Chapter 8

Drugs Acting on the Cardiovascular System

Wendy A. Ware

I. DRUGS USED IN HEART FAILURE THERAPY

A. Introduction

1. **Heart failure** occurs when abnormal cardiac function causes inadequate blood delivery to the tissues or adequate delivery only with elevated cardiac filling pressures. It can involve abnormalities of systolic or diastolic function, or both.
   a. **Congestive heart failure** (CHF) is characterized by high cardiac filling pressure which leads to venous congestion (behind the affected side of the heart) and tissue fluid accumulation. It is a complex clinical syndrome rather than a specific etiologic diagnosis. Although poor contractility often underlies CHF, chronic cardiac overload (volume or pressure) or other injury can also stimulate a cascade of neurohormonal and cardiac responses that eventually lead to congestive signs and further deterioration in function.
      (1) **Left-sided congestive signs** include pulmonary venous congestion and edema (resulting in cough, tachypnea, dyspnea, orthopnea, pulmonary crackles, tiring, hemoptysis, cyanosis). Chronic pulmonary congestion can lead to varying degrees of pulmonary hypertension and sometimes, right-sided CHF signs.
      (2) **Right-sided congestive signs** include systemic venous hypertension, with resulting jugular venous distension, hepatic (and abdominal visceral) congestion, pleural effusion (resulting in dyspnea, orthopnea, cyanosis), ascites, small pericardial effusions, and sometimes, subcutaneous edema.
   b. **Forward (low output) failure** causes tiring, exertional weakness, syncope, prerenal azotemia, and peripheral cyanosis (from poor cutaneous circulation). Cardiac arrhythmias frequently occur with all manifestations of heart failure. These signs can occur with either left or right heart disease.
2. **Pathophysiology** of heart failure
   a. **Cardiac remodeling** involves changes in myocardial size, shape and stiffness that occur in response to various mechanical, biochemical, and molecular signals induced by the underlying injury or stress.
      (1) **Myocardial hypertrophy**. Changes include myocardial cell hypertrophy, cardiac cell dropout (apoptosis), excess interstitial matrix formation, fibrosis, and abnormal collagen binding between individual myocytes. Increased mechanical forces (ventricular wall stress), as well as various neurohormones (e.g., angiotensin II, norepinephrine, endothelin, aldosterone) and cytokines (e.g., a tumor necrosis factor-α), are stimuli for cardiac remodeling. Myocardial hypertrophy helps normalize wall stress. Systolic pressure loads mainly cause "concentric" hypertrophy, with myocardial fiber thickening; volume loads mainly cause "eccentric" hypertrophy, with myocardial fiber elongation. Hypertrophy can interfere with diastolic function by making the ventricle "stiffer."
      (2) **Frank–Starling mechanism.** Acutely increased filling pressure and end diastolic volume (preload) induce greater force of contraction and help increase overall cardiac output. Valvular insufficiency, arterial hypertension, and ventricular outflow obstruction as well as volume retention lead to increased preload. Compensatory hypertrophy lessens the importance of the Frank–Starling mechanism in stable, chronic heart failure.
   b. **Neurohormonal mechanisms.** Neurohormonal responses contribute to cardiac remodeling and have systemic effects. Excessive activation of neurohormonal "compensatory" mechanisms leads to the clinical syndrome of CHF.

(1) Increased sympathetic nervous tone. Short-term effects of increased contractility, heart rate, and venous return can increase cardiac output. But over time, increased afterload stress and myocardial oxygen requirement, contribute to cellular damage, myocardial fibrosis, and increased potential for cardiac arrhythmias.

(2) Activation of the renin–angiotensin–aldosterone system. Angiotensin II stimulates potent vasoconstriction and aldosterone secretion, and has other important effects. Aldosterone promotes Na^+ and Cl^- reabsorption in the kidney; it also contributes to pathologic remodeling and myocardial fibrosis.

(3) Antidiuretic hormone (vasopression). This hormone directly causes vasoconstriction and also promotes free water reabsorption.

(4) Other substances. Cytokines (e.g., TNF-α), endothelins, and other substances also play a role in abnormal myocardial hypertrophy and/or fibrosis in heart failure.

(5) Endogenous vasodilatory mechanisms. These oppose the vasoconstrictor responses in heart failure and include natriuretic peptides (atrial NP and brain NP, nitric oxide, and vasodilatory prostaglandins). Normally, a balance between vasodilator and vasoconstrictor effects maintains circulatory homeostasis. As heart failure progresses, the influence of the vasoconstrictor mechanisms predominates.

c. Pathophysiologic groups of heart failure. As an aid to choosing therapy, the causes of heart failure can be viewed according to major underlying pathophysiologic mechanism. Nevertheless, several pathophysiologic abnormalities usually coexist; both systolic and diastolic function abnormalities are common in advanced failure.

(1) Myocardial (systolic pump) failure. Dilated cardiomyopathy is the most common cause. Valvular insufficiency may or may not be present initially, but usually develops as the affected ventricle dilates.

(2) Volume overload. A leaky valve or abnormal systemic-to-pulmonary connections are common causes. Cardiac pump function is often maintained well initially, but myocardial contractility deteriorates over time.

(3) Systolic pressure overload. Congenital ventricular outflow obstruction, and systemic or pulmonary hypertension are common causes. Concentric hypertrophy increases ventricular wall thickness and stiffness, and predisposes to ischemia; eventually myocardial contractility declines.

(4) Reduced ventricular compliance with impaired filling (diastolic dysfunction). Examples include hypertrophic and restrictive myocardial disease and pericardial disease. Contractile ability is usually normal initially, but elevated filling pressure leads to congestion and may diminish cardiac output.

B. Overview of heart failure therapy

1. Treatment strategies are aimed at modifying either the results of neurohormonal activation (i.e., Na^+ and water retention) or the activation process itself (e.g., angiotensin-converting enzyme inhibition). Goals are to control edema and effusions, improve cardiac output, reduce cardiac workload, support myocardial function, and manage concurrent arrhythmias. The clinical severity of heart failure influences the treatments used. Animals with heart failure caused by systolic dysfunction (e.g., dilated cardiomyopathy or advanced valvular insufficiency) benefit most from arteriolar vasodilation (reduced afterload) and also positive inotropic support.

a. Acute CHF. Acute CHF is characterized by severe cardiogenic pulmonary edema, with or without pleural and/or abdominal effusions or poor cardiac output. Therapy is aimed at rapidly clearing pulmonary edema, improving oxygenation, and optimizing cardiac output (see Table 8-1).

b. Chronic heart failure. Therapy is tailored to the individual's needs by adjusting dosages, adding or substituting drugs, and modifying lifestyle or diet. Pleural effusion and large-volume ascites that accumulate despite medical therapy are drained to improve respiration. As heart disease progresses, more aggressive

TABLE 8-1. Management of Acute Decompensated Congested Heart Failure*

- Avoid stress!
- Provide cage rest
- Enhance oxygenation:
  - Check airway patency
  - Give supplemental O_2 (avoid >50% for >24 hours)
  - If frothing is evident, suction airways
  - Intubate and mechanically ventilate if needed
  - Perform thoracocentesis if pleural effusion suspected
- Remove alveolar fluid:
  - Initiate diuresis:
    - Furosemide (dogs: 2–5 [–8] mg/kg IV or IM q1–4 hours until respiratory rate decreases, then 1–4 mg/kg q6–12 hours, or 0.6–1 mg/kg/h CRI (see cited text for more information); cats: 1–2 (–4) mg/kg IV or IM q1–4 hours until respiratory rate decreases, then q6–12 hours)
  - Redistribute blood volume:
    - Vasodilators (sodium nitroprusside: 0.5–1 mcg/kg/min (initial) CRI in D5W, titrate upward as needed to 5–15 mcg/kg/min, monitor arterial pressure (see cited text for more information); or 2% nitroglycerin ointment (+/− with hydralazine): dogs: 1/2–1 1/2 inch cutaneously q6 hours; cats: 1/4–1/2 inch cutaneously q6 hours.
    - (± morphine [dogs only, see below])
    - (± phlebotomy [6–10 mL/kg])
- Reduce bronchoconstriction:
  - Aminophylline (dogs: 4–8 mg/kg slow IV, IM, SC or 6–10 mg/kg PO q6–8 hours; cats: 4–8 mg/kg IM, SC, PO q8–12 hours) or similar drug
- Mild sedation to reduce anxiety:
  - Butorphanol (dogs: 0.2–0.3 mg/kg IM; cats: 0.2–0.25 mg/kg IM); or
  - Morphine (dogs: 0.025–0.1 mg/kg IV boluses q2–3 minutes to effect, or 0.1–0.5 mg/kg single IM or SC dose)
  - Acepromazine (cats: 0.05–0.2 mg/kg SC; or 0.05–0.1 mg/kg IM with butorphanol), or
  - Diazepam (cats: 2–5 mg IV; dogs: 5–10 mg IV)
- Reduce afterload:
  - Hydralazine: dogs: initial 0.5–1.0 mg/kg PO, repeat in 2–3 hours (until systolic arterial pressure is 90–110 mm Hg), then q12 hours (avoid nitroprusside); or
  - Enalapril (0.5 mg/kg PO q12–24 hours) or other ACE inhibitor (avoid nitroprusside); or
  - Amlodipine (dogs: 0.1–0.3 mg/kg PO q12–24 hours)
- Increase contractility (if myocardial failure present):
  - Dobutamine† (1–10 mcg/kg/min CRI; start low), or dopamine‡ (dogs: 1–10 mcg/kg/min CRI; cats: 1–5 mcg/kg/min CRI; start low).
  - Amrinone (1–3 mg/kg IV; 10–100 mcg/kg/min CRI), or milrinone (50 mcg/kg IV over 10 minutes initially; 0.375–0.75 mcg/kg/min CRI [human dose]).
  - Pimobendan (PO, see Appendix II), or
  - Digoxin (see Appendix II for PO maintenance dosage); loading dose (see cited text for indications): PO—1 or 2 doses at twice calculated maintenance; dog IV: 0.01–0.02 mg/kg—give 1/4 of this total dose in slow boluses over 2–4 hours to effect; cat IV: 0.005 mg/kg—give 1/2 of total, then 1–2 hours later give 1/4 dose bolus(es), if needed).
- Monitor and manage abnormalities as possible:
  - Respiratory rate, heart rate and rhythm, arterial blood pressure, body weight, urine output, hydration, attitude, serum biochemistry and blood gas analyses, and pulmonary capillary wedge pressure (if available).
- Diastolic dysfunction (e.g., cats with hypertrophic cardiomyopathy):
  - General recommendations, O_2 therapy, and furosemide as above.
  - +/− Nitroglycerin and mild sedation.
  - Consider IV esmolol (200–500 mcg/kg IV over 1 minute, followed by 25–200 mcg/kg CRI) or diltiazem (0.15–0.25 mg/kg over 2–3 minutes IV).

*Adapted from Wendy A. Ware. *Cardiovascular Disease in Small Animal Medicine*. 2007, London, UK, Manson Publishing, p. 171.

†Dilution of 250 mg dobutamine into 500 mL of fluid yields 500 mcg/mL; infusion at 0.6 mL/kg/h provides 5 mcg dobutamine/kg/min.

‡Dopamine is diluted in saline solution, 5% dextrose in water, or lactated Ringer's solution; 40 mg of dopamine into 500 mL of fluid provides 80 mcg/mL; infusion at 0.75 mL/kg/h provides 1 mcg dopamine/kg/min.

therapy is usually needed. Support of myocardial function with pimobendan (or digoxin) is helpful for many dogs, and some cats.

c. Treatment implications for diastolic dysfunction

(1) Hypertrophic cardiomyopathy (HCM). Disease such as HCM, which impairs ventricular filling, is treated with drugs that slow heart rate (to increase filling time and reduce ischemia). Improved cardiac relaxation is also a goal. Diltiazem (Ca^{2+} blocker), a β-adrenergic blocker and/or an angiotensin converting enzyme inhibitor (ACEI) are most commonly used.

(2) Cardiac tamponade. Impaired filling caused by cardiac tamponade or pericardial restriction is treated by pericardiocentesis or pericardiectomy rather than drugs.

C. Diuretics. Diuretic therapy is indicated to control edema and effusions that occur in CHF. Excessive use of diuretics in heart failure exacerbates neurohormonal activation. Diuretics are discussed in more detail in Chapter 9.

1. **Furosemide.** This loop-diuretic is used almost exclusively for animals with cardiogenic edema or effusion.
   - **a. Acute CHF**. Although aggressive furosemide therapy is indicated for acute, fulminant pulmonary edema, the smallest effective doses are used for chronic heart failure therapy.
   - **b. Chronic heart failure. Furosemide should not be used as monotherapy for chronic heart failure management.**
   - **c. Adverse effects** are usually related to excessive fluid and/or electrolyte losses.
2. **Spironolactone.** This K^+-sparing diuretic may be a useful adjunct therapy for chronic refractory heart failure, although it appears to have little diuretic effect in normal dogs.
   - **a.** Aldosterone release can occur despite ACE inhibitor use. Spironolactone's antialdosterone effect may mitigate aldosterone-induced cardiovascular remodeling.
   - **b.** Spironolactone must be used cautiously in patients receiving an ACEI or K^+ supplement, and is absolutely contraindicated in hyperkalemic patients.
   - **c.** Adverse effects relate to excess K^+ retention and GI disturbances. Spironolactone may decrease digoxin clearance.
3. **Thiazide diuretics.** Chlorothiazide or hydrochlorothiazide is occasionally used in combination with furosemide and other therapy for refractory CHF.
   - **a.** Thiazide diuretics decrease renal blood flow and should not be used in the presence of azotemia.

D. Angiotensin converting enzyme inhibitors (ACEIs). This is a group of drugs that, by inhibiting the action of ACE, block the conversion of an inactive precursor peptide (angiotensin I) into the active angiotensin II. In this way, the effects of the renin–angiotensin–aldosterone cascade are opposed. ACE also degrades certain vasodilator kinins, including bradykinin. Most ACEIs (except captopril and lisinopril) are prodrugs which are converted to their active form in the liver. Severe liver dysfunction can interfere with this conversion.

1. **Pharmacologic effects and mechanism of action**
   - **a.** The main benefits of ACEIs arise from reducing the effects of neurohormonal activation (Figure 8-1).
   - **b.** Arteriolar and venous vasodilation
     - **(1)** Inhibition of locally produced ACE within vascular walls may produce a local vasodilatory response, even in the absence of high circulating renin levels.
     - **(2)** The vasodilating effects of ACEIs may be enhanced by vasodilatory kinins normally degraded by ACE.
   - **c.** Inhibition of angiotensin II production decreases aldosterone secretion, a hormone that promotes renal Na^+ retention. ACEI's diuretic effect is modest.
   - **d.** ACEIs may also (potentially) oppose abnormal CV remodeling changes.

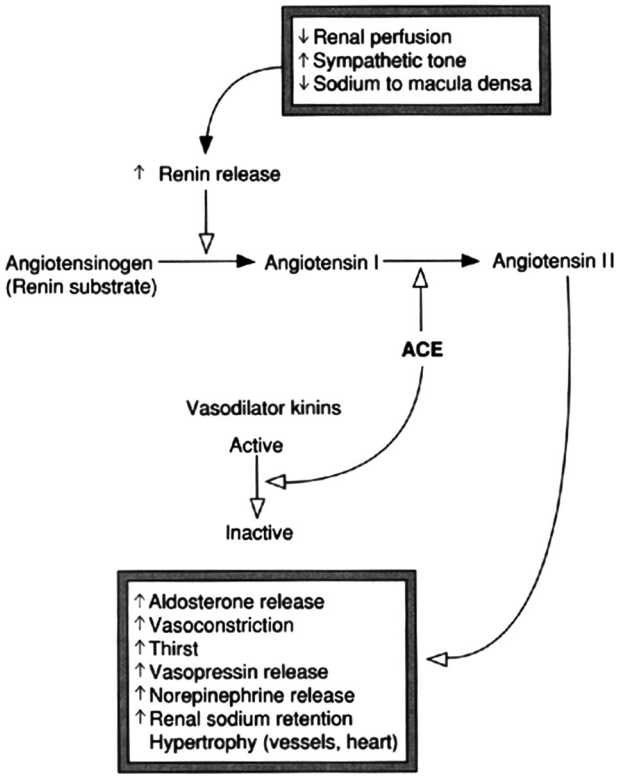

FIGURE 8-1. The renin–angiotensin cascade and effects of angiotensin II. Angiotensin converting enzyme (ACE) catalyzes the conversion of angiotensin I to angiotensin II and degrades vasodilator kinins (e.g., bradykinin). Open arrows—enzymatic reaction.

2. **Therapeutic uses and administration**
   - **a.** An ACEI is indicated for the chronic management of most causes of chronic heart failure, especially dilated cardiomyopathy, chronic valvular insufficiency, and HCM.
   - **b. An ACEI is considered the first choice agent in the management of systemic arterial hypertension in dogs.** An ACEI may also be useful in cats with hypertension.
   - **c.** An ACEI may help slow progression of chronic renal failure in cats, and possibly dogs.
3. **Adverse effects of ACEIs** include hypotension, GI upset, renal function deterioration, and hyperkalemia (especially when used with a K^+-sparing diuretic or K^+ supplement).
   - **a. Azotemia**. If azotemia develops, the diuretic dosage is decreased first. If necessary, the ACEI dose is reduced or the drug discontinued.
4. **ACEI used commonly for CHF management**
   - **a. Enalapril** is the only ACEI licensed for veterinary use.
     - **(1)** Enalapril is well absorbed orally; bioavailability is not decreased by food.
     - **(2)** Enalapril is hydrolyzed in the liver to its most active form, enalaprilat.
     - **(3)** Peak ACE-inhibiting activity occurs within 4–6 hours in dogs. Duration of action is 12–14 hours; effects are minimal by 24 hours after once daily dosing.
     - **(4)** Maximal activity in cats occurs within 2–4 hours after an oral dose; some ACE inhibition (50% of control) persists for 2–3 days.
     - **(5)** Enalapril and its active metabolite are excreted in the urine.
       - **(a)** Significant adverse effects on renal function in dogs with advanced mitral regurgitation are generally not a concern.
       - **(b)** Renal failure and severe CHF prolong the drug's elimination, so reduced dosage or benazepril are used in this situation.

b. Benazepril is often chosen in animals with preexisting renal disease. Benazepril may also slow renal function deterioration and partially mitigate hypertension in cats with renal disease.

(1) Oral administration is absorbed at rate of ~40%, which is not affected by feeding.

(2) Benazepril is metabolized to its active form (benazeprilat) in the liver.

(3) Peak ACE inhibition occurs within 2 hours of PO administration in dogs and cats. Complete ACE inhibition occurs in cats at doses of 0.25–0.5 mg/kg. There is >90% ACE inhibition at 24 hours.

(4) Repeated dosing moderately increases drug plasma concentrations.

(5) Benazepril is eliminated equally in urine and bile in dogs. In cats, ~85% is excreted in the feces and only 15% in the urine.

c. Other ACEIs sometimes used for CHF include captopril, lisinopril, ramipril, quinipril, fosinopril, and imidapril.

(1) Captopril is well absorbed orally (75% bioavailable), but **feeding decreases bioavailability by 30–40%**.

(a) Hemodynamic effects appear within 1 hour, peak in 1–2 hours, and last <4 hours in dogs.

(b) Captopril is excreted in the urine.

(2) Lisinopril is a lysine analog of enalaprilat with direct ACE-inhibiting effects.

(a) Lisinopril is 25–50% bioavailable; absorption is not affected by feeding.

(b) Time to peak effect is 6–8 hours. Once daily dosing appears to be effective.

E. Other vasodilators can further improve cardiac output and reduce edema and effusions in selected heart failure patients. Agents that reduce arteriolar resistance are also used in the treatment of hypertension. Vasodilators can affect arterioles, venous capacitance vessels, or both ("balanced" vasodilators).

1. Introduction

a. Arteriolar dilators decrease systemic vascular resistance, arterial blood pressure, and afterload on the heart by relaxing arteriolar smooth muscle. This helps improve forward cardiac output and can reduce (mitral) regurgitant flow, thereby decreasing left atrial pressure and pulmonary congestion. **An arteriolar or mixed vasodilator drug should be initiated cautiously to avoid hypotension and reflex tachycardia.**

b. Venodilators relax systemic veins, increase venous capacitance, decrease cardiac filling pressures (preload), and reduce pulmonary congestion. They are used mainly in treating acute CHF.

2. Hydralazine

a. Preparation and chemistry. Hydralazine (Apresoline®) is a phthalazine-derivative vasodilating agent.

b. Pharmacologic effects and mechanism of action. Hydralazine directly relaxes arteriolar smooth muscle with little effect on the venous system. Cerebral, coronary, splanchnic, and renal circulations are affected more than skeletal muscle or skin vasculature. Its effect is dependent on intact vascular endothelium.

c. Therapeutic uses and administration. Hydralazine, in combination with furosemide, is especially useful for dogs with mitral insufficiency and severe pulmonary edema by rapidly reducing arterial resistance (afterload). This helps reduce regurgitant volume and pulmonary venous pressure and increase forward cardiac output. Hydralazine has also been used in the treatment of myocardial failure and hypertension.

d. Pharmacokinetics. The drug is rapidly absorbed orally, with onset of action within 1 hour. Peak effect occurs within 3–5 hours and lasts up to 12 hours in dogs. There is extensive first-pass hepatic metabolism of this drug. However, in dogs, increased doses saturate this mechanism and increase bioavailability. A small amount of the drug is excreted unchanged in the urine. The $t_{1/2}$ is 2–4 hours in people. The Cl_T is about 70 mL/min/kg and V_d is 9 L/kg; bioavailability is decreased by over 60% with food.

e. **Adverse effects.** Hypotension is most common. Hydralazine causes significant reflex tachycardia in some animals. The dose should be reduced if this occurs; sometimes adding digoxin or a β-blocker is also necessary. Hydralazine can exacerbate the increased neurohumoral response in heart failure, and enhance Na^+ and water retention. GI upset may also occur, especially in cats.

3. **Amlodipine**
   a. **Preparation and chemistry.** Amlodipine besylate (Norvasc®) is dihydropyridine Ca^{2+} channel blocker.
   b. **Pharmacologic effects and mechanism of action.** Ca^{2+} channel blockers as a group block Ca^{2+} influx across cardiac and vascular smooth muscle cell membranes. Amlodipine mainly has vasodilating effects, with no appreciable cardiac effects.
   c. **Therapeutic uses and administration.** Amlodipine is the drug of first choice for systemic arterial hypertension in cats. It can be a useful adjunct therapeutic agent in hypertensive dogs, and may be effective as a single agent in some. It also is used as adjunct therapy in dogs with refractory CHF (especially from mitral valve disease). It is administered PO.
   d. **Pharmacokinetics.** Plasma $t_{1/2}$ of amlodipine is ~30 hours in dogs, and maximal effects occur 4–7 days after initiating therapy. Oral bioavailability is high (88% in dogs) and peak plasma concentrations are reached 3–8 hours after oral administration; plasma concentrations increase with chronic therapy. The drug undergoes hepatic metabolism, but there is no extensive first-pass elimination; caution is warranted in animals with poor liver function. Excretion is through the urine and feces. Amlodipine's effect on blood pressure lasts ≥24 hours in cats. Amlodipine generally does not have significant effects on serum creatinine concentration or body weight in cats with chronic renal failure.
   e. **Adverse effects.** Hypotension is possible, but less likely than with hydralazine because of the slower onset of action. Infrequently, inappetence, azotemia, lethargy, hypokalemia, reflex tachycardia, or weight loss may occur.

4. **Nitrates**
   a. **Preparation and chemistry.** Commonly used nitrates include **sodium nitroprusside** (for IV infusion), **nitroglycerine** topical ointment (2%), and oral **isosorbide dinitrate.**
   b. **Pharmacologic effects and mechanism of action.** Nitrates cause peripheral vasodilation.
      (1) Nitroprusside is a potent direct dilator of both arteriolar and venous smooth muscle; it reduces afterload as well as preload on the heart. The infused dosage should be titrated to maintain mean arterial pressure above 70 mm Hg.
      (2) Nitroglycerin and isosorbide dinitrate act mainly on the venous system and reduce cardiac filling pressures (preload) by their venodilating effects. They are metabolized in vascular smooth muscle to produce nitric oxide, which indirectly mediates vasodilation via activation of guanylyl cyclase to produce cyclic GMP, which in turn activates protein kinase G to open K^+ channels and close Na^+ channels, thereby inducing hyperpolarization of the muscle.
   c. **Therapeutic uses and administration**
      (1) Sodium nitroprusside is mainly administered IV in the treatment of fulminant CHF; it is sometimes used for acute hypertensive crisis. This agent should only be used when arterial blood pressure and IV infusion rate can be constantly monitored.
      (2) Nitroglycerin. The major indication for nitroglycerin is acute cardiogenic pulmonary edema. Nitroglycerin ointment (2%) is usually applied to the skin of the groin, axillary area, or ear pinna, although the efficacy of this in heart failure is unclear. An application paper or glove is used to avoid skin contact by the person applying the drug. Nitroglycerin ointment or isosorbide dinitrate are used occasionally in chronic CHF management, either combined with standard therapy for refractory CHF, or with hydralazine or amlodipine in animals that cannot tolerate ACEIs.

d. Pharmacokinetics

(1) Sodium nitroprusside's effect on blood pressure last less than 10 minutes, so the drug must be given by intravenous infusion. Nitroprusside is metabolized to a cyanide radical, and then further metabolized in the liver; elimination is via the urine, feces, and exhaled air.

(2) Other nitrates. Because of extensive first-pass hepatic metabolism after oral administration, the transcutaneous route is used most often in animals for other nitrates, although **nitroglycerine** is also well absorbed sublingually. Nitroglycerine ointment (2%) is applied to the patient's skin (usually the groin, axillary area, or ear pinna) every 4–6 hours using application papers or gloves. Onset of action is within 1 hour, with variable duration of effect (e.g., 2–12 hours). The $t_{1/2}$ in dogs is unclear; it is <5 minutes in people, but metabolites have some activity. Dosage and absorption are variable. The self-adhesive, sustained-release preparations may be useful, but have not been systematically evaluated in small animals.

e. Adverse effects. Profound hypotension is the major side effect of sodium nitroprusside. Cyanide toxicity can result from excess or prolonged use (e.g., over 48 hours). Hypotension may result from excessive or inappropriate use of other nitrates as well. Chronic high dosages and frequent application or long acting formulations are most likely to be associated with the development of drug tolerance.

F. Positive inotropic drugs

1. Pimobendan (Vetmedin®)

a. Preparation and chemistry. Pimobendan is a benzimidazole–pyridazinone derivative, nonsympathomimetic, nonglycoside inotropic drug that also has vasodilating properties.

b. Pharmacologic effects and mechanism of action. This drug increases myocardial contractility by increasing myofilament sensitivity to Ca^{2+} and by inhibiting phosphodiesterase III (which breaks down cyclic AMP). The latter mechanism is responsible for pimobendan's vasodilating properties. The drug also appears to have some anticytokine and antithrombotic properties.

c. Therapeutic uses and administration. Pimobendan is approved for use in dogs with CHF from dilated cardiomyopathy or chronic mitral valve disease. It is used in combination with diuretic and other therapy (sometimes including digoxin) as appropriate for the individual case. The total daily oral dose (0.5 mg/kg) is divided (not necessarily equally) and administered BID using a combination of whole and half chewable tablets (or capsules where available).

d. Pharmacokinetics. Pimobendan is metabolized in the liver to an active metabolite. Excretion is mainly through the feces. There is >90% protein binding of both drug and active metabolite. The elimination $t_{1/2}$ for pimobendan and its metabolite are ~0.5 and 2 hours, respectively. There is a wide tissue distribution and there is a delay from the time of peak plasma concentrations to maximal effect on myocardial contractility (dP/dt_{max}). Increased dP/dt_{max} is observed for ≥8 hours after dosing. Inotropic effect may be attenuated by concurrent use of a β- or Ca^{2+}-blocker.

e. Adverse effects. About a third of patients may experience reduced appetite, lethargy, diarrhea, and dyspnea, with fewer dogs exhibiting azotemia, weakness and other signs; however, these signs may be due to the underlying CHF. Sporadic mild increase in serum alkaline phosphatase has occurred, and hyperactivity, hemorrhage, drooling, constipation, and diabetes mellitus have been reported as suspected adverse reactions.

2. Digoxin

a. Preparation and chemistry. Digoxin is a cardiac glycoside. It is essentially the only digitalis glycoside still in clinical use.

b. Pharmacologic effects and mechanism of action

(1) Positive inotropic effect (Figure 8-2). Digoxin competitively binds to and inhibits Na^+, K^+-ATPase at the myocardial cell membrane. Decreased

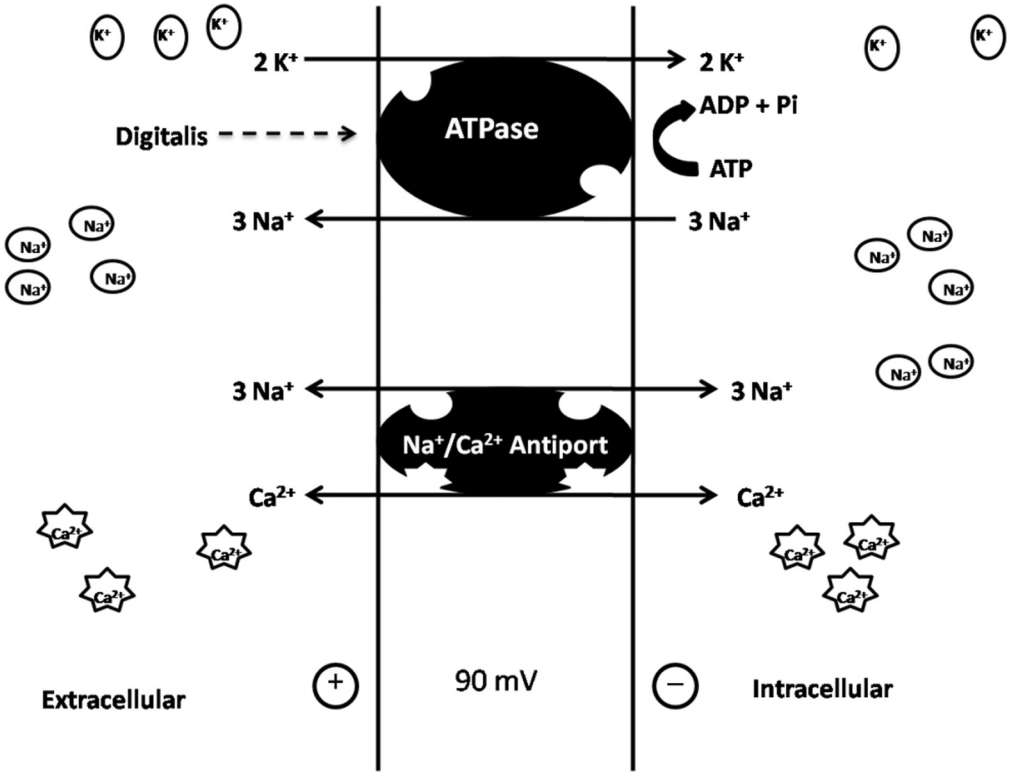

FIGURE 8-2. Digoxin mechanism of action in myocardium. Digoxin-induced inhibition of Na^+, K^+-ATPase leads to an increase in myocardial Na^+ concentration. Through Na^+–Ca^{2+} exchanger, an increase in Ca^{2+} influx is reached. The increase in myocardial Ca^{2+} concentrations enhances the muscle contractility.

extracellular Na^+ transport causes intracellular accumulation, which promotes Ca^{2+} entry via the Na^+–Ca^{2+} exchange. The drug's modest positive inotropic effect results from increased Ca^{2+} available to the contractile proteins.

(2) Antiarrhythmic effects. Digoxin also has some antiarrhythmic effects against supraventricular tachyarrhythmias which are mediated primarily via increased parasympathetic tone to the sinus and A-V nodes and atria. The drug also has some direct effects, which further prolong the conduction time and the refractory period of the A-V node.

(3) Digoxin also improves arterial baroreceptor sensitivity in heart failure, which helps counteract excessive neurohormonal activation.

c. Therapeutic uses and administration

(1) Digoxin is used for its modest positive inotropic effect. Digoxin has generally been used in the treatment of heart failure caused by or associated with myocardial failure, such as dilated cardiomyopathy and advanced, chronic pressure or volume overloads (e.g., aortic insufficiency, long-standing patent ductus arteriosus, mitral, or tricuspid insufficiency). However, this use is being supplanted by pimobendan.

(2) Digoxin is used for its antiarrhythmic effect against supraventricular arrhythmias. It is only moderately effective in slowing the ventricular response rate in atrial fibrillation and does not cause conversion to sinus rhythm.

(3) Digoxin is usually contraindicated in HCM, where it may worsen existing ventricular outflow obstruction; although it has been used when clinical signs of right heart failure develop. Digoxin is generally not useful for patients with pericardial disease. Digoxin is usually contraindicated when sinus

or A-V nodal disease is present; it is relatively contraindicated with most serious ventricular arrhythmias because the drug may exacerbate them.

(4) **Factors affecting dosage.** Conservative doses should be used. Therapy is almost always begun using oral maintenance (rather than IV or loading) doses. There is only a weak correlation between digoxin dose and serum concentration in dogs with heart failure, indicating that other factors are important in determining the serum concentrations of this drug.

(a) **Renal function.** Serum digoxin concentrations are increased in dogs and cats with renal dysfunction because of reduced total body clearance and volume of distribution. There appears to be no correlation between degree of azotemia and serum concentration.

(b) **Body condition.** Since much of the drug is bound to skeletal muscle, animals with reduced muscle mass or cachexia, as well as those with compromised renal function can easily become toxic at the usual calculated doses. In addition, because digoxin has poor lipid solubility the dose should be based on the calculated lean body weight; this is especially important in obese animals.

(c) **Serum concentration measurement.** After 1 week of therapy (or dosage alteration) serum concentrations should be measured.

i The sample is drawn 8–10 hours after the previous dose. If serum concentration is <0.8 ng/mL, the digoxin dose can be increased by ≤30%, and the serum concentration measured the following week.

ii If serum concentration cannot be measured and toxicity is suspected, the drug should be discontinued for 1–2 days, then reinstituted at half of the original dose.

(d) **Therapeutic serum concentration** is considered to be between 0.8 and 2.0 ng/mL. This is reached within 2–4.5 days (with PO dosing every 12 hours) in dogs. In cats, therapeutic serum concentration is achieved with low doses given every 48 hours; concentrations are ~50% higher with the alcohol-based (less palatable) elixir than with tablets. In horses, serum concentrations of 0.5–2.0 ng/mL are achieved within 1–2 hours. Significant enterohepatic recycling may produce a second peak serum concentration in horses.

d. Pharmacokinetics

(1) **Absorption** is ~60% for the tablet form and 75% for the elixir. Absorption is decreased by food, kaolin–pectin compounds, antacids, and malabsorption syndromes. Steady state serum concentrations are achieved in ~7 days for dogs, in ~10 days for cats, and in 3–5 days for horses.

(2) **Fate.** About 27% of the drug in serum is protein bound. Elimination is mainly renal. There is minimal hepatic metabolism. Digoxin $t_{1/2}$ is reported to be 23–39 hours in dogs, 25–78 hours in cats, and 13–23 hours in horses.

e. Adverse effects. Myocardial toxicity is of greater concern than GI toxicity. Fatal myocardial toxicity may occur before other signs develop, especially in patients with myocardial failure. **P-R interval prolongation or signs of GI toxicity should *not* be used to guide progressive dosing of digitalis.** Serum concentration measurement should be used to guide dosing. Loading doses should not be used in myocardial failure.

(1) **Myocardial toxicity** can cause almost any cardiac rhythm disturbance, including ventricular tachyarrhythmias, supraventricular premature complexes and tachycardia, sinus arrest, Mobitz type I second-degree A-V block, and junctional rhythms.

(a) **Calcium overload.** Diastolic sequestration and systolic release of Ca^{2+} may be impaired in diseased myocardial cells. Digoxin use can lead to cellular Ca^{2+} overload and electrical instability.

(b) Toxic levels of digoxin also **increase sympathetic** tone to the heart causing increased automaticity. In addition, the parasympathetic effects of slowed conduction and altered refractory period facilitate the occurrence of re-entrant arrhythmias.

(c) Digoxin also can stimulate spontaneous automaticity of myocardial cells by inducing and potentiating **late after-depolarization**; this is enhanced by cellular stretch, calcium overloading, and hypokalemia.

(2) **GI toxicity.** GI upset is the other major toxicity and may occur before signs of myocardial toxicity develop, especially in patients without myocardial failure. Its signs include anorexia, depression, vomiting, borborygmus, and diarrhea. Direct effects of digitalis on chemoreceptors in the area postrema of the medulla may be the cause of some of the GI signs (e.g., vomiting).

(3) **Factors predisposing to digoxin toxicity**

(a) **Hypokalemia** predisposes to myocardial toxicity by leaving more available binding sites on membrane Na^+, K^+-ATPase for digitalis.

(b) **Renal dysfunction** (see above)

(c) **Hypercalcemia** and **hypernatremia** potentiate both the inotropic and toxic effects of the drug.

(d) **Abnormal thyroid** hormone levels can lead to digitalis toxicity (hyperthyroidism increases the drug's myocardial effects and hypothyroidism reduces its clearance); therefore, dosage reduction may be needed.

(e) **Hypoxia** sensitizes the myocardium to the toxic effects of digitalis.

(f) **Certain drugs** increase digoxin serum concentration. Quinidine displaces the drug from skeletal muscle binding sites and reducing its renal clearance. Verapamil and amiodarone also can increase serum digoxin concentration; other drugs possibly do as well (including diltiazem, prazosin, spironolactone, and triamterene). Drugs affecting hepatic microsomal enzymes may also have effects on digoxin metabolism. Neomycin and sulfasalazine decrease bioavailability.

(4) **Therapy for digitalis toxicity** depends on the signs manifested.

(a) **GI signs** usually respond to drug withdrawal and correction of fluid or electrolyte disturbances.

(b) **Atrioventricular conduction abnormalities** also usually resolve with drug withdrawal, although sometimes an anticholinergic agent is needed.

(c) **Ventricular tachyarrhythmias** in dogs are treated with lidocaine or phenytoin.

i Other therapy includes IV K^+ supplementation (if serum K^+ is <4.0 mEq/L), IV fluid to correct dehydration and maximize renal function, and in some cases, propranolol to help control ventricular tachyarrhythmias (as long as no conduction blocks are present).

ii Oral administration of the steroid-binding resin cholestyramine is only useful very soon after accidental overdosage of digoxin, since this drug undergoes minimal enterohepatic circulation. A preparation of digoxin-specific antigen binding fragments (Digoxin immune Fab; Digibind®) derived from ovine antidigoxin antibodies have been used occasionally for digoxin overdose in dogs.

3. **Dobutamine and dopamine (sympathomimetic agents).** See Chapter 2 for more information.

a. **Preparation and chemistry. Dopamine** (Intropin®) is an endogenous catecholamine that is a precursor to norepinephrine. **Dobutamine** (Dobutrex®) is a synthetic analog of dopamine.

b. **Pharmacologic effects and mechanism of action.** Catecholamines increase contractility and heart rate, especially at higher doses. Stimulation of cardiac β_1-adrenergic receptors (coupled to G_s) activates adenylyl cyclase to increase cyclic AMP synthesis, which stimulates a protein kinase A that in turn activates Ca^{2+} channels, leading to increased Ca^{2+} influx and greater contractility.

(1) **Dopamine** stimulates β- and α-receptors at higher doses. Peripheral vasoconstriction occurs at 10–15 mcg/kg/min. At low doses (less than 2–5 mcg/kg/min IV infusion), it also stimulates vasodilator dopaminergic receptors in the renal, mesenteric, coronary, and cerebral circulations.

(2) **Dobutamine** stimulates β_1-receptors, but has only weak action on β_2- and α-receptors; it does not stimulate dopaminergic receptors. The drug increases

contractility, with minimal effects on heart rate and blood pressure at lower infusion rates (3–7 μg/kg/min).

c. Therapeutic uses and administration

(1) Myocardial failure. Dopamine and dobutamine are used, in conjunction with other therapy, for short-term inotropic and blood pressure support in dogs and cats with myocardial failure. Use of catecholamines for heart failure is limited by the development of β-receptor downregulation. Generally these drugs are given for no more than 3 days.

(2) Hypotension that is not responsive to fluid loading.

(3) Dopamine is also used to increase renal blood flow in acute oliguric renal failure.

d. Pharmacokinetics. The very short $t_{1/2}$ (less than 2 minutes) and extensive hepatic metabolism of the catecholamines used clinically makes them suitable only for IV administration, usually by constant infusion.

e. Adverse effects. At higher doses, dopamine and dobutamine increase heart rate, myocardial oxygen demand, and the risk of inducing ventricular arrhythmias. Development of sinus tachycardia or tachyarrhythmias should prompt a decrease in infusion rate.

(1) Dobutamine is less arrhythmogenic than other catecholamines, but may precipitate supraventricular and ventricular arrhythmias at higher infusion rates (10–20 mcg/kg/min). Cats are more sensitive to dobutamine than dogs and may exhibit seizures or other adverse effects at relatively low dosages.

(2) By increasing renal blood flow, dopamine may enhance the renal clearance of other drugs.

4. Amrinone and **Milrinone** (phosphodiesterase inhibitors)

a. Preparation and chemistry. Amrinone is also known as inamrinone. Amrinone and milrinone are bipyridine cardiac inotropic agents.

b. Pharmacologic effects and mechanism of action. These agents inhibit phosphodiesterase III, an intracellular enzyme that degrades cAMP. They produce vasodilation as well as an increase in myocardial contractility.

c. Therapeutic uses and administration. Amrinone and milrinone are sometimes used for short-term inotropic support in dogs and cats with severe myocardial failure. The drugs are available for IV injection. They can be used concurrently with other types of inotropic agents.

d. Pharmacokinetics. Effects begin within 3 minutes and peak in 10 minutes after IV bolus injection, but are short-lived in normal dogs (<30 minutes). Constant infusion is required for sustained effect. Peak effect using constant rate infusion occurs in ~45 minutes in dogs.

e. Adverse effects

(1) These agents may exacerbate ventricular tachyarrhythmias.

(2) Higher dosages result in greater vasodilation, with reduction of blood pressure and increases in heart rate.

(3) Other adverse effects could include vomiting/diarrhea, hepatotoxicity, thrombocytopenia (with prolonged use).

G. Drugs used in heart disease causing diastolic function. Agents that increase diastolic filling time, reduce myocardial O_2 requirements, and/or facilitate myocardial relaxation are used in the treatment of HCM and other causes of severe hypertrophy.

1. β-Blockers such as atenolol (propranolol, metoprolol, and others) are often used to slow heart rate and reduce myocardial O_2 consumption. See II D and Chapter 2 for more information.

a. Certain β-blockers (e.g., carvedilol, metoprolol) may also be useful in the long-term management of dilated cardiomyopathy and chronic valve disease, but further study is needed.

2. Calcium entry blockers, as a group, cause coronary and systemic vasodilation, enhanced myocardial relaxation, and sometimes, reduced cardiac contractility. **Diltiazem** has been used commonly in cats with HCM (see II D for additional information).

3. **ACE inhibitors** (e.g., enalapril, benazepril) are being increasingly used in the management of CHF from HCM (see above and also Chapter 3).

II. ANTIARRHYTHMIC DRUGS

A. Introduction

1. **Multiple factors underlie the development of cardiac rhythm disturbances.**
   - **a.** Both overt and subclinical changes in cardiac structure or function can alter cell electrophysiologic characteristics in ways that predispose to arrhythmia formation.
     - **(1)** Changes in normal cellular conduction properties or automaticity caused by cardiac structural or physiologic remodeling can predispose to arrhythmia development. Genetic factors and environmental stresses can contribute.
     - **(2)** Additional triggering (e.g., premature stimulus or abrupt change in heart rate) and/or modulating factors (e.g., changes in autonomic tone, circulating catecholamines, ischemia, or electrolyte disturbances) also appear necessary to provoke and sustain rhythm disturbances.
   - **b.** Abnormal rhythms, as well as normal sinus node activity, are influenced by the autonomic nervous system. Many conditions affect prevailing autonomic tone.
2. In general, underlying mechanisms are categorized as disorders of impulse formation, disorders of impulse conduction, or combinations of both. Identifying the specific mechanism for an arrhythmia in the individual patient is often difficult.
   - **a.** Disorders of impulse conduction can cause bradyarrhythmias when conduction fails in the AV node, atria, or SA node, causing asystole or a slow escape rhythm.
   - **b.** Disorders of impulse conduction can also cause tachyarrhythmias when re-entry (re-entrant excitation, circus movement, reciprocating tachycardia) occurs.
   - **c.** Re-entry is a common arrhythmia mechanism.
     - **(1)** It involves an area where conduction is blocked or delayed, but which recovers excitability in time to transmit the depolarizing wave back around so that tissue that had been previously depolarized becomes activated again.
     - **(2)** Re-entry can occur within defined anatomic pathways (anatomic re-entry) or because of functional electrophysiologic changes in adjacent tissues (functional re-entry).
3. The clinical context of the arrhythmia is important.
   - **a.** Some arrhythmias are benign and do not require treatment.
     - **(1)** Ventricular ectopy that develops after thoracic trauma in previously healthy animals generally resolves without therapy.
     - **(2)** Occasional ventricular premature contractions (VPCs) have also been identified in clinically normal animals.
   - **b.** While some arrhythmias are of no clinical consequence, others cause weakness, syncope, or sudden death, especially in animals with underlying disease.
   - **c.** Arrhythmias that compromise cardiac output, arterial blood pressure, and coronary perfusion can promote myocardial ischemia, deterioration of cardiac pump function, and, sometimes, sudden death.
     - **(1)** These arrhythmias tend to be either very rapid (e.g., sustained ventricular or supraventricular tachyarrhythmias) or very slow (e.g., advanced AV block with a slow or unstable ventricular escape rhythm).
     - **(2)** Rapid sustained tachycardia of either supraventricular or ventricular origin reduces cardiac output acutely, and eventually leads to myocardial dysfunction and CHF (tachycardia-induced cardiomyopathy).
4. An arrhythmia may be suspected from the animal's history or identified on physical examination.
   - **a.** An accurate ECG diagnosis is important.

B. Overview of cardiac arrhythmia therapy

1. Therapy is indicated for arrhythmias that cause clinical signs of hemodynamic compromise, and when the patient has a disease known to be associated with sudden arrhythmic death.
   - **a.** Ideal goals of antiarrhythmic drug therapy might be to totally suppress all abnormal beats, and prevent further arrhythmias and sudden death, but these are not often realistic goals.
   - **b.** Successful therapy usually is sufficient reduction in frequency (e.g., by ≥70–80%) or repetitive rate of ectopic beats to restore normal hemodynamic status and eliminate clinical signs.
   - **c.** Even apparently complete arrhythmia suppression does not remove the risk of a lethal arrhythmia and sudden death.
2. Antiarrhythmic drugs may slow the rate of tachycardia, terminate a re-entrant arrhythmia, or prevent abnormal impulse formation or conduction.
   - **a.** These effects can occur through modulation of tissue electrophysiologic properties and/or autonomic nervous system effects.
   - **b.** The traditional (Vaughan Williams) antiarrhythmic drug classification system consists of four classes based on the drug's predominant cardiac electrophysiologic effects (Table 8-2), but this system has shortcomings.
     - **(1)** Class I agents have membrane-stabilizing effects that tend to slow conduction as well as decrease automaticity and excitability.

TABLE 8-2. Antiarrhythmic Drug Classification*

Class	Drug	Mechanism and ECG Effects
I		Decrease fast inward Na^+ current; membrane-stabilizing effects (slowed conduction, decreased excitability and automaticity)
IA	Quinidine, procainamide	Moderately slows conduction, increases action potential duration; can prolong QRS complex and Q-T interval
IB	Lidocaine, mexiletine, phenytoin	Little change in conductivity, decreases action potential duration; QRS complex and Q-T interval unchanged
IC	Flecainide, propafenone	Markedly slows conduction without change in action potential duration
II	Atenolol, propranolol, esmolol, metoprolol, carvedilol, others	β-adrenergic blockade, reduces effects of sympathetic stimulation (no direct myocardial effects at clinical doses)
III	Sotalol, amiodarone, others	Selectively prolongs action potential duration and refractory period; antiadrenergic effects; Q-T interval prolonged
IV	Diltiazem, verapamil	Decreases slow inward Ca^{++} current (greatest effect on SA and AV nodes)
Other agents with antiarrhythmic effects include	Digoxin	Antiarrhythmic action results mainly from indirect autonomic effects, especially increased vagal tone
	Atropine and other anticholinergic drugs	Oppose vagal effects on SA and AV nodes

*Adapted from Wendy A. Ware. *Cardiovascular Disease in Small Animal Medicine*. 2007, London, UK, Manson Publishing, p. 199.

(2) Class II consists of β-adrenergic antagonists, which act by inhibiting catecholamine effects on the heart.
(3) Class III drugs prolong the effective refractory period of cardiac action potentials without decreasing conduction velocity.
(4) Class IV contains calcium-entry blocking drugs. These are most useful for supraventricular tachyarrhythmias; ventricular arrhythmias usually are unresponsive to them.

c. Suggested drug dosages are listed in Appendix II.

3. Therapy for supraventricular tachyarrhythmias

a. Supraventricular premature complexes:
(1) Occasional premature beats do not require antiarrhythmic therapy.
(2) Predisposing factors should be minimized as far as possible.

b. Frequent atrial premature contractions or brief paroxysmal supraventricular tachycardia (SVT):
(1) Digoxin (Table 8-2) is used first in dogs with heart failure and in cats with dilated cardiomyopathy.
(2) A β-blocker or the Ca^{2+} blocker diltiazem can be added if the arrhythmia is not sufficiently controlled with digoxin (along with an ACE inhibitor and furosemide for heart failure).
(3) For cats with HCM or hyperthyroidism a β-blocker (e.g., atenolol or propranolol) is used, although diltiazem could be an alternative.
(4) Recurrent supraventricular tachyarrhythmias that are refractory to these drugs may respond to amiodarone, sotolol, procainamide, quinidine, or a Class IC agent.

c. Acute therapy for sustained or persistent paroxysmal SVT:
(1) A vagal maneuver is tried initially for sustained SVT.
(2) When SVT persists, a Ca^{2+} channel blocker is usually administered next.
(a) Diltiazem (IV or PO loading) is preferred.
(b) Verapamil (IV) is also effective, but is not recommended for dogs with myocardial dysfunction or heart failure because of its greater negative inotropic effect.
(3) A β-blocker given slowly IV (propranolol, esmolol) is an alternative, but also has negative inotropic effects.
(4) IV digoxin is another alternative, but it is generally less effective than Ca^{2+} channel blockers.
(a) Digoxin is not used in pre-excitation syndrome because it can decrease the refractory period of the accessory pathway, although it slows AV conduction.
(5) Lidocaine (IV) can be effective in some cases of SVT caused by an accessory pathway or ectopic atrial focus, although it is most often used for wide-QRS tachyarrhythmias.
(6) If Ca^{2+} channel- or β-blocker or lidocaine therapy does not control persistent SVT, IV procainamide may.
(7) Refractory SVT (AV node-independent) may respond to sotalol or amiodarone.
(8) Once the rhythm is controlled, PO maintenance digoxin and/or diltiazem or a β-blocker are used most often for long-term therapy.
(a) Amiodarone or sotalol are alternative agents in cases refractory to conventional drugs.
(b) Procainamide, quinidine, or a Class IC drug have also been used

d. Atrial fibrillation (AF) is usually associated with marked atrial enlargement, except in large/giant breeds of dog and in large animal species. Because permanent conversion to sinus rhythm is unlikely in most animals with atrial enlargement, the usual goals of therapy are to slow AV conduction and to manage underlying disease.
(1) If rapid HR reduction is indicated, IV diltiazem is recommended because it has less negative inotropic effect than verapamil and propranolol.

(2) Long-term oral therapy usually includes digoxin in dogs (and cats with myocardial failure). But **digoxin alone often does not adequately slow the heart rate animals with heart failure or during exercise.** Either a β-blocker or diltiazem can be added to further slow AV conduction; low initial doses are used and titrated upward to effect.
(3) Amiodarone can be used if additional rate control is needed.
(4) For cats with HCM and AF, diltiazem or a β-blocker is used without digoxin.
(5) When ventricular pre-excitation is present in a patient with AF, AV nodal blocking drugs (Ca^{2+} blockers, digoxin, and possibly β-blockers) should not be used because they can paradoxically increase the ventricular response rate. Amiodarone is recommended in these cases; sotalol or procainamide can also be used.

e. AF in larger animals without signs of heart disease or failure may convert to sinus rhythm, either spontaneously or with drug treatment or electrical cardioversion. Conversion is more likely with AF of recent onset and normal atrial size.
(1) Pharmacologic cardioversion is sometimes achieved with quinidine, but this is only used where this is no or only mild underlying disease.
(2) Alternatively, high-dose diltiazem alone (PO for 3 days) has sometimes been effective in dogs, as has amiodarone, propafenone, and sotolol. Acute onset AF associated with high vagal tone may convert with IV lidocaine.

4. Therapy for ventricular tachyarrhythmias

a. Occasional ventricular premature complexes (VPCs) are usually not treated, especially in an otherwise asymptomatic animal. Moderately frequent, single VPCs of uniform configuration may also not require antiarrhythmic drug treatment, especially if underlying heart function is normal.

b. Acute therapy for ventricular tachycardia
(1) Lidocaine (IV) is usually the first-choice drug for controlling serious ventricular tachyarrhythmias in dogs.
(2) PO sotalol, or mexiletine, or IV amiodarone, can be more effective in some cases. IV amiodarone must be given cautiously because marked hypotension can occur.
(3) Alternatively, procainamide (given IV, IM, or PO) or quinidine (given IM or PO) can be tried. If a single IM or PO loading dose of either drug is effective (within 2 hours), lower doses can be given every 4–6 hours IM or PO.
(4) Addition of a β-blocker or other combination therapy is sometimes effective.
(5) Cats with frequent ventricular tachyarrhythmias are usually given a β-blocker first. Alternatively, low doses of lidocaine can be tried, but cats, are sensitive to the neurotoxic effects of this drug. Procainamide or sotolol can also be used.

c. Chronic oral therapy for ventricular tachyarrhythmias
(1) The same, or similar, drug that was most effective during acute therapy is often continued PO in cases where long-term therapy is needed.
(2) Sustained-release procainamide or mexiletine (Class I agents) can be used alone, or with a β-blocker. β-Blockers may confer some protection against ventricular fibrillation.
(3) Sotolol or amiodarone (Class III agents) may provide greater antifibrillatory protection.

5. Therapy for bradyarrhythmias

a. If the arrhythmia is the result of a drug effect, discontinuation or dosage reduction is also used, as appropriate.

b. Symptomatic bradyarrhythmias (e.g., sinus bradycardia, sick sinus syndrome, atrial standstill, high grade AV block) are initially treated with atropine (or atropine challenge test).

c. If the arrhythmia is responsive to atropine challenge, oral anticholinergic therapy may be useful.

d. An emergency infusion of dopamine or isoproterenol may increase the ventricular escape rate in animals with high-grade AV block, although ventricular tachyarrhythmias may also be provoked

e. Temporary or permanent artificial pacing is indicated when there is inadequate increase in heart rate with medical therapy.

C. Class I agents (membrane stabilizers)

1. **Class I agents (local anesthetics)** slow conduction and decrease automaticity and excitability by their membrane stabilizing effects. Most of these agents are dependent on extracellular K^+ concentration for their effects.
   a. Drugs in Class I have also been subclassified (see Table 8-2).
   b. Concurrent use of a Class I drug and a drug of another class (or even subclass) may increase antiarrhythmic efficacy in cases refractory to a single agent.
   c. Contraindications. All these drugs are contraindicated in the presence of complete heart block, and should be used only cautiously in patients with sinus bradycardia, sick sinus syndrome, and first- or second-degree A-V blocks.
   d. Adverse effects. All antiarrhythmic drugs may cause exacerbation of arrhythmias (proarrhythmic effect), especially the Class IC agents.
2. **Lidocaine**
   a. Preparation and chemistry. Lidocaine HCl is available as an injectable solution of various concentrations. The 2% concentration is most commonly used.
   b. Pharmacologic effects and mechanism of action. Lidocaine has little effect on sinus rate, AV conduction rate, and refractoriness. See Table 8-2, Class IB.
      (1) The electrophysiologic effects of lidocaine (and other Class I drugs) are very dependent on extracellular K^+ concentration; hypokalemia may make the drug ineffective, while hyperkalemia intensifies the drug's depressant effects on cardiac membranes.
      (2) Lidocaine suppresses automaticity in both normal Purkinje fibers and diseased myocardial tissue, slows conduction, and reduces the supernormal period. It has greater effects on diseased and hypoxic cardiac cells.
      (3) Lidocaine produces minimal hemodynamic effects and little to no depression of contractility at therapeutic doses when given slowly IV. Hypotension can be associated with toxic levels.
   c. Therapeutic uses and administration. Lidocaine is used IV mainly to suppress frequent ventricular premature contractions and ventricular tachycardia, although it may convert some cases of SVT.
   d. Pharmacokinetics
      (1) Because of almost complete first-pass hepatic elimination, lidocaine is administered IV, usually as slow boluses followed by constant rate infusion. Antiarrhythmic effects after an IV bolus occur within 2 minutes and disappear within 10–20 minutes.
      (2) Constant rate infusion without a loading dose results in steady state levels in 4–6 hours.
      (3) Lidocaine undergoes rapid hepatic metabolism; some metabolites are active. The $t_{1/2}$ after IV injection is <1 hour in the dog (similar in the cat).
      (4) A V_d of 5.7 L/kg and Cl_T of 62 mL/min/kg are reported for the dog. A V_d of 1.7 L/kg, Cl_T of 64.4 mL/min/kg, and a $t_{1/2}$ of 3.1 hours are reported for the horse.
      (5) Therapeutic plasma concentrations are 2–6 mcg/mL.
      (6) Propranolol, cimetidine, and other drugs which decrease liver blood flow slow the metabolism of lidocaine. Reduced hepatic blood flow associated with heart failure can also predispose to toxicity.
   e. Adverse effects. Central nervous system (CNS) excitation is the most common toxic effect. Signs include agitation, disorientation, muscle twitches, nystagmus, and generalized seizures. Nausea may also occur. Cats are particularly sensitive to the drug's toxic effects and may suffer respiratory arrest along with seizures. Horses are also very sensitive to CNS toxic effects. QRS widening can occur.
3. **Mexiletine**
   a. Preparation and chemistry. Mexiletine HCl is available as oral capsules.

b. Pharmacologic effects and mechanism of action. Mexiletine is similar to lidocaine in its electrophysiologic, hemodynamic, and antiarrhythmic properties (see Table 8-2).

c. Therapeutic uses and administration. Mexiletine is used to suppress frequent ventricular premature contractions and ventricular tachycardia.

d. Pharmacokinetics

(1) Mexiletine appears to have good oral absorption.

(2) The drug is highly protein bound. It undergoes liver metabolism (influenced by liver blood flow) and some renal excretion (which is slower with alkaline urine). The $t_{1/2}$ in dogs is 4.5–7 hours (depending to some degree on urine pH).

(3) Therapeutic serum concentration is thought to be 0.5–2.0 mcg/mL.

e. Adverse effects. Toxic effects are similar to lidocaine. Vomiting, anorexia, tremor, ataxia, disorientation, sinus bradycardia, and thrombocytopenia have been reported in dogs.

4. Procainamide

a. Preparation and chemistry. Procainamide HCl is similar in structure to procaine. It is available as an injectable solution and in tablets or capsules as well as extended release tablets.

b. Pharmacologic effects and mechanism of action (see Table 8-2). Procainamide has both direct (Class IA) and indirect (vagolytic) effects similar to quinidine.

(1) Oral and IM administrations of this drug are not associated with marked hemodynamic effects; however, rapid IV injection can cause significant hypotension and cardiac depression (but less than with IV quinidine).

c. Therapeutic uses and administration. Procainamide is used mainly for frequent ventricular premature contractions and ventricular tachycardia; it also may be effective against some supraventricular tachyarrhythmias.

d. Pharmacokinetics

(1) Procainamide is well absorbed orally in the dog. Procainamide is thought to be 20% protein bound in the dog. The V_d is 1.4–2.1 L/kg in dogs.

(2) Constant IV infusion may be used; steady state is reached in 12–22 hours.

(3) Elimination is by hepatic metabolism as well as renal excretion in proportion to the creatinine clearance. The $t_{1/2}$ is 2.5–4 hours; the sustained release form has a slightly longer $t_{1/2}$ of 3–6 hours in dogs.

(4) The metabolite N-acetylprocainamide is found in horses, but is not present to any significant degree in dogs. In the horse, a V_d of 2.4 L/kg, Cl_T of 3.9 mL/min/kg, and a $t_{1/2}$ of 3–7 hours are reported.

(5) Therapeutic plasma range in dogs is 4–12 mcg/mL.

e. Adverse effects. Procainamide may exacerbate hypotension or heart failure.

(1) The toxic effects are similar to those of quinidine but usually milder. GI upset and prolongation of the PR, QRS, or Q-T intervals can occur.

(2) Increased ventricular response rate to atrial fibrillation can result when used without digoxin, β-blocker, or Ca^{2+} entry blocker.

(3) More serious toxic effects include hypotension, depressed A-V conduction, and worsening of arrhythmias (may result in syncope or ventricular fibrillation).

5. Quinidine

a. Preparation and chemistry. Quinidine is an alkaloid derived from quinine or the cinchona (or related) plants. Gluconate, polygalacturonate, and sulfate salts have been used clinically PO. The gluconate salt is available for injection.

b. Pharmacologic effects and mechanism of action. Quinidine is a Class IA agent (see Table 8-2). The drug's actions result from both direct electrophysiologic and vagolytic effects.

(1) Its indirect (vagolytic) effects, at low doses, may increase sinus node rate or the ventricular response rate to atrial fibrillation by antagonizing the drug's direct effects.

(2) As with other Class I agents, hypokalemia reduces the antiarrhythmic effectiveness of quinidine.

(3) Vasodilation (via α-receptor blockade), cardiac depression, and hypotension result from IV administration. Oral and IM administrations are usually not associated with adverse hemodynamic effects, but could be in patients with underlying cardiac disease.

c. Therapeutic uses and administration. Quinidine is used less commonly than other antiarrhythmic agents now. It can be effective against frequent ventricular tachyarrhythmias; it also may be effective against some supraventricular tachyarrhythmias.

(1) Quinidine may successfully convert recent-onset atrial fibrillation to sinus rhythm in horses, cattle, and large dogs with normal heart size and function.

d. Pharmacokinetics

(1) Quinidine is well absorbed orally with little first-pass hepatic elimination. The sulfate salt is more rapidly absorbed than the gluconate. Peak effect is usually achieved 1–2 hours after oral administration.

(2) The drug is highly protein bound in dogs and cats. In the dog, a V_d of 2.9 L/kg and a Cl_T of 6 mL/min/kg are reported. In the cat, a V_d of 2.2 L/kg and Cl_T of 14.8 mL/min/kg are reported.

(3) There is extensive hepatic metabolism that is not greatly dependent on liver blood flow. Quinidine has a $t_{1/2}$ of ~6 hours in the dog, and ~2 hours in the cat. Anticonvulsants and other drugs which induce hepatic microsomal enzymes can speed the drug's metabolism.

(4) Therapeutic blood levels (2.5–5 mcg/mL) are usually reached in 12–24 hours after PO and IM administration.

(5) Slow-release sulfate, gluconate, and polygalacturonate salts prolong the drug's absorption and elimination. Administration of these q8 hours is probably adequate for dogs, while standard quinidine sulfate should be given q6 hours.

(6) In the horse, a V_d of 2.9–6.3 L/kg, Cl_T of 6–16 mL/min/kg, and a $t_{1/2}$ of 4–7 hours are reported. The drug is usually given by nasogastric tube every 2 hours for up to 5–6 doses to convert atrial fibrillation. From 10 to 50% absorption occurs within 2 hours.

(7) A plasma concentration of 2–4 mcg/mL is thought to be therapeutic.

e. Adverse effects. Quinidine may exacerbate hypotension or heart failure. It should not be administered IV.

(1) Toxicity occurs as an extension of the drug's electrophysiologic and hemodynamic actions. Prolongation of ECG intervals occurs as plasma concentration increases. Marked Q-T prolongation, development of bundle branch block, or QRS widening greater than 25% of the pretreatment value suggest toxicity. All degrees of A-V block and ventricular tachyarrhythmias can also result.

(2) Lethargy, weakness, and CHF can result from the drug's negative inotropic and vasodilatory effects and subsequent hypotension.

(3) Cardiotoxicity and hypotension may be partially reversible by sodium bicarbonate therapy. This temporarily decreases serum K^+ concentration and increases quinidine's binding to albumin. Because of its extensive protein binding, severe hypoalbuminemia can predispose to toxicity.

(4) GI signs (nausea, vomiting, and diarrhea) are common with oral quinidine therapy. Apprehension, depression, diarrhea, and anorexia are common in horses.

(5) Quinidine can precipitate digoxin toxicity when both drugs are used together, as it displaces digoxin from skeletal muscle-binding sites and decreases digoxin's renal clearance.

6. Phenytoin

a. Preparation and chemistry. Phenytoin Na^+ is a hydantoin-derivative available as an injectable solution in a propylene glycol/alcohol vehicle.

b. Pharmacologic effects and mechanism of action. Phenytoin is similar to lidocaine, but it also has some slow calcium channel inhibitory and CNS effects that may contribute to its effectiveness against digitalis-induced arrhythmias.

c. Therapeutic uses and administration. Phenytoin is used in dogs only for the therapy of digitalis-induced ventricular arrhythmias that are not responsive to lidocaine; phenytoin is not used in cats.

d. Pharmacokinetics

(1) Oral bioavailability is poor; the drug is administered slowly IV.

(2) The drug is metabolized in the liver and, by stimulating hepatic microsomal enzymes, may speed its own elimination.

(3) The $t_{1/2}$ of phenytoin is only about 3 hours in the dog; the V_d is 1.2 L/kg and the Cl_T is 4 mL/min/kg. The drug is not used in cats, as the $t_{1/2}$ is very long (>40 hours).

(4) Therapeutic plasma range is 10–16 μg/mL.

e. Adverse effects. The drug has been associated with bradycardia, A-V blocks, ventricular tachycardia, and cardiac arrest.

(1) Rapid IV injection is avoided because the propylene glycol vehicle can depress myocardial contractility and cause vasodilation, hypotension, exacerbation of arrhythmias, and respiratory arrest. Slow IV infusion and oral administration do not cause significant hemodynamic disturbances.

(2) Other toxicity signs include depression, nystagmus, disorientation, and ataxia.

(3) Even low doses can produce toxic serum concentrations in cats.

7. Other Class I drugs. Flecainide and propafenone (Class IC) markedly reduce cardiac conduction velocity; they may depress automaticity in the sinus node and specialized conducting tissues at high doses. Proarrhythmia is a serious potential adverse effect of these Class IC agents. Bradycardia, intraventricular conduction disturbance, and consistent (although transient) hypotension have occurred in dogs, as well as nausea, vomiting, and anorexia. Hypotension from vasodilation and myocardial depression after IV administration can be significant.

D. Class II agents (β-blockers) act by inhibiting catecholamine effects on the heart. They slow heart rate, reduce myocardial oxygen demand, and increase AV conduction time and refractoriness.

1. β-blockers are indicated for supraventricular tachyarrhythmias (including paroxysmal atrial tachycardia and frequent atrial premature complexes) and to slow the ventricular response rate in atrial fibrillation (usually in combination with digoxin).

a. A β-blocker is the drug of first choice in cats for both supra- and ventricular tachyarrhythmias.

b. In dogs, the combination of a β-blocker with a Class I agent often provides better arrhythmia suppression than either alone.

c. β-blockers are also used to decrease heart rate and myocardial O_2 demand in HCM and other causes of myocardial hypertrophy, as well as in the therapy of hypertension.

2. The antiarrhythmic effect of β-blockers relates to β_1-receptor blockade rather than direct electrophysiologic effects.

a. Although β-receptor blockers cause little negative inotropic effect in normal animals, in those with severe underlying myocardial disease (and dependent on increased sympathetic drive to maintain cardiac output) depression of cardiac contractility, conduction, and heart rate can result.

(1) Because the drug's effects are dependent on the level of sympathetic activation, individual response is quite variable.

(2) Initial dosages should be low and titrated upward as needed.

b. β-blockers enhance the depression of A-V conduction produced by digoxin, Class I antiarrhythmic drugs, and calcium entry blockers.

(1) Using a β-blocker and calcium entry blocker simultaneously is not recommended and can lead to marked decreases in heart rate and myocardial contractility.

(2) β-blockers can decrease liver blood flow, leading to reduced elimination of drugs that are highly dependent on liver blood flow for clearance (e.g., lidocaine, phenytoin).

c. Toxicity is usually related to excessive β-blockade, and can lead to bradycardia, heart failure, and hypotension.
(1) Bronchospasm or increased vascular resistance can occur with nonselective β-blockers (β_1 and β_2).
(2) Lipophilic β-blockers (e.g., propranolol) can cause depression and disorientation via CNS effects.
(3) Because of possible β-receptor "up-regulation" (increased number and/or affinity of receptors) during chronic β-blockade, abrupt cessation of therapy could result in serious arrhythmias.
(4) β-blockers may also prevent the appearance of early signs of acute hypoglycemia in diabetics (e.g., tachycardia and blood pressure changes). These drugs also reduce the release of insulin in response to hyperglycemia.

3. Atenolol
a. Preparation and chemistry. Tablets are used most often; an injectable is available.
b. Pharmacologic effects and mechanism of action. Atenolol has β_1-receptor selectivity.
c. Therapeutic uses and administration. See **II D 1**, above. Atenolol is the agent used most often for chronic oral β-blockade.
d. Pharmacokinetics
(1) Oral bioavailability in dogs and cats is about 90%.
(2) Atenolol is excreted in the urine; renal impairment delays clearance. The $t_{1/2}$ of atenolol is slightly over 3 hours in dogs and about 3.5 hours in cats.
(3) Atenolol's β-blocking effects are evident for 12 hours but are gone by 24 hours in normal cats.
e. Adverse effects. Weakness or exacerbation of heart failure can be observed, as with other β-blockers. Adverse CNS effects are unlikely because atenolol is hydrophilic and does not readily cross the blood–brain barrier.

4. Propranolol
a. Preparation and chemistry. Propranolol HCl is available as an injectable solution as well as oral tablets and solution.
b. Pharmacologic effects and mechanism of action. Propranolol is a nonselective β-blocker.
c. Therapeutic uses and administration. Propranolol can be used for acute (IV) or chronic (oral) β-blockade.
d. Pharmacokinetics
(1) Feeding delays the rate of oral absorption and increases the clearance of an intravenous dose (by increasing liver blood flow).
(2) Propranolol has extensive first-pass hepatic metabolism; however, chronic administration and higher doses cause hepatic enzyme saturation and increased bioavailability. Propranolol lowers hepatic blood flow, thereby prolonging its own elimination and that of other drugs dependent on liver blood flow for their metabolism.
(3) The $t_{1/2}$ of propranolol in the dog is only 1.5 hours or less (0.5 to over 4.2 hours in cats), but active metabolites exist. A V_d of 3.3–6.5 L/kg and Cl_T of 34–70 mL/min/kg are reported in the dog. Dosing q8 hours appears to be adequate in both dogs and cats.
(4) In the horse, a V_d of 2.3 L/kg, Cl_T of 12–21 mL/min/kg, and a $t_{1/2}$ of 1.2–1.7 hours are reported. Bioavailability is low.
e. Adverse effects. Propranolol toxicity is usually related to excessive β-blockade. Propranolol and other lipophilic β-blockers can cause depressed attitude and disorientation because of CNS effects.

5. Esmolol
a. Preparation and chemistry. Esmolol HCl is used as an IV injection.
b. Pharmacologic effects and mechanism of action. Esmolol is an ultra-short acting agent that selectively blocks β_1-adrenergic receptors.
c. Therapeutic uses and administration. Esmolol is useful as short-term treatment for acute (usually supraventricular) tachyarrhythmias and CHF from hypertrophic

obstructive cardiomyopathy. Esmolol can be used to test whether a β-blocker would be an effective therapeutic strategy in such cases.

d. Pharmacokinetics

(1) Esmolol is rapidly metabolized by blood esterases. The $t_{1/2}$ is less than 10 minutes.

(2) Steady state occurs in 5 minutes with, or 30 minutes without, a loading dose. Effects dissipate within 10–20 minutes of discontinuing infusion.

e. Adverse effects are minimal because of the drug's brief $t_{1/2}$.

6. Metoprolol

a. Preparation and chemistry. Metoprolol tartrate is available as oral tablets and an injectable. Metoprolol succinate extended release tablets are also available.

b. Pharmacologic effects and mechanism of action. Metoprolol is a β_1-selective agent.

c. Therapeutic uses and administration. Metoprolol (a second-generation β-blocker) has been used as an antiarrhythmic drug. It may be useful as well for long-term heart failure therapy in dogs with stable DCM and chronic valvular disease (see carvedilol, below).

d. Pharmacokinetics

(1) Metoprolol is well absorbed PO, but bioavailability is reduced by a large first-pass effect. There is minimal protein-binding.

(2) The drug is metabolized in the liver and excreted in the urine. $t_{1/2}$ is 1.6 hours in dogs and 1.3 hours in cats.

e. Adverse effects. As for other β-blockers, including exacerbation of CHF.

7. Carvedilol

a. Preparation and chemistry. Carvedilol is available in oral tablet form.

b. Pharmacologic effects and mechanism of action. Carvedilol blocks β_1-, β_2-, and α_1-adrenergic receptors, but is without intrinsic sympathomimetic activity. It also has some other effects (including antioxidant activity, some Ca^{2+} blocking effect, and also promotes vasodilation).

c. Therapeutic uses and administration. This third-generation β-blocker has been effective in people with chronic in heart failure in modulating pathologic cardiac remodeling and reducing mortality with long-term use. It is hoped that carvedilol (or metoprolol) might play a similar beneficial role in dogs; studies to evaluate this are ongoing.

d. Pharmacokinetics

(1) Peak plasma concentrations appear to be quite variable after oral administration.

(2) The drug is eliminated mainly through hepatic metabolism. The $t_{1/2}$ is short (<2 hours) in dogs; but an active metabolite is thought to account for the nonselective β-blocking effect which lasts for 12–24 hours.

e. Adverse effects. As for other β-blockers, including exacerbation of CHF.

8. Other β-blockers are available. Their basic effects are similar, although their relative selectivity for β_1-receptors as well as their pharmacologic characteristics vary.

E. Class III agents prolong action potential duration and effective refractory period without decreasing conduction velocity. They act mainly by inhibiting the repolarizing K^+ channel I_K (delayed rectifier).

1. Sotolol

a. Preparation and chemistry. Sotolol HCl is available as a tablet containing a racemic mixture of the d- and l- isomers.

b. Pharmacologic effects and mechanism of action. Sotalol is a nonselective β-blocker with Class III effects at higher doses. β-Blocking effects (from the l-isomer) occur at lower doses and are about 30% of propranolol's potency. d-Sotalol alone prolongs repolarization but has no β-blocking effect.

c. Therapeutic uses and administration. Sotolol is used mainly for ventricular tachyarrhythmias in dogs. Sotalol has also been used in cats with severe ventricular tachyarrhythmias.

d. Pharmacokinetics
- **(1)** The oral bioavailability of sotalol is high with negligible first-pass effect, but absorption is reduced with food.
- **(2)** Sotolol is eliminated unchanged by the kidneys; renal dysfunction prolongs elimination. The $t_{1/2}$ is about 5 hours in dogs.
- **(3)** Sotalol's β-blocking effects last longer than its plasma $t_{1/2}$.

e. Adverse effects. The drug has minimal hemodynamic effects, although it can cause hypotension.
- **(1)** Although it has less negative inotropic effect than propranolol, sotolol may exacerbate myocardial failure in dogs with DCM.
- **(2)** Other adverse effects of sotalol can include hypotension, depression, nausea, vomiting, diarrhea, and bradycardia.
- **(3)** Slowed sinus rate and first-degree heart block can occur. Sotalol can be proarrhythmic (as can all antiarrhythmic agents).

2. Amiodarone

a. Preparation and chemistry. Amiodarone HCl is an iodinated benzofuran. It is available as an oral tablet and injectable solution.

b. Pharmacologic effects and mechanism of action. Although classified as a Class III agent, it also shares properties with all three other antiarrhythmic drug classes. Besides prolonging the action potential duration and effective refractory period in both atrial and ventricular tissues, it has effects on Na^+, K^+, and Ca^{2+} channels, and has noncompetitive α_1- and β-blocking properties.
- **(1)** Amiodarone's β-blocking effects occur soon after administration, but maximal Class III effects (and prolongation of the action potential and QT interval) are not achieved for weeks with long-term administration.

c. Therapeutic uses and administration. Amiodarone is indicated for refractory tachyarrhythmias of both atrial and ventricular origin.

d. Pharmacokinetics. Amiodarone's pharmacokinetics are complex.
- **(1)** There is a delayed onset of action, and prolonged time (>10 weeks) to steady state. With long-term PO use, the drug concentrates in myocardial and other tissues (especially fat), and an active metabolite (desethylamiodarone) accumulates.
- **(2)** The drug is metabolized in the liver. The $t_{1/2}$ in dogs after a single PO dose is ~7.5 hours, but increases to 3.2 days with long-term use.
- **(3)** Therapeutic serum concentration is thought to be 1–2.5 mcg/mL.

e. Adverse effects
- **(1)** IV use can cause marked hypotension and bradycardia; hypersensitivity-type reactions (with acute angioedema formation) and tremors have also occurred.
- **(2)** Long-term use can be associated with many adverse effects, including depressed appetite, GI upset, pneumonitis leading to pulmonary fibrosis, hepatopathy, thyroid dysfunction, positive Coombs test, thrombocytopenia, and neutropenia. Other adverse effects noted with long-term use in people include corneal microdeposits, photosensitivity, bluish skin discoloration, and peripheral neuropathy.
- **(3)** Amiodarone can increase the serum concentrations of digoxin, diltiazem, and possibly, procainamide and quinidine.

F. Class IV agents (Ca^{2+} channel blockers) reduce cellular Ca^{2+} influx (the slow inward current) by blocking transmembrane L-type Ca^{2+} channels. As a group they can cause coronary and systemic vasodilation, as well as reduced myocardial contractility; but individual agents differ in these effects. Some calcium entry blockers (such as the nondihydropyridine Ca^{2+} channel blockers diltiazem and verapamil) have antiarrhythmic effects. These effects involve tissues dependent on the slow inward Ca^{2+} current. They cause dose-related slowing of the sinus node rate and A-V conduction. Contraindications to Ca^{2+} channel blocker use include sinus bradycardia, AV block, sick sinus syndrome, digoxin toxicity, and myocardial failure (for agents with pronounced negative inotropic effect). They are generally not used with a β-blocker.

1. **Diltiazem**
   a. **Preparation and chemistry.** Diltiazem HCl is a benzothiazepine Ca^{2+} channel blocker. It is available as oral tablets and injectable solution, as well as extended release tablets and capsules.
   b. **Pharmacologic effects and mechanism of action.** Diltiazem slows the sinus node rate, increases AV nodal refractory period, and can block some arrhythmias caused by abnormal automaticity, triggered mechanisms, and re-entry. Diltiazem also causes potent coronary and mild peripheral vasodilation. It has less negative inotropic effect than verapamil.
   c. **Therapeutic uses and administration.** Diltiazem is indicated for supraventricular tachyarrhythmias. It is often combined with digoxin to further slow the ventricular response rate to atrial fibrillation in dogs. **Diltiazem is the Ca^{2+} channel blocker recommended in cats with HCM.**
   d. **Pharmacokinetics**
      (1) Diltiazem's bioavailability is only about 43% in dogs because of extensive first-pass effect. Bioavailability of conventional diltiazem is greater in cats than in dogs.
      (2) Diltiazem is metabolized in the liver; active metabolites exist. Drugs that inhibit hepatic microsomal enzymes (e.g., cimetidine, ketoconazole, chloramphenicol) reduce diltiazem's metabolism.
      (3) Effects peak within 2 hours after PO dosing and last $\geq$6 hours in dogs. The $t_{1/2}$ in dogs is >2 hours, but is longer with chronic PO use because of its enterohepatic circulation.
      (4) The $t_{1/2}$ in cats is 2–3 hours; plasma concentrations peak within 30–90 minutes and effects last for 8 hours.
      (5) The therapeutic range is 50–300 ng/mL.
      (6) A sustained-release preparation (Cardizem-CD®) produces plasma concentrations that peak in 6 hours and remain in the therapeutic range for 24 hours in cats.
      (7) Diltiazem XR is another sustained-release preparation. The 240-mg capsule contains four tablets of 60 mg each. There appears to be much pharmacokinetic variability among individual cats. Sustained-release diltiazem may have lesser efficacy in preventing sinus tachycardia compared with atenolol. Adverse effects may also be more frequent, including anorexia, vomiting, lethargy, and evidence of hepatopathy in cats.
   e. **Adverse effects** are uncommon at therapeutic doses, but anorexia, nausea, bradycardia, and, rarely, other GI, cardiac, or neurologic effects may occur.
      (1) Cats sporadically develop liver enzyme elevation with anorexia. Anorexia and other GI signs are more likely at higher doses**.** Anecdotally, some cats become aggressive or show other personality change when treated with diltiazem.
      (2) The concurrent use of diltiazem (or verapamil) and a β-blocker can cause a sudden fall in the sinus rate or complete heart block.
      (3) Toxic effects can include reduced myocardial contractility, hypotension, depression, lethargy, bradycardia, and AV block.
2. **Other Ca^{2+} blocker drugs**
   a. **Verapamil** HCl (a phenylalkylamine) has the most potent cardiac effects of the clinically used Ca^{2+}-entry blockers.
      (1) Verapamil's $t_{1/2}$ in dogs is ~2.5 hours. It is poorly absorbed and undergoes first-pass hepatic metabolism, resulting in low oral bioavailability. The pharmacokinetics in cats are similar to dogs but are reportedly more variable.
      (2) Verapamil has marked negative inotropic, and some vasodilatory effects which can cause decompensation, hypotension and even death if underlying myocardial disease is present. Verapamil is not used in patients with heart failure.
      (3) Toxic effects of verapamil include sinus bradycardia, AV block, hypotension, reduced myocardial contractility, and cardiogenic shock. The

negative inotropic effects of verapamil may be reversed with IV Ca^{2+} salts, sympathomimetic drugs, or amrinone. Atropine may mitigate bradycardia or AV block precipitated by verapamil. Verapamil reduces the renal clearance of digoxin.

b. Other Ca^{2+} channel blockers (the dihydropyridines) are used for their vasodilating effect in hypertension or chronic heart failure management. Amlodipine besylate is used most often (see p. 197).

G. Other drugs with antiarrhythmic effects

1. **Anticholinergic drugs.** Atropine sulfate and glycopyrrolate are anticholinergic agents that act by antagonism of ACh at muscarinic receptors. They increase sinus rate and AV conduction when excessive vagal tone is present.
   a. Parenteral atropine or glycopyrrolate is indicated for sinus bradycardia or AV block induced by anesthesia, CNS lesions, and certain other diseases or toxicities. See Chapter 2 for more information. An atropine response test is often used in dogs and cats presented with a bradyarrhythmia to determine the extent of vagal influence.
   b. Bradyarrhythmias responsive to parenteral atropine or glycopyrrolate may also respond to oral anticholinergic agents such as propantheline bromide and hyoscyamine sulfate.
   c. Adverse effects of vagolytic drugs include aggravation of paroxysmal supraventricular tachyarrhythmias (as in sick sinus syndrome). Other side effects of anticholinergic therapy include vomiting, diarrhea, dry mouth, keratoconjunctivitis sicca, and drying of respiratory secretions.
2. **Sympathomimetic drugs** (see Chapter 2 for more information)
   a. Isoproterenol is a β-receptor agonist that has been used to treat symptomatic AV block and bradycardia refractory to atropine, although artificial pacing is safer and more effective. Because of its affinity for β_2-receptors, it can cause hypotension and it is not used for treating either heart failure or cardiac arrest. Isoproterenol can be arrhythmogenic, like other catecholamines. Oral administration is not usually effective because of marked first-pass hepatic metabolism. Isoproterenol can cause serious tachyarrhythmias.
   b. Oral terbutaline sulfate, a β_2-receptor agonist, may have a mild stimulatory effect on HR.
   c. The methylxanthine bronchodilators aminophylline and theophylline can increase heart rate in some dogs with sick sinus syndrome when used at higher doses.
3. **Digoxin** is commonly used to treat frequent supraventricular or atrial premature beats and tachycardias. It is also used to slow A-V conduction in atrial fibrillation. See I F 2 for more information.

III. ANTIHYPERTENSIVE DRUGS

A. Introduction

1. Systemic arterial hypertension is often associated with renal disease or hyperadrenocorticism in dogs; other associated conditions include pheochromocytoma, diabetes mellitus, hypothyroidism, and liver disease. Renal disease and hyperthyroidism are the most common associated conditions in cats. Idiopathic (essential) hypertension is uncommon in dogs and cats.
   a. Certain drugs can increase blood pressure, such as glucocorticoids, mineralocorticoids, NSAIDs, phenylpropanolamine, NaCl, and even topical ocular phenylephrine.
   b. High blood pressure can damage capillary beds. The eye, kidney, heart, and brain are particularly vulnerable to damage from chronic hypertension.

2. Systemic arterial hypertension is most often recognized in middle-aged to older dogs and cats, presumably because of the associated disease conditions.
   a. Signs of hypertension relate either to underlying disease or to end-organ damage caused by the hypertension itself. Ocular signs, especially sudden blindness, are the most common presenting complaint.
   b. A diagnosis of arterial hypertension should be confirmed by measuring BP multiple times and on different days. Blood pressure measurements are indicated not only when signs compatible with hypertension are found, but also when a disease associated with hypertension is diagnosed.

B. Overview of antihypertensive therapy

1. Antihypertensive therapy is indicated for animals with severe hypertension and those with clinical signs presumed to be caused by hypertension.
   a. Measured BP in such animals is generally over 180/120 mm Hg.
   b. Some cases are hypertensive emergencies, requiring immediate therapy and intensive monitoring, but most hypertensive animals can be managed more conservatively with oral therapy.
   c. Patients with high BP that persists after treatment for the primary disease, as well as those with evidence of end-organ damage, should be treated.
   d. The goal of therapy is to reduce BP to below 150/95 mm Hg.
2. Several drugs are used as antihypertensive agents in dogs and cats:
   a. Usually one drug is administered at a time, at initially low doses. The animal is monitored to assess efficacy; two or more weeks may be needed to assess whether a significant decrease in BP has occurred.
   b. The drugs used most often are angiotensin-converting enzyme inhibitors (ACEI), the Ca^{2+}-blocker amlodipine, and β-blockers.
      (1) An ACEI is recommended as the initial antihypertensive drug in dogs.
      (2) Amlodipine is recommended as the drug of first-choice in cats, unless hyperthyroidism is the underlying cause. For hyperthyroid-induced hypertension, atenolol or another β-blocker is used first.
      (3) Therapy with a single agent is effective in some cases.
      (4) Combination therapy may be needed for adequate BP control in others.
   c. Hypotension is a potential adverse effect of antihypertensive drugs.
      (1) This usually is evident as periods of lethargy or ataxia.
      (2) Reduced appetite can be another adverse effect.
   d. Ancillary strategies may be helpful, although alone they are unlikely to markedly reduce BP.
      (1) Moderate dietary salt reduction (e.g., $\leq$0.22–0.25% Na^+ on a dry matter basis) is advised for all cases. Although not expected to normalize BP by itself, it may enhance antihypertensive drug effectiveness.
      (2) Weight reduction is usually advised for obese animals.
      (3) Drugs that can potentiate vasoconstriction (e.g., phenylpropanolamine and other α_1-adrenergic agonists), as well as glucocorticoids and progestins should also be avoided when possible.
      (4) A diuretic may help by reducing blood volume in individuals with volume expansion.
         (a) A diuretic alone is rarely effective.
         (b) Diuretics are avoided or used only with caution. in animals with renal disease.
   e. The ability to monitor BP is important when antihypertensive drugs are used. Serial measurements are needed to assess treatment efficacy and avoid hypotension.

C. Vasodilator drugs

1. **Angiotensin converting enzyme inhibitors.** ACEI may help control BP by reducing angiotensin II formation, vasodilator kinin degradation, and/or aldosterone secretion (with its effects on vascular volume).

a. An ACEI is generally the drug of first choice in hypertensive dogs.
b. Hypertension in cats with chronic renal failure is often not responsive to ACEI. But, an ACEI may help mitigate further hypertensive renal damage by preferentially reducing efferent arteriolar constriction and reducing glomerular hypertension
c. See I D for more information about ACEI.

2. Calcium-entry blockers
a. Amlodipine besylate is a long-acting dihydropyridine Ca^{2+}-blocker that causes vasodilation without appreciable cardiac effects.
(1) Amlodipine is the drug of first choice in most hypertensive cats.
(a) Oral bioavailability is high and peak plasma concentrations are reached 3–8 hours after administration (in people); plasma concentrations increase with chronic therapy.
(b) There is no extensive first-pass elimination. The drug undergoes hepatic metabolism; caution is warranted when liver function is poor.
(c) No specific pharmacokinetic data are available in cats. However, transdermal application produces measurable blood levels and pharmacologic effect, although to a lesser degree than with oral dosing. Bioavailability appears lower than with oral dosing.
(d) Amlodipine's $t_{1/2}$ is ~30 hours in dogs; maximal effects occur 4–7 days after initiating therapy.
(2) Amlodipine can be used as adjunctive therapy (or alone) in dogs if an ACEI does not sufficiently control BP.
b. Other agents, such diltiazem (see II F 1) and nifedipine might be useful in hypertensive animals.

3. Other vasodilators
a. Direct-acting vasodilator agents generally produce faster reduction in BP (e.g., nitroprusside, hydralazine).
(1) Nitroprusside can be dosed to effect by constant IV infusion, but arterial pressure should be closely monitored to avoid hypotension (see I E 4).
(2) Hydralazine given IV or PO is an alternative, especially for dogs (see I E 2).
b. α_1-Blockers oppose the vasoconstrictive effects of these α-receptors. **Their main use is for hypertension caused by pheochromocytoma.** After an α-blocker is administered, adjunctive therapy with a β-blocker can help control reflex tachycardia or arrhythmias.
(1) Phenoxybenzamine is a noncompetitive α-blocker used most often for pheochromocytoma-induced hypertension.
(2) Prazosin also has been used in some dogs.
(3) Phentolamine is used IV when hypertensive crisis is related to pheochromocytoma or other cause of catecholamine excess.
(4) Addition of a β-blocker can help mitigate pheochromocytoma-induced tachyarrhythmias, but it should not be administered alone or before an α-blocker is given.

D. Other drugs used for hypertension

1. β-Blockers may reduce blood pressure by slowing heart rate, and decreasing cardiac output and renal renin release (see II D).
a. Atenolol and propranolol have been used most often.
b. A β-blocker is recommended for cats with hyperthyroid-induced hypertension. **But β-blockers are often ineffective as the sole antihypertensive agent in cats with renal disease.**
c. An IV β-blocker (propranolol, esmolol, or labetolol) can be used for emergency treatment.

2. Diuretics may reduce blood pressure by promoting Na^+ and water excretion. Furosemide is usually tried, although hydrochlorothiazide may be helpful in nonazotemic dogs. See Chapter 9 for more information.

Chapter 9

Diuretics

Franklin Ahrens

I. INTRODUCTION

A. Diuretics are drugs that increase urinary loss of sodium ions (Na^+) and water. By shrinking extracellular fluid (ECF) volume, they mobilize edema fluid from the interstitial space and restore normal tissue perfusion and organ function. Their primary clinical use in veterinary medicine is in the prevention and treatment of generalized edema or severe local edema. Causes of generalized edema include congestive heart failure, liver disease, renal disease, or protein-losing enteropathies. The latter three conditions are characterized by low levels of plasma albumin because of the impaired synthesis (liver disease) or excess loss (renal or intestinal disease). The resulting fall in plasma oncotic pressure results in transudation of fluid from plasma to the interstitial space.

Cerebral, pulmonary, ocular, and udder edema are examples of local edema that arises from infection, inflammation, trauma, or poisons.

B. All diuretics act directly on renal tubular epithelia at specific sites in the nephron (Table 9-1). A brief review of ion and water transport in nephron segments is useful in understanding the action of diuretic drugs.

1. **Proximal convoluted tubule** (Figure 9-1). Sixty-five percent of the filtered sodium and water is reabsorbed from this segment. Sodium is absorbed by active transport, coupled transport with glucose and amino acids, and passive diffusion. High concentrations of carbonic anhydrase (CA) in tubule cells generate hydrogen ions ($CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$) which exchange for luminal sodium ions (Na^+–H^+ antiport). Filtered bicarbonate is reabsorbed from the lumen by a reversal of the above reaction (catalyzed by brush border CA) and the diffusion of CO_2 into the proximal tubule cell. Chloride and potassium are passively reabsorbed. Absorption is isosmotic since water is reabsorbed with ions. Activation of the renin–angiotensin system in response to volume depletion or a fall in blood pressure increases sodium and water reabsorption from this segment.
2. **Descending loop of Henle.** Sodium and chloride ions are not reabsorbed but become progressively concentrated in luminal fluid as water is osmotically removed into the hypertonic medullary interstitium.
3. **Thick portion of the ascending loop of Henle** (Figure 9-2). Twenty-five percent of the filtered sodium is reabsorbed in this segment. Sodium, potassium, and chloride are actively transported out of the lumen by a coupled mechanism (Na^+–K^+–$2Cl^-$symport). The tubule epithelium is impermeable to water. The movement of ions but not water out of the lumen in this segment is essential to the countercurrent multiplier system of the kidney which generates the hypertonic-medullary interstitium. Calcium (Ca^{++}) and magnesium (Mg^{++}) are passively reabsorbed via the paracellular pathway. Luminal fluid is hypotonic as it leaves this segment.
4. Early **distal convoluted tubule** (Figure 9-3). Ten percent of filtered sodium is reabsorbed in this segment. Chloride ion is cotransported with sodium. Calcium reabsorption is increased by parathyroid hormone (PTH) acting at this segment of the nephron. The tubule epithelium is impermeable to water and thus there is further dilution of tubular urine.
5. **Late distal tubule and collecting duct** (Figure 9-4). Four percent of filtered sodium is actively reabsorbed in this part of the nephron. Potassium and hydrogen ions are secreted. An increase in the sodium load reaching this segment tends to increase K^+ and H^+ secretions as Na^+ is reabsorbed. Therefore, loop and thiazide diuretics indirectly increase urinary loss of K^+ and H^+ and tend

TABLE 9-1. Site of Actions of Diuretics

Nephron Segment	Diuretic
Proximal convoluted tubule	CA inhibitors (e.g., acetazolamide) Osmotic agents (e.g., mannitol) Xanthines (e.g., aminophylline)
Ascending loop of Henle	Loop diuretics (e.g., furosemide) Osmotic agents
Early distal convoluted tubule	Thiazides (e.g., hydrochlorothiazide)
Late distal tubule and collecting duct	K^+-sparing diuretics (e.g., triamterene or spironolactone)

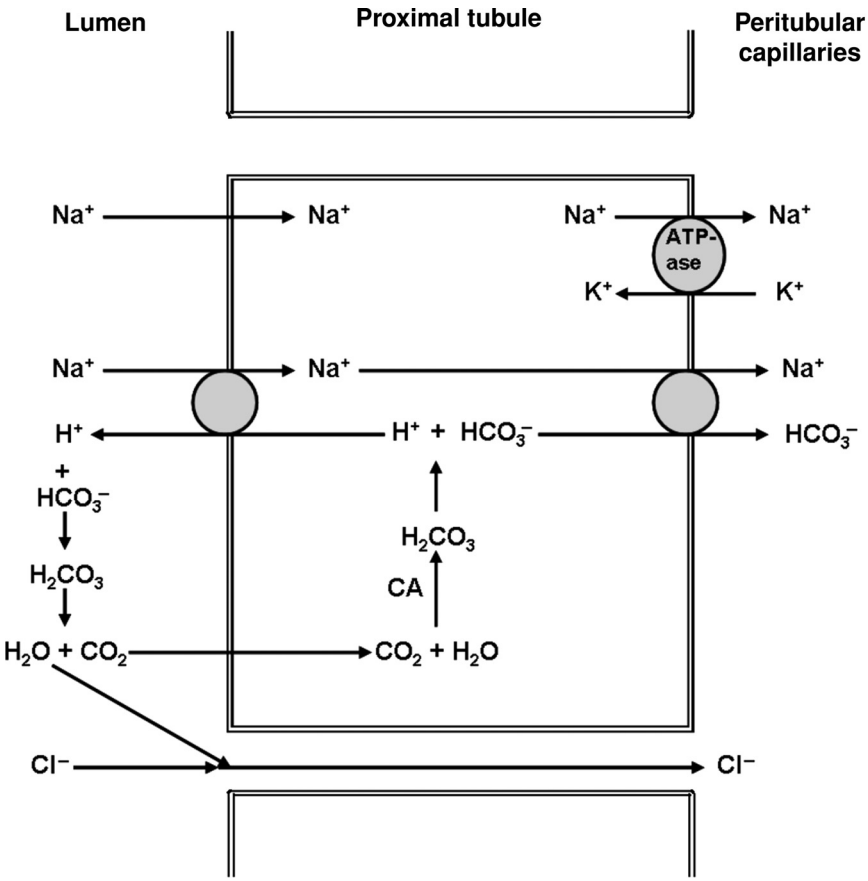

FIGURE 9-1. Electrolyte and water transport in the proximal convoluted tubule. Sodium moves into the cell down its concentration gradient—maintained by the Na^+–K^+-ATPase pump on the basolateral membrane. Sodium is also absorbed by exchange with H^+ at the luminal membrane (antiport). Hydrogen ion combines with filtered bicarbonate to form H_2CO_3, which is converted to H_2O and CO_2 by brush border carbonic anhydrase (CA). The reaction is reversed intracellularly. Diuretics that inhibit CA, such as acetazolamide, increase excretion of Na^+ and HCO_3^-.

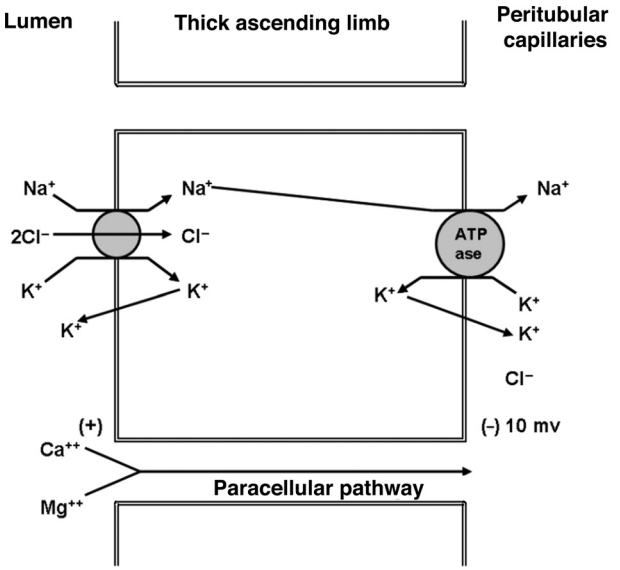

FIGURE 9-2. Electrolyte and water transport in the thick ascending limb of the loop of Henle. The Na^+–K^+–$2Cl^-$ symporter at the luminal membrane moves these ions into the cell. Part of the K^+ diffuses back to the lumen via conductance channels to maintain the lumen-positive transepithelial potential, which provides the driving force for the paracellular absorption of Ca^{++} and Mg^{++}. Inhibition of the symporter by loop diuretics, such as furosemide, increase excretion of Na^+, K^+, Cl^-, Ca^{++}, and Mg^{++}.

to produce hypokalemia and metabolic alkalosis. Aldosterone acts at this segment to increase luminal sodium channels resulting in increased sodium absorption and potassium excretion. Water is reabsorbed only if antidiuretic hormone (ADH) is present.

II. LOOP (HIGH-CEILING) DIURETICS

A. Preparations and chemistry. Furosemide and bumetanide are structurally related to sulfonamides. Ethacrynic acid is a derivation of phenoxyacetic acid. All are carboxylic acids. Furosemide is the most commonly used loop diuretic in veterinary medicine.

B. Mechanism of action. Loop diuretics inhibit electrolyte reabsorption in the thick ascending limb of the loop of Henle. They act at the luminal face of the epithelial cell

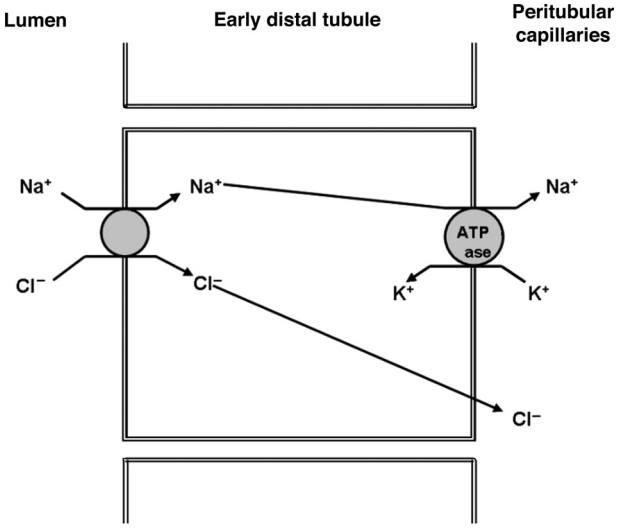

FIGURE 9-3. Absorption of sodium and chloride in the distal convoluted tubule is linked by a Na^+–Cl^- symporter in the luminal membrane. Thiazide diuretics inhibit the symporter and increase excretion of Na^+ and Cl^-.

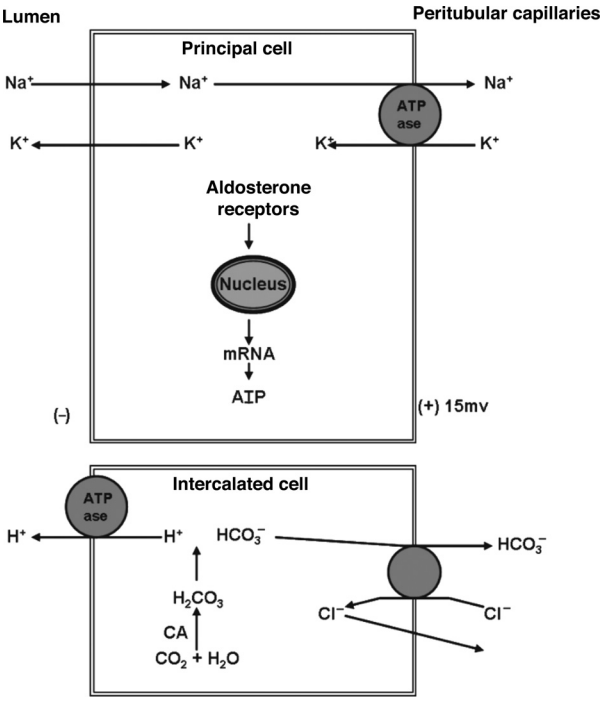

FIGURE 9-4. Electrolyte transport in the distal tubule and collecting duct. In the principal cell, sodium moves down its electrochemical gradient into the cell through Na^+ channels in the luminal membrane. Potassium moves from the cell into the lumen via K^+ channels in the luminal membrane driven by the lumen-negative transepithelial potential. This potential also aids the transport of H^+ into the lumen by the H^+-ATPase pump in the intercalated cell. Potassium-sparing diuretics such as triamterene and amiloride block luminal sodium channels to reduce Na^+ absorption and K^+ excretion. Aldosterone stimulates the production of aldosterone-induced proteins (AIP), which increases luminal sodium channels to increase Na^+ absorption.

to inhibit Na^+–K^+–$2Cl^-$cotransport into the cell. They have a rapid onset of action with peak diuresis greater than other classes of diuretics. Calcium and magnesium ion absorption from the ascending loop of Henle are also inhibited because of the decreased lumen-positive transepithelial potential. Diuretic action is independent of urinary pH. Loop diuretics produce an increase in systemic venous capacitance which may be due to their ability to stimulate prostaglandin release by the juxtaglomerular apparatus.

C. Therapeutic uses

1. Loop diuretics are the drugs of choice for the rapid mobilization of edema fluid arising from congestive heart failure, liver disease, or other causes of generalized edema, and for pulmonary, cerebral, or udder edema.
2. Furosemide increases urinary calcium excretion and is used in the treatment of hypercalcemia and hypercalcuric nephropathy in dogs and cats.
3. Furosemide may be combined with osmotic diuretics such as mannitol to maintain urine flow in severe oliguria and acute renal failure.
4. Furosemide is used for the prevention of exercise-induced pulmonary hemorrhage (EIPH) and epistaxis in racehorses. Its efficacy in this condition may be related to increased blood vessel capacitance and decreased left atrial pressure.

D. Pharmacokinetics.

Furosemide, bumetanide, and ethacrynic acid are well absorbed orally. They are actively secreted into urine by the organic acid transport system of the proximal convoluted tubule and thus rapidly reach their site of action in the loop of Henle. Furosemide is excreted in the urine as unchanged drug (80%) or as the glucuronide (20%). The plasma $t_{1/2}$ is 1–2 hours for most species and the duration of diuresis is 3–6 hours for a single oral dose. If administered intravenously, the onset of diuresis is 2–20 minutes with a duration of 2 hours.

E. Administration

1. For the treatment of edema, furosemide is administered orally or intravenously three times a day for diuresis in dogs and cats and twice a day in cattle and

horses. Treatment for udder edema in cattle should not exceed 48 hours postpartum.
2. For the treatment of oliguric renal failure, furosemide is administered intravenously at hourly intervals until diuresis occurs.
3. For the prevention of EIPH, furosemide is administered intravenously to horses 1–2 hours prior to a race for EIPH prevention. Rules of use are governed by state racing authorities.
4. For the treatment of hypercalcemia or hypercalcuric nephropathy in dogs and cats, furosemide is administered in KCl-supplemented saline, intravenously, once or twice a day.

F. Adverse effects

1. Fluid and electrolyte imbalances (especially hypokalemia) are the most common adverse effects. High or prolonged doses may produce dehydration, muscle weakness, CNS depression, volume depletion, and cardiovascular collapse. Cats are more sensitive than dogs to the effects of loop diuretics and lower doses are used in this species.
2. Loop diuretics may alter electrolyte balance in the endolymph of the inner ear. Deafness is a risk if a potentially ototoxic drug (e.g., an aminoglycoside antibiotic) is administered concomitantly. In such circumstances, another class of diuretic should be employed.
3. Transient granulocytopenia and thrombocytopenia may occur.

III. THIAZIDE DIURETICS (BENZOTHIADIAZIDES)

A. Preparations and chemistry.

The thiazides are heterocyclic compounds whose structure includes a benzene ring with an unsubstituted sulfonamide group ($-SO_2NH_2$).

Chlorothiazide and hydrochlorothiazide are the most common thiazides used in veterinary medicine.

B. Mechanism of action

1. The thiazide diuretics block Na^+–Cl^- cotransport in the early part of distal tubule. Sodium, chloride, magnesium, and potassium ion excretion are increased. Calcium ion excretion is decreased because thiazides increase Ca^{++} absorption in the early distal tubule. Thiazide diuresis tends to be moderate since 90% of the filtered sodium has been reabsorbed from the nephron by the time it reaches the distal segment. Urinary excretion of ions tends to be in physiological ratios and thus distortion of ECF ion balance is minimal.
2. Thiazides are weak inhibitors of CA but at normal doses this does not contribute to their diuretic action.
3. Paradoxically, thiazides *reduce* urine output in diabetes insipidus. The mechanism of this action is unknown but is related to their natriuretic effect.
4. Thiazides may induce hyperglycemia and glycosuria in diabetic or prediabetic states by inhibiting the conversion of proinsulin to insulin.

C. Therapeutic uses

1. Chlorothiazide and hydrochlorothiazide are useful for long-term diuretic therapy in dogs and cats as adjuncts to cardiac drugs in the treatment of congestive heart failure. Hydrochlorothiazide and trichlormethiazide are used in the treatment of udder edema in cattle.
2. Thiazide diuretics are effective in reducing urine output in nephrogenic diabetes insipidus in dogs.
3. Hydrochlorothiazide reduces urinary calcium ion excretion and is used for the treatment of calcium oxalate uroliths in dogs.

D. **Pharmacokinetics.** Pharmacokinetics studies of thiazides in animals have not been reported. In man, oral absorption is 10–20% and 65–75% for chlorothiazide and hydrochlorothiazide, respectively. Onset of diuresis occurs in 2 hours and peaks in 4–6 hours. Duration of action is 6–12 hours. They are not metabolized and are excreted in the urine by active tubular secretion.

E. **Administration**

1. For the treatment of edema in heart failure, chlorothiazide or hydrochlorothiazide is administered orally twice a day in dogs and cats. A diuretic response occurs in 2–3 hours and lasts 6–12 hours.
2. For the treatment of recurrent calcium oxalate uroliths in dogs with hypercalcuria, hydrochlorothiazide is administered orally twice a day.
3. For the treatment of udder edema in cattle, hydrochlorothiazide is administered intravenously or intramuscularly twice a day. Trichlormethiazide is combined with dexamethasone in a proprietary preparation (Naquasone) administered orally once a day.
4. For the treatment of nephrogenic diabetes insipidus, chlorothiazide or hydrochlorothiazide is administered orally twice a day.

F. **Adverse effects.** The moderate diuresis produced by thiazide results in less disturbance of ECF electrolyte balance than other classes of diuretics. Hypokalemia and hypochloremia may develop with high or prolonged doses. Hyperglycemia may occur and may aggravate preexisting diabetes mellitus.

IV. OSMOTIC DIURETICS

A. **Preparations and chemistry.** Mannitol is a six-carbon sugar alcohol prepared as a 20–25% aqueous solution. It is the most important member in this class of diuretics. Glycerol and urea are used less frequently. Dimethyl sulfoxide (DMSO) prepared as a 10% solution in 5% dextrose has been used to treat edema in horses.

B. **Mechanism of action**

1. Osmotic diuretics are filtered at the glomerulus but are poorly reabsorbed from the lumen of the nephron. The presence of these unabsorbed solutes in the proximal tubule causes decreased reabsorption of water, resulting in a large volume of urine. There is a small increase in Na^+ and Cl^- excretion. Mannitol causes an increase in renal medullary blood flow via a prostaglandin-mediated mechanism. This reduces medullary tonicity, decreases extraction of water in the descending loop of Henle, and thus lowers the concentration of NaCl and the passive reabsorption of NaCl in the thick ascending loop of Henle.

C. **Therapeutic uses**

1. For the nonspecific treatment of poisoning in dogs and cats, mannitol is used to induce forced diuresis which hastens the elimination of poisons excreted by the kidney.
2. For the treatment of oliguric renal failure in dogs and cats mannitol is used as an adjunct to furosemide therapy. The osmotic expansion of the plasma increases glomerular filtration volume and maintains urine flow. Urine output must be monitored.
3. For the treatment of increased intraocular pressure of acute glaucoma in dogs and cats, osmotic diuretics such as mannitol or glycerin are used to reduce intraocular pressure.
4. For the treatment of cerebral edema in large and small animals, mannitol is used as an adjunct to furosemide to mobilize edema fluid. In addition to its diuretic

effect, mannitol may prevent the hypovolemic shock commonly observed in cerebral edema.

D. **Pharmacokinetics.** Mannitol is administered intravenously for osmotic diuresis since oral absorption is poor. It distributes to the ECF, is not metabolized, and is excreted by renal glomerular filtration. The plasma $t_{1/2}$ is 1–2 hours.

E. **Administration.** Mannitol solutions (5–20%) are administered by slow intravenous infusions over 15–30 minutes in all species. Doses may be repeated every 6–8 hours.

F. **Adverse effects.** Toxicity is rare but fluid and electrolyte balance and urine output should be monitored, especially in the treatment of oliguric renal failure. Mannitol should not be used in generalized edema or acute pulmonary edema because its saluretic effect is small and because it produces an initial expansion of the ECF which may exacerbate the edema and may cause decompensation in patients with congestive heart failure.

V. CARBONIC ANHYDRASE INHIBITORS

A. **Preparations and chemistry.** Acetazolamide, methazolamide, and dichlorphenamide are sulfonamide derivates.

B. **Mechanism of action.** These agents reversibly inhibit CA enzyme predominantly in the proximal convoluted tubules, causing a reduction in hydrogen ions available for Na^+–H^+ exchange. Carbon dioxide (CO_2) reabsorption from the glomerular filtrate is suppressed, and Na^+–HCO_3^- excretion is increased, resulting in an alkaline urine. To maintain ionic balance, Cl^- is retained by the kidney, resulting in a hyperchloremic acidosis. The resulting metabolic acidosis (low plasma HCO_3^-) eventually induces a refractory state and decreased diuresis.

High concentrations of CA occur in the ciliary process of the eye and the enzyme is involved in aqueous humor formation. CA inhibitors reduce intraocular pressure in glaucoma by decreasing the production of aqueous humor.

C. **Therapeutic uses.** The primary use of CA inhibitors is for reducing the rate of aqueous humor formation in the treatment of glaucoma. They are occasionally used as adjuncts in the treatment of metabolic alkalosis. Their diuretic action is weak and they are seldom used for this purpose now.

D. **Pharmacokinetics.** Acetazolamide and dichlorphenamide are absorbed orally, distributed to tissues with high CA concentrations (renal cortex, eye, and erythrocytes), and excreted by the kidney by active secretion and passive reabsorption. Onset of diuretic action is 30 minutes with a duration of 6–12 hours in small animals. In horses, after IV administration, the distribution $t_{1/2}$ is 60 minutes, and the elimination $t_{1/2}$ is ~7.5 hours. After oral administration in horses, the time to reach peak plasma level is ~2 hours. Bioavailability of acetazolamide in horses is only ~25%.

E. **Administration.** For glaucoma, acetazolamide, methazolamide, ethazolamide, or dichlorphenamide are given orally 2–3 times daily. In acute cases, a single intravenous dose of acetazolamide is given followed by an oral dosage regimen.

F. **Adverse effects.** Toxicity is rare. Gastrointestinal disturbances, especially vomiting, may occur with oral administration. CA inhibitors are contraindicated in the presence of liver disease because they may precipitate hepatic coma by diverting ammonia produced in the kidney from the urine to the systemic circulation as a result of urine alkalinization.

VI. POTASSIUM-SPARING DIURETICS

A. **Preparations and chemistry.** Triamterene and amiloride are cyclic amidines and are organic bases. Spironolactone is a steroid analog of the mineralocorticoid aldosterone.

B. **Mechanism of action.** Triamterene and amiloride inhibit active Na^+ reabsorption in the distal convoluted tubule and collecting duct. This reduces the net driving force for K^+ secretion. They cause a small increase in Na^+ and Cl^- excretion without increasing K^+ excretion. Their action is independent of aldosterone.

Spironolactone is a competitive antagonist of the mineralocorticoid aldosterone. It reduces the aldosterone-mediated Na^+–K^+exchange at the late distal convoluted tubule, increasing Na^+ loss while decreasing K^+ loss. Spironolactone is most effective when circulating aldosterone levels are high.

C. **Therapeutic uses.** Triamterene or amiloride is occasionally used in combination with thiazides or loop diuretics in chronic edema. The combination augments the natriuretic effect while attenuating K^+ loss.

Spironolactone is occasionally used as an adjunct to other diuretics in the treatment of refractory edema if excessive K^+ loss is a concern. Spironolactone is also used to treat adrenal gland tumors to counter the excess mineralocorticoid effects of aldosterone (sodium retention and potassium excretion).

D. **Pharmacokinetics.** Triamterene and amiloride are absorbed orally. Amiloride is excreted unchanged by the kidney. Triamterene is converted by the liver to an active metabolite—hydroxytriamterene. Both drugs are transported by the organic base secretory mechanism in the proximal tubule. Hydroxytriamterene can further form the sulfate conjugate. Peak onset of diuresis is 6–8 hours with a duration of 12–15 hours.

Spironolactone is absorbed orally, bound to plasma proteins, and is extensively metabolized by the liver. The active metabolite, canrenone, has a long half-life (16–20 hours). Diuretic action is prolonged with a duration of 2–3 days.

E. **Administration.** Triamterene is administered orally twice a day in dogs and cats. Amiloride is administered orally once a day.

Spironolactone is administered orally twice a day in dogs and cats.

F. **Adverse effects.** Hyperkalemia can occur and thus K^+ diuretics are not given in combination with one another and are contraindicated in hyperkalemic patients. Hyperkalemia is especially likely in the presence of diabetes mellitus, renal disease, or thromboembolic disease. Gastrointestinal disturbances, including nausea and vomiting, may occur.

VII. METHYLXANTHINES

A. **Mechanism of action.** The methylxanthines include aminophylline, theophylline, caffeine, and theobromine. Their diuretic effect is due to increased renal blood flow and glomerular filtration rate and to inhibition of sodium reabsorption in the proximal convoluted tubule. Diuresis is enhanced by an alkaline urine and thus greater in herbivores than carnivores. They also produce bronchodilation by inhibition of adenosine receptors and are CNS stimulants.

B. **Therapeutic uses.** Methylxanthines are rarely used as diuretics but increased urine output is observed when aminophylline or theophylline is employed as a bronchodilator in respiratory disease therapy.

C. Pharmacokinetics of theophylline

1. **Absorption**. Theophylline bioavailability after oral administration is ~100% when nonsustained release products are used, but is 30–75% if sustained release products are used.
2. **Distribution.** Theophylline is distributed throughout the ECF and body tissues. Because of the low volumes of distribution (0.5–1 L/kg) and theophylline's low lipid solubility, obese patients should be dosed on a lean body weight basis**.**
3. **Elimination.** Theophylline is metabolized primarily in the liver (in humans) to 3-methylxanthine, an active metabolite. Renal clearance contributes only about 10% to the overall plasma clearance of theophylline. The reported elimination $t_{1/2}$ are: dogs, ~6 hours; cats, ~8 hours, pigs, 11 hours; and horses, 12–17 hours.

D. Adverse effects. Methylxanthine may produce excitement, skeletal muscle fasciculation, vomiting, and cardiovascular toxicity including palpitations and hypotension with high or prolonged dosage.

VIII. ACIDIFYING SALTS

A. Mechanism of action. Acidifying salts such as ammonium chloride (NH_4Cl) lower the pH of ECF and urine. The liver converts NH_4Cl to urea, H^+ and Cl^-. Hydrogen ion is buffered by HCO_3^- in plasma and this leads to acidosis. The increased chloride load to the kidney produces urinary loss of Na^+ and Cl^- and a mild diuresis.

B. Therapeutic uses. Ammonium chloride is used for urinary acidification to dissolve uroliths or to prevent their formation. It is also used to enhance the renal excretion of ionizable drugs or poisons by ion trapping in the urine.

C. Administration. Ammonium chloride is administered orally two to three times a day or added to the diet in dogs and cats.

D. Adverse effects. Severe, uncompensated acidosis may result if renal function is impaired. Nausea and gastric irritation may occur with oral dosing. Ammonium chloride is contraindicated in the presence of decreased liver function because of the requirement for its hepatic conversion to urea described under mechanism of action above.

SUGGESTED READING

http://www.drugs.com

Jackson EK. 2006. "Drugs affecting renal and cardiovascular function." In *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. Edited by Brunton LL, Lazo JS, Parker KL. 11th ed., pp. 737–769. New York: McGraw-Hill.

Kochevar DT. 2001. "Diuretics." In *Veterinary Pharmacology and Therapeutics*. Edited by Adams HR. 8th ed., pp. 534–552. Ames, IA: Iowa State University Press.

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Chapter 18

Fluid and Blood Therapy

Walter H. Hsu

I. BIOCHEMICAL BASIS OF FLUID THERAPY

A. Body water

1. **Water content** is 55–60% of body weight in mature animals, 70–75% in immature animals, and 50% in obese animals.
2. **Intracellular fluid (ICF)** represents 40% of the body weight.
3. **Extracellular fluid (ECF)** consists of:
   a. **Plasma water:** 5% of the body weight.
   b. **Interstitial fluid:** 14% of the body weight.
   c. **Transcellular fluid:** 1–6% of the body weight.
4. **Body water turnover**
   a. It is regulated by thirst and drinking control centers and vasopressin (antidiuretic hormone [ADH]), responding to osmolarity and blood volume changes: the higher the osmolarity and the lower the blood volume, the more stimulation of the drinking control centers and vasopressin secretion. As a result, large volume of water is being drunk.
   b. **Body water turnover** is 50–130 mL/kg/day, 65 mL/kg/day in mature animals.
   c. **The role of skin and body surface.** Skin is the largest organ of the body. The smaller the size of an animal, the larger the body surface is; thus, the higher the body water turnover rate. This is why dehydration has a much greater impact on young animals than mature animals.

B. Concept of milliequivalents (mEq)

1. Most of the electrolyte concentrations are expressed as mEq/L; mEq is calculated as mg of chemical divided by its equivalent weight. For example, the equivalent weight of NaCl is 58.5; 1 mEq of NaCl = 58.5 mg.
2. Total concentration of cations in the plasma is equal to that of anions.
3. Calcium and phosphorus in the plasma are measured as mg%, ~50% of plasma calcium is in the free ionized form and ~50% is bound by plasma proteins. Plasma phosphorus is present as $H_2PO_4^-$, HPO_4^{2-}, and PO_4^{3-}.

C. Osmosis and osmolarity

1. **Role of semipermeable membranes in osmosis.** Fluid compartments are separated by semipermeable membranes, which allow free passage of water but restrict particles. Water moves to the compartment with the highest number of particles (osmotic pressure).
2. **Osmolarity** is to describe properties related to the number of particles in solution and is expressed as mOsm/L of body fluid.
3. **Calculation of mOsm/L from mM**
   a. **For electrolyte solutions.** Since NaCl dissociates into two particles, Na^+ and Cl^-, 1 mmol/L (1 mmolar or 1 mM) of NaCl solution yields 2 mOsm/L. A total of 1 mmol of NaCl contains 58.5 mg since its molecular weight is 58.5.
   b. **For nonelectrolyte solutions.** Since glucose does not dissociate, 1 mM of glucose solution yields 1 mOsm/L.
4. **Osmolarity of an isotonic solution is ~300 mOsm/L.** One should be able to determine if a solution in mM is isotonic depending on whether the chemical can dissociate in the solvent. For example, 150 mM NaCl and 300 mM glucose solutions are isotonic.

D. Role of the kidney in water and electrolyte regulation

1. A total of 80–90% of water, Na^+, Cl^-, and so forth, is reabsorbed from the proximal tubule.
2. Information on renal physiology is presented in Chapter 9, I B (Review of nephron ion and water transport).

E. Acid–base regulation

1. **Definition of acid, base, and pH** Acid is a proton (H^+) donor and base is a H^+ acceptor. Thus, HCl is an acid, and HCO_3^- is a base, so is NH_3; chloride (Cl^-) is not an acid and Na^+ is not a base. pH is $-\log [H^+]$. If $[H^+] = 10^{-7}$ M, pH = 7.
2. **Use of Henderson–Hasselbalch equation** to calculate the ratio between base and acid

$$pH = \frac{pKa + \log[A^-]}{[HA]}$$

Since $pKa = 6.1$ for the $[HCO_3^-] - [H_2CO_3]$ pair, and if pH is 7.4:

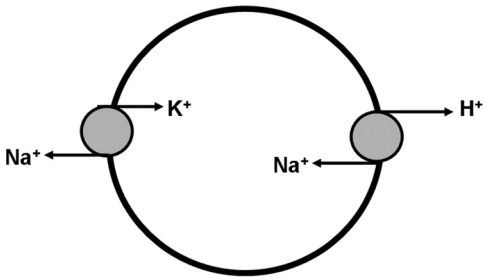
$$7.4 = 6.1 + \log [HCO_3^-]/[H_2CO_3], \text{ the } \log [HCO_3^-]/[H_2CO_3]$$

$$= 1.3; \text{ the antilog of } 1.3 \text{ is } 20$$

$$\text{Thus, } \frac{[HCO_3^-]}{[H_2CO_3]} = \frac{20}{1} \text{ at pH } 7.4.$$

When this ratio is disturbed, the result is either acidosis or alkalosis.

3. **Buffer systems in the body**
   a. **Intrinsic buffering system.** Bicarbonate, hemoglobin, phosphate, and proteins (amino acids) constitute 53, 35, 5, and 7% of the intrinsic buffering system, respectively.
   b. **The cellular component of the buffering system** takes place during the first stage of the abnormality.
      (1) **Na^+–H^+–K^+ exchanges** (Figure 18-1). Normally, H^+ generated during cellular metabolism is removed via Na^+–H^+ antiport, which exports H^+ and imports Na^+. The increased $[Na^+]_i$ will then exchange for $[K^+]_o$ via Na^+, K^+-ATPase. Thus, **the net result of the reaction is one molecule of H^+_{in} exchanges for one molecule of K^+_{out}.** During acidosis (acidemia), this exchange process is inhibited by low pH, and thus more H^+ stays in the cells and more K^+ stays in the ECF. During alkalosis (alkalemia), this exchange is accelerated, and thus more H^+ is lost to the ECF and more K^+ enters the cells.
      (2) **Cl^-–HCO_3^- exchange.** The plasma membranes of animal cells contain an anion exchange protein, which exports HCO_3^- and imports Cl^-. The activity



Hyperkalemia $(\uparrow[K^+]_o) \rightarrow \uparrow[K^+]_i\ [Na^+]_o \rightarrow \uparrow[H^+]_o$
Hypokalemia $(\downarrow[K^+]_o) \rightarrow \downarrow[K^+]_i\ [Na^+]_o \rightarrow \downarrow[H^+]_o$
Acidemia $(\uparrow[H^+]_o) \rightarrow \downarrow[Na^+]_i \rightarrow \downarrow[K^+]_i, \uparrow[K^+]_o$
Alkalemia $(\downarrow[H^+]_o) \rightarrow \uparrow[Na^+]_i \rightarrow \uparrow[K^+]_i, \downarrow[K^+]_o$

FIGURE 18-1. The compensatory mechanisms for acid–base disturbances involving intra- and extracellular H^+, Na^+, and K^+ exchanges. As a result of these exchanges, acidosis and alkalosis can lead to hyperkalemia, and hypokalemia, respectively. By the same token, hyperkalemia and hypokalemia can lead to acidosis and alkalosis, respectively.

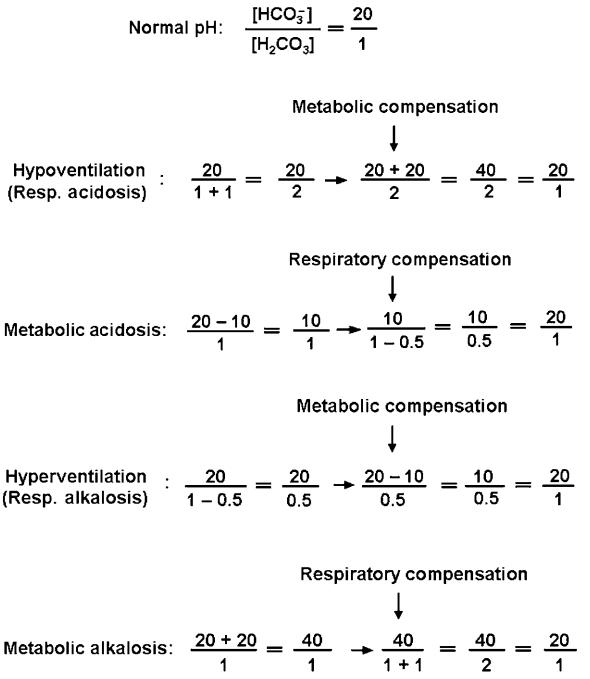


FIGURE 18-2. The compensatory mechanisms for simple acid–base disturbances as explained by the changes in the Henderson–Hasselbalch equation.

of this protein is stimulated to lower intracellular pH once it rises above 7.0 (normal intracellular pH is <7.0). With alkalosis, this exchange process is active and thus more HCO_3^- is expelled to keep the cells less alkaline. With acidosis, this exchange process is inhibited and thus less HCO_3^- is expelled, resulting in the cells being less acidic.

(3) **Renal regulation of H^+ and K^+.** Renal regulation of H^+ and K^+ occurs at the distal renal tubule level, where **one molecular of Na^+ is reabsorbed into the tubular cell at the expense of one molecule of H^+ or K^+. With acidosis, more H^+ than K^+ is expelled (secreted) into the lumen, resulting in hyperkalemia as part of the compensatory process.** By the same token, alkalosis would lead to hypokalemia through this same process.

c. Respiratory and metabolic components

Since H_2CO_3–HCO_3^- is the major buffering system in the body, **respiratory and renal control of the blood CO_2 and HCO_3^- concentrations intends to keep body pH normal. Under normal physiological condition, the ratio of blood [HCO_3^-] and [H_2CO_3] is 20:1, where HCO_3^- is the metabolic component and H_2CO_3 (or dissolved CO_2) is the respiratory component.** This ratio will change by addition or loss of CO_2 and HCO_3^- to the system. Figure 18-2 depicts changes in the ratio of [HCO_3^-] and [H_2CO_3] that might occur during simple acid–base disturbances.

During hypoventilation (respiratory acidosis), retention of CO_2 will lower the ratio. In order to return the ratio to 20:1, the body must retain more HCO_3^- through metabolic compensation.

During metabolic acidosis, loss of HCO_3^- will decrease the ratio. In order to return the ratio to 20:1, body must expel more CO_2 to lower the ratio through respiratory compensation.

These changes in [HCO_3^-]/[H_2CO_3] also account for the compensatory processes during respiratory alkalosis (hyperventilation) and metabolic alkalosis (Figure 18-2).

4. Acid–base parameters and terminology

a. At pH 7.4, the ratio of $\frac{[HCO_3^-]}{[H_2CO_3]} = 20:1$

b. Base deficit/excess is defined as the titratable acid or base, respectively, needed to titrate the blood to a pH of 7.4 under standard conditions of PCO_2 (40 mm Hg), temperature (38°C), and complete hemoglobin oxygenation.

c. Acidemia and alkalemia. Acidemia is defined as arterial pH of <7.35 and alkalemia is defined as arterial pH of >7.45.

d. Anion gap. The difference between the ECF concentration of Na^+ (140 mEq/L) and the sum of the concentrations of HCO_3^- (25 mEq/L) and Cl^- (105 mEq/L). The normal anion gap varies with the species, but is 13–25 in dogs and cats. Metabolic acids contribute to the anion gap. Untreated cases of metabolic acidosis may have high anion gaps.

II. GENERAL CONCEPTS OF FLUID AND ELECTROLYTE THERAPY

A.

Institution of fluid therapy. Fluid therapy should be instituted for the following conditions: dehydration, acid–base disturbances and/or electrolyte imbalances, nutritional problems, and loss of body fluids.

1. Basis for institution of fluid therapy

a. Accurate diagnosis based on clinical examination and laboratory data is important for fluid therapy.

The clinical signs for detection of dehydration include: loss of skin elasticity, dry buccal mucosa and tongue, and sunken eyeballs should be taken into account.

b. Signs of vomiting, diarrhea, abnormal respiratory pattern, and CNS depression or excitation may help with the diagnosis of acid–base disturbances.

c. Blood gas and urine analyses are useful for the precise diagnosis of acid–base and electrolyte disturbances.

2. Dehydration

a. General considerations. Dehydration may be considered in three general categories:

(1) Hypertonic dehydration, which is attributable to loss of pure water or hypotonic fluid.

(2) Isotonic dehydration, which is attributable to loss of isotonic body fluids. However, isotonic dehydration is only seen in acute cases, since with some degree of water replacement, isotonic dehydration will become hypotonic dehydration.

(3) Hypotonic dehydration. The loss of a hypertonic fluid or loss of isotonic fluid with water replacement results in hypotonic dehydration.

b. Causes

(1) Decreases in water intake usually lead to hypertonic dehydration.

(a) Lack of water source.

(b) Disorders and pain of the buccal cavity and pharynx.

(c) CNS disturbances.

(2) Increases in body fluid excretion usually lead to hypotonic dehydration.

(a) Polyuria. Diabetes, nephrosis, hypoaldosteronism, and diuretics. Diabetes insipidus will cause hypertonic dehydration.

(b) Respiratory loss of water during high temperature may lead to hypertonic dehydration.

(c) Profuse sweating in horses.

(d) Vomiting/diarrhea.

(e) Third space loss. Body fluid lost to the body cavities and hollow organs.

c. Role of electrolytes on hydration states and acid–base balance:

(1) ↑ $[Na^+]$ in ECF → water retention

(2) Changes in $[K^+]$ in ECF result in changes in acid–base balance:

(a) ↑ $[K^+]$ in plasma→↑$[K^+]$,↓$[H^+]$ in urine → Acidemia

(b) ↓ $[K^+]$ in plasma→↓$[K^+]$,↑$[H^+]$ in urine → Alkalemia.

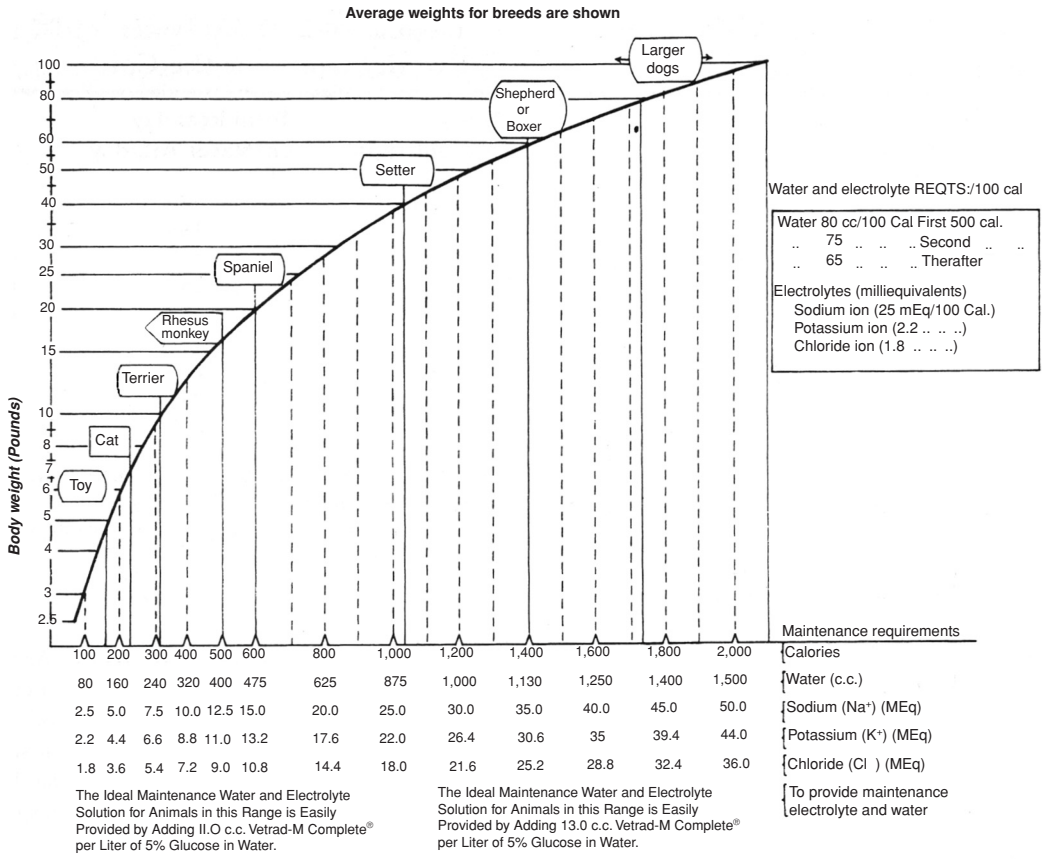


FIGURE 18-3. Daily water, calorie, and electrolyte requirements for dogs and cats. (Reprinted with permission from *Fluid, Electrolyte, and Acid–Base Disorders,* 3rd ed. Edited by DiBartola S. P. Saunders/Elsevier, 2006, Figure 14-1. This figure was modified from Harrison J. B., Sussman H. H., and Pickering D. E. Fluid and electrolyte therapy in small animals. *JAVMA* 137:637–645, 1960, Figure 1.)

d. Role of carbohydrate metabolism on hydration states and acid–base balance:
- **(1)** ↓ Carbohydrate utilization → Hyperglycemia → Glucosuria→ Polyuria → Dehydration
- **(2)** ↓ Carbohydrate utilization →↑ Gluconeogenesis → Ketoacidosis
- **(3)** ↑ Carbohydrate intake (grain overload) in herbivores →↑ Lactic acid production → Acidosis.

e. Treatment (amount of fluid to be used) must be based on the body water maintenance plus replacement of the deficit and ongoing loss
- **(1) Amount of body water maintenance**
  - **(a)** On the basis of body water turnover
  - **(b)** A total of 50–75 mL/kg/day (average 65 mL/kg/day)
  - **(c)** For more precise estimation of water maintenance doses in dogs and cats, see Figure 18-3.
- **(2) Determination of water deficit (dehydration)**
  - **(a)** Dehydration of 4, 6, 8, and 12% (of body weight), only **loss >4%** needs a replacement
  - **(b) A total of 4% dehydration (mild)**
    - **i.** Animals with 4% dehydration have a history of fluid loss, but without significant signs of dehydration.
    - **ii.** No replacement is needed.

(c) A total of 6% dehydration (moderate)

i. Animals with 6% dehydration have decreased skin turgor. In dogs and cats, **when the skin over the lateral thorax is picked into a tented fold, it will return to normal slowly**; in species having tight skin, pinch the dorsal eyelid to do the test.

ii. A decrease in skin elasticity is also seen in cachexia; thus, one cannot conduct this test in cachectic animals.

iii. Animals with 6% dehydration have dull haircoat and **dry mucous membranes.**

(d) About 8–10% dehydration (severe). The animals with 8–10% dehydration have the following signs:

i. The skin lacks pliability. In dogs and cats, when the skin is pinched into a tented fold, it will tent and stay after the pinch is released.

ii. Dry mucous membranes and tongue.

iii. Soft eyeballs that are sunken into the orbit.

iv. Cold extremities.

v. Capillary refill time >3 seconds (normal <2 seconds).

(e) About 12% dehydration (extremely severe). The animals with 12% dehydration have following signs:

i. All the signs seen with 8–10% dehydration.

ii. Circulatory collapse (shock).

(3) Estimation of water deficit. The replacement volume for the initial deficit is estimated according to the following equations:

$$\text{Replacement volume}\,(L) = \%\,\text{dehydration} \times \text{body weight}\,(\text{kg})$$

(4) The composition of replacement fluid should be similar to the volume of fluid lost. For example, if the deficit is due to loss of the electrolyte-rich GI fluid, then a balanced salt solution containing Na^+, K^+, Ca^{2+}, Cl^-, and HCO_3^- (or indirect alkalinizing agents) should be used. See Table 18-1 for the compositions of commonly used replacement fluids of crystalloid in nature. In contrast, if the deficit is due to loss of pure water, volume can be replaced with 5% dextrose (glucose in water) over 24–72 hours. An isotonic solution of 2.5% dextrose and 0.45% NaCl can also be used.

(5) The ongoing loss must be taken into account when estimating the fluid therapy volume. The ongoing loss of fluid via vomiting, diarrhea, and polyuria must be estimated and replaced.

(6) Additional factors need to be considered

(a) Dehydration affects young animals much faster than adult animals.

(b) Old animals with chronic diseases require more water than younger adult animals.

(c) Physical and weather conditions may affect the requirement, particularly when it is hot and humid.

(d) Drugs will alter requirements, particularly diuretics and mineralocorticoids can affect water and electrolyte balances.

(7) The volume to be used for treatment of dehydration is considered an estimate, since it is based on clinical signs to estimate the body water deficit. **Despite the importance of good data collection and application of principles of fluid therapy, the adjustment of volume based on the "reassess" process is needed for each individual case.**

3. Therapy in acid–base disturbances

a. Metabolic acidosis

(1) Causes

(a) Gain of acid. Severe tissue breakdown, grain overload, ketosis, poor tissue perfusion, hyperkalemia, lactic acid overproduction, and drug overdose, for example, acidic NSAIDs, chemical poisonings, for example, ethylene glycol (which is metabolized into oxalic acid in the body).

(b) Loss of base. Severe diarrhea, severe salivation, renal insufficiency, and so forth.

(2) General signs. Hyperpnea, CNS depression.

TABLE 18-1. Composition of Selected Fluid Therapy Solutions

		Characteristics		Ion Composition (mEq/L)						
Type	**Solution**	**pH**	**Osmolarity (mOsm/L)**	**Na^+**	**K^-**	**cl^-**	**Ca^{++}**	**Mg^{++}**	**Glucose (g/L)**	**Alkalinizing Equivalents (mEq/L)**
Replacement										
Acidifying BES	Ringer's	5.4	309	147	4	155	4	0	0	0
Acidifying BES	Normal saline (0.9%)	5.0	308	154	0	154	0	0	0	0
Alkalinizing BES	Lactated Ringer's	6.6	273	130	4	109	3	0	0	28 (lactate)
Alkalinizing BES	Normosol-R	6.6	294	140	5	98	0	3	0	27 (acetate) 23(gluconate)
Alkalinizing BES	Plasma-Lyte A	7.4	294	140	5	98	0	3	0	27 (acetate) 23 (gluconate)
Maintenance										
Acidifying	2.5% dextrose/water in 0.45% saline plus potassium addition (16 mEq/L)	4.5	280	77	16	77	0	0	25	0
	Equal volumes 5% dextrose/water and lactated Ringer's plus potassium addition (16 mEq/L)	5.0	309	65.5	18	55	1.5	0	25	14 (lactate)
	Normosol-M with 5% dextrose	5.0	363	40	13	40	0	3	50	16 (acetate)
	Plasma-Lyte M with 5% dextrose	5.5	377	40	16	40	5	3	50	12 (lactate) 12 (acetate)
Other solutions	5% dextrose/water	4.0	252	0	0	0	0	0	5	0
	50% dextrose/water	4.2	2,780	0	0	0	0	0	50	0
	7.5% saline	—	2,566	1,283	0	1,283	0	0	0	0
	8.4% $NaHCO_3$	—	2000	1,000	0	0	0	0	0	1,000
	14.9% KCl	—	4,000	0	2,000	2,000	0	0	0	0

BES, balanced electrolyte solution.

(3) Laboratory data and pathogenesis. ↑ Blood $[H^+]$, ↓$[HCO_3^-]$ (**Base deficit >4 mEq/L**).

(4) Therapy. Treatment of the underlying disease and the use of alkalinizing agents.

(a) Direct alkalinizing agents: $NaHCO_3$ and THAM (Tris). $NaHCO_3$ is used commonly in animals, but THAM is not frequently used.

i. Advantage of $NaHCO_3$: It directly works to neutralize excess of H^+.

ii. Disadvantages of $NaHCO_3$:

– It has a short shelf life of 2 years in solution. Discard the solution when it is cloudy.

– It cannot be autoclaved, since heat will cause: $2NaHCO_3 \rightarrow Na_2CO_3 + H_2O + CO_2$

– Oral dosing of $NaHCO_3$ decreases gastric acidity, which will interfere with milk clot formation, resulting in poor milk digestion.

(b) Indirect alkalinizing agents. Na lactate, lactated Ringer's, Na gluconate, Na acetate, acetated polyionic solution, and Na citrate. **The most frequently used indirect alkalinizing agents are Na acetate and Na lactate. The onset of alkalinizing action for an indirect agent is ~30 minutes**.

i. How do they alkalinize? See Figure 18-4.

ii. Most of commercial lactate solutions are the mixture of D- and L-forms (racemic form). D-lactate is minimally metabolized, thus is eliminated mostly via renal excretion.

iii. Other indirect agents do not have the problem with D-form of the chemical as with Na lactate.

iv. Lactate is metabolized in the liver (Krebs cycle), whereas Na acetate is used throughout the body, especially by the muscle. Thus, acetate is metabolized to form HCO_3^- more efficiently than lactate.

v. Acetate can induce vasodilation, which may be detrimental when it is administered IV to patients in shock.

vi. Do not use Na lactate in patients with lactic acidosis, who already have had a problem metabolizing lactate.

vii. Do not use Na acetate in patients with ketoacidosis, since acetate can form ketone bodies.

viii. Since the acidotic animals usually have K^+ deficit, supplement of alkalinizing agents with K^+-containing solutions.

ix. Dose of $NaHCO_3$ to be administered, if base deficit (BD) is known: mEq of $NaHCO_3$ administered = BW (kg) × 0.3 × BD

x. The $NaHCO_3$ should be administered via IV infusion for over a few hours, and the blood gas reevaluated before making a decision on further therapy.

xi. Dose of $NaHCO_3$, if base deficit is not known: 1–2 mEq/kg in a balanced electrolyte solution can be administered.

xii. It is rather difficult to over-alkalinize the body using an indirect agent in a patient with normal renal function. Excess $NaHCO_3$ produced can easily be excreted in the urine.

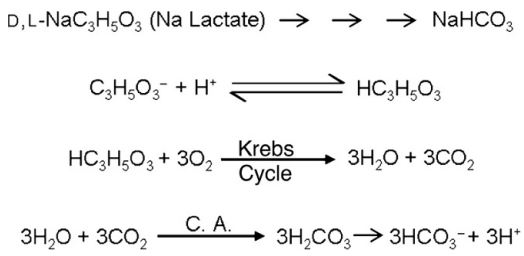


FIGURE 18-4. The metabolism of lactate into bicarbonate by the Krebs cycle.

b. Metabolic alkalosis

(1) Causes. Gain of base, excessive gastric vomiting, GI stasis or obstruction, hypokalemia, excess of aldosterone or diuretics, urea poisoning in cattle, and so forth.

(a) How does GI stasis lead to metabolic alkalosis? $NaHCO_3$ and HCl are produced in the parietal cell of the stomach. Once being made, $NaHCO_3$ is diffused into ECF, and HCl is released into the gastric lumen.

$$H_2CO_3 + NaCl \rightarrow NaHCO_3 + HCl$$

HCl will then be absorbed from the small intestine. GI stasis will prevent/delay the absorption of HCl into the circulation, thereby resulting in metabolic alkalosis.

(b) How does urea poisoning lead to metabolic alkalosis?

$$\underset{\text{Urea}}{CO(NH_2)_2} + H_2O \xrightarrow[\text{Cycle}]{\text{Urea}} 2\,NH_3 + CO_2$$

$$NH_3 + HCl\,(\text{strong acid}) \rightarrow NH_4Cl\,(\text{weak acid})$$

Alkalosis becomes apparent when a large amount of HCl is converted into NH_4Cl.

(2) General signs. Hypopnea, excitation including tetany, tremors, convulsions, and muscle rigidity may or may not be seen.

(3) Laboratory data. ↓ blood $[H^+]$, ↑$[HCO_3^-]$ (Base excess >4 mEq/L), alkaluria or paradoxical aciduria (particularly in the presence of hyponatremia).

(4) Therapy

(a) Treat etiology

(b) Chloride-responsive alkalosis. NaCl, KCl + NaCl, Ringer's solution, NH_4Cl + NaCl. It is best to use solutions containing NaCl and KCl, since affected animals usually have K^+ deficit.

(c) Chloride-resistant alkalosis. This is usually due to hyperaldosteronism, and thus the mineralocorticoid receptor antagonist spironolactone can be used to treat Cl^--resistant alkalosis. However, this condition is rarely seen in animals.

(d) H_2-antihistamines or omeprazole, an H^+ blocker, to stop the loss of H^+ into the GI tract. See Chapters 3 and 11 for more information about these drugs.

(e) Oral KCl in patients with heart failure receiving furosemide, who may have hypokalemia.

(5) How does NH_4Cl acidify the body?

Through urea cycle:

$$2NH_4Cl + CO_2 \Leftrightarrow \underset{\text{(urea)}}{CO(NH_2)_2} + H_2O + 2HCl$$

(6) How does NaCl acidify the body?

(a) Normal renal function. Reabsorption in distal tubule: $Cl^- > HCO_3^-$.

(b) Supplying a large volume of normal saline → More Cl^- than HCO_3^- is reabsorbed from the distal tubule →↑ plasma $[Cl^-]$, ↓ plasma $[HCO_3^-]$.

c. Respiratory acidosis

(1) Causes. Respiratory distress/pulmonary diseases, CNS depression resulting in inhibition of the respiratory center (disease or drug overdose), and so forth.

(2) General signs. Respiratory distress, cyanosis, CNS depression, and tachycardia.

(3) Laboratory data. ↑ Blood $[H^+]$, P_aCO_2 (>45 mm Hg).

(4) Therapy. Proper ventilation, alkalinizing agent is optional and can be used when ventilation alone will not correct the condition (e.g., pulmonary obstructions).

d. Respiratory alkalosis

(1) Causes. Overheat, fever, hyperventilation (particularly if there is overactive positive pressure ventilation during anesthesia), central neurologic disease, CNS stimulant overdose, and salicylate poisoning/overdose.

(2) General signs. Hyperpnea with and without panting, CNS stimulation with and without tremors/spasms/convulsions.

(3) Laboratory data. ↓ Blood $[H^+]$, ↓P_aCO_2 (<35 mm Hg).

(4) Therapy. Correction of hyperventilation; underlying etiologic factors must be eliminated; administration of sedatives may help in cases of CNS excitation; administration of an acidifying agent is optional.

e. Mixed acid–base disturbances occur much more frequently because of the development of compensation processes. Treatment may convert one type of acid–base disturbance into another; close monitoring is necessary. **At arterial blood pH of <7.2 or >7.6, then steps must be taken to correct the pH imbalance.**

f. In cases of combined metabolic and respiratory acidosis (which is a very severe form of acidosis), one must try to restore ventilation as the top priority; subsequently, an alkalinizing agent preferably $NaHCO_3$ can be administered to help raise blood pH. In the presence of high P_aCO_2, $NaHCO_3$ cannot work effectively as an alkalinizing agent.

g. In the field situation, if acid–base status is unclear, Ringer's solution should be administered. Lactated Ringer's solution or an acetated polyionic solution is the second choice.

h. Hypokalemia

(1) Causes. Reduced intake, loss via the GI tract, kidney, loss of interstitial fluid, excess of aldosterone or diuretics, and so forth.

(2) General signs. CNS depression and weak muscle contraction are attributable to hyperpolarization of the excitable membranes, cardiac arrhythmia.

(3) Laboratory data. ↓ Blood $[K^+]$, $[H^+]$,↑$[HCO_3^-]$, ↑Urine$[H^+]$, ↓$[HCO_3^-]$.

(4) Electrocardiogram (ECG) findings in hypokalemia-induced cardiac arrhythmia:

(a) ↑ Amplitude of QRS complex and P wave.

(b) Prolongation of QT interval.

(c) Flattened or inverted T waves.

(5) Mechanisms underlying hypokalemia-induced cardiac arrhythmia. Hypokalemia evokes an increase in myocardial $[Na^+]$ via Na^+, K^+-ATPase mechanism. High myocardial $[Na^+]$ increases Ca^{2+} influx via the Na^+–Ca^{2+} exchange mechanism (see Chapter 8, Figure 8-2). **Most of the ECG findings are attributable to the increase in myocardial $[Ca^{2+}]$.**

(6) Therapy for hypokalemia

(a) Only for severe acute hypokalemia **(<2.5 mEq/L)** or chronic hypokalemia.

(b) KCl or K gluconate, PO, SC, or IV **(≤0.5 mEq/kg/h). Parenteral fluids containing KCl (≤35 mEq/L) can be used safely by the SC route.**

(c) Watch out for KCl-induced hyperkalemia by monitoring signs of hyperkalemia.

(7) Drug interaction. Severe cardiac arrhythmias may occur in patients with hypokalemia when given digoxin.

i. Hyperkalemia

(1) Causes. Reduced urinary excretion, acidosis, hypoadrenocorticism, diabetes mellitus (early phase), excessive cell/tissue damage, increased intake, and so forth.

(2) General signs

(a) Increased neuromuscular excitability.

(b) Skeletal muscle twitching, irritability, and muscle weakness.

(c) Cardiac disturbances due to decreased resting membrane potential and a decreased myocardial $[Ca^{2+}]$.

(3) Laboratory data. Similar to metabolic acidosis.

(4) Therapy for hyperkalemia
- **(a)** Ca gluconate administration to replenish myocardial [Ca^{2+}]
- **(b)** Cation-exchange resin
- **(c)** Peritoneal dialysis
- **(d)** Diuretic administration
- **(e)** $NaHCO_3$ (1–2 mEq/kg) or dextrose to effect; insulin for diabetes mellitus.

B. Route and rate of administration

1. Oral route

a. Advantages
- **(1)** Rapid administration is possible.
- **(2)** Adverse reactions are minimal.
- **(3)** Economical.
- **(4)** Caloric needs may be easily met.

b. Disadvantages
- **(1)** May be contraindicated if GI disease is present.
- **(2)** Utilization is slower than by some other routes.

2. Intravenous route

a. Advantages
- **(1)** Rapid dispersion of fluid occurs.
- **(2)** Precise dosage is possible.
- **(3)** Hypertonic or hypotonic solution may be administered.

b. Disadvantages
- **(1)** The procedure may be time-consuming.
- **(2)** A limited number of sites are available.
- **(3)** A greater chance of adverse reactions.

c. Rates of intravenous infusion
- **(1)** If the heart, lungs, and kidneys are normal, the maximal rate of administration is **90 mL/kg/h** for an isotonic solution.
- **(2)** Rate of infusion should be high if the fluid loss was rapid and should be low if the fluid loss was gradual/slow. **Infusion rate of 15 mL/kg/h is appropriate for most cases.**
- **(3)** Rapid administration of glucose (>4 mg/kg/min) will result in hyperglycemia.
- **(4)** Rate of infusion should be slowed down after the first hour of administration especially if anuria is present (a catheter should be placed in urinary bladder in critically ill patients). Every attempt must be made to establish renal function. After ≥4 hours of infusion without urine flow, the rate of infusion must be decreased to 2 mL/kg/h.
- **(5) Watch for adverse reactions due to pulmonary edema and vagal stimulation. Central venous pressure (CVP) monitoring may aid in avoiding a volume overload (normal CVP is 0–3 cm of water). The infusion rate should be adjusted for each patient.**

3. Subcutaneous route

a. Advantages
- **(1)** It is convenient.
- **(2)** Solution with high K^+ concentrations, for example, 35 mEq/L may be given using this route.
- **(3)** Large quantities of a warm solution can be given to dogs and cats, particularly to very young or small size animals (hypodermoclysis).

b. Disadvantages
- **(1)** Limited to isotonic solutions.
- **(2)** Irritating solutions cannot be given.
- **(3)** Absorption may be poor in patients with edema or shock.
- **(4)** Five percent glucose, SC, is not a good idea, especially in animals in shock.

4. Intraperitoneal route

a. Advantage. Relatively rapid absorption.

b. Disadvantages
(1) May induce peritonitis or injury to viscera.
(2) Limited to isotonic solutions.

5. Rectal route
a. Advantage. It is convenient, especially in very young or small size animals, for example, birds. It is a viable alternative for fluid resuscitation in hypovolemic shock. This easy and noninvasive method of fluid replacement may be useful when standard IV access is impossible. Warm the solution to facilitate the absorption.
b. Disadvantages
(1) Erratic absorption.
(2) Contraindicated if diarrhea is present.

6. Intramedullary route. This is a rarely used route of fluid administration.
a. Advantages
(1) Rapid absorption.
(2) May be easier than IV route in neonates and birds.
b. Disadvantages
(1) May cause osteomyelitis.
(2) The procedure may be painful.

C. Products for fluid therapy

1. Crystalloids (Table 18-1)
a. Replacement solutions. Ringer's, normal saline, lactated Ringer's, acetated polyionic solutions (Normosol-R®; Plasma-Lyte A®).
b. The composition of the replacement fluids should reflect the composition of the fluid lost. For example, if the loss is due to diarrhea, then a solution containing Na^+, K^+, Cl^-, and HCO_3^- with concentrations similar to those of the body fluid should be administered.
c. Maintenance fluids are needed when a patient does not voluntarily ingest adequate amount of food and water to keep up with the daily maintenance dose requirements.
d. For the practical purpose, the maintenance fluid can be infused at the dose of 50–75 mL/kg/24 h for mature animals and 75–130 mL/kg/24 h for immature/young animals; the high dose of 130 mL/kg/24 h is reserved for very young animals.
e. Maintenance solutions (diluted electrolyte solutions using dextrose/water). These solutions usually contain high K^+ (13–18 mEq/L) and low Na^+ (40–80 mEq/L). Other factors affecting body water maintenance should be taken into consideration (see II A2 e (6)].
f. Other solutions: 5% dextrose, 50% dextrose, 7.5% saline, 8.4% (1 M) $NaHCO_3$, 14.9% (1 M) KCl, 5 M Na lactate, 2 M Na acetate, and so forth.

2. Colloids (plasma expanders)
a. General consideration
(1) The critical distribution of body water between plasma and interstitial fluid is maintained in part by the colloid osmotic pressure (COP) of plasma proteins, primarily albumin. This force pulls and holds body water into capillaries and balances the hydrostatic pressure driving water out. This forms the basis for IV colloid therapy.
(2) The crystalloids do not exert COP, and they are minimally retained in the vascular space, since they are small molecules. As a result, crystalloids cause much smaller volume of expansion than colloids.
b. Therapeutic uses
(1) Colloids are usually included in fluid regimens for small-volume resuscitation during shock (see below), management of hemorrhage, and improvement of microcirculatory flow and capillary integrity during systemic inflammatory response syndrome.

TABLE 18-2. Activity of Colloids on Plasma Expansion

Fluid (1 liter)	Plasma Volume Expansion (liter)	Expansion Duration (hours)
Plasma	1.000	
L. Ringer's	0.194	2
6% Hetastarch	0.710	24–36
6% Dextran 70	0.800	24
10% Dextran 40	1.000	4–6

L. Ringer's, Lactated Ringer's solution.

(2) Colloids must be used in combination with a crystalloid solution to replenish the interstitial and ICF deficits. In fact, the appropriate use of colloids can reduce the required amount of crystalloid solution by 40–60%.

(3) Care must be taken to adjust the amount and rate of all fluids to prevent overload and edema. COP can be monitored by using a colloid osmometer (normal being 20–25 mm Hg).

a. Preparations. Plasma, dextran 40, dextran 70, hetastarch, and polygelatins (Table 18-2).

(1) Dextrans

(a) These are polysaccharides produced by *Leuconostoc* bacteria. Dextrans 40 and 70 have sizes of 40 and 70 kDa, respectively.

(b) Dextrans 40 and 70 have plasma $t_{1/2}$ of 1–3 and 2–6 hours, respectively.

(c) Elimination. In normal dogs, 70% of the dextran 40 dose and 40% of the dextran 70 dose are excreted unchanged within 24 hours. The remaining dextrans are metabolized slowly to glucose by hepatic dextranase. Some of the molecules can remain in the body for weeks after administration.

(2) Hetastarch

(a) It is a synthetic glucose polymer. It is very slowly metabolized by α-amylase if size is >59 kDa, whereas smaller molecules (<59 kDa) are excreted by the kidneys or taken up by macrophages and slowly metabolized by lysozymes.

(b) In dogs, 24 hours after administration, ~40% of hetastarch remains in the plasma and ~30% is excreted in the urine.

(3) Polygelatins

(a) Gelatins are prepared by degradation of bovine collagen and are available in several forms, oxypolygelatin, succinated gelatin, and urea-linked gelatin. 5% oxypolygelatin is the only polygelatin available in the United States for fluid therapy.

(b) The plasma $t_{1/2}$ of oxypolygelatin is ~24 hours.

(c) Gelatins are metabolized by proteolytic enzymes in the liver with ~70 and ~15% of the end products being excreted in the urine and feces, respectively.

b. Rate of colloid infusion

(1) In acute situations, for example, shock or hemorrhage, 10–40 mL/kg IV bolus to effect, followed by a constant-rate infusion (CRI) to maintain a mean arterial pressure (MAP) of 80 mm Hg.

(2) In chronic situations, use CRI to maintain MAP of 80 mm Hg.

(3) Since cats are more likely to show signs of allergic reactions, especially when synthetic colloids are infused rapidly, only small volumes are infused at slower rates (5 mL/kg increments given over 5–10 minutes, repeated to effect at ≤20 mL/kg).

c. Adverse effects

(1) Volume expansion may dilute blood constituents.

(2) Rapid volume expansion may be detrimental to patients with acute renal failure or congestive heart failure.

(3) Dextran 40 may cause acute renal failure.
(4) Colloids may cause antigen–antibody reactions (<0.1% in humans).
(5) Dextrans and hetastarch may interfere with **fibrin clot formation by diluting and reducing clotting factors and interfering with platelet function. Thus, they should not be used before or during major surgery. However, some hetastarch preparations have Ca^{2+} in the medium, which may reduce clotting abnormalities. Gelatins have less anticoagulatory effects than other colloids**.

3. **Hypertonic solutions** (e.g., 7.5% NaCl)
   a. **Therapeutic uses.** These solutions are used for the resuscitation of animals suffering from shock (plasma volume expansion), and treatment of head injury and burns.
   b. **Hypertonic solutions are used in combination with colloids**; for example, 7% NaCl–6% dextran 70 (4–8 mL/kg).
   c. **Other actions.** Hypertonic solutions decrease afterload (due to vasodilatation), increase catecholamine release, and increase oxygen delivery to the heart. Hypertonic solutions could have positive inotropic effects and immunomodulatory effects.
   d. **Adverse effects.** Volume overload and edema.
   e. **Contraindications.** Patients with hypernatremia or coagulation problems should not receive hypertonic solutions.

D. **Parenteral nutritional therapy.** It is used in animals who cannot voluntarily consume food because of a GI, pancreatic, or hepatic disease. This technique is to prevent malnutrition and to treat animals that are malnourished.

1. **Total parenteral nutrition (TPN).** The IV infusion of glucose, lipid, amino acids, trace elements, and vitamins (usually only B-complex) in adequate amounts to meet the nutritional needs.
2. **Partial parenteral nutrition**. In some cases, enteral nutrition is provided in combination with parenteral nutrition. These animals are more likely to survive compared with animals not receiving any enteral nutrition.
3. **Most companion animals receive parenteral nutrition for short time, average 3–4 days**. Occasionally, parenteral nutrition is administered for prolonged periods, but the risk/benefit ratio must be considered for these cases.
4. **Two premises for performing TPN because of the administration of hypertonic solutions (700–1,000 mOsm/L):**
   a. **Infusion into a large bore vein, that is, the jugular vein.**
   b. **Continuous (24 hours) infusion of the solution.**
5. **Formulation of parenteral nutrition requirements**
   a. **Calorie requirements.** The determination of daily calorie requirement in each dog or cat can be performed by using the information in Figure 18-3 or by calculating the resting energy requirement (RER) in Figure 18-5.
      (1) One should avoid using the linear regression in Figure 18-5 for animals >25 kg, since it will overestimate their energy requirement; the exponential regression can estimate more precisely their calorie needs than the linear regression.
      (2) Sources for calories: Glucose (dextrose) and lipid are major sources for calories. Glucose and lipid generate 4 and 9 kcal/g, respectively.
      (3) The maintenance doses of calories in dogs and cats are presented in Figure 18-3. For example, a 10-kg dog would require 700 kcal for daily maintenance, which can be generated by 175 g of glucose or 78 g of lipid. Glucose is usually used for the supply of calories. However, lipid solution can provide essential fatty acids.
      (4) For the calorie requirements, 50% dextrose instead of 5% should be used; the latter is too diluted to meet the daily maintenance requirement.
      (5) **The glucose infusion rate should be ≤4 mg/kg/min to avoid hyperglycemia.** In diabetic patients, the insulin dose will require adjustment in order to maintain normoglycemia.

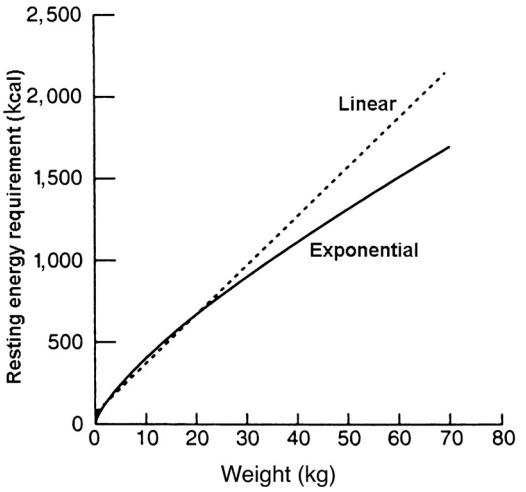


FIGURE 18-5. Comparison of resting energy requirements (RERs), as calculated using a linear equation [(30 × body weight) + 70] versus an exponential equation [70 (body weight)$^{0.75}$]. Note that the equations yield similar results for animals weighing between 3 and 25 kg. For animals that weight >25 kg, the linear equation overestimates the animal's RER. (Reprint with permission from *Fluid, Electrolyte, and Acid-Base Disorders*, 3rd ed. Edited by DiBartola S. P. Saunders/Elsevier, 2006, Figure 25-5.)

6. **Amino acid requirements.** Animals need a nitrogen source to induce positive nitrogen balance and essential amino acids; these requirements can be met by using an amino acid solution that is available 3.5–15% (Aminosyn®, Travasol®, Noramine®, FreAmine®, and ProcalAmine®) containing all essential amino acids, except taurine. Most amino acid solutions are available in two formulations: one with electrolytes and one without.
   a. **Dosages: 40–50 mg amino acids/kcal/day for dogs and 60 mg/kcal/day for cats** (**Note: dosage is based on kcal requirement, but not body weight**).
   b. Animals with large draining wound or hypoproteinemia should use higher quantity of amino acids than heretofore recommended.
   c. The amino acid dosages should be reduced in patients with protein intolerance, for example, those with hepatic encephalopathy or renal failure.
   d. **Calories must be provided at the same time** to prevent the gluconeogenesis from amino acids.
7. **Lipid requirements.** Lipid emulsions are occasionally used in TPN as an energy source and to provide essential fatty acids.
   a. **Lipid generates 9 kcal/g**. The lipid preparations used include soybean oil/safflower oil, egg yolk phospholipids, glycerin, and water.
   b. Since high doses of lipid can cause immunosuppression via granulocyte and reticuloendothelial cell dysfunction, and inflammation due to increased formation of eicosanoids, the **doses should be limited to 2 g/kg/day**. Patients with high blood levels of triglyceride should not receive a lipid emulsion.
   c. Animals have a need for essential fatty acids; **dogs need linoleic acid and cats need arachidonic acid**. The fatty acids can be provided by a lipid emulsion. In parenteral nutrition, fatty acids are usually not required, unless the animals remain on prolonged nutritional treatment.
8. **Other nutritional requirements**. Electrolytes, vitamin B-complex, and trace elements may be added to the parenteral nutrition. Because most animals are on short duration of parenteral nutrition, fat-soluble vitamins are usually not included in the formulation. Adjustments to the nutritional plan may include Na^+ restriction for cardiac patients, protein restriction for encephalopathic patients, and end-stage renal failure patients.
9. **Problems associate with parenteral nutrition** include infection (sepsis), hyperglycemia, and mechanical complications.

III. BLOOD THERAPY

A. Blood transfusions

1. **Major indications for whole blood therapy**
   a. **Hemorrhage or shock**: Keep in mind that **normal blood volume is ~75 mL/kg** and **normal plasma volume is ~50 mL/kg**
   b. **Anemia**
   c. **Coagulation abnormalities**
   d. **Provision of antibodies**
2. **Donor selection. To find a healthy donor with compatible erythrocytes.**
   a. **Three strong hemagglutinin antigens in dogs**: **dog erythrocyte antigen** (**DEA) 1.1, DEA1.2, and DEA7; DEA7 is an isoantibody** and is active only below 37°C. **The ideal dog blood donor has to be healthy, and should be free of these strong hemagglutinin antigens**.
   b. **Two hemagglutinin antigens in cats**
      (1) **A and B: These are isoantibodies.**
      (2) **Type A (anti-B)**: Weak; Siamese and 99% of domestic cats in the United States.
      (3) **Type B (anti-A)**: Cats with type B blood have strong anti-A antibody; 20% of pure bred cats are type B. One milliliter of type A blood given to a type B cat can be fatal, even without prior sensitization. Type A kittens born to and allowed to nurse from type B queens suffer from neonatal isoerythrolysis.
      (4) **Type AB (no antibody)**: 0.1% of cats in the United States belong to type AB.
   c. **For horses, male ponies with no previous history of blood transfusion can serve as donors**, if cross-matching technique is not practical in the field.
   d. **Other species also have isoantibodies; one can do cross-matching to determine agglutination** (see below).
   e. **Cross-matching technique**
      (1) **Major technique:** Potential donor's RBCs are mixed with recipient's serum to determine agglutination.
      (2) **Minor technique:** Potential donor's serum is mixed with recipient's RBCs to determine agglutination.
3. **Blood collection and storage**
   a. **Collection**: 20% of blood from a donor at 2–4 weeks intervals.
   b. Collection in plastic bags with an anticoagulant solution: **CPD (citrate–phosphate–dextrose) or CPDA-1 (citrate–phosphate–dextrose–adenine)**. CPDA-1 is the most commonly used anticoagulant in human medicine for the collection and storage of whole blood. The commercially available canine and feline whole blood products (from Animal Blood Bank, Inc.) are also preserved in CDPA-1.
   c. **CPD or CDPA-1: 14 mL is needed to collect 100 mL of blood.**
   d. **The blood using CPD and CPDA-1 as the anticoagulant can be preserved for 3 and 7 weeks, respectively, at 4°C.**
   e. **Sterile (autoclaved) 3.5% Na citrate** solution can be used as an inexpensive anticoagulant, particularly in large animals (1 part of 3.5% Na citrate to 9 parts of blood). The blood collected using Na citrate should be utilized as soon as possible, since it does not have any additives (dextrose, phosphate, or adenosine) to preserve the blood cells.
   f. **Sodium citrate may induce vomiting** in nonherbivores.
   g. **Plasma** can be separated from blood cells before the bag of blood is expired.
   h. **Heparin** should not be used as an anticoagulant to collect blood for transfusion. Heparin has following problems.
      (1) Heparinized blood cannot be stored, since heparin is inactivated in 24–48 hours in the blood.
      (2) Heparin activates platelets, rendering them nonfunctional.

4. **Administration and dosages**
   a. **Administer when PCV <20%.**
   b. The blood should be filtered to remove possible blood clots and warmed to 37°C before being transfused into a recipient.
   c. One should conduct cross-matching whenever possible before administration.
   d. Administer IV, IP, or intramedullary.
   e. Dosages: **10–20 mL/kg** or using the formula: **mL of blood infused = 1 mL/lb × % PCV change desired.**
   f. **Rate of administration** depends on clinical signs and the dose: **60 mL/min (large animals), 5–10 mL/min (small animals), and 40–50 mL/30 min (cats).**
5. **Plasma**
   a. **Therapeutic uses.** Plasma is used to expand plasma volume, or to increase plasma proteins, for example, albumin and globulin in patients with hepatic dysfunction, and to provide clotting factors and platelets.
   b. **Preparations.** Plasma is available either as a fresh or frozen preparation.
      (1) Fresh plasma **contains platelets** and clotting factors, and must be used within 4 hours of preparation because of the risk of bacterial contamination at room temperature.
      (2) Fresh frozen plasma contains clotting factors (freeze at <–40°C, good for 1 year; at −20°C, good for 3 months), which are destroyed if the unit has been thawed for >8 hours, **but contains no platelets.**
   c. **Administration**
      (1) **Administer when serum albumin concentration is <1.5 g/dL.**
      (2) **Dosages**: **5–10 mL/kg, IV infusion.**
6. **Adverse effects.** Hemoglobinemia, hemoglobinuria, jaundice, thrombocytopenia, leucopenia, fever, emesis, incontinence, urticaria and/or weakness, hypocalcemic tetany, and circulatory overload. Neonatal animals may develop hemolysis after nursing due to the development of antibodies to erythrocyte antigen in the colostrum.
7. **Interspecies transfusion** is prohibited because of incompatibility.
8. **Polymerized bovine hemoglobin (Oxyglobin®)**
   a. **Preparation**: 13 g/dL in lactated Ringer's solution.
   b. **Therapeutic uses.** For the treatment of anemia in dogs: 30 mL/kg, IV, at a rate of ≤10 mL/kg/h. **It is particularly useful in dogs with autoimmune hemolytic anemia shortly before an immunosuppressant is given.**
   c. **Elimination $t_{1/2}$: 30–40 hours** (90% being eliminated in 5–7 days).
   d. **Adverse effects.** Discoloration/GI and CV disturbances, pulmonary edema, anaphylaxis, and death.
   e. **Contraindications.** Do not use this product in patients with a cardiac or renal disease.
   f. **Warnings**
      (1) Do not use this product repeatedly in the same dog, since the repeated use of this product can cause anaphylaxis.
      (2) Must finish the product within 4 days once it is opened; otherwise, it may form methemoglobin.

IV. SPECIAL TOPICS IN FLUID THERAPY

A. Horses

1. Cases of severe diarrhea, shock, intestinal obstruction, or esophageal obstruction may predispose to severe metabolic acidosis.
2. The respiratory acidosis may be associated with inhalation anesthesia.
3. A severe hyponatremia may be associated with dehydration.
4. A severe hyperkalemia (plasma K^+ concentrations of ≥7 mEq/L) may be associated with acidosis in foals.

B. Cattle

1. The metabolic alkalosis may be associated with an abomasal disease.
2. A severe metabolic acidosis and dehydration and sometimes severe hyperkalemia may be associated with grain overload and calf diarrhea.
3. A severe K^+ deficit may be present in anorectic animals.
4. The oral fluid therapy should be administered to treat neonatal diarrhea whenever possible.

C. Problems seen in all species

1. **Effects of anesthesia and surgery**
   - **a.** Anesthetic and surgical effects
     - **(1)** General anesthetics depress the cardiovascular system and the glomerular filtration rate.
     - **(2)** Inhalation anesthetics cause vasodilatation.
     - **(3)** Fluid loss may increase during general anesthesia and surgery.
     - **(4)** Third spacing may occur during surgery.
     - **(5)** IV fluids cause reduction in plasma protein concentrations and blood cell counts.
     - **(6)** Patients may have volume overload and hypertension during postsurgical period.
2. **Heat exhaustion and prostration.** Excessive heat will cause the loss of a large amount of NaCl from the ECF. As a result, K^+ is released from the cells to compensate for the loss of Na^+. Renal excretion of NaCl diminishes, but water excretion continues. The body has a severe deficit of Na^+, K^+, Cl^-, and dehydration. Hyperventilation in response to heat may lead to respiratory alkalosis. All measures are needed to lower the high body temperature. In addition, an electrolyte solution (e.g., Ringer's, lactated Ringer's, or acetated polyionic solution) should be administered. If hypertonic dehydration, maintenance crystalloid solutions with low Na^+ and high K^+ should be administered.
3. **Burns.** With burns, more electrolyte than water is lost, which leads to hypotonic dehydration. Hypertonic solution can be used to treat patients with burns.

D. Oral fluid therapy in neonatal calf and piglet diarrhea

1. **Generation considerations.** Oral fluids are indicated for the correction of diarrhea-associated dehydration in neonatal animals that still retain the suck reflex.
   - **a.** In general, neonatal animals that can stand and have a suck reflex are good candidates for oral fluid therapy. Calves that are weak and have poor suck reflex often benefit from oral fluids, but they may have to be administered via the stomach tube.
   - **b.** Recumbent neonatal calves that do not have suck reflex and/or show rapidly progressing signs of severe dehydration should not be treated with oral fluid; instead, they should be treated with IV fluids. As a rule of thumb, neonatal animals not clinically improved within 1–2 hours of oral fluid administration are likely candidates for IV fluid administration.
   - **c.** The effectiveness of oral fluids depends on their composition, the severity of the condition under treatment, and the aggressiveness of the treatment regimen. Oral crystalloid solutions containing electrolytes, glucose, glycine, and alkalinizing agents are highly efficacious in treating calves and piglets with severe diarrhea. Table 18-3 shows the composition of four commercially available preparations.
     - **(1) Utilization of the action of cotransporters** (glucose–Na^+, amino acid–Na^+) into the gut mucosa. Rehydration depends on Na^+ absorption. Numerous glucose–Na^+ and amino acid–Na^+ cotransporters are found in the gut mucosa. These cotransporters are stimulated by glucose and neutral amino acids, respectively, to facilitate the transport of glucose, amino acids, and Na^+. Glycine is the neutral amino acid most frequently used in oral crystalloid solutions.

TABLE 18-3. Composition of Four Oral Electrolyte Solutions Designed to Be Fed to Diarrheic Calves

Product	Glucose (mmol/L)	Glycine (mmol/L)	Na^+ (mEq/L)	K^+ (mEq/L)	Cl^- (mEq/L)	AlkalinizingAbility (mEq/L)	HCO_3^- (mEq/L)	Citrate (mEq/L)	Acetate (mEq/L)
Electrolyte Powder®	110	0	139	10	101	48	48*	0	0
Electrolyte with Thickener®	220	25	184	38	46	110	110*	0	0
Hydra-Lyte®	405	16	118	30	45	103	0	4	99
Resorb®	120	44	78	17	78	0	0	1	0

*Interferes with milk clotting.

(2) **Inclusion of alkalinizing agents.** $NaHCO_3$ and the indirect alkalinizing agents Na acetate, Na gluconate, and Na citrate are used in oral fluids. The addition of alkalinizing agents to the oral fluids has decreased the mortality in neonatal calves and piglets. Alkalinizing agents are usually added to the oral fluids at the rate of 40–100 mEq/L.
   (a) $NaHCO_3$ can directly neutralize acid, but it also decreases gastric/abomasal) acidity, which may predispose to bacterial overgrowth in the small intestine, and may interfere with milk digestion by preventing its clot formation.
   (b) The advantage of indirect alkalinizing agents is that they will not affect gut pH. The disadvantage of indirect alkalinizing agents is decreased utilization in diarrheic animals with severe dehydration.

(3) **Inclusion of KCl.** In diarrheic neonatal animals, there is a severe K^+ deficit. The addition of KCl to the oral fluids may save the life of neonatal animals. KCl is usually found in the oral fluids at the rate of 10–40 mEq/L.

(4) **Inclusion of gelling agents.** These agents are found in some of the commercial preparations (e.g., Electrolyte with Thickener®). They are indigestible mucopolysaccharides. Despite claims that they can slow down the flow and elimination of oral fluids, which reduce the severity of diarrhea, no scientific evidence supports these claims.

(5) **Milk consumption.** Milk is the most easily digestible food source for neonatal animals and should be reintroduced early in the treatment of diarrhea. It provides the most nutrition of all types; it provides calories, protein, vitamins, minerals, and water. Milk contains 500–600 kcal/L. Studies have shown that enterocyte repair is increased in diarrheic calves after they drank milk. Frequent milk feedings (1 liter, 2–4 times a day), in addition to oral fluid therapy, usually facilitates the recovery from calf diarrhea rather well.

(6) **Dosages of oral fluids.** The diarrheic neonatal calves should be fed with oral fluids 2–4 times a day with total intake of 4 liters.

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