinus heart rate, slowed atrioventricular conduction)	Chronic symptomatic heart failure • rapid ventricular rate in atrial fibrillation • has not been definitively shown to reduce mortality	Oral, parenteral • duration 36–40 h • *Toxicity:* Nausea, vomiting, diarrhea • cardiac arrhythmias
VASODILATORS				
Venodilators: • Isosorbide dinitrate	Releases nitric oxide (NO) • activates guanylyl cyclase (see Chapter 12)	Venodilation • reduces preload and ventricular stretch	Acute and chronic heart failure • angina	Oral • 4–6 h duration • *Toxicity:* Postural hypotension, tachycardia, headache • *Interactions:* Additive with other vasodilators and synergistic with phosphodiesterase type 5 inhibitors
Arteriolar dilators: • Hydralazine	Probably increases NO synthesis in endothelium (see Chapter 11)	Reduces blood pressure and afterload • results in increased cardiac output	Hydralazine plus nitrates have reduced mortality	Oral • 8–12 h duration • *Toxicity:* Tachycardia, fluid retention, lupus-like syndrome
Combined arteriolar and venodilator: • Nitroprusside	Releases NO spontaneously • activates guanylyl cyclase	Marked vasodilation • reduces preload and afterload	Acute cardiac decompensation • hypertensive emergencies (malignant hypertension)	IV only • duration 1–2 min • *Toxicity:* Excessive hypotension, thiocyanate and cyanide toxicity • *Interactions:* Additive with other vasodilators
BETA-ADRENOCEPTOR AGONISTS				
• Dobutamine	$Beta_1$-selective agonist • increases cAMP synthesis	Increases cardiac contractility, output	Acute decompensated heart failure • intermittent therapy in chronic failure reduces symptoms	IV only • duration a few minutes • *Toxicity:* Arrhythmias • *Interactions:* Additive with other sympathomimetics
• Dopamine	Dopamine receptor agonist • higher doses activate β and α adrenoceptors	Increases renal blood flow • higher doses increase cardiac force and blood pressure	Acute decompensated heart failure • shock	IV only • duration a few minutes • *Toxicity:* Arrhythmias • *Interactions:* Additive with sympathomimetics

(*continued*)

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
BIPYRIDINES				
• Inamrinone, milrinone	Phosphodiesterase type 3 inhibitors • decrease cAMP breakdown	Vasodilators; lower peripheral vascular resistance • also increase cardiac contractility	Acute decompensated heart failure • increase mortality in chronic failure	IV only • duration 3–6 h • *Toxicity:* Arrhythmias • *Interactions:* Additive with other arrhythmogenic agents
NATRIURETIC PEPTIDE				
• Nesiritide	Activates BNP receptors, increases cGMP	Vasodilation • diuresis	Acute decompensated failure • has not been shown to reduce mortality	IV only • duration 18 minutes • *Toxicity:* Renal damage, hypotension, may increase mortality

PREPARATIONS AVAILABLE

DIURETICS

See Chapter 15.

DIGITALIS

Digoxin (generic, Lanoxicaps, Lanoxin)
Oral: 0.125, 0.25 mg tablets; 0.05, 0.1, 0.2 mg capsules*; 0.05 mg/mL elixir
Parenteral: 0.1, 0.25 mg/mL for injection

DIGITALIS ANTIBODY

Digoxin immune fab (ovine) (Digibind, DigiFab)
Parenteral: 38 or 40 mg per vial with 75 mg sorbitol lyophilized powder to reconstitute for IV injection. Each vial will bind approximately 0.5 mg digoxin or digitoxin.

SYMPATHOMIMETICS MOST COMMONLY USED IN CONGESTIVE HEART FAILURE

Dobutamine (generic)
Parenteral: 12.5 mg/mL for IV infusion

Dopamine (generic, Intropin)
Parenteral: 40, 80, 160 mg/mL for IV injection; 80, 160, 320 mg/dL in 5% dextrose for IV infusion

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Benazepril (generic, Lotensin)
Oral: 5, 10, 20, 40 mg tablets

Captopril (generic, Capoten)
Oral: 12.5, 25, 50, 100 mg tablets

Enalapril (generic, Vasotec, Vasotec I.V.)
Oral: 2.5, 5, 10, 20 mg tablets
Parenteral: 1.25 mg enalaprilat/mL

Fosinopril (generic, Monopril)
Oral: 10, 20, 40 mg tablets

Lisinopril (generic, Prinivil, Zestril)
Oral: 2.5, 5, 10, 20, 30, 40 mg tablets

Moexipril (generic, Univasc)
Oral: 7.5, 15 mg tablets

Perindopril (Aceon)
Oral: 2, 4, 8 mg tablets

Quinapril (generic, Accupril)
Oral: 5, 10, 20, 40 mg tablets

Ramipril (Altace)
Oral: 1.25, 2.5, 5, 10 mg capsules

Trandolapril (Mavik)
Oral: 1, 2, 4 mg tablets

ANGIOTENSIN RECEPTOR BLOCKERS

Candesartan (Atacand)
Oral: 4, 8, 16, 32 mg tablets

Eprosartan (Teveten)
Oral: 600 mg tablets

Irbesartan (Avapro)
Oral: 75, 150, 300 mg tablets

Losartan (Cozaar)
Oral: 25, 50, 100 mg tablets

Olmesartan (Benicar)
Oral: 5, 20, 40 mg tablets

Telmisartan (Micardis)
Oral: 20, 40, 80 mg tablets

Valsartan (Diovan)
Oral: 40, 80, 160, 320 mg tablets

BETA BLOCKERS THAT HAVE REDUCED MORTALITY IN HEART FAILURE

Bisoprolol (generic, Zebeta, off-label use)
Oral: 5, 10 mg tablets

Carvedilol (Coreg)
Oral: 3.125, 6.25, 12.5, 25 mg tablets; 10, 20, 40, 80 mg extended-release capsules

Metoprolol (Lopressor, Toprol XL)
Oral: 50, 100 mg tablets; 25, 50, 100, 200 mg extended-release tablets
Parenteral: 1 mg/mL for IV injection

Nebivolol (Bystolic)
Oral: 2.5, 5, 10 mg tablets

ALDOSTERONE ANTAGONISTS

Spironolactone (generic, Aldactone)
Oral: 25, 50 mg tablets

Eplerenone (Inspra)
Oral: 25, 50 mg tablets

OTHER DRUGS

Hydralazine (generic) (see Chapter 11)

Isosorbide dinitrate (see Chapter 12)

Nitroglycerine (see Chapter 12)

Hydralazine plus isosorbide dinitrate fixed dose (BiDil)
Oral: 37.5 mg hydralazine + 20 mg isosorbide dinitrate tablets

Inamrinone (generic)
Parenteral: 5 mg/mL for IV injection

Milrinone (generic, Primacor)
Parenteral: 1 mg/mL for IV injection

Nesiritide (Natrecor)
Parenteral: 1.58 mg powder to reconstitute for IV injection

Bosentan (Tracleer)
Oral: 62.5, 125 mg tablets

*Digoxin capsules (Lanoxicaps) have greater bioavailability than digoxin tablets.

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CASE STUDY ANSWER

The patient has a low ejection fraction with systolic heart failure. He was placed on a low-sodium diet and treated with a diuretic (furosemide 40 mg twice daily). On this therapy, he was less short of breath on exertion and could also lie flat without dyspnea. An angiotensin-converting enzyme (ACE) inhibitor was added (enalapril 20 mg twice daily), and over the next few weeks, he continued to feel better. Because of continued shortness of breath on exercise, digoxin 0.25 mg/d was added with a further improvement in exercise tolerance. Addition of a β blocker and eplerenone is being considered.

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CHAPTER 14

Agents Used in Cardiac Arrhythmias

Joseph R. Hume, PhD, &
Augustus O. Grant, MD, PhD

CASE STUDY

A 69-year-old retired teacher presents with a 1-month history of palpitations, intermittent shortness of breath, and fatigue. She has a history of hypertension. An ECG shows atrial fibrillation with a ventricular response of 122 bpm and signs of left ventricular hypertrophy. She is anticoagulated with warfarin and started on sustained-release metoprolol 50 mg/d. After 7 days, her rhythm reverts to normal sinus spontaneously. However, over the ensuing month, she continues to have intermittent palpitations and fatigue. Continuous ECG recording over a 48-hour period documents paroxysms of atrial fibrillation with heart rates of 88–114 bpm. An echocardiogram shows a left ventricular ejection fraction of 38% with no localized wall motion abnormality. At this stage, would you initiate treatment with an antiarrhythmic drug to maintain normal sinus rhythm, and if so, what drug would you choose?

Cardiac arrhythmias are a common problem in clinical practice, occurring in up to 25% of patients treated with digitalis, 50% of anesthetized patients, and over 80% of patients with acute myocardial infarction. Arrhythmias may require treatment because rhythms that are too rapid, too slow, or asynchronous can reduce cardiac output. Some arrhythmias can precipitate more serious or even lethal rhythm disturbances; for example, early premature ventricular depolarizations can precipitate ventricular fibrillation. In such patients, antiarrhythmic drugs may be lifesaving. On the other hand, the hazards of antiarrhythmic drugs—and in particular the fact that they can *precipitate* lethal arrhythmias in some patients—has led to a reevaluation of their relative risks and benefits. In general, treatment of asymptomatic or minimally symptomatic arrhythmias should be avoided for this reason.

Arrhythmias can be treated with the drugs discussed in this chapter and with nonpharmacologic therapies such as pacemakers, cardioversion, catheter ablation, and surgery. This chapter describes the pharmacology of drugs that suppress arrhythmias by a direct action on the cardiac cell membrane. Other modes of therapy are discussed briefly (see Box: The Nonpharmacologic Therapy of Cardiac Arrhythmias).

ELECTROPHYSIOLOGY OF NORMAL CARDIAC RHYTHM

The electrical impulse that triggers a normal cardiac contraction originates at regular intervals in the sinoatrial (SA) node (Figure 14–1), usually at a frequency of 60–100 bpm. This impulse spreads rapidly through the atria and enters the atrioventricular (AV) node, which is normally the only conduction pathway between the atria and ventricles. Conduction through the AV node is slow, requiring about 0.15 seconds. (This delay provides time for atrial contraction to propel blood into the ventricles.) The impulse then propagates over the His-Purkinje system and invades all parts of the ventricles, beginning with the endocardial surface near the apex and ending with the epicardial surface at the base of the heart. Ventricular activation is complete in less than 0.1 seconds; therefore, contraction of all of the ventricular muscle is normally synchronous and hemodynamically effective.

Arrhythmias consist of cardiac depolarizations that deviate from the above description in one or more aspects: there is an abnormality in the site of origin of the impulse, its rate or regularity, or its conduction.

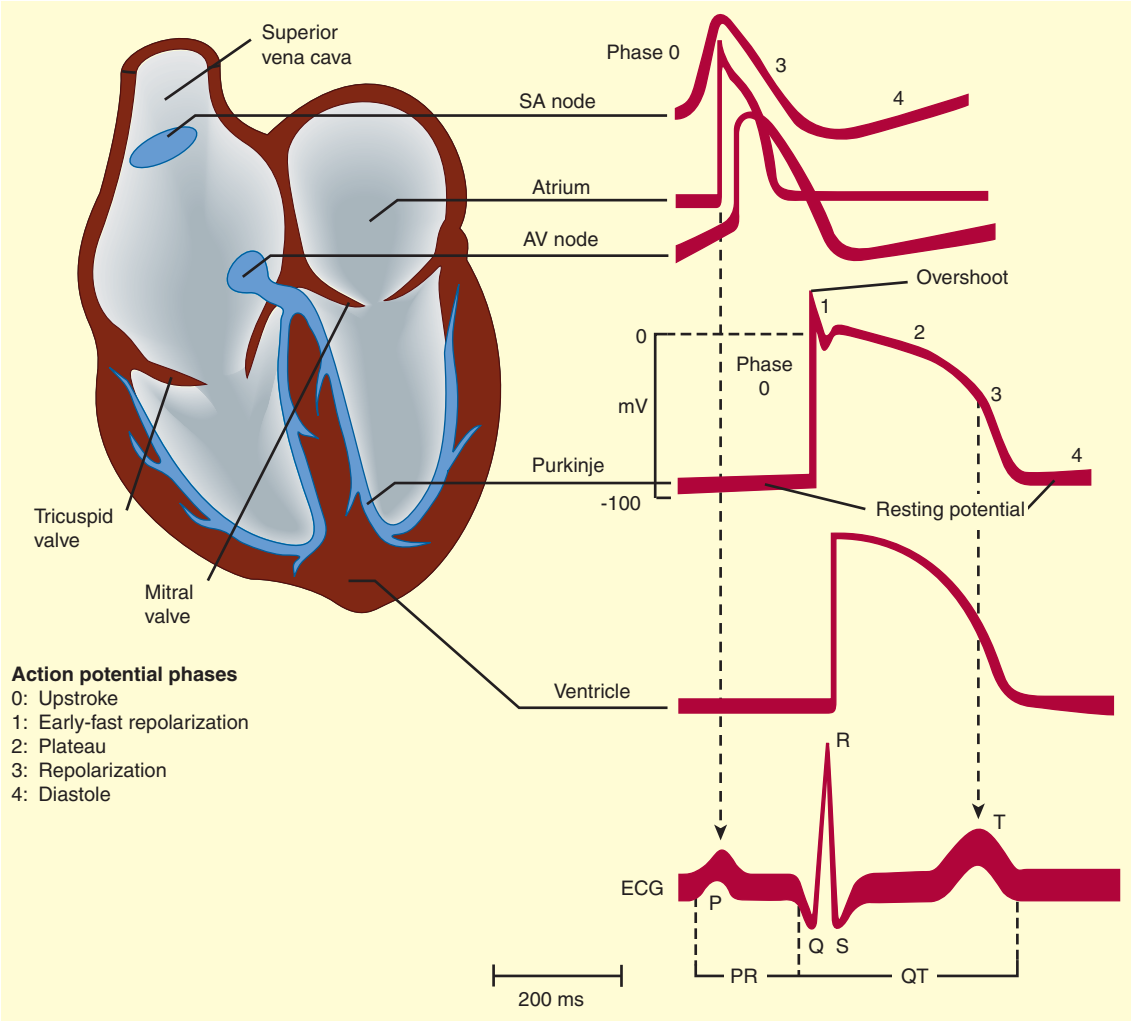


FIGURE 14–1 Schematic representation of the heart and normal cardiac electrical activity (intracellular recordings from areas indicated and ECG). Sinoatrial (SA) node, atrioventricular (AV) node, and Purkinje cells display pacemaker activity (phase 4 depolarization). The ECG is the body surface manifestation of the depolarization and repolarization waves of the heart. The P wave is generated by atrial depolarization, the QRS by ventricular muscle depolarization, and the T wave by ventricular repolarization. Thus, the PR interval is a measure of conduction time from atrium to ventricle, and the QRS duration indicates the time required for all of the ventricular cells to be activated (ie, the intraventricular conduction time). The QT interval reflects the duration of the ventricular action potential.

Ionic Basis of Membrane Electrical Activity

The transmembrane potential of cardiac cells is determined by the concentrations of several ions—chiefly sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), and chloride (Cl^-)—on either side of the membrane and the permeability of the membrane to each ion. These water-soluble ions are unable to freely diffuse across the lipid cell membrane in response to their electrical and concentration gradients; they require aqueous channels (specific pore-forming proteins) for such diffusion. Thus, ions move across cell membranes in response to their gradients only at specific times during the cardiac cycle when these ion channels are open. The movements of the ions produce currents that form the basis of the cardiac action potential. Individual channels are relatively ion-specific, and the flux of ions through them is controlled by "gates" (flexible portions of the peptide chains that make up the channel proteins). Each type of channel has its own type of gate (sodium, calcium, and some potassium channels are each thought to have two types of gates). The channels primarily responsible for the cardiac action potential (sodium, calcium, and several potassium) are opened and closed ("gated") by voltage changes across the cell membrane; that is, they are voltage-sensitive. Most are also modulated by ion concentrations and metabolic conditions, and some potassium channels are primarily ligand- rather than voltage-gated.

All the ionic currents that are currently thought to contribute to the cardiac action potential are illustrated in Figure 14–2. At rest, most cells are not significantly permeable to sodium, but at the start of each action potential, they become quite permeable (see below). In electrophysiologic terms, the conductance of the fast sodium

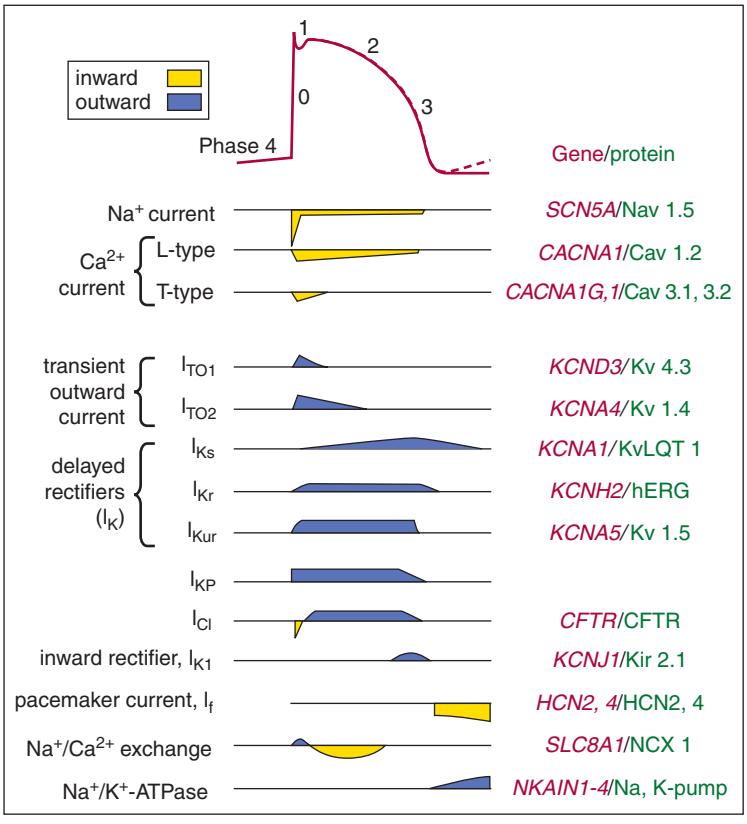


FIGURE 14–2 Schematic diagram of the ion permeability changes and transport processes that occur during an action potential and the diastolic period following it. Yellow indicates inward (depolarizing) membrane currents; blue indicates outward (repolarizing) membrane currents. Multiple subtypes of potassium and calcium currents, with different sensitivities to blocking drugs, have been identified. The right side of the figure lists the genes and proteins responsible for each type of channel or transporter.

channel suddenly increases in response to a depolarizing stimulus. Similarly, calcium enters and potassium leaves the cell with each action potential. Therefore, in addition to ion channels, the cell must have mechanisms to maintain stable transmembrane ionic conditions by establishing and maintaining ion gradients. The most important of these active mechanisms is the sodium pump, Na^+/K^+-ATPase, described in Chapter 13. This pump and other active ion carriers contribute indirectly to the transmembrane potential by maintaining the gradients necessary for diffusion through channels. In addition, some pumps and exchangers produce net current flow (eg, by exchanging three Na^+ for two K^+ ions) and hence are termed "electrogenic."

When the cardiac cell membrane becomes permeable to a specific ion (ie, when the channels selective for that ion are open), movement of that ion across the cell membrane is determined by Ohm's law: current = voltage ÷ resistance, or current = voltage × conductance. Conductance is determined by the properties of the individual ion channel protein. The voltage term is the difference between the actual membrane potential and the reversal potential for that ion (the membrane potential at which no current would flow even if channels were open). For example, in the case of sodium in a cardiac cell at rest, there is a substantial concentration gradient (140 mmol/L Na^+ outside; 10–15 mmol/L Na^+ inside) and an electrical gradient (0 mV outside; −90 mV inside) that would drive Na^+ into cells. Sodium does not enter the cell at rest because sodium channels are closed; when sodium channels open, the very large influx of Na^+ accounts for phase 0 depolarization of the action potential. The situation for K^+ in the resting cardiac cell is quite different. Here, the concentration gradient (140 mmol/L inside; 4 mmol/L outside) would drive the ion out of the cell, but the electrical gradient would drive it in; that is, the inward gradient is in equilibrium with the outward gradient. In fact, certain potassium channels ("inward rectifier" channels) are open in the resting cell, but little current flows through them because of this balance. The equilibrium, or **reversal potential,** for ions is determined by the **Nernst equation:**

$$E_{ion} = 61 \times \log\left(\frac{C_e}{C_i}\right)$$

where C_e and C_i are the extracellular and intracellular concentrations, respectively, multiplied by their activity coefficients. Note that raising extracellular potassium makes E_K less negative. When this occurs, the membrane depolarizes until the new E_K is reached. Thus, extracellular potassium concentration and inward rectifier channel function are the major factors determining the membrane potential of the resting cardiac cell. The conditions required for application of the Nernst equation are approximated at the peak of

the overshoot (using sodium concentrations) and during rest (using potassium concentrations) in most nonpacemaker cardiac cells. If the permeability is significant for both potassium and sodium, the Nernst equation is not a good predictor of membrane potential, but the **Goldman-Hodgkin-Katz equation** may be used:

$$E_{mem} = 61 \times \log\left(\frac{P_K \times K_e + P_{Na} \times Na_e}{P_K \times K_i + P_{Na} \times Na_i}\right)$$

In pacemaker cells (whether normal or ectopic), spontaneous depolarization (the pacemaker potential) occurs during diastole (phase 4, Figure 14–1). This depolarization results from a gradual increase of depolarizing current through special hyperpolarization-activated ion channels (I_f, also called I_h) in pacemaker cells. The effect of changing extracellular potassium is more complex in a pacemaker cell than it is in a nonpacemaker cell because the effect on permeability to potassium is much more important in a pacemaker (see Box: Effects of Potassium). In a pacemaker—especially an ectopic one—the end result of an increase in extracellular potassium is usually to slow or stop the pacemaker. Conversely, hypokalemia often facilitates ectopic pacemakers.

The Active Cell Membrane

In normal atrial, Purkinje, and ventricular cells, the action potential upstroke (phase 0) is dependent on sodium current. From a functional point of view, it is convenient to describe the behavior of the sodium current in terms of three channel states (Figure 14–3). The cardiac sodium channel protein has been

Effects of Potassium

The effects of changes in serum potassium on cardiac action potential duration, pacemaker rate, and arrhythmias can appear somewhat paradoxical if changes are predicted based solely on a consideration of changes in the potassium *electrochemical gradient*. In the heart, however, changes in serum potassium concentration have the additional effect of altering potassium *conductance* (increased extracellular potassium increases potassium conductance) independent of simple changes in electrochemical driving force, and this effect often predominates. As a result, the actual observed effects of ***hyperkalemia*** include reduced action potential duration, slowed conduction, decreased pacemaker rate, and decreased pacemaker arrhythmogenesis. Conversely, the actual observed effects of ***hypokalemia*** include prolonged action potential duration, increased pacemaker rate, and increased pacemaker arrhythmogenesis. Furthermore, pacemaker rate and arrhythmias involving ectopic pacemaker cells appear to be more sensitive to changes in serum potassium concentration, compared with cells of the sinoatrial node. These effects of serum potassium on the heart probably contribute to the observed increased sensitivity to potassium channel-blocking antiarrhythmic agents (quinidine or sotalol) during hypokalemia, eg, accentuated action potential prolongation and tendency to cause torsades de pointes.

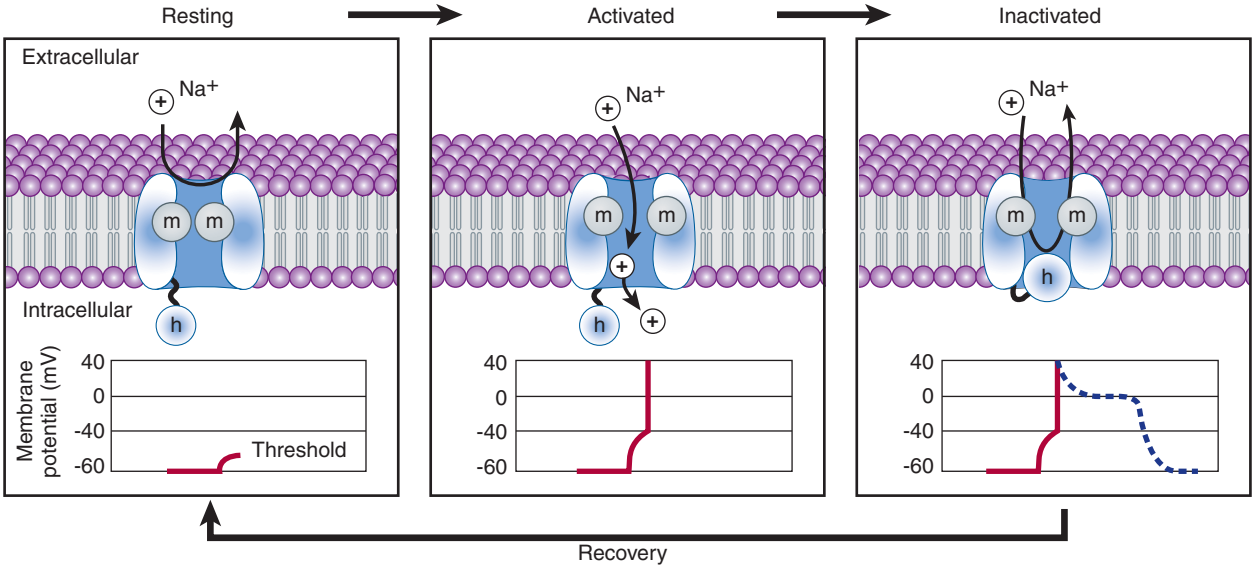


FIGURE 14–3 A schematic representation of Na^+ channels cycling through different conformational states during the cardiac action potential. Transitions between resting, activated, and inactivated states are dependent on membrane potential and time. The activation gate is shown as *m* and the inactivation gate as *h*. Potentials typical for each state are shown under each channel schematic as a function of time. The dashed line indicates that part of the action potential during which most Na^+ channels are completely or partially inactivated and unavailable for reactivation.

cloned, and it is now recognized that these channel states actually represent different protein conformations. In addition, regions of the protein that confer specific behaviors, such as voltage sensing, pore formation, and inactivation, are now being identified. The gates described below and in Figure 14–3 represent such regions.

Depolarization to the threshold voltage results in opening of the activation (*m*) gates of sodium channels (Figure 14–3, middle). If the inactivation (*h*) gates of these channels have not already closed, the channels are now open or activated, and sodium permeability is markedly increased, greatly exceeding the permeability for any other ion. Extracellular sodium therefore diffuses down its electrochemical gradient into the cell, and the membrane potential very rapidly approaches the sodium equilibrium potential, E_{Na} (about +70 mV when Na_e = 140 mmol/L and Na_i = 10 mmol/L). This intense sodium current is very brief because opening of the *m* gates upon depolarization is promptly followed by closure of the *h* gates and inactivation of the sodium channels (Figure 14–3, right).

Most calcium channels become activated and inactivated in what appears to be the same way as sodium channels, but in the case of the most common type of cardiac calcium channel (the "L" type), the transitions occur more slowly and at more positive potentials. The action potential plateau (phases 1 and 2) reflects the turning off of most of the sodium current, the waxing and waning of calcium current, and the slow development of a repolarizing potassium current.

Final repolarization (phase 3) of the action potential results from completion of sodium and calcium channel inactivation and the growth of potassium permeability, so that the membrane potential once again approaches the potassium equilibrium potential. The major potassium currents involved in phase 3 repolarization include a rapidly activating potassium current (I_{Kr}) and a slowly activating potassium current (I_{Ks}). These two potassium currents are sometimes discussed together as "I_K." It is noteworthy that a different potassium current, distinct from I_{Kr} and I_{Ks}, may control repolarization in SA nodal cells. This explains why some drugs that block either I_{Kr} or I_{Ks} may prolong repolarization in Purkinje and ventricular cells, but have little effect on SA nodal repolarization (see Box: Molecular & Genetic Basis of Cardiac Arrhythmias).

The Effect of Resting Potential on Action Potentials

A key factor in the pathophysiology of arrhythmias and the actions of antiarrhythmic drugs is the relation between the resting potential of a cell and the action potentials that can be evoked in it (Figure 14–4, left panel). Because the inactivation gates of sodium channels in the resting membrane close over the potential range –75 to –55 mV, fewer sodium channels are "available" for diffusion of sodium ions when an action potential is evoked from a resting potential of –60 mV than when it is evoked from a resting potential of –80 mV. Important consequences of the reduction in peak sodium permeability include reduced maximum upstroke velocity (called $\dot{V}_{max}$, for maximum rate of change of membrane voltage), reduced action potential amplitude, reduced excitability, and reduced conduction velocity.

During the plateau of the action potential, most sodium channels are inactivated. Upon repolarization, recovery from inactivation takes place (in the terminology of Figure 14–3, the *h* gates reopen), making the channels again available for excitation. The time between phase 0 and sufficient recovery of sodium channels in phase 3 to permit a new propagated response to an external stimulus is the **refractory period.** Changes in refractoriness (determined by either altered recovery from inactivation or altered action potential duration) can be important in the genesis or suppression of certain arrhythmias. Another important effect of less negative resting potential is prolongation of this recovery time, as shown in Figure 14–4 (right panel). The prolongation of recovery time is reflected in an increase in the effective refractory period.

A brief, sudden, depolarizing stimulus, whether caused by a propagating action potential or by an external electrode arrangement, causes the opening of large numbers of activation gates before a significant number of inactivation gates can close. In contrast, slow reduction (depolarization) of the resting potential, whether brought about by hyperkalemia, sodium pump blockade, or ischemic cell damage, results in depressed sodium currents during the upstrokes of action potentials. Depolarization of the resting potential to levels positive to –55 mV abolishes sodium currents, since all sodium channels are inactivated. However, such severely depolarized cells have been found to support special action potentials under circumstances that increase calcium permeability or decrease potassium permeability. These "slow responses"—slow upstroke velocity and slow conduction—depend on a calcium inward current and constitute the normal electrical activity in the SA and AV nodes, since these tissues have a normal resting potential in the range of –50 to –70 mV. Slow responses may also be important for certain arrhythmias.

Modern techniques of molecular biology and electrophysiology can identify multiple subtypes of calcium and potassium channels. One way in which such subtypes may differ is in sensitivity to drug effects, so drugs targeting specific channel subtypes may be developed in the future.

MECHANISMS OF ARRHYTHMIAS

Many factors can precipitate or exacerbate arrhythmias: ischemia, hypoxia, acidosis or alkalosis, electrolyte abnormalities, excessive catecholamine exposure, autonomic influences, drug toxicity (eg, digitalis or antiarrhythmic drugs), overstretching of cardiac fibers, and the presence of scarred or otherwise diseased tissue. However, all arrhythmias result from (1) disturbances in impulse formation, (2) disturbances in impulse conduction, or (3) both.

Disturbances of Impulse Formation

The interval between depolarizations of a pacemaker cell is the sum of the duration of the action potential and the duration of the diastolic interval. Shortening of either duration results in an

Molecular & Genetic Basis of Cardiac Arrhythmias

It is now possible to define the molecular basis of several congenital and acquired cardiac arrhythmias. The best example is the polymorphic ventricular tachycardia known as torsades de pointes (shown in Figure 14–8), which is associated with prolongation of the QT interval (especially at the onset of the tachycardia), syncope, and sudden death. This must represent prolongation of the action potential of at least some ventricular cells (Figure 14–1). The effect can, in theory, be attributed to either increased inward current (gain of function) or decreased outward current (loss of function) during the plateau of the action potential. In fact, recent molecular genetic studies have identified up to 300 different mutations in at least eight ion channel genes that produce the congenital long QT (LQT) syndrome (Table 14–1), and different mutations may have different clinical implications. Loss-of-function mutations in potassium channel genes produce decreases in outward repolarizing current and are responsible for LQT subtypes 1, 2, 5, 6, and 7. *HERG* and *KCNE2* (*MiRP1*) genes encode subunits of the rapid delayed rectifier potassium current (I_{Kr}), whereas *KCNQ1* and *KCNE1* (*minK*) encode subunits of the slow delayed rectifier potassium current (I_{Ks}). *KCNJ2* encodes an inwardly rectifying potassium current (I_{Kir}). In contrast, gain-of-function mutations in the sodium channel gene (*SCN5A*) or calcium channel gene (*CACNA1c*) cause increases in inward plateau current and are responsible for LQT subtypes 3 and 8, respectively.

Molecular genetic studies have identified the reason why congenital and acquired cases of torsades de pointes can be so strikingly similar. The potassium channel I_{Kr} (encoded by *HERG*) is blocked or modified by many drugs (eg, quinidine, sotalol) or electrolyte abnormalities (hypokalemia, hypomagnesemia, hypocalcemia) that also produce torsades de pointes. Thus, the identification of the precise molecular mechanisms underlying various forms of the LQT syndromes now raises the possibility that specific therapies may be developed for individuals with defined molecular abnormalities. Indeed, preliminary reports suggest that the sodium channel blocker mexiletine can correct the clinical manifestations of congenital LQT subtype 3 syndrome. It is likely that torsades de pointes originates from triggered upstrokes arising from early afterdepolarizations (Figure 14–5). Thus, therapy is directed at correcting hypokalemia, eliminating triggered upstrokes (eg, by using β blockers or magnesium), or shortening the action potential (eg, by increasing heart rate with isoproterenol or pacing)—or all of these.

The molecular basis of several other congenital cardiac arrhythmias associated with sudden death has also recently been identified. Three forms of short QT syndrome have been identified that are linked to gain-of-function mutations in three different potassium channel genes (*KCNH2*, *KCNQ1*, and *KCNJ2*). Catecholaminergic polymorphic ventricular tachycardia, a disease that is characterized by stress- or emotion-induced syncope, can be caused by genetic mutations in two different proteins in the sarcoplasmic reticulum that control intracellular calcium homeostasis. Mutations in two different ion channel genes (*HCN4* and *SCN5A*) have been linked to congenital forms of sick sinus syndrome. The Brugada syndrome, which is characterized by ventricular fibrillation associated with persistent ST-segment elevation, and progressive cardiac conduction disorder (PCCD), characterized by impaired conduction in the His-Purkinje system and right or left bundle block leading to complete atrioventricular block, have both been linked to several loss-of-function mutations in the sodium channel gene, *SCN5A*. At least one form of familial atrial fibrillation is caused by a gain-of-function mutation in the potassium channel gene, *KCNQ1*.

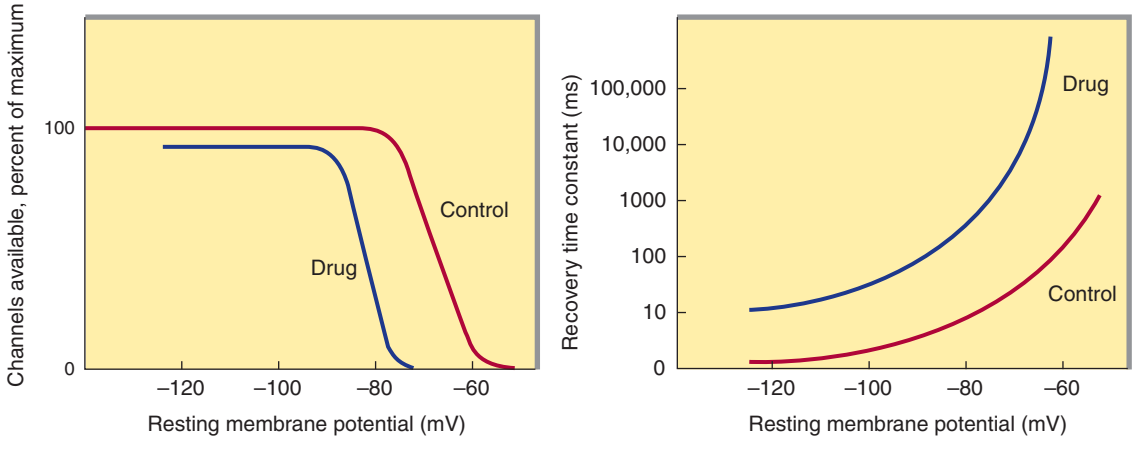


FIGURE 14–4 Dependence of sodium channel function on the membrane potential preceding the stimulus. **Left:** The fraction of sodium channels available for opening in response to a stimulus is determined by the membrane potential immediately preceding the stimulus. The decrease in the fraction available when the resting potential is depolarized in the absence of a drug (control curve) results from the voltage-dependent closure of *h* gates in the channels. The curve labeled *Drug* illustrates the effect of a typical local anesthetic antiarrhythmic drug. Most sodium channels are inactivated during the plateau of the action potential. **Right:** The time constant for recovery from inactivation after repolarization also depends on the resting potential. In the absence of drug, recovery occurs in less than 10 ms at normal resting potentials (−85 to −95 mV). Depolarized cells recover more slowly (note logarithmic scale). In the presence of a sodium channel-blocking drug, the time constant of recovery is increased, but the increase is far greater at depolarized potentials than at more negative ones.

TABLE 14–1 Molecular and genetic basis of some cardiac arrhythmias.

Type	Chromosome Involved	Defective Gene	Ion Channel or Proteins Affected	Result
LQT-1	11	*KCNQ1*	I_{Ks}	LF
LQT-2	7	*KCNH2* (*HERG*)	I_{Kr}	LF
LQT-3	3	*SCN5A*	I_{Na}	GF
LQT-4	4	Ankyrin-B[1]		LF
LQT-5	21	*KCNE1* (*minK*)	I_{Ks}	LF
LQT-6	21	*KCNE2* (*MiRP1*)	I_{Kr}	LF
LQT-7[2]	17	*KCNJ2*	I_{Kir}	LF
LQT-8[3]	12	*CACNA1c*	I_{Ca}	GF
SQT-1	7	*KCNH2*	I_{Kr}	GF
SQT-2	11	*KCNQ1*	I_{Ks}	GF
SQT-3	17	*KCNJ2*	I_{Kir}	GF
CPVT-1[4]	1	*hRyR2*	Ryanodine receptor	GF
CPVT-2	1	*CASQ2*	Calsequestrin	LF
Sick sinus syndrome	15 or 3	*HCN4 or SCN5A*[5]		LF
Brugada syndrome	3	*SCN5A*	I_{Na}	LF
PCCD	3	*SCN5A*	I_{Na}	LF
Familial atrial fibrillation	11	*KCNQ1*	I_{Ks}	GF

[1]Ankyrins are intracellular proteins that associate with a variety of transport proteins including Na^+ channels, Na^+/K^+-ATPase, Na^+, Ca^{2+} exchange, and Ca^{2+} release channels.

[2]Also known as Andersen syndrome.

[3]Also known as Timothy syndrome; multiple organ dysfunction, including autism.

[4]CPVT, catecholaminergic polymorphic ventricular tachycardia; mutations in intracellular ryanodine Ca^{2+} release channel or the Ca^{2+} buffer protein, calsequestrin, may result in enhanced sarcoplasmic reticulum Ca^{2+} leakage or enhanced Ca^{2+} release during adrenergic stimulation, causing triggered arrhythmogenesis.

[5]*HCN4* encodes a pacemaker current in sinoatrial nodal cells; mutations in sodium channel gene (*SCN5A*) cause conduction defects.

GF, gain of function; LF, loss of function; LQT, long QT syndrome; PCCD, progressive cardiac conduction disorder; SQT, short QT syndrome.

increase in pacemaker rate. The more important of the two, diastolic interval, is determined primarily by the slope of phase 4 depolarization (pacemaker potential). Vagal discharge and β-receptor–blocking drugs slow normal pacemaker rate by reducing the phase 4 slope (acetylcholine also makes the maximum diastolic potential more negative). Acceleration of pacemaker discharge is often brought about by increased phase 4 depolarization slope, which can be caused by hypokalemia, β-adrenoceptor stimulation, positive chronotropic drugs, fiber stretch, acidosis, and partial depolarization by currents of injury.

Latent pacemakers (cells that show slow phase 4 depolarization even under normal conditions, eg, some Purkinje fibers) are particularly prone to acceleration by the above mechanisms. However, all cardiac cells, including normally quiescent atrial and ventricular cells, may show repetitive pacemaker activity when depolarized under appropriate conditions, especially if hypokalemia is also present.

Afterdepolarizations (Figure 14–5) are transient depolarizations that interrupt phase 3 **(early afterdepolarizations, EADs)** or phase 4 **(delayed afterdepolarizations, DADs)**. EADs are usually exacerbated at *slow* heart rates and are thought to contribute to the development of long QT-related arrhythmias (see Box: Molecular & Genetic Basis of Cardiac Arrhythmias). DADs, on the other hand, often occur when intracellular calcium is increased (see Chapter 13). They are exacerbated by *fast* heart rates and are thought to be responsible for some arrhythmias related to digitalis excess, to catecholamines, and to myocardial ischemia.

Disturbances of Impulse Conduction

Severely depressed conduction may result in simple **block,** eg, AV nodal block or bundle branch block. Because parasympathetic control of AV conduction is significant, partial AV block is sometimes relieved by atropine. Another common abnormality of conduction is **reentry** (also known as "circus movement"), in which one impulse reenters and excites areas of the heart more than once (Figure 14–6).

The path of the reentering impulse may be confined to very small areas, eg, within or near the AV node, or it may involve large portions of the atrial or ventricular walls. Some forms of reentry are strictly anatomically determined; for example, in Wolff-Parkinson-White syndrome, the reentry circuit consists of atrial tissue, the AV node, ventricular tissue, and an accessory AV connection (bundle of Kent, a bypass tract). In other cases (eg, atrial or ventricular fibrillation),

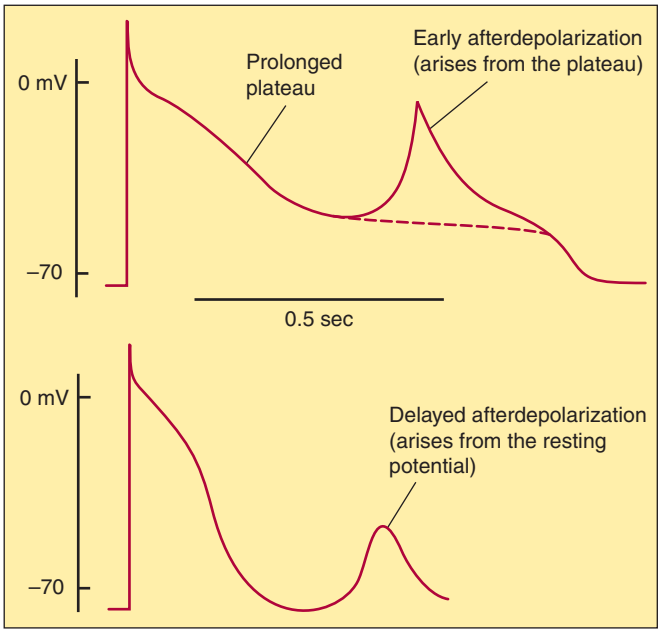


FIGURE 14–5 Two forms of abnormal activity, early (**top**) and delayed afterdepolarizations (**bottom**). In both cases, abnormal depolarizations arise during or after a normally evoked action potential. They are therefore often referred to as "triggered" automaticity; that is, they require a normal action potential for their initiation.

multiple reentry circuits, determined by the varying properties of the cardiac tissue, may meander through the heart in apparently random paths. The circulating impulse often gives off "daughter impulses" that can spread to the rest of the heart. Depending on how many round trips through the pathway the reentrant impulse makes before dying out, the arrhythmia may be manifest as one or a few extra beats or as a sustained tachycardia.

For reentry to occur, three conditions must coexist, as indicated in Figure 14–6. (1) There must be an obstacle (anatomic or physiologic) to homogeneous conduction, thus establishing a circuit around which the reentrant wavefront can propagate. (2) There must be unidirectional block at some point in the circuit; that is, conduction must die out in one direction but continue in the opposite direction (as shown in Figure 14–6, the impulse can gradually decrease as it invades progressively more depolarized tissue until it finally blocks—a process known as decremental conduction). (3) Conduction time around the circuit must be long enough that the retrograde impulse does not enter refractory tissue as it travels around the obstacle; that is, the conduction time must exceed the effective refractory period. It is important to note that reentry depends on conduction that has been depressed by some critical amount, usually as a result of injury or ischemia. If conduction velocity is too slow, bidirectional block rather than unidirectional block occurs; if the reentering impulse is too weak, conduction may fail, or the impulse may arrive so late that it collides with the next regular impulse. On the other hand, if conduction is too rapid—ie, almost normal—bidirectional conduction rather than unidirectional block will occur. Even in the presence of unidirectional block, if the impulse travels around the obstacle too rapidly, it will reach tissue that is still refractory. Representative electrocardiograms of important arrhythmias are shown in Figures 14–7 and 14–8.

Slowing of conduction may be due to depression of sodium current, depression of calcium current (the latter especially in the AV node), or both. Drugs that abolish reentry usually work by

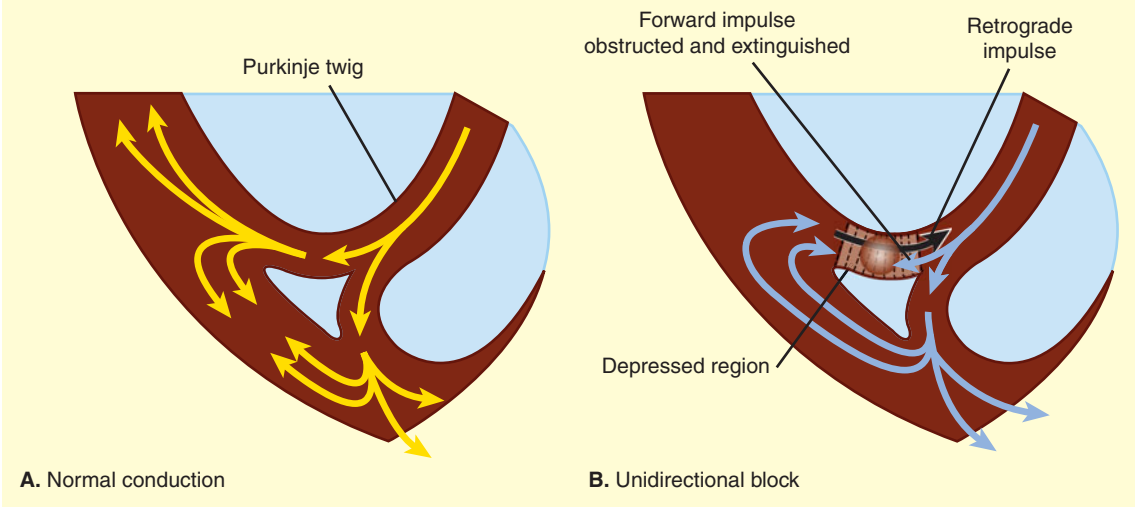


FIGURE 14–6 Schematic diagram of a reentry circuit that might occur in small bifurcating branches of the Purkinje system where they enter the ventricular wall. **A:** Normally, electrical excitation branches around the circuit, is transmitted to the ventricular branches, and becomes extinguished at the other end of the circuit due to collision of impulses. **B:** An area of unidirectional block develops in one of the branches, preventing anterograde impulse transmission at the site of block, but the retrograde impulse may be propagated through the site of block if the impulse finds excitable tissue; that is, the refractory period is shorter than the conduction time. This impulse then reexcites tissue it had previously passed through, and a reentry arrhythmia is established.

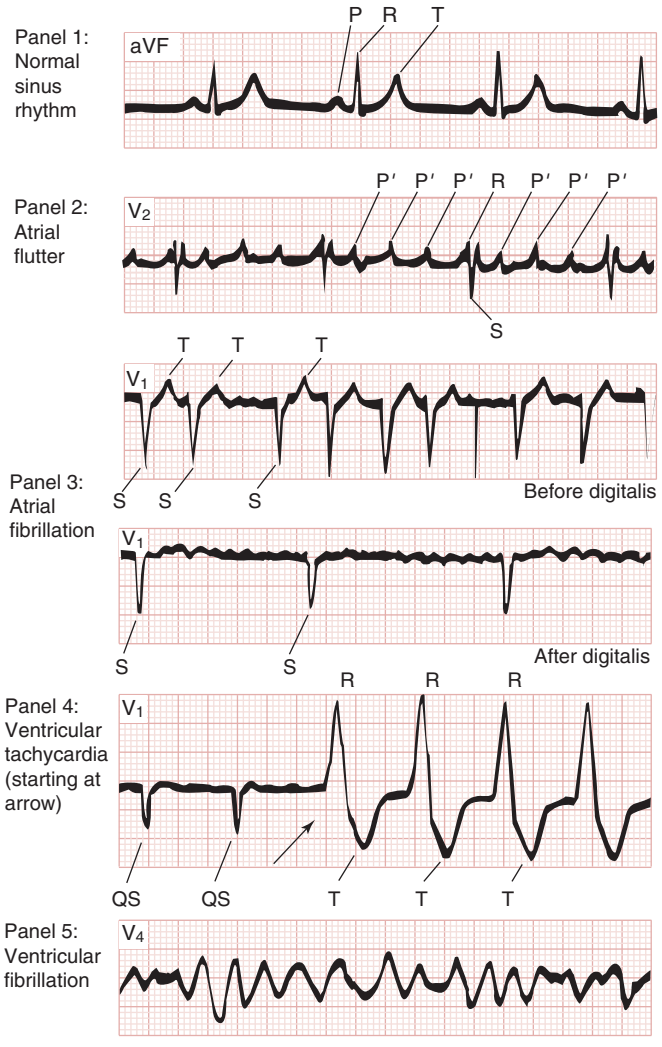


FIGURE 14–7 Electrocardiograms of normal sinus rhythm and some common arrhythmias. Major deflections (P, Q, R, S, and T) are labeled in each electrocardiographic record except in panel 5, in which electrical activity is completely disorganized and none of these deflections is recognizable. (Modified and reproduced, with permission, from Goldman MJ: *Principles of Clinical Electrocardiography*, 11th ed. McGraw-Hill, 1982.)

further slowing depressed conduction (by blocking the sodium or calcium current) and causing bidirectional block. In theory, accelerating conduction (by increasing sodium or calcium current) would also be effective, but only under unusual circumstances does this mechanism explain the action of any available drug.

Lengthening (or shortening) of the refractory period may also make reentry less likely. The longer the refractory period in tissue near the site of block, the greater the chance that the tissue will still be refractory when reentry is attempted. (Alternatively, the shorter the refractory period in the depressed region, the less likely it is that unidirectional block will occur.) Thus, increased dispersion of refractoriness is one contributor to reentry, and drugs may suppress arrhythmias by reducing such dispersion.

BASIC PHARMACOLOGY OF THE ANTIARRHYTHMIC AGENTS

Mechanisms of Action

Arrhythmias are caused by abnormal pacemaker activity or abnormal impulse propagation. Thus, the aim of therapy of the arrhythmias is to reduce ectopic pacemaker activity and modify conduction or refractoriness in reentry circuits to disable circus movement. The major pharmacologic mechanisms currently available for accomplishing these goals are (1) sodium channel blockade, (2) blockade of sympathetic autonomic effects in the heart, (3) prolongation of the effective refractory period, and (4) calcium channel blockade.

Antiarrhythmic drugs decrease the automaticity of ectopic pacemakers more than that of the SA node. They also reduce conduction and excitability and increase the refractory period to a greater extent in depolarized tissue than in normally polarized tissue. This is accomplished chiefly by selectively blocking the sodium or calcium channels of depolarized cells (Figure 14–9). Therapeutically useful channel-blocking drugs bind readily to activated channels (ie, during phase 0) or inactivated channels (ie, during phase 2) but bind poorly or not at all to rested channels. Therefore, these drugs block electrical activity when there is a fast tachycardia (many channel activations and inactivations per unit time) or when there is significant loss of resting potential (many inactivated channels during rest). This type of drug action is often described as **use-dependent** or **state-dependent;** that is, channels that are being used frequently, or in an inactivated state, are more susceptible to block. Channels in normal cells that become blocked by a drug during normal activation-inactivation cycles will rapidly lose the drug from the receptors during the resting portion of the cycle (Figure 14–9). Channels in myocardium that is chronically depolarized (ie, has a resting potential more positive than –75 mV) recover from block very slowly if at all (see also right panel, Figure 14–4).

In cells with abnormal automaticity, most of these drugs reduce the phase 4 slope by blocking either sodium or calcium channels, thereby reducing the ratio of sodium (or calcium) permeability to potassium permeability. As a result, the membrane potential during phase 4 stabilizes closer to the potassium equilibrium potential. In addition, some agents may increase the threshold (make it more positive). β-Adrenoceptor–blocking drugs indirectly reduce the phase 4 slope by blocking the positive chronotropic action of norepinephrine in the heart.

In reentry arrhythmias, which depend on critically depressed conduction, most antiarrhythmic agents slow conduction further by one or both of two mechanisms: (1) steady-state reduction in the number of available unblocked channels, which reduces the excitatory currents to a level below that required for propagation (Figure 14–4, left); and (2) prolongation of recovery time of the channels still able to reach the rested and available state, which increases the effective refractory period (Figure 14–4, right). As a result, early extrasystoles are unable to propagate at all; later impulses propagate more slowly and are subject to bidirectional conduction block.

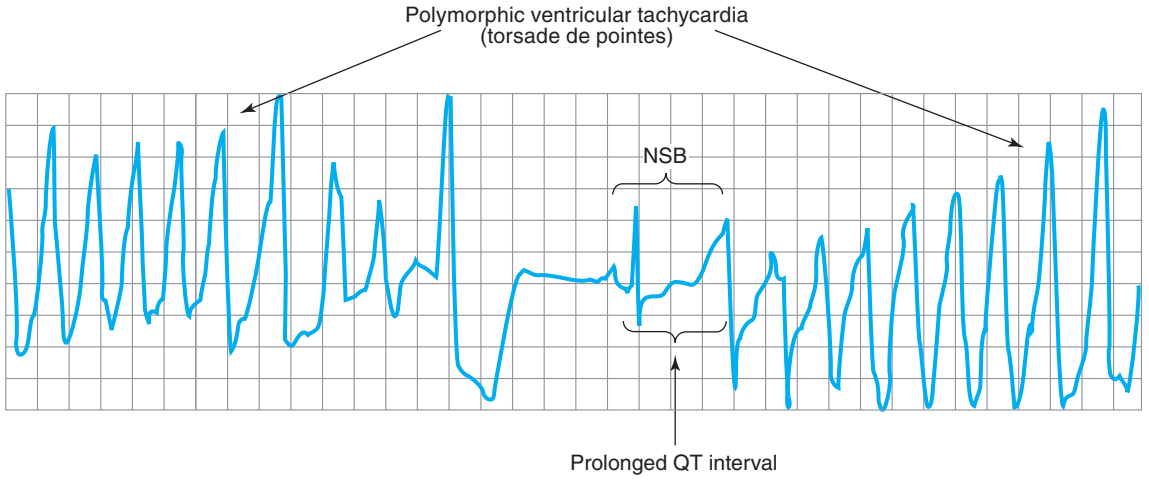


FIGURE 14–8 Electrocardiogram from a patient with the long QT syndrome during two episodes of torsades de pointes. The polymorphic ventricular tachycardia is seen at the start of this tracing and spontaneously halts at the middle of the panel. A single normal sinus beat (NSB) with an extremely prolonged QT interval follows, succeeded immediately by another episode of ventricular tachycardia of the torsades type. The usual symptoms include dizziness or transient loss of consciousness. (Reproduced, with permission, from *Basic and Clinical Pharmacology*, 10th edition, McGraw-Hill, 2007.)

By these mechanisms, antiarrhythmic drugs can suppress ectopic automaticity and abnormal conduction occurring in depolarized cells—rendering them electrically silent—while minimally affecting the electrical activity in normally polarized parts of the heart. However, as dosage is increased, these agents also depress conduction in normal tissue, eventually resulting in *drug-induced* arrhythmias. Furthermore, a drug concentration that is therapeutic (antiarrhythmic) under the initial circumstances of treatment may become "proarrhythmic" (arrhythmogenic) during fast heart rates (more development of block), acidosis (slower recovery from block for most drugs), hyperkalemia, or ischemia.

SPECIFIC ANTIARRHYTHMIC AGENTS

The most widely used scheme for the classification of antiarrhythmic drug actions recognizes four classes:

1. Class 1 action is sodium channel blockade. Subclasses of this action reflect effects on the action potential duration (APD) and the kinetics of sodium channel blockade. Drugs with class 1A action prolong the APD and dissociate from the channel with intermediate kinetics; drugs with class 1B action shorten the APD in some tissues of the heart and dissociate from the channel with rapid kinetics; and drugs with class 1C action have minimal effects on the APD and dissociate from the channel with slow kinetics.
2. Class 2 action is sympatholytic. Drugs with this action reduce β-adrenergic activity in the heart.
3. Class 3 action manifests as prolongation of the APD. Most drugs with this action block the rapid component of the delayed rectifier potassium current, I_{Kr}.
4. Class 4 action is blockade of the cardiac calcium current. This action slows conduction in regions where the action potential upstroke is calcium dependent, eg, the SA and AV nodes.

A given drug may have multiple classes of action as indicated by its membrane and electrocardiographic (ECG) effects (Tables 14–2 and 14–3). For example, amiodarone shares all four classes of action. Drugs are usually discussed according to the predominant class of action. Certain antiarrhythmic agents, eg, adenosine and magnesium, do not fit readily into this scheme and are described separately.

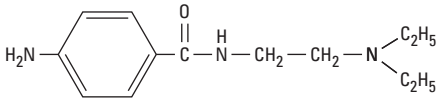
SODIUM CHANNEL-BLOCKING DRUGS (CLASS 1)

Drugs with local anesthetic action block sodium channels and reduce the sodium current, I_{Na}. They are the oldest group of antiarrhythmic drugs and are still widely used.

PROCAINAMIDE (SUBGROUP 1A)

Cardiac Effects

By blocking sodium channels, procainamide slows the upstroke of the action potential, slows conduction, and prolongs the QRS duration of the ECG. The drug also prolongs the APD (a class 3 action) by nonspecific blockade of potassium channels. The drug may be somewhat less effective than quinidine (see below) in suppressing abnormal ectopic pacemaker activity but more effective in blocking sodium channels in depolarized cells.



Procainamide

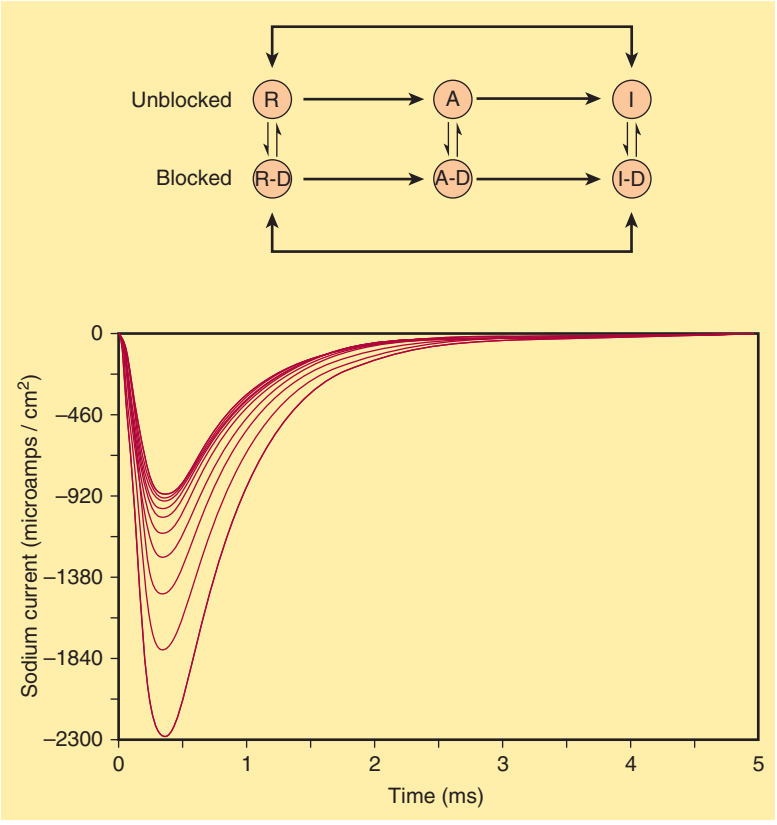


FIGURE 14–9 State- and frequency-dependent block of sodium channels by antiarrhythmic drugs. **Top:** Diagram of a mechanism for the selective depressant action of antiarrhythmic drugs on sodium channels. The upper portion of the figure shows the population of channels moving through a cycle of activity during an action potential in the absence of drugs: R (rested) → A (activated) → I (inactivated). Recovery takes place via the I → R pathway. Antiarrhythmic drugs (D) that act by blocking sodium channels can bind to their receptors in the channels, as shown by the vertical arrows, to form drug-channel complexes, indicated as R-D, A-D, and I-D. Binding of the drugs to the receptor varies with the state of the channel. Most sodium channel blockers bind to the active and inactivated channel receptor much more strongly than to the rested channel. Furthermore, recovery from the I-D state to the R-D state is much slower than from I to R. As a result, rapid activity (more activations and inactivations) and depolarization of the resting potential (more channels in the I state) will favor blockade of the channels and selectively suppress arrhythmic cells. **Bottom:** Progressive reduction of inward sodium current (downward deflections) in the presence of a lidocaine derivative. The largest curve is the initial sodium current elicited by a depolarizing voltage step; subsequent sodium current amplitudes are progressively reduced owing to prior accumulated block and block during each depolarization. (Adapted, with permission, from Starmer FC, Grant AO, Strauss HC: Mechanisms of use-dependent block of sodium channels in excitable membranes by local anesthetics. Biophys J 1984;46:15.)

Procainamide has direct depressant actions on SA and AV nodes, and these actions are only slightly counterbalanced by drug-induced vagal block.

Extracardiac Effects

Procainamide has ganglion-blocking properties. This action reduces peripheral vascular resistance and can cause hypotension, particularly with intravenous use. However, in therapeutic concentrations, its peripheral vascular effects are less prominent than those of quinidine. Hypotension is usually associated with excessively rapid procainamide infusion or the presence of severe underlying left ventricular dysfunction.

Toxicity

Procainamide's cardiotoxic effects include excessive action potential prolongation, QT-interval prolongation, and induction of torsades de pointes arrhythmia and syncope. Excessive slowing of conduction can also occur. New arrhythmias can be precipitated.

A troublesome adverse effect of long-term procainamide therapy is a syndrome resembling lupus erythematosus and usually consisting of arthralgia and arthritis. In some patients, pleuritis, pericarditis, or parenchymal pulmonary disease also occurs. Renal lupus is rarely induced by procainamide. During long-term therapy, serologic abnormalities (eg, increased antinuclear antibody titer) occur in nearly all patients, and in the absence of symptoms, these are not an indication to stop drug therapy. Approximately one third of patients receiving long-term procainamide therapy develop these reversible lupus-related symptoms.

Other adverse effects include nausea and diarrhea (in about 10% of cases), rash, fever, hepatitis (< 5%), and agranulocytosis (approximately 0.2%).

TABLE 14–2 Membrane actions of antiarrhythmic drugs.

Drug	Block of Sodium Channels		Refractory Period		Calcium Channel Blockade	Effect on Pacemaker Activity	Sympatholytic Action
	Normal Cells	Depolarized Cells	Normal Cells	Depolarized Cells			
Adenosine	0	0	0	0	+	0	+
Amiodarone	+	+++	↑↑	↑↑	+	↓↓	+
Diltiazem	0	0	0	0	+++	↓↓	0
Disopyramide	+	+++	↑	↑↑	+	↓	0
Dofetilide	0	0	↑	?	0	0	0
Dronedarone	+	+	na	na	+	na	+
Esmolol	0	+	0	na	0	↓↓	+++
Flecainide	+	+++	0	↑	0	↓↓	0
Ibutilide	0	0	↑	?	0	0	0
Lidocaine	0	+++	↓	↑↑	0	↓↓	0
Mexiletine	0	+++	0	↑↑	0	↓↓	0
Procainamide	+	+++	↑	↑↑↑	0	↓	+
Propafenone	+	++	↑	↑↑	+	↓↓	+
Propranolol	0	+	↓	↑↑	0	↓↓	+++
Quinidine	+	++	↑	↑↑	0	↓↓	+
Sotalol	0	0	↑↑	↑↑↑	0	↓↓	++
Verapamil	0	+	0	↑	+++	↓↓	+
Vernakalant	+	+	+	+	na	0	na

na, data not available.

Pharmacokinetics & Dosage

Procainamide can be administered safely by intravenous and intramuscular routes and is well absorbed orally. A metabolite (*N*-acetylprocainamide, NAPA) has class 3 activity. Excessive accumulation of NAPA has been implicated in torsades de pointes during procainamide therapy, especially in patients with renal failure. Some individuals rapidly acetylate procainamide and develop high levels of NAPA. The lupus syndrome appears to be less common in these patients.

Procainamide is eliminated by hepatic metabolism to NAPA and by renal elimination. Its half-life is only 3–4 hours, which necessitates frequent dosing or use of a slow-release formulation (the usual practice). NAPA is eliminated by the kidneys. Thus, procainamide dosage must be reduced in patients with renal failure. The reduced volume of distribution and renal clearance associated with heart failure also require reduction in dosage. The half-life of NAPA is considerably longer than that of procainamide, and it therefore accumulates more slowly. Thus, it is important to measure plasma levels of both procainamide and NAPA, especially in patients with circulatory or renal impairment.

If a rapid procainamide effect is needed, an intravenous loading dose of up to 12 mg/kg can be given at a rate of 0.3 mg/kg/min or less rapidly. This dose is followed by a maintenance dosage of 2–5 mg/min, with careful monitoring of plasma levels. The risk of gastrointestinal (GI) or cardiac toxicity rises at plasma concentrations greater than 8 mcg/mL or NAPA concentrations greater than 20 mcg/mL.

To control ventricular arrhythmias, a total procainamide dosage of 2–5 g/d is usually required. In an occasional patient who accumulates high levels of NAPA, less frequent dosing may be possible. This is also possible in renal disease, where procainamide elimination is slowed.

Therapeutic Use

Procainamide is effective against most atrial and ventricular arrhythmias. However, many clinicians attempt to avoid long-term therapy because of the requirement for frequent dosing and the common occurrence of lupus-related effects. Procainamide is the drug of second or third choice (after lidocaine or amiodarone) in most coronary care units for the treatment of sustained ventricular arrhythmias associated with acute myocardial infarction.

QUINIDINE (SUBGROUP 1A)

Cardiac Effects

Quinidine has actions similar to those of procainamide: it slows the upstroke of the action potential, slows conduction, and prolongs

TABLE 14–3 Clinical pharmacologic properties of antiarrhythmic drugs.

Drug	Effect on SA Nodal Rate	Effect on AV Nodal Refractory Period	PR Interval	QRS Duration	QT Interval	Usefulness in Arrhythmias		Half-Life
						Supra–ventricular	Ventricular	
Adenosine	↓↑	↑↑↑	↑↑↑	0	0	++++	?	< 10 s
Amiodarone	↓↓[1]	↑↑	Variable	↑	↑↑↑↑	+++	+++	(weeks)
Diltiazem	↑↓	↑↑	↑	0	0	+++	–	4–8 h
Disopyramide	↑↓[1,2]	↑↓[2]	↑↓[2]	↑↑	↑↑	+	+++	7–8 h
Dofetilide	↓(?)	0	0	0	↑↑	++	None	7 h
Dronedarone					↑	+++	–	24 h
Esmolol	↓↓	↑↑	↑↑	0	0	+	+	10 min
Flecainide	None,↓	↑	↑	↑↑↑	0	+[3]	++++	20 h
Ibutilide	↓ (?)	0	0	0	↑↑	++	?	6 h
Lidocaine	None[1]	None	0	0	0	None[4]	+++	1–2 h
Mexiletine	None[1]	None	0	0	0	None	+++	12 h
Procainamide	↓[1]	↑↓[2]	↑↓[2]	↑↑	↑↑	+	+++	3–4 h
Propafenone	0, ↓	↑	↑	↑↑↑	0	+	+++	5–7 h
Propranolol	↓↓	↑↑	↑↑	0	0	+	+	5 h
Quinidine	↑↓[1,2]	↑↓[2]	↑↓[2]	↑↑	↑↑	+	+++	6 h
Sotalol	↓↓	↑↑	↑↑	0	↑↑↑	+++	+++	7 h
Verapamil	↓↓	↑↑	↑↑	0	0	+++	–	7 h
Vernakalant		↑	↑			+++	–	2 h

[1]May suppress diseased sinus nodes.

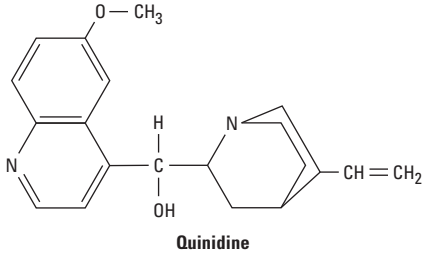
[2]Anticholinergic effect and direct depressant action.

[3]Especially in Wolff-Parkinson-White syndrome.

[4]May be effective in atrial arrhythmias caused by digitalis.

[5]Half-life of active metabolites much longer.

the QRS duration of the ECG, by blockade of sodium channels. The drug also prolongs the action potential duration by blockade of several potassium channels. Its toxic cardiac effects include excessive QT-interval prolongation and induction of torsades de pointes arrhythmia. Toxic concentrations of quinidine also produce excessive sodium channel blockade with slowed conduction throughout the heart.



Quinidine

Extracardiac Effects

Adverse GI effects of diarrhea, nausea, and vomiting are observed in one third to one half of patients. A syndrome of headache, dizziness, and tinnitus **(cinchonism)** is observed at toxic drug concentrations. Idiosyncratic or immunologic reactions, including thrombocytopenia, hepatitis, angioneurotic edema, and fever, are observed rarely.

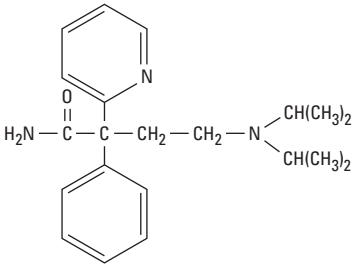
Pharmacokinetics & Therapeutic Use

Quinidine is readily absorbed from the GI tract and eliminated by hepatic metabolism. It is rarely used because of cardiac and extracardiac adverse effects and the availability of better-tolerated antiarrhythmic drugs.

DISOPYRAMIDE (SUBGROUP 1A)

Cardiac Effects

The effects of disopyramide are very similar to those of procainamide and quinidine. Its cardiac antimuscarinic effects are even more marked than those of quinidine. Therefore, a drug that slows AV conduction should be administered with disopyramide when treating atrial flutter or fibrillation.



Disopyramide

Toxicity

Toxic concentrations of disopyramide can precipitate all of the electrophysiologic disturbances described under quinidine. As a result of its negative inotropic effect, disopyramide may precipitate heart failure de novo or in patients with preexisting depression of left ventricular function. Because of this effect, disopyramide is not used as a first-line antiarrhythmic agent in the USA. It should not be used in patients with heart failure.

Disopyramide's atropine-like activity accounts for most of its symptomatic adverse effects: urinary retention (most often, but not exclusively, in male patients with prostatic hyperplasia), dry mouth, blurred vision, constipation, and worsening of preexisting glaucoma. These effects may require discontinuation of the drug.

Pharmacokinetics & Dosage

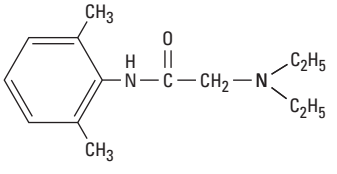
In the USA, disopyramide is only available for oral use. The typical oral dosage of disopyramide is 150 mg three times a day, but up to 1 g/d has been used. In patients with renal impairment, dosage must be reduced. Because of the danger of precipitating heart failure, loading doses are not recommended.

Therapeutic Use

Although disopyramide has been shown to be effective in a variety of supraventricular arrhythmias, in the USA it is approved only for the treatment of ventricular arrhythmias.

LIDOCAINE (SUBGROUP 1B)

Lidocaine has a low incidence of toxicity and a high degree of effectiveness in arrhythmias associated with acute myocardial infarction. It is used only by the intravenous route.



Lidocaine

Cardiac Effects

Lidocaine blocks activated and inactivated sodium channels with rapid kinetics (Figure 14–10); the inactivated state block ensures greater effects on cells with long action potentials such as Purkinje and ventricular cells, compared with atrial cells. The rapid kinetics at normal resting potentials result in recovery from block between action potentials and no effect on conduction. The increased inactivation and slower unbinding kinetics result in the selective depression of conduction in depolarized cells. Little effect is seen on the ECG in normal sinus rhythm.

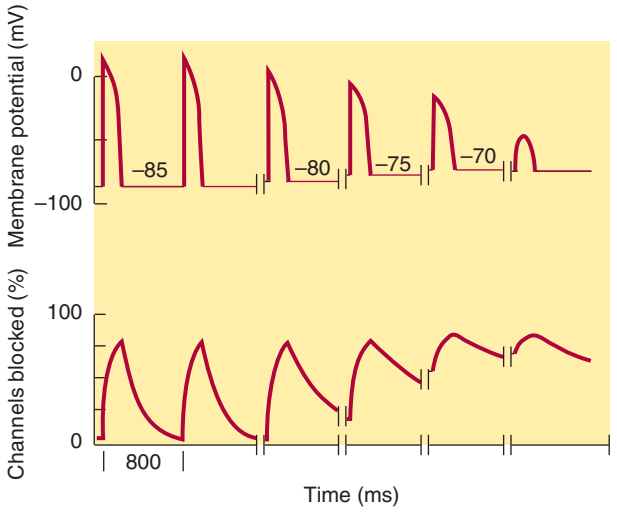


FIGURE 14–10 Computer simulation of the effect of resting membrane potential on the blocking and unblocking of sodium channels by lidocaine as the membrane depolarizes. **Upper tracing:** Action potentials in a ventricular muscle cell. **Lower tracing:** Percentage of channels blocked by the drug. An 800 ms time segment is shown. Extra passage of time is indicated by breaks in the traces. **Left side:** At the normal resting potential of –85 mV, the drug combines with open (activated) and inactivated channels during each action potential, but block is rapidly reversed during diastole because the affinity of the drug for its receptor is so low when the channel recovers to the resting state at –85 mV. **Middle:** Metabolic injury is simulated, eg, ischemia due to coronary occlusion, that causes gradual depolarization over time. With subsequent action potentials arising from more depolarized potentials, the fraction of channels blocked increases because more channels remain in the inactivated state at less negative potentials (Figure 14–4, left), and the time constant for unblocking during diastole rapidly increases at less negative resting potentials (Figure 14–4, right). **Right:** Because of marked drug binding, conduction block and loss of excitability in this tissue result; that is, the "sick" (depolarized) tissue is selectively suppressed.

Toxicity

Lidocaine is one of the least cardiotoxic of the currently used sodium channel blockers. Proarrhythmic effects, including SA node arrest, worsening of impaired conduction, and ventricular arrhythmias, are uncommon with lidocaine use. In large doses, especially in patients with preexisting heart failure, lidocaine may cause hypotension—partly by depressing myocardial contractility.

Lidocaine's most common adverse effects—like those of other local anesthetics—are neurologic: paresthesias, tremor, nausea of central origin, lightheadedness, hearing disturbances, slurred speech, and convulsions. These occur most commonly in elderly or otherwise vulnerable patients or when a bolus of the drug is given too

rapidly. The effects are dose-related and usually short-lived; seizures respond to intravenous diazepam. In general, if plasma levels above 9 mcg/mL are avoided, lidocaine is well tolerated.

Pharmacokinetics & Dosage

Because of its extensive first-pass hepatic metabolism, only 3% of orally administered lidocaine appears in the plasma. Thus, lidocaine must be given parenterally. Lidocaine has a half-life of 1–2 hours. In adults, a loading dose of 150–200 mg administered over about 15 minutes (as a single infusion or as a series of slow boluses) should be followed by a maintenance infusion of 2–4 mg/min to achieve a therapeutic plasma level of 2–6 mcg/mL. Determination of lidocaine plasma levels is of great value in adjusting the infusion rate. Occasional patients with myocardial infarction or other acute illness require (and tolerate) higher concentrations. This may be due to increased plasma α_1-acid glycoprotein, an acute-phase reactant protein that binds lidocaine, making less free drug available to exert its pharmacologic effects.

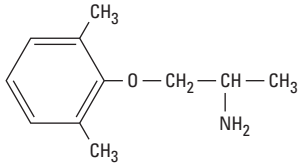
In patients with heart failure, lidocaine's volume of distribution and total body clearance may both be decreased. Therefore, both loading and maintenance doses should be decreased. Since these effects counterbalance each other, the half-life may not be increased as much as predicted from clearance changes alone. In patients with liver disease, plasma clearance is markedly reduced and the volume of distribution is often increased; the elimination half-life in such cases may be increased threefold or more. In liver disease, the maintenance dose should be decreased, but usual loading doses can be given. Elimination half-life determines the time to steady state. Although steady-state concentrations may be achieved in 8–10 hours in normal patients and patients with heart failure, 24–36 hours may be required in those with liver disease. Drugs that decrease liver blood flow (eg, propranolol, cimetidine) reduce lidocaine clearance and so increase the risk of toxicity unless infusion rates are decreased. With infusions lasting more than 24 hours, clearance falls and plasma concentrations rise. Renal disease has no major effect on lidocaine disposition.

Therapeutic Use

Lidocaine is the agent of choice for termination of ventricular tachycardia and prevention of ventricular fibrillation after cardioversion in the setting of acute ischemia. However, routine *prophylactic* use of lidocaine in this setting may actually increase total mortality, possibly by increasing the incidence of asystole, and is not the standard of care. Most physicians administer IV lidocaine only to patients with arrhythmias.

MEXILETINE (SUBGROUP 1B)

Mexiletine is an orally active congener of lidocaine. Its electrophysiologic and antiarrhythmic actions are similar to those of lidocaine. (The anticonvulsant phenytoin [see Chapter 24] also exerts similar electrophysiologic effects and has been used as an antiarrhythmic.) Mexiletine is used in the treatment of ventricular arrhythmias. The elimination half-life is 8–20 hours and permits administration two or three times per day. The usual daily dosage of mexiletine is 600–1200 mg/d. Dose-related adverse effects are seen frequently at therapeutic dosage. These are predominantly neurologic, including tremor, blurred vision, and lethargy. Nausea is also a common effect.

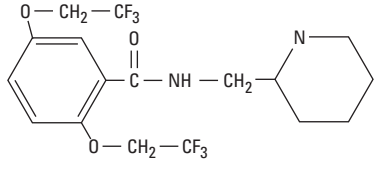


Mexiletine

Mexiletine has also shown significant efficacy in relieving chronic pain, especially pain due to diabetic neuropathy and nerve injury. The usual dosage is 450–750 mg/d orally. This application is off label.

FLECAINIDE (SUBGROUP 1C)

Flecainide is a potent blocker of sodium and potassium channels with slow unblocking kinetics. (Note that although it does block certain potassium channels, it does not prolong the action potential or the QT interval.) It is currently used for patients with otherwise normal hearts who have supraventricular arrhythmias. It has no antimuscarinic effects.



Flecainide

Flecainide is very effective in suppressing premature ventricular contractions. However, it may cause severe exacerbation of arrhythmia even when normal doses are administered to patients with preexisting ventricular tachyarrhythmias and those with a previous myocardial infarction and ventricular ectopy. This was dramatically demonstrated in the Cardiac Arrhythmia Suppression Trial (CAST), which was terminated prematurely because of a two and one-half-fold increase in mortality rate in the patients receiving flecainide and similar group 1C drugs. Flecainide is well absorbed and has a half-life of approximately 20 hours. Elimination is both by hepatic metabolism and by the kidney. The usual dosage of flecainide is 100–200 mg twice a day.

PROPAFENONE (SUBGROUP 1C)

Propafenone has some structural similarities to propranolol and possesses weak β-blocking activity. Its spectrum of action is very similar to that of quinidine, but it does not prolong the action potential. Its sodium channel-blocking kinetics are similar to that of flecainide. Propafenone is metabolized in the liver, with an

average half-life of 5–7 hours. The usual daily dosage of propafenone is 450–900 mg in three divided doses. The drug is used primarily for supraventricular arrhythmias. The most common adverse effects are a metallic taste and constipation; arrhythmia exacerbation can also occur.

MORICIZINE (SUBGROUP 1C)

Moricizine is an antiarrhythmic phenothiazine derivative that was used for treatment of ventricular arrhythmias. It is a relatively potent sodium channel blocker that does not prolong action potential duration. Moricizine has been withdrawn from the US market.

BETA-ADRENOCEPTOR–BLOCKING DRUGS (CLASS 2)

Cardiac Effects

Propranolol and similar drugs have antiarrhythmic properties by virtue of their β-receptor–blocking action and direct membrane effects. As described in Chapter 10, some of these drugs have selectivity for cardiac β_1 receptors, some have intrinsic sympathomimetic activity, some have marked direct membrane effects, and some prolong the cardiac action potential. The relative contributions of the β-blocking and direct membrane effects to the antiarrhythmic effects of these drugs are not fully known. Although β blockers are fairly well tolerated, their efficacy for suppression of ventricular ectopic depolarizations is lower than that of sodium channel blockers. However, there is good evidence that these agents can prevent recurrent infarction and sudden death in patients recovering from acute myocardial infarction (see Chapter 10).

Esmolol is a short-acting β blocker used primarily as an antiarrhythmic drug for intraoperative and other acute arrhythmias. See Chapter 10 for more information. **Sotalol** is a nonselective β-blocking drug that prolongs the action potential (class 3 action).

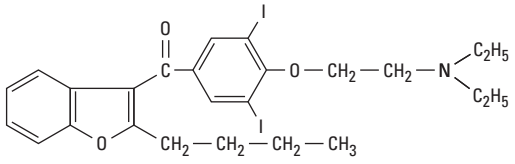
DRUGS THAT PROLONG EFFECTIVE REFRACTORY PERIOD BY PROLONGING THE ACTION POTENTIAL (CLASS 3)

These drugs prolong action potentials, usually by blocking potassium channels in cardiac muscle or by enhancing inward current, eg, through sodium channels. Action potential prolongation by most of these drugs often exhibits the undesirable property of "reverse use-dependence": action potential prolongation is least marked at fast rates (where it is desirable) and most marked at slow rates, where it can contribute to the risk of torsades de pointes.

Although most drugs in the class evoke QT prolongation, there is considerable variability among drugs in their proarrhythmic tendency to cause torsades de pointes despite significant QT-interval prolongation. Recent studies suggest that excessive QT prolongation alone may not be the best predictor of drug-induced torsades de pointes. Other important factors in addition to QT prolongation include action potential stability and development of a triangular shape (triangulation), reverse use-dependence, and dispersion of repolarization.

AMIODARONE

In the USA, amiodarone is approved for oral and intravenous use to treat serious ventricular arrhythmias. However, the drug is also highly effective for the treatment of supraventricular arrhythmias such as atrial fibrillation. As a result of its broad spectrum of antiarrhythmic action, it is very extensively used for a wide variety of arrhythmias. Amiodarone has unusual pharmacokinetics and important extracardiac adverse effects. **Dronedarone,** an analog that lacks iodine atoms, recently received Food and Drug Administration approval for the treatment of atrial flutter and fibrillation. **Celivarone** is another noniodinated benzofuran derivative similar to dronedarone that is currently undergoing clinical trials for the prevention of ventricular tachycardia recurrence.



Amiodarone

Cardiac Effects

Amiodarone markedly prolongs the action potential duration (and the QT interval on the ECG) by blockade of I_{Kr}. During chronic administration, I_{Ks} is also blocked. The action potential duration is prolonged uniformly over a wide range of heart rates; that is, the drug does not have reverse use-dependent action. In spite of its present classification as a class 3 agent, amiodarone also significantly blocks inactivated sodium channels. Its action potential-prolonging action reinforces this effect. Amiodarone also has weak adrenergic and calcium channel-blocking actions. Consequences of these actions include slowing of the heart rate and AV node conduction. The broad spectrum of actions may account for its relatively high efficacy and its low incidence of torsades de pointes despite significant QT-interval prolongation.

Extracardiac Effects

Amiodarone causes peripheral vasodilation. This action is prominent after intravenous administration and may be related to the action of the vehicle.

Toxicity

Amiodarone may produce symptomatic bradycardia and heart block in patients with preexisting sinus or AV node disease. The drug accumulates in many tissues, including the heart (10–50 times more so than in plasma), lung, liver, and skin, and is concentrated in tears. Dose-related pulmonary toxicity is the most important adverse effect. Even on a low dose of 200 mg/d or less, fatal pulmonary fibrosis may be observed in 1% of patients.

Abnormal liver function tests and hypersensitivity hepatitis may develop during amiodarone treatment and liver function tests should be monitored regularly. The skin deposits result in a photodermatitis and a gray-blue skin discoloration in sun-exposed areas, eg, the malar regions. After a few weeks of treatment, asymptomatic corneal microdeposits are present in virtually all patients treated with amiodarone. Halos develop in the peripheral visual fields of some patients. Drug discontinuation is usually not required. Rarely, an optic neuritis may progress to blindness.

Amiodarone blocks the peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3). It is also a potential source of large amounts of inorganic iodine. Amiodarone may result in hypothyroidism or hyperthyroidism. Thyroid function should be evaluated before initiating treatment and should be monitored periodically. Because effects have been described in virtually every organ system, amiodarone treatment should be reevaluated whenever new symptoms develop in a patient, including arrhythmia aggravation.

Pharmacokinetics

Amiodarone is variably absorbed with a bioavailability of 35–65%. It undergoes hepatic metabolism, and the major metabolite, desethylamiodarone, is bioactive. The elimination half-life is complex, with a rapid component of 3–10 days (50% of the drug) and a slower component of several weeks. After discontinuation of the drug, effects are maintained for 1–3 months. Measurable tissue levels may be observed up to 1 year after discontinuation. A total loading dose of 10 g is usually achieved with 0.8–1.2 g daily doses. The maintenance dose is 200–400 mg daily. Pharmacologic effects may be achieved rapidly by intravenous loading. QT-prolonging effect is modest with this route of administration, whereas bradycardia and AV block may be significant.

Amiodarone has many important drug interactions, and all medications should be reviewed when the drug is initiated and when the dose is adjusted. Amiodarone is a substrate for liver cytochrome CYP3A4, and its levels are increased by drugs that inhibit this enzyme, eg, the histamine H_2 blocker cimetidine. Drugs that induce CYP3A4, eg, rifampin, decrease amiodarone concentration when coadministered. Amiodarone inhibits several cytochrome P450 enzymes and may result in high levels of many drugs, including statins, digoxin, and warfarin. The dose of warfarin should be reduced by one third to one half following initiation of amiodarone, and prothrombin times should be closely monitored.

Therapeutic Use

Low doses (100–200 mg/d) of amiodarone are effective in maintaining normal sinus rhythm in patients with atrial fibrillation. The drug is effective in the prevention of recurrent ventricular tachycardia. It is not associated with an increase in mortality in patients with coronary artery disease or heart failure. In many centers, the implanted cardioverter-defibrillator (ICD) has succeeded drug therapy as the primary treatment modality for ventricular tachycardia, but amiodarone may be used for ventricular tachycardia as adjuvant therapy to decrease the frequency of uncomfortable cardioverter defibrillator discharges. The drug increases the pacing and defibrillation threshold and these devices require retesting after a maintenance dose has been achieved.

DRONEDARONE

Dronedarone is a structural analog of amiodarone in which the iodine atoms have been removed from the phenyl ring and a methanesulfonyl group added to the benzofuran ring. The design was intended to eliminate action of the parent drug on thyroxine metabolism and to modify the half-life of the drug. No thyroid dysfunction or pulmonary toxicity has been reported in short-term studies. However, liver toxicity, including two severe cases requiring liver transplantation, has been reported. Like amiodarone, dronedarone has multichannel actions, including blocking I_{Kr}, I_{Ks}, I_{Ca}, and I_{Na}. It also has β-adrenergic–blocking action. The drug has a half-life of 24 hours and can be administered twice daily at a fixed dose of 400 mg. Dronedarone absorption increases twofold to threefold when taken with food, and this information should be communicated to patients as a part of the dosing instructions. Dronedarone elimination is primarily non-renal. However, it inhibits tubular secretion of creatinine, resulting in a 10–20% increase in serum creatinine. However, because glomerular filtration rate is unchanged, no adjustments are required. Dronedarone is both a substrate and an inhibitor of CY3A4 and should not be co-administered with potent inhibitors of this enzyme, such as the azole and similar antifungal agents, and protease inhibitors.

Dronedarone restores sinus rhythm in a small percentage of patients (< 15%) with atrial fibrillation. It produces a 10- to 15-bpm reduction of the ventricular rate compared to placebo. Dronedarone doubled the interval between episodes of atrial fibrillation recurrence in patients with paroxysmal atrial fibrillation. Initial studies suggested a reduction in mortality or hospitalization in patients with atrial fibrillation. However, a study of dronedarone's effects in permanent atrial fibrillation was terminated in 2011 because of increased risk of death, stroke, and heart failure. Similarly, a trial of dronedarone in advanced heart failure was terminated prematurely because of an increase in mortality. The drug carries a "black box" warning against its use in acute decompensated or advanced (class IV) heart failure.

VERNAKALANT

The limited success of highly specific drugs that target single ion channels and the efficacy of multi-ion channel blockers such as amiodarone have shifted the emphasis in antiarrhythmic drug development to the latter class of drugs. Vernakalant is a multi-ion channel blocker that was developed for the treatment of atrial fibrillation.

Vernakalant prolongs the atrial effective refractory period and slows conduction over the AV node. Ventricular effective refractory period is unchanged. In the maximal clinical dose of 1800 mg/day, vernakalant does not change the QT interval on the ECG. Vernakalant blocks I_{Kur}, I_{ACh}, and I_{to}. These currents play key roles in atrial repolarization and their block accounts for the prolongation of the atrial effective refractory period. The drug is a less potent blocker of I_{Kr} and, as a result, produces less APD prolongation in the ventricle; that is, the APD-prolonging effect is relatively atrium specific. Vernakalant also produces use-dependent block of the sodium channel. Recovery from block is fast, such

that significant blockade is observed only at fast rates or at low membrane potentials. In the therapeutic concentration range, vernakalant has no effect on heart rate.

Toxicity

Adverse effects of vernakalant include dysgeusia (disturbance of taste), sneezing, paresthesia, cough, and hypotension.

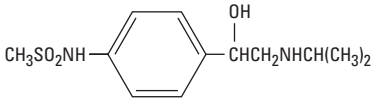
Pharmacokinetics & Therapeutic Uses

Pharmacokinetic data for vernakalant are limited. After IV administration, the drug is metabolized in the liver by CYP2D6 with a half-life of 2 hours. However, on an oral regimen of 900 mg twice daily, a sustained blood concentration was observed over a 12-hour interval. Clinical trials with the oral drug have used a twice-daily dosing regimen.

Intravenous vernakalant is effective in converting recent-onset atrial fibrillation to normal sinus rhythm in 50% of patients. Final approval for this purpose is pending. The drug is undergoing clinical trials for maintenance of normal sinus rhythm in patients with paroxysmal or persistent atrial fibrillation.

SOTALOL

Sotalol has both β-adrenergic receptor-blocking (class 2) and action potential-prolonging (class 3) actions. The drug is formulated as a racemic mixture of D- and L-sotalol. All the β-adrenergic–blocking activity resides in the L-isomer; the D- and L-isomers share action potential prolonging actions. Beta-adrenergic–blocking action is not cardioselective and is maximal at doses below those required for action potential prolongation.



Sotalol

Sotalol is well absorbed orally with bioavailability of approximately 100%. It is not metabolized in the liver and is not bound to plasma proteins. Excretion is predominantly by the kidneys in the unchanged form with a half-life of approximately 12 hours. Because of its relatively simple pharmacokinetics, solatol exhibits few direct drug interactions. Its most significant cardiac adverse effect is an extension of its pharmacologic action: a dose-related incidence of torsades de pointes that approaches 6% at the highest recommended daily dose. Patients with overt heart failure may experience further depression of left ventricular function during treatment with sotalol.

Sotalol is approved for the treatment of life-threatening ventricular arrhythmias and the maintenance of sinus rhythm in patients with atrial fibrillation. It is also approved for treatment of supraventricular and ventricular arrhythmias in the pediatric age group. Sotalol decreases the threshold for cardiac defibrillation.

DOFETILIDE

Dofetilide has class 3 action potential prolonging action. This action is effected by a dose-dependent blockade of the rapid component of the delayed rectifier potassium current (I_{Kr}) and the blockade of I_{Kr} increases in hypokalemia. Dofetilide produces no relevant blockade of the other potassium channels or the sodium channel. Because of the slow rate of recovery from blockade, the extent of blockade shows little dependence on stimulation frequency. However, dofetilide does show less action potential prolongation at rapid rates because of the increased importance of other potassium channels such as I_{Ks} at higher frequencies.

Dofetilide is 100% bioavailable. Verapamil increases peak plasma dofetilide concentration by increasing intestinal blood flow. Eighty percent of an oral dose is eliminated unchanged by the kidneys; the remainder is eliminated in the urine as inactive metabolites. Inhibitors of the renal cation secretion mechanism, eg, cimetidine, prolong the half-life of dofetilide. Since the QT-prolonging effects and risks of ventricular proarrhythmia are directly related to plasma concentration, dofetilide dosage must be based on the estimated creatinine clearance. Treatment with dofetilide should be initiated in hospital after baseline measurement of the rate-corrected QT interval (QT_c) and serum electrolytes. A baseline QT_c of > 450 ms (500 ms in the presence of an intraventricular conduction delay), bradycardia of < 50 bpm, and hypokalemia are relative contraindications to its use.

Dofetilide is approved for the maintenance of normal sinus rhythm in patients with atrial fibrillation. It is also effective in restoring normal sinus rhythm in patients with atrial fibrillation.

IBUTILIDE

Ibutilide, like dofetilide, slows cardiac depolarization by blockade of the rapid component (I_{Kr}) of the delayed rectifier potassium current. Activation of slow inward sodium current has also been suggested as an additional mechanism of action potential prolongation. After intravenous administration, ibutilide is rapidly cleared by hepatic metabolism. The metabolites are excreted by the kidney. The elimination half-life averages 6 hours.

Intravenous ibutilide is used for the acute conversion of atrial flutter and atrial fibrillation to normal sinus rhythm. The drug is more effective in atrial flutter than atrial fibrillation, with a mean time to termination of 20 minutes. The most important adverse effect is excessive QT-interval prolongation and torsades de pointes. Patients require continuous ECG monitoring for 4 hours after ibutilide infusion or until QT_c returns to baseline.

CALCIUM CHANNEL-BLOCKING DRUGS (CLASS 4)

These drugs, of which verapamil is the prototype, were first introduced as antianginal agents and are discussed in greater detail in Chapter 12. Verapamil and diltiazem also have antiarrhythmic

effects. The dihydropyridines (eg, nifedipine) do not share antiarrhythmic efficacy and may *precipitate* arrhythmias.

VERAPAMIL

Cardiac Effects

Verapamil blocks both activated and inactivated L-type calcium channels. Thus, its effect is more marked in tissues that fire frequently, those that are less completely polarized at rest, and those in which activation depends exclusively on the calcium current, such as the SA and AV nodes. AV nodal conduction time and effective refractory period are consistently prolonged by therapeutic concentrations. Verapamil usually slows the SA node by its direct action, but its hypotensive action may occasionally result in a small reflex increase of SA rate.

Verapamil can suppress both early and delayed afterdepolarizations and may antagonize slow responses arising in severely depolarized tissue.

Extracardiac Effects

Verapamil causes peripheral vasodilation, which may be beneficial in hypertension and peripheral vasospastic disorders. Its effects on smooth muscle produce a number of extracardiac effects (see Chapter 12).

Toxicity

Verapamil's cardiotoxic effects are dose-related and usually avoidable. A common error has been to administer intravenous verapamil to a patient with ventricular tachycardia misdiagnosed as supraventricular tachycardia. In this setting, hypotension and ventricular fibrillation can occur. Verapamil's negative inotropic effects may limit its clinical usefulness in diseased hearts (see Chapter 12). Verapamil can induce AV block when used in large doses or in patients with AV nodal disease. This block can be treated with atropine and β-receptor stimulants.

Adverse extracardiac effects include constipation, lassitude, nervousness, and peripheral edema.

Pharmacokinetics & Dosage

The half-life of verapamil is approximately 7 hours. It is extensively metabolized by the liver; after oral administration, its bioavailability is only about 20%. Therefore, verapamil must be administered with caution in patients with hepatic dysfunction or impaired hepatic perfusion.

In adult patients without heart failure or SA or AV nodal disease, parenteral verapamil can be used to terminate supraventricular tachycardia, although adenosine is the agent of first choice. Verapamil dosage is an initial bolus of 5 mg administered over 2–5 minutes, followed a few minutes later by a second 5 mg bolus if needed. Thereafter, doses of 5–10 mg can be administered every 4–6 hours, or a constant infusion of 0.4 mcg/kg/min may be used.

Effective oral dosages are higher than intravenous dosage because of first-pass metabolism and range from 120 mg to 640 mg daily, divided into three or four doses.

Therapeutic Use

Supraventricular tachycardia is the major arrhythmia indication for verapamil. Adenosine or verapamil are preferred over older treatments (propranolol, digoxin, edrophonium, and vasoconstrictor agents) and cardioversion for termination. Verapamil can also reduce the ventricular rate in atrial fibrillation and flutter. It only rarely converts atrial flutter and fibrillation to sinus rhythm. Verapamil is occasionally useful in ventricular arrhythmias. However, intravenous verapamil in a patient with sustained ventricular tachycardia can cause hemodynamic collapse.

DILTIAZEM

Diltiazem appears to be similar in efficacy to verapamil in the management of supraventricular arrhythmias, including rate control in atrial fibrillation. An intravenous form of diltiazem is available for the latter indication and causes hypotension or bradyarrhythmias relatively infrequently.

MISCELLANEOUS ANTIARRHYTHMIC AGENTS

Certain agents used for the treatment of arrhythmias do not fit the conventional class 1–4 organization. These include digitalis (discussed in Chapter 13), adenosine, magnesium, and potassium. It is also becoming clear that certain nonantiarrhythmic drugs, such as drugs acting on the renin-angiotensin-aldosterone system, fish oil, and statins, can reduce recurrence of tachycardias and fibrillation in patients with coronary heart disease or congestive heart failure.

ADENOSINE

Mechanism & Clinical Use

Adenosine is a nucleoside that occurs naturally throughout the body. Its half-life in the blood is less than 10 seconds. Its mechanism of action involves activation of an inward rectifier K^+ current and inhibition of calcium current. The results of these actions are marked hyperpolarization and suppression of calcium-dependent action potentials. When given as a bolus dose, adenosine directly inhibits AV nodal conduction and increases the AV nodal refractory period but has lesser effects on the SA node. Adenosine is currently the drug of choice for prompt conversion of paroxysmal supraventricular tachycardia to sinus rhythm because of its high efficacy (90–95%) and very short duration of action. It is usually given in a bolus dose of 6 mg followed, if necessary, by a dose of 12 mg. An uncommon variant of ventricular tachycardia is adenosine-sensitive. The drug is less effective in the presence of adenosine receptor blockers such as theophylline or caffeine, and its effects are potentiated by adenosine uptake inhibitors such as dipyridamole.

The Nonpharmacologic Therapy of Cardiac Arrhythmias

It was recognized over 100 years ago that reentry in simple in vitro models (eg, rings of conducting tissues) was permanently interrupted by transecting the reentry circuit. This concept is now applied in cardiac arrhythmias with defined anatomic pathways—eg, atrioventricular reentry using accessory pathways, atrioventricular node reentry, atrial flutter, and some forms of ventricular tachycardia—by treatment with **radiofrequency catheter ablation** or extreme cold, **cryoablation.** Mapping of reentrant pathways and ablation can be carried out by means of catheters threaded into the heart from peripheral arteries and veins. Recent studies have shown that paroxysmal and persistent atrial fibrillation may arise from one of the pulmonary veins. Both forms of atrial fibrillation can be cured by electrically isolating the pulmonary veins by radiofrequency catheter ablation or during concomitant cardiac surgery.

Another form of nonpharmacologic therapy is the **implantable cardioverter-defibrillator (ICD),** a device that can automatically detect and treat potentially fatal arrhythmias such as ventricular fibrillation. ICDs are now widely used in patients who have been resuscitated from such arrhythmias, and several trials have shown that ICD treatment reduces mortality in patients with coronary artery disease who have an ejection fraction ≤ 30% and in patients with class II or III heart failure and no prior history of arrhythmias. The increasing use of nonpharmacologic antiarrhythmic therapies reflects both advances in the relevant technologies and an increasing appreciation of the dangers of long-term therapy with currently available drugs.

Toxicity

Adenosine causes flushing in about 20% of patients and shortness of breath or chest burning (perhaps related to bronchospasm) in over 10%. Induction of high-grade AV block may occur but is very short-lived. Atrial fibrillation may occur. Less common toxicities include headache, hypotension, nausea, and paresthesias.

MAGNESIUM

Originally used for patients with digitalis-induced arrhythmias who were hypomagnesemic, magnesium infusion has been found to have antiarrhythmic effects in some patients with normal serum magnesium levels. The mechanisms of these effects are not known, but magnesium is recognized to influence Na^+/K^+-ATPase, sodium channels, certain potassium channels, and calcium channels. Magnesium therapy appears to be indicated in patients with digitalis-induced arrhythmias if hypomagnesemia is present; it is also indicated in some patients with torsades de pointes even if serum magnesium is normal. The usual dosage is 1 g (as sulfate) given intravenously over 20 minutes and repeated once if necessary. A full understanding of the action and indications for the use of magnesium as an antiarrhythmic drug awaits further investigation.

POTASSIUM

The significance of the potassium ion concentrations inside and outside the cardiac cell membrane was discussed earlier in this chapter. The effects of increasing serum K^+ can be summarized as (1) a resting potential depolarizing action and (2) a membrane potential stabilizing action, the latter caused by increased potassium permeability. Hypokalemia results in an increased risk of early and delayed afterdepolarizations, and ectopic pacemaker activity, especially in the presence of digitalis. Hyperkalemia depresses ectopic pacemakers (severe hyperkalemia is required to suppress the SA node) and slows conduction. Because both insufficient and excess potassium is potentially arrhythmogenic, potassium therapy is directed toward normalizing potassium gradients and pools in the body.

■ PRINCIPLES IN THE CLINICAL USE OF ANTIARRHYTHMIC AGENTS

The margin between efficacy and toxicity is particularly narrow for antiarrhythmic drugs. Risks and benefits must be carefully considered (see Box: Antiarrhythmic Drug-Use Principles Applied to Atrial Fibrillation).

Pretreatment Evaluation

Several important steps must be taken before initiation of any antiarrhythmic therapy:

1. **Eliminate the cause.** Precipitating factors must be recognized and eliminated if possible. These include not only abnormalities of internal homeostasis, such as hypoxia or electrolyte abnormalities (especially hypokalemia or hypomagnesemia), but also drug therapy and underlying disease states such as hyperthyroidism or cardiac disease. It is important to separate this abnormal substrate from triggering factors, such as myocardial ischemia or acute cardiac dilation, which may be treatable and reversible by different means.
2. **Make a firm diagnosis.** A firm arrhythmia diagnosis should be established. For example, the misuse of verapamil in patients with ventricular tachycardia mistakenly diagnosed as supraventricular tachycardia can lead to catastrophic hypotension and cardiac arrest. As increasingly sophisticated methods to characterize underlying arrhythmia mechanisms become available and are validated, it may be possible to direct certain drugs toward specific arrhythmia mechanisms.
3. **Determine the baseline condition.** Underlying heart disease is a critical determinant of drug selection for a particular arrhythmia in a particular patient. A key question is whether the heart is structurally abnormal. Few antiarrhythmic drugs have documented safety in patients with congestive heart failure or ischemic heart disease. In fact, some drugs pose a documented proarrhythmic risk in certain disease states, eg, class 1C drugs in patients with ischemic heart disease. A reliable baseline should be established against which to judge the efficacy of any

Antiarrhythmic Drug-Use Principles Applied to Atrial Fibrillation

Atrial fibrillation is the most common sustained arrhythmia observed clinically. Its prevalence increases from ~ 0.5% in individuals younger than 65 years of age to 10% in individuals older than 80. Diagnosis is usually straightforward by means of an ECG. The ECG may also enable the identification of a prior myocardial infarction, left ventricular hypertrophy, and ventricular pre-excitation. Hyperthyroidism is an important treatable cause of atrial fibrillation, and a thyroid panel should be obtained at the time of diagnosis to exclude this possibility. With the clinical history and physical examination as a guide, the presence and extent of the underlying heart disease should be evaluated, preferably using noninvasive techniques such as echocardiography.

Treatment of atrial fibrillation is initiated to relieve patient symptoms and prevent the complications of thromboembolism and tachycardia-induced heart failure, the result of prolonged uncontrolled heart rates. The initial treatment objective is control of the ventricular rate. This is usually achieved by use of a calcium channel-blocking drug alone or in combination with a β-adrenergic blocker. Digoxin may be of value in the presence of heart failure. A second objective is a restoration and maintenance of normal sinus rhythm. Several studies show that rate control (maintenance of ventricular rate in the range of 60–80 bpm) has a better benefit-to-risk outcome than rhythm control (conversion to normal sinus rhythm) in the long-term health of patients with atrial fibrillation. If rhythm control is deemed desirable, sinus rhythm is usually restored by DC cardioversion in the USA; in some countries, a class 1 antiarrhythmic drug is used initially. For patients with paroxysmal atrial fibrillation, normal sinus rhythm may be restored with a single large oral dose of propafenone or flecainide, provided that safety is initially documented in a monitored setting. Intravenous ibutilide can restore sinus rhythm promptly. For restoration of sinus rhythm in an emergency, eg, atrial fibrillation associated with hypotension or angina, DC cardioversion is the preferred modality. A class 1 or class 3 antiarrhythmic drug is then used to maintain normal sinus rhythm.

subsequent antiarrhythmic intervention. Several methods are now available for such baseline quantification. These include prolonged ambulatory monitoring, electrophysiologic studies that reproduce a target arrhythmia, reproduction of a target arrhythmia by treadmill exercise, or the use of transtelephonic monitoring for recording of sporadic but symptomatic arrhythmias.

4. **Question the need for therapy.** The mere identification of an abnormality of cardiac rhythm does not necessarily require that the arrhythmia be treated. An excellent justification for conservative treatment was provided by the Cardiac Arrhythmia Suppression Trial (CAST) referred to earlier.

Benefits & Risks

The benefits of antiarrhythmic therapy are actually relatively difficult to establish. Two types of benefits can be envisioned: reduction of arrhythmia-related symptoms, such as palpitations, syncope, or cardiac arrest; and reduction in long-term mortality in asymptomatic patients. Among drugs discussed here, only β blockers have been definitely associated with reduction of mortality in relatively asymptomatic patients, and the mechanism underlying this effect is not established (see Chapter 10).

Antiarrhythmic therapy carries with it a number of risks. In some cases, the risk of an adverse reaction is clearly related to high dosages or plasma concentrations. Examples include lidocaine-induced tremor or quinidine-induced cinchonism. In other cases, adverse reactions are unrelated to high plasma concentrations (eg, procainamide-induced agranulocytosis). For many serious adverse reactions to antiarrhythmic drugs, the *combination* of drug therapy and the underlying heart disease appears important.

Several specific syndromes of arrhythmia provocation by antiarrhythmic drugs have also been identified, each with its underlying pathophysiologic mechanism and risk factors. Drugs such as quinidine, sotalol, ibutilide, and dofetilide, which act—at least in part—by slowing repolarization and prolonging cardiac action potentials, can result in marked QT prolongation and torsades de pointes. Treatment for torsades requires recognition of the arrhythmia, withdrawal of any offending agent, correction of hypokalemia, and treatment with maneuvers to increase heart rate (pacing or isoproterenol); intravenous magnesium also appears effective, even in patients with normal magnesium levels.

Drugs that markedly slow conduction, such as flecainide, or high concentrations of quinidine, can result in an increased frequency of reentry arrhythmias, notably ventricular tachycardia in patients with prior myocardial infarction in whom a potential reentry circuit may be present. Treatment here consists of recognition, withdrawal of the offending agent, and intravenous sodium.

Conduct of Antiarrhythmic Therapy

The urgency of the clinical situation determines the route and rate of drug initiation. When immediate drug action is required, the intravenous route is preferred. Therapeutic drug levels can be achieved by administration of multiple *slow* intravenous boluses. Drug therapy can be considered effective when the target arrhythmia is suppressed (according to the measure used to quantify it at baseline) and toxicities are absent. Conversely, drug therapy should not be considered ineffective unless toxicities occur at a time when arrhythmias are not suppressed.

Monitoring plasma drug concentrations can be a useful adjunct to managing antiarrhythmic therapy. Plasma drug concentrations are also important in establishing compliance during long-term therapy as well as in detecting drug interactions that may result in very high concentrations at low drug dosages or very low concentrations at high dosages.

SUMMARY Antiarrhythmic Drugs

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
CLASS 1A				
• Procainamide	I_{Na} (primary) and I_{Kr} (secondary) blockade	Slows conduction velocity and pacemaker rate • prolongs action potential duration and dissociates from I_{Na} channel with intermediate kinetics • direct depressant effects on sinoatrial (SA) and atrioventricular (AV) nodes	Most atrial and ventricular arrhythmias • drug of second choice for most sustained ventricular arrhythmias associated with acute myocardial infarction	Oral, IV, IM • eliminated by hepatic metabolism to *N*-acetylprocainamide (NAPA; see text) and renal elimination • NAPA implicated in torsades de pointes in patients with renal failure • *Toxicity:* Hypotension • long-term therapy produces reversible lupus-related symptoms
• *Quinidine: Similar to procainamide but more toxic (cinchonism, torsades); rarely used in arrhythmias; see Chapter 52 for malaria*				
• *Disopyramide: Similar to procainamide but significant antimuscarinic effects; may precipitate heart failure; not commonly used*				
CLASS 1B				
• Lidocaine	Sodium channel (I_{Na}) blockade	Blocks activated and inactivated channels with fast kinetics • does not prolong and may shorten action potential	Terminate ventricular tachycardias and prevent ventricular fibrillation after cardioversion	IV • first-pass hepatic metabolism • reduce dose in patients with heart failure or liver disease • *Toxicity:* Neurologic symptoms
• *Mexiletine: Orally active congener of lidocaine; used in ventricular arrhythmias, chronic pain syndromes*				
CLASS 1C				
• Flecainide	Sodium channel (I_{Na}) blockade	Dissociates from channel with slow kinetics • no change in action potential duration	Supraventricular arrhythmias in patients with normal heart • do not use in ischemic conditions (post-myocardial infarction)	Oral • hepatic and kidney metabolism • half life ~ 20 h • *Toxicity:* Proarrhythmic
• *Propafenone: Orally active, weak β-blocking activity; supraventricular arrhythmias; hepatic metabolism*				
• *Moricizine: Phenothiazine derivative, orally active; ventricular arrhythmias, proarrhythmic. Withdrawn in USA.*				
CLASS 2				
• Propranolol	β-Adrenoceptor blockade	Direct membrane effects (sodium channel block) and prolongation of action potential duration • slows SA node automaticity and AV nodal conduction velocity	Atrial arrhythmias and prevention of recurrent infarction and sudden death	Oral, parenteral • duration 4–6 h • *Toxicity:* Asthma, AV blockade, acute heart failure • *Interactions:* With other cardiac depressants and hypotensive drugs
• *Esmolol: Short-acting, IV only; used for intraoperative and other acute arrhythmias*				
CLASS 3				
• Amiodarone	Blocks I_{Kr}, I_{Na}, $I_{Ca\text{-}L}$ channels, β adrenoceptors	Prolongs action potential duration and QT interval • slows heart rate and AV node conduction • low incidence of torsades de pointes	Serious ventricular arrhythmias and supraventricular arrhythmias	Oral, IV • variable absorption and tissue accumulation • hepatic metabolism, elimination complex and slow • *Toxicity:* Bradycardia and heart block in diseased heart, peripheral vasodilation, pulmonary and hepatic toxicity • hyper- or hypothyroidism. • *Interactions:* Many, based on CYP metabolism
• Dofetilide	I_{Kr} block	Prolongs action potential, effective refractory period	Maintenance or restoration of sinus rhythm in atrial fibrillation	Oral • renal excretion • *Toxicity:* Torsades de pointes (initiate in hospital) • *Interactions:* Additive with other QT-prolonging drugs
• *Sotalol: β-Adrenergic and I_{Kr} blocker, direct action potential prolongation properties, use for ventricular arrhythmias, atrial fibrillation*				
• *Ibutilide: Potassium channel blocker, may activate inward current; IV use for conversion in atrial flutter and fibrillation*				
• *Dronedarone: Amiodarone derivative; multichannel actions, reduces mortality in patients with atrial fibrillation*				
• *Vernakalant: Investigational, multichannel actions in atria, prolongs atrial refractoriness, effective in atrial fibrillation*				

(*continued*)

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
CLASS 4				
• Verapamil	Calcium channel ($I_{Ca\text{-}L}$ type) blockade	Slows SA node automaticity and AV nodal conduction velocity • decreases cardiac contractility • reduces blood pressure	Supraventricular tachycardias, hypertension, angina	Oral, IV • hepatic metabolism • caution in patients with hepatic dysfunction • *Toxicity & Interactions*: See Chapter 12
• *Diltiazem: Equivalent to verapamil*				
MISCELLANEOUS				
• Adenosine	Activates inward rectifier I_K • blocks I_{Ca}	Very brief, usually complete AV blockade	Paroxysmal supraventricular tachycardias	IV only • duration 10–15 seconds• *Toxicity:* Flushing, chest tightness, dizziness • *Interactions:* Minimal
• Magnesium	Poorly understood • interacts with Na^+/K^+-ATPase, K^+, and Ca^{2+} channels	Normalizes or increases plasma Mg^{2+}	Torsades de pointes • digitalis-induced arrhythmias	IV • duration dependent on dosage • *Toxicity:* Muscle weakness in overdose
• Potassium	Increases K^+ permeability, K^+ currents	Slows ectopic pacemakers • slows conduction velocity in heart	Digitalis-induced arrhythmias • arrhythmias associated with hypokalemia	Oral, IV • *Toxicity:* Reentrant arrhythmias, fibrillation or arrest in overdose

PREPARATIONS AVAILABLE

SODIUM CHANNEL BLOCKERS

Disopyramide (generic, Norpace)
Oral: 100, 150 mg capsules
Oral controlled-release (generic, Norpace CR): 100, 150 capsules

Flecainide (generic, Tambocor)
Oral: 50, 100, 150 mg tablets

Lidocaine (generic, Xylocaine)
Parenteral: 100 mg/mL for IM injection; 10, 20 mg/mL for IV injection; 40, 100, 200 mg/mL for IV admixtures; 2, 4, 8 mg/mL premixed IV (5% D/W) solution

Mexiletine (Mexitil)
Oral: 150, 200, 250 mg capsules

Procainamide (generic, Pronestyl, others)
Oral: 250, 375, 500 mg tablets and capsules
Oral sustained-release (generic, Procan-SR): 250, 500, 750, 1000 mg tablets
Parenteral: 500 mg/mL for injection

Propafenone (generic, Rythmol)
Oral: 150, 225, 300 mg tablets, capsules

Quinidine sulfate [83% quinidine base] (generic)
Oral: 200, 300 mg tablets
Oral sustained-release (Quinidex Extentabs): 300 mg tablets

Quinidine gluconate [62% quinidine base] (generic)
Oral sustained-release: 324 mg tablets
Parenteral: 80 mg/mL for injection

Quinidine polygalacturonate [60% quinidine base] (Cardioquin)
Oral: 275 mg tablets

BETA BLOCKERS LABELED FOR USE AS ANTIARRHYTHMICS

Acebutolol (generic, Sectral)
Oral: 200, 400 mg capsules

Esmolol (Brevibloc)
Parenteral: 10 mg/mL, 250 mg/mL for IV injection

Propranolol (generic, Inderal)
Oral: 10, 20, 40, 60, 80, 90 mg tablets
Oral sustained-release: 60, 80, 120, 160 mg capsules
Oral solution: 4, 8 mg/mL
Parenteral: 1 mg/mL for injection

ACTION POTENTIAL-PROLONGING AGENTS

Amiodarone (generic, Cordarone)
Oral: 100, 200, 400 mg tablets
Parenteral: 150 mg/3 mL for IV infusion

Dofetilide (Tikosyn)
Oral: 125, 250, 500 mcg capsules

Dronedarone (Multac)
Oral: 400 mg tablets

Ibutilide (Corvert)
Parenteral: 0.1 g/mL solution for IV infusion

Sotalol (generic, Betapace)
Oral: 80, 120, 160, 240 mg capsules

CALCIUM CHANNEL BLOCKERS

Diltiazem (generic, Cardizem, Dilacor)
Oral: 30, 60, 90, 120 mg tablets; 60, 90, 120, 180, 240, 300, 340, 420 mg extended- or sustained-release capsules (*not labeled for use in arrhythmias*)
Parenteral: 5 mg/mL for IV injection

Verapamil (generic, Calan, Isoptin)
Oral: 40, 80, 120 mg tablets
Oral sustained-release (Calan SR, Isoptin SR): 100, 120, 180, 240 mg capsules
Parenteral: 5 mg/2 mL for injection

MISCELLANEOUS

Adenosine (generic, Adenocard)
Parenteral: 3 mg/mL for injection

Magnesium sulfate
Parenteral: 125, 500 mg/mL for IV infusion

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CASE STUDY ANSWER

The patient has significant symptoms during recurrent episodes of atrial fibrillation. The peak heart rate is not particularly high. Maintenance of sinus rhythm appears to be important in this patient. The echocardiogram demonstrates impairment of left ventricular function. Selection of a drug that is tolerated in heart failure and has documented ability to convert or prevent atrial fibrillation, eg, dofetilide or amiodarone, would be appropriate.

CHAPTER 15

Diuretic Agents

Harlan E. Ives, MD, PhD

CASE STUDY

A 65-year-old man comes to the emergency department with severe shortness of breath. His wife reports that he has long known that he is hypertensive but never had symptoms, so he refused to take antihypertensive medications. During the last month, he has noted increasing ankle edema, reduced exercise tolerance, and difficulty sleeping lying down, but he reports no episodes of chest pain or discomfort. He now has pitting edema to the knees and is acutely uncomfortable lying down. Vital signs include blood pressure 190/140 mm Hg, pulse 120 bpm, and respiratory rate 20/min. Chest auscultation reveals loud rhonchi, but an electrocardiogram is negative except for evidence of left ventricular hypertrophy. He is given a diuretic intravenously and admitted to intensive care. What diuretic would be most appropriate for this man's case of acute pulmonary edema associated with heart failure? What are the possible toxicities of this therapy?

Abnormalities in fluid volume and electrolyte composition are common and important clinical disorders. Drugs that block specific transport functions of the renal tubules are valuable clinical tools in the treatment of these disorders. Although various agents that increase urine volume (diuretics) have been described since antiquity, it was not until 1937 that carbonic anhydrase inhibitors were first described and not until 1957 that a much more useful and powerful diuretic agent (chlorothiazide) became available.

Technically, a "diuretic" is an agent that increases urine volume, whereas a "natriuretic" causes an increase in renal sodium excretion and an "aquaretic" increases excretion of solute-free water. Because natriuretics almost always also increase water excretion, they are usually called diuretics. Osmotic diuretics and antidiuretic hormone antagonists (see Agents That Alter Water Excretion) are aquaretics that are not directly natriuretic.

This chapter is divided into three sections. The first section covers major renal tubule transport mechanisms. The nephron is divided structurally and functionally into several segments (Figure 15–1, Table 15–1). Several autacoids, which exert multiple, complex events on renal physiologic processes (adenosine, prostaglandins, and urodilatin, a renal autacoid closely related to atrial natriuretic peptide), are also discussed. The second section describes the pharmacology of diuretic agents. Many diuretics exert their effects on specific membrane transport proteins in renal tubular epithelial cells. Other diuretics exert osmotic effects that prevent water reabsorption (mannitol), inhibit enzymes (acetazolamide), or interfere with hormone receptors in renal epithelial cells (vaptans, or vasopressin antagonists). The physiology of each nephron segment is closely linked to the basic pharmacology of the drugs acting there, which is discussed in the second section. The third section of the chapter describes the clinical applications of diuretics.

RENAL TUBULE TRANSPORT MECHANISMS

PROXIMAL TUBULE

Sodium bicarbonate ($NaHCO_3$), sodium chloride (NaCl), glucose, amino acids, and other organic solutes are reabsorbed via specific transport systems in the early proximal tubule (proximal convoluted tubule, PCT). Potassium ions (K^+) are reabsorbed via the paracellular pathway. Water is reabsorbed passively, maintaining the osmolality of proximal tubular fluid at a nearly constant level. As tubule fluid is processed along the length of the proximal tubule, the luminal concentrations of these solutes decrease relative to the concentration of inulin, an experimental marker that is filtered but neither secreted nor absorbed by renal tubules. Approximately 66% of filtered sodium ions (Na^+), 85% of the $NaHCO_3$, 65% of the K^+, 60% of the water, and virtually all of the filtered glucose and amino acids are reabsorbed in the proximal tubule.

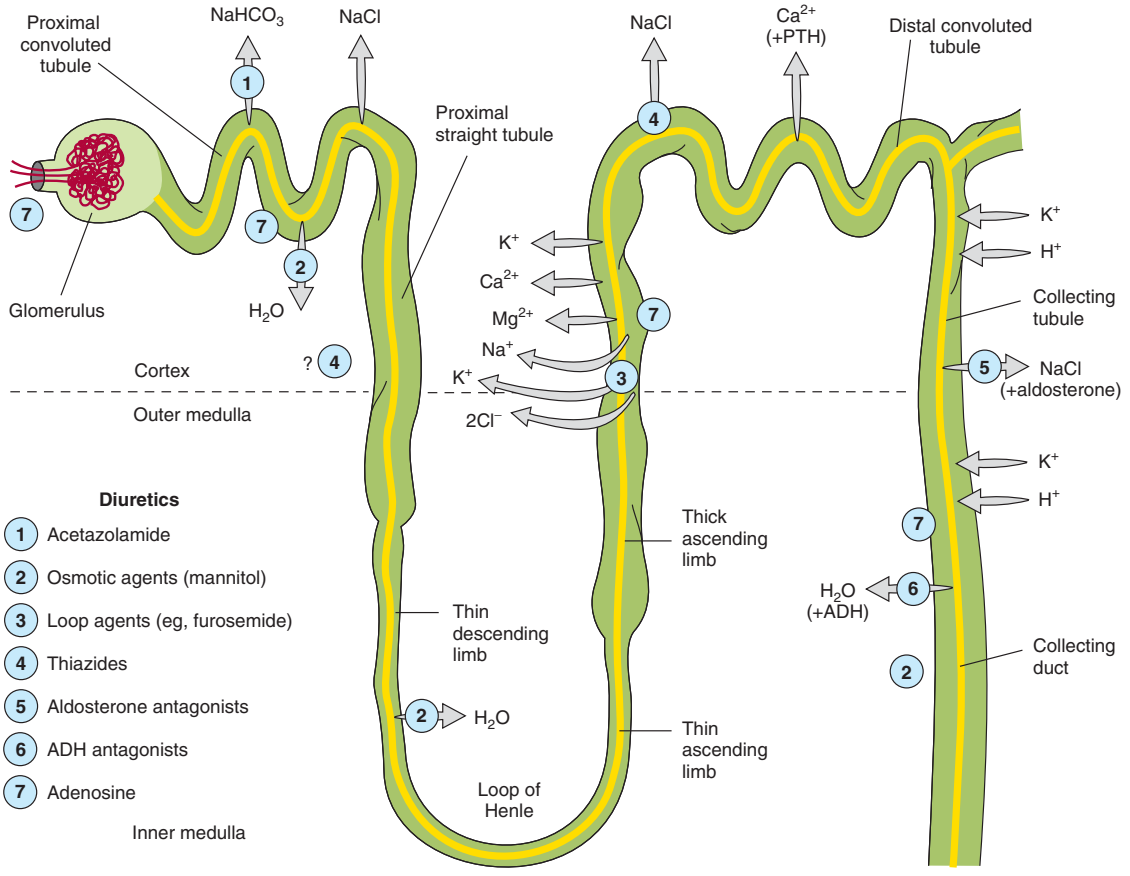

FIGURE 15–1 Tubule transport systems and sites of action of diuretics. ADH, antidiuretic hormone; PTH, parathyroid hormone.

TABLE 15–1 Major segments of the nephron and their functions.

Segment	Functions	Water Permeability	Primary Transporters and Drug Targets at Apical Membrane	Diuretic with Major Action
Glomerulus	Formation of glomerular filtrate	Extremely high	None	None
Proximal convoluted tubule (PCT)	Reabsorption of 65% of filtered $Na^+/K^+/CA^{2+}$, and Mg^{2+}; 85% of $NaHCO_3$, and nearly 100% of glucose and amino acids. Isosmotic reabsorption of water.	Very high	Na/H^1 (NHE3), carbonic anhydrase	Carbonic anhydrase inhibitors Adenosine antagonists (under investigation)
Proximal tubule, straight segments	Secretion and reabsorption of organic acids and bases, including uric acid and most diuretics	Very high	Acid (eg, uric acid) and base transporters	None
Thin descending limb of Henle's loop	Passive reabsorption of water	High	Aquaporins	None
Thick ascending limb of Henle's loop (TAL)	Active reabsorption of 15–25% of filtered $Na^+/K^+/Cl^-$; secondary reabsorption of Ca^{2+} and Mg^{2+}	Very low	Na/K/2Cl (NKCC2)	Loop diuretics
Distal convoluted tubule (DCT)	Active reabsorption of 4–8% of filtered Na^+ and Cl^-; Ca^{2+} reabsorption under parathyroid hormone control	Very low	Na/Cl (NCC)	Thiazides
Cortical collecting tubule (CCT)	Na^+ reabsorption (2–5%) coupled to K^+ and H^+ secretion	Variable[2]	Na channels (ENaC), K channels,[1] H^+ transporter,[1] aquaporins	K^+-sparing diuretics Adenosine antagonists (under investigation)
Medullary collecting duct	Water reabsorption under vasopressin control	Variable[2]	Aquaporins	Vasopressin antagonists

[1]Not a target of currently available drugs.
[2]Controlled by vasopressin activity.

Of the various solutes reabsorbed in the proximal tubule, the most relevant to diuretic action are $NaHCO_3$ and NaCl. Of the currently available diuretics, only one group (carbonic anhydrase inhibitors, which block $NaHCO_3$ reabsorption) acts predominantly in the PCT. In view of the large quantity of NaCl absorbed in this segment, a drug that specifically blocked proximal tubular absorption of NaCl could be a particularly powerful diuretic. Adenosine receptor antagonists, which are currently under intense clinical investigation, act mainly in the PCT and appear to induce a NaCl, rather than a $NaHCO_3$ diuresis. Sodium bicarbonate reabsorption by the PCT is initiated by the action of a Na^+/H^+ exchanger (NHE3) located in the luminal membrane of the proximal tubule epithelial cell (Figure 15–2). This transport system allows Na^+ to enter the cell from the tubular lumen in exchange for a proton (H^+) from inside the cell. As in all portions of the nephron, Na^+/K^+-ATPase in the basolateral membrane pumps the reabsorbed Na^+ into the interstitium so as to maintain a low intracellular Na^+ concentration. The H^+ secreted into the lumen combines with bicarbonate (HCO_3^-) to form H_2CO_3 (carbonic acid), which is rapidly dehydrated to CO_2 and H_2O by carbonic anhydrase. Carbon dioxide produced by dehydration of H_2CO_3 enters the proximal tubule cell by simple diffusion where it is then rehydrated back to H_2CO_3, also facilitated by intracellular carbonic anhydrase. After dissociation of H_2CO_3, the H^+ is available for transport by the Na^+/H^+ exchanger, and the HCO_3^- is transported out of the cell by a basolateral membrane transporter (Figure 15–2). Bicarbonate reabsorption by the proximal tubule is thus dependent on carbonic anhydrase activity. This enzyme can be inhibited by acetazolamide and other carbonic anhydrase inhibitors.

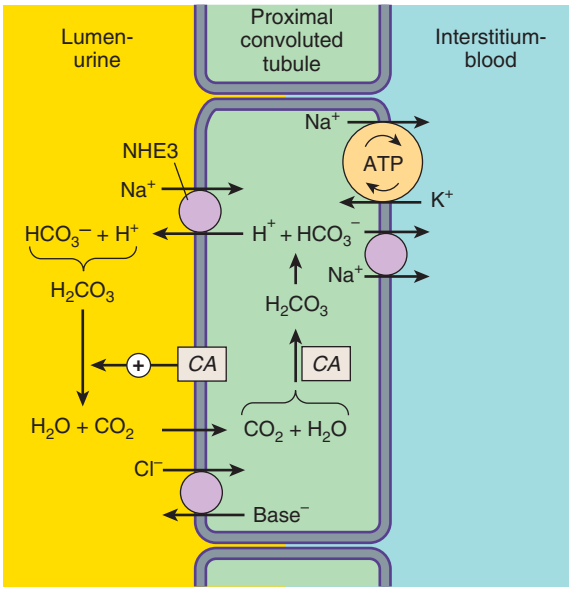

FIGURE 15–2 Apical membrane Na^+/H^+ exchange (via NHE3) and bicarbonate reabsorption in the proximal convoluted tubule cell. Na^+/K^+-ATPase is present in the basolateral membrane to maintain intracellular sodium and potassium levels within the normal range. Because of rapid equilibration, concentrations of the solutes are approximately equal in the interstitial fluid and the blood. Carbonic anhydrase (CA) is found in other locations in addition to the brush border of the luminal membrane.

Adenosine, which is released as a result of hypoxia and ATP consumption, is a molecule with four different receptors and complex effects on Na^+ transport in several segments of the nephron. Although it reduces glomerular filtration rate (GFR) to decrease energy consumption by the kidney, adenosine actually increases proximal reabsorption of Na^+ via stimulation of NHE3 activity. A new class of drugs, the adenosine A_1-receptor antagonists, have recently been found to significantly blunt both proximal tubule NHE3 activity and collecting duct NaCl reabsorption, and to have potent vasomotor effects in the renal microvasculature (see below, under Autacoids, Pharmacology of Diuretic Agents, and under Heart Failure).

Because HCO_3^- and organic solutes have been largely removed from the tubular fluid in the late proximal tubule, the residual luminal fluid contains predominantly NaCl. Under these conditions, Na^+ reabsorption continues, but the H^+ secreted by the Na^+/H^+ exchanger can no longer bind to HCO_3^-. Free H^+ causes luminal pH to fall, activating a poorly defined Cl^-/base exchanger (Figure 15–2). The net effect of parallel Na^+/H^+ exchange and Cl^-/base exchange is NaCl reabsorption. As yet, there are no diuretic agents that are known to act on this conjoint process.

Water is reabsorbed in the PCT in response to osmotic forces, so luminal fluid osmolality remains nearly constant along its length, and an impermeant solute like inulin rises in concentration as water is reabsorbed. If large amounts of an impermeant solute such as mannitol (an osmotic diuretic) are present in the tubular fluid, water reabsorption causes the concentration of the solute to rise, so that as salt concentrations become diminished further, water reabsorption is prevented.

Organic acid secretory systems are located in the middle third of the straight part of the proximal tubule (S_2 segment). These systems secrete a variety of organic acids (uric acid, nonsteroidal anti-inflammatory drugs [NSAIDs], diuretics, antibiotics, etc) into the luminal fluid from the blood. These systems thus help deliver diuretics to the luminal side of the tubule, where most of them act. Organic base secretory systems (creatinine, choline, etc) are also present, in the early (S_1) and middle (S_2) segments of the proximal tubule.

LOOP OF HENLE

At the boundary between the inner and outer stripes of the outer medulla, the proximal tubule empties into the thin descending limb of Henle's loop. Water is extracted from the descending limb of this loop by osmotic forces found in the hypertonic medullary interstitium. As in the proximal tubule, impermeant luminal solutes such as mannitol oppose this water extraction and thus have aquaretic activity. The thin *ascending* limb is relatively water-impermeable but is permeable to some solutes.

The thick ascending limb (TAL), which follows the thin limb of Henle's loop, actively reabsorbs NaCl from the lumen (about 25% of the filtered sodium), but unlike the proximal tubule and the thin descending limb of Henle's loop, it is nearly impermeable to water.

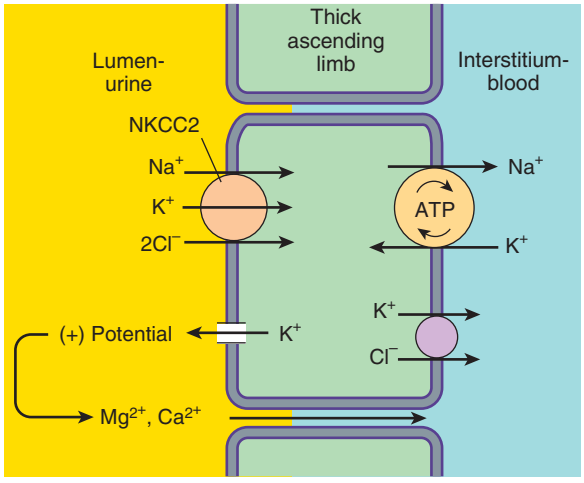

FIGURE 15–3 Ion transport pathways across the luminal and basolateral membranes of the thick ascending limb cell. The lumen positive electrical potential created by K^+ back diffusion drives divalent (and monovalent) cation reabsorption via the paracellular pathway. NKCC2 is the primary transporter in the luminal membrane.

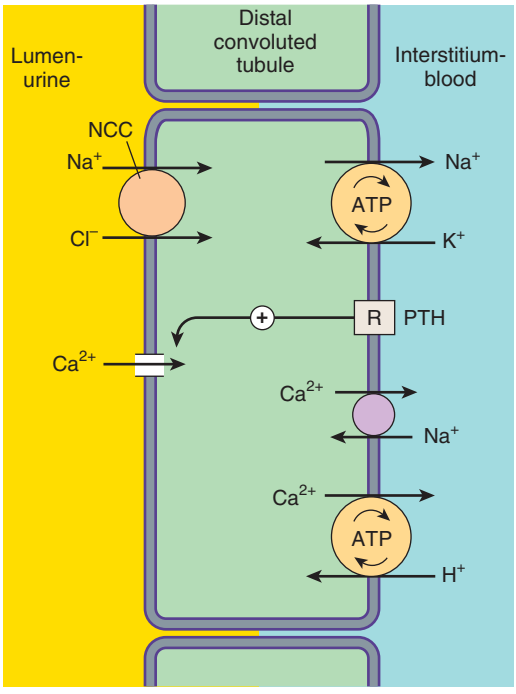

FIGURE 15–4 Ion transport pathways across the luminal and basolateral membranes of the distal convoluted tubule cell. As in all tubular cells, Na^+/K^+ ATPase is present in the basolateral membrane. NCC is the primary sodium and chloride transporter in the luminal membrane. (R, parathyroid hormone [PTH] receptor.)

Salt reabsorption in the TAL therefore dilutes the tubular fluid, and it is called a *diluting segment*. Medullary portions of the TAL contribute to medullary hypertonicity and thereby also play an important role in concentration of urine by the collecting duct.

The NaCl transport system in the luminal membrane of the TAL is a $Na^+/K^+/2Cl^-$ cotransporter (called NKCC2 or NK2CL) (Figure 15–3). This transporter is selectively blocked by diuretic agents known as "loop" diuretics (see later in chapter). Although the $Na^+/K^+/2Cl^-$ transporter is itself electrically neutral (two cations and two anions are cotransported), the action of the transporter contributes to excess K^+ accumulation within the cell. Back diffusion of this K^+ into the tubular lumen causes a lumen-positive electrical potential that provides the driving force for reabsorption of cations—including magnesium and calcium—via the paracellular pathway. Thus, inhibition of salt transport in the TAL by loop diuretics, which reduces the lumen-positive potential, causes an increase in urinary excretion of divalent cations in addition to NaCl.

DISTAL CONVOLUTED TUBULE

Only about 10% of the filtered NaCl is reabsorbed in the distal convoluted tubule (DCT). Like the TAL of Henle's loop, this segment is relatively impermeable to water, and NaCl reabsorption further dilutes the tubular fluid. The mechanism of NaCl transport in the DCT is an electrically neutral thiazide-sensitive Na^+ and Cl^- cotransporter (NCC, Figure 15–4).

Because K^+ does not recycle across the apical membrane of the DCT as it does in the TAL, there is no lumen-positive potential in this segment, and Ca^{2+} and Mg^{2+} are not driven out of the tubular lumen by electrical forces. Instead, Ca^{2+} is actively reabsorbed by the DCT epithelial cell via an apical Ca^{2+} channel and basolateral Na^+/Ca^{2+} exchanger (Figure 15–4). This process is regulated by parathyroid hormone.

COLLECTING TUBULE SYSTEM

The collecting tubule system that connects the DCT to the renal pelvis and the ureter consists of several sequential tubular segments: the connecting tubule, the collecting tubule, and the collecting duct (formed by the connection of two or more collecting tubules). Although these tubule segments may be anatomically distinct, the physiologic gradations are more gradual, and in terms of diuretic activity it is easier to think of this complex as a single segment of the nephron containing several distinct cell types. The collecting tubule system is responsible for only 2–5% of NaCl reabsorption by the kidney. Despite this small contribution, it plays an important role in renal physiology and in diuretic action. As the final site of NaCl reabsorption, the collecting system is responsible for tight regulation of body fluid volume and for determining the final Na^+ concentration of the urine. Furthermore, the collecting system is the site at which mineralocorticoids exert a significant influence. Lastly, this is the most important site of K^+ secretion by the kidney and the site at which virtually all diuretic-induced changes in K^+ balance occur.

The mechanism of NaCl reabsorption in the collecting tubule system is distinct from the mechanisms found in other tubule segments. The **principal cells** are the major sites of Na^+, K^+, and water transport (Figures 15–5 and 15–6), and the **intercalated cells** (α, β) are the primary sites of H^+ (α cells) or bicarbonate (β cells) secretion. The α and β intercalated cells are very similar, except that the membrane locations of the H^+-ATPase and Cl/HCO_3^- exchanger are reversed. Principal cells do not contain apical

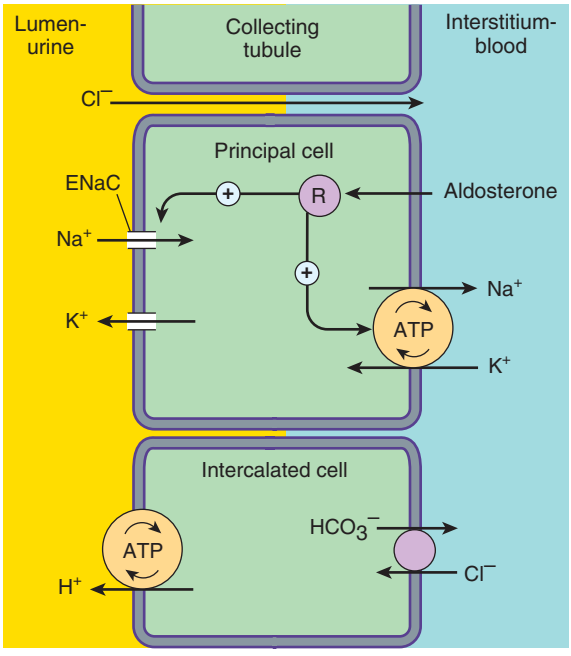

FIGURE 15–5 Ion transport pathways across the luminal and basolateral membranes of collecting tubule and collecting duct cells. Inward diffusion of Na^+ via the epithelial sodium channel (ENaC) leaves a lumen-negative potential, which drives reabsorption of Cl^- and efflux of K^+. (R, aldosterone receptor.)

cotransport systems for Na^+ and other ions, unlike cells in other nephron segments. Principal cell membranes exhibit separate ion channels for Na^+ and K^+. Since these channels exclude anions, transport of Na^+ or K^+ leads to a net movement of charge across the membrane. Because Na^+ entry into the principal cell predominates over K^+ secretion into the lumen, a 10–50 mV lumen-negative electrical potential develops. Sodium that enters the principal cell from the tubular fluid is then transported back to the blood via the basolateral Na^+/K^+-ATPase (Figure 15–5). The 10–50 mV lumen-negative electrical potential drives the transport of Cl^- back to the blood via the paracellular pathway and draws K^+ out of cells through the apical membrane K^+ channel. Thus, there is an important relationship between Na^+ delivery to the collecting tubule system and the resulting secretion of K^+. Upstream diuretics increase Na^+ delivery to this site and enhance K^+ secretion. If Na^+ is delivered to the collecting system with an anion that cannot be reabsorbed as readily as Cl^- (eg, HCO_3^-), the lumen-negative potential is increased, and K^+ secretion is enhanced. This mechanism, combined with enhanced aldosterone secretion due to volume depletion, is the basis for most diuretic-induced K^+ wasting. Adenosine antagonists, which act upstream at the proximal tubule, but also at the collecting duct, are perhaps the only diuretics that violate this principle (see below). Reabsorption of Na^+ via the epithelial Na channel (ENaC) and its coupled secretion of K^+ is regulated by aldosterone. This steroid hormone, through its actions on gene transcription, increases the activity of both apical membrane channels and the basolateral Na^+/K^+-ATPase. This leads to an increase in the transepithelial electrical potential and a dramatic increase in both Na^+ reabsorption and K^+ secretion.

The collecting tubule system is also the site at which the final urine concentration is determined. In addition to their role in control of Na^+ absorption and K^+ secretion (Figure 15–5), principal cells also contain a regulated system of water channels (Figure 15–6). Antidiuretic hormone (ADH, also called arginine vasopressin, AVP) controls the permeability of these cells to water by regulating the insertion of pre-formed water channels (aquaporin-2, AQP2) into the apical membrane. Vasopressin receptors in the vasculature and central nervous system (CNS) are V_1 receptors, and those in the kidney are V_2 receptors. V_2 receptors act via a G protein-coupled, cAMP-mediated process. In the absence of ADH, the collecting tubule (and duct) is impermeable to water, and dilute urine is produced. ADH markedly increases water permeability, and this leads to the formation of a more concentrated final urine. ADH also stimulates the insertion of urea transporter UT1 molecules into the apical membranes of collecting duct cells in the medulla.

Urea concentration in the medulla plays an important role maintaining the high osmolarity of the medulla and in the concentration of urine. ADH secretion is regulated by serum osmolality and by volume status. A new class of drugs, the vaptans (see under Agents That Alter Water Excretion), are ADH antagonists.

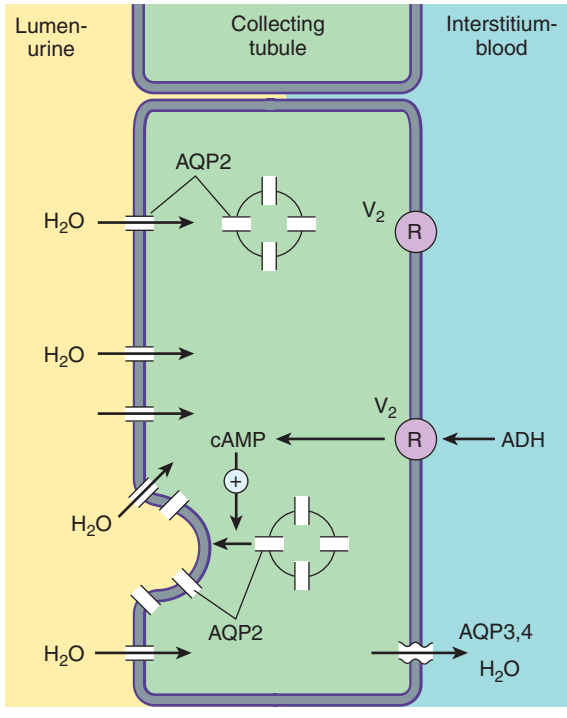

FIGURE 15–6 Water transport across the luminal and basolateral membranes of collecting duct cells. Above, low water permeability exists in the absence of antidiuretic hormone (ADH). Below, in the presence of ADH, aquaporins are inserted into the apical membrane, greatly increasing water permeability. (AQP2, apical aquaporin water channels; AQP3,4, basolateral aquaporin water channels; V_2, vasopressin V_2 receptor.)

RENAL AUTACOIDS

A number of locally produced compounds exhibit physiologic effects within the kidney and are therefore referred to as *autacoids*, or *paracrine factors*. Several of these autacoids (adenosine, the prostaglandins, and urodilatin) appear to have important effects on the pharmacology of diuretics. Since these effects are complex, they will be treated independently of the individual tubule segments discussed above.

ADENOSINE

Adenosine is an unphosphorylated ribonucleoside whose actions in the kidney have been intensively studied. As in all tissues, renal adenosine concentrations rise in response to hypoxia and ATP consumption. In most tissues, hypoxia results in compensatory vasodilation and, if cardiac output is sufficient, increased blood flow. The kidney has different requirements because increased blood flow leads to an increase in GFR and greater solute delivery to the tubules. This increased delivery would increase tubule work and ATP consumption. In contrast, in the hypoxic kidney, adenosine actually decreases blood flow and GFR. Because the medulla is always more hypoxic than the cortex, adenosine increases Na^+ reabsorption from the reduced flow in the cortex, so that delivery to medullary segments will be even further reduced.

There are four distinct adenosine receptors (A_1, A_{2a}, A_{2b}, and A_3), all of which have been found in the kidney. However, probably only one of these (A_1) is of importance with regard to the pharmacology of diuretics. The adenosine A_1 receptor is found on the pre-glomerular afferent arteriole, as well as the PCT and most other tubule segments. Adenosine is known to affect ion transport in the PCT, the medullary TAL, and collecting tubules. In addition, adenosine (via A_1 receptors on the afferent arteriole) reduces blood flow to the glomerulus (and GFR) and is also the key signaling molecule in the process of tubuloglomerular feedback (see below, under Heart Failure).

In addition to its effects on GFR, adenosine significantly alters Na^+ transport in several segments. In the proximal tubule, adenosine has a biphasic effect on NHE3 activity: enhancement at low concentrations and inhibition at very high concentrations. However, adenosine receptor antagonists have generally been found to block the enhancement of NHE3 activity and thus exhibit diuretic activity (see below). It is particularly interesting that unlike other diuretics that act upstream of the collecting tubules, adenosine antagonists do not cause wasting of K. This important finding suggests that in addition to their effects on NHE3, adenosine antagonists must also blunt K^+ secretion in the cortical collecting tubule. Adenosine A_1 receptors have been found in the collecting tubule, but the precise mechanism by which adenosine blunts K^+ secretion is not well understood.

PROSTAGLANDINS

Prostaglandins are autacoids that contribute importantly to renal physiology, and to the function of many other organs (see Chapter 18). Five prostaglandin subtypes (PGE_2, PGI_2, PGD_2, $PGF_{2\alpha}$, and thromboxane [TXA_2] are synthesized in the kidney and have receptors in this organ. The role of some of these receptors in renal physiology is not yet completely understood. However, PGE_2 (acting on EP_1, EP_3, and possibly EP_2) has been shown to play a role in the activity of certain diuretics. Among its many actions, PGE_2 blunts Na^+ reabsorption in the TAL of Henle's loop and ADH-mediated water transport in collecting tubules. These actions of PGE_2 contribute significantly to the diuretic efficacy of loop diuretics. Blockade of prostaglandin synthesis with NSAIDs can therefore interfere with loop diuretic activity.

PEPTIDES

There is growing interest in the natriuretic peptides (ANP, BNP, and CNP, see Chapter 17), which induce natriuresis through several different mechanisms. ANP and BNP are synthesized in the heart, while CNP comes primarily from the CNS. Some of these peptides exert both vascular effects (see Chapter 17) and sodium transport effects in the kidney, which participate in causing natriuresis. A fourth natriuretic peptide, urodilatin, is structurally very similar to ANP but is synthesized and functions only in the kidney. Urodilatin is made in distal tubule epithelial cells and blunts Na^+ reabsorption through effects on Na^+ uptake channels and Na^+/K^+-ATPase at the downstream collecting tubule system. In addition, through effects on vascular smooth muscle, it reduces glomerular afferent and increases glomerular efferent vasomotor tone. These effects cause an increase in GFR, which adds to the natriuretic activity. Ularitide is a recombinant peptide that mimics the activity of urodilatin. It is currently under intense investigation and may become available for clinical use in the near future.

The cardiac peptides ANP and BNP have pronounced systemic vascular effects. The receptors ANP_A and ANP_B, also known as NPR_A and NPR_B, are transmembrane molecules with guanylyl cyclase catalytic activity at the cytoplasmic domains. Of interest, both peptides increase GFR through effects on glomerular arteriolar vasomotor tone and also exhibit diuretic activity. CNP has very little diuretic activity. Three agents in this group are in clinical use or under investigation: nesiritide (BNP), carperitide (ANP, available only in Japan), and ularitide (urodilatin, under investigation). Intravenous ularitide has been studied extensively for use in acute heart failure. It can dramatically improve cardiovascular parameters and promote diuresis without reducing creatinine clearance. There is also evidence that nesiritide (simulating BNP) may enhance the activity of other diuretics while helping to maintain stable renal function.

BASIC PHARMACOLOGY OF DIURETIC AGENTS

CARBONIC ANHYDRASE INHIBITORS

Carbonic anhydrase is present in many nephron sites, but the predominant location of this enzyme is the epithelial cells of the PCT (Figure 15–2), where it catalyzes the dehydration of H_2CO_3

to CO_2 at the luminal membrane and rehydration of CO_2 to H_2CO_3 in the cytoplasm as previously described. By blocking carbonic anhydrase, inhibitors blunt $NaHCO_3$ reabsorption and cause diuresis.

Carbonic anhydrase inhibitors were the forerunners of modern diuretics. They were discovered in 1937 when it was found that bacteriostatic sulfonamides caused an alkaline diuresis and hyperchloremic metabolic acidosis. With the development of newer agents, carbonic anhydrase inhibitors are now rarely used as diuretics, but they still have several specific applications that are discussed below. The prototypical carbonic anhydrase inhibitor is **acetazolamide**.

Pharmacokinetics

The carbonic anhydrase inhibitors are well absorbed after oral administration. An increase in urine pH from the HCO_3^- diuresis is apparent within 30 minutes, is maximal at 2 hours, and persists for 12 hours after a single dose. Excretion of the drug is by secretion in the proximal tubule S_2 segment. Therefore, dosing must be reduced in renal insufficiency.

Pharmacodynamics

Inhibition of carbonic anhydrase activity profoundly depresses HCO_3^- reabsorption in the PCT. At its maximal safe dosage, 85% of the HCO_3^- reabsorptive capacity of the superficial PCT is inhibited. Some HCO_3^- can still be absorbed at other nephron sites by carbonic anhydrase–independent mechanisms, so the overall effect of maximal acetazolamide dosage is only about 45% inhibition of whole kidney HCO_3^- reabsorption. Nevertheless, carbonic anhydrase inhibition causes significant HCO_3^- losses and hyperchloremic metabolic acidosis (Table 15–2). Because of reduced HCO_3^- in the glomerular filtrate and the fact that HCO_3^- depletion leads to enhanced NaCl reabsorption by the remainder of the nephron, the diuretic efficacy of acetazolamide decreases significantly with use over several days.

At present, the major clinical applications of acetazolamide involve carbonic anhydrase–dependent HCO_3^- and fluid transport at sites other than the kidney. The ciliary body of the eye secretes HCO_3^- from the blood into the aqueous humor. Likewise, formation of cerebrospinal fluid by the choroid plexus involves HCO_3^- secretion. Although these processes remove HCO_3^- from the blood (the direction opposite of that in the proximal tubule), they are similarly inhibited by carbonic anhydrase inhibitors.

TABLE 15–2 Changes in urinary electrolyte patterns and body pH in response to diuretic drugs.

Group	Urinary Electrolytes			
	NaCl	*$NaHCO_3$*	*K^+*	Body pH
Carbonic anhydrase inhibitors	+	+++	+	↓
Loop agents	++++	0	+	↑
Thiazides	++	+	+	↑
Loop agents plus thiazides	+++++	+	++	↑
K^+-sparing agents	+	(+)	–	↓

+, increase; –, decrease; 0, no change; ↓, acidosis; ↑, alkalosis.

TABLE 15–3 Carbonic anhydrase inhibitors used orally in the treatment of glaucoma.

Drug	Usual Oral Dosage
Dichlorphenamide	50 mg 1–3 times daily
Methazolamide	50–100 mg 2–3 times daily

Clinical Indications & Dosage (Table 15–3)

A. Glaucoma

The reduction of aqueous humor formation by carbonic anhydrase inhibitors decreases the intraocular pressure. This effect is valuable in the management of glaucoma, making it the most common indication for use of carbonic anhydrase inhibitors. Topically active agents, which reduce intraocular pressure without producing renal or systemic effects, are available (dorzolamide, brinzolamide).

B. Urinary Alkalinization

Uric acid and cystine are relatively insoluble and may form stones in acidic urine. Therefore, in cystinuria, a disorder of cystine reabsorption, solubility of cystine can be enhanced by increasing urinary pH from 7.0 to 7.5 with carbonic anhydrase inhibitors. In the case of uric acid, pH needs to be raised only to 6.0 or 6.5. In the absence of HCO_3^- administration, these effects of acetazolamide last only 2–3 days, so prolonged therapy requires oral HCO_3^-. Excessive urinary alkalinization can lead to stone formation from calcium salts (see below), so urine pH should be followed during treatment with acetazolamide.

C. Metabolic Alkalosis

Metabolic alkalosis is generally treated by correction of abnormalities in total body K^+, intravascular volume, or mineralocorticoid levels. However, when the alkalosis is due to excessive use of diuretics in patients with severe heart failure, replacement of intravascular volume may be contraindicated. In these cases, acetazolamide can be useful in correcting the alkalosis as well as producing a small additional diuresis for correction of volume overload. Acetazolamide can also be used to rapidly correct the metabolic alkalosis that may appear following the correction of respiratory acidosis.

D. Acute Mountain Sickness

Weakness, dizziness, insomnia, headache, and nausea can occur in mountain travelers who rapidly ascend above 3000 m. The symptoms are usually mild and last for a few days. In more serious cases,

rapidly progressing pulmonary or cerebral edema can be life-threatening. By decreasing cerebrospinal fluid formation and by decreasing the pH of the cerebrospinal fluid and brain, acetazolamide can increase ventilation and diminish symptoms of mountain sickness. This mild metabolic central and cerebrospinal fluid (CSF) acidosis is also useful in the treatment of sleep apnea.

E. Other Uses

Carbonic anhydrase inhibitors have been used as adjuvants in the treatment of epilepsy and in some forms of hypokalemic periodic paralysis. They are also useful in treating patients with CSF leakage (usually caused by tumor or head trauma, but often idiopathic). By reducing the rate of CSF formation and intracranial pressure, carbonic anhydrase inhibitors can significantly slow the rate of CSF leakage. Finally, they also increase urinary phosphate excretion during severe hyperphosphatemia.

Toxicity

A. Hyperchloremic Metabolic Acidosis

Acidosis predictably results from chronic reduction of body HCO_3^- stores by carbonic anhydrase inhibitors (Table 15–2) and limits the diuretic efficacy of these drugs to 2 or 3 days. Unlike the diuretic effect, acidosis persists as long as the drug is continued.

B. Renal Stones

Phosphaturia and hypercalciuria occur during the bicarbonaturic response to inhibitors of carbonic anhydrase. Renal excretion of solubilizing factors (eg, citrate) may also decline with chronic use. Calcium salts are relatively insoluble at alkaline pH, which means that the potential for renal stone formation from these salts is enhanced.

C. Renal Potassium Wasting

Potassium (K^+) wasting can occur because the increased Na^+ presented to the collecting tubule (with HCO_3^-) is partially reabsorbed, increasing the lumen-negative electrical potential in that segment and enhancing K^+ secretion. This effect can be counteracted by simultaneous administration of potassium chloride or a K^+-sparing diuretic. Potassium wasting is theoretically a problem with any diuretic that presents increased Na^+ delivery to the collecting tubule. However, the new adenosine A_1-receptor antagonists (see below) appear to avoid this toxicity by blunting Na^+ reabsorption in the collecting tubules as well as the proximal tubules.

D. Other Toxicities

Drowsiness and paresthesias are common following large doses of acetazolamide. Carbonic anhydrase inhibitors may accumulate in patients with renal failure, leading to nervous system toxicity. Hypersensitivity reactions (fever, rashes, bone marrow suppression, and interstitial nephritis) may also occur.

Contraindications

Carbonic anhydrase inhibitor–induced alkalinization of the urine decreases urinary excretion of NH_4^+ (by converting it to rapidly reabsorbed NH_3) and may contribute to the development of **hyperammonemia** and **hepatic encephalopathy** in patients with cirrhosis.

ADENOSINE A_1-RECEPTOR ANTAGONISTS

In addition to their potentially beneficial effect in preventing tubuloglomerular feedback (see below, under Heart Failure), adenosine receptor antagonists interfere with the activation of NHE3 in the PCT and the adenosine-mediated enhancement of collecting tubule K^+ secretion. Thus, adenosine receptor antagonists should be very useful diuretics.

Caffeine and theophylline have long been known to be weak diuretics because of their modest and nonspecific inhibition of adenosine receptors. A more selective A_1 antagonist, rolofylline, was recently withdrawn from study because of CNS toxicity and unexpected negative effects on GFR. However, newer adenosine inhibitors that are much more potent and more specific have been synthesized. Several of these (Aventri [BG9928], SLV320, and BG9719) are under study and if found to be less toxic than rolofylline, may become available as diuretics that avoid the diuretic effects of K^+ wasting and decreased GFR resulting from tubuloglomerular feedback.

LOOP DIURETICS

Loop diuretics selectively inhibit NaCl reabsorption in the TAL. Because of the large NaCl absorptive capacity of this segment and the fact that the diuretic action of these drugs is not limited by development of acidosis, as is the case with the carbonic anhydrase inhibitors, loop diuretics are the most efficacious diuretic agents currently available.

Chemistry

The two prototypical drugs of this group are **furosemide** and **ethacrynic acid.** The structures of these diuretics are shown in Figure 15–7. In addition to furosemide, **bumetanide** and **torsemide** are sulfonamide loop diuretics.

Ethacrynic acid—not a sulfonamide derivative—is a phenoxyacetic acid derivative containing an adjacent ketone and methylene group (Figure 15–7). The methylene group (shaded in figure) forms an adduct with the free sulfhydryl group of cysteine. The cysteine adduct appears to be an active form of the drug.

Organic **mercurial diuretics** also inhibit salt transport in the TAL but are no longer used because of their toxicity.

Pharmacokinetics

The loop diuretics are rapidly absorbed. They are eliminated by the kidney by glomerular filtration and tubular secretion. Absorption of oral torsemide is more rapid (1 hour) than that of furosemide (2–3 hours) and is nearly as complete as with intravenous administration. The duration of effect for furosemide is usually 2–3 hours. The effect of torsemide lasts 4–6 hours. Half-life

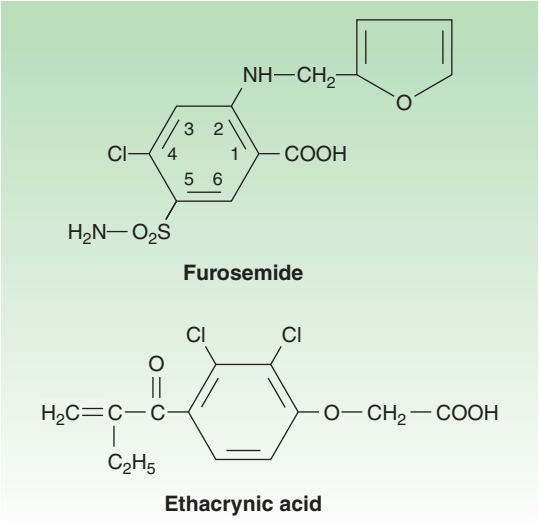

FIGURE 15–7 Two loop diuretics. The shaded methylene group on ethacrynic acid is reactive and may combine with free sulfhydryl groups.

depends on renal function. Since loop agents act on the luminal side of the tubule, their diuretic activity correlates with their secretion by the proximal tubule. Reduction in the secretion of loop diuretics may result from simultaneous administration of agents such as NSAIDs or probenecid, which compete for weak acid secretion in the proximal tubule. Metabolites of ethacrynic acid and furosemide have been identified, but it is not known if they have any diuretic activity. Torsemide has at least one active metabolite with a half-life considerably longer than that of the parent compound.

Pharmacodynamics

Loop diuretics inhibit NKCC2, the luminal $Na^+/K^+/2Cl^-$ transporter in the TAL of Henle's loop. By inhibiting this transporter, the loop diuretics reduce the reabsorption of NaCl and also diminish the lumen-positive potential that comes from K^+ recycling (Figure 15–3). This positive potential normally drives divalent cation reabsorption in the TAL (Figure 15–3), and by reducing this potential, loop diuretics cause an increase in Mg^{2+} and Ca^{2+} excretion. Prolonged use can cause significant hypomagnesemia in some patients. Since vitamin D–induced intestinal absorption and parathyroid hormone-induced renal reabsorption of Ca^{2+} can be increased, loop diuretics do not generally cause *hypocalcemia.* However, in disorders that cause hypercalcemia, Ca^{2+} excretion can be usefully enhanced by treatment with loop diuretics combined with saline infusions.

Loop diuretics have also been shown to induce expression of one of the cyclooxygenases (COX-2), which participates in the synthesis of prostaglandins from arachidonic acid. At least one of these prostaglandins, PGE_2, inhibits salt transport in the TAL and thus participates in the renal actions of loop diuretics. NSAIDs (eg, indomethacin), which blunt cyclooxygenase activity, can interfere with the actions of loop diuretics by reducing prostaglandin synthesis in the kidney. This interference is minimal in otherwise normal subjects but may be significant in patients with nephrotic syndrome or hepatic cirrhosis.

Loop agents have direct effects on blood flow through several vascular beds. Furosemide increases renal blood flow via prostaglandin actions on kidney vasculature. Both furosemide and ethacrynic acid have also been shown to reduce pulmonary congestion and left ventricular filling pressures in heart failure before a measurable increase in urinary output occurs. These effects on peripheral vascular tone are also due to release of renal prostaglandins that were induced by the diuretics.

TABLE 15–4 Typical dosages of loop diuretics.

Drug	Total Daily Oral Dose[1]
Bumetanide	0.5–2 mg
Ethacrynic acid	50–200 mg
Furosemide	20–80 mg
Torsemide	5–20 mg

[1] As single dose or in two divided doses.

Clinical Indications & Dosage (Table 15–4)

The most important indications for the use of the loop diuretics include **acute pulmonary edema, other edematous conditions,** and **acute hypercalcemia.** The use of loop diuretics in these conditions is discussed below in Clinical Pharmacology. Other indications for loop diuretics include hyperkalemia, acute renal failure, and anion overdose.

A. Hyperkalemia

In mild hyperkalemia—or after acute management of severe hyperkalemia by other measures—loop diuretics can significantly enhance urinary excretion of K^+. This response is enhanced by simultaneous NaCl and water administration.

B. Acute Renal Failure

Loop agents can increase the rate of urine flow and enhance K^+ excretion in acute renal failure. However, they cannot prevent or shorten the duration of renal failure. If a large pigment load has precipitated acute renal failure (or threatens to), loop agents may help flush out intratubular casts and ameliorate intratubular obstruction. On the other hand, loop agents can actually worsen cast formation in myeloma and light chain nephropathy because increased distal Cl^- concentration enhances secretion of Tamm-Horsfall protein, which then aggregates with myeloma Bence Jones proteins.

C. Anion Overdose

Loop diuretics are useful in treating toxic ingestions of bromide, fluoride, and iodide, which are reabsorbed in the TAL. Saline solution must be administered to replace urinary losses of Na^+ and to provide Cl^-, so as to avoid extracellular fluid volume depletion.

Toxicity

A. Hypokalemic Metabolic Alkalosis

By inhibiting salt reabsorption in the TAL, loop diuretics increase Na^+ delivery to the collecting duct. Increased delivery leads to increased secretion of K^+ and H^+ by the duct, causing hypokalemic metabolic alkalosis (Table 15–2). This toxicity is a function of the magnitude of the diuresis and can be reversed by K^+ replacement and correction of hypovolemia.

B. Ototoxicity

Loop diuretics occasionally cause dose-related hearing loss that is usually reversible. It is most common in patients who have diminished renal function or who are also receiving other ototoxic agents such as aminoglycoside antibiotics.

C. Hyperuricemia

Loop diuretics can cause hyperuricemia and precipitate attacks of gout. This is caused by hypovolemia-associated enhancement of uric acid reabsorption in the proximal tubule. It may be prevented by using lower doses to avoid development of hypovolemia.

D. Hypomagnesemia

Magnesium depletion is a predictable consequence of the chronic use of loop agents and occurs most often in patients with dietary magnesium deficiency. It can be reversed by administration of oral magnesium preparations.

E. Allergic and Other Reactions

All loop diuretics, with the exception of ethacrynic acid, are sulfonamides. Therefore, skin rash, eosinophilia, and less often, interstitial nephritis are occasional adverse effects of these drugs. This toxicity usually resolves rapidly after drug withdrawal. Allergic reactions are much less common with ethacrynic acid.

Because Henle's loop is indirectly responsible for water reabsorption by the downstream collecting duct, loop diuretics can cause severe dehydration. Hyponatremia is less common than with the thiazides (see below), but patients who increase water intake in response to hypovolemia-induced thirst can become severely hyponatremic with loop agents. Loop agents can cause hypercalciuria, which can lead to mild hypocalcemia and secondary hyperparathyroidism. On the other hand, loop agents can have the opposite effect (hypercalcemia) in volume-depleted patients who have another—previously occult—cause for hypercalcemia, such as metastatic breast or squamous cell lung carcinoma.

Contraindications

Furosemide, bumetanide, and torsemide may exhibit allergic cross-reactivity in patients who are sensitive to other sulfonamides, but this appears to be very rare. Overzealous use of any diuretic is dangerous in hepatic cirrhosis, borderline renal failure, or heart failure.

THIAZIDES

The thiazide diuretics were discovered in 1957, as a result of efforts to synthesize more potent carbonic anhydrase inhibitors. It subsequently became clear that the thiazides inhibit NaCl, rather than $NaHCO_3^-$ transport and that their action was predominantly in the DCT, rather than the PCT. Some members of this group retain significant carbonic anhydrase inhibitory activity (eg, chlorthalidone). The prototypical thiazide is **hydrochlorothiazide (HCTZ).**

Chemistry & Pharmacokinetics

Like carbonic anhydrase inhibitors and three loop diuretics, all of the thiazides have an unsubstituted sulfonamide group (Figure 15–8).

All thiazides can be administered orally, but there are differences in their metabolism. Chlorothiazide, the parent of the group, is not very lipid-soluble and must be given in relatively large doses. It is the only thiazide available for parenteral administration. HCTZ is considerably more potent and should be used in much lower doses (Table 15–5). Chlorthalidone is slowly absorbed and has a longer duration of action. Although indapamide is excreted primarily by the biliary system, enough of the active form is cleared by the kidney to exert its diuretic effect in the DCT.

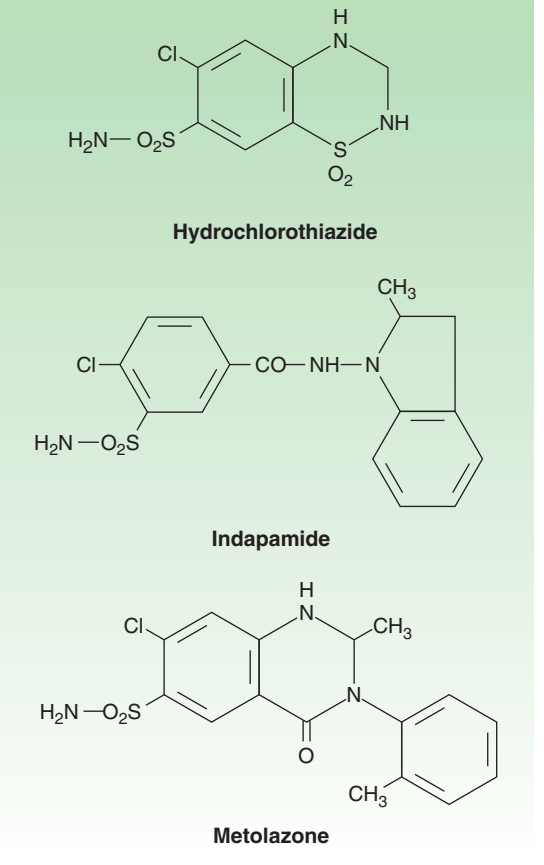

FIGURE 15–8 Hydrochlorothiazide and related agents.

All thiazides are secreted by the organic acid secretory system in the proximal tubule and compete with the secretion of uric acid by that system. As a result, thiazide use may blunt uric acid secretion and elevate serum uric acid level.

Pharmacodynamics

Thiazides inhibit NaCl reabsorption from the luminal side of epithelial cells in the DCT by blocking the Na^+/Cl^- transporter (NCC). In contrast to the situation in the TAL, in which loop diuretics inhibit Ca^{2+} reabsorption, thiazides actually enhance Ca^{2+} reabsorption. This enhancement has been postulated to result from effects in both the proximal and distal convoluted tubules. In the proximal tubule, thiazide-induced volume depletion leads to enhanced Na^+ and passive Ca^{2+} reabsorption. In the DCT, lowering of intracellular Na^+ by thiazide-induced blockade of Na^+ entry enhances Na^+/Ca^{2+} exchange in the basolateral membrane (Figure 15–4), and increases overall reabsorption of Ca^{2+}. Although thiazides rarely cause hypercalcemia as the result of this enhanced reabsorption, they can unmask hypercalcemia due to other causes (eg, hyperparathyroidism, carcinoma, sarcoidosis). Thiazides are useful in the treatment of kidney stones caused by hypercalciuria.

The action of thiazides depends in part on renal prostaglandin production. As described for loop diuretics, the actions of thiazides can also be inhibited by NSAIDs under certain conditions.

Clinical Indications & Dosage (Table 15–5)

The major indications for thiazide diuretics are (1) hypertension, (2) heart failure, (3) nephrolithiasis due to idiopathic hypercalciuria, and (4) nephrogenic diabetes insipidus. Use of the thiazides in each of these conditions is described below in Clinical Pharmacology of Diuretic Agents.

TABLE 15–5 Thiazides and related diuretics.

Drug	Total Daily Oral Dose	Frequency of Daily Administration
Bendroflumethiazide	2.5–10 mg	Single dose
Chlorothiazide	0.5–2 g	Two divided doses
Chlorthalidone[1]	25–50 mg	Single dose
Hydrochlorothiazide	25–100 mg	Single dose
Hydroflumethiazide	12.5–50 mg	Two divided doses
Indapamide[1]	2.5–10 mg	Single dose
Methyclothiazide	2.5–10 mg	Single dose
Metolazone[1]	2.5–10 mg	Single dose
Polythiazide	1–4 mg	Single dose
Quinethazone[1]	25–100 mg	Single dose
Trichlormethiazide	1–4 mg	Single dose

[1]Not a thiazide but a sulfonamide qualitatively similar to the thiazides.

Toxicity

A. Hypokalemic Metabolic Alkalosis and Hyperuricemia

These toxicities are similar to those observed with loop diuretics (see previous text and Table 15–2).

B. Impaired Carbohydrate Tolerance

Hyperglycemia may occur in patients who are overtly diabetic or who have even mildly abnormal glucose tolerance tests. The effect is due to both impaired pancreatic release of insulin and diminished tissue utilization of glucose. Hyperglycemia may be partially reversible with correction of hypokalemia.

C. Hyperlipidemia

Thiazides cause a 5–15% increase in total serum cholesterol and low-density lipoproteins (LDLs). These levels may return toward baseline after prolonged use.

D. Hyponatremia

Hyponatremia is an important adverse effect of thiazide diuretics. It is caused by a combination of hypovolemia-induced elevation of ADH, reduction in the diluting capacity of the kidney, and increased thirst. It can be prevented by reducing the dose of the drug or limiting water intake.

E. Allergic Reactions

The thiazides are sulfonamides and share cross-reactivity with other members of this chemical group. Photosensitivity or generalized dermatitis occurs rarely. Serious allergic reactions are extremely rare but do include hemolytic anemia, thrombocytopenia, and acute necrotizing pancreatitis.

F. Other Toxicities

Weakness, fatigability, and paresthesias similar to those of carbonic anhydrase inhibitors may occur. Impotence has been reported but is probably related to volume depletion.

Contraindications

Excessive use of any diuretic is dangerous in patients with hepatic cirrhosis, borderline renal failure, or heart failure (see text that follows).

POTASSIUM-SPARING DIURETICS

Potassium-sparing diuretics prevent K^+ secretion by antagonizing the effects of aldosterone in collecting tubules. Inhibition may occur by direct pharmacologic antagonism of mineralocorticoid receptors **(spironolactone, eplerenone)** or by inhibition of Na^+ influx through ion channels in the luminal membrane **(amiloride, triamterene).** This latter property appears to be shared by adenosine antagonists, which primarily blunt Na^+ reabsorption in the PCT, but also blunt Na^+ reabsorption and K^+ secretion in collecting tubules. Finally, ularitide (recombinant urodilatin), which is currently still under investigation, blunts Na^+ uptake

and Na^+/K^+-ATPase in collecting tubules and increases GFR through its vascular effects. Nesiritide, which is now commercially available for intravenous use only, increases GFR and blunts Na^+ reabsorption in both proximal and collecting tubules.

Chemistry & Pharmacokinetics

The structures of spironolactone and amiloride are shown in Figure 15–9.

Spironolactone is a synthetic steroid that acts as a competitive antagonist to aldosterone. Onset and duration of its action are determined by the kinetics of the aldosterone response in the target tissue. Substantial inactivation of spironolactone occurs in the liver. Overall, spironolactone has a rather slow onset of action, requiring several days before full therapeutic effect is achieved. Eplerenone is a spironolactone analog with much greater selectivity for the mineralocorticoid receptor. It is several hundredfold less active on androgen and progesterone receptors than spironolactone, and therefore, eplerenone has considerably fewer adverse effects.

Amiloride and triamterene are direct inhibitors of Na^+ influx in the CCT (cortical collecting tubule). Triamterene is metabolized in the liver, but renal excretion is a major route of elimination for the active form and the metabolites. Because triamterene is extensively metabolized, it has a shorter half-life and must be given more frequently than amiloride (which is not metabolized).

Pharmacodynamics

Potassium-sparing diuretics reduce Na^+ absorption in the collecting tubules and ducts. Potassium absorption (and K^+ secretion) at this site is regulated by aldosterone, as described above. Aldosterone antagonists interfere with this process. Similar effects are observed with respect to H^+ handling by the intercalated cells of the collecting tubule, in part explaining the metabolic acidosis seen with aldosterone antagonists (Table 15–2).

Spironolactone and eplerenone bind to mineralocorticoid receptors and blunt aldosterone activity. Amiloride and triamterene do not block aldosterone, but instead directly interfere with Na^+ entry through the epithelial Na^+ channels (ENaC, Figure 15-5), in the apical membrane of the collecting tubule. Since K^+ secretion is coupled with Na^+ entry in this segment, these agents are also effective K^+-sparing diuretics.

The actions of the aldosterone antagonists depend on renal prostaglandin production. The actions of K^+-sparing diuretics can be inhibited by NSAIDs under certain conditions.

Clinical Indications & Dosage (Table 15–6)

Potassium-sparing diuretics are most useful in states of mineralocorticoid excess or hyperaldosteronism (also called aldosteronism), due either to primary hypersecretion (Conn's syndrome, ectopic adrenocorticotropic hormone production) or secondary hyperaldosteronism (evoked by heart failure, hepatic cirrhosis, nephrotic syndrome, or other conditions associated with diminished effective intravascular volume). Use of diuretics such as thiazides or loop agents can cause or exacerbate volume contraction and may cause secondary hyperaldosteronism. In the setting of enhanced mineralocorticoid secretion and excessive delivery of Na^+ to distal nephron sites, renal K^+ wasting occurs. Potassium-sparing diuretics of either type may be used in this setting to blunt the K^+ secretory response.

It has also been found that low doses of eplerenone (25–50 mg/d) may interfere with some of the fibrotic and inflammatory effects of aldosterone. By doing so, it can slow the progression of albuminuria in diabetic patients. More important is that eplerenone has been found to reduce myocardial perfusion defects after myocardial infarction. In one clinical study, eplerenone reduced

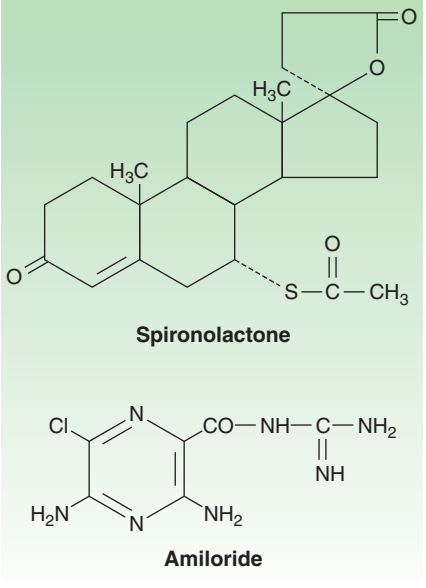

FIGURE 15–9 Potassium-sparing diuretics.

TABLE 15–6 Potassium-sparing diuretics and combination preparations.

Trade Name	Potassium-Sparing Agent	Hydrochlorothiazide
Aldactazide	Spironolactone 25 mg	50 mg
Aldactone	Spironolactone 25, 50, or 100 mg	…
Dyazide	Triamterene 37.5 mg	25 mg
Dyrenium	Triamterene 50 or 100 mg	…
Inspra[1]	Eplerenone 25, 50, or 100 mg	…
Maxzide	Triamterene 75 mg	50 mg
Maxzide-25 mg	Triamterene 37.5 mg	25 mg
Midamor	Amiloride 5 mg	…
Moduretic	Amiloride 5 mg	50 mg

[1]Eplerenone is currently approved for use only in hypertension.

mortality rate by 15% (compared with placebo) in patients with mild to moderate heart failure after myocardial infarction.

Toxicity

A. Hyperkalemia

Unlike most other diuretics, K^+-sparing diuretics reduce urinary excretion of K^+ (Table 15–2) and can cause mild, moderate, or even life-threatening hyperkalemia. The risk of this complication is greatly increased by renal disease (in which maximal K^+ excretion may be reduced) or by the use of other drugs that reduce or inhibit renin (β blockers, NSAIDs, aliskiren) or angiotensin II activity (angiotensin-converting enzyme inhibitors, angiotensin receptor inhibitors). Since most other diuretic agents lead to K^+ losses, hyperkalemia is more common when K^+-sparing diuretics are used as the sole diuretic agent, especially in patients with renal insufficiency. With fixed-dosage combinations of K^+-sparing and thiazide diuretics, the thiazide-induced hypokalemia and metabolic alkalosis are ameliorated. However, because of variations in the bioavailability of the components of fixed-dosage forms, the thiazide-associated adverse effects often predominate. Therefore, it is generally preferable to adjust the doses of the two drugs separately.

B. Hyperchloremic Metabolic Acidosis

By inhibiting H^+ secretion in parallel with K^+ secretion, the K^+-sparing diuretics can cause acidosis similar to that seen with type IV renal tubular acidosis.

C. Gynecomastia

Synthetic steroids may cause endocrine abnormalities by actions on other steroid receptors. Gynecomastia, impotence, and benign prostatic hyperplasia (very rare) all have been reported with spironolactone. Such effects have not been reported with eplerenone, presumably because it is much more selective than spironolactone for the mineralocorticoid receptor and virtually inactive on androgen or progesterone receptors.

D. Acute Renal Failure

The combination of triamterene with indomethacin has been reported to cause acute renal failure. This has not been reported with other K^+-sparing diuretics.

E. Kidney Stones

Triamterene is only slightly soluble and may precipitate in the urine, causing kidney stones.

Contraindications

Potassium-sparing agents can cause severe, even fatal, hyperkalemia in susceptible patients. Patients with chronic renal insufficiency are especially vulnerable and should rarely be treated with these diuretics. Oral K^+ administration should be discontinued if K^+-sparing diuretics are administered. Concomitant use of other agents that blunt the renin-angiotensin system (β blockers, ACE inhibitors, ARBs) increases the likelihood of hyperkalemia. Patients with liver disease may have impaired metabolism of triamterene and spironolactone, so dosing must be carefully adjusted. Strong CYP3A4 inhibitors (eg, erythromycin, fluconazole, diltiazem, and grapefruit juice) can markedly increase blood levels of eplerenone, but not spironolactone.

AGENTS THAT ALTER WATER EXCRETION (AQUARETICS)

OSMOTIC DIURETICS

The proximal tubule and descending limb of Henle's loop are freely permeable to water (Table 15–1). Any osmotically active agent that is filtered by the glomerulus but not reabsorbed causes water to be retained in these segments and promotes a water diuresis. Such agents can be used to reduce intracranial pressure and to promote prompt removal of renal toxins. The prototypic osmotic diuretic is **mannitol.** Glucose is not used clinically as a diuretic but frequently causes osmotic diuresis (glycosuria) in patients with hyperglycemia.

Pharmacokinetics

Mannitol is poorly absorbed by the GI tract, and when administered orally, it causes osmotic diarrhea rather than diuresis. For systemic effect, mannitol must be given intravenously. Mannitol is not metabolized and is excreted by glomerular filtration within 30–60 minutes, without any important tubular reabsorption or secretion. It must be used cautiously in patients with even mild renal insufficiency (see below).

Pharmacodynamics

Osmotic diuretics have their major effect in the proximal tubule and the descending limb of Henle's loop. Through osmotic effects, they also oppose the action of ADH in the collecting tubule. The presence of a nonreabsorbable solute such as mannitol prevents the normal absorption of water by interposing a countervailing osmotic force. As a result, urine volume increases. The increase in urine flow rate decreases the contact time between fluid and the tubular epithelium, thus reducing Na^+ as well as water reabsorption. The resulting natriuresis is of lesser magnitude than the water diuresis, leading eventually to excessive water loss and hypernatremia.

Clinical Indications & Dosage

A. Increase of Urine Volume

Osmotic diuretics are used to increase water excretion in preference to sodium excretion. This effect can be useful when avid Na^+ retention limits the response to conventional agents. It can be used to maintain urine volume and to prevent anuria that might otherwise result from presentation of large pigment loads to the kidney (eg, from hemolysis or rhabdomyolysis). Some oliguric patients do not respond to osmotic diuretics. Therefore, a test dose of mannitol

(12.5 g intravenously) should be given before starting a continuous infusion. Mannitol should not be continued unless there is an increase in urine flow rate to more than 50 mL/h during the 3 hours after the test dose. Mannitol (12.5–25 g intravenously) can be repeated every 1–2 hours to maintain urine flow rate greater than 100 mL/h. Prolonged use of mannitol is not advised.

B. Reduction of Intracranial and Intraocular Pressure

Osmotic diuretics alter Starling forces so that water leaves cells and reduces intracellular volume. This effect is used to reduce intracranial pressure in neurologic conditions and to reduce intraocular pressure before ophthalmologic procedures. A dose of 1–2 g/kg mannitol is administered intravenously. Intracranial pressure, which must be monitored, should fall in 60–90 minutes.

Toxicity

A. Extracellular Volume Expansion

Mannitol is rapidly distributed in the extracellular compartment and extracts water from cells. Prior to the diuresis, this leads to expansion of the extracellular volume and hyponatremia. This effect can complicate heart failure and may produce florid pulmonary edema. Headache, nausea, and vomiting are commonly observed in patients treated with osmotic diuretics.

B. Dehydration, Hyperkalemia, and Hypernatremia

Excessive use of mannitol without adequate water replacement can ultimately lead to severe dehydration, free water losses, and hypernatremia. As water is extracted from cells, intracellular K^+ concentration rises, leading to cellular losses and hyperkalemia. These complications can be avoided by careful attention to serum ion composition and fluid balance.

C. Hyponatremia

When used in patients with severe renal impairment, parenterally administered mannitol cannot be excreted and is retained intravenously. This causes osmotic extraction of water from cells, leading to hyponatremia.

ANTIDIURETIC HORMONE (ADH, VASOPRESSIN) AGONISTS

Vasopressin and **desmopressin** are used in the treatment of central diabetes insipidus. They are discussed in Chapter 37. Their renal action appears to be mediated primarily via V_2 ADH receptors, although V_{1a} receptors may also be involved.

ANTIDIURETIC HORMONE ANTAGONISTS

A variety of medical conditions, including congestive heart failure (CHF) and the syndrome of inappropriate ADH secretion (SIADH), cause water retention as a result of excessive ADH secretion. Patients with CHF who are on diuretics frequently develop hyponatremia secondary to excessive ADH secretion. Dangerous hyponatremia can result.

Until recently, two nonselective agents, lithium (discussed in Chapter 29) and demeclocycline (a tetracycline antimicrobial drug discussed in Chapter 44), were used for their well-known interference with ADH activity. The mechanism for this interference has not been completely determined for either of these agents. Demeclocycline is used more often than lithium because of the many side effects of lithium administration. However, demeclocycline is now being rapidly replaced by several specific ADH receptor antagonists (vaptans), which have yielded encouraging clinical results.

There are three known vasopressin receptors, V_{1a}, V_{1b}, and V_2. V_1 receptors are expressed in the vasculature and CNS, while V_2 receptors are expressed specifically in the kidney. **Conivaptan** (currently available only for intravenous use) exhibits activity against both V_{1a} and V_2 receptors (see below). The oral agents **tolvaptan,** lixivaptan, and satavaptan are selectively active against the V_2 receptor. Lixivaptan and satavaptan are still under clinical investigation, but tolvaptan, which recently received Food and Drug Administration approval, is very effective in treatment of hyponatremia and as an adjunct to standard diuretic therapy in patients with CHF.

Pharmacokinetics

The half-life of conivaptan and demeclocycline is 5–10 hours, while that of tolvaptan is 12–24 hours.

Pharmacodynamics

Antidiuretic hormone antagonists inhibit the effects of ADH in the collecting tubule. Conivaptan and tolvaptan are direct ADH receptor antagonists, while both lithium and demeclocycline reduce ADH-induced cAMP by mechanisms that are not yet completely clarified.

Clinical Indications & Dosage

A. Syndrome of Inappropriate ADH Secretion

Antidiuretic hormone antagonists are used to manage SIADH when water restriction has failed to correct the abnormality. This generally occurs in the outpatient setting, where water restriction cannot be enforced, but can occur in the hospital when large quantities of intravenous fluid are needed for other purposes. Demeclocycline (600–1200 mg/d) or tolvaptan (15–60 mg/d) can be used for SIADH. Appropriate plasma levels of demeclocycline (2 mcg/mL) should be maintained by monitoring, but tolvaptan levels are not routinely monitored. Unlike demeclocycline or tolvaptan, conivaptan is administered intravenously and is not suitable for chronic use in outpatients. Lixivaptan and satavaptan may also soon be available for oral use.

B. Other Causes of Elevated Antidiuretic Hormone

Antidiuretic hormone is also elevated in response to diminished effective circulating blood volume, as often occurs in heart failure. When treatment by volume replacement is not desirable, hyponatremia may

result. As for SIADH, water restriction is often the treatment of choice. In patients with heart failure, this approach is often unsuccessful in view of increased thirst and the large number of oral medications being used. For patients with heart failure, intravenous conivaptan may be particularly useful because it has been found that the blockade of V_{1a} receptors by this drug leads to decreased peripheral vascular resistance and increased cardiac output.

Toxicity

A. Nephrogenic Diabetes Insipidus

If serum Na^+ is not monitored closely, any ADH antagonist can cause severe hypernatremia and nephrogenic diabetes insipidus. If lithium is being used for a psychiatric disorder, nephrogenic diabetes insipidus can be treated with a thiazide diuretic or amiloride (see Diabetes Insipidus, below).

B. Renal Failure

Both lithium and demeclocycline have been reported to cause acute renal failure. Long-term lithium therapy may also cause chronic interstitial nephritis.

C. Other

Dry mouth and thirst are common with many of these drugs. Tolvaptan may cause hypotension. Multiple adverse effects associated with lithium therapy have been found and are discussed in Chapter 29. Demeclocycline should be avoided in patients with liver disease (see Chapter 44) and in children younger than 12 years.

DIURETIC COMBINATIONS

LOOP AGENTS & THIAZIDES

Some patients are refractory to the usual dose of loop diuretics or become refractory after an initial response. Since these agents have a short half-life (2–6 hours), refractoriness may be due to an excessive interval between doses. Renal Na^+ retention may be greatly increased during the time period when the drug is no longer active. After the dosing interval for loop agents is minimized or the dose is maximized, the use of two drugs acting at different nephron sites may exhibit dramatic synergy. Loop agents and thiazides in combination often produce diuresis when neither agent acting alone is even minimally effective. There are several reasons for this phenomenon.

First, salt reabsorption in either the TAL or the DCT can increase when the other is blocked. Inhibition of both can therefore produce more than an additive diuretic response. Second, thiazide diuretics often produce a mild natriuresis in the proximal tubule that is usually masked by increased reabsorption in the TAL. The combination of loop diuretics and thiazides can therefore block Na^+ reabsorption, to some extent, from all three segments.

Metolazone is the thiazide-like drug usually used in patients refractory to loop agents alone, but it is likely that other thiazides would be as effective. Moreover, metolazone is available only in an oral preparation, whereas chlorothiazide can be given parenterally.

The combination of loop diuretics and thiazides can mobilize large amounts of fluid, even in patients who have not responded to single agents. Therefore, close hemodynamic monitoring is essential. Routine outpatient use is not recommended. Furthermore, K^+ wasting is extremely common and may require parenteral K^+ administration with careful monitoring of fluid and electrolyte status.

POTASSIUM-SPARING DIURETICS & PROXIMAL TUBULE DIURETICS, LOOP AGENTS, OR THIAZIDES

Hypokalemia often develops in patients taking carbonic anhydrase inhibitors, loop diuretics, or thiazides. This can usually be managed by dietary NaCl restriction or by taking dietary KCl supplements. When hypokalemia cannot be managed in this way, the addition of a K^+-sparing diuretic can significantly lower K^+ excretion. Although this approach is generally safe, it should be avoided in patients with renal insufficiency and in those receiving angiotensin antagonists such as ACE inhibitors, in whom life-threatening hyperkalemia can develop in response to K^+-sparing diuretics. It is not yet known whether adenosine receptor antagonists, which are K^+-sparing diuretics (but which act primarily in the proximal tubule), will cause hyperkalemia.

CLINICAL PHARMACOLOGY OF DIURETIC AGENTS

A summary of the effects of diuretics on urinary electrolyte excretion is shown in Table 15–2.

EDEMATOUS STATES

A common reason for diuretic use is for reduction of peripheral or pulmonary edema that has accumulated as a result of cardiac, renal, or vascular diseases that reduce blood flow to the kidney. This reduction is sensed as insufficient effective arterial blood volume and leads to salt and water retention, which expands blood volume and eventually causes edema formation. Judicious use of diuretics can mobilize this interstitial edema without significant reductions in plasma volume. However, excessive diuretic therapy may compromise the effective arterial blood volume and reduce the perfusion of vital organs. Therefore, the use of diuretics to mobilize edema requires careful monitoring of the patient's hemodynamic status and an understanding of the pathophysiology of the underlying illness.

HEART FAILURE

When cardiac output is reduced by heart failure, the resultant changes in blood pressure and blood flow to the kidney are sensed as hypovolemia and lead to renal retention of salt and water. This

physiologic response initially increases intravascular volume and venous return to the heart and may partially restore the cardiac output toward normal (see Chapter 13).

If the underlying disease causes cardiac output to deteriorate despite expansion of plasma volume, the kidney continues to retain salt and water, which then leaks from the vasculature and becomes interstitial or pulmonary edema. At this point, diuretic use becomes necessary to reduce the accumulation of edema, particularly in the lungs. Reduction of pulmonary vascular congestion with diuretics may actually improve oxygenation and thereby improve myocardial function. Reduction of preload can reduce the size of the heart, allowing it to work at a more efficient fiber length. Edema associated with heart failure is generally managed with loop diuretics. In some instances, salt and water retention may become so severe that a combination of thiazides and loop diuretics is necessary.

In treating the heart failure patient with diuretics, it must always be remembered that cardiac output in these patients is being maintained in part by high filling pressures. Therefore, excessive use of diuretics may diminish venous return and further impair cardiac output. This is especially critical in right ventricular heart failure. Systemic, rather than pulmonary vascular, congestion is the hallmark of this disorder. Diuretic-induced volume contraction predictably reduces venous return and can severely compromise cardiac output if left ventricular filling pressure is reduced below 15 mm Hg (see Chapter 13). Reduction in cardiac output, resulting from either left or right ventricular dysfunction, also eventually leads to renal dysfunction resulting from reduced perfusion pressures.

Increased delivery of salt to the TAL leads to activation of the macula densa and a reduction in GFR by tubuloglomerular feedback. The mechanism of this feedback is secretion of adenosine by macula densa cells, which causes afferent arteriolar vasoconstriction through activation of A_1 adenosine receptors on the afferent arteriole. This vasoconstriction reduces GFR. Tubuloglomerular feedback–mediated reduction in GFR exacerbates the reduction that was initially caused by decreased cardiac output. Recent work with adenosine receptor antagonists has shown that it may soon be possible to circumvent this complication of diuretic therapy in heart failure patients by blunting tubuloglomerular feedback.

Diuretic-induced metabolic alkalosis, exacerbated by hypokalemia, is another adverse effect that may further compromise cardiac function. This complication can be treated with replacement of K^+ and restoration of intravascular volume with saline; however, severe heart failure may preclude the use of saline even in patients who have received excessive diuretic therapy. In these cases, adjunctive use of acetazolamide helps to correct the alkalosis.

Another serious toxicity of diuretic use in the cardiac patient is hypokalemia. Hypokalemia can exacerbate underlying cardiac arrhythmias and contribute to digitalis toxicity. This can usually be avoided by having the patient reduce Na^+ intake while taking diuretics, thus decreasing Na^+ delivery to the K^+-secreting collecting tubule. Patients who are noncompliant with a low Na^+ diet must take oral KCl supplements or a K^+-sparing diuretic.

KIDNEY DISEASE AND RENAL FAILURE

A variety of diseases interfere with the kidney's critical role in volume homeostasis. Although some renal disorders cause salt wasting, most cause retention of salt and water. When renal failure is severe (GFR < 5 mL/min), diuretic agents are of little benefit, because glomerular filtration is insufficient to generate or sustain a natriuretic response. However, a large number of patients, and even dialysis patients, with milder degrees of renal insufficiency (GFR of 5–15 mL/min), can be treated with diuretics when they retain excessive volumes of fluid between dialysis treatments.

There is still interest in the question as to whether diuretic therapy can alter the severity or the outcome of acute renal failure. This is because "nonoliguric" forms of acute renal insufficiency have better outcomes than "oliguric" (< 400–500 mL/24 h urine output) acute renal failure. Almost all studies of this question have shown that diuretic therapy helps in the short-term fluid management of these patients with acute renal failure, but that it has no impact on the long-term outcome.

Many glomerular diseases, such as those associated with diabetes mellitus or systemic lupus erythematosus, exhibit renal retention of salt and water. The cause of this sodium retention is not precisely known, but it probably involves disordered regulation of the renal microcirculation and tubular function through release of vasoconstrictors, prostaglandins, cytokines, and other mediators. When edema or hypertension develops in these patients, diuretic therapy can be very effective.

Certain forms of renal disease, particularly diabetic nephropathy, are frequently associated with development of hyperkalemia at a relatively early stage of renal failure. In these cases, a thiazide or loop diuretic will enhance K^+ excretion by increasing delivery of salt to the K^+-secreting collecting tubule.

Patients with renal diseases leading to the nephrotic syndrome often present complex problems in volume management. These patients may exhibit fluid retention in the form of ascites or edema but have reduced plasma volume due to reduced plasma oncotic pressures. This is very often the case in patients with "minimal change" nephropathy. In these patients, diuretic use may cause further reductions in plasma volume that can impair GFR and may lead to orthostatic hypotension. Most other causes of nephrotic syndrome are associated with primary retention of salt and water by the kidney, leading to expanded plasma volume and hypertension despite the low plasma oncotic pressure. In these cases, diuretic therapy may be beneficial in controlling the volume-dependent component of hypertension.

In choosing a diuretic for the patient with kidney disease, there are a number of important limitations. Acetazolamide must usually be avoided because it causes $NaHCO_3$ excretion and can exacerbate acidosis. Potassium-sparing diuretics may cause hyperkalemia. Thiazide diuretics were previously thought to be ineffective when GFR falls below 30 mL/min. More recently, it has been found that thiazides, which are of little benefit when used alone, can be used to significantly reduce the dose of loop diuretics needed to promote diuresis in a patient with GFR of 5–15 mL/min. Thus, high-dose loop diuretics (up to

500 mg of furosemide/d) or a combination of metolazone (5–10 mg/d) and much smaller doses of furosemide (40–80 mg/d) may be useful in treating volume overload in dialysis or predialysis patients. There has been some interest in the use of osmotic diuretics such as mannitol, because this drug can shrink swollen epithelial cells and may theoretically reduce tubular obstruction. Unfortunately, there is no evidence that mannitol can prevent ischemic or toxic acute renal failure. Mannitol may be useful in the management of hemoglobinuria or myoglobinuria. Lastly, although excessive use of diuretics can impair renal function in all patients, the consequences are obviously more serious in patients with underlying renal disease.

HEPATIC CIRRHOSIS

Liver disease is often associated with edema and ascites in conjunction with elevated portal hydrostatic pressures and reduced plasma oncotic pressures. Mechanisms for retention of Na^+ by the kidney in this setting include diminished renal perfusion (from systemic vascular alterations), diminished plasma volume (due to ascites formation), and diminished oncotic pressure (hypoalbuminemia). In addition, there may be primary Na^+ retention due to elevated plasma aldosterone levels.

When ascites and edema become severe, diuretic therapy can be very useful. However, cirrhotic patients are often resistant to loop diuretics because of decreased secretion of the drug into the tubular fluid and because of high aldosterone levels. In contrast, cirrhotic edema is unusually responsive to spironolactone and eplerenone. The combination of loop diuretics and an aldosterone receptor antagonist may be useful in some patients. However, considerable caution is necessary in the use of aldosterone antagonists in cirrhotic patients with even mild renal insufficiency because of the potential for causing serious hyperkalemia.

It is important to note that, even more than in heart failure, overly aggressive use of diuretics in this setting can be disastrous. Vigorous diuretic therapy can cause marked depletion of intravascular volume, hypokalemia, and metabolic alkalosis. Hepatorenal syndrome and hepatic encephalopathy are the unfortunate consequences of excessive diuretic use in the cirrhotic patient.

IDIOPATHIC EDEMA

Idiopathic edema (fluctuating salt retention and edema) is a syndrome found most often in 20–30 year-old women. Despite intensive study, the pathophysiology remains obscure. Some studies suggest that surreptitious, intermittent diuretic use may actually contribute to the syndrome and should be ruled out before additional therapy is pursued. While spironolactone has been used for idiopathic edema, it should probably be managed with moderate salt restriction alone if possible. Compression stockings have also been used but appear to be of variable benefit.

NONEDEMATOUS STATES

HYPERTENSION

The diuretic and mild vasodilator actions of the thiazides are useful in treating virtually all patients with essential hypertension and may be sufficient in many. Although hydrochlorothiazide is the most widely used diuretic for hypertension, chlorthalidone may be more effective because of its much longer half-life. Loop diuretics are usually reserved for patients with mild renal insufficiency (GFR < 30–40 mL/min) or heart failure. Moderate restriction of dietary Na^+ intake (60–100 mEq/d) has been shown to potentiate the effects of diuretics in essential hypertension and to lessen renal K^+ wasting. A K^+-sparing diuretic can be added to reduce K^+ wasting.

There has been debate about whether thiazides should be used as the initial therapy in treatment of hypertension. Their relatively mild efficacy sometimes limits their use as monotherapy. However, a very large study of over 30,000 participants has shown that inexpensive diuretics like thiazides result in outcomes that are similar or superior to those found with ACE inhibitor or calcium channel-blocker therapy. This important result reinforces the importance of thiazide therapy in hypertension.

Although diuretics are often successful as monotherapy, they also play an important role in patients who require multiple drugs to control blood pressure. Diuretics enhance the efficacy of many agents, particularly ACE inhibitors. Patients being treated with powerful vasodilators such as hydralazine or minoxidil usually require simultaneous diuretics because the vasodilators cause significant salt and water retention.

NEPHROLITHIASIS

Approximately two thirds of kidney stones contain Ca^{2+} phosphate or Ca^{2+} oxalate. While there are numerous medical conditions (hyperparathyroidism, hypervitaminosis D, sarcoidosis, malignancies, etc) that cause hypercalciuria, many patients with such stones exhibit a defect in proximal tubular Ca^{2+} reabsorption. This can be treated with thiazide diuretics, which enhance Ca^{2+} reabsorption in the DCT and thus reduce the urinary Ca^{2+} concentration. Fluid intake should be increased, but salt intake must be reduced, since excess dietary NaCl will overwhelm the hypocalciuric effect of thiazides. Dietary Ca^{2+} should not be restricted, as this can lead to negative total body Ca^{2+} balance. Calcium stones may also be caused by increased intestinal absorption of Ca^{2+}, or they may be idiopathic. In these situations, thiazides are also effective but should be used as adjunctive therapy with other measures.

HYPERCALCEMIA

Hypercalcemia can be a medical emergency (see Chapter 42). Because loop diuretics reduce Ca^{2+} reabsorption significantly, they can be quite effective in promoting Ca^{2+} diuresis. However, loop diuretics alone can cause marked volume contraction. If this occurs, loop diuretics are ineffective (and potentially counterproductive)

because Ca^{2+} reabsorption in the proximal tubule would be enhanced. Thus, saline must be administered simultaneously with loop diuretics if an effective Ca^{2+} diuresis is to be maintained. The usual approach is to infuse normal saline and furosemide (80–120 mg) intravenously. Once the diuresis begins, the rate of saline infusion can be matched with the urine flow rate to avoid volume depletion. Potassium chloride may be added to the saline infusion as needed.

DIABETES INSIPIDUS

Diabetes insipidus is due to either deficient production of ADH (neurogenic or central diabetes insipidus) or inadequate responsiveness to ADH (nephrogenic diabetes insipidus [NDI]). Administration of supplementary ADH or one of its analogs is effective only in central diabetes insipidus. Thiazide diuretics can reduce polyuria and polydipsia in both types of diabetes insipidus. Lithium, used in the treatment of manic-depressive disorder, is a common cause of NDI, and thiazide diuretics have been found to be very helpful in treating it. This seemingly paradoxic beneficial effect of thiazides was previously thought to be mediated through plasma volume reduction, with an associated fall in GFR, leading to enhanced proximal reabsorption of NaCl and water and decreased delivery of fluid to the downstream diluting segments. However, in the case of Li^+-induced NDI, it is now known that HCTZ causes increased osmolality in the inner medulla (papilla) and a partial correction of the Li^+-induced reduction in aquaporin-2 expression. HCTZ also leads to increased expression of Na^+ transporters in the DCT and CCT segments of the nephron. Thus, the maximum volume of dilute urine that can be produced is significantly reduced in NDI. Dietary sodium restriction can potentiate the beneficial effects of thiazides on urine volume in this setting. Serum Li^+ levels must be carefully monitored in these patients, because diuretics may reduce renal clearance of Li^+ and raise plasma Li^+ levels into the toxic range (see Chapter 29). Lithium-induced polyuria can also be partially reversed by amiloride, which blocks Li^+ entry into collecting duct cells, much as it blocks Na^+ entry. As mentioned above, thiazides are also beneficial in other forms of nephrogenic diabetes insipidus. It is not yet clear whether this is via the same mechanism that has been found in Li^+-induced NDI.

SUMMARY Diuretic Agents

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
CARBONIC ANHYDRASE INHIBITORS				
• Acetazolamide, others	Inhibition of the enzyme prevents dehydration of H_2CO_3 and hydration of CO_2 in the proximal convoluted tubule	Reduces reabsorption of HCO_3^-, causing self-limited diuresis • hyperchloremic metabolic acidosis reduces body pH, reduces intraocular pressure	Glaucoma, mountain sickness, edema with alkalosis	Oral and topical preparations available • duration of action ~ 8–12 h • *Toxicity:* Metabolic acidosis, renal stones, hyperammonemia in cirrhotics
• *Brinzolamide, dorzolamide: Topical for glaucoma*				
LOOP DIURETICS				
• Furosemide	Inhibition of the Na/K/2Cl transporter in the ascending limb of Henle's loop	Marked increase in NaCl excretion, some K wasting, hypokalemic metabolic alkalosis, increased urine Ca and Mg	Pulmonary edema, peripheral edema, hypertension, acute hypercalcemia or hyperkalemia, acute renal failure, anion overdose	Oral and parenteral preparations • duration of action 2–4 h • *Toxicity:* Ototoxicity, hypovolemia, K wasting, hyperuricemia, hypomagnesemia
• *Bumetanide, torsemide: Sulfonamide loop agents like furosemide*				
• *Ethacrynic acid: Not a sulfonamide but has typical loop activity and some uricosuric action*				
THIAZIDES				
• Hydrochlorothiazide	Inhibition of the Na/Cl transporter in the distal convoluted tubule	Modest increase in NaCl excretion • some K wasting • hypokalemic metabolic alkalosis • decreased urine Ca	Hypertension, mild heart failure, nephrolithiasis, nephrogenic diabetes insipidus	Oral • duration 8–12 h • *Toxicity:* Hypokalemic metabolic alkalosis, hyperuricemia, hyperglycemia, hyponatremia
• *Metolazone: Popular for use with loop agents for synergistic effects*				
• *Chlorothiazide: Only parenteral thiazide available (IV)*				
• *Chlorthalidone: Long half-life (50–60 h) due to binding to red blood cells*				

(*continued*)

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
POTASSIUM-SPARING DIURETICS				
• Spironolactone	Pharmacologic antagonist of aldosterone in collecting tubules • weak antagonism of androgen receptors	Reduces Na retention and K wasting in kidney • poorly understood antagonism of aldosterone in heart and vessels	Aldosteronism from any cause • hypokalemia due to other diuretics • postmyocardial infarction	Slow onset and offset of effect • duration 24–48 h •*Toxicity:* Hyperkalemia, gynecomastia (spironolactone, not eplerenone) • additive interaction with other K-retaining drugs
• Amiloride	Blocks epithelial sodium channels in collecting tubules	Reduces Na retention and K wasting • increases lithium clearance	Hypokalemia from other diuretics • reduces lithium-induced polyuria	Orally active • duration 24 h • *Toxicity:* Hyperkalemic metabolic acidosis
• *Eplerenone: Like spironolactone, more selective for aldosterone receptor*				
• *Triamterene: Mechanism like amiloride, much less potent, more toxic*				
OSMOTIC DIURETICS				
• Mannitol	Physical osmotic effect on tissue water distribution because it is retained in the vascular compartment	Marked increase in urine flow, reduced brain volume, decreased intraocular pressure, initial hyponatremia, then hypernatremia	Renal failure due to increased solute load (rhabdomyolysis, chemotherapy), increased intracranial pressure, glaucoma	IV administration • *Toxicity:* Nausea, vomiting, headache
VASOPRESSIN (ADH) ANTAGONISTS				
• Conivaptan	Antagonist at V_{1a} and V_2 ADH receptors	Reduces water reabsorption, increases plasma Na concentration, vasodilation	Hyponatremia, congestive heart failure	IV only, usually continuous • *Toxicity:* Infusion site reactions, thirst, polyuria, hypernatremia
• Tolvaptan	Selective antagonist at V_2 ADH receptors	Reduces water reabsorption, increases plasma Na concentration	Hyponatremia, SIADH	Oral • duration 12–24 h • *Toxicity:* Polyuria (frequency), thirst, hypernatremia

PREPARATIONS AVAILABLE

Acetazolamide (generic, Diamox)
Oral: 125, 250 mg tablets
Oral sustained-release: 500 mg capsules
Parenteral: 500 mg powder for injection

Amiloride (generic, Midamor, combination drugs[1])
Oral: 5 mg tablets

Bendroflumethiazide (Naturetin, combination drugs[1])
Oral: 5, 10 mg tablets

Brinzolamide (Azopt) (For ocular conditions)
Ophthalmic: 1% suspension

Bumetanide (generic, Bumex)
Oral: 0.5, 1, 2 mg tablets
Parenteral: 0.5 mg/2 mL ampule for IV or IM injection

Chlorothiazide (generic, Diuril)
Oral: 250, 500 mg tablets; 250 mg/5 mL oral suspension
Parenteral: 500 mg for injection

Chlorthalidone (generic, Hygroton, Thalitone, combination drugs[1])
Oral: 25, 50, 100 mg tablets

Conivaptan (Vaprisol)
Parenteral: 5 mg/mL; 20 mg/100 mL D5W for IV injection

Demeclocycline (Declomycin)
Oral: 150 mg tablets and capsules; 300 mg tablets

Dichlorphenamide (Daranide)
Oral: 50 mg tablets

Dorzolamide (Trusopt) (For ocular conditions)
Ophthalmic: 2% solution

Eplerenone (Inspra)
Oral: 25, 50 mg tablets

Ethacrynic acid (Edecrin)
Oral: 25, 50 mg tablets
Parenteral: 50 mg IV injection

Furosemide (generic, Lasix, others)
Oral: 20, 40, 80 mg tablets; 8, 10 mg/mL oral solutions
Parenteral: 10 mg/mL for IM or IV injection

Hydrochlorothiazide (generic, Esidrix, Hydro-DIURIL, combination drugs[1])
Oral: 12.5 mg capsules; 25, 50, 100 mg tablets; 10, 100 mg/mL solution

Hydroflumethiazide (generic, Saluron)
Oral: 50 mg tablets

Indapamide (generic, Lozol)
Oral: 1.25, 2.5 mg tablets

Mannitol (generic, Osmitrol)
Parenteral: 5, 10, 15, 20% solution, for injection

Methazolamide (generic, Neptazane) (For ocular conditions)
Oral: 25, 50 mg tablets

Methyclothiazide (generic, Aquatensen, Enduron)
Oral: 2.5, 5 mg tablets

Metolazone (Mykrox, Zaroxolyn) (Note: Bioavailability of Mykrox is greater than that of Zaroxolyn.)
Oral: 0.5 (Mykrox); 2.5, 5, 10 mg (Zaroxolyn) tablets

Nesiritide (Natrecor)
Parenteral: 1.5 mg vial for dilution into 250 mL IV solution (6 mcg/mL)

Polythiazide (Renese, combination drugs[1])
Oral: 1, 2, 4 mg tablets

Quinethazone (Hydromox)
Oral: 50 mg tablets

Spironolactone (generic, Aldactone , combination drugs[1])
Oral: 25, 50, 100 mg tablets

Tolvaptan (Samsca)
Oral: 15, 30 mg tablets

Torsemide (Demadex)
Oral: 5, 10, 20, 100 mg tablets
Parenteral: 10 mg/mL for injection

Triamterene (Dyrenium)
Oral: 50, 100 mg capsules

Trichlormethiazide (generic, Diurese, Naqua, others)
Oral: 2, 4 mg tablets

[1]Combination drugs: see Table 15-6

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CASE STUDY ANSWER

The diuretic most commonly used for congestive heart failure is a loop diuretic like furosemide, which is administered IV, in a dosage of 40 mg, followed if necessary by oral administration, 20–80 mg/24 h. For this patient, furosemide would probably be needed chronically, since it blunts the symptoms of congestive heart failure but does not reverse the ventricular damage that caused the symptoms. A common problem when beginning effective diuretic treatment is a reduction of glomerular filtration rate. Other adverse effects of loop diuretics include hypokalemia, metabolic alkalosis, ototoxicity, hyperuricemia, hypomagnesemia, and allergic reactions.