Pharmacologic Treatment of Hypertension

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This chapter reviews the currently available classes of drugs used in the treatment of hypertension. To best appreciate the complexity of selecting an antihypertensive agent, an understanding of the pathophysiology of hypertension and the pharmacology of the various drug classes used to treat it is required. A thorough understanding of these mechanisms is necessary to appreciate more fully the workings of specific antihypertensive agents. Among the factors that modulate high blood pressure, there is considerable overlap. The drug treatment of hypertension takes advantage of these integrated mechanisms to alter favorably the hemodynamic pattern associated with high blood pressure.

CHAPTER 7

Pathogenesis of Hypertension

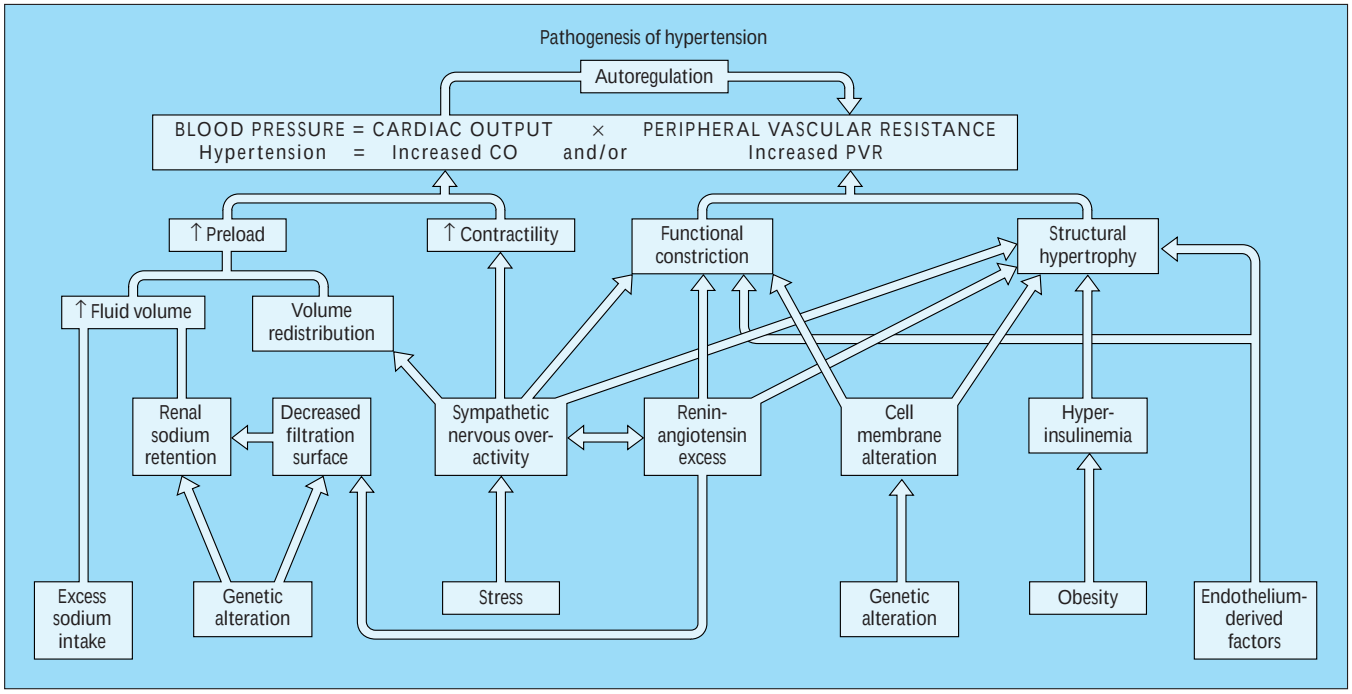

FIGURE 7-1

Pathogenesis of hypertension. Mean arterial pressure (MAP) is the product of cardiac output (CO) and peripheral vascular resistance (PVR). There are a large number of control mechanisms involved in every type of hypertension. (*From* Kaplan [1]; with permission.)

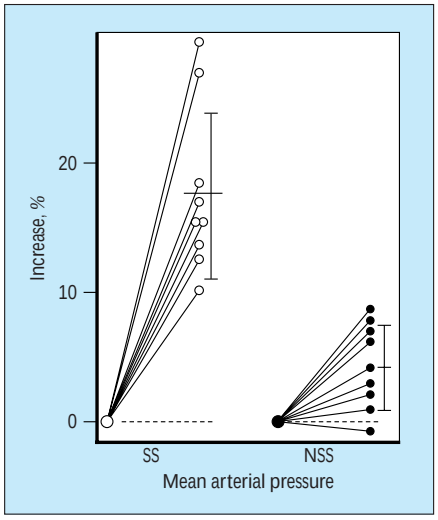

FIGURE 7-2

Blood pressure changes and diet. Many hypertensive patients appear to be sodium sensitive, as first suggested by studies in 19 hypertensive subjects who were observed after "normal" (109 mmol/d), "low" (9 mmol/d), and "high" (249 mmol/d) sodium intake [2]. This figure shows the percent increase in mean blood pressure in salt-sensitive (SS) and non–salt-sensitive (NSS) patients with hypertension when their diet was changed from low sodium to high sodium. *Vertical lines* indicate mean ± standard deviation. (*From* Kawasaki *et al.* [2]; with permission.)

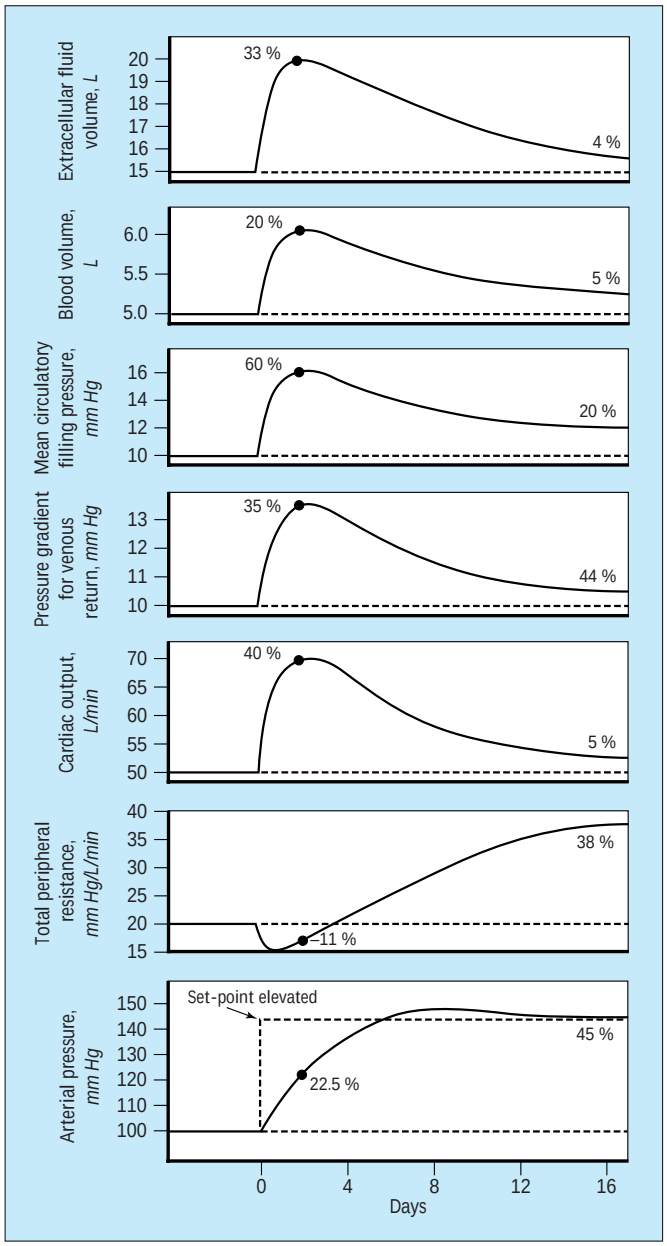

FIGURE 7-3

Cardiac output. An increase in cardiac output has been suggested as a mechanism for hypertension, particularly in its early borderline phase [3,4]. Sodium and water retention have been theorized to be the initiating events. Sequential changes following salt loading are depicted [3]. The resultant high cardiac output perfuses the peripheral tissues in excess of their metabolic requirements, resulting in a normal autoregulatory (vasoconstrictor) pressure. The early phase of high cardiac output and normal peripheral vascular resistance gradually changes to the characteristic feature of the sustained hypertensive state: normal cardiac output and high peripheral vascular resistance. Shown here are segmental changes in the important cardiovascular hemodynamic variables in the first few weeks following the onset of short-term salt-loading hypertension. Note especially that the arterial pressure increases ahead of the increase in total peripheral resistance. (*From* Guyton and coworkers [3]; with permission.)

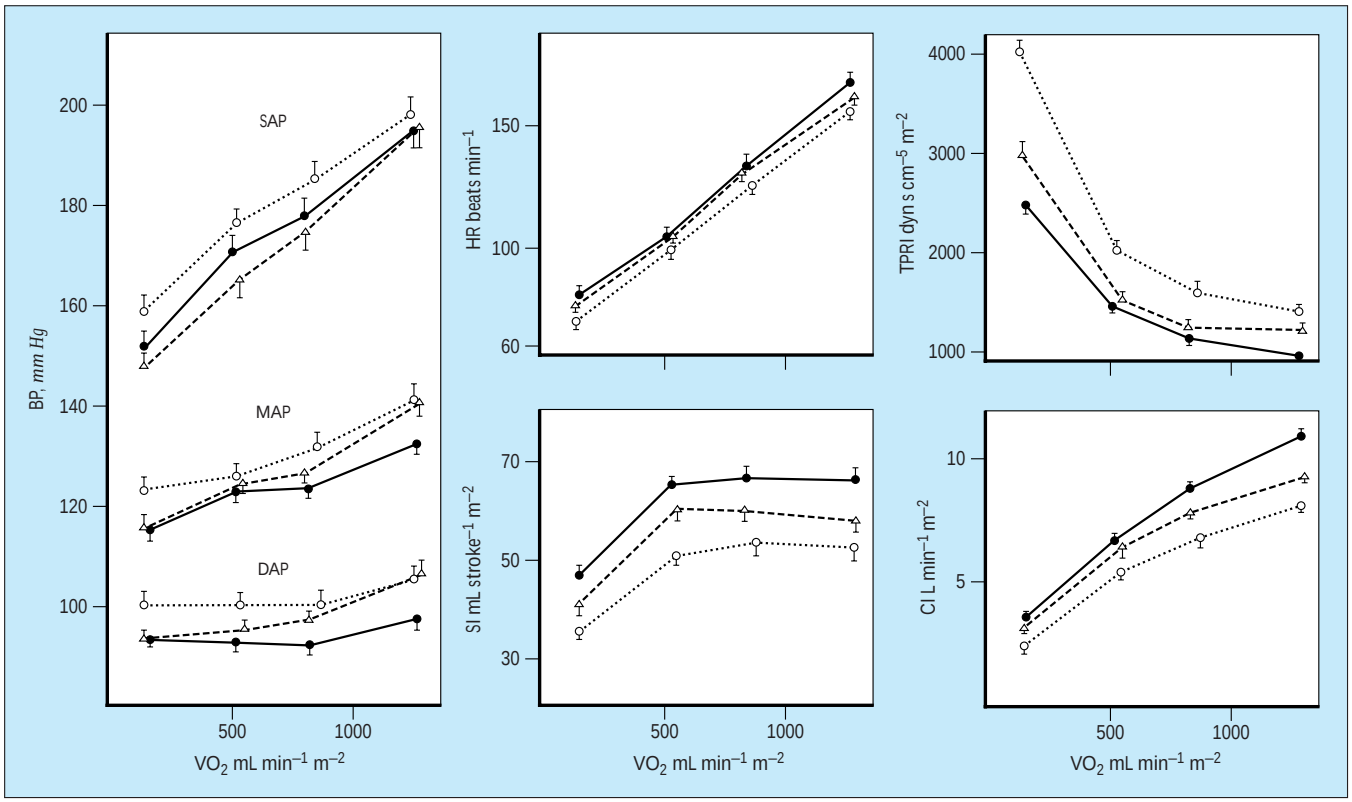

FIGURE 7-4

Peripheral vascular resistance. Most established cases of hypertension are associated with an increase in peripheral vascular resistance [5]. These alterations may be related to a functional constriction, the type observed under the influence of circulating or tissue-generated vasoconstrictors, or may be a result of structural alterations in the blood vessel. *Solid line* indicates values at start of the study [9]; *dashed line* indicates results after 10 years; *dotted line* indicates results after 20 years. BP—blood pressure; CI—cardiac index; DAP—diastolic arterial blood pressure; HR—heart rate; MAP—mean arterial pressure; SAP—systolic arterial blood pressure; SI—stroke index; TPRI—total peripheral resistance index; VO_2—oxygen consumption. (*From* Lund-Johansen [5]; with permission.)

Classes of Antihypertensive Drugs and Their Side Effects

CLASSES OF ANTIHYPERTENSIVE DRUGS

Diuretics: benzothiadiazides, loop, and potassium-sparing
β-adrenergic and α_1/β-adrenergic antagonists
Central α_2-adrenergic agonists
Central/peripheral adrenergic neuronal-blocking agent
Peripheral α_1-adrenergic antagonists
Moderately selective peripheral α_1-adrenergic antagonist
Peripheral adrenergic neuronal blocking agents
Direct-acting vasodilators
Calcium antagonists
Angiotensin-converting enzyme inhibitors
Tyrosine hydroxylase inhibitor
Angiotensin II receptor antagonists

FIGURE 7-5
Classes of antihypertensive drugs. There are 12 currently available classes of antihypertensive agents.

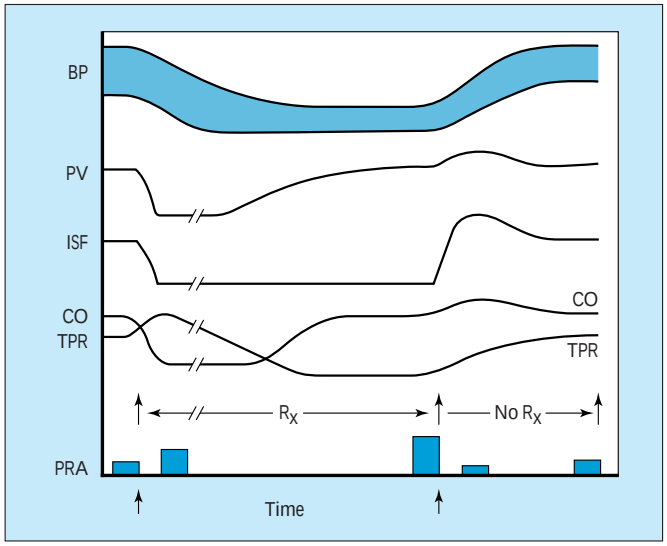

FIGURE 7-6
Hemodynamic response to diuretics. Diuretics reduce mean arterial pressure by their initial natriuretic effect [6]. Acutely, this is achieved by a reduction in cardiac output mediated by a reduction in plasma and extracellular fluid volumes [7]. Initially, peripheral vascular resistance is increased, mediated in part by stimulation of the renin-angiotensin system. During sustained diuretic therapy, cardiac output returns to pretreatment levels, probably reflecting restoration of plasma volume. Chronic blood pressure control now correlates with a reduction in peripheral vascular resistance. BP—blood pressure; CO—cardiac output; ISF—interstitial fluid; PRA—plasma renin activity; PV—plasma volume; Rx—treatment; TPR—total peripheral resistance. (*Adapted from* Tarazi [7].)

A. DIURETICS: BENZOTHIADIAZIDES (PARTIAL LIST) AND RELATED DIURETICS

Generic (trade) name	First dose, mg	Usual dose	Maximum dose	Duration of action, h
Hydrochlorothiazide (G) (Hydrodiuril, Microzide)	12.5	12.5–50 mg QD	100	6–12
Chlorthalidone (G) (Hygroton)	12.5	12.5–50 mg QD	100	48–72
Indapamide (Lozol)	1.25	2.5–5.0 mg	5	15–18
Metolazone				
(Mykrox)*;	0.5	0.5–1.0	1	12–24
(Zaroxolyn)	2.5	2.5–10 mg QD	20	12–24

*Marketed only for treatment of hypertension.
(G)—generic available.

B. DIURETICS: LOOP

Generic (trade) name	First dose, mg	Usual dose	Maximum dose	Duration of action, h
Bumetanide (G) (Bumex)	0.5	0.5–2 mg bid	10	4–6
Ethacrynic Acid (Edecrin)	25	25–50 mg bid	200	6–8
Furosemide (G) (Lasix)	20	20–120 mg bid	600	6–8
Torsemide (Demadex)	5	5–50 mg bid	100	6–8

(G)—generic available.

C. DIURETICS: POTASSIUM-SPARING DIURETICS

Generic (trade) name	First dose, mg	Usual dose	Maximum dose	Duration of action, h
Spironolactone (G) (Aldactone)	25	50–1 00 mg QD	400	48–72
Amiloride (G) (Midamor)	5	5–10 mg QD	20	24
Triamterene (G) (Dyrenium)	50	50-100 mg bid	300	7–9

(G)—generic available.

FIGURE 7-7

A–C. Diuretics: benzothiadiazides and related agents, loop diuretics, and potassium-sparing agents. A partial list of benzothiadiazides and their related agents is given [6]. With the exception of indapamide and metolazone, their dose-response curves are shallow; they should not be used when the glomerular filtration rate is less than 30 mL/min/1.73 m^2. The second group listed is loop diuretics. Because of their steep dose-response curves and natriuretic potency, they are especially useful when the glomerular filtration rate is less than 30 mL/min/1.73 m^2. The third group is the potassium-sparing diuretics. The major therapeutic use of these drugs is to attenuate the loss of potassium induced by the other diuretics.

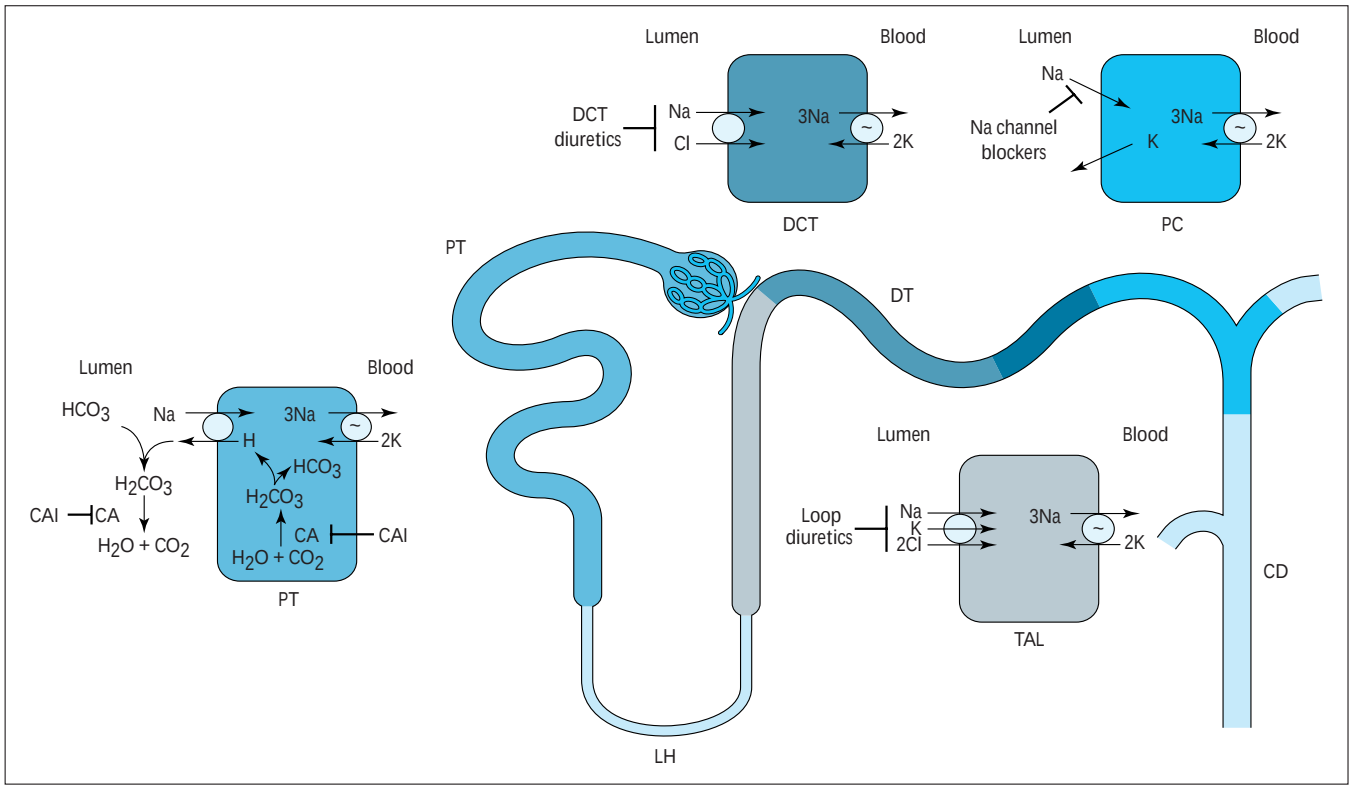

FIGURE 7-8

Mechanisms of action of diuretics. This figure depicts the major sites and mechanisms of action of diuretic drugs [8]. The diuretic/natriuretic action of benzothiadiazide-type diuretics is predicated on their gaining access to the luminal side of the distal convoluted tubule and inhibiting Na^+ - Cl^- cotransport by competing for the chloride site.

The diuretic/natriuretic action of loop diuretics is predicated on their gaining access to the luminal side of the thick ascending limb of the loop of Henle and inhibiting Na^+ - K^+ -$2Cl^-$ electroneutral cotransport by competing for the chloride site.

The diuretic/natriuretic action of potassium-sparing diuretics is predicated on their gaining access to the luminal side of the principal cells located in the late distal tubule and cortical collecting duct and blocking luminal sodium channels. Because Na^+ uptake is blocked, the lumen negative voltage is reduced, inhibiting K^+ secretion. The potassium-sparing diuretic spironolactone does this indirectly by competing with aldosterone for its cytosolic receptor. CA—carbonic anhydrase; CAI—carbonic anhydrase inhibitor; CD—collecting duct; DCT—distal convoluted tubule; DT—distal tubule; LH—loop of Henle; PC—principal cell; PT—proximal tubule; TAL—thick ascending limb. (*From* Ellison [8]; with permission.)

THE SIDE EFFECT PROFILE OF DIURETIC THERAPY

Side effects	Mechanisms
Thiazide-type diuretic	
Azotemia	Enhanced proximal fluid and urea reabsorption secondary to volume depletion
Hypochloremia, hypokalemia, metabolic alkalosis	Increased delivery of sodium to distal tubule facilitating Na^+-K^+ and Na^+-H^+ exchange; increased net acid excretion; increased urinary flow rate; secondary aldosteronism
Hypomagnesemia	Increase fractional Mg^{2+} excretion by inhibiting reabsorption in ascending limb of loop of Henle
Hyponatremia	Impaired free water clearance (distal cortical diluting segment)
Hypercalcemia	May reflect an increased protein-bound fraction secondary to volume depletion
Hyperuricemia	Impair enhanced proximal fluid and urate reabsorption secondary to volume depletion
Carbohydrate intolerance	Hypokalemia impairing insulin secretion; decreased insulin sensitivity
Hyperlipidemia	
Increased total triglyceride	May be due to extracellular fluid depletion
Increased total cholesterol	
Loop-type diuretics	
Ototoxicity	High plasma concentration of furosemide or ethacrynic acid
Hypocalcemia	Increase fractional excretion of calcium by interfering with reabsorption in loop of Henle
Potassium-sparing diuretics	
Hyperkalemia	Blocks potassium excretion
Decreased sexual function, gynecomastia, menstrual irregularity, hirsutism	Spironolactone only; lower circulatory testosterone levels by increasing metabolic clearance and/or preventing compensatory rise in testicular androgen production
Renal stone	Triamterene only

FIGURE 7-9

The side effect profile of diuretic therapy. The complications of diuretic therapy are typically related to dose and duration of therapy, and they decrease with lower dosages. This table lists the most common side effects of diuretics and their proposed mechanism of action [6].

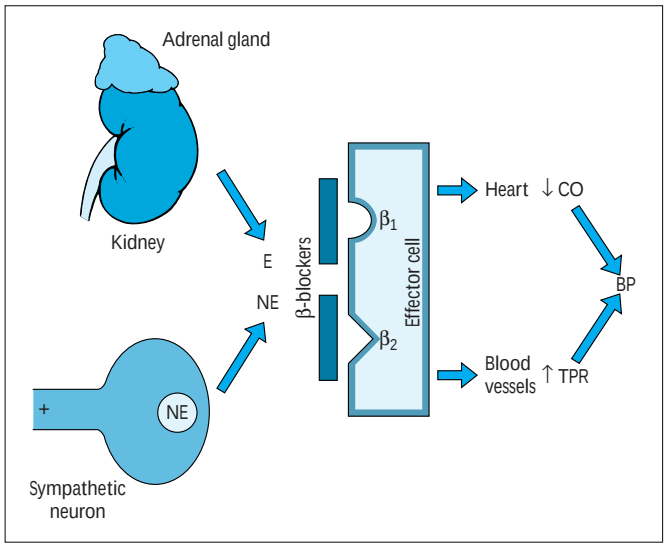

FIGURE 7-10

β-adrenergic antagonists. β-adrenergic antagonists attenuate sympathetic activity through competitive antagonism of catecholamines at both β_1- and β_2-adrenergic receptors [6,9]. In the absence of partial agonist activity (PAA), the acute systemic hemodynamic effects are a decrease in heart rate and cardiac output and an increase in peripheral vascular resistance proportional to the degree of cardiodepression; blood pressure is unchanged. Chronically, there is a gradual decrease in blood pressure proportional to the fall in peripheral vascular resistance, which is dependent on the degree of cardiac sympathetic drive. β-adrenergic antagonists with sufficient partial agonist activity to maintain heart rate and cardiac output may not evoke acute reflex vasoconstriction: Blood pressure falls proportional to the decrease in peripheral resistance (*see* Fig. 7-11) [10]. BP—blood pressure; CO—cardiac output; E—epinephrine; NE—norepinephrine; TPR—total peripheral resistance.

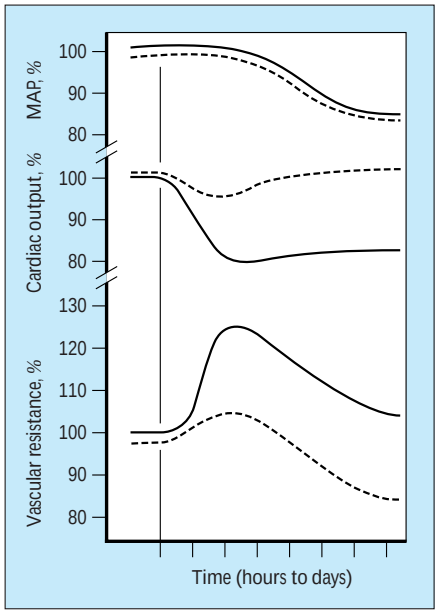

FIGURE 7-11

Hemodynamic changes associated with β-adrenergic blockade. Time course of hemodynamic changes after treatment with a β-adrenergic blocker devoid of partial agonist activity (PAA) (*solid line*) as compared with hemodynamic changes after administration of a β-adrenergic blocker with sufficient PAA to replace basal sympathetic tone (*eg*, pindolol) (*broken line*). MAP—mean arterial pressure. (*From* Man in't Veld and Schalekamp [10]; with permission.)

A. DOSING SCHEDULES FOR β-ADRENERGIC ANTAGONISTS: NON-SELECTIVE (β_1 AND β_2) ADRENERGIC ANTAGONISTS THAT LACK PARTIAL AGONIST ACTIVITY

Generic (trade) name	First dose, mg	Usual daily dose, mg	Maximum daily dose, mg	Duration of action, h
Nadolol (G)	40	40–240 QD	320	>24
(Corgard)				
Propranolol (G)				
(Inderal)	40	40–120 bid	480	>12
(Inderal LA)	80	80–240 QD	480	>12
Timolol (G)				
(Blockadren)	10	10–30 bid	60	>12

G—generic available.

B. DOSING SCHEDULES FOR β-ADRENERGIC ANTAGONISTS: NON-SELECTIVE (β_1 AND β_2) ADRENERGIC ANTAGONISTS WITH PARTIAL AGONIST ACTIVITY

Generic (trade) name	First dose, mg	Usual daily dose, mg	Maximum daily dose, mg	Duration of action, h
Pindolol (G)	5	10–30 bid	60	12
(Visken)				
Carteolol	2.5	2.5–10 QD	10	24
(Cartrol)				
Penbutolol	10	10–20 QD	40	24
(Levatol)				

G—generic available.

C: DOSING SCHEDULES FOR β-ADRENERGIC ANTAGONISTS: β_1-SELECTIVE ADRENERGIC ANTAGONISTS THAT LACK PARTIAL AGONIST ACTIVITY

Generic (trade) name	First dose, mg	Usual daily dose, mg	Maximum daily dose, mg	Duration of action, h
Atenolol (G)	50	50–100 QD	200	24
(Tenormin)				
Metoprolol Tartrate (G)	50	50–150 bid	400	12
(Lopressor)				
Metoprolol Succinate	50	100–300 QD	400	12
(Toprol-XL)				
Betaxolol	5	10–20 QD	40	>24
(Kerlone)				
Bisoprolol	5	5–20 QD	40	12
(Zebeta)				

G—generic available.

FIGURE 7-12

Dosing schedules for β-adrenergic antagonists. **A**, Nonselective β-adrenergic antagonists that lack partial agonist activity. **B**, Nonselective β-adrenergic antagonists with partial agonist activity. **C**, β_1-selective adrenergic antagonists that lack partial agonist activity.

(Continued on next page)

D. DOSING SCHEDULES FOR β-ADRENERGIC ANTAGONISTS: β_1-SELECTIVE ADRENERGIC ANTAGONISTS WITH WEAK PARTIAL AGONIST ACTIVITY

Generic (trade) name	First dose, mg	Usual daily dose, mg	Maximum daily dose, mg	Duration of action, h
Acebutolol (Sectrol)	200	400–800 QD	1200	24

E. DOSING SCHEDULES FOR β-ADRENERGIC ANTAGONISTS: α_1-NONSELECTIVE β-ADRENERGIC ANTAGONISTS LABETALOL (G)

Generic (trade) name	First dose, mg	Usual daily dose, mg	Maximum daily dose, mg	Duration of action, h
Labetalol (G) (Normodyne) (Trandate)	100	100-600 bid	2400	12
Carvedilol (Coreg)	6.25	6.25-25 bid	50	6

G—generic available.

FIGURE 7-12 (*Continued*)

D, β_1-selective adrenergic antagonists with weak partial agonist activity. **E**, α_1-nonselective β-adrenergic antagonists.

PHARMACOKINETICS OF β-ADRENERGIC ANTAGONISTS

	Solubility	Absorption	First-pass hepatic metabolism	Peak concentration, h	Active metabolite	Plasma half-life, h	Dose reduction in renal failure
Nadolol	Hydrophilic	30%–40%	<10%	2–4	None	20–24	Yes
Propranolol	Lipophilic	>90%	60%	1–3	Yes	3–4	No
Propranolol LA	Lipophilic	>90%	80%	6	Yes	10	No
Timolol	Lipophilic	>90%	50%	1–2	None	3–4	No
Pindolol	Lipophilic	>90%	<10%	1–2	None	3–4	Yes
Carteolol	Hydrophilic	>90%	<10%	1–3	Yes	5–6	Yes
Penbutolol	Lipophilic	>90%	<10%	2–3	Yes	5	Yes
Atenolol	Hydrophilic	50–60%	<10%	2–4	None	6–7	Yes
Metoprolol tartrate	Lipophilic	>90%	50%	1–2	None	3–7	No
Metoprolol succinate	Lipophilic	>90%	50%	7	None	3–7	No
Betaxolol	Lipophilic	>90%	<10%	1.5–6	None	14–22	Yes
Bisoprolol	Equal	>90%	20%	2–4	None	9–12	Yes
Acebutolol	Lipophilic	70%	30%	2–4	Yes	3–4	Yes
Labetalol	Lipophilic	>90%	60%	1–2	None	3–4	No
Carvedilol	Lipophilic	>90	70–80%	1–2	Yes	7–10	No

FIGURE 7-13
Pharmacokinetics of β-adrenergic antagonists.

THE SIDE EFFECT PROFILE OF β-ADRENERGIC ANTAGONISTS

Side effects	Mechanisms
Bronchospasm	Blockade of β_2-adrenergic receptors; increased airway resistance
Bradycardia	Blockade of atrial β_1/β_2-adrenergic receptors; decrease in heart rate
Congestive heart failure; decrease in exercise tolerance	Blockade of ventricular β_1-adrenergic receptors
Claudication	Blockade of peripheral vascular β_2-adrenergic receptors
Constipation, dyspepsia	Blockade of gastrointestinal β_1/β_2-adrenergic receptors; decreased motility and relaxation of sphincter tone
Central nervous system manifestations (sleep disturbances, depression)	Blockade of CNS β_1/β_2-adrenergic receptors
Sexual dysfunction (impotence, decrease libido)	Unknown
Impaired glucose tolerance	Impaired β_2-adrenergic–mediated islet cell insulin secretion; increase hepatic glucose, and/or decrease insulin-stimulated glucose disposal
Prolonged insulin-induced hypoglycemia	Block epinephrine-mediated counterregulatory mechanisms
Hepatocellular necrosis	Labetalol only, idiosyncratic reaction
Withdrawal syndrome Unstable angina Myocardial infarction	Acute overshoot in heart rate with increased myocardial oxygen demand due to increase in number and/or sensitivity of β-adrenergic receptors during chronic blockade
Dyslipidemia Increased total triglycerides Decreased high-density lipoproteins cholesterol	Increased α-adrenergic tone; reduced lipoprotein lipase activity

FIGURE 7-14
The side effect profile of β-adrenergic antagonists. The side effect profile of beta-blockers is related to the specific blockade of β_1 or β_2 receptors. This table lists the more common side effects and their proposed mechanism(s) of action [6,9].

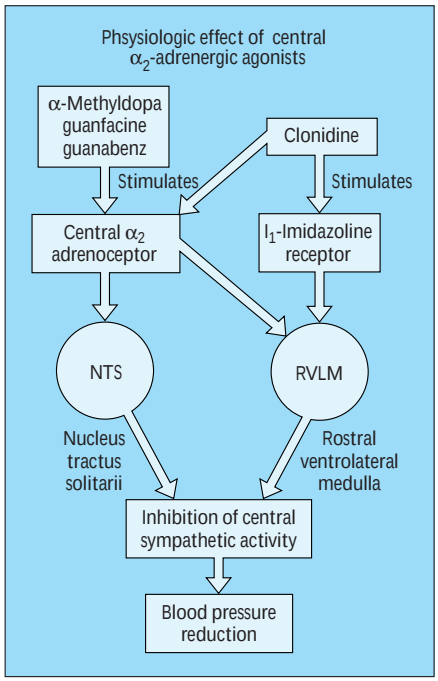

FIGURE 7-15

Central α_2-adrenergic agonists. Central α_2-adrenergic agonists cross the blood-brain barrier and stimulate α_2-adrenergic receptors in the vasomotor center of the brain stem [6,9]. Stimulation of these receptors decreases sympathetic tone, brain turnover of norepinephrine, and central sympathetic outflow and activity of the preganglionic sympathetic nerves. The net effect is a reduction in norepinephrine release. The central α_2-adrenergic agonist clonidine also binds to imidazole receptors in the brain; activation of these receptors inhibits central sympathetic outflow. Central α_2-adrenergic agonists may also stimulate the peripheral α_2-adrenergic receptors that mediate vasoconstriction; this effect predominates at high plasma drug concentrations and may precipitate an increase in blood pressure. The usual physiologic effect is a decrease in peripheral resistance and slowing of the heart rate; however, output is either unchanged or mildly decreased. Preservation of cardiovascular reflexes prevents postural hypotension.

CENTRAL α2-ADRENERGIC ANTAGONISTS

Generic (trade) name	First dose, mg	Usual daily dose	Maximum daily dose	Duration of action
α-Methyldopa (G) (Aldomet)	250	250–1000 mg bid	3000	24–48 h
Clonidine (G) (Catapres)	0.1	0.1–0.6 mg bid/tid	2.4	6–8 h
Clonidine TTS (Catapres-TTS)	2.5 mg (TTS-1)	2.5–7.5 mg (TTS–1 to TTS–3) qwk	15 mg (TTS-3x2) 9 wk	7 d
Guanabenz (Wytensin)	4	4–16 mg bid	64	12 h
Guanfacine (Tenex)	1	1–3 mg QD	3	36 h

G—generic available; TTS—transdermal patch.

FIGURE 7-16

Central α_2-adrenergic agonists. α-Methyldopa is a methyl-substituted amino acid that is active only after decarboxylation and conversion to α-methyl-norepinephrine. The antihypertensive effect results from accumulation of α_2-adrenergic receptors, displacing and competing with endogenous catecholamines. Methyldopa is absorbed poorly (<50%); peak plasma concentrations occur in 2 to 4 hours. It is metabolized in the liver and excreted in the urine mainly as the inactive O-sulfate conjugate. The plasma half-life of methyldopa (1 to 2 hours) and its metabolites is prolonged in patients with renal insufficiency; dose reduction is required.

Clonidine, an imidazoline derivative, acts by stimulating either central α_2-adrenergic receptors or imidazole receptors. Clonidine may be administered orally or by a transdermal delivery system (TTS). When given orally, it is absorbed well (>75%); peak plasma concentrations occur in 3 to 5 hours. Clonidine is metabolized mainly in the liver; fecal excretion ranges from 15% to 30%, and 40% to 60% is excreted unchanged in the urine. In patients with renal insufficiency, the plasma half-life (12 to 16 hours) may be extended to more than 40 hours; dose reduction is required. When clonidine is administered transdermally, therapeutic plasma levels are achieved within 2 to 3 days.

Guanabenz, a guanidine derivative, is highly selective for central α_2-adrenergic receptors. It is absorbed well (>75%); peak plasma levels are reached in 2 to 5 hours. Guanabenz undergoes extensive hepatic metabolism; less than 2% is excreted unchanged in the urine. The plasma half-life (approximately 6 hours) is not prolonged in patients with renal insufficiency.

Guanfacine is a phenylacetyl-guanidine derivative with a longer plasma half-life than guanabenz. It is absorbed well (>90%); peak plasma concentrations are reached in 1 to 4 hours. The drug is primarily metabolized in the liver. Guanfacine and its metabolites are excreted primarily by the kidneys; 24% to 37% is excreted as unchanged drug in the urine. The plasma half-life (15 to 17 hours) is not prolonged in patients with renal insufficiency [6,9].

THE SIDE EFFECT PROFILE OF CENTRAL α_2-ADRENERGIC AGONISTS

Side effects	Mechanisms
Sedation/drowsiness	Stimulation of α_2-adrenergic receptors in the brain
Xerostoniia (dry mouth)	Centrally mediated inhibition of cholinergic transmission
Gynecomastia in men, galactorrhea in women	Reduced central dopaminergic inhibition of prolactin release (methyldopa only)
Drug fever, hepatotoxicity, positive Coombs test with or without hemolytic anemia	Long-term tissue toxicity (methyldopa only)
Sexual dysfunction, depression, decreased mental acuity	Stimulation of α_2-adrenergic receptor in the brain
"Overshoot hypertension" Restlessness Insomnia Headache Tremor Anxiety Nausea and vomiting A feeling of impending doom	Acute excessive sympathetic discharge in the face of chronic downregulation of central α_2-adrenergic receptors in an inhibitory circuit during chronic treatment when treatment is stopped

FIGURE 7-17

The side effect profile of central α_2-adrenergic agonists. The side effect profile of these agents is diverse [6,9].

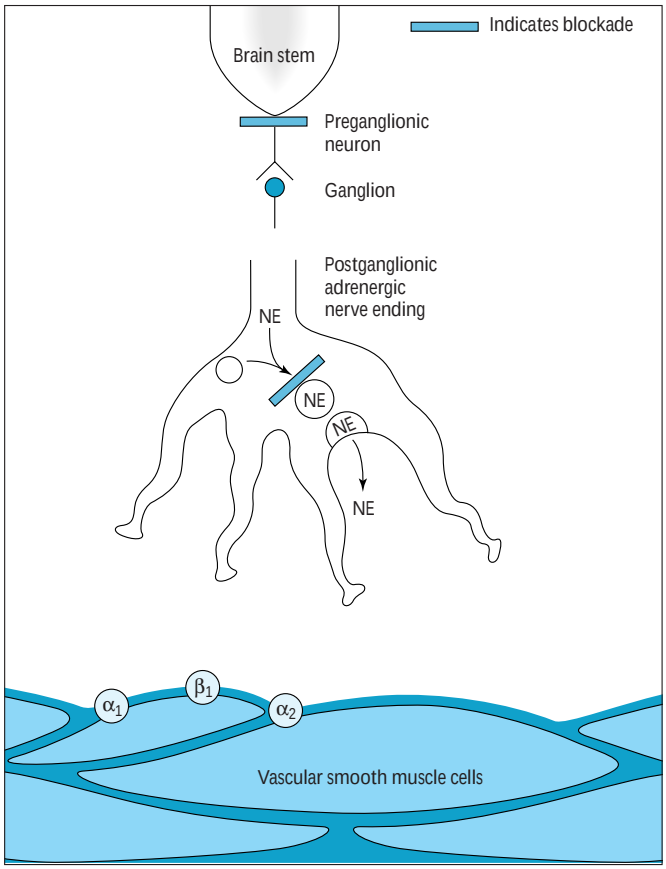

FIGURE 7-18

Central and peripheral adrenergic neuronal blocking agents. Rauwolfia alkaloids act both within the central nervous system and in the peripheral sympathetic nervous system [6,9]. They effectively deplete stores of norepinephrine (NE) by competitively inhibiting the uptake of dopamine by storage granules and by preventing the incorporation of norepinephrine into the protective chromaffin granules; the free catecholamines are destroyed by monoamine oxidase. The predominant pharmacologic effect is a marked decrease in peripheral resistance; heart rate and cardiac output are either unchanged or mildly decreased.

CENTRAL PERIPHERAL ADRENERGIC-NEURONAL BLOCKING AGENT

Generic (trade) name	First dose, mg	Usual daily dose, mg	Maximum daily dose, mg	Duration of action
Reserpine (G) (Serpasil)	0.1	0.1–.25 QD	0.5	2–3 wk

FIGURE 7-19

Central and peripheral adrenergic neuronal blocking agents. Reserpine is the most popular rauwolfia product used. It is absorbed poorly (approximately 30%); peak plasma concentrations occur in 1 to 2 hours. Catecholamine depletion begins within 1 hour of drug administration and is maximal in 24 hours. Catecholamines are restored slowly. Chronic doses of reserpine are cumulative. Blood pressure is maximally lowered 2 to 3 weeks after beginning therapy. Reserpine is metabolized by the liver; 60% of an oral dose is recovered in the feces. Less than 1% is excreted in the urine as unchanged drug. The plasma half-life (12 to 16 days) is not prolonged in patients with renal insufficiency.

THE SIDE EFFECT PROFILE OF RESERPINE

Side effects	Mechanisms
Altered CNS function Inability to concentrate Decrease mental acuity Sedation Sleep disturbance Depression	Depletion of serotonin and/or catecholamine
Nasal congestion/rhinitis	Cholinergic effects
Increased GI motility, increased gastric acid secretion	Cholinergic effects
Increased appetite/weight gain	Unknown
Sexual dysfunction Impotence Decreased libido	Unknown

FIGURE 7-20

The side effect profile of the central and peripheral adrenergic neuronal blocking agents [10,13]. Reserpine is contraindicated in patients with a history of depression or peptic ulcer disease. CNS—central nervous system; GI—gastrointestinal.

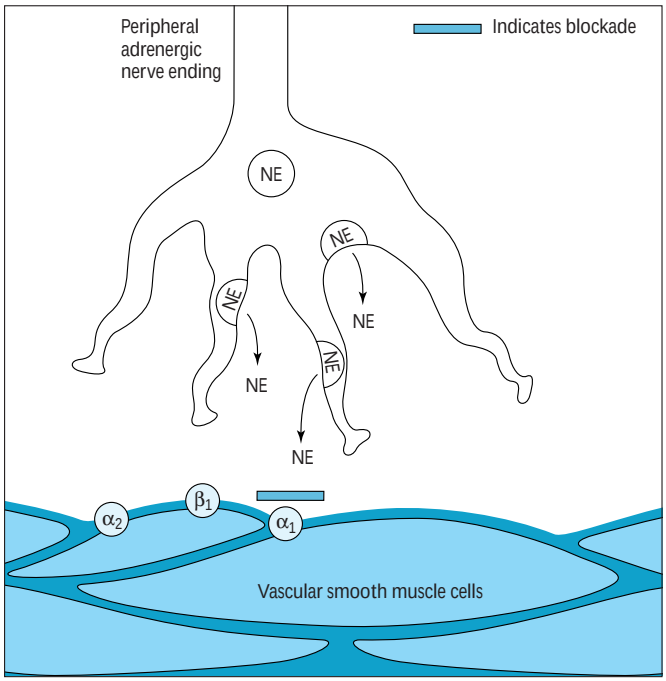

FIGURE 7-21

Peripheral α_1-adrenergic antagonists. α_1-Adrenergic antagonists induce dilation of both resistance (arterial) and capacitance (venous) vessels by selectively inhibiting postjunctional α_1-adrenergic receptors [6,9]. The net physiologic effect is a decrease in peripheral resistance; reflex tachycardia and the attendant increase in cardiac output do not predictably occur. This is due to their low affinity for prejunctional α_2-adrenergic receptors, which modulate the local control of norepinephrine release from sympathetic nerve terminals by a negative feedback mechanism (*see* Fig. 7-22) [11]. NE—norepinephrine.

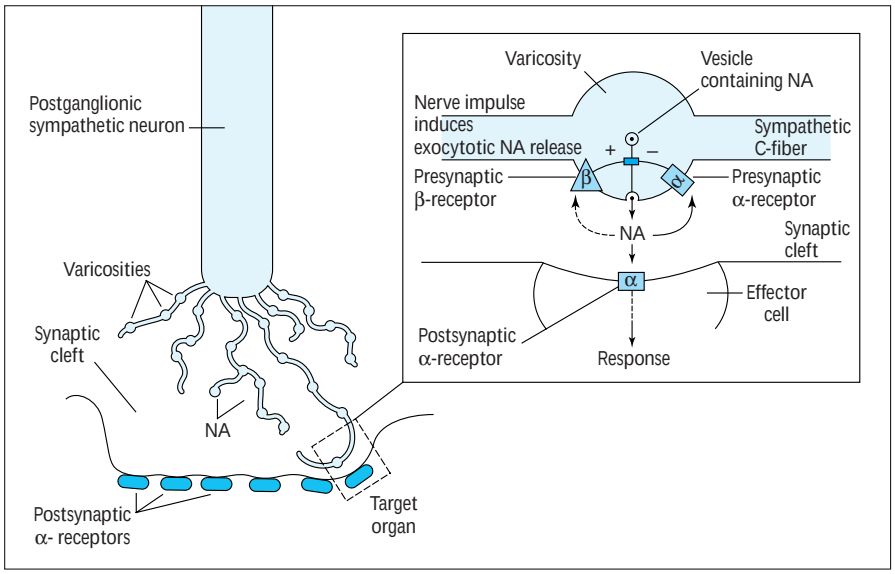

FIGURE 7-22

Adrenergic synapse. Nerve activity releases the endogenous neurotransmitter noradrenaline (NA) and also adrenaline from the varicosities. Noradrenaline and adrenaline reach the postsynaptic α-adrenoceptors (or β-adrenoceptors) on the cell membrane of the target organ by diffusion. On receptor stimulation, a physiologic or pharmacologic effect is initiated. Presynaptic α_2-adrenoceptors on the membrane (*enlarged area*), when activated by endogenous noradrenaline as well as by exogenous agonists, inhibit the amount of transmitter noradrenaline released per nerve impulse. Conversely, the stimulation of presynaptic β_2-receptors enhances noradrenaline release from the varicosities. Once noradrenaline has been released, it travels through the synaptic cleft and reaches both α- and β-adrenoceptors at postsynaptic sites, causing physiologic effects such as vasoconstriction or tachycardia. (*Adapted from* Van Zwieten [11].)

PERIPHERAL α_1-ADRENERGIC ANTAGONISTS

Generic (trade) name	First dose, mg	Usual daily dose, mg	Maximum daily dose, mg	Duration of action
Prazosin (G) (Minipress)	1	2-6 bid/tid	20	6-12 w
Terazosin (Hytrin)	1	2-5 QD/bid	20	12-24 h
Doxazosin (Cardura)	1	2-4 QD	16	24 h

G—generic available.

FIGURE 7-23

Peripheral α_1-adrenergic antagonists. Prazosin is a lipophilic highly selective α_1-adrenergic antagonist. It is absorbed well (approximately 90%) but undergoes variable first-pass hepatic metabolism. Peak plasma concentrations occur in 2 to 3 hours. It is extensively metabolized by the liver and predominantly excreted in the feces. The plasma half-life of prazosin (2 to 4 hours) is not prolonged in patients with renal insufficiency.

Terazosin is a water-soluble quinazoline analogue of prazosin with about one third of its potency. It is completely absorbed and undergoes minimal first-pass hepatic metabolism. Peak plasma concentrations occur in 1 to 2 hours. It is extensively metabolized by the liver and predominantly excreted in the feces. The plasma half-life of terazosin (approximately 12 hours) is not prolonged in patients with renal insufficiency.

Doxazosin is also a water-soluble quinazoline analogue of prazosin, with about half its potency. It is absorbed well but undergoes significant first-pass hepatic metabolism; bioavailability is approximately 65%. Peak concentrations occur in 2 to 3 hours. It is extensively metabolized by the liver and primarily eliminated in the feces. The plasma half-life of doxazosin (approximately 22 hours) is not prolonged in patients with renal insufficiency [6,9].

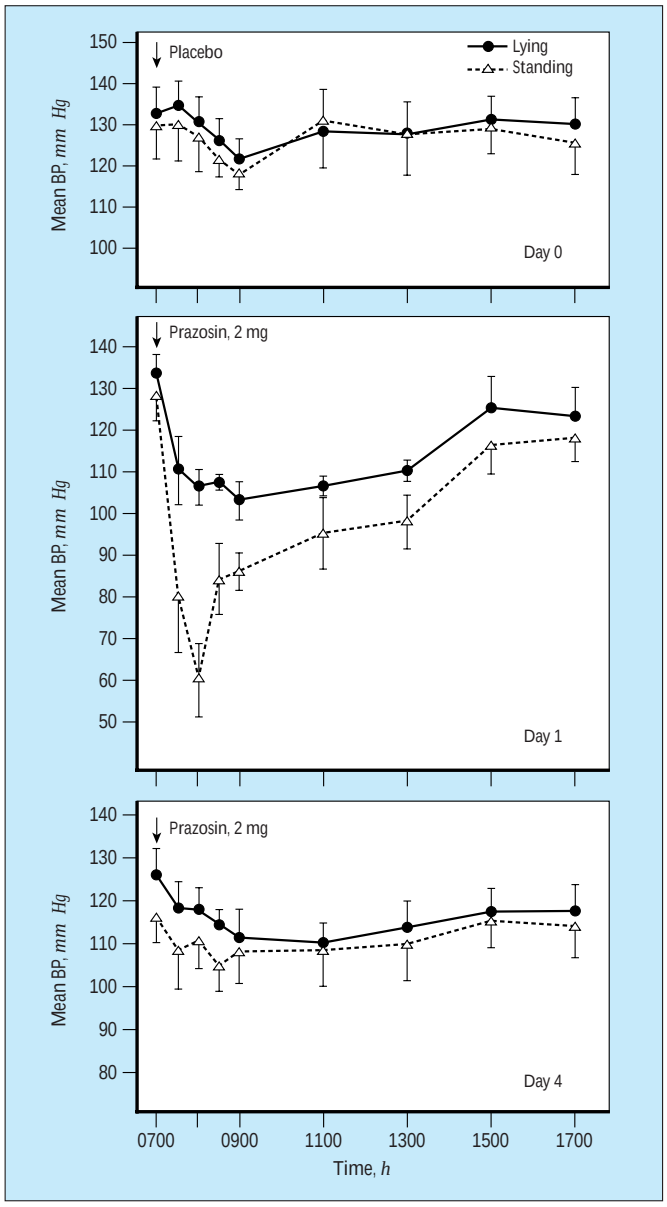

FIGURE 7-24

The side effect profile of the peripheral α_1-adrenergic antagonists. α_1-Adrenergic antagonists are associated with relatively few side effects [6,9]; the most striking is the "first-dose effect" [12]. It occurs 30 to 90 minutes after the first dose and is dose dependent. It is minimized by initiating therapy in the evening and by careful dose titration. The "first-dose effect" is exaggerated by fasting, upright posture, volume contraction, concurrent β-adrenergic antagonism, or excessive catecholamine activity (*eg*, pheochromocytoma). (*From* Graham and coworkers [12]; with permission.)

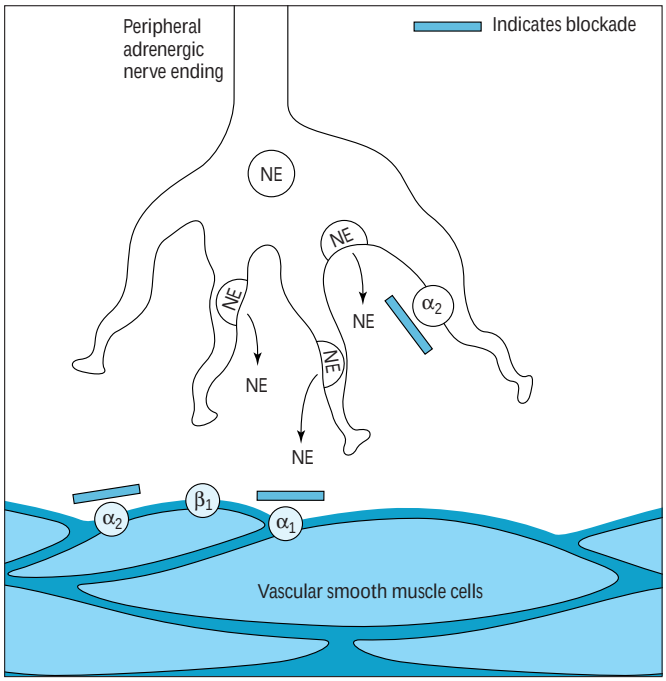

FIGURE 7-25

Moderately selective peripheral α_1-adrenergic antagonists. Phenoxybenzamine is a moderately selective peripheral α_1-adrenergic antagonist [6,9]. It is 100 times more potent at α_1-adrenergic receptors than at α_2-adrenergic receptors. Phenoxybenzamine binds covalently to α-adrenergic receptors, interfering with the capacity of sympathomimetic amines to initiate action at these sites. Phenoxybenzamine also increases the rate of turnover of norepinephrine (NE) owing to increased tyrosine hydroxylase activity, and it increases the amount of norepinephrine released by each nerve impulse owing to blockade of presynaptic α_2-adrenergic receptors [11]. The net physiologic effect is a decrease in peripheral resistance and increases in heart rate and cardiac output. Postural hypotension may be prominent, related to blockade of compensatory responses to upright posture and hypovolemia. The degree of vasodilation is dependent on the degree of adrenergic vascular tone.

MODERATELY SELECTIVE PERIPHERAL α_1-ADRENERGIC ANTAGONIST

Generic (trade) name	First dose, mg	Usual daily dose, mg	Maximum of action, mg	Duration of action
Phenoxybenzamine (Dibenzyline)	10	20-40 bid	120	3–4 d

FIGURE 7-26

Moderately selective peripheral α_1-adrenergic antagonists. Phenoxybenzamine is the only drug in its class. Absorption is variable and incomplete (20% to 30%). Peak blockade occurs in 3 to 4 hours. Its plasma half-life is 24 hours. The duration of action is approximately 3 to 4 days. Phenoxybenzamine is primarily used in the management of preoperative or inoperative pheochromocytoma. Efficacy is dependent on the degree of underlying excessive α-adrenergic vascular tone [6,9].

THE SIDE EFFECT PROFILE OF PHENOXYBENZAMINE

Side effects	Mechanisms
Nasal congestion	α-adrenergic receptor blockade
Miosis	α-adrenergic receptor blockade
Sedation	Unknown
Weakness, lassitude	Impairment of compensatory vasoconstriction producing orthostatic hypotension
Sexual dysfunction Inhibition of ejaculation	α-adrenergic receptor blockade
Tachycardia	Uninhibited effects of epinephrine, norepinephrine and direct or reflex sympathetic nerve stimulation on the heart

FIGURE 7-27

The side effect profile of phenoxybenzamine. The common side effects are listed [6,9].

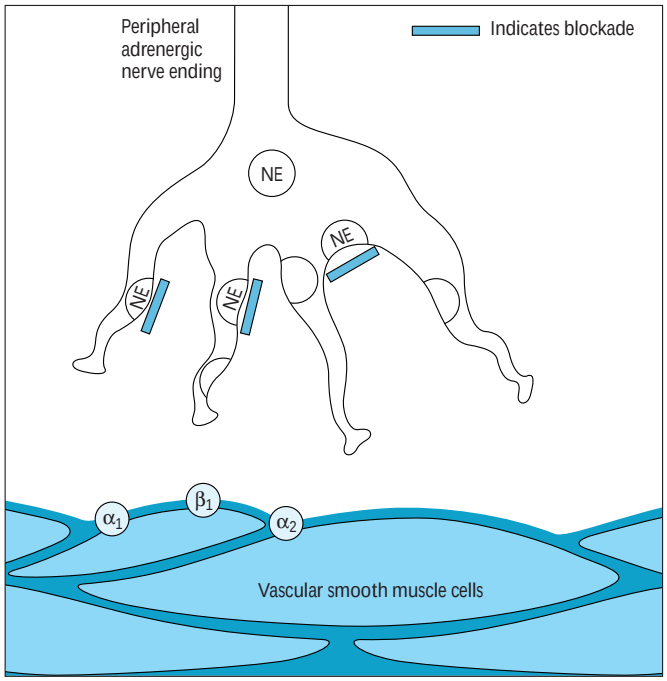

FIGURE 7-28

Peripheral adrenergic neuronal blocking agents. Peripheral adrenergic neuronal blocking agents are selectively concentrated in the adrenergic nerve terminal by an active transport mechanism, or "norepinephrine pump" [6,9]. They act by interfering with the release of norepinephrine (NE) from neuronal storage sites in response to nerve stimulation and by depleting norepinephrine from nerve endings. Acutely, cardiac output is reduced, caused by diminished venous return and by blockade of sympathetic β-adrenergic effects on the heart; peripheral resistance is unchanged. Following chronic therapy, peripheral resistance is decreased, along with modest decreases in heart rate and cardiac output.

PERIPHERAL ADRENERGIC-NEURONAL BLOCKING AGENTS

Generic (trade) name	First dose, mg	Usual daily dose, mg	Maximum daily dose, mg	Duration of action
Guanethidine (Ismelin)	10	25–75 QD	150	7–21 d
Guanadrel (Hylorel)	5	10–50 bid	150	4–14 h

FIGURE 7-29

Peripheral adrenergic neuronal blocking agents. Guanethidine is the prototype peripheral adrenergic neuronal blocking agent. Absorption is incomplete and variable; only 3% to 30% is absorbed over 12 hours. Peak plasma levels are reached in 6 hours. The drug rapidly leaves the plasma for extravascular storage sites, including sympathetic neurons. Guanethidine is eliminated with a plasma half-life of 4 to 8 days, a time course that corresponds with its antihypertensive effect. Approximately 24% of the drug is excreted unchanged in the urine; the remainder is metabolized by the liver into more polar, less active, metabolites that are excreted in the urine and feces. When therapy is initiated or the dosage is changed, three half-lives (approximately 15 days) are required to accumulate 87.5% of a steady-state level. By administering loading doses of guanethidine at 6-hour intervals (the nearly maximal effect from a single oral dose), blood pressure can be lowered in 1 to 3 days. In patients with severe renal insufficiency, drug excretion is decreased; dose reduction is required.

Guanadrel is a guanethidine derivative with a short therapeutic half-life. Absorption is greater than 85%; peak plasma concentrations are reached in 1 to 2 hours. Guanadrel is metabolized by the liver. Elimination occurs through the kidney; approximately 40% of the drug is excreted unchanged in the urine. In patients with renal insufficiency, the plasma half-life (10 to 12 hours) is prolonged; dose reduction is required [6,9].

THE SIDE EFFECT PROFILE OF PERIPHERAL ADRENERGIC-NEURONAL BLOCKING AGENTS

Side effects	Mechanisms
Decrease renal function (GFR)	Decreased renal perfusion; effect is magnified in the upright position
Fluid retention/weight gain	Decreased filtered load and fractional excretion of sodium; diuretic should be used in combination
Dizziness/weakness Syncope	Postural hypotension accentuated by hot weather, alcohol ingestion, and/or physical exercise
Intestinal cramping/diarrhea	Unopposed parasympathetic activity, increasing gastrointestinal motility
Sexual dysfunction Retrograde ejaculation Impotence Decreased libido	Inhibition of bladder neck closure, unknown
Sinus bradycardia Atrioventricular block	Interferes with cardiac sympathetic compensating reflexes
Bronchospasm	Catecholamine depletion aggravates airway resistance
Congestive heart failure	Decreased cardiac output

FIGURE 7-30

The side effect profile of peripheral adrenergic neuronal blocking agents. The specific side effects of this class are related to either excessive sympathetic blockade or a relative increase in parasympathetic activity. GFR—glomerular filtration rate.

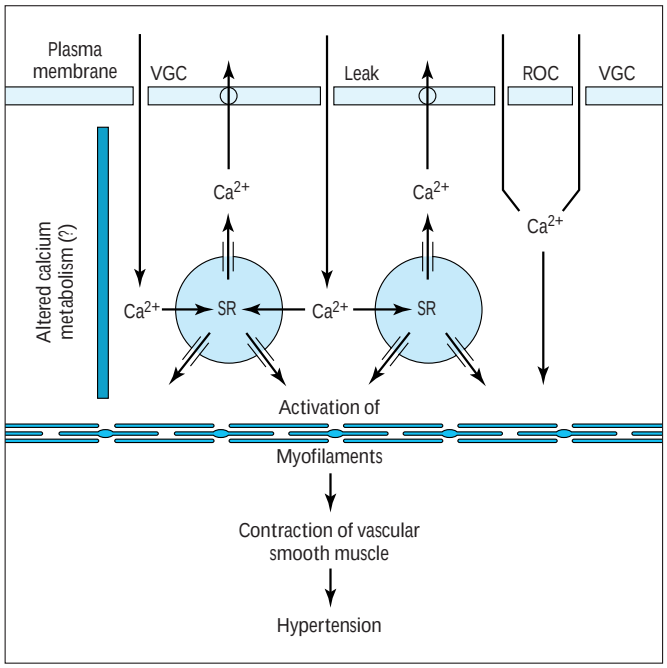

FIGURE 7-31

Direct-acting vasodilators. Direct-acting vasodilators may have an effect on both arterial resistance and venous capacitance vessels; however, the currently available oral drugs are highly selective for resistance vessels [6,9]. Their specific mechanism of vascular relaxation and reason for selectivity are unknown. By altering cellular calcium metabolism, they interfere with the calcium movements responsible for initiating or maintaining a contractile state. The net physiologic effect is a decrease in peripheral vascular resistance associated with increases in heart rate and cardiac output. These increases in heart rate and cardiac output are related directly to sympathetic stimulation and indirectly to the baroreceptor reflex response. ROC—receptor-operated channel; SR—sarcoplasmic reticulum; VGC—voltage-gaited channels.

DIRECT-ACTING VASODILATORS

Generic (trade) name	First dose, mg	Usual daily dose, mg	Maximum daily dose, mg	Duration of action, h
Hydralazine (G) (Apresoline)	10	50–100 bid/tid	300	10–12
Minoxidil (G) (Loniten)	5	10–20 QD/bid	80	75

G—generic available.

FIGURE 7-32

Direct-acting vasodilators. Hydralazine is the prototype of direct-acting vasodilators. Absorption is more than 90%. Peak plasma levels occur within 1 hour but may vary widely among individuals. This is because hydralazine is subject to polymorphic acetylation; slow acetylators have higher plasma levels and require lower drug doses to maintain blood pressure control compared with rapid acetylators. Bioavailability for slow acetylators ranges from 30% to 35%; bioavailability for rapid acetylators ranges from 10% to 16%. Hydralazine undergoes extensive hepatic metabolism; it is mainly excreted in the urine in the form of metabolites or as unchanged drug. The plasma half-life is 3 to 7 hours. Dose reduction may be required in the slow acetylator with renal insufficiency.

Minoxidil is a substantially more potent direct-acting vasodilator than hydralazine. Absorption is greater than 95%. Peak plasma levels occur within 1 hour. Following a single oral dose, blood pressure declines within 15 minutes, reaches a nadir between 2 and 4 hours, and recovers at an arithmetically linear rate of 30% per day. Approximately 90% is metabolized by conjugation with glucuronic acid and by conversion to more polar products. Known metabolites, which are less pharmacologically active than minoxidil, are excreted in the urine. The plasma half-life of minoxidil is approximately 4 hours; dose adjustments are unnecessary in patients with renal insufficiency. Minoxidil and its metabolites are removed by hemodialysis and peritoneal dialysis; replacement therapy is required [6,9].

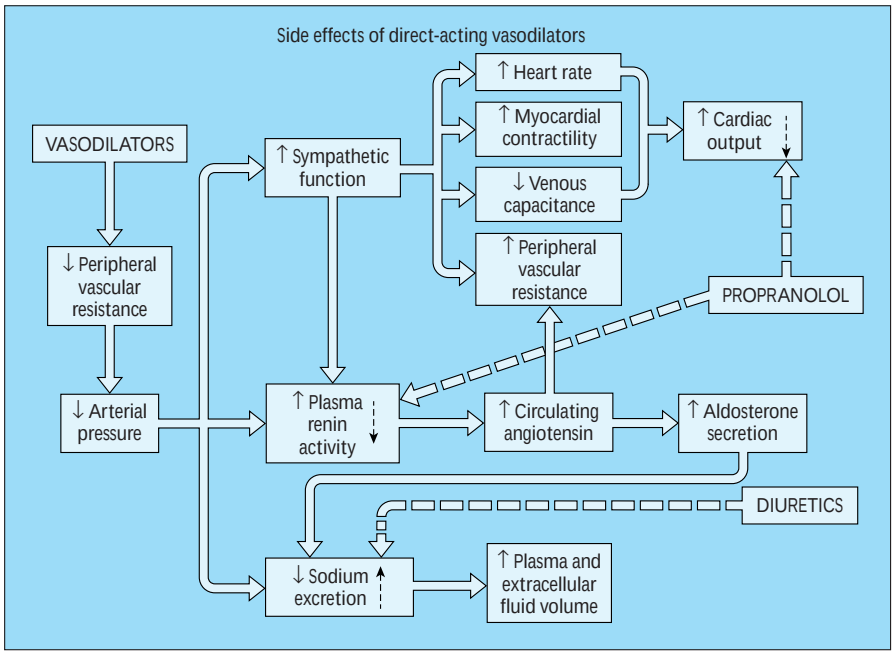

FIGURE 7-33

The side effect profile of direct-acting vasodilators. The most common and most serious effects of hydralazine and minoxidil are related to their direct or reflex-mediated hemodynamic actions, including flushing, headache, palpitations, anginal attacks, and electrocardiographic changes of myocardial ischemia [6,9]. These effects may be prevented by concurrent administration of a β-adrenergic antagonist. Sodium retention with expansion of extracellular fluid volume is a significant problem. Large doses of potent diuretics may be required to prevent fluid retention and the development of pseudotolerance [13]. (*From* Koch-Weser [13]; with permission.)

Repeated administration of hydralazine can lead to a reversible syndrome that resembles disseminated lupus erythematosus. The incidence is dose dependent; it rarely occurs in patients receiving less than 200 mg/day. Hypertrichosis is a common troublesome but reversible side effect of minoxidil; it develops during the first 3 to 6 weeks of therapy in approximately 80% of patients.

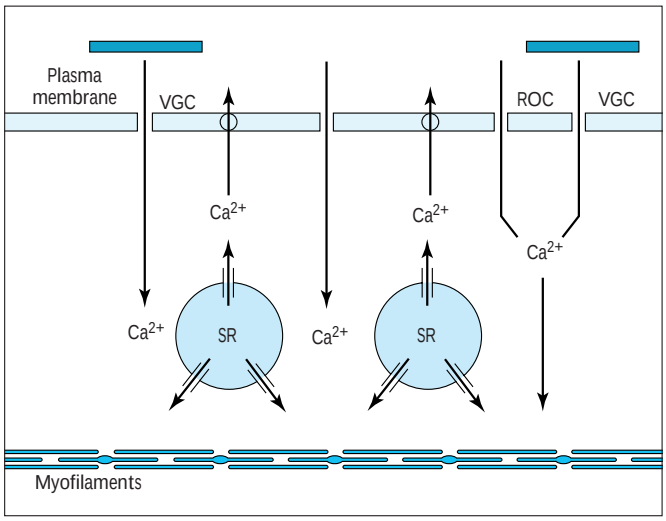

FIGURE 7-34

Calcium antagonists. The calcium antagonists share a common antihypertensive mechanism of action: inhibition of calcium ion movement into smooth muscle cells of resistance arterioles through L-type (long-lasting) voltage-operated channels [6,9]. The ability of these drugs to bind to voltage-operated channels, causing closure of the gate and subsequent inhibition of calcium flux from the extracellular to the intracellular space, inhibits the essential role of calcium as an intracellular messenger, uncoupling excitation to contraction. Calcium ions may also enter cells through receptor-operated channels. The opening of these channels is induced by binding neurohumoral mediators to specific receptors on the cell membrane. Calcium antagonists inhibit the calcium influx triggered by the stimulation of either α-adrenergic or angiotensin II receptors in a dose-dependent manner, inhibiting the influence of α-adrenergic agonist and angiotensin II on vascular smooth muscle tone. The net physiologic effect is a decrease in vascular resistance.

Although all the calcium antagonists share a basic mechanism of action, they are a highly heterogeneous group of compounds that differ markedly in their chemical structure, pharmacologic effects on tissue specificity, pharmacologic behavior side-effect profile, and clinical indications [6,9,14]. Because of this, calcium antagonists have been subdivided into several distinct classes: phenylalkamines, dihydropyridines, and benzothiazepines. ROC—receptor-operated channel; SR—sarcoplasmic reticulum; VGC—voltage-gaited channels.

A. DOSING SCHEDULES FOR CALCIUM ANTAGONISTS: PHENYLALKAMINE DERIVATIVE

Generic (trade) name	First dose, mg	Usual dose, mg	Maximum daily dose, mg	Duration of action, h
Verapamil (G) (Isoptin, Calan)	80	80–120 tid	480	8
Verapamil SR (Isoptin SR, Calan SR)	90	90–240 bid	480	12–24
Verapamil SR—pellet (Veralan)	120	240–480 QD	480	24
Verapamil COER-24 (Covera HS)	180	180–480 qhs	480	24

G—generic available.

B. DOSING SCHEDULES FOR CALCIUM ANTAGONISTS: DIHYDROPYRIDINE DERIVATIVES

Generic (trade) name	First dose, mg	Usual dose, mg	Maximum daily dose, mg	Duration of action, h
Amlodipine (Norvasc)	5	5–10 QD	10	24
Felodipine (Plendil)	5	5–1 0 QD	20	24
Isradipine (DynaCirc)	2.5	2.5-5 bid	20	12
Isradipine CR (DynaCirc CR)	5	5–20 QD	20	24
Nicardipine SR (Cardine SR)	30	30–60 bid	120	12
Nifedipine Caps (G) (Procardia)	10	10–30 tid/qid	120	4–6
Nifedipine ER (Adalat CC)	30	30–90 QD	120	24
Nifedipine GITS (Procardia XL)	30	30–90 QD	120	24
Nisoldipine (Sular)	20	20–40 QD	60	24

G—generic available.

C. DOSING SCHEDULES FOR CALCIUM ANTAGONISTS: BENZODIAZEPINE DERIVATIVE

Generic (trade) name	First dose, mg	Usual dose, mg	Maximum daily dose, mg	Duration of action, h
Diltiazem (G) (Cardizem)	60	60–120 tid/qid	480	8
Diltiazem SR (Cardizem SR)	180	120–240 bid	480	12
Diltiazem CD (Cardizem CD)	180	240–480 QD	480	24
Diltiazem XR (Dilacor XR)	180	180–480 QD	480	24
Diltiazem ER (Tiazac)	180	180–480 QD	480	24

G—generic available.

FIGURE 7-35

A–C. Dosing schedules for calcium antagonists: phenylalkamine derivatives, dihydropyridine derivatives, and benzothiazepine derivatives.

PHARMACOKINETICS OF CALCIUM ANTAGONISTS

	Absorption, %	First-pass hepatic	Peak concentration	Route of elimination	Active metabolite	Plasma half-life, h	Dose reduction
Verapamil	>90	70%–80%	1–2 h (tablet) 5 h (SR caplet) 7–9 h (SR pellet) 11 h (COER)	Liver	Yes	4–12 (tablet) 12 (SR pellet)	No
Amlodipine	>90	Minimal	6–12 h	Liver	No	30–50	No
Felodipine	>90	Extensive	2.5–5 h	Liver	No	11–16	No
Isradipine	>90	Extensive	1–2 h (tablet) 7–18 h (CR)	Liver	No	8	No
Nicardipine	>90	Extensive	1–4 h (SR)	Liver	No	8–9	No
Nifedipine	>90	20%–30%	<30 min (cap) 2.5–5 h (ER) 6 h GITS)	Liver	No	2 24 24	No
Nisoldipine	>85	Extensive	6–12 h	Liver	Yes	7–12	No
Diltiazem	>80	50%	2–3 h (tablet) 6–11 h (SR) 10–14 h (CD) 4–6 h (XR) 7 h (ER)	Liver	Yes	4–6 5–7 5–8 5–10 4–10	Yes

FIGURE 7-36
Pharmacokinetics of the calcium antagonists: phenylalkamine derivatives, dihydropyridine derivatives, and benzothiazepine derivatives.

THE SIDE EFFECTS PROFILE OF CALCIUM ANTAGONISTS

Side effects	Mechanism
Dihydropyridine Headache, flushing, palpitation, edema	Potent peripheral vasodilator
Phenylalkylamine Constipation Bradycardia, AV block congestive heart failure	Negative inotropic, dromotropic, chronotropic effects
Benzodiazepine Bradyarrhythmia, AV block congestive heart failure	Negative inotropic, dromotropic, chronotropic effects

FIGURE 7-37
The side effect profile of calcium antagonists [10,13,18]. AV—atrioventricular.

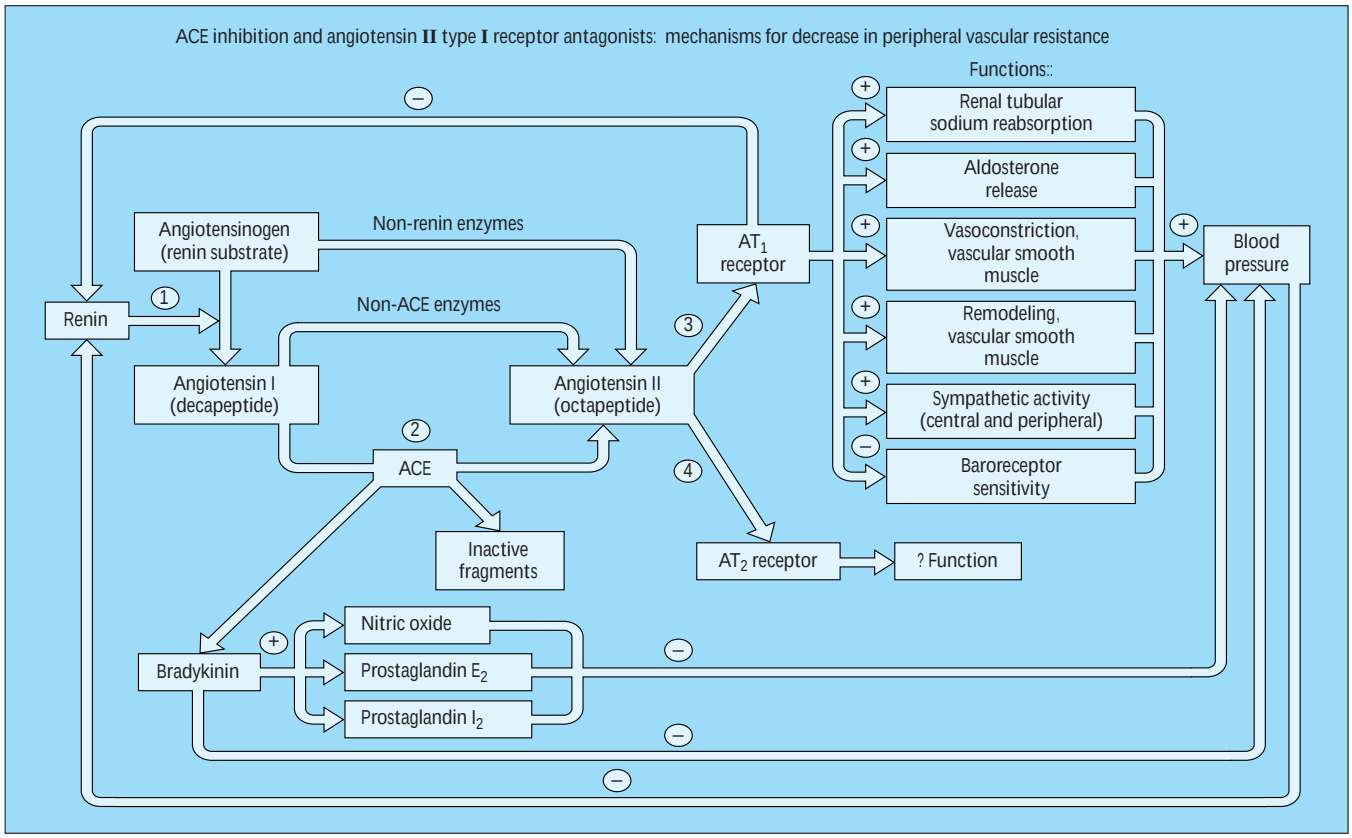

FIGURE 7-38

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II type I receptor antagonists. Angiotensin-converting enzyme inhibitors and angiotensin II type I receptor antagonists lower blood pressure by decreasing peripheral vascular resistance; there is usually little change in heart rate or cardiac output [6,9,15]. Mechanisms proposed for the observed decrease in peripheral resistance are shown [15]. Sites of pharmacologic blockade in the renin angiotensin system: 1) renin inhibitors, 2) ACE inhibitors, 3) angiotensin II type I receptor antagonists, 4) angiotensin II type II receptor antagonists.

A. DOSING SCHEDULES FOR SULFHYDRYL-CONTAINING ACE INHIBITOR

Generic (trade) name	First dose, mg	Usual dose, mg	Maximum dose, mg	Duration of action, h
Captopril (G) (Capoten)	12.5	12.5–50 bid/tid	150	6–12

B. DOSING SCHEDULES FOR CARBOXYL-CONTAINING ACE INHIBITORS

Generic (trade) name	First dose, mg	Usual dose, mg	Maximum dose, mg	Duration of action, h
Benazepril (Lotensin)	10	10–20 QD	40	24
Enalapril (Vasotec)	5	5–10 QD/bid	40	12–24
Lisinopril (Prinivil,Zestril)	10	20–40 QD	40	24
Moexipril (Univasc)	7.5	7.5–15 QD/bid	30	24
Quinapril (Accupril)	5–10	20–40 QD	40	24
Ramipril (Altace)	2.5	2.5–20 QD/bid	40	24
Trandolapril (Mavik)	1	2–4 QD	8	24

C. DOSING SCHEDULES FOR PHOSPHINIC ACID–CONTAINING ACE INHIBITOR

Generic (trade) name	First dose, mg	Usual dose, mg	Maximum dose, mg	Duration of action, h
Fosinopril (Monopril)	10	20–40 QD/bid	40	24

G—generic available.

FIGURE 7-39

A–C. Classification of and dosing schedule for angiotensin-converting enzyme (ACE) inhibitors. Angiotensin-converting enzyme inhibitors differ in prodrug status, ACE affinity, potency, molecular weight and conformation, and lipophilicity [6,9]. They are generally classified into one of three main chemical classes according to the ligand of the zinc ion of ACE: sulfhydryl, carboxyl, or phosphinic acid.

PHARMACOKINETICS OF ACE INHIBITORS

	Absorption, %	Prodrug	Peak concentration (active component), h	Route of elimination	Plasma half-life, h	Dose reduction (renal disease)
Captopril	60–75	No	1	Kidney	2	Yes
Benazepril	37	Yes	1–2	Kidney/liver	10–11	Yes
Enalapril	55–75	Yes	3–4	Kidney	11	Yes
Lisinopril	25	Yes	6–8	Kidney	12	Yes
Moexipril	> 20	Yes	1–2	Kidney	2–9	Yes
Quinapril	60	Yes	2	Kidney	25	Yes
Ramipril	50–60	Yes	2–4	Kidney/liver	13–17	Yes
Trandolapril	70	Yes	4–10	Kidney/liver	16–24	Yes
Fosinopril	36	Yes	3	Kidney/liver	12	No

FIGURE 7-40
Pharmacokinetics of angiotensin-converting enzyme (ACE) inhibitors: sulfhydryl-containing, carboxyl-containing, and phosphinic acid–containing.

THE SIDE EFFECTS PROFILE OF ACE INHIBITORS

Side effects	Mechanisms
Cough, angioedema Laryngeal edema	Potentiation of tissue kinins
Lightheadedness, syncope	Excessive hypotension in patients with high basal peripheral vascular resistance—high renin states, like volume contraction, impaired cardiac output
Hyperkalemia	Decreased aldosterone; potassium-containing salt substitutes and supplements should be avoided
Acute renal failure	Extreme hypotension with impaired efferent arteriolar autoregulation

FIGURE 7-41
The side effect profile of angiotensin-converting enzyme (ACE) inhibitors. ACE inhibitors are well tolerated; there are few side effects [6,9].

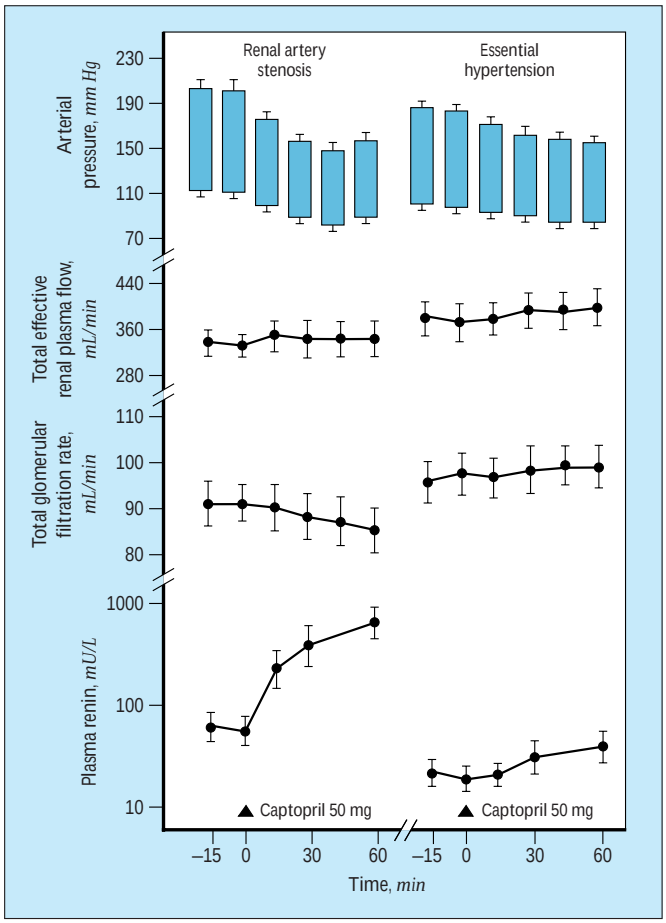

FIGURE 7-42

Angiotensin-converting enzyme (ACE) inhibition in acute renal failure. ACE inhibitors may produce functional renal insufficiency in patients with essential hypertension and hypertensive nephrosclerosis, in patients with severe bilateral renal artery stenosis, or in patients with stenosis of the renal artery of a solitary kidney. The postulated mechanism for this effect is diminished renal blood flow (decrease in systemic pressure, compromising flow through a fixed stenosis) in combination with diminished postglomerular capillary resistance (*ie*, decrease in angiotensin II–mediated efferent arteriolar tone). In unilateral renal artery stenosis, a drop in the critical perfusion and filtration pressures may result in a marked drop in single-kidney glomerular filtration rate (GFR); however, the contralateral kidney may show an increase in both effective renal plasma flow (ERPF) and GFR due to attenuation of the intrarenal effects of angiotensin II on vascular resistance and mesangial tone. Thus, total "net" GFR may be normal, giving the false appearance of stability [16]. Although ACE inhibition may invariably decrease the GFR of the stenotic kidney, it is unlikely to cause renal ischemia owing to preservation of ERPF; GFR usually returns to pretreatment values following cessation of therapy.

Shown is the effect of captopril (50 mg) on total clearances of ^{131}I-sodium iodohippurate (ERPF) and ^{126}I-thalamate (GFR) in 14 patients with unilateral renal artery stenosis and in 17 patients with essential hypertension. The effects after 60 minutes of captopril on systolic and diastolic intra-arterial pressure ($P < 0.001$) and of renin were significant. (*From* Wenting and coworkers [16]; with permission.)

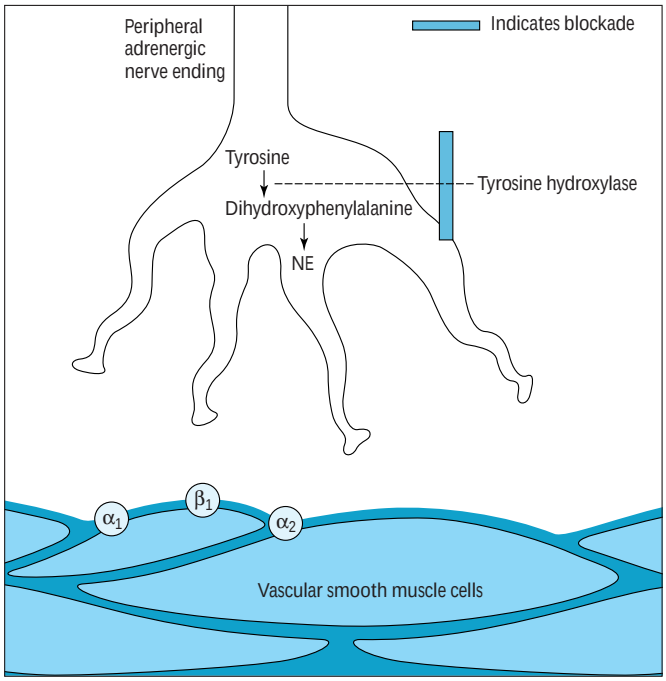

FIGURE 7-43

Tyrosine hydroxylase inhibitor. Metyrosine (α-methyl-para-tyrosine) is an inhibitor of tyrosine hydroxylase, the enzyme that catalyzes the conversion of tyrosine to dihydroxyphenylalanine [6,9]. Because this first step is rate limiting, blockade of tyrosine hydroxylase activity results in decreased endogenous levels of circulating catecholamines. In patients with excessive production of catecholamines, metyrosine reduces biosynthesis 36% to 79%; the net physiologic effect is a decrease in peripheral vascular resistance and increases in heart rate and cardiac output resulting from the vasodilation. The degree of vasodilation is dependent on the degree of blockade of adrenergic vascular tone. NE—norepinephrine.

TYROSINE HYDROXYLASE INHIBITOR

Generic (trade) name	First dose, mg	Usual daily dose, mg	Maximum dose, mg	Duration of action, h
Metyrosine (Demser)	250	25 qid	1000 qid	3–4

FIGURE 7-44

Tyrosine hydroxylase inhibitor. Metyrosine is the only drug in its class. The initial recommended dose is 1 g/d, given in divided doses. This may be increased by 250 to 500 mg daily to a maximum of 4 g/d. The usual effective dosage is 2 to 3 g/d. The maximum biochemical effect occurs within 2 to 3 days. In hypertensive patients in whom there is a response, blood pressure decreases progressively during the first days of therapy. In patients who are usually normotensive, the dose should be titrated to the amount that will reduce circulating or urinary catecholamines by 50% or more. Following discontinuation of therapy, the clinical and biochemical effects may persist 2 to 4 days. Metyrosine is variably absorbed from the gastrointestinal tract; bioavailability ranges from 45% to 90%. Peak plasma concentrations are reached in 1 to 3 hours. The plasma half-life is 3 to 4 hours. Metyrosine is not metabolized; the unchanged drug is recovered in the urine. Drug dosage should be reduced in patients with renal insufficiency. Metyrosine is exclusively used in the management of preoperative or inoperative pheochromocytoma [6,9].

THE SIDE EFFECTS PROFILE OF METYROSINE

Side effects	Mechanisms
CNS symptoms	Depletion of CNS dopamine
Sedation	
Extrapyramidal signs	
Drooling	
Speech difficulty	
Tremor	
Trismus	
Parkinsonian syndrome	
Psychic dysfunction	
Anxiety	
Depression	
Disorientation	
Confusion	
Crystalluria, uroliathiasis	Poor urine solubility
Diarrhea	Direct irritant to bowel mucosa
Insomnia (temporary)	Following drug withdrawal

FIGURE 7-45

The side effect profile of metyrosine. The adverse reactions observed with metyrosine are primarily related to the central nervous system and are typically dose dependent [6,9]. Metyrosine crystalluria (needles or rods), which is due to the poor solubility of the drug in the urine, has been observed in patients receiving doses greater than 4 g/d. To minimize this risk, patients should be well hydrated. CNS—central nervous system.

ANGIOTENSIN II RECEPTOR ANTAGONISTS

Generic (trade) name	First dose, mg	Usual dose, mg	Maximum dose, mg	Duration of action, h
Losartan (Cozaar)	50	50–100 QD/bid	100	12–24
Valsartan (Diovan)	80	80–160 QD	320	24
Irbesaftan (Avapro)	150	150–300 QD	300	24

FIGURE 7-46

Angiotensin II receptor antagonists. These drugs antagonize angiotensin II–induced biologic actions, including proximal sodium reabsorption, aldosterone release, smooth muscle vasoconstriction, vascular remodeling, and baroreceptor sensitivity. Antihypertensive efficacy appears dependent on an activated renin-angiotensin system; bilateral nephrectomy and volume expansion abolish their activity. Losartan is a nonpeptide, specific angiotensin II receptor antagonist acting on the antagonist AT_1 subtype receptor. Peak response occurs within 6 hours of dosing. It is readily absorbed; peak plasma concentrations are achieved within 1 hour. It has a relatively short terminal half-life of 1.5 to 2.5 hours. Oral bioavailability is approximately 33%. Losartan undergoes extensive first-pass hepatic metabolism to the predominant circulatory form of the drug Exp-3174. This metabolite is 15 to 30 times more potent than losartan with a longer half-life (between 4 and 9 hours). The metabolite is cleared equally by the liver and the kidney; there may be enhanced hepatic clearance in renal insufficiency [15]. Dose reduction is not required in patients with renal insufficiency.

Valsartan is a nonpeptide, specific angiotensin II antagonist acting on the AT_1 subtype receptor. Peak response occurs within 6 hours of dosing. Peak plasma concentrations are reached 2 to 4 hours after dosing. The average elimination half-life is about 6 hours. Oral bioavailability is approximately 25%. Dose reduction is not required in patients with renal insufficiency [15].

Irebsartan is a nonpeptide, specific angiotensin II antagonist acting on the AT_1 subtype receptor. Peak response occurs in 4 to 8 hours. There is no active metabolite. Dose reduction is not required in patients with renal insufficiency [15].

THE SIDE EFFECTS PROFILE OF ANGIOTENSIN II RECEPTOR ANTAGONISTS

Side effects	Mechanisms
Hyperkalemia	Blockade of angiotensin II Reduced aldosterone secretion
Acute renal dysfunction	Hypotension with impaired efferent anteriolar autoregulation

FIGURE 7-47

The side effect profile of angiotensin II receptor antagonists. Angiotensin II receptor antagonists are well tolerated. In contrast to the angiotensin-converting enzyme (ACE) inhibitors, cough and angioedema are rarely (if at all) associated with this class of antihypertensive drug. Similar to ACE inhibitors, however, hyperkalemia and acute renal failure may occur in patients at risk [15].

Prevention and Treatment of High Blood Pressure

JNC VI CLASSIFICATION OF HYPERTENSION

Category*	Systolic (mm Hg)		Diastolic (mm Hg)
Optimal†	<120	and	<80
Normal	<130	and	<85
High normal	130–139	or	85–89
Hypertension‡			
Stage 1	140/159	or	90/99
Stage 2	160/179	or	100/109
Stage 3	≥-180	or	≥110

*Not taking anithypertensive drugs and not acutely ill. When systolic and diastolic blood pressures fall into different categories, the higher category should be selected to classify the individual's blood pressure status. For example, 160/92 mm Hg should be classified as stage 2 hypertension, and 174/120 mm Hg should be classified as stage 3 hypertension. Isolated systolic hypertension is defined as systolic blood pressure of 140 mm Hg or greater and diastolic blood pressure of less than below 90 mm Hg and staged appropriately (*eg*, 170/82 mm Hg is defined as stage 2 isolated hypertension). In addition to classifying stages of hypertension on the basis of average blood pressure levels, clinicians should specify presence of target organ disease and additional risk factors. This specifically is important for risk classification.

†Optimal blood pressure with respect to cardiovascular risk is below 120/80 mm Hg. Unusually low readings should be evaluated for clinical significance.

‡Based on the average of two or more readings taken at each of two or more visits after an initial screening. JNC—Joint National Committee.

FIGURE 7-48

Prevention and treatment of high blood pressure. The aim of antihypertensive therapy is risk reduction. Since the relationship between blood pressure and cardiovascular risk is continuous, the goal of treatment might be the maximum tolerated reduction in blood pressure. There is controversy concerning what constitutes hypertension and how far systolic or diastolic blood pressure should be lowered, however. The Sixth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) [17] provides a new classification of hypertension and recommends that risk stratification be used to determine if lifestyle modification or drug therapy with adjunctive lifestyle modification be initiated according to the patient's blood pressure classification (*see* Fig. 7-50). Major risk factors include smoking, dyslipidemia, diabetes mellitus, an age of 60 or older, male sex or postmenopausal state for women, and a family history of cardiovascular disease in women younger than 65 and in men younger than 55. Target organ damage includes heart disease (left ventricular hypertrophy, angina pectoris, prior myocardial infarction, heart failure), stroke or transient ischemic attack, and nephropathy. Prevention and management of hypertension-related morbidity and mortality may best be accomplished by achieving a systolic blood pressure below 140 mm Hg and a diastolic blood pressure below 90 mm Hg; lower if tolerable. Recently, more aggressive blood pressure control has been advocated in patients with renal disease and hypertension, particularly in those patients with a urinary protein excretion of greater than 1 g/d. Blood pressure control in the range of 125/80 mm Hg (mean arterial pressure of 108 mm Hg) has been shown to slow the progression of renal disease [18,19]. This targeted blood pressure control may therefore be advisable in the majority of patients with hypertension. Regardless, each patient should be treated according to their cerebrovascular, cardiovascular, or renal risks; their specific pathophysiology or target organ damage; and their concurrent disease states. A uniform blood pressure goal (target) probably does not exist for all hypertensive patients, and lower may not always be better.

JNC VI DECISION ANALYSIS FOR TREATMENT

Blood pressure stages (mm Hg)	Risk group A (no risk factors, no TOD/CCD)*	Risk group B (at least 1 risk factor, not including diabetes; no TOD/ CCD)	Risk Group C (TOD/CCD and/or diabetes, with or without other risk factors)†
High normal (130–139/85–89)	Lifestyle modification	Lifestyle modification	Drug therapy‡
Stage 1 (140–159/90–99)	Lifestyle modification (up to 12 months)	Lifestyle modification (up to 6 months)	Drug therapy
Stages 2 and 3 (>160/≥100)	Drug therapy	Drug therapy	Drug therapy

Lifestyle modification should be adjunctive therapy for all patients recommended for pharmacologic therapy.
*TOD/CCD indicates target organ disease/clinical cardiovascular disease.
†For patients with multiple risk factors, clinicians should consider drugs as initial therapy plus lifestyle modifications.
‡For those with heart failure, renal insufficiency, or diabetes.

FIGURE 7-49
Decision analysis for treatment based on the Sixth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) [17].

CRITERIA FOR INITIAL DRUG THERAPY

Reduce peripheral vascular resistance
No sodium retention
No compromise in regional blood flow
No stimulation of the renin-angiotensin-aldosterone system
Favorable profile with concomitant diseases
Once a day dosing
Favorable adverse effect profile
Cost effective (low direct and indirect cost)

FIGURE 7-50
Selection of initial drug therapy. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) recommends that either a diuretic or a β-blocker be chosen as initial drug therapy, based on numerous randomized controlled trials that show reduction in morbidity and mortality with these agents [17]. Not all authorities agree with this recommendation.

In selecting an initial drug therapy to treat a hypertensive patient, several criteria should be met [6,9]. The drug should decrease peripheral resistance, the pathophysiologic hallmark of all hypertensive diseases. It should not produce sodium retention with attendant pseudotolerance. The drug should neither stimulate nor suppress the heart, nor should it compromise regional blood flow to target organs such as the heart, brain, or the kidney. It should not stimulate the renin-angiotensin-aldosterone axis. Drug selection should consider concomitant diseases such as arteriosclerotic cardiovascular and peripheral vascular disease, chronic obstructive pulmonary disease, diabetes mellitus, hypertensive cardiovascular disease, congestive heart failure, and hyperlipidemia. Drug dosing should be infrequent. The drug's side effect profile, including its effect on physical state, emotional well-being, sexual and social function, and cognitive activity, should be favorable. Drug costs, both direct and indirect, should be reasonable. It is readily apparent that no current class of antihypertensive drug fulfills all these criteria.

CANDIDATES FOR INITIAL DRUG THERAPY OF MILD TO MODERATE HYPERTENSIVE DISEASE

	ACE inhibitors	α_1-adrenergic antagonists	Angiotensin II type I receptor antagonists	β_1-adrenergic antagonists	Calcium antagonists	Thiazide-type diuretics
Peripheral vascular resistance	Decrease	Decrease	Decrease	Decrease	Decrease	Decrease
Sodium homeostasis						
Urinary sodium excretion	Increase/no change	May decrease	Increase/no change	No change	Increase/no change	Increase
Extracellular fluid volume	No change	May increase	No change	No change	No change	Decrease
Pseudotolerance	No	No	No	No	No	No
Target organ function						
Heart rate, cardiac output	No change	May increase	No change	Decrease	Class specific	No change
Cerebral function	Preserve	Preserve	Preserve	Preserve	Preserve	Preserve
Renal function (GFR)	No change/increase	No change	No change	No change/decrease	No change/increase	No change
Renin-angiotensin-aldosterone						
Plasma renin activity	Increase	No change	Increase	Decrease	No change	Increase
Plasma angiotensin II	Decrease	No change	Increase	Decrease	No change	Increase
Plasma aldosterone	Decrease/no change	No change	Decrease/no change	Decrease/no change	No change	Increase
Concurrent disease efficacy						
Coronary disease	No effect	No effect	No effect	Benefit	Benefit	No effect
Peripheral vascular disease	No effect	No effect	No effect	May aggravate	May benefit	No effect
Obstructive airway disease	No effect	No effect	No effect	May aggravate	No effect	No effect
Diabetes mellitus	May benefit	No effect	May benefit	May aggravate	No effect	May aggravate
Dyslipidemia	No effect	Benefit	No effect	May aggravate	No effect	Aggravate
Systolic dysfunction	Benefit	No effect	Benefit	May aggravate	No effect	Benefit

FIGURE 7-51

Options for monotherapy. Given the drugs that we have and their pharmacologic profiles, what are the best classes for initial drug therapy? Alphabetically, they include 1) angiotensin-converting enzyme (ACE) inhibitors, 2) α_1-adrenergic antagonists, 3) angiotensin II type I receptor antagonists, 4) β_1-adrenergic antagonists, 5) calcium antagonists, and 6) thiazide-type diuretics [6,9,15]. All these drugs, given as monotherapy, are effective in lowering blood pressure in 50% to 60% of patients with mild to moderate hypertension. β_1-adrenergic antagonists, ACE inhibitors, and angiotensin II receptor antagonists are less efficacious in blacks than in whites.

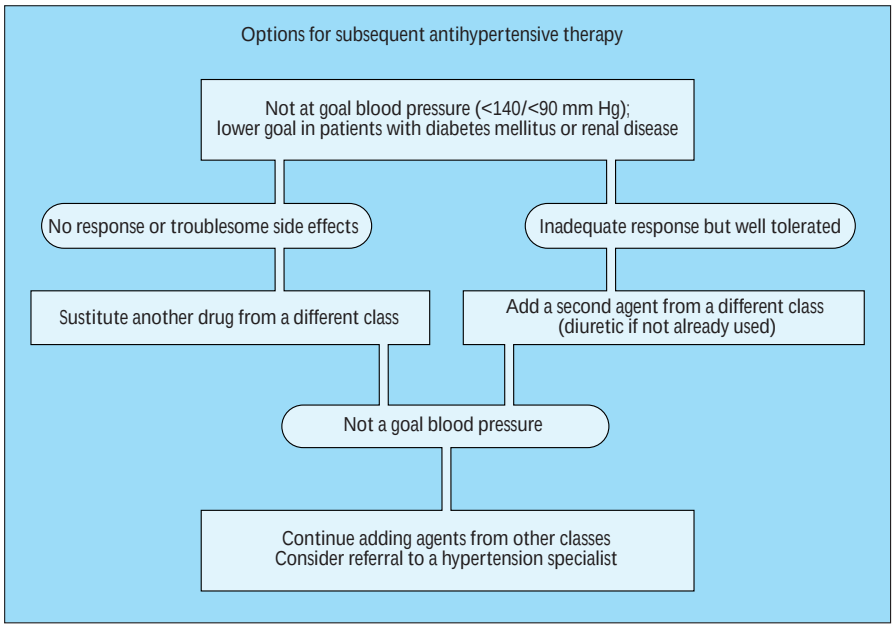

FIGURE 7-52

Options for subsequent antihypertensive therapy. The majority of patients with mild to moderate hypertension can be controlled with one drug. If, after a 1- to 3-month interval, the response to the initial choice of therapy is inadequate, however, three options for subsequent antihypertensive drug therapy may be considered: 1) increase the dose of the initial drug, 2) discontinue the initial drug and substitute a drug from another class, or 3) add a drug from another class (combination therapy). Recommendations from the Sixth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) are provided [17].

COMBINATION THERAPIES

Mild to moderate (stage 1 or 2) hypertension

Addition of low-dose thiazide-type diuretic to:
- ACE inhibitor
- β_1-adrenergic antagonist
- α_1-adrenergic antagonist
- Angiotensin III receptor antagonist
- Severe (Stage 3) hypertension

Classic triple drug therapy
- Diuretic
- β_1-adrenergic antagonist
- Direct-acting vasodilator
- ACE inhibitor plus calcium antagonist
- β_1-adrenergic antagonist plus α_1-adrenergic antagonist
- β_1-adrenergic antagonist plus dihydropyridine calcium antagonist

FIGURE 7-53

Combination therapies. If a second drug is required, the addition of a low-dose thiazide-type diuretic to a nondiuretic drug will usually enhance the effectiveness of the first drug [6,9,17]. Newly developed formulations, using combinations of low doses of two agents from different classes, are available and effective and may minimize the likelihood of a dose-dependent adverse effect. The fixed doses used in these formulations were chosen to control mild to moderate (JNC VI stage 1 or 2) hypertension. More severe (JNC VI stage 3) cases of hypertension that are unresponsive to this therapeutic strategy may respond either to a variety of combination therapies given together as separate formulations or to classic triple-drug therapy (*ie*, diuretic, β-adrenergic antagonist, and direct-acting vasodilator) [6,9]. ACE—angiotensin-converting enzyme; JNC—Joint National Committee.

JNC VI LIFE STYLE MODIFICATIONS

Lose weight if overweight

Limit alcohol intake to no more than 1 oz (30 mL) ethanol (*eg*, 24 oz [720 mL] beer, 10 oz [300 mL] wine, or 2 oz [60 mL] 100-proof whiskey) per day or 0.5 oz (15 mL) ethanol per day for women and lighter weight people

Increase aerobic physical activity (30 to 45 minutes most days of the week)

Reduce sodium intake to no more than 100 mmol/d (2.4 g sodium or 6 g sodium chloride)

Maintain adequate intake of dietary potassium (approximately 90 mmol/d)

Maintain adequate intake of dietary calcium and magnesium for general health

Stop smoking and reduce intake of dietary saturated fat and cholesterol for overall cardiovascular health

FIGURE 7-54

Follow-up in antihypertensive therapy. During follow-up visits, pharmacologic therapy should be reconfirmed or readjusted. As a rule, antihypertensive therapy should be maintained indefinitely. Cessation of therapy in patients who were correctly diagnosed as hypertensive is usually (but not always) followed by a return of blood pressure to pretreatment levels. After blood pressure has been controlled for 1 year and at least four visits, however, attempts should be made to reduce antihypertensive drug therapy "in a deliberate, slow, and progressive manner;" such "step-down therapy" may be successful in patients following lifestyle modification [17]. Patients for whom drug therapy has been reduced or discontinued should have regular follow-up, since blood pressure may increase again to hypertensive levels. JNC—Joint National Committee.

CAUSES OF RESISTANT HYPERTENSION

Patient's failure to adhere to drug therapy

Physician's failure to diagnose a secondary cause of hypertension
- Renal parenchymal hypertension
- Renovascular hypertension
- Mineralocorticoid excess state (*eg*, primary aldosteronism)
- Pheochromocytoma
- Drug-induced hypertension (*eg*, sympathomimetic, cyclosporine)
- Illicit substances (*eg*, cocaine, anabolic steroids)
- Glucocortoid excess state (*eg*, Cushing's syndrome)
- Coarctation of the aorta
- Hormonal disturbances (*eg*, thyroid, parathyroid, growth hormone, serotonin)
- Neurologic syndromes (*eg*, Guillain-Barré syndrome, porphyria, sleep apnea)

Physician's failure to recognize an adverse drug–drug interaction
- See Physician's Desk Reference

Physician's failure to recognize the development of secondary drug resistance
- Sodium retention with pseudotolerance, secondary to diuretic resistance or excess sodium intake
- Increased heart rate, cardiac output secondary to drug-induced reflex tachycardia
- Increased peripheral vascular resistance secondary to drug-induced stimulation of the renin-angiotensin system

FIGURE 7-55

Resistant hypertension. Causes of failure to achieve or sustain control of blood pressure with drug therapy are listed [6,9].

DIURETIC RESISTANCE

Problem	Mechanism	Solution
Limits active transport of diuretics into proximal tubular fluid, reducing inhibitory effect at a more distal intraluminal membrane site	Reduced renal blood flow	Use of large doses of a diuretic and appropriate dosing interval to achieve a therapeutic tubular drug concentration
Limits absolute amount of sodium filtered	Reduced glomerular filtration rate	Use loop diuretics with steep dose response curve and/or block multiple sites of sodium reabsorption: loop diuretic with thiazide-like diuretic
Sodium recaptured at late distal tubule and collecting duct	Secondary hyperaldosteronism	Addition of a potassium-sparing diuretic to above, to maintain urine sodium/potassium ratio > 1

FIGURE 7-56

Diuretic resistance. Diuretic resistance may result from patient noncompliance, impaired bioavailability in an edematous syndrome, impaired diuretic secretion by the proximal tubule, protein binding in the tubule lumen (*eg*, nephrotic syndrome), reduced glomerular filtration rate, or enhanced sodium chloride reabsorption [7,8]. Resultant fluid retention will attenuate the effectiveness of most antihypertensive drugs. Renal mechanisms, problems, and solutions are provided in this table [6,8,9].

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