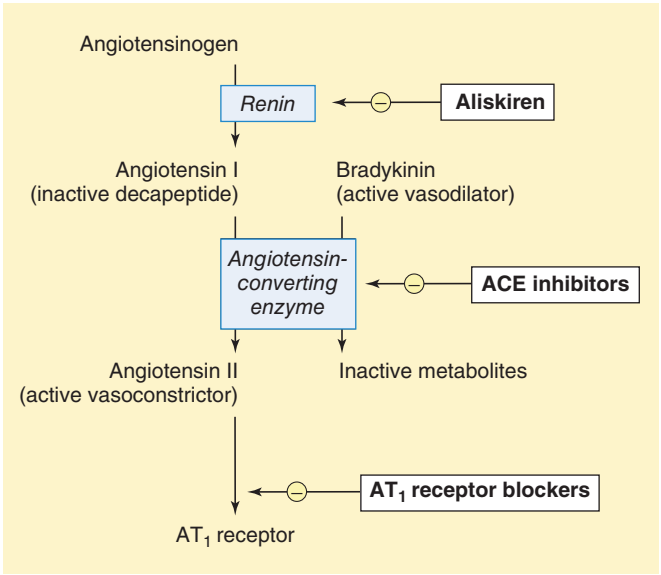


QUESTIONS

1. A 32-year-old woman with hypertension wishes to become pregnant. Her physician informs her that she will have to switch to another antihypertensive drug. Which of the following drugs is absolutely contraindicated in pregnancy?
(A) Atenolol
(B) Losartan
(C) Methyldopa
(D) Nifedipine
(E) Propranolol

2. A patient is admitted to the emergency department with severe tachycardia after a drug overdose. His family reports that he has been depressed about his hypertension. Which one of the following drugs increases the heart rate in a dose-dependent manner?
(A) Captopril
(B) Hydrochlorothiazide
(C) Losartan
(D) Minoxidil
(E) Verapamil

3. Which one of the following is characteristic of nifedipine treatment in patients with essential hypertension?
(A) Competitively blocks angiotensin II at its receptor
(B) Decreases calcium efflux from skeletal muscle
(C) Decreases renin concentration in the blood
(D) Decreases calcium influx into smooth muscle
(E) Increases calcium excretion in the urine

4. A 73-year-old man with a history of a recent change in his treatment for moderately severe hypertension is brought to the emergency department because of a fall at home. Which of the following drug groups is most likely to cause postural hypotension and thus an increased risk of falls?
(A) ACE inhibitors
(B) $Alpha_1$-selective receptor blockers
(C) Arteriolar dilators
(D) $Beta_1$-selective receptor blockers
(E) Calcium channel blockers

5. A significant number of patients started on ACE inhibitor therapy for hypertension are intolerant and must be switched to a different class of drug. What is the most common manifestation of this intolerance?
(A) Angioedema
(B) Glaucoma
(C) Headache
(D) Incessant cough
(E) Ventricular arrhythmias

6. Which one of the following is a significant unwanted effect of the drug named?
(A) Constipation with verapamil
(B) Heart failure with hydralazine
(C) Hemolytic anemia with atenolol
(D) Hypokalemia with aliskiren
(E) Lupus-like syndrome with hydrochlorothiazide

7. Comparison of prazosin with atenolol shows that
(A) Both decrease heart rate
(B) Both increase cardiac output
(C) Both increase renin secretion
(D) Both increase sympathetic outflow from the CNS
(E) Both produce orthostatic hypotension

8. A patient with hypertension and angina is referred for treatment. Metoprolol and verapamil are among the drugs considered. Both metoprolol and verapamil are associated with which one of the following?
(A) Diarrhea
(B) Hypoglycemia
(C) Increased PR interval
(D) Tachycardia
(E) Thyrotoxicosis

9. A 45-year-old man is brought to the emergency department with mental obtundation. He is found to have a blood pressure of 220/160 and retinal hemorrhages. Which one of the following is used in severe hypertensive emergencies, is short-acting, acts on a G-protein-coupled receptor, and must be given by intravenous infusion?
(A) Aliskiren
(B) Captopril
(C) Fenoldopam
(D) Hydralazine
(E) Losartan
(F) Metoprolol
(G) Nitroprusside
(H) Prazosin
(I) Propranolol

10. Which of the following is very short acting and acts by releasing nitric oxide?
(A) Atenolol
(B) Captopril
(C) Diltiazem
(D) Fenoldopam
(E) Hydrochlorothiazide
(F) Losartan
(G) Minoxidil
(H) Nitroprusside
(I) Prazosin

ANSWERS

1. Methyldopa is often recommended in pregnant patients because it has a good safety record. Calcium channel blockers (choice **D**) and β blockers (choices **A** and **E**) are not contraindicated. In contrast, ACE inhibitors and ARBs (choice **B**) have been shown to be teratogenic, causing severe renal abnormalities in the fetus. The answer is **B**.

2. ACE inhibitors (choice **A**), ARBs (choice **C**), and diuretics (choice **B**) do not significantly increase heart rate. Although dihydropyridine calcium channel blockers do not usually reduce rate markedly (and may increase it), verapamil (choice **E**) and diltiazem do inhibit the sinoatrial node and predictably decrease rate. Other direct vasodilators (choice **D**) regularly *increase* heart rate, and minoxidil, a very efficacious vasodilator, causes severe tachycardia that must be controlled with β blockers. The answer is **D.**

3. Nifedipine is a prototype L-type calcium channel blocker and lowers blood pressure by reducing calcium influx into vascular smooth muscle. It has no effect on angiotensin-converting enzyme. Calcium efflux from skeletal muscle cells does not involve the L-type Ca^{2+} channel. The plasma renin level may *increase* as a result of the compensatory response to reduced blood pressure. Calcium channel blockers have negligible effects on urine calcium. The answer is **D.**

4. Drug-induced postural (orthostatic) hypotension is usually due to venous pooling or excessive diuresis and inadequate blood volume. Venous pooling is normally prevented by α-receptor activation in vascular smooth muscle; thus, orthostatic hypotension may be caused or exacerbated by α_1 blockers, eg, prazosin. The answer is **B.**

5. Chronic, intolerable cough is an important adverse effect of captopril and other ACE inhibitors. It may be associated with increased bradykinin levels because ARBs are not as frequently associated with cough. The ACE inhibitors are very commonly used in hypertensive diabetic patients because of their proven benefits in *reducing* diabetic renal damage. The ACE inhibitors are not associated with glaucoma; angioedema is not as common as cough; and headache and arrhythmias are rare. The answer is **D.**

6. Hydralazine (choice **B**) is sometimes *used* in heart failure. Beta blockers (choice **C**) are not associated with hematologic abnormalities, but methyldopa is. The thiazide diuretics (choice **E**) often cause mild hyperglycemia, hyperuricemia, and hyperlipidemia but not lupus; hydralazine is associated with a lupus-like syndrome. Aliskiren (choice **D**) and other inhibitors of the renin-angiotensin-aldosterone system may cause *hyper*kalemia, not hypokalemia. Verapamil (choice **A**) often causes constipation, probably by blocking L-type calcium channels in the colon. The answer is **A.**

7. Atenolol, but not prazosin, may decrease heart rate (choice **A**). Prazosin—but not atenolol—may increase cardiac output, a compensatory effect (choice **B**). Prazosin may increase renin output (a compensatory response), but β blockers inhibit its release by the kidney (choice **C**). By reducing blood pressure, both may increase central sympathetic outflow (a compensatory response). Beta blockers do not cause orthostatic hypotension. The answer is **D.**

8. Neither β blockers nor calcium channel blockers cause diarrhea. Hypoglycemia is not a common effect of any of the antihypertensive drugs. Thyroid disorders are not associated with either drug group. However, calcium blockers, especially verapamil and diltiazem, and β blockers are associated with depression of calcium-dependent processes in the heart, for example, contractility, heart rate, and atrioventricular conduction. Therefore, *bradycardia* and increased PR interval may be expected. The dihydropyridines do not often cause cardiac depression, probably because they evoke increased sympathetic outflow as a result of their dominant vascular effects. The answer is **C.**

9. Fenoldopam, nitroprusside, and propranolol are the drugs in the list that have been used in hypertensive emergencies. Fenoldopam and nitroprusside are used by infusion only, but nitroprusside releases nitric oxide, which acts on intracellular guanylyl cyclase. The answer is **C.**

10. The two agents in this list that act via a nitric oxide mechanism are hydralazine and nitroprusside (see Table 11–2). However, hydralazine has a duration of action of hours, whereas nitroprusside acts for seconds to minutes and must be given by intravenous infusion. The answer is **H.**

SKILL KEEPER 1 ANSWER: DEVELOPMENT OF NEW ANTIHYPERTENSIVE DRUGS (SEE CHAPTER 1)

The FDA requires a broad range of animal data, provided by the developer in an investigational new drug (IND) application, before clinical trials can be started. These data must show that the drug has the expected effects on blood pressure in animals and has low and well-defined toxicity in at least two species. A new drug application (NDA) must be submitted and approved before marketing can begin. This application usually requires data on pharmacokinetics in normal volunteers (phase 1), efficacy and safety in a small group of closely observed patients (phase 2), and efficacy and safety in a much larger group of patients under conditions of actual use (phase 3). For drugs intended for highly lethal diseases (cancer, the more dangerous infectious diseases, etc), the FDA may allow modified and accelerated or combined-phase "adaptive" clinical trials.

SKILL KEEPER 2 ANSWER: COMPENSATORY RESPONSES TO ANTIHYPERTENSIVE DRUGS (SEE CHAPTER 6)

The compensatory responses to hydralazine are tachycardia and salt and water retention. These responses are generated by the baroreceptor and renin-angiotensin-aldosterone mechanisms summarized in Figures 6–4 and 11–1. The motor limb of the sympathetic response consists of outflow from the vasomotor center to the heart and vessels, as shown in Figure 11–2. You should be able to reproduce these diagrams from memory.

CHECKLIST

When you complete this chapter, you should be able to:

- ❑ List 4 major groups of antihypertensive drugs, and give examples of drugs in each group. (Renin inhibitors are not considered an independent major group; can you name the one available drug that acts by this mechanism?)
- ❑ Describe the compensatory responses, if any, to each of the 4 major types of antihypertensive drugs.
- ❑ List the major sites of action of sympathoplegic drugs in research or clinical use, and give examples of drugs that act at each site.
- ❑ List the 4 mechanisms of action of vasodilator drugs.
- ❑ List the major antihypertensive vasodilator drugs and describe their effects.
- ❑ Describe the differences between the 2 types of angiotensin antagonists.
- ❑ List the major toxicities of the prototype antihypertensive agents.

QUESTIONS

Questions 1–4. A 57-year-old woman presents to her primary care physician with a complaint of severe chest pain when she walks uphill in cold weather. The pain disappears when she rests. She has a 40-pack-year history of smoking but her plasma lipids are within the normal range. After evaluation and discussion of treatment options, a decision is made to treat her with nitroglycerin.

1. Which of the following is a common direct or reflex effect of nitroglycerin?
(A) Decreased heart rate
(B) Decreased venous capacitance
(C) Increased afterload
(D) Increased cardiac force
(E) Increased diastolic myocardial fiber tension

2. In advising the patient about the adverse effects she may notice, you point out that nitroglycerin in moderate doses often produces certain symptoms. Which of the following effects might occur due to the mechanism listed?
(A) Constipation due to reduced colonic activity
(B) Dizziness due to reduced cardiac force of contraction
(C) Diuresis due to sympathetic discharge
(D) Headache due to meningeal vasodilation
(E) Hypertension due to reflex tachycardia

3. One year later, the patient returns complaining that her nitroglycerin works well when she takes it for an acute attack but that she is now having more frequent attacks and would like something to *prevent* them. Useful drugs for the prophylaxis of angina of effort include
(A) Amyl nitrite
(B) Esmolol
(C) Sublingual isosorbide dinitrate
(D) Sublingual nitroglycerin
(E) Verapamil

4. If a β blocker were to be used for prophylaxis in this patient, what is the most probable mechanism of action in angina?
(A) Block of exercise-induced tachycardia
(B) Decreased end-diastolic ventricular volume
(C) Increased double product
(D) Increased cardiac force
(E) Decreased ventricular ejection time

5. A new 60-year-old patient presents to the medical clinic with hypertension and angina. He is 1.8 meters tall with a waist measurement of 1.1 m. Weight is 97 kg, blood pressure is 150/95, and pulse is 85. In considering adverse effects of possible drugs for these conditions, you note that an adverse effect that nitroglycerin and prazosin have in common is
(A) Bradycardia
(B) Impaired sexual function
(C) Lupus erythematosus syndrome
(D) Orthostatic hypotension
(E) Weight gain

6. A 25-year-old man is admitted to the emergency department with a brownish cyanotic appearance, marked shortness of breath, and hypotension. He has needle marks in both arms. Which of the following is most likely to cause methemoglobinemia?
(A) Amyl nitrite
(B) Isosorbide dinitrate
(C) Isosorbide mononitrate
(D) Nitroglycerin
(E) Sodium cyanide

7. Another patient is admitted to the emergency department after a drug overdose. He is noted to have hypotension and severe bradycardia. He has been receiving therapy for hypertension and angina. Which of the following drugs in high doses causes bradycardia?
(A) Amlodipine
(B) Isosorbide dinitrate
(C) Nitroglycerin
(D) Prazosin
(E) Verapamil

8. A 45-year-old woman with hyperlipidemia and frequent migraine headaches develops angina of effort. Which of the following is relatively contraindicated because of her migraines?
(A) Amlodipine
(B) Diltiazem
(C) Metoprolol
(D) Nitroglycerin
(E) Verapamil

9. When nitrates are used in combination with other drugs for the treatment of angina, which one of the following combinations results in additive effects on the variable specified?
(A) Beta blockers and nitrates on end-diastolic cardiac size
(B) Beta blockers and nitrates on heart rate
(C) Beta blockers and nitrates on venous tone
(D) Calcium channel blockers and β blockers on cardiac force
(E) Calcium channel blockers and nitrates on heart rate

10. Certain drugs can cause severe hypotension when combined with nitrates. Which of the following interacts with nitroglycerin by inhibiting the metabolism of cGMP?
(A) Atenolol
(B) Hydralazine
(C) Isosorbide mononitrate
(D) Nifedipine
(E) Ranolazine
(F) Sildenafil
(G) Terbutaline

ANSWERS

1. Nitroglycerin *increases* heart rate and venous capacitance and *decreases* afterload and diastolic fiber tension. It increases cardiac contractile force because the decrease in blood pressure evokes a compensatory increase in sympathetic discharge. The answer is **D.**

2. The nitrates relax many types of smooth muscle, but the effect on motility in the colon is insignificant. Nitroglycerin causes hypotension as a result of arterial and venous dilation. Dilation of arteries in the meninges has no effect on central nervous system function but does cause headache. The answer is **D.**

3. The calcium channel blockers and the β blockers are generally effective in reducing the number of attacks of angina of effort, and most have durations of 4–8 h. Oral and transdermal nitrates have similar or longer durations. Amyl nitrite and the sublingual nitrates have short durations of action (a few minutes to 30 min). Esmolol (an intravenous β blocker) must be given intravenously and also has a very short duration of action. Thus, nitrites, sublingual nitrates, and esmolol are of no value in prophylaxis. The answer is **E.**

4. Propranolol blocks tachycardia but has none of the other effects listed. Only revascularization increases double product; drugs that decrease cardiac work increase exercise time by decreasing double product. The answer is **A.**

5. Both drugs cause venodilation and reduce venous return sufficiently to cause some degree of postural hypotension. Bradycardia, lupus, and urinary retention occur with neither of them, but prazosin has been used to relieve urinary retention in men with prostatic hyperplasia. While this patient has a high body mass index of 29.9, weight gain is not a risk with either drug. The answer is **D.**

6. Read carefully! Nitrites, not nitrates, cause methemoglobinemia in adults. Methemoglobinemia is deliberately induced in one of the treatments of cyanide poisoning. Amyl nitrite and isobutyl nitrite, obtained as street drugs, have been heavily used as sex-enhancers. The answer is **A.**

7. Isosorbide dinitrate (like all the nitrates) and prazosin can cause reflex tachycardia. Amlodipine, a dihydropyridine calcium channel blocker, causes much more vasodilation than cardiac depression and may also cause reflex tachycardia. Verapamil typically slows heart rate and high doses may cause severe bradycardia. The answer is **E.**

8. Acute migraine headache is associated with vasodilation of meningeal arteries. Of the drugs listed, only nitroglycerin is commonly associated with headache. In fact, calcium channel blockers and β blockers have been used with some success as *prophylaxis* for migraine. The answer is **D.**

9. The effects of β blockers and nitrates on heart size, force, venous tone, and heart rate are *opposite*. The effects of β blockers and calcium channel blockers on heart size, force, and rate are the same. The answer is **D.**

10. Sildenafil inhibits phosphodiesterase 5, an enzyme that inactivates cGMP. The nitrates (via nitric oxide) increase the synthesis of cGMP. This combination is synergistic. The answer is **F.**

SKILL KEEPER ANSWER: NIFEDIPINE CARDIOTOXICITY (SEE CHAPTER 6)

Several studies have suggested that patients receiving prompt-release nifedipine may have an increased risk of myocardial infarction. Slow-release formulations do not seem to impose this risk. These observations have been explained as follows: Rapid-acting vasodilators—such as nifedipine in its prompt-release formulation—cause significant and sudden reduction in blood pressure. The drop in blood pressure evokes increased sympathetic outflow to the cardiovascular system and increases heart rate and force of contraction by the mechanism shown in Figure 6–4. These changes can markedly increase cardiac oxygen requirement. If coronary blood flow does not increase sufficiently to match the increased requirement, ischemia and infarction can result.

CHECKLIST

When you complete this chapter, you should be able to:

- ❑ Describe the pathophysiology of effort angina and vasospastic angina and the major determinants of cardiac oxygen consumption.
- ❑ List the strategies and drug targets for relief of anginal pain.
- ❑ Contrast the therapeutic and adverse effects of nitrates, β blockers, and calcium channel blockers when used for angina.
- ❑ Explain why the combination of a nitrate with a β blocker or a calcium channel blocker may be more effective than either alone.
- ❑ Explain why the combination of a nitrate and sildenafil is potentially dangerous.
- ❑ Contrast the effects of medical therapy and surgical therapy of angina.

QUESTIONS

Questions 1–2. A 73-year-old man with an inadequate response to other drugs is to receive digoxin for chronic heart failure. He is in normal sinus rhythm with a heart rate of 88 and blood pressure of 135/85 mm Hg.

1. Which of the following is the best-documented mechanism of beneficial action of cardiac glycosides?
(A) A decrease in calcium uptake by the sarcoplasmic reticulum
(B) An increase in a late transmembrane sodium current
(C) A modification of the actin molecule
(D) An increase in systolic cytoplasmic calcium levels
(E) A block of cardiac β adrenoceptors

2. After your patient has been receiving digoxin for 3 weeks, he presents to the emergency department with an arrhythmia. Which one of the following is most likely to contribute to the arrhythmogenic effect of digoxin?
(A) Increased parasympathetic discharge
(B) Increased intracellular calcium
(C) Decreased sympathetic discharge
(D) Decreased intracellular ATP
(E) Increased extracellular potassium

3. A patient who has been taking digoxin for several years for atrial fibrillation and chronic heart failure is about to receive atropine for another condition. A common effect of digoxin (at therapeutic blood levels) that can be almost entirely blocked by atropine is
(A) Decreased appetite
(B) Headaches
(C) Increased atrial contractility
(D) Increased PR interval on ECG
(E) Tachycardia

4. A 65-year-old woman has been admitted to the coronary care unit with a left ventricular myocardial infarction. She develops acute severe heart failure with marked pulmonary edema, but no evidence of peripheral edema. Which one of the following drugs would be most useful?
(A) Digoxin
(B) Furosemide
(C) Minoxidil
(D) Propranolol
(E) Spironolactone

5. A 72-year-old woman has long-standing heart failure. Which one of the following drugs has been shown to reduce mortality in chronic heart failure?
(A) Atenolol
(B) Digoxin
(C) Furosemide
(D) Nitroprusside
(E) Spironolactone

6. Which of the following drugs increases the plasma levels of endogenous BNP and also blocks angiotensin receptors?
(A) Furosemide
(B) Losartan
(C) Nesiritide
(D) Sacubitril
(E) Spironolactone

7. Which one of the following drugs is associated with clinically useful or physiologically important positive inotropic effect?
(A) Captopril
(B) Dobutamine
(C) Enalapril
(D) Losartan
(E) Nesiritide

8. A 68-year-old man with a history of chronic heart failure goes on vacation and abandons his low-salt diet. Three days later, he develops severe shortness of breath and is admitted to the local hospital emergency department with significant pulmonary edema. The first-line drug of choice in most cases of acute decompensation in patients with chronic heart failure is
(A) Atenolol
(B) Captopril
(C) Carvedilol
(D) Digoxin
(E) Diltiazem
(F) Dobutamine
(G) Enalapril
(H) Furosemide
(I) Metoprolol
(J) Spironolactone

9. Which of the following has been shown to prolong life in patients with chronic congestive failure in spite of having a negative inotropic effect on cardiac contractility?
(A) Carvedilol
(B) Digoxin
(C) Dobutamine
(D) Enalapril
(E) Furosemide

10. A 5-year-old child was vomiting and was brought to the emergency department with sinus arrest and a ventricular rate of 35 bpm. An empty bottle of his uncle's digoxin was found where he was playing. Which of the following is the drug of choice in treating a severe overdose of digoxin?
(A) Digoxin antibodies
(B) Lidocaine infusion
(C) Magnesium infusion
(D) Phenytoin by mouth
(E) Potassium by mouth

ANSWERS

1. Digitalis does not decrease calcium uptake by the sarcoplasmic reticulum or increase sodium current; it does not modify actin. Cardiac adrenoceptors are not affected. The most accurate description of digitalis's mechanism in this list is that it increases systolic cytoplasmic calcium by inhibiting Na^+/K^+ transport by the ATPase sodium pump and indirectly altering Na^+/Ca^{2+} exchange. The answer is **D.**

2. The effects of digitalis include increased vagal action on the heart (not arrhythmogenic) and increased intracellular calcium, including calcium overload, the most important cause of toxicity. Decreased sympathetic discharge and increased extracellular potassium and magnesium *reduce* digitalis arrhythmogenesis. The answer is **B.**

3. The parasympathomimetic effects of digitalis can be blocked by muscarinic blockers such as atropine. The only parasympathomimetic effect in the list provided is increased PR interval, a manifestation of slowed AV conduction. The answer is **D.**

4. Acute severe congestive failure with pulmonary edema often requires a vasodilator that reduces intravascular pressures in the lungs. Furosemide has such vasodilating actions in the context of acute failure in addition to its diuretic effect. Pulmonary edema also involves a shift of fluid from the intravascular compartment to the lungs. Minoxidil would decrease arterial pressure and increase the heart rate excessively. Digoxin has a slow onset of action and lacks vasodilating effects. Spironolactone is useful in chronic failure but not in acute pulmonary edema. Pulmonary vasodilation and removal of edema fluid by diuresis are accomplished by furosemide. The answer is **B.**

5. Of the drugs listed, only spironolactone has been shown to reduce mortality in this highly lethal disease. Digoxin, furosemide, and nitroprusside are used in the management of symptoms. The answer is **E.**

6. Furosemide has no significant effect on peptide metabolism and does not block AT_1 receptors. Losartan blocks AT_1 receptors but has no effect on peptide metabolism. Nesiritide is a synthetic BNP and does not block AT_1 receptors. Spironolactone blocks the aldosterone receptor in the kidney. Only sacubitril/valsartan has the combined effect listed in the stem of this question. The answer is **D.**

7. Although they are extremely useful in heart failure, ACE inhibitors (eg, captopril, enalapril), and angiotensin receptor blockers (ARBs, eg, losartan) have no positive inotropic effect on the heart. Nesiritide is a vasodilator with diuretic effects and renal toxicity. Dobutamine is a β_1-selective adrenoceptor agonist. The answer is **B.**

8. In both acute and chronic failure and systolic (HFrEF) and diastolic heart failure (HFpEF), the initial treatment of choice is usually furosemide. The answer is **H.**

9. Several β blockers, including carvedilol, have been shown to prolong life in heart failure patients even though these drugs may have a negative inotropic action on the heart. Their benefits presumably result from some other β-mediated effect, and at least one other β blocker has failed to show a mortality benefit. The answer is **A.**

10. The drug of choice in severe, massive overdose with any cardiac glycoside is digoxin antibody, Digibind. The other drugs listed are used in moderate overdosage associated with increased automaticity. The answer is **A.**

SKILL KEEPER ANSWER: MAINTENANCE DOSE CALCULATIONS (SEE CHAPTER 3)

Maintenance dosage is equal to CL × Cp ÷ F, so
Maintenance dosage for a patient with normal renal function
= 7 L/h × 1 ng/mL ÷ 0.7 = 7 L/h × 1 mcg/L ÷ 0.7
= 10 mcg/h × 24 h/d = 240 mcg/d = 0.24 mg/d.
But this patient has only 30% of normal renal function, so
CL (total) = 0.3 × CL (renal [60% of total])
+ CL (liver [40% of total])
CL (total) = 0.3 × 0.6 × 7 L/h + 0.4 × 7 L/h, and
CL (total) = 1.26 L/h + 2.8 L/h = 4.06 L/h, and
Maintenance dosage = 4.06 L/h × 1 mcg/L ÷ 0.7
= 5.8 mcg/h = 139 mcg/d = 0.14 mg/d

QUESTIONS

Questions 1 and 2. A 76-year-old retired postal worker with rheumatoid arthritis and chronic heart disease presents with a cardiac arrhythmia and is being considered for treatment with procainamide. She is already receiving an ACE inhibitor, digoxin, and hydrochlorothiazide for her cardiac condition.

1. In deciding on a treatment regimen with procainamide for this patient, which of the following statements is *most* correct?
(A) A probable drug interaction with digoxin suggests that digoxin blood levels should be obtained before and after starting procainamide.
(B) Hyperkalemia should be avoided to reduce the likelihood of procainamide toxicity.
(C) Procainamide cannot be used if the patient has asthma because it has a β-blocking effect.
(D) Procainamide cannot be used if the patient has angina because it has a β-agonist effect.
(E) Procainamide is not active by the oral route.

2. If this patient should take an overdose and manifest severe acute procainamide toxicity with markedly prolonged QRS, which of the following should be given immediately?
(A) A calcium chelator such as EDTA
(B) Adenosine
(C) Nitroprusside
(D) Potassium chloride
(E) Sodium lactate

3. A 54-year-old airline pilot is admitted to the emergency department with chest pain and a rapid heart rhythm. The ECG shows an inferior myocardial infarction and ventricular tachycardia. Amiodarone is ordered. Amiodarone
(A) Decreases PR interval in normal sinus rhythm
(B) Increases action potential duration
(C) Increases contractility
(D) Often causes liver function abnormalities
(E) Reduces resting potential

4. A 36-year-old woman with a history of poorly controlled thyrotoxicosis has recurrent episodes of tachycardia with severe shortness of breath. During elective surgery to remove her thyroid, she develops a heart rate of 200 with a slightly decreased blood pressure. Which of the following drugs would be *most* suitable?
(A) Amiodarone
(B) Disopyramide
(C) Esmolol
(D) Quinidine
(E) Verapamil

5. A 16-year-old girl has paroxysmal attacks of rapid heart rate with palpitations and shortness of breath. These episodes occasionally terminate spontaneously but often require a visit to the emergency department of the local hospital. Her ECG during these episodes reveals an AV nodal tachycardia. Which of the following drugs would be most suitable for prophylaxis of future episodes of acute AV nodal tachycardia?
(A) Adenosine
(B) Amiodarone
(C) Flecainide
(D) Propranolol
(E) Verapamil

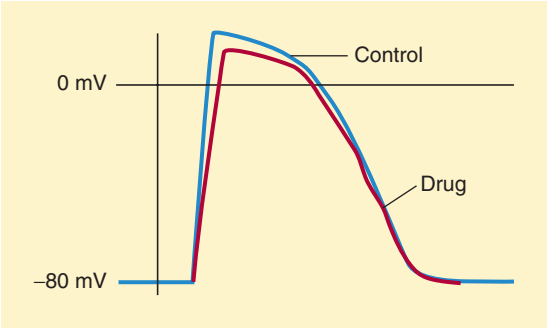
6. A 55-year-old man is admitted to the emergency department and is found to have an abnormal ECG. Overdose of an antiarrhythmic drug is considered. Which of the following drugs is correctly paired with its ECG effects?
(A) Quinidine: Increased PR and decreased QT intervals
(B) Flecainide: Increased QRS interval
(C) Verapamil: Decreased PR interval
(D) Lidocaine: Decreased QRS and PR interval
(E) Metoprolol: Increased QRS duration

7. A 60-year-old woman comes to the emergency department with atypical chest pain. Her ECG reveals ventricular tachycardia with rare normal sinus beats, and ST-segment elevation. Troponin C levels are markedly increased, suggesting myocardial damage. A diagnosis of myocardial infarction is made, and the woman is admitted to the cardiac intensive care unit. Her arrhythmia will probably be treated initially with
(A) Adenosine
(B) Digoxin
(C) Lidocaine
(D) Quinidine
(E) Verapamil

8. Which of the following drugs slows conduction through the AV node and has a duration of action of 10–20 seconds?
(A) Adenosine
(B) Amiodarone
(C) Diltiazem
(D) Esmolol
(E) Flecainide
(F) Lidocaine
(G) Mexiletine
(H) Procainamide
(I) Quinidine

9. When working in outlying areas, this 62-year-old rancher is away from his house for 12–14 h at a time. He has an arrhythmia that requires chronic therapy. Which of the following has the longest half-life of all antiarrhythmic drugs?
(A) Adenosine
(B) Amiodarone
(C) Disopyramide
(D) Esmolol
(E) Flecainide
(F) Lidocaine
(G) Mexiletine
(H) Procainamide
(I) Quinidine
(J) Verapamil

10. A drug was tested in the electrophysiology laboratory to determine its effects on the cardiac action potential in normal ventricular cells. The results are shown in the diagram.



Which of the following drugs does this agent most resemble?
(A) Amiodarone
(B) Flecainide
(C) Mexiletine
(D) Procainamide
(E) Verapamil

ANSWERS

1. Hyperkalemia facilitates procainamide toxicity. Procainamide is active by the oral route and has a duration of action of 2–4 h (in the prompt-release form). Procainamide has no significant documented interaction with digoxin and no significant β-agonist or β-blocking action. The answer is **B.**

2. The most effective therapy for procainamide (and quinidine) toxicity appears to be concentrated sodium lactate. This drug may (1) increase sodium current by increasing the sodium ion gradient and (2) reduce drug-receptor binding by alkalinizing the tissue. The answer is **E.**

3. Amiodarone typically decreases contractility only slightly; it prolongs the PR and QRS interval, as well as the QT interval and action potential duration; and it has no effect on the resting potential. Its major toxicity is pulmonary fibrosis, not liver toxicity. The answer is **B.**

4. This patient is suffering from a typical perisurgical arrhythmia, exacerbated by her thyroid disorder. Beta blockers are the most effective agents in acute thyrotoxic arrhythmias. While β blockers are used to decrease blood pressure in hypertension, this patient's lowered blood pressure is probably due to the arrhythmia and will normalize when the tachycardia is converted to normal sinus rhythm. Esmolol is a parenteral, rapid-acting β blocker (see Chapter 10). The answer is **C.**

5. Calcium channel blockers are effective in both treating and preventing supraventricular AV nodal tachycardias. They are orally active and have a duration of action of several hours. Adenosine is very effective in most acute nodal tachycardias and is less toxic because of its extremely short duration of action. However, it is not useful for chronic prophylaxis because it must be given IV and has a very short duration of action. The answer is **E.**

6. All the associations listed are incorrect except flecainide (see Table 14–1). Group 1C drugs block sodium channels but have little effect on K^+ and Ca^{2+} channels. The answer is **B.**

7. Lidocaine has limited applications as an antiarrhythmic drug, but emergency treatment of myocardial infarction arrhythmias is one of the most important. Procainamide or amiodarone are used as alternative drugs in this situation. Lidocaine is also useful in digoxin-induced arrhythmias. After recovery from the acute phase of a myocardial infarction, β blockers are used for 2 years or more to prevent sudden death arrhythmias. The answer is **C.**

8. Adenosine is a very short-acting parenteral agent often used for AV nodal arrhythmias. Diltiazem also slows AV conduction and aborts AV nodal arrhythmias but has a duration of hours, not seconds. (Beta blockers also slow AV conduction but have much smaller effects on calcium channels.) The answer is **A.**

9. Amiodarone has the longest half-life of all the antiarrhythmics (weeks). The answer is **B.**

10. The drug effect shown in the diagram includes slowing of the upstroke of the AP but no significant change in repolarization or AP duration. This is most typical of group 1C drugs. The answer is **B,** flecainide.

QUESTIONS

1. A 70-year-old retired businessman with a history of chronic heart failure has been taking digoxin and furosemide. He is now admitted with a history of vomiting, acute decompensated heart failure, and metabolic derangements. He has marked peripheral edema and metabolic alkalosis (pH, 7.50; pCO_2, 45; HCO_3, 36; Na^+, 140). Which of the following drugs is *most* appropriate for the treatment of his edema?
(A) Acetazolamide
(B) Digoxin
(C) Eplerenone
(D) Hydrochlorothiazide
(E) Tolvaptan

2. A 50-year-old man has a history of frequent episodes of renal colic with calcium-containing renal stones. A careful workup indicates that he has a defect in proximal tubular calcium reabsorption, which results in high concentrations of calcium salts in the tubular urine. The most useful diuretic agent in the treatment of recurrent calcium stones is
(A) Chlorthalidone
(B) Diazoxide
(C) Ethacrynic acid
(D) Mannitol
(E) Spironolactone

3. Which of the following is an important effect of chronic therapy with loop diuretics?
(A) Decreased urinary excretion of calcium
(B) Elevation of blood pressure
(C) Elevation of pulmonary vascular pressure
(D) Metabolic alkalosis
(E) Teratogenic action in pregnancy

4. Which drug is correctly associated with its actions in the following table? (+ indicates increase and – indicates decrease.)

Choice	Drug	Urine Na^+	Urine K^+	Metabolic change
(A)	Acetazolamide	+++	+	Alkalosis
(B)	Furosemide	++	–	Alkalosis
(C)	Hydrochlorothiazide	+	++	Acidosis
(D)	Spironolactone	+	–	Acidosis
(E)	Mannitol	–	++	Alkalosis

5. Which of the following diuretics would be most useful in the acute treatment of a comatose patient with traumatic brain injury and cerebral edema?
(A) Acetazolamide
(B) Amiloride
(C) Chlorthalidone
(D) Furosemide
(E) Mannitol

6. A 62-year-old man with advanced prostate cancer is admitted to the emergency department with mental obtundation. An electrolyte panel shows a serum calcium of 16.5 (normal 8.5–10.5 mg/dL). Which of the following therapies would be most useful in the management of severe hypercalcemia?
(A) Acetazolamide plus saline infusion
(B) Furosemide plus saline infusion
(C) Hydrochlorothiazide plus saline infusion
(D) Mannitol plus saline infusion
(E) Spironolactone plus saline infusion

7. A 60-year-old patient complains of paresthesias and occasional nausea associated with one of the drugs she is taking. She is found to have hyperchloremic metabolic acidosis. She is probably taking
(A) Acetazolamide for glaucoma
(B) Amiloride for edema associated with aldosteronism
(C) Furosemide for severe hypertension and heart failure
(D) Hydrochlorothiazide for hypertension
(E) Mannitol for cerebral edema

8. A 70-year-old woman is admitted to the emergency department because of a "fainting spell" at home. She appears to have suffered no trauma from her fall, but her blood pressure is 120/60 when lying down and 60/20 when she sits up. Neurologic examination and an ECG are within normal limits when she is lying down. Questioning reveals that she has recently started taking "water pills" (diuretics) for a heart condition. Which of the following drugs is the most likely cause of her fainting spell?
(A) Acetazolamide
(B) Amiloride
(C) Furosemide
(D) Hydrochlorothiazide
(E) Spironolactone

9. A 58-year-old woman with lung cancer has abnormally low serum osmolality and hyponatremia. A drug that increases the formation of dilute urine and is used to treat SIADH is
(A) Acetazolamide
(B) Amiloride
(C) Desmopressin
(D) Ethacrynic acid
(E) Furosemide
(F) Hydrochlorothiazide
(G) Mannitol
(H) Spironolactone
(I) Triamterene
(J) Tolvaptan

10. A graduate student is planning to make a high-altitude climb in South America while on vacation. He will not have time to acclimate slowly to altitude. A drug that is useful in preventing high-altitude sickness is
(A) Acetazolamide
(B) Amiloride
(C) Demeclocycline
(D) Desmopressin
(E) Ethacrynic acid

ANSWERS

1. Although acetazolamide is rarely used in heart failure, carbonic anhydrase inhibitors are quite valuable in patients with edema *and* metabolic alkalosis. The high bicarbonate levels in these patients make them particularly susceptible to the action of carbonic anhydrase inhibitors. Digoxin is useful in chronic systolic failure but is not first-line therapy and may cause vomiting, with depletion of stomach acid and reduced serum chloride; increasing the digoxin dose might cause arrhythmias. Tolvaptan might be useful if the patient were hyponatremic. Hydrochlorothiazide and eplerenone are not adequate for first-line therapy of edema in acute heart failure. The answer is **A.**
2. The thiazides are useful in the prevention of calcium stones because these drugs reduce tubular calcium concentration, probably by increasing passive proximal tubular and distal convoluted tubule reabsorption of calcium. In contrast, the loop agents (choice **C**) facilitate calcium excretion. Diazoxide is a thiazide-like vasodilator drug but has no diuretic action; in fact, it may cause sodium retention. It is used in hypertension and insulinoma (see Chapter 11). The answer is **A.**
3. Loop diuretics *increase* urinary calcium excretion and *decrease* blood pressure (in hypertension) and pulmonary vascular pressure (in congestive heart failure). They have no recognized teratogenic action. They cause metabolic alkalosis (Table 15–1). Loop diuretics also cause ototoxicity. The answer is **D.**
4. Acetazolamide causes metabolic acidosis. Furosemide causes a marked increase in sodium and a moderate increase in potassium excretion. Thiazides cause alkalosis and a greater increase in sodium than potassium excretion. Mannitol causes a small increase in both sodium and potassium excretion and no change in body pH. Spironolactone causes the changes indicated. The answer is **D.**
5. An osmotic agent is needed to remove water from the cells of the edematous brain and reduce intracranial pressure rapidly. The answer is **E.**
6. Diuretic therapy of hypercalcemia requires a reduction in calcium reabsorption in the thick ascending limb, an effect of loop diuretics. However, a loop diuretic alone would reduce blood volume around the remaining calcium so that serum calcium would not decrease appropriately. Therefore, a saline infusion should accompany the loop diuretic. The answer is **B.**
7. Paresthesias and gastrointestinal distress are common adverse effects of acetazolamide, especially when it is taken chronically, as in glaucoma. The observation that the patient has metabolic acidosis also suggests the use of a carbonic anhydrase inhibitor like acetazolamide. The answer is **A.**
8. The case history suggests that the syncope (fainting) is associated with diuretic use. Complications of diuretics that can result in syncope include both postural hypotension (which this patient exhibits) due to excessive reduction of blood volume and arrhythmias due to excessive potassium loss. Potassium wasting is more common with thiazides (because of their long duration of action), but these drugs rarely cause reduction of blood volume sufficient to result in orthostatic hypotension. The answer is **C,** furosemide.
9. Retention of water with hyponatremia and inability to form dilute urine in the fully hydrated condition is characteristic of SIADH. Antagonists of ADH are needed to treat this condition. The answer is **J,** tolvaptan.
10. Carbonic anhydrase inhibitors are useful for the prevention of altitude sickness. The answer is **A.**

SKILL KEEPER ANSWER: DIGITALIS AND DIURETICS (SEE CHAPTER 13)

Digoxin toxicity is facilitated by hypokalemia. Therefore, potassium-wasting diuretics (eg, loop agents, thiazides), which are often needed in heart failure, can increase the risk of a fatal digitalis arrhythmia. Carbonic anhydrase inhibitors, though also potassium-wasting agents, are rarely used for their systemic and diuretic effects and are therefore less likely to be involved in digitalis toxicity. The potassium-sparing diuretics, in contrast to the other groups, can be useful in preventing such interactions with digitalis but may cause hyperkalemia, which can be arrhythmogenic.

CHECKLIST

When you complete this chapter, you should be able to:

- ❑ List 5 major types of diuretics and relate them to their sites of action.
- ❑ Describe 2 drugs that reduce potassium loss during sodium diuresis.
- ❑ Describe a therapy that reduces calcium excretion in patients who have recurrent urinary stones.
- ❑ Describe a treatment for severe acute hypercalcemia in a patient with advanced carcinoma.
- ❑ Describe a method for reducing urine volume in nephrogenic diabetes insipidus.
- ❑ Describe a method for increasing water excretion in SIADH secretion.
- ❑ Describe a group of drugs that reduce glucose reabsorption in the nephron and cause a concomitant diuresis.
- ❑ List the major applications and the toxicities of acetazolamide, thiazides, loop diuretics, and potassium-sparing diuretics.

QUESTIONS

1. PJ is a 5-year-old boy. At his checkup, the pediatrician notices cutaneous xanthomas and orders a lipid panel. Repeated measures confirm that the patient's serum cholesterol levels are high (936 mg/dL). Further testing confirms a diagnosis of homozygous familial hypercholesterolemia. Which of the following interventions will be **least** effective in this patient?
(A) Atorvastatin
(B) Ezetimibe
(C) Lomitapide
(D) Mipomersen
(E) Niacin

2. A 46-year-old woman with a history of hyperlipidemia was treated with a drug. The chart below shows the results of the patient's fasting lipid panel before treatment and 6 mo after initiating drug therapy. Normal values are also shown. Which of the following drugs is most likely to be the one that this patient received?
(A) Colestipol
(B) Ezetimibe
(C) Gemfibrozil
(D) Lovastatin
(E) Niacin

Time of Lipid Measurement	Triglyceride	Total Cholesterol	LDL Cholesterol	VLDL Cholesterol	HDL Cholesterol
Before treatment	1000	640	120	500	20
Six months after starting treatment	300	280	90	150	40
Normal values	<150	<200	<130	<30	>35

Questions 3–6. A 35-year-old woman appears to have familial combined hyperlipidemia. Her serum concentrations of total cholesterol, LDL cholesterol, and triglyceride are elevated. Her serum concentration of HDL cholesterol is somewhat reduced.

3. Which of the following drugs is most likely to increase this patient's triglyceride and VLDL cholesterol concentrations when used as monotherapy?
(A) Atorvastatin
(B) Cholestyramine
(C) Ezetimibe
(D) Gemfibrozil
(E) Niacin

4. If this patient is pregnant, which of the following drugs should be avoided because of a risk of harming the fetus?
(A) Cholestyramine
(B) Ezetimibe
(C) Fenofibrate
(D) Niacin
(E) Pravastatin

5. The patient is started on gemfibrozil. Which of the following is a major mechanism of gemfibrozil's action?
(A) Increased excretion of bile acid salts
(B) Increased expression of high-affinity LDL receptors
(C) Increased secretion of VLDL by the liver
(D) Increased triglyceride hydrolysis by lipoprotein lipase
(E) Reduced uptake of dietary cholesterol

6. Which of the following is a major toxicity associated with gemfibrozil therapy?
(A) Bloating and constipation
(B) Cholelithiasis
(C) Hyperuricemia
(D) Liver damage
(E) Severe cardiac arrhythmia

Questions 7–10. A 43-year-old man has heterozygous familial hypercholesterolemia. His serum concentrations of total cholesterol and LDL are markedly elevated. His serum concentration of HDL cholesterol, VLDL cholesterol, and triglycerides are normal or slightly elevated. The patient's mother and older brother died of myocardial infarctions before the age of 50. This patient recently experienced mild chest pain when walking upstairs and has been diagnosed as having angina of effort. The patient is somewhat overweight. He drinks alcohol most evenings and smokes about 1 pack of cigarettes per week.

7. Consumption of alcohol is associated with which of the following changes in serum lipid concentrations?
(A) Decreased chylomicrons
(B) Decreased HDL cholesterol
(C) Decreased VLDL cholesterol
(D) Increased LDL cholesterol
(E) Increased triglyceride

8. If the patient has a history of gout, which of the following drugs is most likely to exacerbate this condition?
(A) Colestipol
(B) Ezetimibe
(C) Gemfibrozil
(D) Niacin
(E) Simvastatin

9. After being counseled about lifestyle and dietary changes, the patient was started on atorvastatin. During his treatment with atorvastatin, it is important to routinely monitor serum concentrations of which of the following?
(A) Blood urea nitrogen
(B) Alanine and aspartate aminotransferase
(C) Platelets
(D) Red blood cells
(E) Uric acid

10. Six months after beginning atorvastatin, the patient's total and LDL cholesterol concentrations remained above normal, and he continued to have anginal attacks despite good adherence to his antianginal medications. His physician decided to add ezetimibe. Which of the following is the most accurate description of ezetimibe's mechanism of an action?
(A) Decreased lipid synthesis in adipose tissue
(B) Decreased secretion of VLDL by the liver
(C) Decreased gastrointestinal absorption of cholesterol
(D) Increased endocytosis of HDL by the liver
(E) Increased lipid hydrolysis by lipoprotein lipase

ANSWERS

1. Homozygous familial hypercholesterolemia is caused by mutations leading to dysfunctional LDL receptors incapable of taking up LDL from the bloodstream. Options **B–E** would have a cholesterol-lowering effect. Lomitapide and mipomersen are specifically indicated for patients with familial hypercholesterolemia. Reductase inhibitors such as atorvastatin rely on functional LDL receptors to achieve a LDL-lowering effect and thus will not work in patients with homozygous familial hypercholesterolemia. The answer is **A.**

2. This patient presents with striking hypertriglyceridemia, elevated VLDL cholesterol, and depressed HDL cholesterol. Six months after drug treatment was initiated, her triglyceride and VLDL cholesterol have dropped dramatically and her HDL cholesterol level has doubled. The drug that is most likely to have achieved all of these desirable changes, particularly the large increase in HDL cholesterol, is niacin. Although gemfibrozil lowers triglyceride and VLDL concentrations, it does not cause such large increases in HDL cholesterol and decreases in LDL cholesterol. The answer is **E.**

3. In some patients with familial combined hyperlipidemia and elevated VLDL, the resins increase VLDL and triglyceride concentrations even though they also lower LDL cholesterol. The answer is **B.**

4. The HMG-CoA reductase inhibitors are contraindicated in pregnancy because of the risk of teratogenic effects. The answer is **E.**

5. A major mechanism recognized for gemfibrozil is increased activity of the lipoprotein lipase associated with capillary endothelial cells. Gemfibrozil and other fibrates decrease VLDL secretion, presumably by stimulating hepatic fatty acid oxidation. The answer is **D.**

6. A major toxicity of the fibrates is increased risk of gallstone formation, which may be due to enhanced biliary excretion of cholesterol. The answer is **B.**

7. Chronic ethanol ingestion can increase serum concentrations of VLDL and triglycerides. This is one of the factors that places patients with alcoholism at risk of pancreatitis. Chronic ethanol ingestion also has the possibly beneficial effect of raising, not decreasing, serum HDL concentrations. The answer is **E.**

8. Niacin can exacerbate both hyperuricemia and glucose intolerance. The answer is **D.**

9. The 2 primary adverse effects of the HMG-CoA reductase inhibitors are hepatotoxicity and myopathy. Patients taking these drugs should have liver function tests performed before starting therapy, and at regular intervals as needed during therapy. Serum concentrations of alanine and aspartate aminotransferase are used as markers of hepatocellular toxicity. The answer is **B.**

10. The major recognized effect of ezetimibe is inhibition of absorption of cholesterol in the intestine. The answer is **C.**

SKILL KEEPER ANSWERS: ANGINA (SEE CHAPTER 12)

1. *The 3 major forms of angina are (1) angina of effort, which is associated with a fixed plaque that partially occludes 1 or more coronary arteries; (2) vasospastic angina, which involves unpredictably timed, reversible coronary spasm; and (3) unstable angina, which often immediately precedes a myocardial infarction and requires emergency treatment.*

2. *The 3 major drug groups used in angina are nitrates, calcium channel blockers, and β blockers. Nitrates are used in all 3 types of angina. Calcium channel blockers are useful for treatment of angina of effort and vasospastic angina. They can be added to β blockers and nitroglycerin in patients with refractory unstable angina. β blockers are not useful in vasospastic angina or for an acute attack of angina of effort. They are primarily used for prophylaxis of angina of effort and also in emergency treatment of acute coronary syndromes.*