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Digitalis, Positive Inotropes, and Vasodilators

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An understanding of the pharmacokinetic and pharmacodynamic characteristics of cardiac drugs is essential for veterinarians who treat cardiovascular disease. Cardiac disease is often severe and life-threatening events must be managed with these drugs. Also, states of cardiac dysfunction that are amenable to drug therapy are common in dogs and cats. This chapter considers some of the more important drugs used in therapeutic management of cardiac disorders, with focus on those that affect basic aspects of cardiovascular function, including positive inotropes, inodilators, and vasodilators. Antiarrhythmic drugs are covered in Chapter 22. Other classes of drugs that elicit prominent cardiac responses (e.g., adrenergic and cholinergic agents) are discussed in Chapter 8, while off-loading therapies, other than vasodilators and inodilators (i.e., diuretics) are discussed in Chapter 24.

Basic Aspects of Cardiac Function

The primary pathways by which the cardiovascular system can increase or decrease cardiac output, based on need, include changes in heart rate, adjustments in myocardial contractility, an intrinsic response of the cardiac muscle to changes in muscle length, and optimization of vascular size (vasodilation and vasoconstriction). This physiological (neurohormonal) control is via pressure sensors, the central nervous system, sympathetic and parasympathetic nervous systems (SNS, PSNS), and the renin–angiotensin–aldosterone system (RAAS). The control systems involved are of considerable importance to pharmacology because the net response of the heart and vascular system is to these regulatory systems and the drugs administered often provide their effect via stimulating or blunting these systems.

Intrinsic Regulation

Contractile response of cardiac muscle to a change in its own length is the primary mechanism whereby the heart adjusts its pumping activity under normal physiological conditions (Fozzard, 1976). When venous return increases, the contractile function in the healthy heart increases, thereby pumping an increased volume of blood into the arterial system. This fundamental capability of the heart to autoregulate its pumping capacity in response to end-diastolic filling is referred to as the *Frank–Starling law of the heart* (Frank, 1895; Starling, 1918). This force–length relationship is primarily a result of an increase in calcium sensitivity as the initial sarcomere length increases. The relationship between preload (end-diastolic filling) and cardiac output under basal conditions and under dominance by the sympathetic and parasympathetic nervous systems is shown in Figure 21.1.

Regulation by the Nervous System

The autonomic nervous system regulates the cardiovascular system mainly by adjusting heart rate, vascular volume, and myocardial contractility. Details concerning cardiac effects and mechanisms of action of the sympathetic neurotransmitter norepinephrine (NE) and the parasympathetic neurotransmitter acetylcholine (ACh) are found in Chapters 6–8.

The intrinsic heart rate is determined via blockade of both arms of the autonomic nervous system. When an animal is at rest, the PSNS is likely dominant, as the resting heart rate is lower than the intrinsic heart rate. Patients with heart failure often have higher resting heart rates and less heart rate variability, suggesting that the SNS is likely dominant over the PSNS at rest. Sympathetic stimulation of cardiac muscle (via endogenous NE and certain pharmacological agents) can markedly increase the force of contraction, irrespective of end-diastolic muscle length. A change in contractile strength that is independent of muscle length is referred to as a change in contractility or inotropy. In the presence of inotropic stimulation by the sympathetic system, cardiac output at each level of ventricular filling is enhanced over the basal state (Figure 21.1). Conversely, parasympathetic nerves exert their primary influences

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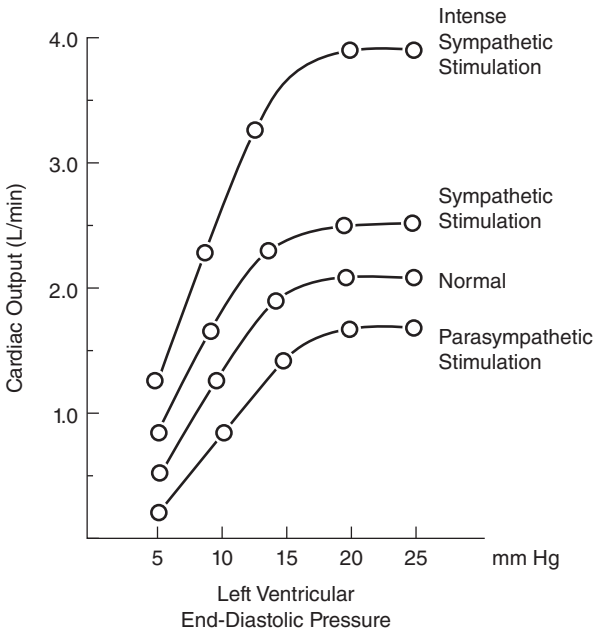

Figure 21.1 Frank–Starling law of the heart. As end-diastolic ventricular volume (preload) increases, the myofiber is stretched, enhancing the contractile state of the muscle; cardiac output is thus increased. The cardiac output curve can be influenced by different degrees of sympathetic and parasympathetic stimulation.

on cardiac output, not by changing the inotropic state, but by slowing heart rate and, with that, increasing ventricular filling time. Vagal discharge, however, when it produces bradycardia, decreases cardiac output at all levels of venous return and stretch on myocardial fibers (Figure 21.1). In contrast, sympathetic stimulation produces an increase in heart rate. Within physiological limits, cardiac output increases proportionately to the change in heart rate. Importantly, myocardial blood flow is decreased in rapid tachycardia, while myocardial oxygen needs are increased.

Myocardial oxygen demand (MVO_2) varies directly with three main factors: heart rate, myocardial wall tension, and inotropic state. Myocardial wall tension is directly related to ventricular radius (cardiac size) and intraventricular pressure and indirectly related to wall thickness (i.e., the law of Laplace). Primary determinants of ventricular wall tension are preload (i.e., end-diastolic volume and stretch) and afterload (determined by cardiac luminal size, wall thickness, and systemic blood pressure). By reducing pre- or afterload, certain drugs can elicit marked reduction in cardiac work (and MVO_2) without direct inotropic action on the heart muscle cell.

Cellular Concepts

The basic contractile unit of a heart muscle cell is the sarcomere, composed of actin (thin filament) and myosin (thick filament) proteins. A protein assembly unit, associated with the actin molecule, composed of tropomyosin and troponin, regulates activation of the filaments. Availability of ionized calcium (Ca^{++}) in the vicinity of troponin is the obligate modulator of the diastole–systole contraction cycle. Binding of Ca^{++} to a high-affinity subunit of the troponin molecule evokes the movement of tropomyosin from its diastolic blocking position on actin. Cross-linkages or "cross-bridges" are formed between projections of the myosin molecules and exposed sites on actin. As cross-bridges are formed, the thick and thin filaments slide over each other, and contraction occurs. Calcium delivery to the myofibrils is initiated by bioelectric events at the cell membrane, represented by the cardiac action potential.

Excitation–Contraction Coupling

L-type Ca^{++} channels are opened as the wave of depolarization travels down the T tubules, leading to the release of a small amount of Ca^{++}. This Ca^{++} triggers the activation of Ca^{++} release channels on the sarcoplasmic reticulum (SR) and causes the release of relatively large amounts of Ca^{++} into the cytosol (Opie, 2001; Fabiato and Fabiato, 1979).

Two separate pathways of movement of superficial Ca^{++} are believed to be involved (Langer, 1976, 1980; Parker and Adams, 1977). The primary electrogenic route is associated with the previously discussed triggered Ca^{++} release from the SR. An additional influx of Ca^{++} is linked with a Ca^{++}–Na^{+} exchange across the sarcolemma. A schematic representation of excitation–contraction coupling in mammalian heart muscle is shown in Figure 21.2.

Relaxation

During repolarization, Ca^{++} is actively sequestered by the SR, which avidly binds and stores myoplasmic Ca^{++} with affinity greater than troponin. Relaxation occurs as Ca^{++} moves to the SR from troponin binding sites on the myofibrils, and the cytoplasmic Ca^{++} concentration decreases below the threshold required to trigger actin–myosin cross-bridge formation (Figure 21.2). Since this is an energy-requiring process, relaxation is somewhat a misnomer for the changes that occur during diastole.

Maintenance of Electrolyte Gradients

There is a net influx of Na^{+} and Ca^{++} and efflux of K^{+} with each action potential. Membrane-bound enzymes act as pumps to relocate ions and prevent their improper accumulation (Gadsby, 1984). Sodium–potassium–activated adenosine triphosphatase (Na^{+},K^{+}-ATPase), localized in the cell membrane, propels Na^{+} out of and K^{+} into the cell, against their respective concentration gradients. Excess intracellular Ca^{++} is pumped out of the cell by systems localized in regions of the SR in close approximation

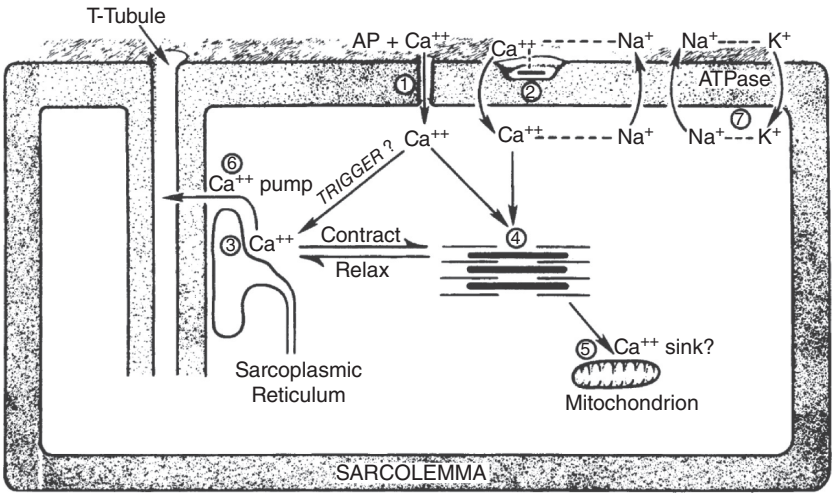

Figure 21.2 Schematic representation of cellular ion movements controlling excitation–contraction coupling in heart muscle. An action potential (AP) instigates the inward movement of Ca^{++} through slow Ca^{++} channels of the sarcolemma (1). Inward-moving calcium fills sarcoplasmic reticulum stores of the cation and also serves as a trigger to release additional Ca^{++} from storage sites of the sarcoplasmic reticulum (3). These Ca^{++} sources and that resulting from Na^{+}–Ca^{++} exchanges across the sarcolemma (2) activate the contractile proteins (4). Relaxation occurs as calcium is sequestered at storage sites of sarcoplasmic reticulum (3). Mitochondrion (5). Ca^{++} is pumped out of the cell (6). Altered sodium pump activity (7) may also affect sodium concentrations available from Na^{+}–Ca^{++} exchange. Source: Parker and Adams, 1977.

to the sarcolemma (Figure 21.2). A sarcolemmal Ca^{++}-ATPase also contributes to extrusion of Ca^{++}.

Positive Inotropes and Inodilators

Digitalis and Related Cardiac Glycosides

Digitalis and several closely allied chemicals are derived from the purple foxglove plant (*Digitalis purpurea*), other related species of the figwort family, and some plant species unrelated to digitalis.

Chemistry and Sources

Chemical and structure–activity relationships of the digitalis glycosides are quite complex, but several basic similarities are retained in the different compounds. The nomenclature is based on botanical origins rather than chemical structure. Digitalis is the dried leaf of the purple foxglove plant. Digitoxin, digoxin, and gitoxin also can be extracted from the leaf of a related plant, *D. lanata,* the woolly foxglove. Strophanthidin and ouabain are glycosides contained in the seeds of *Strophanthus* sp. Digitoxin and ouabain have been removed from the commercial market and only digoxin will be discussed here. Because of considerable pharmacological similarities between the different glycosides, the collective term *digitalis* has been used to designate the entire group of drugs, including digoxin. Often, *digitalis* and *digoxin* are used interchangeably by cardiologists. The term *glycoside* in general refers to a compound linked by an oxygen atom to a sugar molecule(s). The basic steroid-type nucleus is a cyclopentanoperhydrophenanthrene, to which is attached an unsaturated lactone ring at carbon atom 17 (C-17). The sugar molecules usually are attached at C-3; they influence water solubility, cell penetrability, duration of action, and other pharmacokinetic characteristics. The cardioactivity of the molecule resides principally in the aglycone moiety, but the positive myocardial actions of these entities are somewhat less potent and of lesser duration than the parent glycoside.

Cardiovascular Effects

Improved myocardial contractility was once considered to be the most important trait of the glycosides and, indeed, is the primary action on which the hemodynamic benefits depend. Today however, neuroendocrine (neurohormonal) effects, including reduced SNS activity and heart rate control, are believed to be of most important in treating heart failure.

Myocardial Contractility

The ability of cardiac glycosides to increase contractility has been demonstrated in a multitude of experimental preparations with results that validate a direct effect on contractile strength, independent of changes in resting fiber length, heart rate, or afterload. The positive inotropic action of cardiac glycosides is most pronounced in the hypodynamic or failing heart, though it is less than with other inotropic agents, such as dobutamine. Digitalis was shown in one study to provide a 24% increase in cardiac index versus 34% with dobutamine CRI (continuous rate infusion; ~3 μg/kg/min), meaning that the latter has a 42% greater inotropic effect than digoxin (Vatner et al., 1974).

Cellular Mechanisms of Inotropic Action

One of digitalis' proposed actions in congestive failure is a positive cardiac inotropic effect, but significance of this effect has diminished after examining results of several investigations. The second restorative action is neurohormonal normalization, thought by many to be the more important of known and postulated mechanisms of digitalis' clinical benefits (see Section Neuroendocrine Effects) (Ferguson, 1989).

Inhibition of Na^+,K^+-ATPase: The Mg^{++}-dependent Na^+,K^+-ATPase of the cell membrane supplies energy for the active pumping of Na^+ outward and K^+ inward against their large concentration gradients (Figure 21.2). The Na^+,K^+-ATPase is believed to be the cellular receptor for digitalis glycosides (Schwartz, 1977; Akera and Ng, 1991; Schatzmann, 1953). Inhibition of Na^+,K^+-ATPase by digitalis results in progressive reduction of $(K^+)_i$ as the ability of the pump to transport K^+ inward and Na^+ outward progressively fails (Fozzard and Sheets, 1985; Katz et al., 1985). A decrease in $(K^+)_i$ and/or an increase in $(K^+)_o$ reduces resting membrane potential to a less negative value, which can lead to increased automaticity and eventually impaired conduction and excitability. Inhibition of ATPase and resulting depletion of $(K^+)_i$ are responsible for the *arrhythmogenic properties* of digitalis.

The *inotropic effect* involves activation of a Na^+–Ca^{++} exchange mechanism through accumulation of $(Na^+)_i$. Baker et al. (1969) demonstrated with the giant squid axon that an increase in $(Na^+)_i$ enhanced the uptake of Ca^{++} by a Na^+–Ca^{++} exchange process. This mechanism seems to be operative in other excitable tissues and has been evoked as the link between inhibition of Na^+,K^+-ATPase and digitalis inotropy in the heart (Langer, 1977). The sequence of events can be visualized to include the following progression: digitalis interacts with and inhibits cell membrane Na^+,K^+-ATPase, outward pumping of Na^+ is slowed, $(Na^+)_i$ accumulates, increased $(Na^+)_i$ augments transmembrane exchange of intracellular Na^+ for extracellular Ca^{++}, $(Ca^{++})_i$ is increased, and Ca^{++} delivery to the contractile proteins is increased; thus the positive inotropic effect is gained. Dominance of Na^+–K^+ exchange and augmentation of Na^+–Ca^{++} exchange, with digitalis' inhibition of ATPase is demonstrated in Figure 21.3.

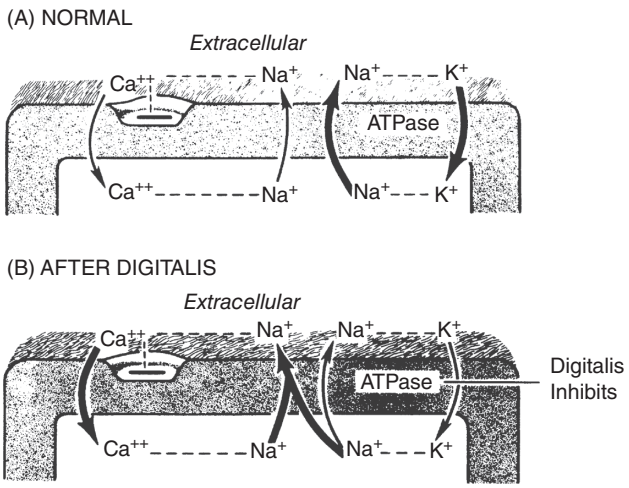

Figure 21.3 Schematic representation of a proposed mechanism for the positive inotropic action of cardiac glycosides. Inhibition of Na^+,K^+–ATPase (sodium pump) by digitalis results in increased intracellular concentrations of sodium available for exchange with calcium. Heavy arrows designate the dominant pathway of ion exchange during normal conditions (A) and after inhibition by digitalis of Na^+,K^+–ATPase (B). Adapted from Langer, 1976; Source: Parker and Adams, 1977.

Cardiac output

Digitalis glycosides increase contractility in both the normal and failing myocardium. However, the change in cardiac output is influenced by the functional status of the cardiovascular system.

Normal heart: Output of the normal heart increases minimally and may even decrease slightly after treatment with digitalis (Braunwald, 1985). Total peripheral resistance is increased by digitalis in the normal subject as a result of a centrally mediated increase in sympathetic vasomotor tone and direct vasoconstrictor effect. Impedance of the arterial circuit to ventricular ejection (afterload) is thereby increased, which attenuates the expected increase in cardiac output produced by the positive inotropic effect.

Failing heart: The work capacity of the failing ventricle at any given end-diastolic volume or pressure is inadequate to generate a normal stroke volume (Figure 21.4). The ejection fraction is diminished accordingly, which increases residual blood in the ventricle after systole (Moalic et al., 1993). If diastolic filling continues at a near normal rate, the ventricle will dilate to accommodate increased end-diastolic volume. With the administration of digitalis, the above processes are reversed. Digitalis-increased myocardial contractility augments work capacity of the ventricle, at any given end-diastolic filling pressure, as illustrated in Figure 21.4, where ventricular function curves derived in the prefailure state (normal) are compared with curves derived from congestive failure patients prior to and after digitalis therapy. Digitalis shifts the complete ventricular function curve upward in the direction of improved contractility (Mason, 1973; Braunwald, 1985). Systolic emptying is now more complete (increased ejection fraction) and, therefore, residual ventricular volume is diminished. Cardiac output increases and the size of the heart is reduced.

Digitalis' augmentation of myocardial contractility and normalization of baroreceptor function favorably affect vasomotor tone, evoking peripheral vasodilation with diminished outflow impedance (afterload). Additionally, improved cardiac performance increases venous return to the heart, thereby increasing preload and further enhancing cardiac performance by the Frank–Starling mechanism. This sequence of events continues to dominate as peripheral perfusion and tissue oxygenation improve, and it compensates for the direct vasoconstrictor effect of digitalis. The increase in cardiac output persists as long as the state of myocardial compensation prevails.

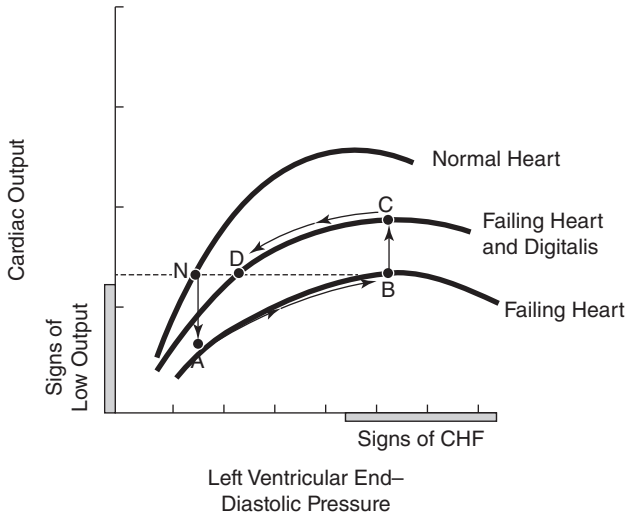

Figure 21.4 Diagrammatic representation of how changes in left ventricular filling influence cardiac output by the Frank–Starling mechanism in a normal heart and in a failing heart before and after digitalis. The points N to D represent in sequence: N–A, normal cardiac output falls to A because of initial contractile depression from congestive heart failure (CHF); A–B, shift to higher end-diastolic filling and thus higher cardiac output in accord with the Frank–Starling law; B–C, increase in contractility after digitalization; C–D, reduction in use of Frank–Starling compensation, which digitalis allows. N, B, and D: identical cardiac output on the vertical axis but achieved at different end-diastolic filling pressure on the horizontal axis. Levels of cardiac output and end-diastolic filling associated with signs of low output (e.g., fatigue) or CHF (e.g., dyspnea, edema) are represented by the dotted areas. Source: Adapted from Mason, 1973.

Cardiac Energy Metabolism

Digitalis increases oxygen consumption proportionately with increased contractile force in nonfailing cardiac muscle (Lee and Klaus, 1971); but patients with heart failure do not show an increase in the myocardial oxygen consumption because of the slowing of heart rate and the reversal of SNS-derived vasoconstriction.

These seemingly contradictory data can be reconciled by comparing the cardiodynamics of digitalis in normal and failing hearts. The heart with a normal ventricular volume responds to digitalis with increase in oxygen consumption commensurate with increase in contractility. Increased oxygen consumption is the direct result of increased contractility, in accordance with the concept that MVO_2 is influenced directly by the inotropic state, heart rate, and wall tension. Ventricular wall tension is directly proportional to ventricular pressure and radius (tension = (pressure × radius)/wall thickness; the Laplace relation). Tension will decrease if either pressure or radius is reduced. In the failing and dilated heart, reduction in cardiac size secondary to the inotropic action of digitalis therapy leads to a significant reduction in wall tension, which in turn leads to decreased MVO_2. The ultimate determinant of cardiac output is then a balance of the positive effect of increased preload on force of contraction and its negative effect on afterload, by reduction in cardiac chamber size (Laplace relation). Blood pressure normalization after cardiac glycoside therapy is secondary to cardiodynamic improvement in the congestive failure patient (Figure 21.4).

Neuroendocrine Effects

In heart failure patients, a lowering of heart rate accompanies the positive inotropic effect. This is apparently the result of a *neuroendocrine effect* and has been recognized as perhaps more important than the positive inotropic effects at therapeutic dosages. It also appears that the neuroendocrine effects are independent from the positive inotropic action and occur at lower serum digoxin levels (<1 ng/ml) (Ferguson, 1989). Neuroendocrine effects are achieved through digitalis' increase (normalization) in the baroreceptor reflex sensitivity that has been lost, presumably because of high levels of circulating aldosterone, during heart failure (Weber, 2001). Digitalis restores baroreceptor sensitivity and thereby decreases sympathetic tone in patients with heart failure (Quest and Gillis, 1971; McRitchie and Vatner, 1976; Zucker et al., 1980; Ferrari et al., 1981). The neuroendocrine effects also are attributed to direct pharmacological vagal stimulation (parasympathomimetic effect) (Thames et al., 1982). The neuroendocrine effects are responsible for a decrease in sinus rate, afterload, and speed of atrioventricular (AV) impulse conduction, thereby reducing cardiac work and MVO_2. Ahmed and Pitt have shown that the positive effects of digoxin are maintained and survival benefits enhanced at serum digoxin concentrations of 0.7–0.9 ng/ml, *but not higher* (Ahmed et al., 2006a,b; Ahmed et al., 2008), for both systolic and diastolic failure.

Excitability and Automaticity

As described earlier the increased excitability of digoxin on the heart is caused by ion fluxes and changes in K^+ conductance. Pacemaker cells are characterized by phase 4 spontaneous depolarization (normal automaticity), which moves diastolic potential to the threshold required for activation of phase 0, causing spontaneous depolarization (see Chapter 22). Therapeutic doses of cardiac glycosides increase vagal tone and decrease sympathetic tone, decreasing the slope of spontaneous diastolic depolarization of the sinoatrial pacemaker. This reduces the firing frequency of the sinoatrial node, and hence heart rate. After pretreatment with atropine, or with relatively high doses of digitalis, the nonvagal effects dominate, and an increase in automaticity is observed; this response is prevalent in the specialized conducting systems of atria and, especially, the ventricles. A typical transmembrane potential recording of a subsidiary pacemaker cell prior to and after digitalis is shown in Figure 21.5. This increased automaticity evoked by cardiac glycosides is due to an accelerated rate of spontaneous

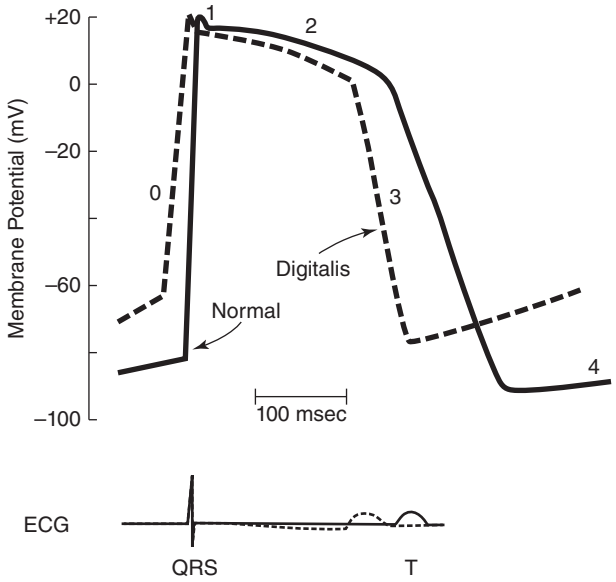

Figure 21.5 Electrophysiological effects of digitalis on transmembrane potential of a subsidiary pacemaker cell. Digitalis (i) decreases (less negative) the maximal diastolic potential, (ii) decreases the maximal rate of depolarization of phase 0, V_{max}, and (iii) enhances automaticity by increasing the slope of phase 4 spontaneous depolarization. (i) and (ii) lead to decreased conduction velocity and, in conjunction with (iii), can lead to arrhythmias of both impulse formation and impulse conduction. Source: Adapted from Mason et al., 1971.

diastolic depolarization. The normally latent pacemaker activities of cells within the ventricular conducting system are thereby magnified, leading to ectopic ventricular beats as an important early sign of digitalis toxicity. In contrast, muscle fibers in atria and ventricles can be depolarized to the point of inexcitability, without demonstrating spontaneous impulse generation. If excitability of ventricular muscle falls sufficiently, concomitant with increased frequency of ectopic impulses from specialized conduction fibers, the tendency for ventricular fibrillation is promoted.

The clinical significance of the "delayed afterdepolarizations" sometimes seen with digitalis toxicity is not completely resolved. These oscillations of the transmembrane potential initially are subthreshold and appear spontaneously during diastole after a usual action potential. These afterdepolarizations can, however, reach threshold as toxicity worsens, with the resulting extrasystoles contributing to ectopic arrhythmias associated with digitalis intoxication.

Impulse Conduction and Refractory Periods

The dominant effect of digitalis on impulse conduction is to slow conduction velocity by both vagal and nonvagal mechanisms. This response is particularly prevalent in the AV node and contributes importantly to the beneficial effects of digitalis in controlling ventricular rate during atrial fibrillation and flutter. Antiarrhythmic agents are discussed further in Chapter 22 of this book.

Digitalis Effects During Atrial Fibrillation and Flutter

During atrial fibrillation, the ventricular rate is rapid and dysrhythmic, as a result of rapid transmission of impulses through the AV node. This contributes further to cardiac dysfunction by promoting incomplete ventricular filling and ejection. Because digitalis prolongs the refractory period and delays impulse conduction through the AV node, fewer impulses will effectively reach the ventricle. Thus ventricular response rate is reduced to a slower, more physiological level (Ferguson et al., 1989).

Similar benefits are gained during atrial flutter. Digitalis can slow this rhythm or convert it to atrial fibrillation. Ventricular rate is still decreased, however, through prolonged AV refractoriness and slowed impulse conduction. Conversion of atrial flutter to fibrillation by digitalis is viewed optimistically because ventricular rate is controlled more easily during fibrillation than during flutter. It has been shown that the combination of digoxin and the Ca^{++} channel blocker, diltiazem (which also slows conduction through the AV node), is more effective at slowing the ventricular response to atrial fibrillation than is either drug alone (Gelzer et al., 2009).

Effects on the Electrocardiogram

The multiplicity of electrophysiological effects of cardiac glycosides on myocardial tissues can be expressed as equally complex changes in the electrocardiogram (ECG). Most conduction disturbances and dysrhythmias can be produced in normal individuals by administration of cardiac glycosides.

Congestive failure patients with sinus tachycardia or other supraventricular tachyarrhythmias usually demonstrate return toward more normal ECG patterns after digitalization. Rapid ventricular rates associated with atrial fibrillation or flutter are typically, but often inadequately, reduced by digitalis. Prolonged PR intervals, reflecting delayed AV conduction, are relatively common ECG features of digitalized dogs. Conversely, a lengthened PR interval is not necessarily a prerequisite for the therapeutic response.

Kidneys and Diuresis

After digitalization, reflex vasoconstriction decreases as cardiac output and hemodynamics are improved. Renal blood flow and glomerular filtration rate increase and stimuli for increased release of aldosterone are diminished. A fall in aldosterone secretion can be measured after digitalization in the dog with congestive failure (Figure 21.5). Diuresis results as salt and water retention by the kidneys is decreased. Diuresis, with lowering of capillary hydrostatic pressure, moves interstitial fluid back into the vascular space, providing relief from

edema. Diuresis is not a prominent feature of digitalis therapy if edema does not accompany the congestive failure syndrome. Similarly, digitalis does not evoke diuresis if edema is not cardiogenic. Thus the diuretic response to digitalis is secondary to circulatory improvement and is not from a direct effect on the kidney, and is virtually never adequate without concurrent loop diuretic therapy (Robinson, 1972).

Pharmacokinetics

Dog: The absorption of digoxin after oral administration of an elixir usually is uniform, up to 75–90%, with peak serum concentrations attained in 45–60 minutes (Krasula et al., 1976). With tablets, the peak serum concentration is less, and occurs somewhat later (90 minutes). After IV administration, the maximal positive inotropic responses to digoxin were obtained within 60 minutes after injection (Hamlin et al., 1971). Breznock (1973, 1975) reported that the plasma half-life value for digoxin was 38.9 and 55.9 hours in different studies. Others report approximate digoxin half-lives varying from 24 to 31 hours, with a median of 30 hours for six studies (Barr et al., 1972; Doherty, 1973; Breznock, 1973, 1975; Hahn, 1977; DeRick et al., 1978). The importance of interpatient variability is exemplified in a study that found the half-life for digoxin in dogs at steady state varied from 14.4 to 46.5 hours (DeRick et al., 1978). These variables strengthen the need for adoption of individual dosage regimens, depending on the patient's response and, especially, evaluation of the serum digoxin concentration (SDC).

Digoxin is 25% protein bound (Breznock, 1973) and urinary excretion seems to be the most important route of elimination. Digitalis glycosides and their biotransformation products can follow an enterohepatic cycle, in which compounds are excreted by the liver into bile and some parent glycoside and metabolites are subsequently reabsorbed. See Section Digitalis in Cats.

Horse: The pharmacokinetics in horses have been studied because digoxin is occasionally considered for congestive heart failure and supraventricular arrhythmias in these animals (Sweeney et al., 1993). After oral administration of 44 µg/kg, the oral absorption was approximately 23%, with a peak concentration of 2.2 ng/ml (Brumbaugh et al., 1983). The half-life was approximately 17 hours based on mean serum concentrations. The authors presented oral doses needed to attain predicted steady-state serum concentrations that ranged from 28 µg/kg to 64 µg/kg loading dose, followed by 11–25 µg/kg maintenance dose every 12 hours. The specific dose depends on the therapeutic target concentrations cited in their paper (Brumbaugh et al., 1983).

Digitalis Toxicity

Plasma concentrations: In humans and dogs, therapeutic and toxic serum drug concentrations (SDCs) are in the range of 0.8–1.6 ng/ml and greater than 2.4 ng/ml, respectively (Moe and Farah, 1975). In dogs, concentrations from 0.8 to 2.4 ng/ml have been considered to be therapeutic, whereas SDC greater than 2.5–3 ng/ml are associated with increased probability of toxicosis. Nontoxic digoxin plasma concentrations have been determined for horses (0.5–2 ng/ml; Button et al., 1980); for cats (≤2.3 ng/ml; Erichsen et al., 1980); and for dogs (≤2.5 ng/ml; DeRick et al., 1978). Toxicity signs are generally mild or absent when serum digoxin concentrations are less than 2.5 ng/ml; moderate with SDC of 2.5–6 ng/ml; and severe, even fatal, when SDC exceeds 6 ng/ml (Fillmore and Detweiler, 1973; Teske et al., 1976).

Today, with the knowledge that neurohormonal and clinical benefits occur at much lower serum concentrations than needed for inotropic benefit (Ahmed et al., 2006a, 2006b; Ahmed et al., 2008) digoxin toxicity is much less a problem. In nonemergent situations, the authors advocate an initial low dosage, relying upon *other drugs discussed in this chapter* to control immediate signs. This is followed by uptitration of digoxin dosage over 2–3 weeks, using serum concentrations taken 8 hours posttreatment with a target SDC of 0.8–1.2 ng/ml. If kidney function declines, dose adjustments may be necessary to prevent accumulation of high concentrations of digoxin.

Clinical signs: Digitalis intoxication is characterized by clinical signs varying from mild gastrointestinal upset to neurological signs and death (Detweiler, 1977; Tilley, 1979). Relative inappetance, depression, and loose stools are common side effects, which are often self-limiting. Vomiting, however, is viewed more seriously, especially if protracted diarrhea is an accompaniment and these individuals should be examined for additional evidence of toxicity. Lethal outcomes are most often due to cardiac arrhythmias. The authors emphasize that the presence of any sign that can be seen with toxicosis should be considered to indicate toxicosis and action taken. This ideally triggers an office visit, SDC measurement, and serum biochemistry to evaluate kidney values. An ECG should be examined in dogs suspected of digoxin toxicity. The effects of digoxin on the ECG were described in Section Effects on the Electrocardiogram. Occurrence of ECG abnormalities necessitates: complete withdrawal of digitalis therapy; measurement of SDC; possibly other medical intervention; and reduction in dosage when reinstituted.

Electrolyte Involvement: Low K^+ concentration potentiates digitalis arrhythmogenicity and lessens efficacy of

its treatment, whereas excess K^+ antagonizes arrhythmogenic activity. The antiarrhythmic activity of K^+ in digitalis intoxication is probably related to inhibition by the cation of glycoside binding to the Na^+,K^+-ATPase.

Treatment: Discontinuing digoxin administration is the first step to treat toxicity. Serum drug concentrations and ECG should be evaluated. Other drugs can be considered to replace digoxin in treatment (other drugs discussed in this chapter).

Digoxin immune FAB (Digibind®): This is an ovine source of antidigoxin antibodies. This treatment has been used in animals but is expensive. One vial contains 38 mg digoxin immune FAB and will neutralize 500 µg of digoxin. Animals will improve quickly after administration. After therapy with Digibind, free digoxin levels decreased whereas bound digoxin (to FAB) levels will rise.

Antiarrhythmic therapy: *Antiarrhythmic therapy for digitalis intoxication is not specific and treatment of specific arrhythmias is handled elsewhere* (see Chapter 22). Atropine may be helpful in cases with severe sinus bradycardia or AV block. In the presence of AV block, therapy with beta-blockers and calcium channel blockers should be avoided. Quinidine should be avoided as it may actually cause an increase in plasma concentrations of digoxin, probably by blocking the efflux transporter, p-glycoprotein (Discussed in Chapter 22).

Therapeutic Indications for Digitalis

Congestive heart failure: Controversy exists relative to the actual survival benefits of digitalis glycosides in the long-term therapeutic management of cardiac disease in animal and human patients (Hamlin et al., 1973; Patterson et al., 1973; Braunwald, 1985; Kittleson et al., 1985a). In man, no study has ever shown *overall* improvement in survival with digitalis therapy. However, improvement in quality of life and reduction in hospitalization have been demonstrated (Packer et al., 1993;Digitalis Investigation Group, 1997;Whitbeck et al., 2013). With low serum digoxin levels (0.5–0.9 ng/ml) there was a benefit, which was lost at higher serum levels (Ahmed et al., 2006a,b; Ahmed et al., 2008).

Cardiac glycosides are theoretically indicated in *systolic* heart failure of any etiology. New inodilator drugs (pimobendan discussed in Section Inodilators: Pimobendan) have largely taken the place of digitalis in managing heart failure in animals.

Atrial arrhythmias: Many specialists use digoxin (often with diltiazem) to control the heart rate in atrial fibrillation, when there is a rapid ventricular response (Gelzeret al., 2009).This therapeutic choice is made easier if heart failure is also present, especially with evidence of poor systolic function (e.g., dilated cardiomyopathy). However, digoxin does not produce conversion to a sinus rhythm, but reduces ventricular rate by slowing AV conduction (Meijler, 1985).

Precautions: The authors do not initiate digoxin treatment unless rate control is needed and/or if inotropic support is needed and finances precluded the use of other positive inotropic agents. Digitalis therapy is not used in the presence of heart block or ventricular tachycardia.

Digoxin should not be used to reduce heart rate when sinus tachycardia is present without evidence of heart failure. Tachycardia, associated with other conditions, such as fever, thyrotoxicosis, pain, anxiety, or even cardiac conditions, such as pericardial effusion with tamponade or with hypertrophic cardiomyopathy (HCM), is not amenable to digitalis therapy.

Clinical Practice

Generally, digoxin is initiated at the low end of the dose range listed below, then increased gradually if necessary to achieve the desired therapeutic outcome. If toxicity is observed, monitoring and assessment – as described in this chapter – should be used to adjust the dosage or make a determination about discontinuing digoxin administration. A listing of average digitalis glycoside dosages is provided in formularies for dogs and cats (Tables 21.1 and 21.2). The dosage regimens published for dogs have used both a mg/kg and mg/m^2 dosing schedule, the latter based on body surface area. There is some evidence that dosing on a body surface area basis may be safer than mg/kg dosing (Kittleson, 1983).

Parenteral schedules: IV administration increases the likelihood for toxicity, including life-threatening arrhythmias, and this route is rarely used for administration. Digoxin is sufficiently absorbed by the oral route that IV administration is not ordinarily necessary. Intravenous dosing regimens are provided in previous editions of this book.

Digitalis in Cats

There are less data on administration of digoxin to cats compared to dogs. There are no studies of survival or quality of life (Atkins et al., 1988, 1989, 1990); however, there are evaluated clinically relevant aspects of digitalis therapy in cats.

The effect of concurrent therapies on digoxin pharmacokinetics was measured and results presented in Table 21.3. The study showed that other drugs can affect digoxin through unidentified mechanisms. The authors also compared results between the 10 and 20-day evaluations, indicating that at steady state there is no effect

Table 21.1 Medical management of factors contributing to signs of systolic heart failure in dogs. Source: Adapted from Atkins CE. Atrioventricular valvular insufficiency. In Allen DG (ed): *Small Animal Medicine,* Lippincott, 1992.

Factor	Strategy	Agent and dosage
Fluid retention/ excessive preload	Salt restriction	Senior diet, renal diet or, late in course, heart (heavily salt-restricted) diet
	Diuresis	Furosemide 1–4 mg/kg SID–TID, IV, IM, SC, or PO or CRI at 0.66 mg/kg/min
		Torsemide 0.2 mg/kg PO SID–TID
		Hydrochlorothiazide or aldactazide 2–4 mg/kg QID–BID PO
		Chlorthiazide 20–40 mg/kg BID PO
		Spironolactone 2.0 mg/kg SID PO
	Venodilation	Triamterene 2–4 mg/kg/day PO
		Nitroglycerin 2% ointment 0.5 cm per 5kg TID topically for 1st 24 hours
		Captopril 0.5–2 mg/kg TID PO
		Enalapril 0.5 mg/kg SID–BID PO
		Benazepril 0.25–0.5 mg/kg SID PO
		Prazosin 1 mg TID if <15 kg; 2 mg TID if >15 kg
		Sodium nitroprusside 1–5 µg/kg/min IV
Neurohormonal aberration	Blunt RAAS	Captopril 0.5–2 mg/kg TID PO
		Enalapril 0.5–1 mg/kg SID–BID PO
		Benazepril 0.25–0.5 mg/kg SID PO
		Spironolactone 2.0 mg/kg/day PO
		Angiotensin II receptor blocker (e.g., losartan) dosage TBD
	Blunt SNS	Digoxin 0.005–0.01 mg/kg or 0.22 mg/m^2 body surface BID PO for maintenance
		Propranolol 5–40 mg TID PO
		Atenolol 0.25–1 mg/kg PO[b]
		Carvedilol 0.1–0.2 mg/kg SID PO, increasing to 0.5–1mg/kg BID over 6 weeks
Increased afterload	Arterial vasodilation	Hydralazine 1–3 mg/kg BID PO
		Captopril 0.5–2 mg/kg TID PO
		Enalapril 0.5 mg/kg SID–BID PO
		Benazepril 0.25–0.5 mg/kg SID PO
		Prazosin 1 mg TID PO if <15 kg; 2 mg TID if >15 kg PO
		Sodium nitroprusside 1–5 µg/kg/min IV
		Diltiazem 0.1–0.2 mg/kg IV slowly; 0.5–1.5 mg/kg TID PO
		Amlodipine 0.1–0.2 mg/kg SID–BID PO
		Sildenafil 0.5–1 mg/kg SID–BID PO
Diminished contractility[a]	Positive inotropic support	Digoxin 0.005–0.01 mg/kg or 0.22 mg/m^2 body surface BID PO for maintenance
		Rapid oral: 0.01 mg/kg BID to 0.02 mg/kg TID for 1 day, then to maintenance
		Rapid IV: 001–0.02 mg/kg given one half IV immediately and one-fourth IV at 30 to 60-min intervals PRN
		Dobutamine 1.5–20 µg/kg/min IV for <72 hours
		Dopamine 2–10 µg/kg/min IV for <72 hours
		Amrinone 1–3 mg/kg IV followed by 10–100 µg/kg/min
		Pimobendan 0.25 mg/kg BID PO

[a]In most instances of mitral insufficiency, positive inotropic support is unnecessary.
[b]Calcium channel (verapamil and diltiazem) and beta-blockers (propranolol, esmolol, atenolol) should be used with caution in patients in heart failure.
SID, once daily; BID, twice daily; TID, three times daily; QID, four times daily; IM, intramuscularly; IV, intravenously; SC, subcutaneously; PO, per os; PRN, as needed; RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous systems.

of duration of therapy on pharmacokinetics in normal cats (Atkins et al., 1988). Pharmacokinetics were also examined in cats with compensated dilated cardiomyopathy (DCM) compared with six clinically normal cats (Atkins et al., 1989) at a dosage of 0.01 mg/kg, q 48 h for 10 days. There were no differences between control and heart failure cats. Other studies have shown hemodynamic improvement in cats with heart failure due to DCM (Atkins et al., 1990).

One can conclude from these studies, and others, that digoxin is effective in cats with DCM, when given q 48 h, that concurrent treatment alters pharmacokinetics, predisposing to toxicity, but that the heart failure state per se and prolonged therapy does not further affect these parameters. The recommended dosage for cats in heart failure is 0.007 mg/kg q 48 h and SDC should be determined at steady state, 8 hours posttreatment, with a goal of 0.8–1.2 ng/ml.

Table 21.2 Feline formulary

Drug	Trade Name[a]	Formulation(s)[b]	Dosage	Use
Amlodipine	Norvasc	1.25 mg tablets	0.625 mg PO QD–BID	Antihypertensive
Diltiazem	Cardizem	30 mg tablets	7.5 mg PO TID	Lusitrope, Vasodilator, Negative chronotrope
Diltiazem - LA				
	Dilacor XR	180, 240 mg capsule	30 mg PO BID	*same*
	Cardizem CD	180, 240 mg capsule	45 mg PO QD	*same*
Enalapril	Enacard (Vasotec)	1, 2.5, 5 mg tablet	0.5 mg/kg PO QD	ACEI (CHF, Hypertension)
Benazepril	Lotensin (Foretkor)	5, 10 mg tablet	0.25–0.5 mg/kg PO QD–BID	*same*
Atenolol	Tenormin	25 mg tablet	6.25–12.5 mg PO QD	Negative chronotrope, Antiarrhythmic, Lusitrope, Antihypertensive
Esmolol	Brevibloc	10, 250 mg/ml injectable	50–500 (100 usually) µg/kg IV	*same*
Sotalol	Betapace	80 mg tablet	2 mg/kg PO BID	Antiarrhythmic
Procainamide	Pronestyl, Procan SR	250 mg tablet100 mg/ml injectable	2–5 mg/kg PO BID–TID	Antiarrhythmic
Furosemide	Lasix	12.5 mg tablet 50 mg/ml injectable	1–4 mg/kg PO BID–q 48 h; 0.5–2 mg/kg SQ, IM, IV PRN	Diuretic
Nitroglycerin	Nitrol, Nitro-Bid	2% ointment	2–5 cm topically TID for 24 h	Venodilator (CHF)
Warfarin	Coumadin	1, 2, 2.5, 4 mg tablet	0.1–0.2 mg QD	Anticoagulant
Heparin		Multiple	250–300 U/kg SQ TID	Anticoagulant
LMW Heparin	Fragmin	2500 U/0.2 ml	100 U/kg SQ QD	Anticoagulant
Aspirin	Plavix	81 mg	40–80 mg q 72 h	Anticoagulant
Clopidogrel		75 mg	17.5 mg daily	Anticoagulant
Digoxin	Lanoxin	0.05 mg/ml elixir 0.125 mg tablet	0.007 mg/kg PO q 48 h (check serum [digoxin])	Positive inotrope, Negative chronotrope (CHF, SVT)
Taurine		250 mg tablet	250 mg PO QD	Taurine deficiency
Cyproheptadine	Periactin	4 mg tablet	2 mg BID	Prevent SAE vasoconstriction (?)

[a]Selected name brands, some available as generic.
[b]Most appropriate formulations for cats; other sizes available for many drugs.
BID, twice daily; TID, three times daily; IM, intramuscularly; IV, intravenously; SQ, subcutaneously; PO, per os; PRN, as needed.

Table 21.3 Digoxin pharmacokinetic properties in cats after treatment with digoxin tablets (0.01 mg/kg of body weight, q 48 h). Source: Adapted from Atkins et al., 1988.

	Group 1 (n = 6)		Group 2 (n = 3)	
Variable	**DXN alone**	**DXN, FRS, ASA**	**DXN 10 days**	**DXN 20 days**
Peak [DXN] (ng/ml)	2.1 ± 0.35 (0.95 to 3.69)	3.3* ± 0.60 (1.31 to 5.64)	1.8 ± 0.38 (1.11 to 2.69)	1.4 ± 0.08 (1.31 to 1.63)
8-Hour [DXN] (ng/ml)	1.4 ± 0.35 (0.56 to 3.03)	2.5 ± 0.64 (0.63 to 5.01)	1.1 ± 0.33 (0.58 to 1.91)	0.8 ± 0.29 (0.58 to 1.71)
Mean [DXN] (ng/ml)	1.1 ± 0.22 (0.44 to 1.85)	2.2* ± 0.57 (0.55 to 4.15)	0.93 ± 0.2 (0.57 to 1.41)	0.69 ± 0.1 (0.54 to 0.95)
t (hours)	40.1 ± 11.7 (13.2 to 99)	81.8* ± 21.8 (30.1 to 173)	61.8 ± 24.0 (23 to 119.6)	47.7 ± 13.8 (24.7 to 80.7)
Oral clearance (L/h.kg)	0.15 ± 0.035 (0.05 to 0.27)	0.07* ± 0.02 (0.01 to 0.17)	0.10 ± 0.02 (0.08 to 0.14)	0.16 ± 0.04 (0.07 to 0.24)
Hours [DXN] in toxic range	3 ± 1.7 (0 to 6)	24.7* ± 9.8 (0 to 48)	2 ± 1.6 (0 to 6)	0 ± 0 (0)

*Significantly different from that value within the same group ($P < 0.05$).
ASA, aspirin; DXN, digoxin; FRS, furosemide.

Preparations

Digoxin, USP – cardiotonic glycoside from *D. lanata*.
Digoxin Injection, USP – digoxin in 10% alcohol; injections, 0.5 mg/2 ml.
Digoxin Tablets, USP – tablets, 0.25 and 0.5 mg.
Digoxin Solution – digoxin, 0.05 mg/ml in oral solution.

Sympathomimetic Agents: Dobutamine and Dopamine

Sympathomimetic drugs, such as dobutamine and dopamine, can be used to support cardiac function and blood pressure acutely. Veterinary cardiologists have most often employed dobutamine for the emergency management of heart failure in dogs; there is less support for administration of dopamine.

Dobutamine

This agent, a synthetic sympathomimetic, produces improvement in cardiac performance by complexing primarily with myocardial β_1 receptors, which, through second messengers, increase intracellular calcium and, thereby, myocardial contractility. There is both agonist and antagonist effects on α receptors, the clinical effects of which are uncertain. Dobutamine is unique as a SNS-agonist as it has relatively little effect on heart rate, is minimally proarrhythmic, and has a very short half-life (1–2 minutes). The short half-life allows for quick adjustment of dose rates and if the infusion is discontinued the effects quickly dissipate. The short half-life also requires that it be administered as a constant rate infusion (CRI). Additionally, it results in down-regulation of β_1 receptors 48–72 hours after its institution, rendering the drug ineffective after this time. Furthermore, there is concern that the positive dromotropic effect of dobutamine in dogs with atrial fibrillation, not receiving digitalis, may increase AV nodal conduction to a degree that a life-threatening ventricular response rate may result in ventricular fibrillation. There are no clinical trials involving dobutamine in natural canine heart disease, but anecdotal evidence that it may be helpful for the acute management of heart failure in hospitalized patients.

Dobutamine is beneficial for emergency management of DCM, without atrial fibrillation or other supraventricular tachycardia. It provides inotropic support without increasing heart rate and can be life-saving when there is profound myocardial systolic dysfunction. There is no evidence of benefit for treatment of long-standing mitral valve regurgitation.

Dopamine

Dopamine, unlike dobutamine, is not a synthetic catecholamine, occurring naturally and formed endogenously from L-Dopa. It has a significant first pass effect and very short half-life, dictating that it can only be administered IV with a CRI. It has two known receptor subtypes with which it interacts (DA_1 and DA_2). DA_1 subserves vasodilation in the renal, cerebral, mesenteric, and coronary vasculature. DA_2 stimulation inhibits norepinephrine release from the postsynaptic nerves and autonomic ganglia. However, dopamine also stimulates β_1- and $\alpha_{1,2}$-adrenoreceptors, with the expected positive inotropic, chronotropic, dromotropic, and vasoconstrictive effects.

With this wide spectrum of effects, it is not surprising that clinical effects vary with dosage. At a low dosage (0.5–1 μg/kg/min), dopamine stimulates DA_1 only, thereby lowering blood pressure, without other hemodynamic effects. At intermediate dosages, cardiac benefits are recognized, with variable effects on heart rate, a lack of reduction in pulmonary capillary wedge pressure, but positive effects on cardiac output and renal blood flow. At high doses, vasoconstriction may be observed with increased cardiac afterload. Dopamine does not dilate capacitance vascular beds, so is sometimes accompanied by venodilators (nitroglycerin or nitroprusside) or by dobutamine. Concerns at this dosage range include arrhythmias and tachycardia. High dosages (2–10 μg/kg/min in normal humans to >50 μg/kg/min in shock patients) produce, in addition to tachycardia and arrhythmia, elevation of blood pressure and systemic vascular resistance through α_1 and α_2-adrenoreceptor stimulation with resultant vasoconstriction (Horowitz et al., 1962; Sprung et al., 1984). This is desirable only in shock management and should be preceded by fluid therapy to correct deficits.

In veterinary medicine, dopamine has found its greatest utility in the management of hypotension during anesthesia and treating noncardiogenic shock. Sisson and Kittleson (1999) recommend a starting dosage of 2 μg/kg/min, with upward titration or retreat as the clinical situation dictates. The ultimate dosage typically ranges from 1 to 8 μg/kg/min, administered by CRI (in 5% D/W, using an infusion pump to avoid excessive volumes in heart failure patients). Although it has been used, at low doses, to stimulate DA receptors, dilate renal vessels, and treat acute kidney disease, it has not been shown to produce these benefits in animal studies.

Preparations: Supplied in 5-ml vials containing 40, 80, 160 mg/ml.

Inodilators: Pimobendan

Agents that have both vasodilatory and positive inotropic properties are classified as *inodilators* (Opie, 2001). Historically, short-term management of acute or decompensated heart failure characterized by systolic dysfunction benefited from a combination of dobutamine (positive inotrope) and nitroprusside (vasodilator). Inodilators

combine these properties and agents such as pimobendan, which is available in an oral formulation, make chronic therapy a possibility. Levosimendan, another drug from this class having been investigated in animals, is not available for clinical use at this time.

Clinical Application

Pimobendan is a novel agent with properties useful in the clinical management of canine heart failure secondary to either DCM or myxomatous mitral valvular disease (MMVD). The efficacy of pimobendan in the treatment of heart failure, arising from DCM and MMVD, has been evaluated more thoroughly in dogs than have other cardioactive medications to date.

In dogs (English Cocker spaniels and Doberman Pinschers) with DCM and heart failure pimobendan was associated with a significant improvement in heart disease class (modified New York Heart Association [NYHA] functional class; overall, median NYHA 2 to NYHA 3), regardless of breed (Figure 21.6, Table 21.4). Other agents (furosemide, enalapril, and digoxin) also were allowed. However, only in the Doberman pinschers was there a significant survival benefit (Fuentes, 2004).

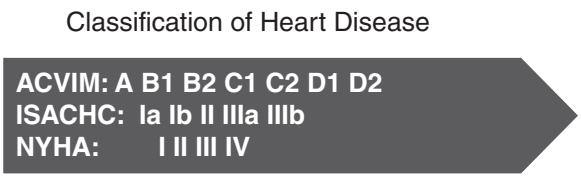

Figure 21.6 The American College of Veterinary Internal Medicine Cardiac Disease Classification Scheme (ACVIM), the International Small Animal Cardiac Health Council (ISACHC) and New York Heart Association adaptation are categorically compared. See Table 21.4 for description. Source: Atkins et al. 2009.

Several high-quality studies have been performed on dogs with heart failure caused by cardiomyopathy or mitral valve disease (Lombard et al., 2006; O'Grady et al., 2008; Häggström et al., 2008; Summerfield et al., 2012). The results of these studies showed that pimobendan was effective, increased survival, and had a favorable safety profile. Some studies were multiinstitution, high-quality studies, for example, the QUEST trial (Häggström et al., 2008), the PROTECT study (Summerfield et al.,

Table 21.4 Functional classification schemes of cardiac disease in dogs

A. Modified New York Heart Association (NYHA) system (American)	
Class I	Includes patients with asymptomatic heart disease (typically murmur only)
Class II	Includes patients with signs of cardiac dysfunction only with strenuous exercise
Class III	Includes patients with heart disease that causes clinical signs with routine daily activities or mild exercise
Class IV	Includes patients with heart disease that causes severe clinical signs even at rest
B. International Small Cardiac Health Council (ISACHC) system	
Class I	The asymptomatic patient: Class IA: Signs of heart disease are present, but no signs of compensation (volume or pressure load ventricular hypertrophy) are evident Class IB: Signs of heart disease are present and signs of compensation (volume or pressure overload ventricular hypertrophy) are detected radiographically or echocardiographically
Class II	Mild-to- moderate heart failure; clinical signs of heart failure are evident at rest or with mild exercise, and adversely affect the quality of life
Class III	Advanced heart failure; clinical signs of advanced heart failure are immediately obvious: Class IIIA Home care is possible Class IIIB Hospitalization is recommended (cardiogenic shock, life-threatening pulmonary edema, or a large pleural effusion
C. American College of Veterinary Internal Medicine (ACVIM) scheme (adapted from American Heart Association and American College of Cardiology)	
Class A	Includes asymptomatic patients with no sign of cardiac disease but believed to be at risk because of genetic, environmental, or infectious causes
Class B1	Includes asymptomatic patients with heart disease, typically identified by the finding of a heart murmur, but without evidence of cardiac enlargement
Class B2	Includes asymptomatic patients with heart disease, typically identified by the finding of a heart murmur, which have evidence of hemodynamically significant valve regurgitation, evident by the finding of cardiac enlargement
Class C1	Includes patients with past or current clinical signs of heart failure, associated with structural heart disease, and requiring hospitalization
Class C2	Includes patients with past or current clinical signs of heart failure, associated with structural heart disease, which can be released from the hospital or which do not require hospitalization
Class D1	Includes patients in heart failure due to end-stage cardiac disease, which are refractory to standard therapy (requiring advanced or specialized treatment), requiring hospitalization
Class D2	Includes patients in heart failure due to end-stage cardiac disease, which are refractory to standard therapy (requiring advanced or specialized treatment) but that can be managed as outpatients

2012), and the EPIC trial. The EPIC study is a prospective trial, evaluating 360 client-owned dogs. EPIC, standing for evaluation of pimobendan in dogs with cardiomegaly caused by preclinical mitral valve disease, is a double-blind, randomized, placebo-controlled clinical trial, evaluating the effectiveness of pimobendan in the prevention of the onset of signs of congestive heart failure in dogs with cardiac enlargement secondary to preclinical myxomatous mitral valve disease. Preliminary results indicate that pimobendan is clearly beneficial and did not raise any concern over the administration of pimobendan.

In randomized prospective clinical trials, pimobendan has been proven to be safe and effective in heart failure secondary to both DCM (Doberman pinschers) and MMVD, as well as in asymptomatic DCM (Doberman pinschers) and MMVD. Pimobendan has been approved for use in dogs with congestive heart failure, beginning in 2000 in many countries around the world.

Pimobendan in cats: There are only a few studies to define the clinical use in cat. It produced improved survival in cats with nontaurine responsive dilated cardiomyopathy without adverse effects (Hambrook and Bennett, 2012). It improved survival and was well-tolerated in cats with congestive heart failure caused by cardiomyopathy (MacGregor et al., 2011; Reina-Doreste et al., 2014; Gordon et al., 2012). The pharmacokinetics have been performed in cats (Hanzlicek et al., 2012). The pharmacokinetic studies showed a rapid oral absorption and elimination half-life of 1.3 hours (mean). In other animals, pimobendan is metabolized (demethylated) to desmethylpimobendan, which is active and responsible for some of the cardiovascular effects. An observation from the feline pharmacokinetic study is that some cats may not be capable of metabolizing the parent drug to an active metabolite. The implications of the differences in metabolism among cats is undetermined until additional study results are available. The dosage is the same as in the dog, 0.25–0.3 mg/kg, q 12 h, oral. Administration of large oral tablets designed for dogs can be a challenge in cats.

Mechanism of Action

Inotropy: Pimobendan is a benzimidazole pyridazinone derivative that has effects as a positive inotrope and balanced arteriovenous dilator. In failing hearts it exerts its positive inotropic effects primarily through sensitization of the cardiac contractile apparatus to intracellular calcium. As a phosphodiesterase (PDE) III inhibitor, it can potentially increase intracellular calcium concentration and increase myocardial oxygen consumption. However, the cardiac PDE effects of pimobendan are reportedly minimal at pharmacological doses in dogs with heart disease, which is a major advantage relative to other inotropic PDE inhibitors such as milrinone. Pimobendan's calcium sensitization of the contractile apparatus is achieved by enhancement of the interaction between calcium and troponin C complex resulting in a positive inotropic effect that enhances systolic function, but does not increase myocardial oxygen consumption. The major advantage of pimobendan is its relative lack of the arrhythmogenic activity that is associated with positive inotropes whose sole mechanism of action is to increase myocardial intracellular calcium or cyclic AMP concentrations.

Vasodilation: Phosphodiesterase III and V are found in vascular smooth muscle. Inhibitors of PDE III, such as pimobendan, result in balanced vasodilation (combination of venous and arterial dilation) leading to a reduction of both cardiac preload and afterload, a cornerstone of therapy in heart failure. In addition, pimobendan may have some PDE V inhibitory effects. PDE V concentrations are relatively high in the vascular smooth muscle of pulmonary arteries; therefore, PDE V inhibition may ameliorate elevations in pulmonary artery pressure (pulmonary hypertension) that tend to parallel long-standing elevations in left atrial pressure, a clinically important complication of CVD. (Sildenafil is a specific PDE-V inhibitor, discussed in Section Phosphodiesterase V Inhibitors: Sildenafil.)

Cytokine modulation: The significance of alterations in proinflammatory cytokines, such as tumor necrosis factor-α and interleukins 1-b and 6, on the progression of heart failure has been documented in several forms of heart disease. Maladaptive alterations in these cytokine concentrations are associated with increased morbidity and mortality; pimobendan has demonstrated beneficial modulation of several such cytokines in models of heart failure (Iwasaki et al., 1999). Anecdotally, many clinicians feel that this results in attitude and appetite improvement beyond what is seen with control of heart failure alone.

Antiplatelet effects: In the dog, pimobendan has in vitro antithrombotic effects, but only at drug concentrations much higher than what can be clinically attained. Therefore, pimobendan's antiplatelet effects in the dog neither contributes to its therapeutic benefit nor confers risk of bleeding (Shipley et al., 2013).

Positive lusitropic effects: Via PDE III inhibition in cardiomyocytes, pimobendan increased intracellular cAMP, facilitating phosphorylation of receptors on the sarcoplasmic reticulum. Diastolic reuptake of calcium is thus enhanced, and the speed of relaxation increased, indicating a positive lusitropic property. Two small studies in the human and dog support this positive lusitropic

property of pimobendan (Asanoi et al., 1994; Ishiki et al., 2000).

Pharmacokinetics

Pimobendan's absorption is rapid, with peak plasma levels achieved within an hour of oral administration. Thus, although pimobendan is an oral preparation, it can provide rapid, short-term support to dogs with emergent, acute-onset or decompensated heart failure. The elimination half-life in dogs is approximately 1 hour or less (Bell et al., 2015; Yata et al., 2016). Oral bioavailability is 60–65%, and as high as 70% (Bell et al., 2015), but because it is reduced in the presence of food, pimobendan should be administered at least 1 hour after feeding until steady state is reached. Pimobendan is water insoluble, highly protein bound (90%–95%), excreted into bile, and eliminated in the feces. Pimobendan is metabolized (demethylated) in the liver and the major metabolite desmethylpimobendan (UDCG-212) is a more potent inhibitor of PDE III (vasodilation) than pimobendan and has a half-life slightly longer than the parent drug (Yata et al., 2016) (as discussed in Section Pimobendan in Cats, cats may not produce this metabolite).

Adverse Effects

Pimobendan is well tolerated in dogs, including in animals with heart disease (Fuentes, 2004). There were initial concerns that it could produce worsening of (fatal) arrhythmias, or increase risk of atrial fibrillation in dogs with cardiomyopathy. In subsequent studies (Lake-Bakaar et al., 2015) these concerns were dismissed and no prospective, randomized, blinded trial has reported an increase in the frequency of arrhythmias in veterinary patients. Veterinary studies report improved quality and quantity of life, arguing against clinically important side effects, when pimobendan is used for treatment of canine heart failure. Furthermore, the necessity for even higher pimobendan dosages (≥0.3 mg/kg TID) in dogs that have entered ACVIM class D heart disease, have provided significant survival benefit and, in the authors' opinion, better quality of life (Ames et al., 2013). Even at very high (10 times recommended dosage) accidental over-dosing, adverse signs have been relatively modest in severity (Reinker et al., 2012). The database (November 2004 to April 2010) of an animal poison control center was searched for cases involving pimobendan toxicosis. Seven dogs that ingested between 2.6 mg/kg and 21.3 mg/kg were evaluated. Clinical signs consisted of cardiovascular abnormalities, including severe tachycardia (4/7), hypotension (2/7), and hypertension (2/7). In two dogs, no clinical signs were seen. All dogs were released from the hospital within 24 hours, although one died 3 days later.

As for all positive inotropic agents, pimobendan is *relatively* contraindicated in patients with outflow tract obstruction (e.g., HCM, subaortic stenosis, pulmonic stenosis). The inotropic effect may negatively affect dogs with early valvular lesions. In a study in asymptomatic dogs with mitral valve disease (Chetboul et al., 2007), pimobendan worsened mitral valve lesions and indices of cardiac function in dogs treated with pimobendan, compared to the group treated with the angiotensin-converting enzyme (ACE) inhibitor benazepril. The authors of the study proposed that the cardiotoxic effects were caused by an exaggerated pharmacodynamic effect, rather than from intrinsic toxicity. The importance of this finding has been diminished with the advent of the premature closing of the EPIC study (asymptomatic MMVD), discussed above.

Formulations and Dosing

Pimobendan is supplied as hard gelatin capsules (most countries) containing 1.25, 2.5, or 5 mg pimobendan. In the USA it is approved as a chewable formulation in four sizes: Vetmedin® 1.25, 2.5, 5, and 10 mg. It is not stable in suspension and should not be reformulated in this manner. The labeled dose recommendation is 0.25–0.3 mg/kg q 12 h. Initial efficacy may be enhanced by administration on an empty stomach but once steady-state is reached (a few days) it can be administered with food. Oral pimobendan solution (3.5 mg/ml and 1 mg/ml) is available in some countries (Bell et al., 2015; Yata et al., 2016). Levosimendan has been investigated as agent for treating heart failure in dogs. At this time, it is not available for clinical use.

Inotropic Agents: Inamrinone and Milrinone

Inamrinone (formerly amrinone) and milrinone are bipyridine derivatives commonly referred to as nonglycoside, noncatecholamine inotropic drugs. These compounds were discovered during an investigative search for cardiac stimulant agents that could be used to replace digitalis in the therapy of heart failure (Alousi et al., 1979). Numerous studies confirmed that inamrinone and milrinone evoke both a positive inotropic action in the heart and a peripheral vasodilator effect. The mechanism of action of the bipyridines is dissimilar to that of digitalis and does not involve adrenergic or other cell surface receptors. Rather, the cardiac inotropic and peripheral vasodilator actions of inamrinone and milrinone involve inhibition of the type III cyclic nucleotide phosphodiesterase enzyme. This enzyme is responsible for the selective metabolism of cAMP; hence, inhibition of type III phosphodiesterase by inamrinone or milrinone results in the accumulation of intracellular cAMP in cardiac and vascular tissues. Cyclic AMP subserves a positive inotropic response in myocardium and a vasodilator response in blood vessels. Because of concurrent inotropic and vasodilator actions, considerable attention

has been focused first on inamrinone and later on milrinone as alternatives to digitalis in managing congestive heart failure patients (Mancini et al., 1985; Colucci et al., 1986a, 1986b).

Inamrinone (amrinone)

Although inamrinone increased cardiac contractile force and left ventricular pressure with relatively small changes in heart rate and systemic blood pressure in experimental dogs it has not been used clinically except as a last resort when other treatments have failed (Alousi et al., 1979). Adverse effects in people have prevented its routine use (Massie et al., 1985).

Milrinone

Milrinone is a structural congener of inamrinone, and the former is 20–30 times more potent than the latter. Initial studies suggested that milrinone might be relatively free of adverse side effects and could potentially be helpful in the management of heart failure in humans (Colucci et al., 1986a,b). However, studies in human patients with moderately severe heart failure indicated that milrinone was less effective than digoxin, and the combination of milrinone and digoxin was no more effective than digoxin alone. Moreover, milrinone administration was associated with an increased incidence of both ventricular and supraventricular tachyarrhythmias (DiBianco et al., 1989). In the OPTIME-CHF trial, milrinone administration had a bidirectional effect, worsening the outcome in patients with ischemic heart disease and having a neutral to beneficial effect in those with nonischemic heart disease (Felker et al., 2003).

Tachyarrhythmias were predictable as side effects of milrinone and other type III phosphodiesterase inhibitors inasmuch as their mechanism of action depends upon accumulation of cAMP. Hence, the initial enthusiasm for cardiac uses of milrinone and other type III phosphodiesterase inhibitors has decreased (Massie et al., 1985; DiBianco et al., 1989).

There is evidence that milrinone may be safe and effective in dogs with spontaneous heart failure (Kittleson et al., 1985b). Dogs may respond favorably to treatment with milrinone as the sole therapeutic agent. Positive effects were sustained for the 4 weeks of the study; however, heart failure worsened when milrinone was withdrawn but improved when the drug was reinstituted. The only apparent adverse reactions were asymptomatic ventricular dysrhythmias in two dogs. These investigators concluded that milrinone may be an effective drug for treating myocardial failure in the dog when administered orally twice daily in 0.5–1 mg/kg doses.

Clinical Use

Despite experience with oral milrinone in dogs, there is currently no approved oral formulation available. Milrinone lactate (Primacor®) is available as an injectable solution in a strength of 200 µg/ml. Milrinone is little used by veterinary cardiologists (Bonagura, 2010). Inamrinone is supplied only as an intravenous solution.

Angiotensin-Converting Enzyme Inhibitors: Enalapril Maleate and Benazepril, and Mineralocorticoid Receptor Blockers, Spironolactone

Recognition of the contribution of the renin–angiotensin–aldosterone system (RAAS) to the pathophysiology of congestive heart failure led to development of the angiotensin-converting enzyme inhibitors (ACEIs), such as captopril, enalapril, benazepril, ramipril, lisinopril, imidapril, temocapril, quinapril, alacecapril, etc. (Jackson, 2006).

Mechanisms of Action

Reduced renal perfusion during heart failure and other pathological and physiological situations evokes renin release from the juxtaglomerular apparatus (Figure 21.7).

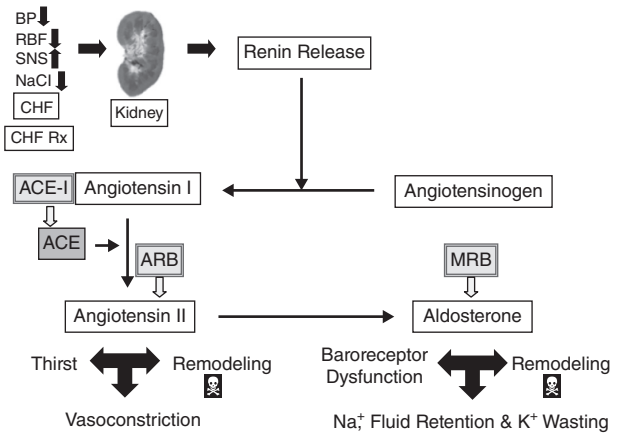

Figure 21.7 Reduction in blood pressure (BP), renal blood flow (RBF), and serum sodium concentration (NaCl), as well as activation of the sympathetic nervous system (SNS), the state of heart failure (CHF) and its treatment cause renin to be released by the juxtaglomerular apparatus, starting the cascade with angiotensinogen being converted to angiotensin I. This is followed by its conversion to angiotensin II by angiotensin converting-enzyme (ACE), and finally by stimulating the adrenal gland to secrete aldosterone. When chronic and excessive, the terminal hormones produced are toxic, particularly to heart failure patients, causing vasoconstriction, pathological remodeling of the myocardium and vessels, sodium and fluid retention, potassium wasting, and baroreceptor dysfunction. Blunting this cascade has become a major part of the treatment of cardiac disease in man and animals, using ACE-inhibitors (ACE-I), angiotensin II receptor blockers (ARB), and mineralocorticoid receptor blockers (MRB, e.g., spironolactone).

As discussed in Chapter 24, renin synthesizes the formation of angiotensin I from angiotensinogen. Angiotensin I is relatively inactive; however, it is cleaved by ACE into the potent vasoconstrictor and stimulator of aldosterone release, angiotensin II. Thus, by inhibiting ACE, ACEIs decrease the formation of angiotensin II and, through this mechanism, evoke peripheral vasodilation (relatively weak "mixed" or "balanced," arteriolar and venous, dilation). Angiotensin II-mediated release of aldosterone also is decreased by ACEI, thus facilitating sodium excretion and diuresis. Blockade of angiotensin II and aldosterone production blunts the negative effect of pathological remodeling of the heart, vasculature, and kidney in states of pathological RAAS activation (heart failure, renal failure, hypertension, and in response to off-loading therapies, such as vasodilators and diuretics)(Weber and Brilla, 1991; Schiffrin, 2006; Brown and Vaughan, 1998).

ACE is a relatively nonselective enzyme, not only converting angiotensin I to angiotensin II, but cleaving and thereby inactivating the bradykinin molecule as well. While the other effects of ACE are harmful in disease states, the increase in bradykinin is helpful as it blocks RAAS-induced vasoconstriction (via prostaglandins) and pathological remodeling.

The ACEIs commonly used in veterinary medicine, with the exception of captopril and lisinopril, are administered orally as prodrugs and converted to their active form in the liver (enalaprilat and benazeprilat). At this time, there is no clear superior ACEI, although captopril has clearly been surpassed in terms of convenience and because of its propensity to produce gastrointestinal upset.

Adverse Effects

ACEIs have the potential to produce symptomatic hypotension. This is due to the mixed vasodilatory effect of this group of drugs and is typically observed when ACEIs are used in conjunction with other off-loading therapies, such as vasodilators, diuretics, and sodium restriction. Hypotension is reversed by altering drug therapies but may be problematic in producing azotemia, inappetance, weakness, lassitude, and precipitating digitalis intoxication by reducing renal elimination. Other than at dosages 50–100 times those clinically recommended, the ACEIs are not directly nephrotoxic. The major impact of ACEI on the kidney, with clinically relevant dosages, is through production of hypotension, thereby reducing the kidney perfusion pressure and glomerular filtration rate, resulting in worsening of azotemia (MacDonald et al., 1987).

Less-common side effects include coughing and angioedema. While well-documented in people, there are no reports of these phenomena in animals. The cause for coughing is unclear, but is thought to be related to increased levels of bradykinin or resultant prostaglandins.

Veterinary clinicians have had experience with enalapril, captopril, benazepril, lisinopril, imidapril, alacepril, and ramapril. Of these, only enalapril has been extensively studied and is licensed for use in management of heart failure in the USA and benazepril has been marketed in Europe, Canada, South America, and Asia. We have learned through clinical experience with ACEIs (mainly captopril, enalapril, and benazepril in the USA) that their impact on kidney function is minimal, even in the face of severe heart failure. When azotemia is observed, ACEIs are usually administered in conjunction with diuretics and sodium restriction, often with resultant hypotension. Typically, diuretic cessation or reduction in the dosage results in the reversal of azotemia (Wynckel et al., 1998). In studies of enalapril in NYHA phase III and IV heart disease (moderate to severe heart failure), due to mitral valve regurgitation and DCM, there was actually a lower incidence of azotemia in the enalapril-treated group than the placebo-treated group (IMPROVE – Sisson et al., 1995; Cove Study Group, 1995; LIVE – Ettinger et al., 1998; Merck-Agvet, 1994). Furthermore, in a study of enalapril's role in the delay or prevention of heart failure due to naturally occurring MMVD, enalapril, at the standard dosage of 0.5 mg/kg daily, had no effect on serum creatinine concentrations as compared to placebo (Atkins et al., 2002). In fact, it is now well accepted that ACEI, administered chronically to both human and veterinary patients with naturally occurring and experimental renal failure, are beneficial (Abraham et al., 1988; Brown et al., 1999; Praga et al., 1992; Maschio et al., 1996; Grauer et al., 2000; Watanabe et al., 1999; Miller et al., 1999). Mechanisms for this improvement are postulated to be the antihypertensive effect, reduction of angiotensin II-induced mesangial cell proliferation, and renal vasodilatory effects of ACEI, the latter related to a fall in renal filtration pressure and proteinuria (Abraham et al., 1988; Praga et al., 1992; Maschio et al., 1996). Enalapril has recently been shown to reduce urine protein loss and reduce blood pressure in naturally occurring canine glomerulonephritis (Grauer et al., 2000). Likewise, benazepril reduced azotemia and proteinuria in a short-term study of experimental and naturally occurring renal insufficiency in cats(Watanabe et al., 1999) and lowered blood urea nitrogen (BUN) and creatinine concentrations and blood pressure in cats with polycystic kidney disease (Miller et al., 1999).

Efficacy

ACEIs represent a cornerstone in the chronic management of heart failure. By inhibiting the conversion of angiotensin I to angiotensin II (Jackson, 2006), they

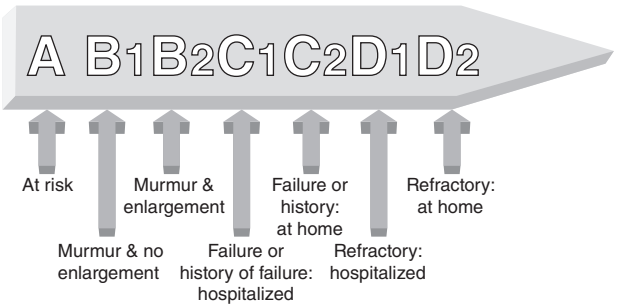

Figure 21.8 The American College of Veterinary Internal Medicine Cardiac Disease Classification scheme. Source: Atkins et al. 2009.

reduce the undesirable effects of angiotensin II (vasoconstriction; pathological remodeling with cardiomyocyte death and replacement; de novo fibrosis; and increased thirst) and aldosterone (pathological remodeling; sodium retention and potassium wasting; and baroreceptor dysfunction) recognized in congestive heart failure, hypertension, and glomerular disease.

They are indicated in virtually all cases of systolic heart failure. In subclinical MMVD (NYHA 1, ISAHC 1a and 1b, ACVIM B1 and B2) (Figures 21.8, 21.9, Table 21.4) RAAS suppression is known to be useful in asymptomatic dogs in ISAHC 1b, ACVIM B2, after there is cardiac remodeling (enlargement). ACEIs have proven useful in the management of systemic hypertension, clinical and subclinical cardiac disease, and proteinuric

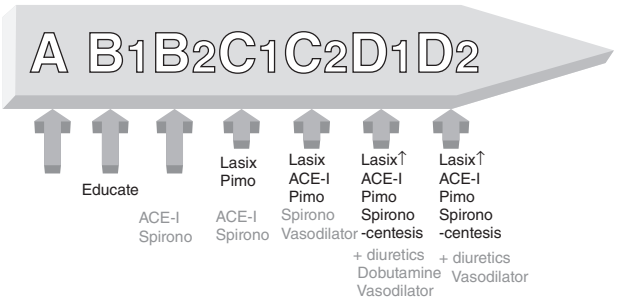

Figure 21.9 The American College of Veterinary Internal Medicine Classification Scheme with recommendations of the Consensus Committee on management of myxomatous mitral valve disease in dogs. Unanimous recommendations of the Committee are in bold black type, while the grey type represents the majority recommendations of that group, as well as the recommendations of the authors. Since the ACVIM Consensus Panel made its recommendations, two studies have been published which will likely impact this scheme. A European study demonstrated that the combination of benazepril and spironolactone were efficacious in treating dogs with heart failure (Bernay et al., 2010). The EPIC Trial demonstrated that pimobendan was effective in dogs in Stage B2 heart disease, prolonging the time to heart failure or cardiac death (Boswood et al., 2016). ACE-I, angiotensin converting-enzyme inhibitor; Spirono, spironolactone; Pimo, pimobendan; -centesis, thoracocentesis and/or abdominocentesis; Lasix, furosemide. Source: Atkins et al. 2009.

renal disease (Grauer et al., 2000; Atkins and Haggstrom, 2012; O'Grady et al., 2009).

In NYHA phase III and IV heart disease in dogs (moderate to severe heart failure; Table 21.4), due to MMVD or DCM, enalapril improved survival by >100% as well as reducing pulmonary edema and, improving quality of life scores (IMPROVE – Sisson et al., 1995; Cove Study Group, 1995; LIVE – Ettinger et al., 1998). Exercise capacity is also improved in dogs with experimental mitral insufficiency (Hamlin et al., 1996).Benazepril has likewise been shown to improve survival (BENCH Study Group, 1999). The multicenter trials cited examined the ability of ACE inhibition to augment digitalis and diuretic therapy, rather than therapeutic benefits from enalapril alone. Nevertheless, these studies yielded convincing evidence that inhibition of ACE with enalapril improves quality of life and delays mortality in dogs with heart failure. It is clear that enalapril (and, likely the ACEI class) is beneficial in the management of heart failure when added to conventional therapy. There has been virtually no study of ACEI and inodilators being used together.

Preclinical heart disease: Enalapril has been studied in two placebo-controlled, randomized, double-blind clinical trials assessing its ability to slow the progression to heart failure in dogs with MMVD. The two studies were similarly designed, utilizing asymptomatic MMVD patients, the onset of pulmonary edema as the primary endpoint, and the ACEI, enalapril, versus placebo in a double-blinded, prospective trial (SVEP – Kvart et al., 2002; VETPROOF – Atkins et al., 2007). The SVEP trial and the VETPROOF had differing results because of differing study design. Both studies are useful to our understanding of the role of ACEI prior to the onset of heart failure in MMVD. Results of the SVEP trial argue strongly that, at the dosage evaluated, there is little to no benefit with ACE inhibition in a population of dogs with (107) and without (122) radiographic evidence of remodeling. The 5-year VETPROOF demonstrates a modest benefit in delaying the onset of heart failure with an additional 3-year follow-up substudy demonstrating a treatment benefit in delaying all-cause mortality; the latter study should ideally be repeated, with all-cause mortality as the primary endpoint. In the all-cause mortality substudy of 96 study participants followed to their deaths, it was demonstrated that a longer-term benefit (9 months) with ACEI therapy ($P < 0.02$) (Atkins and Keene, 2009).

Feline studies: In a retrospective study of cats presenting with HCM, enalapril therapy improved echocardiographic parameters (Rush et al., 1998). However, a larger prospective, blinded study (MacDonald et al., 2006), in which ramipril, administered for 1 year to Maine Coon

and Maine Coon cross-bred cats with HCM, did not lead to a significant difference in LV mass, diastolic function, or BNP or aldosterone concentrations when were compared to controls.

Drug Interactions

A complete list of pharmacokinetic drug interactions is provided in the manuscript by Shionoiri (1993). Interactions that affect renal function are covered by Loboz and Shenfield (2005). ACEIs are used with other cardiovascular drugs (including diuretics) safely. However, ACEIs will potentiate the effect of diuretics and these drugs should be used together cautiously. Often times, the dosage of diuretic can (and should) be reduced with concomitant ACEI therapy.

When ACEIs are administered concurrently with nonsteroidal antiinflammatory drugs (NSAIDs), the latter may diminish ACEIs beneficial effect by blocking formation of prostaglandin, as some of the antihypertensive effect of ACEI is caused by generation of prostaglandins (Guazzi et al., 1998; Davie et al., 2000). NSAIDs also have been suggested to increase the risk of kidney injury (Loboz and Shenfield, 2005). Only one study examining this combination has been published for dogs, in which it was concluded in that tepoxalin did not alter renal function in healthy Beagle dogs receiving an ACEI (Fuselier et al., 2005). This has not been determined for other NSAIDs.

Use of ACE Inhibitors in Chronic Kidney Disease

As reviewed by Lefebvre and Toutain (2004), ACEIs can be beneficial in chronic kidney disease (CKD) because they reduce intraglomerular pressure, slow progression of lesions, and decrease proteinuria. These authors have documented the changes in disposition of ACEI in animals with renal impairment (Lefebvre and Toutain, 2004; Lefebvre et al. 2006). In dogs and cats, enalaprilat (active metabolite of enalapril) is predominantly cleared by the kidneys. Benazeprilat is excreted in the bile as well as in the urine, while enalaprilat is excreted solely by the kidneys. In the situation of renal dysfunction, benazeprilat serum concentrations are essentially unchanged from those expected in normal dogs (Toutain et al., 2000). Enalaprilat serum concentrations, however, with no alternative route for elimination, are elevated in the situation of renal dysfunction. Therefore, under these circumstances, benazepril is more predictable in terms of serum concentrations.

In cats with reduction in glomerular filtration rate, there was no alteration in clearance of benazeprilat(Lefebvre et al., 1999; Toutain et al., 2000; Brown et al., 2001).

ACE Inhibitors Currently in Use

Enalapril (Enacard®, Vasotec®, generic) has been approved for the treatment of heart failure in dogs in most countries, including the USA (Enacard®), but is no longer marketed in this country and the human generic drug is used. The dosage of enalapril used in the treatment of heart failure is 0.25–0.5 mg/kg q 12–24 h PO, whereas for systemic hypertension and proteinuria there is a wider rage of 0.25–1.0 mg/kg q 12–24 h PO. The dosage in cats is 0.25–0.5 mg/kg q 12–24 h.

Benazepril (Fortekor®, Lotensin®) has been approved for use in dogs in Canada, Europe (Fortekor®), South America, and Asia, and has been investigated in the USA for use in cats and dogs, at a dosage of 0.25–0.5 mg/kg q 12–24 h PO. Imidapril has been approved for the treatment of heart failure in dogs in the UK (Prilium®) at 0.25 mg/kg q 24 h PO. Ramipril (Altace®, Vasotop®) has been approved for use in dogs in the UK (Vasotop®). The dosage is 0.125–0.25 mg/kg q 24 h PO (starting at the lower end of the dose range and titrating upwards). Lisinopril (Prinivil®, Zestril®) has also been investigated in animals, but is not in common use. The dosage used in dogs is 0.5 mg/kg q 12–24 h, PO. The dosage in cats is 0.25–0.5 mg/kg q 24 h.

A combination of benazepril and spironolactone (Cardalis®) has now been approved for use in the EU for dogs in heart failure. This should provide a useful and convenient addition to the arsenal for management of heart failure, hypertension, and possibly proteinuric renal disease. US studies are in progress at the time of this writing. Cardalis® is supplied as 2.5 : 10, 5 : 20, 10 : 80 (mg benazepril : mg spironolactone) chewable tablets for once-daily use.

Mineralocorticoid Receptor Blockers

At the time of this writing, there are two mineralocorticoid receptor blockers on the market, eplerenone and spironolactone. Eplerinone is a human drug used to avoid some of the endocrine side effects of spironolactone. It is not used in veterinary medicine and is expensive, therefore will not be included in this discussion.

Spironolactone is a synthetic 17-lactone drug that is a competitive aldosterone receptor (mineralocorticoid receptor blocker, MRB). The result of this antagonism of mineralocorticoid receptor in distal renal tubule cells is an increase in urinary Na^+ and H_2O excretion and a decrease in K^+ excretion. In the dog, spironolactone is relatively quickly absorbed through the gastrointestinal tract into the plasma and is then converted to several active metabolites (Sadée, 1972; Karim et al., 1976). The bioavailability in the dog is highest when given with food, reaching 80–90% (Guyonnet et al., 2010). Using an experimental model of hyperaldosteronism, mimicking that in

heart failure, Guyonnet and colleagues (2010) found that the spironolactone dosage of 2 mg/kg once daily restored the urinary Na^+/K^+ ratio to near normal.From this result and analysis of pharmacokinetic and pharmacodynamic data from this preclinical trial, the authors suggested that the optimal dosage of spironolactone in the dog is 2 mg/kg once daily.

As a weak, potassium-sparing diuretic (diuretics are discussed in Chapter 24), spironolactone was initially used to provide sequential nephron blockade and combat hypokalemia resulting from the use of loop and thiazide diuretics. However, current use focuses on the antagonism of aldosterone, which may have long-term benefits. Aldosterone has been implicated in the pathological remodeling (inflammation, hypertrophy, fibrosis) of cardiovascular and renal tissues (Ovaert et al., 2009; Hezzell et al., 2012). Because of this, the primary rationale for adding spironolactone as adjunctive therapy for heart failure is now mineralocorticoid receptor (specifically, aldosterone) blockade. Mineralocorticoid receptor blockade is now considered standard of care in humans with heart failure and low ejection fraction (McMurray et al., 2012; Yancy et al., 2013). The benefit seen with additional RAAS blockade in heart failure supports the concept of aldosterone breakthrough, discussed in Section Clinical Use. A similar study in 212 dogs with naturally occurring MMVD and heart failure showed a 69% reduction in risk of cardiac morbidity and mortality when spironolactone was added to standard therapy (ACEI, furosemide, with or without digoxin), as compared standard therapy alone (Bernay et al., 2010). A separate safety analysis of dogs involved in the aforementioned study showed that dogs receiving spironolactone, in addition to standard therapy, were not at higher risk of adverse events (death from renal disease, variations in serum Na^+, K^+, urea nitrogen, and creatinine) when compared to dogs receiving placebo and standard therapy (Lefebvre et al., 2013). Finally, spironolactone in combination with ACEI therapy appears to be safe when used to treat dogs with naturally occurring asymptomatic MMVD, as well those with occult DCM, without preexisting azotemia (Thomason et al., 2007, 2014).

Clinical Use

A consensus statement of the American College of Veterinary Internal Medicine, generating guidelines for the therapy of dogs with MMVD (Atkins et al., 2009), recommended the use of spironolactone as an adjunctive therapy in dogs with ACVIM stage D2 (refractory, with home therapy possible) heart failure (Figures 21.9 and 21.10). A majority of panelists also used spironolactone in the therapy of stage C2 (dogs previously stabilized with in-hospital heart failure therapy or clinical signs of heart failure, mild enough to be treated at home (Figure 21.9). A minority of panelists advocated the use spironolactone

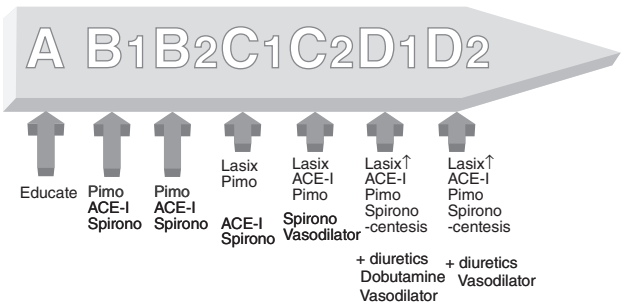

Figure 21.10 The American College of Veterinary Internal Medicine Cardiac Disease Classification scheme with the authors' treatment recommendations for dilated cardiomyopathy. See Figure 21.9 for abbreviations.

in dogs with ACVIM stage B2 (cardiac enlargement, but prior to onset of heart failure) MMVD.

Spironolactone is approved within the European Union as adjunctive therapy in the treatment of canine heart failure, secondary to MMVD. Clinical trials are currently underway to evaluate the effects of spironolactone in combination with ACEI in the treatment of stage B2 and C1 MMVD dogs (ongoing US placebo-controlled, double-blind study of spironolactone and benazepril versus benazepril alone in dogs with MMVD and first-time heart failure, sponsored by CEVA Santa Animale with expected completion in 2017) (Borgarelli, 2011). There is no consensus regarding the use of spironolactone in other diseases, such as DCM and congenital heart disease, despite its having been used for decades to treat canine heart failure, secondary to a variety of causes.

Preliminary data from the authors' clinics suggest that aldosterone breakthrough occurs in dogs with heart failure due to naturally occurring heart disease and that the incidence is approximately 40%. Furthermore, it appears that aldosterone breakthrough may occur quite early in the disease course (Bomback and Klemmer, 2007; Lantis et al., 2014). Monitoring of urine aldosterone : creatinine (Gardner et al., 2007), may therefore help optimize an individual patient's pharmacotherapy and improve RAAS blockade (i.e., determine if spironolactone should be added as an adjunctive therapy).

Use in cats: Aldosterone has been found to be elevated in Maine Coon cats with asymptomatic HCM (MacDonald et al., 2006) and the use of spironolactone (2 mg/kg/day for 4 months) in the therapy of asymptomatic HCM in cats has been evaluated (MacDonald et al., 2008). Unfortunately, this study did not show reduction in left ventricular mass or improvement in an echocardiographic parameter of diastolic function and four of the 13 spironolactone-treated cats developed ulcerative facial dermatitis. A double-blinded, placebo-controlled clinical trial, evaluating the use of spironolactone in cats with heart failure due to HCM is currently

under way (James et al., 2013). It is worth noting that, at interim analysis (n = 16 cats enrolled), no cat receiving spironolactone (1.3–2.2 mg/kg once daily) had experienced ulcerative facial dermatitis.

In conclusion, based on clinical and research data, the authors utilize spironolactone in virtually all instances in which ACEIs are employed. This would include dogs with ACVIM stage B2 MMVD (cardiac enlargement, but prior to onset of congestive heart failure (pulmonary edema); Figure 21.10); dogs with ACVIM stage C2 and D2 MMVD (at-home therapy of congestive heart failure; Figure 21.10); in systemic hypertension; in occult and florid DCM; and in proteinuric renal disease. At the current time, as data on MRB efficacy are pending, we do not feel that there is adequate evidence for the routine use of spironolactone in cats at this time.

Other Vasodilators: Prazosin, Hydralazine, Calcium Channel Blockers, Nitrovasodilators, Sildenafil, and Carvedilol

Vasodilators are characterized as: (i) "venous dilators" or "venodilators" (preload reducing), with nitroglycerin being a prime example – useful for signs of congestion; (ii) "arteriolar dilators" or "arteriodilators" (afterload reducing) include hydralazine and amlodipine – useful for low output signs (and for signs of congestion); and (iii) "mixed" or "balanced" vasodilators, which dilate both arterioles and veins, include the ACEIs, prazosin, pimobendan, and nitroprusside, useful for both congestive and low output signs. All, except pimobendan, also have the potential to cause hypotension and, hence, impaired renal perfusion. When used with other offloading therapies (e.g., furosemide), hypotension and azotemia are more likely to result.

This group of drugs has been used extensively as treatment for heart failure to "off-load" or "unload" the failing heart (Hamlin, 1977; Zelis et al., 1979; Remme, 1993). The rationale is that decreasing the work load of the heart is better for the patient than administering a positive inotropic agent with toxic potential (i.e., digitalis) and which typically increases MVO_2 (inodilators, such as pimobendan, being an exception). If systemic arterial pressure (a component of left ventricular afterload) is reduced by a vasodilator drug, the left ventricle ejects blood into a circuit with lowered resistance. Further, peripheral venodilation diverts blood from the pulmonary to the systemic vasculature. This response is antagonistic to the formation of pulmonary edema, because it tends to restrict venous return to the heart (i.e., ventricular preload). Left ventricular size and wall tension decrease in response to reduction in ventricular preload and afterload. Myocardial oxygen demands decrease accordingly as the workload of the heart is reduced; cardiac output and hemodynamics should improve (Packer, 1984; Abrams, 1985).

Before initiating vasodilator therapy in treating congestive failure in animals, the clinician should be aware of potential problems; for example it has been assumed that drug-induced vasodilation would automatically increase peripheral perfusion and thereby increase oxygen availability to all tissues. However, vasodilator agents of the nitroglycerin type exert a predominant reduction in peripheral venous resistance as compared to arteriolar resistance. Pooling of blood in the venous capacitance beds in no way ensures increased perfusion of all tissues. Vasodilators are beneficial to the failing heart because they decrease cardiac workload, not by directly improving peripheral perfusion but because of vascular dilation. Furthermore, if arterial pressure is critically decreased, blood flow through the coronary and renal vascular beds may be compromised further. Reflex tachycardia accompanied by increased myocardial oxygen demand is another potential problem associated with fall in systemic blood pressure.

Prazosin

Prazosin (Minipress) is an α_1-adrenergic selective blocking agent (Chapter 7). Prazosin can be an effective vasodilator through the adrenergic blocking properties on vascular smooth muscle, but it is little used in veterinary cardiology. This drug may be useful in the treatment of renal hypertension (Zimmerman and Largent, 1983) and treatment of vesicourethral reflex dyssynergia in dogs (Haagsman et al., 2013). In dogs, prazosin undergoes hepatic metabolism with biliary excretion being the major route of elimination and 50% metabolized through first-past metabolism. Urinary excretion of this drug appears to be low (Rubin et al., 1979).

Hydralazine Hydrochloride

Hydralazine hydrochloride, USP (Apresoline®), is an arteriolar dilator that has undergone limited study in dogs with volume-overload heart failure (Kittleson et al., 1983; Häggström et al., 1996) and experimental heartworm disease with pulmonary hypertension (Atkins et al., 1994). Through its effect on systemic arterial beds, hydralazine reduces impedance, peripheral and pulmonary vascular resistance, and lowers impedance to left ventricular ejection. Stroke volume and cardiac output increase proportionately, thereby initiating hemodynamic improvement.

Beneficial effects of hydralazine are manifested in the management of congestive heart failure, secondary to MMVD. In this pathophysiological state, forward left

ventricular stroke volume is reduced owing to a regurgitant fraction being pumped backward through the incompetent AV valve into the left atrium. By lowering systemic impedance to left ventricular ejection, hydralazine increases forward stroke volume and thereby reduces the regurgitant fraction. End-systolic volume and cardiac size are reduced because more blood is pumped from the cardiac chambers per beat. Reduction in cardiac size leads to commensurate decreases in wall tension (afterload) and myocardial oxygen consumption. Also, importantly, it reduces the size of the orifice of the incompetent mitral valve and hemodynamic improvement has been demonstrated in dogs with volume-overload congestive heart failure, caused by mitral valve regurgitation (Kittleson et al., 1983; Häggström et al., 1996). However, there are no outcome trials published to date. Hydralazine is likely effective in other volume overload states such as patent ductus arteriosus, aortic insufficiency, or septal defects.

Pharmacokinetics

Hydralazine is absorbed rapidly after oral administration in dogs, its onset of action is within 1 hour, and peak response at 3–5 hours. The drug undergoes extensive hepatic metabolism during its initial passage through the liver. Administration of hydralazine with food in dogs reduces its bioavailability (Semple et al., 1990). There is evidence that uremia in some way affects biotransformation of hydralazine, so that blood concentrations may increase in uremic patients.

Clinical Use

A recommended dosage for hydralazine in dogs involves the initial oral administration of 1 mg/kg; this dose can be adjusted upward, depending upon evidence of clinical improvement, but should not exceed 3 mg/kg. Although doses have been published for cats, it is not currently recommended for treatment.

The therapeutic response in dogs generally lasts 11–13 hours; thus twice-daily administration is suggested as the standard (Kittleson, 1983).

Adverse Effects

Important adverse effects of hydralazine therapy in humans are tachycardia and hypotension. It was reported that hypotension was not a problem in dogs when hydralazine dosage was titrated carefully against signs of clinical improvement; however, tachycardia does seem to be a common untoward development in dogs, treated with hydralazine (Kittleson et al., 1983). Because tachycardia increases myocardial oxygen consumption and may lead to cardiac decompensation, heart rate should be monitored during therapeutic implementation with hydralazine or any other vasodilating drug.

Concomitant administration of a beta-blocking drug might reduce the reflex tachycardia produced by hypotensive reactions to hydralazine. On the other hand, the potential negative inotropic response to cardiac beta-receptor blockade may exacerbate heart failure and/or worsen hypotension (see Chapter 7).

Calcium Channel Blocking Drugs

These agents suppress calcium ion (Ca^{++}) influx through plasma membrane channels in cardiac tissues, vascular smooth muscle, and other excitable cell types (Katz, 1985; Allert and Adams, 1987; Opie, 1984). The resulting decrease in intracellular Ca^{++} concentration leads to characteristic changes in physiological activity of affected tissues, including reduction in myocardial contractility, vasodilation in coronary and peripheral arterial beds, lowered impedance to left ventricular ejection, reduced myocardial oxygen demand, and slowed AV impulse conduction. Because of this diverse pharmacological profile, Ca^{++} channel blockers have been studied extensively for therapeutic application in a wide spectrum of cardiovascular disorders. Drugs of this group have been approved for the management of ischemic heart disease, hypertension, and some forms of cardiac dysrhythmias in human medicine. Other indications in people include obstructive cardiomyopathies, asthma, and cerebral ischemia (Stone and Antmann, 1983; Conti et al., 1985). Less is known about the clinical application of Ca^{++} channel blockade in veterinary medicine (Adams, 1986; Novotny and Adams, 1986; Johnson, 1985; Bright, 1992). The greatest experience has been with amlodipine, primarily in the management of systemic hypertension (Henik, 1997; Snyder, 1994) and with diltiazem, used to slow AV conduction (Gelzer et al., 2009) (thereby slowing ventricular response to atrial fibrillation or supraventricular tachycardia); to break supraventricular tachycardia; and as a lusitropic agent in cats with HCM (Bright, 1992). Amlodipine is also used in the treatment of heart failure to unload the ventricle(s), reducing cardiac size, reducing AV valvular insufficiency, improving forward cardiac output, and reducing impingement of an enlarged heart on the airways. The rationale for Ca^{++} channel blocking drugs in cardiovascular therapeutics in animals was summarized by Allert and Adams (1987). The use of Ca^{++} blocking agents as Class IV antiarrhythmics and electrophysiological properties in treating supraventricular tachyarrhythmias is addressed in Chapter 22.

Fundamentals of Ca^{++} Channel Blockade

Channel blockers are a heterogenous group of drugs that can be classified into two groups. The dihydropyridine calcium channel blockers (amlodipine, nifedipine) have greater vascular selectivity whereas the nondihydropyridine calcium channel blockers (diltiazem, verapamil)

have greater selectivity for nodal and myocardial tissues. Their commonality is that they all selectively inhibit the L-type Ca^{++} channel – preventing its opening in smooth muscle and/or the myocardium. The dihydropyridine group (verapamil and diltiazem) are discussed more extensively in Chapter 22 of this book.

The calcium channels are protein moieties embedded within and spanning the permeability barrier of the phospholipid plasma membrane biolayer. Calcium channel blocking drugs induce negative inotropic effects in the heart by reducing transsarcolemmal influx of activator Ca^{++}.

Contraction of vascular smooth muscle is mediated by Ca^{++} and also depends on the influx of Ca^{++} through cell membrane channels (Somlyo, 1985). Therefore, Ca^{++} channel blockade in the vasculature evokes smooth muscle relaxation and a vasodilatory response. The resultant peripheral vasodilation, and accompanying decrease in peripheral vascular resistance, lowers impedance to left ventricular ejection, thereby reducing ventricular wall tension (afterload) during ejection.

Adverse Effects

Although the negative inotropic effects and vasodilator actions of Ca^{++} channel blockade can benefit hemodynamics by reducing cardiac workload, these same cardiovascular depressant responses obviously carry the risk of exacerbating hypotensive crisis. Adverse circulatory side effects of Ca^{++} channel blockade include a negative inotropic effect, with reduced cardiac output and hypotension, particularly with concurrent off-loading therapies (diuretics, ACEIs, vasodilators). This combination of effects can result in decompensation of preclinical or compensated heart failure Hypotension may also complicate treatment of patients *not* in danger of heart failure, resulting in lassitude, anorexia, collapse, and azotemia. Other potential side effects are sinus bradycardia and heart block, attributable to direct depression of sinoatrial firing rate and AV conduction, respectively.

Clinical Use

Antiarrhythmic applications are discussed in Chapter 22. For example, diltiazem is a common treatment for controlling heart rate in cats with HCM (Bright, 1992), and can be used in dogs for treating atrial fibrillation. When considered for HCM in cats, long-acting diltiazem is an attractive alternative. Based on the author's work (Johnson et al., 1996), conventional diltiazem should be administered at 7.5 mg TID and long-acting diltiazem at 45 mg q 24 h.

Dilacor® XR has the advantage of availability in capsules which contain three or four time-release tablets, as compared to the granules of the long-acting form. Based on studies with this product (Wall et al., 2005), either 30 or 60 mg of extended-release diltiazem tablets PO, once daily, can be administered, but Dilacor® XR administered at 30 mg BID can be effective without the untoward events.

Because other vasodilator drugs are available in veterinary medicine, (discussed in this chapter) amlodipine is rarely used in the management of heart failure. Amlodipine is the preferred drug for management of systemic hypertension in cats because it is longer-acting than other dihydropyridines (Snyder, 1994).

Nitrovasodilators: Nitroglycerin, Isosorbide Dinitrate, and Nitroprusside

The organic nitrates are nitrogen esters that exert their effect by acting as an exogenous source for nitric oxide. Nitric oxide is now known to be endothelium-derived relaxing factor (EDRF), an endogenous vasodilator. The nitrate vasodilators are esters of nitrous acid. They are metabolized to inorganic nitrite and denitrated metabolites.

Mechanism of Action

Nitrites, organic nitrates, and nitroso compounds all act to activate the enzyme *guanylate cyclase*. The resultant increase in intracellular cyclic-GMP (3,5-guanosine monophosphate) subsequently acts to inhibit contraction of vascular smooth muscle. This mechanism may involve a decrease in the availability of intracellular Ca^{++} in vascular smooth muscle cells or may interfere with the myosin–actin interaction (Opie and Gersch, 2009). Nitrates may also stimulate synthesis of the vasodilator prostaglandins, PGI_2 and PGE. Nitrates relax smooth muscle in both arteries and veins, but they are often used clinically as *preload* reducers. They decrease myocardial O_2 requirements (decrease workload of heart) and pool blood in the splanchnic vessels to reduce congestive signs in heart failure. They are commonly used to manage human patients with angina pectoris (chest pain caused by coronary artery disease), as coronary vasodilators and possibly by reducing cardiac work through reduction in preload.

Pharmacokinetics

Nitroglycerin and other nitrovasodilators are metabolized quickly with half-lives of only a few minutes. Nitrates have significant *first-pass effects*, and metabolites are one-tenth or less the potency of the parent drug. These drugs are, therefore, administered either topically, sublingually, or intravenously to avoid first-pass metabolism by the liver. In dogs receiving topical 2% nitroglycerin ointment applied to the pinnae at a dosage of 0.25 cm/kg or an equal amount of petrolatum, splenic dimension increased by an average of 7% in treated dogs as compared to no change in the placebo-treated dogs

(Parameswaran et al., 1999). Enlargement of the spleen was apparent at approximately 8 minutes, peaking at approximately 15 minutes. This occurred without elevation in splenic pressure, indicating relaxation of vascular smooth muscle in the spleen.

Nitrovasodilators in Clinical Use

Nitrovasodilators are available as ointments, creams, sublingual tablet, lingual spray, or buccal tablet.

Nitroglycerin (NitroBid®, Nitrol®, Minitran®, Nitro-Dur® and generic) is applied topically (as a 2% cream, 2% ointment, or 0.2, 0.4, 0.6, and 0.8 mg/h patch), The half-life is 1–3 minutes. An international group of veterinary cardiologists (ISACHC, 2006) recommends a topical nitroglycerin dosage of 4–15 mg q 6–12 h for dogs and 3–4 mg q 6–12 h for cats. It is usually applied to an area on the patient that lacks hair and where the patient will not lick it off (such as pinnae of ears or shaved portion of the body; most patients receiving nitroglycerin are not grooming). This topical formulation of nitrate vasodilation, administered TID, is preferred by the authors to supplement management of acute heart failure.

Isosorbide dinitrate (Isordil®) is available as an oral tablet (even though it has poor systemic availability), topical ointment, and lingual spray at a dosage is 2.5–5.0 mg/dog). Isosorbide mononitrate (IS-5-MN) may have better absorption and longer half-life. At both IV and PO doses of 3 mg/kg of IS-5-MN, the main metabolite of isosorbide-dinitrate, showed that the decrease in systolic blood pressure was closely correlated with the log plasma concentration (Sponer et al., 1984). Bioavailability was estimated at 71.5%. The half-lives for the distribution and elimination phases were approximately 6 minutes and 1.5 hours, respectively, the latter being only one-third of that obtained in man. Subsequently, dogs were given five different dosages of IS-5-MN orally (3.125–50 mg/dog) and showed a peak plasma concentration and area under the curve proportional to the dosage, whereas the terminal half-life did not differ markedly. The minimum plasma concentration for a hemodynamic effect was estimated to be 100 ng/ml.

Some studies in experimental dogs using oral administration of long-acting isosorbide dinitrate at 1–2 mg/kg had beneficial effects (Yamamoto et al., 2013). However, others have found less promising results. Adin and associates evaluated 5-isosorbide dinitrate in normal dogs and dogs in heart failure, using a dosage of 2, 3, and 4 mg/kg PO or placebo on separate days (Adin et al., 2001). Investigators were unable to detect a shift in blood volume with oral 5-isosorbide dinitrate administration at any dose tested in either group, despite adequate drug levels. The authors questioned the benefit of this compound in the treatment of dogs with congestive heart failure.

Sodium nitroprusside (Nipride®) is a potent, direct-acting mixed vasodilator, administered as a CRI because of its short half-life. Tolerance does not develop to nitroprusside, relative to other nitrate compounds, because it provides intracellular nitric oxide. It is administered, in 5% dextrose, at an infusion rate of 0.5–10 μg/kg/min (beginning at the lower dosage and titrating upwards, as needed) to veterinary patients, while monitoring blood pressure to avoid hypotension. The risk of hypotension can be lessened and additional benefit realized when used with dobutamine infusion or pimobendan PO or IV. It is supplemental to loop diuretic administration, lowering left and right heart filling pressures, systemic and pulmonary vascular resistance, ventricular afterload, and pulmonary edema. Cyanide toxicity can develop in patients in which renal elimination is compromised because sodium nitroprusside is rapidly metabolized to cyanide and thiocyanate.

Although there are limited publications on its effect and use in normal dogs or those in congestive heart failure, the ACVIM Consensus Committee on MMVD reached consensus on its use emergent congestive heart failure (ACVIM Stages C and D; Figure 21.8, 21.9) (Atkins et al., 2009). A small case series showed benefit with nitroprusside infusion in dogs with fulminant, unresponsive (furosemide, nitroglycerin, and oxygen, with no mention of ACEIs or inotropic agents) pulmonary edema due to MMVD (Greer et al., 2004). Eight of 10 dogs were released from the hospital, seven receiving from 1 to 3 (mean 1.75) μg/kg/h and one receiving 5 μg/kg/h. Infusion was reduced or stopped if blood pressure fell below 90 mmHg. Infusions were continued for an average of 14 hours and tapered over 2–3 hours.

Clinical Uses

In people, the organic nitrates are primarily used for the relief of anginal pain (angina pectoris) (Parker and Adams, 1977). Their use in veterinary medicine is limited because the dosage forms available can be inconvenient to use and the duration of action is brief. Nevertheless, they may be helpful for vasodilation and the acute treatment of pulmonary edema associated with congestive heart failure. Topical nitroglycerin ointment (2%) is typically used in a semiquantitative fashion:

cats: 0.3 cm strip (1/8 inch),
small dogs: 0.6–1.2 cm strip (1/4 to 1/2 inch),
medium dogs: 1.2–2.5 cm strip (1/2 to 1 inch),
large dogs: 2.5–5.0 cm strip (1 to 2 inch).

It is applied topically (usually to the inner ear flap) q 8 h, for the acute management of congestive heart failure. After 24 hours, because of concerns or tolerance, the drug is stopped if the patient's condition allows, or withdrawn for 8 hours and then continued at the same dosage at "8 hours on – 8 hours off". The drug is rarely dispensed

but, if so, it can be used to treat orthopnea in heart failure patients, by administering it at bedtime once daily. Owners should be instructed to wear exam gloves when applying the ointment and to wash hands thoroughly afterwards.

Tolerance

Tolerance to nitrovasodilators develops with repeated administration. The mechanism is suspected to be a progressive depletion of sulfhydral groups necessary for the formation of nitric oxide. Efficacy is improved if the drug is used intermittently instead of continuously because intermittent use allows time for regeneration of sulfhydral groups. Optimum intermittent use is to provide a nitrate free interval of 8 hours or more during the day.

Adverse Effects

The most common and limiting side effect of these drugs is hypotension. Methemoglobinemia can occur with accumulation of nitrites but, both this and cyanide poisoning are extremely uncommon, as this therapy is usually used in the short-term management of acute heart failure requiring hospitalization.

Phosphodiesterase V Inhibitors: Sildenafil

Sildenafil (Viagra®) is an orally active PDE V inhibitor. Phosphodiesterase V is found in relatively high concentration in lung and penile erectile tissue and levels are elevated in humans with pulmonary hypertension (PHT). Type V phosphodiesterase inhibitors prevent degradation of cyclic guanosinemonophosphate-specific phosphodiesterase-5 (cGMP), resulting in relaxation of smooth muscle in pulmonary vasculature and, to a lesser degree, systemic vessels. This enhances nitric oxide-mediated pulmonary vasodilation and may provide additional beneficial effects on vascular remodeling and cardiac function (Takimoto et al., 2005). However, a canine study looking specifically at sildenafil's effect on cardiac function did not demonstrate inotropic benefit (Dias-Junior et al., 2006).

Pulmonary hypertension, a clinically important disease associated with high morbidity and mortality in dogs, is most often a sequelae of other disease processes (chronic obstructive pulmonary disease and heartworm disease), thereby requiring a balanced therapeutic approach which targets both the underlying disease and palliation of clinical signs. An important goal of therapy is to reduce pulmonary artery pressures. Early vasodilators, however, have had no preferential effect on pulmonary vasculature and thus have had questionable benefit, as well as the potential to worsen the clinical signs of pulmonary hypertension by producing systemic hypotension.

Sildenafil is currently the most extensively researched of the PDE V inhibitors, and has been shown to improve erections, as well as exercise tolerance and quality of life in humans with PHT, resulting in FDA approval for its use in erectile dysfunction and PHT. Although, still expensive, sildenafil is now available as a generic preparation.

Pharmacokinetics

There are little published data on sildenafil in the dog. Incompletely described pharmacokinetic properties include T_{max} of 1 hour or less. Bioavailability is attenuated by presystemic hepatic metabolism. The volume of distribution is 5.2 l/kg, with plasma protein binding of 84%. The dog has an elimination half-life of 6.1 hours. After single oral or intravenous doses of [^{14}C]-sildenafil, the majority of radioactivity was excreted in the feces (Walker, 1999; Sugiyama, 2001; Al-Mohizea et al., 2015).

In normal human subjects, sildenafil is rapidly absorbed after oral administration, with absolute bioavailability of about 40%, due to the extensive first-pass metabolism. It is eliminated predominantly by hepatic metabolism (mainly by cytochrome P450 3A4) and is converted to an active form. Sildenafil and its metabolite have terminal half-lives of approximately 4–5 hours. The maximum observed plasma concentration of sildenafil is reached within 30–120 minutes (median 60 minutes) of an oral dosing in a fasting state (Al-Ghazawi et al., 2010).

Efficacy

Well-controlled dose studies of vasodilator effects of sildenafil are lacking in the veterinary literature; however, there are three small clinical studies, one being placebo controlled (Dias-Junior et al., 2006; Bach et al., 2006; Kellum and Stepien, 2007). The dose used is approximately 2 mg/kg sildenafil every 8–24 hours. These studies show improvement in pulmonary hypertension or quality of life scores.

In naturally occurring PHT in dogs with concurrent MMVD, dosage of 1 mg/kg TID sildenafil (Brown et al., 2010), with concomitant but variable use of furosemide, enalapril, pimobendan, digoxin, spironolactone, and thiazide diuretics, produced improvements in pulmonary pressures. Exercise capacity was significantly greater and quality of life scores significantly higher in dogs receiving sildenafil than in dogs receiving placebo. The authors concluded that sildenafil decreases systolic pulmonary arterial pressure in dogs with PAH and its use is associated with increased exercise capacity and quality of life, when compared to treatment with placebo. No adverse effects were noted.

Because of the variability and complexity of the potential causes of PHT, additional harmful effects of the

underlying disease, and the systemic response to pulmonary hypertension (e.g., congestive heart failure), sildenafil is often used in combination with other medications, including conventional heart failure therapeutics, such as diuretics, ACEIs, and pimobendan (Hoskins, 2006). While adverse side effects with long-term therapy have been minimal or unrecognized, long-term studies are lacking.

Carvedilol

This compound has been approved for use in humans to treat hypertension and heart failure. Antiarrhythmic effects are discussed in Chapter 22. It is both a nonselective β_1 and β_2-receptor antagonist and an α_1-receptor antagonist (see Chapters 7 and 22 for more complete discussion). The ratio of β_1/β_2 to α_1-receptor antagonist potency for carvedilol is 10 : 1. Thus, this agent should reduce myocardial workload by lowering heart rate and peripheral vascular resistance. Carvedilol is also an antioxidant and its beta-blocking effects have potential beyond heart rate control and vasodilation. It is well accepted in human medicine that beta-blockers (carvedilol and others) play a role in heart failure management, improving survival, quality of life, cardiac health, and exercise capacity (Packer et al., 1996).The mechanism for this is the blunting of SNS activity, because SNS has multiple harmful effects, including: production of tachycardia and arrhythmias; vasoconstriction with increased afterload; RAAS activation; and myocardial remodeling, apoptotic cell death, and fibrosis.

Uechi et al. (2002) reported that in dogs with experimental mitral valve regurgitation, carvedilol (0.2 mg/kg) decreased heart rate, whereas renal function, arterial blood pressure, and left ventricular contractile function were unaffected. Carvedilol (0.4 mg/kg) decreased heart rate, blood pressure, and renal function. The tachycardic response to isoproterenol was significantly diminished for 36 hours by 0.4 mg/kg carvedilol versus 24 hours with 0.2 mg/kg. The authors determined that carvedilol should be initiated at less than 0.2 mg/kg and titrated up to 0.4 mg/kg for dogs in heart failure.

Because of beta-blockers' negative inotropic effect, they are typically (or always) started prior to heart failure or at least during remission. The dosage is gradually increased until the target (25 mg BID in DCM, or approximately 0.5–1 mg/kg) is reached or the dog can no longer tolerate the drug. If the latter occurs, the dosage is backed off to the previously tolerated dosage and maintained or again carefully increased once stabilization has occurred. Carvedilol and other beta-blockers are typically used in conjunction with other agents used in treating heart failure. Preliminary studies in dogs with MMVD show promise with this agent (Arsenault et al., 2005; Gordon et al., 2005, 2006); however, absorption of carvedilol varies markedly between individuals, making dosage determination difficult (Uechi et al., 2002). Furthermore, the only placebo-controlled, double-blind study of a beta-blocker (bisoprolol) in veterinary medicine failed to show a benefit in slowing the progression to heart failure in dogs with asymptomatic MMVD (Keene et al., 2012). The use of beta-blockers in DCM is still advocated, though their use has not been evaluated in dogs with this affliction.

Ancillary Therapy in Congestive Heart Failure

Diuretics

Diuretics are covered in Chapter 24. The use of potent loop-acting diuretics (furosemide, torsemide, bumetanide) are the mainstay of the management of congestive heart failure in man and animals. Today, in dogs, their use is supplemented with ACEIs and pimobendan in most cases ("triple therapy"). The authors advocate "quadruple therapy," adding spironolactone to any drug regimen, which employs ACEIs. This is because of the phenomenon termed aldosterone breakthrough, described in Section Mineralocorticoid Receptor Blockers, Clinical Use. Furthermore, the authors do not prescribe furosemide as a monotherapy, because of its RAAS-activating properties, similar to that of vasodilators. An ACEI virtually always accompanies the use of furosemide in the authors' clinics.

Patients receiving diuretics should be carefully monitored. Pronounced diuresis can reduce blood volume to the extent that dehydration lowers preload, such that ventricular performance is inadequate. A reduced ventricular filling pressure (preload) is good on the one hand because it reduces wall tension, myocardial oxygen demand, and the propensity for edema formation. Conversely, this reduction in venous return – without concurrent positive inotropic effects – may well lead to reduced cardiac output, which results in reduction in renal perfusion, azotemia, and reduced clearance of certain drugs. Furthermore, inappetance and/or vomiting contribute further to dehydration and electrolyte loss. Hypokalemia is one of the more important concerns in this setting, as potassium levels fall with anorexia, polyuria, excessive diuresis, and emesis. This is, however, counteracted with potassium supplementation, ACEIs, and MRB (spironolactone). Serum electrolyte and renal values (BUN and serum creatinine) should be monitored, along with body weight, state of hydration (skin turgor, packed cell volume, total protein, serum albumin and sodium).

Overview of the Management of Cardiovascular Disease

Type of Heart Disease and Related Hemodynamic Abnormalities

The sympathetic nervous system and RAAS are both activated in heart failure and even before its onset. In virtually all cases, this activation is detrimental to cardiac patients.

In MMVD, contractility is at least partially maintained until the patient reaches terminal stages of illness. But recent studies of pulmonary transit time of blood (time required to traverse the lungs and reach the left atrium) indicate that subtle changes are present much earlier. These dogs have generally not been thought to require inotropic support but, today, pimobendan has been shown to be useful in the management of MMVD-induced congestive heart failure.

In heart failure, preload and afterload are both elevated and should be reduced. Heart rate varies but is usually high and can be reduced with digoxin, for example, and simply by managing heart failure and normalizing the autonomic forces on the cardiovascular system.

Dogs with DCM have similar abnormalities except that contractility is always diminished and often, profoundly so. This requires inotropic support in the emergency room with dobutamine CRI, digoxin IV or PO, or IV or PO pimobendan and chronically with pimobendan PO, with or without digoxin (Figure 21.10).

Cats with HCM suffer diastolic failure and increased preload and afterload, often with elevated heart rate. Afterload increase is not as severe as in eccentrically hypertrophied hearts, as discussed above for MMVD and DCM, because the concentric hypertrophy of HCM (and hypertension) is adaptive in terms of afterload (LaPlace relationship, in which chamber radius increases and wall thickness reduces afterload). Systolic function is thought to be adequate in most cases. Therapy is different with treatment of rapid heart rate, diastolic failure (lusitropic and negative chronotropic drugs), and congestion.

Pressure overload, due most often to systemic hypertension, pulmonary hypertension (heartworm disease, etc), and obstructive disease (SAS, PS, coarctation of the aorta, etc.), also produces heart failure with increased afterload, normal, elevated or decreased preload, and increased heart rate, as in heart failure of other causes.

Severity of Heart Disease

There are numerous classification schemes in veterinary medicine for the categorization of severity of cardiac disease (Atkins and Haagstrom, 2012). Two of these (Figure 21.8), the ISACHC (International Small Animal Cardiac Health Council) and ACVIM (American College of Veterinary Internal Medicine), are most commonly in use today (ISACHC, 1994; Atkins et al., 2009).

The ISACHC classification consists of four categories (Ia, Ib, II, and III), which are schematized in Figure 21.6 and described in Table 21.4. The ACVIM classification of cardiac disease, which was adapted from the American College of Cardiology/American Heart Association classification system, depicted in Figure 21.8, uses an A through D categorization of cardiac disease and does not rely heavily upon exercise tolerance as a criterion, a weakness of previous schemes. It also includes a category (A) for dogs without heart disease but who are at risk (e.g., Cavalier King Charles Spaniels at risk to develop MMVD). Category B includes dogs with mild heart disease, without (B1) and with (B2) cardiomegaly, but without present or historical evidence of congestive heart failure. Category C includes dogs with signs of heart failure, either hospitalized (C1) or treated at home (C2) and is similar to category D, which includes refractory or end-stage heart failure patients, treated in the hospital (D1) or at home (D2). Obviously, this categorization is fluid, with patients able to move back and forth between the stages of heart disease, with decompensation, with disease progression, and with successful treatment.

Choice of Pharmacological Agents, Based on Signs

One can also pick agents based on pathological responses seen in individual patients, for example, congestion, tachycardia, poor systolic function, and arrhythmia. In Tables 21.1 and 21.2 drugs are classified as to the type of abnormality for which they are likely to be indicated, with the suggested dosage.

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22

Antiarrhythmic Agents

Kathryn M. Meurs and Jim E. Riviere

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An arrhythmia is typically defined as an abnormality in the rate, regularity, or site of origin of the electrical impulse of the heart, or a disruption in impulse conduction such that the normal sequence of atrial and ventricular activation is changed. In many cases cardiac arrhythmias have no clinical importance, and in some cases are considered normal findings (sinus arrhythmia in the dog). However, arrhythmias that lead to very slow or rapid heart rates or very irregular heart rates can have significant clinical implications, particularly if cardiac disease is present. The decision to treat a cardiac arrhythmia with an antiarrhythmic should be based on many factors including heart rate, type of arrhythmia, presence or absence of clinical signs such as syncope or exercise intolerance, and presence of underlying heart disease. Arrhythmias in the face of underlying heart disease, particularly with myocardial dysfunction (dilated cardiomyopathy, etc.) can be likely to lead to the development of clinical signs, including sudden death. Although there are many antiarrhythmics, only a small number have been well studied and shown to be effective in veterinary medicine and this chapter will concentrate on those. This chapter focuses on the more common antiarrhythmic agents used in veterinary medicine and introduces their principal pharmacodynamic actions on cardiac rate and rhythm.

Rhythmicity of the Heart

Normal cardiac rhythmicity is maintained by (i) dominance of a single pacemaker discharging regularly with the highest frequency, (ii) rapid and uniform conduction through normal routes of impulse conduction, and (iii) long and uniform duration of the action potential and refractory period of cardiac myofibers. In addition, duration of the Purkinje fiber action potential normally outlasts that of the ventricular muscle, thus providing a safety factor preventing reentry and reexcitation of the Purkinje system by the muscle action potential. A disturbance in any of the preceding factors can be arrhythmogenic, for example an inappropriate increase in automaticity of normally latent pacemaker cells, abbreviation of the refractory period, slowing of conduction velocity, or disparate refractory periods of adjacent fibers. Likewise, treatment of arrhythmias with the drugs discussed in this chapter is aimed at correcting these disturbances by altering cardiac pacemaker threshold, sodium, potassium, and/or calcium currents.

Arrhythmias often are associated with: imbalance of the parasympathetic and sympathetic branches of the autonomic nervous system; changes in serum electrolyte concentrations, especially potassium and calcium ions (K^+ and Ca^{++}); hypoxemia; acidosis; changes in concentration of carbon dioxide; excessive stretch of cardiac tissue; mechanical trauma; myocardial disease states such as congestive heart failure and viral myocarditis; numerous drugs; and ischemia and infarction of the heart muscle. Chapters 6, 7, and 8 on the autonomic system and the introduction to cardiac function in Chapter 21 should be consulted for an appropriate background in these areas.

Hemodynamic instability occurring during cardiac arrhythmias results from alterations in heart rate, changing the regularity of heartbeats, and losing atrial assistance in ventricular filling. Electromechanical synchrony of the cardiac chambers is thereby lost, culminating in ineffectual filling and ejection of the ventricles and hemodynamic deterioration of the patient. Antiarrhythmic drugs suppress arrhythmias and help restore hemodynamic stability by altering basic electrophysiological processes in the heart.

Electrophysiological Properties of Cardiac Cells

The classification system for clinically useful antiarrhythmic drugs is based mainly on the predominant pharmacological effects of a drug on the action potential of cardiac cells (Vaughn Williams, 1984; Adams, 1986). Accordingly, a useful understanding of antiarrhythmic drug actions and affiliated nomenclature depends first on

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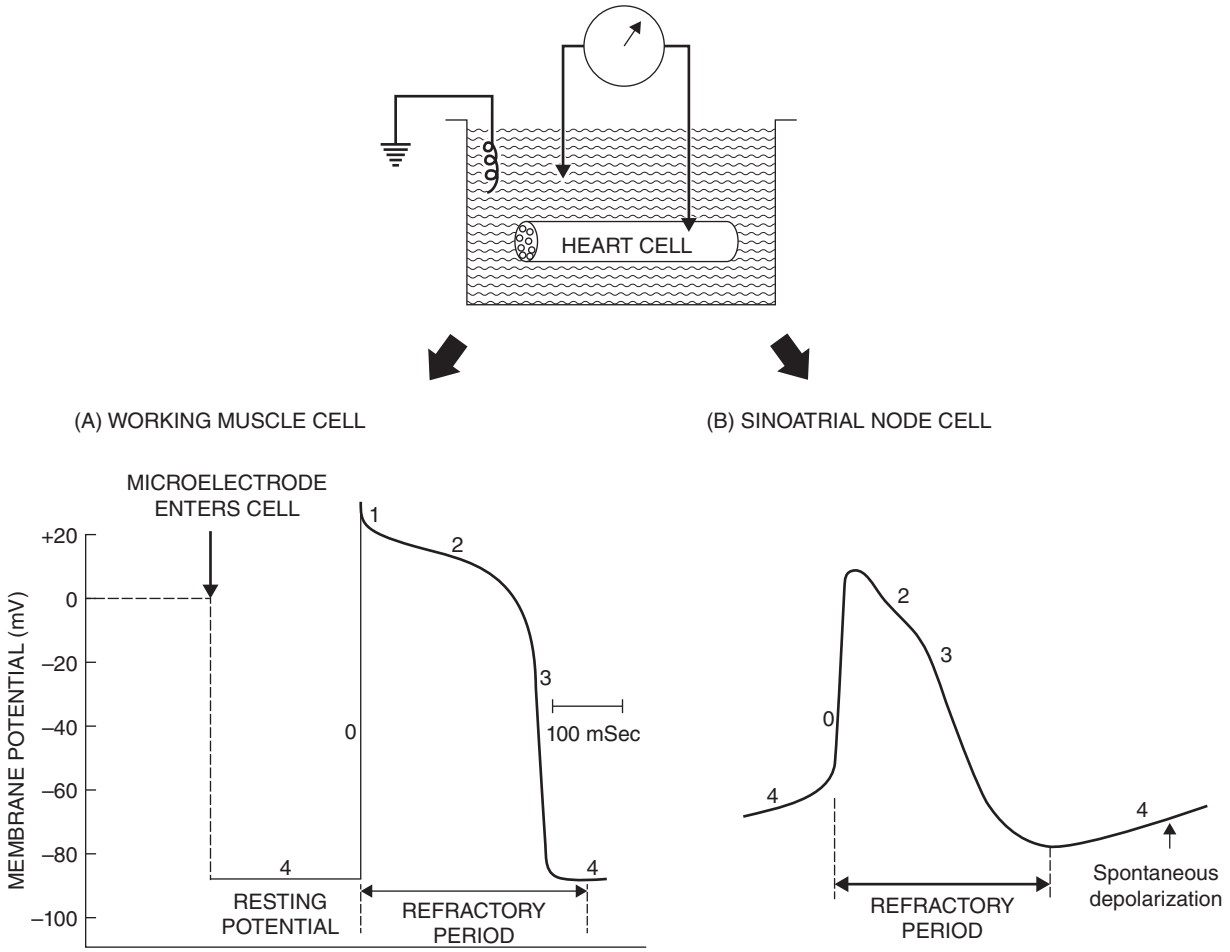

Figure 22.1 Cardiac action potentials recorded from a working myocardial cell (A) and a sinoatrial pacemaker cell (B). The nonautomatic working muscle cell (A) exhibits a constant phase 4 resting potential during diastole, whereas the automatic cell (B) undergoes spontaneous depolarization during phase 4, leading to threshold and spontaneous excitation. The cell is inexcitable or poorly responsive to additional stimuli during much of the action potential, and this refractory period helps prevent premature excitation. See text for further details. Source: Adams, 1986.

a good comprehension of basic bioelectric properties of the heart. An overview of salient features of this topic is outlined here relative to action potentials of cardiac cells and types of cardiac arrhythmogenesis.

Action Potentials of Cardiac Cells

The electrical activity of individual heart muscle cells can be recorded with a microelectrode capable of entering the intracellular space of a single cell, as shown schematically in Figure 22.1. Some of the common terms used to describe the configuration and ionic determinants of cardiac action potential components are defined here (Adams, 1986):

1) Membrane potential is the voltage difference across the cell membrane, that is the difference in electrical voltage between the intracellular and extracellular spaces. By convention, the resting membrane potential is defined as the charge inside the cell relative to the extracellular side, in which case the resting potential is a negative charge. An increase in resting membrane potential would therefore designate a more negative intracellular charge (e.g., an increase from −70 to −90 mV), while a decrease in resting membrane potential would designate a less negative intracellular charge (e.g., a decrease from −70 to −50 mV).
2) Depolarization is the loss or decrease in electronegativity of the intracellular space, for example a decrease in membrane potential from −90 to −50 mV (partial depolarization) or from −90 to 0 mV (complete depolarization).
3) Hyperpolarization is an increase in electronegativity of the intracellular space.
4) Inward current is the change in electrical charge across the cell membrane that results from influx of positively charged ions or, alternatively, from efflux of negatively charged ions.

5) Spontaneous depolarization of automatic cells is a physiological and progressive decrease in resting potential during diastole, leading spontaneously to threshold and automatic firing.
6) Threshold potential is the membrane potential required for excitation of the cell, initiating the action potential and affiliated cellular responses.
7) Phase 0 is the rapid depolarization phase of the action potential of the excited cell, mediated by a rapid inward current carried by Na^+ through fast sodium channels of the cell membrane.
8) Phase 1 is the initial early repolarization phase of the action potential.
9) Phase 2 is the plateau phase of the action potential, mediated in part by a slow inward current carried by Ca^{++} through slow calcium channels of the cell membrane.
10) Phase 3 is the rapid repolarization phase of the action potential, returning membrane potential to the diastolic level.
11) Phase 4 is the membrane potential during diastole; it is constant in working muscle cells but undergoes spontaneous depolarization in cells with automaticity.
12) Refractory period is that early and late interval of the action potential during which excitability of the cell is essentially absent (functional refractory period) or depressed (relative refractory period), respectively.
13) Depressed fast sodium ion (Na^+) responses are slowly rising phase 0 depolarizations due either to premature excitation during the relative refractory period of normal cells or excitation of sick cells with low diastolic potentials; depressed fast Na^+ response action potentials develop cardiac impulses that propagate poorly with reduced conduction velocity.
14) Slow Ca^{++} responses are analogous to the slow inward Ca^{++} current during phase 2; this term is used to describe the very slowly rising phase 0 depolarizations mediated by Ca^{++} when the fast Na^+ channels are inoperative. Slow Ca^{++} action potentials develop cardiac impulses that propagate poorly with extremely slow conduction.

When a cardiac cell is stimulated, the electrical potential measured across the cell membrane undergoes a depolarization and repolarization cycle that can be differentiated into five sequential components. These components are referred to as phases 0, 1, 2, 3, and 4 (Figure 22.1). The precise morphology of the 5 phases of the cardiac action potential varies with the anatomic region of the heart. A schematic diagram illustrating the configuration of action potentials derived from sinoatrial (SA) tissue, atrial muscle (AM), Purkinje fibers (PF), and ventricular muscle (VM) is depicted in Figure 22.2 along with corresponding waveforms of the electrocardiogram

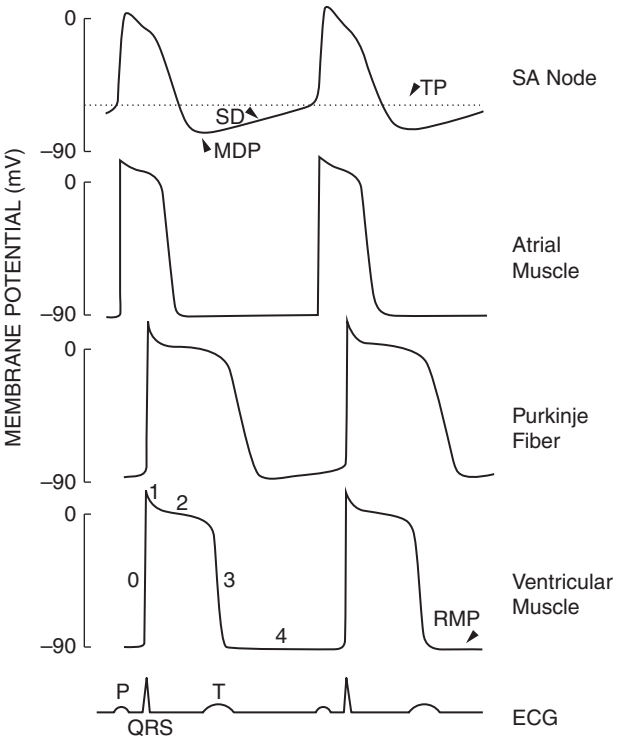

Figure 22.2 Schematic diagrams demonstrating the temporal relationships between transmembrane action potentials recorded from cells of the sinoatrial node (SA), atrial muscle, Purkinje fibers, and ventricular muscle (see text for discussion). Modeled after Trautwein, 1963. Source: Adams, 1986.

(ECG). Action potentials of a sinoatrial pacemaker cell (Figure 22.1B) and a typical working heart muscle cell (Figure 22.1A) will be addressed as examples of cardiac tissue with and without normal automaticity, respectively.

Working heart muscle cells: Electrical diastole is designated by phase 4 of the cardiac action potential (Figure 22.1A); this resting membrane potential is steady at about −90 mV. Polarization across the cell membrane is maintained primarily because of the unequal distribution of K^+ inside and outside the cell. The Na^+,K^+-adenosine triphosphatase transport system maintains high intracellular K^+ relative to extracellular K^+, and the cell membrane is selectively permeable to K^+ during phase 4 diastole when compared to other ions such as Na^+ or Ca^{++}. When the cell is stimulated to its particular threshold level, however, the selective permeability characteristics of the cell membrane to K^+ are momentarily lost. Other ions now cross the sarcolemma and produce the typical depolarization–repolarization cycle that comprises the action potential (Figure 22.1).

Phase 0 of the action potential reflects the extremely rapid depolarization spike produced by Na^+ rushing into

the cell through specific "fast Na^+ channels" or passageways of the sarcolemma. Phase 0 is terminated as early (phase 1) and delayed (phase 3) repolarization occur, restoring the membrane potential to its resting diastolic level of phase 4 (Figure 22.1). The cell is refractory to additional stimuli during the early and intermediate phase of the action potential cycle; it is only partially responsive if stimulated prior to complete repolarization and return to normal phase 4 diastolic potential.

The phase 2 plateau of the action potential partially represents a brief anomalous delay in restoration of K^+ permeability (Figure 22.1). A critically important component of phase 2 comprises an influx of Ca^{++} through specific "slow Ca^{++} channels" or "slow cation channels" of the cell membrane. This slow inward Ca^{++} current is the mechanism whereby membrane excitation is coupled to activation of the contractile elements of heart muscle cells (Parker and Adams, 1977). The influx of Ca^{++} during phase 2 triggers a release of greater amounts of Ca^{++} from intracellular storage sites, and the increased cytosolic Ca^{++} proportionately activates the contractile machinery of the myocardial cells.

Sinoatrial pacemaker cells: Unlike working myocardial cells, automatic cells do not exhibit a clearly definable resting membrane potential during phase 4. Instead, phase 4 is characterized by a slow spontaneous depolarization to threshold potential (Figure 22.1B), thereby discharging automatically and leading into the more rapid depolarization of phase 0. However, the slope of phase 0 depolarization of SA pacemaker cells is much less than that of working muscle cells (Figures 22.1, 22.2). This distinction may be explained by a component of slow Ca^{++} influx in the genesis of phase 0 depolarization in these types of automatic cells (Adams, 1986). Cells with normal automaticity (i.e., spontaneous phase 4 depolarization) also are found in specialized atrial conduction tracts, the distal region of the AV node, AV valves, and PF.

Classification of Arrhythmogenic Mechanisms

The basic mechanisms involved in genesis of cardiac arrhythmias involve abnormalities of impulse formation (i.e., arrhythmias caused by changes in automaticity), impulse conduction (i.e., arrhythmias caused by reentry phenomena), and a combination of automaticity and reentry (Singh et al., 1980; Binah and Rosen, 1984).

Disturbances in Automaticity

The action potential from the SA node, AM, PF, and VM are shown in Figure 22.2. The five phases of the action potential (0, 1, 2, 3, 4) are numbered in the first complex of VM. Notice spontaneous depolarization (SD), maximal diastolic potential (MDP), and threshold potential (TP) in the automatic cells of SA and PF. The resting membrane potential (RMP) is shown in the nonautomatic cells of the AM and VM. The P wave of the ECG corresponds to depolarization of SA and AM, while the QRS complex and T wave correspond to depolarization and repolarization, respectively, of ventricular cells (Figure 22.2).

Automatic cells of the SA node normally are the dominant pacemaker, reaching threshold first with the resultant propagating impulse exciting all other potential pacemaker cells before they spontaneously attain threshold values (Figure 22.2). If automaticity of the SA node is depressed or the spontaneous firing rate in some other tissue (latent pacemaker) is accelerated, regions of the heart other than the SA node may serve as the pacemaker and initiate ectopic impulses. Examples are shown in Figure 22.3.

Automaticity is enhanced when the slope of phase 4 SD is increased (e.g., from a to b in I of Figure 22.3); this decreases the time required to reach TP, thereby increasing the frequency of spontaneous discharge. The result is an increase in heart rate when the SA pacemaker is involved or emergence of ectopic beats if a normally latent pacemaker is involved. By decreasing the slope of spontaneous depolarization (e.g., from b to a or from a to

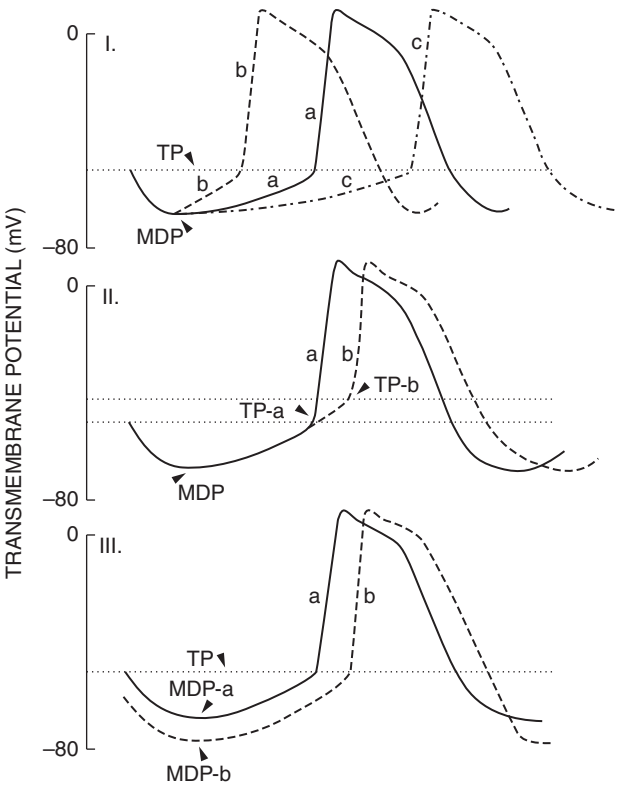

Figure 22.3 Schematic representations of transmembrane action potentials of cardiac cells with the property of automaticity and potential mechanisms whereby antiarrhythmic drugs can influence automaticity (see text for discussion). Source: Adapted from Hoffman and Cranefield, 1960; Mason et al., 1973.

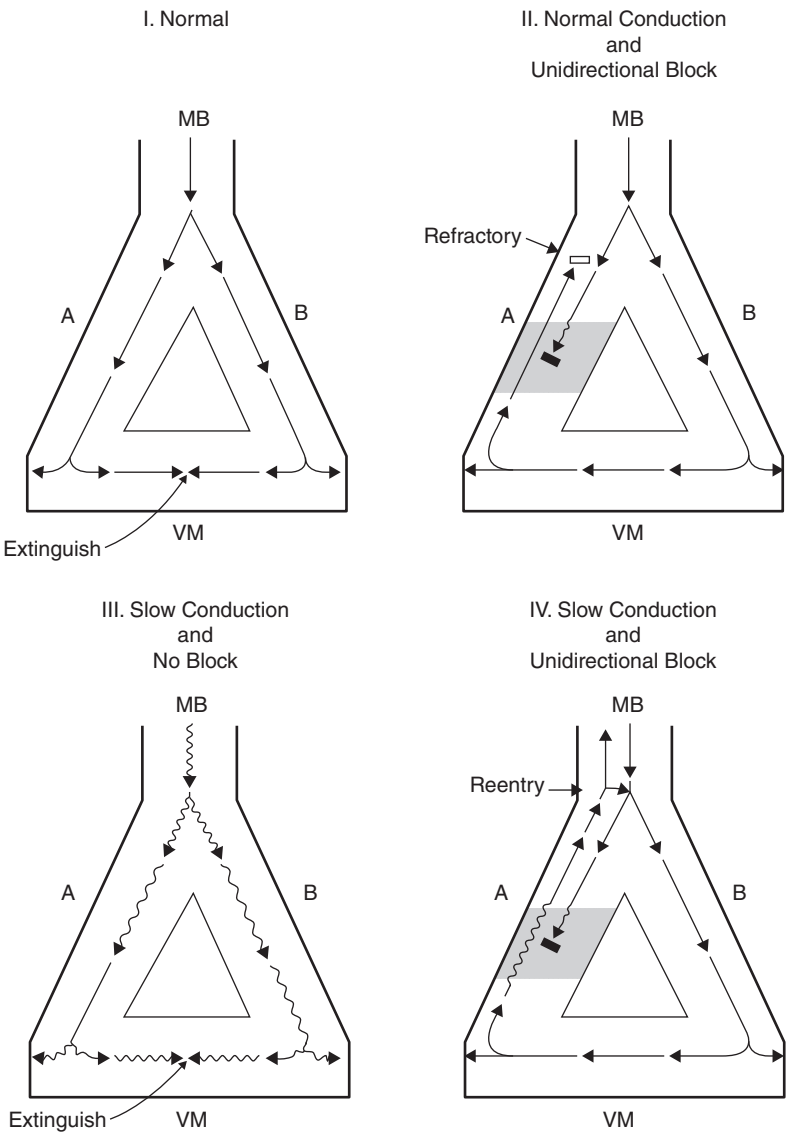

Figure 22.4 Schematic representations of potential mechanisms involved in cardiac arrhythmias caused by reentry phenomena. I. Normal. The cardiac impulse (arrows) exits a main bundle branch (MB) of the Purkinje system and enters terminal Purkinje branches A and B. The impulse uniformly and rapidly excites a segment of ventricular muscle (VM) and would be extinguished within the VM due to refractoriness of the cells just excited. II. Normal conduction and unidirectional block. Because of an area of damaged tissue (shaded area) that blocks antegrade conduction in branch A, the impulse traversing branch B and the VM will excite branch A. The impulse will traverse branch A and the area of unidirectional block through a retrograde pathway; however, since it is conducted at a normally fast speed, it will encounter refractory cells (open square) and be extinguished. III. Slow conduction velocity and no block. Although the cardiac impulse may be conducted at an abnormally slow velocity (wavy arrows), the lack of unidirectional conduction block causes the impulse to arrive at refractory cells and extinguish. IV. Slow conduction and unidirectional block. Same as II but the speed of impulse conduction through the area of unidirectional block (wavy arrows), and perhaps through B and VM as well, is so slow that the impulse encounters cells after their refractory period. Thus the impulse can reenter the conduction pathway, thereby establishing perpetual reexcitation. Modeled after Cranefield, 1973; Mason et al., 1973. Source: Adams, 1986.

c in I of Figure 22.3), drugs can depress ectopic foci and restore normal sinus rhythm without affecting MDP or TP. If a drug raises TP to less negative values (e.g., from TP-a to TP-b in II of Figure 22.3), additional time will be required to reach TP, thereby depressing automaticity. By increasing the MDP (e.g., from MDP-a to MDP-b in III of Figure 22.3), a drug can suppress automaticity because additional time would be required before TP is attained.

Disturbances in Impulse Conduction

Arrhythmias caused by disturbances in impulse conduction are thought to be associated with a phenomenon of reentry or circus movement. The concept of reentry is based on very slow conduction velocity, an area of the heart demonstrating unidirectional block of impulse conduction and perhaps an abnormally brief refractory period (Schmidt and Erlanger, 1929; Wit et al., 1972, 1974). This theory holds that a cardiac impulse can travel circuitously around an anatomic loop of fibers in which slowed conduction velocity and brief refractoriness permit the impulse to arrive at cells that are no longer refractory, thereby permitting perpetual reexcitation.

A schematic demonstration of impulse reentry at a junctional region between PF and ventricular muscle is shown in Figure 22.4 (Adams, 1986). Conduction can be significantly slowed by pathological lesions in the heart tissue. Because of slowed conduction, a reentry stimulus can excite tissue that would have otherwise been refractory. Reentry theoretically could be controlled by a drug that either creates bidirectional block or bidirectional conduction through the region of cells causing the unidirectional block; accelerates speed of impulse conduction, thus returning the impulse to the site of reentry when cells are still refractory; prolongs action potential duration of normal cells, thereby extending their refractory period; or exhibits a combination of the above actions.

Other forms of cardiac electrophysiological disturbances, in addition to primary abnormalities of impulse conduction and automaticity, may be important. Examples include abnormal excitability, early/late afterdepolarizations, and triggered electrical activities. These types of abnormalities overlap mechanistically with disturbances of automaticity and impulse conduction. Arrhythmias arising from primary automaticity and conduction abnormalities are adequate for modeling the classes of antiarrhythmic drugs relative to their effects on cardiac action potential characteristics and arrhythmogenesis.

Antiarrhythmic Drugs

Based on mechanisms described above, particularly with respect to ion conduction across cardiac cell membranes, antiarrhythimic drugs can be classified using the traditional Vaughn Williams classification scheme discussed in Section Electrophysiological Properties of Cardiac Cells. This classification is presented in Table 22.1.

Antiarrhythmic drugs are divided into Classes I to IV in this system. Although the clinical importance of this classification scheme has been debated (see Vaughn Williams, 1992), some familiarity with the system is still of value. Some drugs (e.g., digoxin, anticholinergic agents, vagolytics, sympathomimetics) are not classified by this system.

Class I antiarrhythmics block fast sodium channels in the myocardial cell membrane resulting in a decrease in the upstroke velocity of the action potential in atrial and ventricular myocardium and Purkinje cells. By decreasing the upstroke velocity, class I antiarrhythmics slow conduction velocity in normal and abnormal cardiac tissue. Class I drugs also prolong the refractory period and can be effective at abolishing reentrant tachyarrhythmias. Class I agents have variable effects on repolarization. Some of them prolong repolarization while others shorten it or have no effect. Class I agents are also subdivided into classes IA, IB, and IC based on differences in electrophysiological and antiarrhythmic differences (Keefe et al., 1981).

Class IA antiarrhythmics depress conduction in normal and abnormal cardiac tissue and prolong repolarization. Examples used in veterinary medicine are procainamide and quinidine.

Class IB antiarrhythmics have a greater impact on conduction velocity and effective refractory period in abnormal cardiac tissue than in normal tissue. Additionally, their effect is most profound in Purkinje fibers and they have very little effect on the sinus node, atrioventricular node, or cardiac contractility. Examples used in veterinary medicine are lidocaine and mexiletine.

Class IC antiarrhythmics include encainide and flecainide. They are rarely, if ever, used in veterinary medicine. Flecanide was withdrawn from the market after adverse effects were reported in people.

Class II antiarrhythmics are the β-adrenergic receptor blockers. These include atenolol, propranolol, and sotalol. Sotalol is also considered a Class III due to its unique combination of beta-blocking and potassium channel blocking mechanisms.

Table 22.1 Classification of antiarrhythmic drugs based on mechanism of action: Vaughn Williams classification system. Source: Data from Vaughn Williams, 1984.

Class	Drug	Effect on Na^+ channels	Effect on K^+ channels	Effect on Ca^{++} channels	Effect on action potential
Class Ia	Local anesthetics Procainamide Quinidine	Depresses	Depresses	–	Lengthens action potential Increases refractory period
Class Ib	Local anesthetics Lidocaine Mexiletine	Depresses	Depresses	–	Does not increase refractory period as Class Ia drugs
Class II	β_1-adrenergic blockers Propranolol Atenolol Metoprolol	Depresses	–	Depresses	Suppresses SA, AV node Decreases rate
Class III	Potassium channel blockers Amiodarone Sotalol[a]	–	Depresses	–	Prolongs refractory period Lengthens action potential
Class IV	Calcium-channel blockers Verapamil Diltiazem	–	–	Depresses	Suppresses SA, AV node Decreases rate

[a]Sotalol also has beta-blocking (Class II) properties.

Table 22.2 Dose recommendations for drugs used to treat cardiac arrhythmias

Amiodarone	Dogs: 8–10 mg/kg, orally, twice daily be given for one week and then reduced to 5–10 mg/kg PO once daily thereafter
Atenolol	Dogs: 0.25–1.0 mg/kg, orally, twice daily Cats: 6.25–12.5 mg/dog, orally, twice daily
Atropine sulfate	Dogs and cats: 0.02–0.04 mg/kg, subcutaneously every 4–6 hours, or as a single injection for atropine challenge
Digoxin	Dogs: 0.005 mg/kg, orally, twice daily Cats: 0.008–0.01 mg/kg orally, every 48 hours
Diltiazem	Dogs: 0.5–1.5 mg/kg, orally every 8 hours Cats: 1.75–2.4 mg/kg, orally every 8 hours
Esmolol	0.05–0.1 mg/kg intravenously given slowly
Isoproterenol	1 mg diluted in 500 ml of 5% dextrose of Ringer's solution and infuse intravenously at 0.5–1 ml/min or to effect
Lidocaine	Dogs: 2–4 mg/kg, intravenously Cats: 0.25–0.75 mg/kg, intravenously
Mexiletine	Dogs: 5–7 mg/kg, orally, every 8 hours.
Procainamide	Dogs: 10–30 mg/kg, orally, every 6 hours Cats: 3–8 mg/kg, orally, every 6 hours
Propantheline	0.25–0.5 mg/kg, orally, every 8–12 hours
Quinidine	Horses: 22 mg/kg, via nasogastric tube, every 2 hours until conversion to sinus rhythm, a cumulative dose of 88–132 mg/kg had been administered
Sotalol	Dogs: 1–2 mg/kg, orally, every 12 hours Cats: 1–2 mg/kg, orally, every 12 hours
Terbutaline	Dogs: 1.25–5 mg/dog, orally, every 8 hours Cats: 0.1–0.2 mg/kg, orally, every 12 hours

Class III antiarrhythmics prolong the action potential and increase the refractory period. Examples used in veterinary medicine are amiodarone and sotalol.

Class IV antiarrhythmics are the calcium channel blockers. The most common example is diltiazem.

A practical approach to consider which antiarrhythmic to administer is to begin by diagnosing the rhythm abnormality and selecting a drug based on the underlying heart rate or arrhythmia. Initial therapy should be directed at correcting specific etiologies; for example if serum electrolyte abnormalities are responsible, obviously these should be corrected before an antiarrhythmic drug is introduced. Dose recommendations are provided in Table 22.2.

Bradyarrhythmias

Bradyarrhythmias are arrhythmias with heart rates that are below the normal range. Sinus bradycardia may be due to systemic issues including hypothermia, hypothyroidism, and issues that lead to high vagal tone. Sick sinus syndrome and atrioventricular block are bradyarrhythmias that are typically a result of sinus node or atrioventricular node issues. These arrhythmias may be responsive to drugs that can increase heart rate, termed positive chronotropic drugs. However, if they are not responsive to medical therapy, a pacemaker may be needed.

Two mechanisms for increasing heart rate are to decrease vagal tone (vagolytics) or increase sympathetic tone by stimulation of the β-adrenergic receptors in the sinus or atrioventricular nodes (sympathomimetic adrenergic drugs).

Vagolytics such as atropine and propantheline bromide are commonly used to treat bradyarrhythmias that are a result of high vagal tone. These drugs were introduced in Chapter 8. Atropine is frequently used acutely in anesthetized patients in which a bradycardia is observed. It can also be used to determine how responsive a bradyarrhythmia might be to a vagolytic treatment by doing an atropine challenge. In these cases, atropine may be given at a dose of at 0.4 mg/kg subcutaneously and the heart rate rechecked in 30 minutes. An increase in heart rate after the atropine challenge indicates that the arrhythmia may have a component of high vagal tone and may be responsive to an oral vagolytic or sympathomimetic.

Propantheline Bromide

Mechanism of action and pharmacology: Propantheline bromide is an antimuscarinic agent with similar actions to atropine, but it exists in an oral formulation and may be appropriate for chronic use. Propantheline is primarily metabolized in the gastrointestinal tract and liver and is not completely absorbed after oral administration. There is likely a variable rate of absorption among dogs. Because of the lack of specific information regarding oral absorption and onset of action, it is recommended that each case be closely monitored and doses adjusted as needed.

Side effects, adverse effects, and tolerance: As a vagolytic, propantheline could be expected to lead to sinus tachycardia, increased salivation, and vomiting.

Clinical use: In small animal medicine, propantheline can be used an oral treatment for atropine challenge responsive bradyarrhythmias including sick sinus syndrome and possibly second-degree atrioventricular block. However, it may not be as effective as the sympathomimetics described below and is not used as commonly.

Clinical monitoring: Propantheline is used most commonly to increase heart rate in dogs with bradycardias that are responsive to atropine, and response to therapy is variable (Rishniw and Thomas, 2000). Heart rate and rhythm should be monitored with electrocardiography to monitor for a response to therapy. Owners should be

advised of possible clinical signs including increased salivation and vomiting.

Isoproterenol

Mechanism of action and pharmacology: Isoproterenol is a sympathomimetic, introduced in Chapter 7, that increases heart rate by stimulating both the β_1 and β_2 receptors in the sinus and atrioventricular node. Although an oral form is available, isoproterenol is most commonly used intravenously for short-term treatment. The intravenous form is very rapid acting and the effect is decreased rapidly after discontinuation.

Side effects, adverse effects, and tolerance: As a stimulant of the β receptors, isoproterenol can lead to tachycardia, increased contractility, hypotension, and arrhythmias, particularly if underlying heart disease is present. However, the side effects will be rapidly reduced after decreasing the dose or by discontinuing the infusion. Although chronic administration is unlikely, long-term exposure can induce congestive heart failure in dogs.

Clinical use: Isoproterenol can be given intravenously for patients with emergency bradycardias (atrioventricular block, sick sinus syndrome) while waiting for surgical intervention with a pacemaker.

Clinical monitoring: Isoproterenol can lead to hypotension as well as cardiac arrhythmias; therefore, blood pressure monitoring and continuous electrocardiography should be performed for the duration of infusion. This also helps determine if the dose should be adjusted for an improved heart rate response.

Tachyarrhythmias

Sinus Tachycardia

Sinus tachycardia is typically a response to low blood pressure, pain, sepsis, fever, or low cardiac output. Note that many of these are systemic issues rather than a primary cardiac issue and do not require specific antiarrhythmic drug treatment. Sinus tachycardia can also be associated with congestive heart failure as a response to low cardiac output. Because sinus tachycardia is most commonly a sign of underlying systemic or cardiac disease, the primary cause should be addressed by correcting underlying problems. Treatments include administration of fluids if needed to correct blood pressure, considering pain relief, and if the sinus tachycardia is secondary to low cardiac output and heart disease, treating the heart disease with cardiac drugs including pimobenden and angiotensin-converting enzyme inhibitors (ACE-inhibitors) as indicated and fully discussed in Chapter 21.

Supraventricular Tachyarrhythmias

In small animals, supraventricular tachyarrhythmias are usually caused by primary cardiac disease and secondary atrial enlargement, and are not likely to completely resolve with antiarrhythmic drug treatment. Therefore, treatment is directed at slowing the rapid conduction through the atrioventricular node with one of three options: digitalis, a calcium channel blocker or a β-adrenergic receptor blocker.

Digoxin

Mechanism of action and pharmacology: Digoxin's mechanism as an antiarrhythmic is predominantly due to a parasympathetic effect (vagomimetic effect) on the sinus node, atrioventricular node and atrial tissue. This class of drugs has been extensively discussed in Chapter 21. This impact slows conduction through the atrioventricular node and increases vagal tone to the ventricle (Ettinger, 2010). The pharmacokinetics have been described in several veterinary species, which has defined the distribution, elimination, and recommendations for dosage regimens. The dose of digoxin is based on the animal's lean body weight because it is preferentially distributed to muscle instead of fat. It is metabolized by the liver and excreted by the kidney. Dose adjustments based on clinical monitoring should be done in patients with both cardiac and kidney disease.

Adverse effects, adverse effects, and tolerance: The most common clinical signs are gastrointestinal and include nausea, loss of appetite, vomiting, and diarrhea. Cardiac arrhythmias may also develop including atrioventricular block, ventricular premature complexes, and tachycardia. Hypokalemia can exacerbate the toxicity.

Clinical use: The most common antiarrhythmic use of digoxin is for the treatment of supraventricular tachycardia by slowing conduction through the atrioventricular node and slowing the ventricular response rate. However, in many cases, the reduction in heart rate is not significant to have clinical importance and it may be necessary to add on a Class IV (calcium channel blocker), typically diltiazem, or a Class II (β-adrenergic receptor blocker), typically atenolol (Gelzer et al., 2009). In cases with congestive heart failure or significant myocardial dysfunction, it may be reasonable to first give digoxin to decrease the heart rate since it is also a positive inotrope (diltiazem and atenolol are negative inotropes). Once the heart disease is more stable, atenolol or diltiazem may be added

on to improve the heart rate reduction and to obtain a target rate closer to 150 beats per minute.

Clinical monitoring: As mentioned in Chapter 21, there is tremendous patient variability for digoxin toxicity and individual patient factors including obesity, ascites, hypoalbunimea, renal disease, and thyroid status can all be involved (Merrett, 2000). Due to the difficulty in predicting digoxin toxicity, it is prudent to measure serum levels 10–14 days after starting digoxin. Samples should ideally be drawn 6–8 hours postadministration. Most clinicians aim for a target range of 0.8 – 1.2 ng/ml for dogs (Trepanier, 2013), although some dogs may show clinical signs of toxicity even within the therapeutic range and others will not act at all toxic even when their level is above this range. There is anecdotal evidence that management of atrial fibrillation requires higher concentrations than for treatment of heart failure, but this has not been confirmed through clinical trials. If signs of toxicity develop, digoxin should be completely discontinued for 48 hours before restarting at half of the previous dose. Cats can be particularly sensitive to digoxin and should be started at the low end of the dose. Fortunately, cats infrequently develop significant supraventricular tachycardia and the use of digoxin for this purpose in the cat is relatively uncommon. Digoxin is also used in horses but most commonly in combination with quinidine for the treatment of atrial fibrillation. Since individual animals have such variation in the likelihood of the development of toxicity, owners should always be advised of possible clinical signs of toxicity so that they can watch them if they develop before serum levels are measured.

Calcium Channel Blockers

Mechanism of action and pharmacology: In veterinary medicine, both verapamil and diltiazem are calcium channel blockers (Class IV agents, Table 22.1) that have been used for their antiarrhythmic activity. However, diltiazem is used more commonly due to a much lower level of effects. Diltiazem is an L-type calcium channel blocker that works by inhibiting the transmembrane influx of extracellular calcium ions into myocardial cells and vascular smooth muscle without altering serum calcium concentrations (Tidholm, 2010). It slows the sinus node depolarization rate as well as atrioventricular node conduction and depolarization rate. It can have a use-dependent rate and therefore has a more profound ability to decrease the ventricular rate with faster heart rates (Pariaut, 2014).

Side effects, adverse effects, and tolerance: Adverse effects of diltiazem are fairly rare in the dog although bradycardia and atrioventricular block could develop. In cats, gastrointestinal signs, including vomiting and anorexia have been observed, but are fairly uncommon. Diltiazem is a negative inotrope by virtue of the Ca^{++} channel blockade. This action could potentially produce cardiac decompensation if administered to animals with significant myocardial dysfunction. However, this is uncommon.

Clinical use: As an antiarrhythmic, the most commonly used calcium channel blocker for veterinary medicine is diltiazem and it is used most commonly to treat supraventricular tachycardia.

Clinical monitoring: Diltiazem is used primarily to slow the ventricular response rate in supraventricular tachycardia so assessment of heart rate is important to determine if the effective dose is being provided. An in-house electrocardiogram for 3–5 minutes is an inexpensive way to occasionally monitor the heart rate and rhythm, but it may not give an accurate representation of the resting heart rate when the animal is relaxed in a home setting. Therefore, many clinicians prefer to monitor heart rate control with a 24-hour Holter monitor after 10–14 days of treatment.

Beta-Adrenergic Receptor Blockers

Beta-adrenergic receptor blockers (beta-blocker, Class II agents, Table 22.1) are predominantly used as an antiarrhythmic for supraventricular tachycardias, although they may be helpful in some cases for treating ventricular tachyarrhythmias particularly if sympathetic tone is involved. Additionally, sotalol, a combination beta-blocker and potassium channel blocker (Class II and Class III agent, Table 22.1) is a very effective ventricular antiarrhythmic.

For treatment of supraventricular arrhythmias, beta-blockers are most commonly used to alter the electrophysiological properties of the atrioventricular node and to decrease the ventricular response rate. Additionally they can prolong the time that the atrioventricular junction is refractory to further stimulation, which is particularly helpful to disrupt reentrant circuits that use the atrioventricular node as part of the reentry circuit.

Beta-blockers are classified according to the β-adrenergic receptors that they block (see Chapters 6 and 7). Beta-blockers can selectively block the β_1 receptors, or nonselectively block both β_1 and β_2 receptors, or partially block β_1 receptors. The most commonly used selective beta-blocker for supraventricular tachycardia in veterinary medicine is atenolol. Esmolol, also a selective β_1-blocker, has a very short half-life and can be given intravenously to disrupt very rapid supraventricular tachycardias. Sotalol is a combination beta-blocker and potassium channel blocker that can be used effectively for both supraventricular and ventricular tachycardias. A few other beta-blockers are used in veterinary medicine

for their negative inotropic effect or for cardioprotective strategies, including propranolol, metoprolol, and carvedilol. These are much less commonly used as antiarrhythmics.

Atenolol

Pharmacology: Atenolol is a specific β1-adrenergic blocking drug.

Side effects, adverse effects, and tolerance: Very high doses of atenolol can produce bradycardia although this is uncommonly observed. Due to its β-receptor blocking effects, atenolol is a negative inotrope and could exacerbate heart failure or myocardial dysfunction in patients with low cardiac reserve. It should be administered cautiously when these issues are present.

Clinical use: Atenolol is most commonly used in conjunction with digoxin to slow the heart rate in patients with atrial fibrillation or other rapid supraventricular tachycardias.

Clinical monitoring: As for diltiazem, ideally a Holter monitor would be used to monitor heart rate control after 10–14 days of treatment.

Esmolol

Pharmacology: Esmolol is an ultrashort-acting (half-life <10 minutes) β_1 blocker used commonly for intravenous administration. Steady state β-blockade is produced within 10–20 minutes after starting intravenous administration of esmolol in dogs. After discontinuation of drug administration, no detectable β-blockade is apparent at 20 minutes postinfusion, regardless of the dose administered.

Side effects, adverse effects, and tolerance: Esmolol can cause sinus bradycardia and decrease myocardial function so it should be used with care in patients with congestive heart failure or underlying systolic function. Additionally, it can sometimes stop the tachyarrhythmia quite abruptly leading to sinus arrest so careful monitoring is warranted while infusing.

Clinical use: As an antiarrhythmic, esmolol is primarily used for acute termination of very rapid supraventricular tachycardias.

Clinical monitoring: A continuous electrocardiogram should be monitored while infusing esmolol to observe for the onset of bradycardia or acute discontinuation of the supraventricular arrhythmia. An advantage of esmolol is that the half-life is very short; therefore, if adverse effects are observed, termination of the infusion will ordinarily result in attenuation of effects quickly. In cases of the abrupt occurrence of sinus arrest, sometimes epinephrine is needed to increase the sinus rate.

Sotalol

Mechanism of action and pharmacology: Sotalol is a nonselective beta-blocker and potassium channel blocker (Class II and Class III; Table 22.1).

Side effects, adverse effects, and tolerance: As for any beta-blocker, the heart rate is expected to decrease with sotalol administration. It also prolongs the AV nodal refractory period and the PR interval because of its beta-blocking effect and can sometimes produce mild atrioventricular block. Because it is a beta-blocker, a decrease in myocardial contractility is expected but it should not produce adverse effects in patients with normal heart function. Additionally, as an antiarrhythmic, sotalol does have a potential to be proarrhythmic although this would appear to be fairly uncommon in comparison to some of the older antiarrhythmics such as procainamide.

Clinical use: As a beta-blocker and potassium channel blocker sotalol is effective for both supraventricular and ventricular tachyarrhythmias and can be particularly helpful for patients with both types of arrhythmias.

Clinical monitoring: Ideally a 24-hour Holter monitor should be performed after 10–14 days of treatment to evaluate the efficacy and the heart rate control.

Ventricular Tachycardia

The efficacy of an antiarrhythmic on a ventricular tachyarrhythmia likely depends on the mechanism of the arrhythmia. The most likely possible mechanisms for ventricular arrhythmia development include reentry, and triggered and abnormal automaticity. Unfortunately, the mechanism of the arrhythmia cannot be detected from the clinical aspects of a case and it is not possible to select the antiarrhythmic based on a known mechanism for arrhythmia development. Instead, the antiarrhythmic is typically selected from a small number of available antiarrhythmics with tolerable safety profile.

The goals of treating a ventricular tachyarrhythmia are to decrease the number of abnormal ventricular complexes, as well as the complexity of the arrhythmia, and to hopefully reduce clinical signs (generally syncope) and the risk of sudden cardiac death. The most commonly used ventricular antiarrhythmics (sotalol and mexiletine) are effective at reducing the number of ventricular premature complexes (VPCs) and the complexity of the

arrhythmia, and some veterinary cardiologists believe that they do decrease episodes of syncope. However, the overall effect of the antiarrhythmics on preventing sudden cardiac death in veterinary medicine is undetermined.

Procainamide

Mechanism of action and pharmacology: Procainamide is a Class IA antiarrhythmic that decreases myocardial excitability, slows conduction velocity, and prolongs refractory period in the atria, ventricles and His-Purkinje system. In humans and other animals, when procainamide is metabolized, an active metabolite is formed, *N*-acetylprocainamide (NAPA), which has moderate antiarrhythmic effects (Class III antiarrhythmic effects). Dogs are the only mammals that do not produce this metabolite (Papich et al., 1986), which may explain why higher concentrations and higher doses are needed to control arrhythmias compared to people.

Side effects, adverse effects, and tolerance: Procainamide can be proarrhythmic. In one canine study, 50% of the dogs showed an increase in VPC number after 14–21 days of oral procainamide (Meurs, 2002). Procainamide can also have mild negative inotropic effects, but this is rarely a clinically significant issue unless the patient has underlying myocardial disease. Other adverse effects can include gastrointestinal signs (vomiting, diarrhea), widening of QRS and QT intervals, and hypotension. Adverse effects are usually dose related. An important adverse effect in people from procainamide is drug-induced lupus. People who are slow metabolizers have a higher incidence of this adverse effect, but it has not been reported in dogs. People are also susceptible to arrhythmias related to long Q-T syndromes, which can be serious (Class III antiarrhythmic effect). Because of these problems in people, the drug is rarely, if ever, used in human medicine and most dosage forms are no longer available.

Clinical use: Procainamide has been used for treatment of ventricular and supraventricular arrhythmias. However, because of serious adverse effects noted above, particularly the proarrhythmia aspect, it is rarely the first choice for either. It can be used to treat very rapid ventricular arrhythmias in which an intravenous route for dosing may be needed, but it should be injected slowly over 10–20 minutes and has a wide dosing range. Therefore, it is usually the second choice for acute treatment of ventricular tachyarrhythmia in comparison to lidocaine (see Section Lidocaine).

Clinical monitoring: Due to the proarrhythmic effect that can be observed, a continuous electrocardiogram should be monitored during infusion of the intravenous form. If the oral formulation is used, a 24-hour Holter monitor should be evaluated after 14–21 days of therapy to make sure that the arrhythmia has improved and not become worse.

Quinidine

Quinidine is now rarely used in small animals. Its primary use in veterinary medicine at this time is for management of atrial fibrillation in the horse.

Mechanism of action and pharmacology: Quinidine is a Class IA antiarrhythmic that decreases the rate of phase 0 depolarization of cardiac cells and also decreases the slope of spontaneous depolarization of Purkinje fibers. Its main benefit for atrial fibrillation is its ability to prolong the effective refractory period of atrial muscle but it also can prolong the effective refractory period of ventricular muscle with relatively less effect on the refractory period of normal pacemaker cells. The capability of quinidine to directly prolong the refractory period of atrial fibers is thought to account for its ability to convert atrial fibrillation to sinus rhythm. However, quinidine also has an atropine-like activity (vagolytic) that leads to improved AV conduction. Therefore, a complication of using quinidine for treating supraventricular tachyarrhythmias is that it can actually result in an increase in ventricular rate before the atrial dysrhythmia itself is controlled. This characteristic seems to be particularly prevalent when quinidine is administered by the intravenous route.

Side effects, adverse effects, and tolerance: The most common side effects of quinidine are cardiovascular and gastrointestinal and can be quite dramatic requiring careful monitoring of horses being treated with the drug. Cardiovascular effects include hypotension, prolongation of the QRS and QT complex, arrhythmias, and decreased contractility. Horses with concurrent systolic dysfunction could advance into congestive heart failure because of effects on myocardial function. Tachyarrhythmias, including both supraventricular and ventricular, and subsequent sudden death have been reported. Quinidine can also lead to urticarial wheals, colic like symptoms, inflammation of the nasal mucosa with respiratory difficulty, and laminitis (Detweiler, 1977). Quinidine is also a well-known inhibitor of P-glycoprotein, a membrane pump that can be important for clearance of some drugs (Fromm et al., 1999). This interaction is attributed to causing the increased (and potentially toxic) concentrations of digoxin when the drugs are administered concurrently. Because of the well-known effects of quinidine on P-glycoprotein, this drug is often considered as a probe to investigate P-glycoprotein-mediated drug interactions.

Clinical use: The primary use of quinidine is for the treatment of atrial fibrillation in horses (Reef et al., 1995). The use in small animals has declined because of lack of oral dosage forms and adverse effects. When used in horses, quinidine is typically administered via nasogastric tube every 2 hours until conversion to sinus rhythm or a cumulative dose of 88–132 mg/kg, or adverse or toxic effects from the drug. Because of the risk of tachyarrhythmias, increased atrioventricular conduction and decreased contractility, digoxin should be administered before quinidine treatment if the horse has evidence of systolic dysfunction, was prone to tachycardia or had a previous history of sustained tachycardia. Digoxin will help slow atrioventricular conduction and control the ventricular rate in atrial fibrillation and flutter. However, care should be exercised in the concomitant use of digoxin and quinidine, since the latter may substantially increase the plasma concentration of the former (Leahey et al., 1978; Fromm et al., 1999). A study has suggested that addition of digoxin to quinidine might improve the atrial fibrillation conversion rate (Lotstra et al., 2015).

Clinical monitoring: The significant clinical signs that can be observed with quinidine lead to a the need for significant monitoring while treating, including blood pressure monitoring, electrocardiography for evidence of arrhythmias or prolongation of the QRS and QT complexes, and measurement of quinidine levels. The detection of significant adverse effects should lead to discontinuation of quinidine and measurement of a plasma quinidine level.

Lidocaine

Lidocaine is perhaps the most common agent administered IV for acute treatment of ventricular arrhythmias.

Mechanism of action and pharmacology: Lidocaine is a Class IB antiarrhythmic that acts to decrease the rate of ventricular firing, action potential duration and absolute refractory period, and increasing relative refractory period. It has very little effect on atrioventricular node or His-Purkinje conduction. It has a very rapid onset (within a few minutes) when given as an intravenous bolus and can last for more than 10 minutes. However, if continued use is indicated, a continuous rate infusion (CRI) can be provided. To avoid the time to reach steady-state concentrations in dogs, a loading dose may be administered (2–4 mg/kg IV) followed by a CRI of 25–75 µg/kg per minute IV. Lidocaine has a very high first-pass metabolism in the liver and is not effective if administered orally. Mexiletine (discussed in Section Mexiletine) is chemically modified to avoid the first-pass effects and can be administered orally.

Side effects, adverse effects, and tolerance: The side effects of lidocaine are most frequently neurological including depression, seizures, and vomiting, particularly at the high end of the dose. Since it is so short acting, the signs usually resolve once the CRI is discontinued. If clinical signs are severe, the infusion should be decreased or discontinued. If seizures develop they can generally be controlled with diazepam but they usually resolve as soon as the lidocaine infusion rate is decreased or discontinued. If further treatment is indicated, it may be worth considering a change to a different intravenous ventricular antiarrhythmic like procainamide. Cats tend to be much more sensitive to the neurological and cardiac effects of lidocaine and its use in this species is not recommended by cardiologists.

Clinical use: Lidocaine is most useful for acutely converting a ventricular arrhythmia to sinus rhythm. Lidocaine is most effective when the serum potassium level of the patient is at the high normal range; therefore, potassium supplementation should be considered for optimal efficacy if the patient is hypokalemic. However, lidocaine is not useful for chronic therapy since it cannot be given orally, so if continued antiarrhythmics are needed, it is necessary to change to an oral antiarrhythmic such as sotalol or mexiletine. Because of the rapid onset and offset of action of intravenous lidocaine, the first and second dose of the oral antiarrhythmic is often given before discontinuing the intravenous lidocaine. This allows the new antiarrhythmic to begin to develop effective serum levels before removing the lidocaine.

If a ventricular arrhythmia is poorly responsive to lidocaine, consider reevaluation of the serum potassium level and possible supplementation since potassium levels should be in the high normal range for maximum lidocaine effect. Additionally, sometimes decreased levels of myocardial magnesium may be associated with ventricular arrhythmias and magnesium supplementation may be helpful. Finally, since the efficacy of an antiarrhythmic is often dependent on the underlying mechanism of the arrhythmia (which is rarely known), it is sometimes prudent to switch to a different antiarrhythmic. If the response to lidocaine appears to be insufficient and the potassium level is appropriate, it may be reasonable to consider switching to intravenous procainamide.

Another clinical use of lidocaine is to treat pain syndromes and intestinal postoperative ileus in horses (Malone et al., 2006). The effect is likely not via a prokinetic action on the intestine (Milligan, et al., 2007), but by improving repair of the intestinal mucosa in the postoperative period. Lidocaine is also included in clinical infusion protocols, often combined with other agents such as ketamine and morphine ("MLK") to treat perioperative pain.

Clinical monitoring: A continuous electrocardiogram should be observed while treating with lidocaine to observe for efficacy. Additionally, the patient should be observed for neurological signs.

Mexiletine

Mechanism of action and pharmacology: Mexiletine is similar to lidocaine in that it inhibits the inward sodium current and reduces the rate of rise of the action potential. Mexiletine can also interrupt reentry circuits by slowing conduction and depressing membrane responsiveness.

Side effects, adverse effects, and tolerance: Mexilitine can cause similar neurological effects to lidocaine including nausea, anorexia, vomiting, and depression, as well as bradycardia. As with all antiarrhythmics, it can be proarrhythmic but this appears to be quite uncommon. However, overall mexiletine is actually very safe has become a popular and effective ventricular antiarrhythmic. The most common adverse effect noted in animals is gastrointestinal with some mild loss of appetite or vomiting. Cardiologists have observed that giving mexiletine with at least a small meal may alleviate these gastrointestinal effects.

Clinical use: Mexiletine is most useful for chronic management of ventricular arrhythmias and appears to be able to reduce both the number of ventricular premature beats as well as the complexity (runs, bigeminy, etc.) of the arrhythmia. However, in cases that are refractory to management with mexiletine, success is frequently achieved by combination therapy with sotalol. Since mexiletine and sotalol are in different classes of antiarrhythmics they have different mechanisms of action and appear to have a synergistic effect when given together. One of the adverse electrophysiological effects of sotalol is increased action potential duration (Class III effect) and mexiletine may also counteract the adverse effects of sotalol on the action potential duration.

Because it suppresses sodium channels in activated neurons, another use of mexiletine in people – but not reported in animals – is its use for treating chronic pain. It is used to treat pain caused by diabetic neuropathy and nerve injury and much lower doses than the antiarrhythmic dose.

Clinical monitoring: Ideally a 24-hour Holter monitor should be performed after 10–14 days of treatment to monitor for efficacy. The goal would be to have at least an 85% reduction in VPC number and a reduction in complexity (for example, from runs to singles).

Amiodarone

Mechanism of action and pharmacology: Amiodarone is classified as a Class III antiarrhythmic agent (Table 22.1) that prolongs action potential duration and refractory period. It has a high degree of side effects and is typically reserved for use in very difficult to treat arrhythmias that are not responsive to sotalol, mexiletine, or the combination of both. Amiodarone can be used to treat both supraventricular and ventricular tachycardias.

Amiodarone is a complex antiarrhythmic that shows properties of all four of the main classes. It is structurally related to levothyroxine and has high iodine content. It is metabolized to desethylamiodarone in the dog. Desethylamiodarone has important antiarrhythmic effects because of its ability to block fast sodium channels. Amiodarone has unusual pharmacokinetics. After repeated administration, the drug has a long half-life of 3.2 days in the dog. It is very lipophilic and accumulates in adipose tissue up to 300 times the plasma concentration. Once drug administration is discontinued, amiodarone is cleared rapidly from all tissues except adipose tissue. Although it can be given intravenously as well as orally, it is most commonly given orally.

Side effects, adverse effects, and tolerance: Amiodarone can have a number of adverse effects including anorexia and vomiting. Additionally, quite severe cases of neutropenia, thrombocytopenia, and hepatotoxicity have been observed. In many cases, the adverse effects are thought to be dose related and reversible if discontinued early enough, although some deaths have been reported (Kraus et al., 2009). There are reports that Doberman dogs are more prone to adverse effects than other breeds. Alternatively, the adverse effects in dogs may be caused by the drug vehicle, Polysorbate 80, which is known to elicit allergic-like adverse reactions in dogs caused by histamine release. Pretreatment with antihistamines can be considered if these adverse effects are observed.

Clinical use: Amiodarone has been used to treat both atrial fibrillation and ventricular tachyarrhythmias in the dog (Saunders et al., 2006) and atrial fibrillation in horses. However, due to the frequency of significant adverse effects, including hepatotoxicity and neutropenia, which require careful monitoring, amiodarone is often withheld for the treatment of refractory arrhythmias that are not responsive to the safer antiarrhythmics, including sotalol or mexiletine, alone or in combination.

Clinical monitoring: Careful monitoring of liver enzymes, white blood cell and platelet counts should be done on a regular basis with consideration of discontinuing amiodarone if the liver enzymes are elevated or cell counts are down. Amiodarone serum level measurement

is available, although how to use this to guide therapy in veterinary medicine is not yet well understood. A 24-hour Holter monitor should be performed after 10–14 days of treatment to monitor for efficacy.

Sotalol

Mechanism of action and pharmacology: As described above in Section Supraventricular Tachyarrhythmias, sotalol is a nonselective, weak beta-blocker and potassium channel blocker (Class II and III; Table 22.1). It is also very effective for treating ventricular tachyarrhythmias.

Side effects, adverse effects, and tolerance: Sotalol can prolong the AV nodal refractory period and the PR interval and can sometimes lead to mild atrioventricular block. Because it is a β-blocker, a decrease in myocardial contractility is expected but is uncommon, particularly in patients with normal heart function. Additionally, as an antiarrhythmic, sotalol does have a potential to be proarrhythmic although this is fairly uncommon.

Clinical use: For ventricular arrhythmias it has been shown to decrease the number and complexity of ventricular arrhythmias as well as syncope (Meurs, 2002). It is a very effective and safe ventricular antiarrhythmic for veterinary medicine. It is frequently given in conjunction with mexiletine for refractory arrhythmias.

Clinical monitoring: Ideally a 24-hour Holter monitor should be performed after 10–14 days of treatment to monitor for efficacy.

Conclusion

Although in many cases cardiac arrhythmias have no clinical importance and do not require treatment, cardiac arrhythmias can lead to the development of significant clinical signs including sudden cardiac death and do sometimes require antiarrhythmic therapy. The decision to treat a cardiac arrhythmia with an antiarrhythmic should be based on many factors including heart rate, type of arrhythmia, presence or absence of clinical signs such as syncope or exercise intolerance, and presence of underlying heart disease. Although there are many antiarrhythmics, only a small number have been well studied and shown to be effective and safe in veterinary medicine. Selection of the antiarrhythmic should be based on the type of arrhythmia, risk of clinical signs, and side effects of the available antiarrhythmics. The perfect antiarrhythmic does not exist and it may be necessary to try more than one, and to consider combinations when appropriate.

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23

Principles of Acid–Base Balance: Fluid and Electrolyte Therapy, Blood Substitutes

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Composition and Distribution of Body Fluids

Units of Measure

The units of measure commonly utilized in discussion of fluid balance are presented in Table 23.1. Ions or electrolytes combine according to valence (charge) rather than molecular weight. Hence in the case of univalent ions, 1 mM = 1 mEq. One mM of a divalent ion provides 2 mEq. By expressing most electrolyte concentrations in milliequivalents per liter (mEq/l), and comparing the concentration of cations to anions in the body, it becomes clear that electroneutrality exists. Although extracellular cations are often more completely documented in the course of clinical investigations, anions, particularly chloride and bicarbonate, are the electrical counterbalance. Some electrolytes are measured in millimoles per liter (mM/l) because they exist in variable states of protein binding or valence. An example is total calcium, because protein binding confounds any simple assessment of ionized fraction. Phosphorus exists in variable proportions of phosphate and monohydrogen and dihydrogen phosphate, so no valence can be assigned and calculation of milliequivalence is therefore inaccurate. Since mEq/l are the most common and informative unit of comparison for most electrolytes, conversion formulas are also provided in Table 23.1.

Solutes exert an osmotic effect in solution that is dependent only on the number of particles in solution, not on molecular weight or valence. Hence for nondissociable substances, 1 osmole contains 1 mole of substance. If a substance dissociates in solution, the number of osmoles is increased according to the number of particles generated per mole of dissociated substance. For example, each mmol of a completely dissociated NaCl solution yields 2 mOsm. Osmolarity refers to the number of osmoles per liter, and osmolality indicates the number of osmoles per kilogram of solvent (Rose, 1989). In physiological systems the difference between these two is usually small. The concept of osmolality explains why solutions of diverse chemical and electrical composition (e.g., 5% dextrose, 0.9% NaCl, and 1.3% sodium bicarbonate) can all be considered isotonic. For mammals, isotonic solutions equal approximately 300 mOsm.

Body Fluid Compartments

Semipermeable membranes separate most body compartments, allowing the free passage of water and selected solutes. The effective osmolality, or tonicity, of a solution is related to the ability of a solute to attract water and to sustain an increase in osmotic pressure as a result of water movement. For example, two substances with equal ability to attract water down a concentration gradient and across a semipermeable membrane may have very different effects on osmotic pressure, depending upon the movement of the substance itself through the semipermeable membrane. While the measured osmolality of a solution includes all osmoles, whether effective or ineffective, tonicity of a solution relates only to effective osmolality. For example, a solution containing 300 mOsm of nonpenetrating NaCl and 100 mOsm of urea, which can cross plasma membranes, would have a total osmolarity of 400 mOsm and would be hyperosmotic. However, if one put red blood cells in this solution, they would not shrink or swell, because the urea would diffuse into the cells and reach equilibrium inside and outside the cells. Thus, both extracellular and intracellular solutions would have the same osmolarity. There would be no difference in the water concentration across the membrane and no change in cell volume. The solution is therefore considered isotonic.

Ultimately all fluids within the body are in dynamic equilibrium, but it is helpful during fluid therapy to consider body water as existing in several compartments since critical fluid shifts can and do occur. Determination of the volumes of these compartments is problematic, as can be deduced from the large number of different methods that have been used to estimate these volumes (Kohn and DiBartola, 1992). The most common method for assessment of volume in body fluid compartments

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Companion Website: www.wiley.com/go/riviere/pharmacology

Table 23.1 Units of measure and conversions commonly used in fluid therapy

Term	Abbreviation	Description and conversion
Molecular (formula) weight	MW	Sum of atomic weights of all elements in a chemical formula
Millimole	mmol (mM)	Molecular (formula) weight of a substance in mg, equals 1 mM
Milliequivalent	mEq	Weight, in mg, of an element that combines or replaces 1 mg (1 mmol) of hydrogen (H^+)
Milliosmole	mOsm	Always contains 6.0×10^{23} molecules and equals 1 mmol of a nondissociable substance
Milliequivalent per liter	mEq/l	= mmol/l × valence = [(mg/dl × 10)/MW] × valence

depends upon intravenous administration of a known amount of a dye or radioisotope-tagged substance that distributes only in the compartment of interest. This is followed by assessment of dye or radioisotope concentration in the compartment. Ideally, the indicator substance must distribute rapidly and homogeneously, remain in the space to be measured, not be metabolized or bound, and be nontoxic. The volume of distribution (Vd) of a drug, or in this case a volume marker, may be derived according to the same principles of pharmacokinetics described in Chapter 3.

Total body water (TBW) is approximated at 60% of body weight, but this figure varies from 50 to 75% depending upon age, lean body mass, and individual animal variations. Since fat is lower in water content than lean tissue, obesity is associated with decreased TBW (approximately 50%). To avoid overhydration of obese patients, fluid requirements are best estimated based on lean body mass. Very young animals are about 70–75% water, with TBW declining with advancing age. Table 23.2 provides estimates of selected volumes in dogs. TBW is broadly divided into two types: intracellular (ICF) and extracellular fluid (ECF). The ECF is further divided into four subcompartments: plasma volume, interstitial lymph fluid, transcellular fluid, and fluid present in dense connective tissue and bone. Table 23.3 provides experimentally derived blood volumes as percentages of body weight for various species.

Transcellular fluid is found in diverse locations, including cerebrospinal fluid, pleural cavity, gastrointestinal tract, bladder, synovia, aqueous humor, and peritoneal cavity. Transcellular volumes vary greatly from monogastrics (1–6%) to horses and ruminants (10–15%), dependent largely upon the amount of fluid sequestered in the gastrointestinal tract. Transcellular volumes are not readily mobilized during volume deficits but are of importance in terms of drug disposition and equilibrium. In certain disease processes, transcellular fluids may accumulate, causing ascites, hydropericardium, hydrothorax, synovitis, or other conditions, depending on the location of fluid accumulation.

Fluid and Electrolyte Distribution

Body solutes are not distributed homogeneously throughout TBW. Like drugs, every solute has a defined space or volume of distribution that can be assessed experimentally. As with estimation of body compartment volumes, determination of solute distribution is limited by the features of the labeled solute used. Because

Table 23.2 Approximate volumes of selected fluid compartments in the dog. Source: Data from Kohn and DiBartola, 1992.

Compartment	% Body weight	Method
Total body water (TBW)	60	Indicator substance
Extracellular fluid (ECF)	20–27	Indicator substance
Red blood cells (RBC)	3	Counted + calculations
Plasma volume (PV)	5	Indicator substance
Total blood volume (BV)	5.7–10	Calculated: RBC volume + PV
Interstitial lymph fluid	15	Calculated: ECF − BV
Transcellular fluid	1–6	Estimated
Bone and dense connective tissue	5	Estimated
Intracellular fluid (ICF)	33–40	TBW − ECF

Table 23.3 Approximate values for blood volumes of various animals expressed as percentages of body weight. Values represent averages from approximately 30 references.

Species	Total blood volume	Plasma volume	RBC volume
Dogs	8.5	4.5	4.0
Cats	6.7	4.7	2.0
Chickens	6.5	4.5	2.0
Cattle	5.7	3.8	1.9
Goats	7.0	5.4	1.6
Horses			
Draft	7.0	4.0	3.0
Thoroughbred	10.0	6.0	4.0
Saddle	7.7	5.2	2.5
Pigs	7.5	4.8	2.7
Sheep	6.5	4.5	2.0

Table 23.4 Approximate average concentrations of cations and anions in plasma in normal mammals. Source: Gross, 1994. Reproduced with permission of Springer.

Cations	mEq/l	Anions	mEq/l
Sodium	135–160	Chloride	110–125
Potassium	3–5	Bicarbonate	18–22
Calcium (total calcium 5–10 mM/l)	4–6	Phosphate	1–3[a]
Magnesium	1–3	Sulfate	1–2
Trace elements	1	Lactate	1–2
		Other organic acids	3–5
		Protein	10–16
Total	144–175		144–175

[a]Phosphate exists in variable proportions of phosphate and monohydrogen and dihydrogen phosphate, so no valance can be identified and the number of mEq/l is therefore an estimate (Gross, 1994).

normal vascular endothelium is largely impermeable to formed blood elements and plasma protein, these cells and solutes are usually limited to the plasma. Vascular endothelium is freely permeable to ionic solutes, and the concentration of these ions is almost the same in interstitial as in plasma fluid. Table 23.4 provides estimations of ion composition in plasma of normal mammals.

The volume of ICF and ECF compartments is determined by the number of osmotically active particles in each space. ECF osmolality can be estimated from the following formula (Rose, 1989):

$$\text{ECF osmolality (mOsm/kg)} = 2([Na^+] + [K^+]) + \text{glucose}/18 + \text{blood urea nitrogen(BUN)}/2.8$$

Because cell membranes are permeable to urea and K^+, these substances contribute only ineffective osmoles, as described earlier. At normal blood glucose concentrations, Na^+ is the primary determinant of effective ECF osmolality. Because Na^+ is the most abundant and osmotically active ECF cation, maintenance of an extracellular-to-intracellular sodium gradient is critical and is accomplished by the cell membrane Na^+,K^+-adenosine triphosphatase (ATPase) pump. This pump is also responsible for maintaining appropriate concentrations of intracellular K^+. Because K^+ is the most abundant intracellular cation, the ratio of intracellular-to-extracellular K^+ concentration is the major determinant of the resting cell membrane potential (−70 to −90 mV). Because all body fluid spaces are isotonic with one another, the effective osmolality of the ICF, and indeed TBW, must be equal to that of the ECF. Acute addition or loss of fluid and/or solutes from the body inevitably results in alterations in compartment volumes and tonicity. Homeostatic shifts of fluid between compartments must then occur to return the system to isotonicity.

The critical distribution of water between the plasma and the interstitium is maintained by the colloidal osmotic pressure of plasma protein (oncotic pressure). This is the force that draws water into the capillaries and balances the hydrostatic pressure driving water out. These so-called "Starling forces" describe the capillary balance between forces that favor filtration of water from plasma and those that retain vascular volume:

$$\text{Net filtration (NF)} = K_f[(P_{cap} - P_{if}) - (\pi_p - \pi_{if})]$$

where K_f represents permeability of the capillary wall, P represents hydrostatic pressure in the capillaries (P_{cap}) (blood) or tissues (P_{if}) (interstitial fluid), and π represents oncotic pressure generated by plasma protein (π_p) or filtered proteins and glycosaminoglycans in the interstitium (π_{if}). Applying Starling's relationships yields the prediction that hypoproteinemia (decreased π_p) will increase loss of vascular fluid and that water depletion (with a relative increase in π_p and a decrease in P_{cap}) will promote reabsorption of interstitial fluid into the vasculature (Kohn and DiBartola, 1992). The volume of intracellular water in a given tissue is maintained by intracellular protein. As plasma water decreases, plasma protein competes with intracellular protein for water, resulting in cellular dehydration. Clinical alterations in plasma osmolality may be assessed by comparing measured osmolality in a patient to calculated serum osmolality as determined using Na^+, K^+, glucose, and BUN measurements (see the ECF osmolality equation provided above). Observed changes in the osmolal gap (difference between measured osmolality and the osmolality calculated from normal concentrations) may be useful in determining the presence of unmeasured osmoles associated with toxic substances such as ethylene glycol. The osmolal gap may also be useful in assessing shifts in plasma sodium concentration (Kohn and DiBartola, 1992).

The number of cations in the ECF must equal the number of anions in order to maintain electroneutrality. In practice, only selected cations and anions are routinely measured in a clinical setting. Calculation of the difference between the commonly measured cations and anions in ECF yields the unmeasured anions, or anion gap (Oh and Carrol, 1977; Emmett and Narins, 1977). The anion gap calculation can be useful in assessing the

etiology of metabolic acidosis and will be discussed in this context subsequently.

Water, Sodium, and Chloride

Homeostasis

Daily intake of water, nutrients, and minerals is normally balanced by daily excretion of these substances. Water turnover is the term used to describe input and output of body water over a given period of time. Values for water turnover, per 24 hours, in various domestic animals resting in cages or stalls range from about 40 to 132 ml/kg/day. The range is influenced by species, age, and physiological state (Adolph, 1939; Smith, 1970 unpublished data). Extremes of temperature, psychological state, disease, and other variables may change water demands markedly. Water turnover in mature dogs is approximated as 40–60 ml/kg/day, while immature and lactating animals may turn over approximately twice this amount (Muir and DiBartola, 1983). Maintenance fluid needs are defined as the volume of fluid required daily to maintain an animal in zero fluid balance, that is, no net gain or loss of water.

Normal water intake occurs in response to thirst, which is stimulated by plasma hypertonicity and/or contracted ECF volume. Plasma hypertonicity, the primary stimulus, prompts osmoreceptors in the supraoptic and paraventricular nuclei of the hypothalamus to release vasopressin, also called antidiuretic hormone (ADH), which is released into the circulation at the level of the pituitary neurohypophysis. Binding of vasopressin to receptors in the distal nephron and renal collecting duct cells activates adenylyl cyclase and increases intracellular cyclic AMP. A protein kinase cascade initiated by activation of protein kinase A results in opening of luminal water pores in the tubule cell. Permeability of the collecting duct to water and reabsorption of water increase. Sustained release of vasopressin depends additionally upon calcium cycling across the plasma membrane and activation of protein kinase C–dependent pathways. Prostaglandins inhibit the renal response to vasopressin. Drugs with anticyclooxygenase activity that inhibit prostaglandin synthesis thereby enhance the action of endogenous vasopressin. Figure 23.1 summarizes the effects of selected drugs and electrolytes on vasopressin release and action.

If ECF volume and renal perfusion decrease, volume receptors in the renal juxtaglomerular apparatus respond, causing the secretion (or release) of renin, which converts angiotensinogen to angiotensin I. This is the rate-limiting step in the renin–angiotensin system. Angiotensin I is activated to the potent vasoconstrictor angiotensin II in the lung and in endothelial cells throughout the body by angiotensin-converting enzyme (ACE). Angiotensin II stimulates the zona glomerulosa of the adrenal cortex to secrete aldosterone, which, in turn, causes increased reabsorption of sodium from the distal nephron with excretion of K^+ and H^+. Due to the increased concentration of sodium, plasma becomes hypertonic, causing vasopressin release and water retention.

Water intake occurs in response not only to thirst but also to hunger. Water content of food may be as low as 10% (dry food) or as high as 90% (succulent green pasture). Canned pet foods generally contain more than 70% water, and semimoist foods are intermediate (20–40% water) (Lewis and Morris, 1987). Intake of dietary water is governed centrally by appetite control mechanisms rather than by fluid and electrolyte homeostasis. In addition to water intake related to eating and drinking, metabolic water is produced endogenously by catabolism of proteins, fats, and carbohydrates (approximately 5 ml/kg/day) and represents about 10–15% of total water intake in dogs and cats (Anderson, 1983).

Normal water loss occurs via urine, fecal water, and saliva (sensible loss), with insensible losses occurring via evaporation from cutaneous and respiratory epithelia. Insensible losses account for TBW elimination of about 15–30 ml/kg/day in healthy, sedentary animals in a thermoneutral environment (Kohn and DiBartola, 1992).

Metabolic rate, and therefore a portion of daily water turnover, are directly proportional to the ratio of body surface area to total volume. For example, the surface area to volume ratio in a puppy is much larger than in an adult dog and the puppy has a higher basal metabolic rate. Both lead to a much greater evaporative loss of water from the skin per unit volume. Hence, daily water turnover per unit body weight may be nearly twice that of the adult animal. Small, immature animals are therefore at greater risk for insensible water loss than large, mature animals.

The most important and predictable loss of water in healthy, sedentary animals, in a thermoneutral environment, occurs via the urine. Urinary losses can vary from 2 to 20 ml/kg/day. Daily urinary water losses may be divided into obligatory water loss and free water loss (Kohn and DiBartola, 1992). Obligatory water loss represents water eliminated in order to excrete the daily renal solute load. The renal solute load is derived from dietary sources of protein and minerals and consists of urea, Na^+, K^+, Ca^{++}, Mg^{++}, NH_4^+, and other cations, and PO_4^{3-}, Cl^-, SO_4^{2-}, and other anions. Hence, daily renal solute load is a function of the quantity and composition of food ingested. Urea accounts for two-thirds of the urinary solute load in dogs (O'Connor and Potts, 1969).

In normal animals increased urine solute load is eliminated by an increase in urine volume (obligatory water

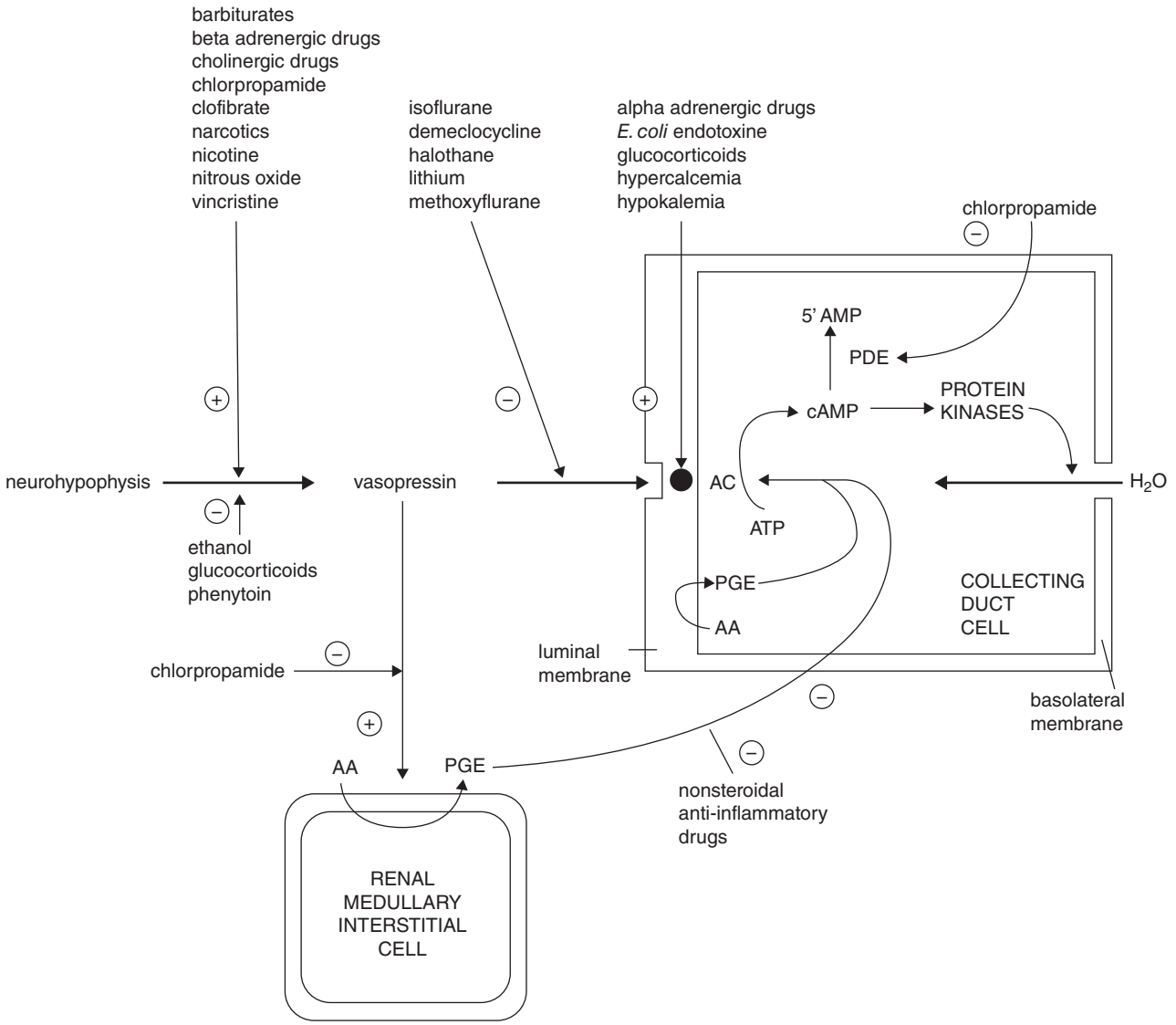

Figure 23.1 Effects of drugs and electrolytes on vasopressin release and mechanisms of cellular action. AA, arachidonic acid; AC, adenylyl cyclase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; PDE, phosphodiesterase; PGE, prostaglandin E. Source: Adapted from DiBartola 1992c. Reproduced with permission of Elsevier.

loss) rather than a marked increase in urine osmolality. Hence, urine osmolality is not generally maximized in order to accomplish steady-state elimination of solutes. Obligatory renal water loss is clinically important for removal of renal solutes but also because this type of water loss will continue even in states of relative water deficit. Free water loss represents water excreted unaccompanied by solute. Excretion of free water is controlled by vasopressin and increases during relative water excess or hypotonicity and decreases during water deficit or hypertonicity. Obligatory fecal water loss occurs in order to excrete fecal solutes. Fecal losses ordinarily account for 2–5% of TBW losses and vary with the species. Feces typically contain 50–80% water (Kohn and DiBartola, 1992).

Renal Regulation of Sodium, Chloride, and Water Excretion

Elimination or conservation of body water and solutes via the kidneys depends upon the processes of glomerular filtration and renal tubular reabsorption and secretion. A major mechanism for conservation of water is urine concentration. The canine kidney can concentrate urine to as much as 2400 mOsm, compared to 1200–1400 mOsm achieved in human urine. Elimination of substances via the urine depends upon renal clearance of each substance from the plasma. The volume of plasma that must be filtered each minute to account for the amount of substance appearing in the urine each minute under steady-state conditions defines renal clearance of that substance.

As much as 20% of cardiac output is directed to the kidneys, with blood entering a renal glomerulus through an afferent arteriole and leaving through an efferent arteriole. Resistance changes in afferent and efferent capillaries regulate glomerular filtration rate (GFR). For discussions of normal and abnormal renal physiological function the reader is referred to any standard physiology text. An understanding of the complexities of renal function is crucial to the understanding of water, acid–base, and electrolyte balances.

As glomerular filtrate flows through the tubules, most of the water (greater than 90%) and varying amounts of solute are reabsorbed into the peritubular capillaries. The composition of the tubular reabsorbate closely approximates that of ECF. Reabsorption is largely achieved by transport of electrolytes and other solutes in two steps: (i) absorption of solutes from tubular fluid into tubular cells and (ii) movement of solutes from tubular cells into the ECF. Several types of transport account for tubular reabsorption of solutes, including passive transport (simple diffusion), facilitated diffusion, active transport, and cotransport. These mechanisms are discussed in more detail in the context of diuretic drugs (Chapter 24) and are summarized in Figure 23.2, which depicts some of the functional processes for regulation of salt and water transport in different segments of the nephron.

As much as 60–65% of filtered solute is reabsorbed in the proximal tubule accompanied by osmotically proportional amounts of water. The tubular fluid at the distal portion of the proximal tubule becomes slightly hypoosmotic. Passive reabsorption of substances, especially sodium and chloride, continues in the thin segment of the loop of Henle. The thick ascending limb of the loop of Henle and the distal convoluted tubule are relatively impermeable to water but actively reabsorb solute. Sodium and chloride enter tubular cells in the thick ascending limb of Henle's loop by crossing the luminal membrane coupled to potassium in a proportion of 1 Na^+ : 1 K^+ : 2 Cl^-. Sodium is then actively extruded across the basolateral membrane to maintain intracellular sodium at low levels. Potassium and chloride leave the tubular cell passively. Two consequences of this are decreased concentration of sodium and chloride in the tubular lumen and increased concentration of each in interstitial fluid. A concentration gradient across the tubular epithelium is established, and this becomes multiplied in a longitudinal direction by the countercurrent mechanism. The collecting ducts are responsive to vasopressin, and in its presence the ducts become highly permeable to water. Tubular fluid equilibrates with hyperosmotic interstitium, and hypertonic (concentrated) urine results. In the absence of vasopressin, the

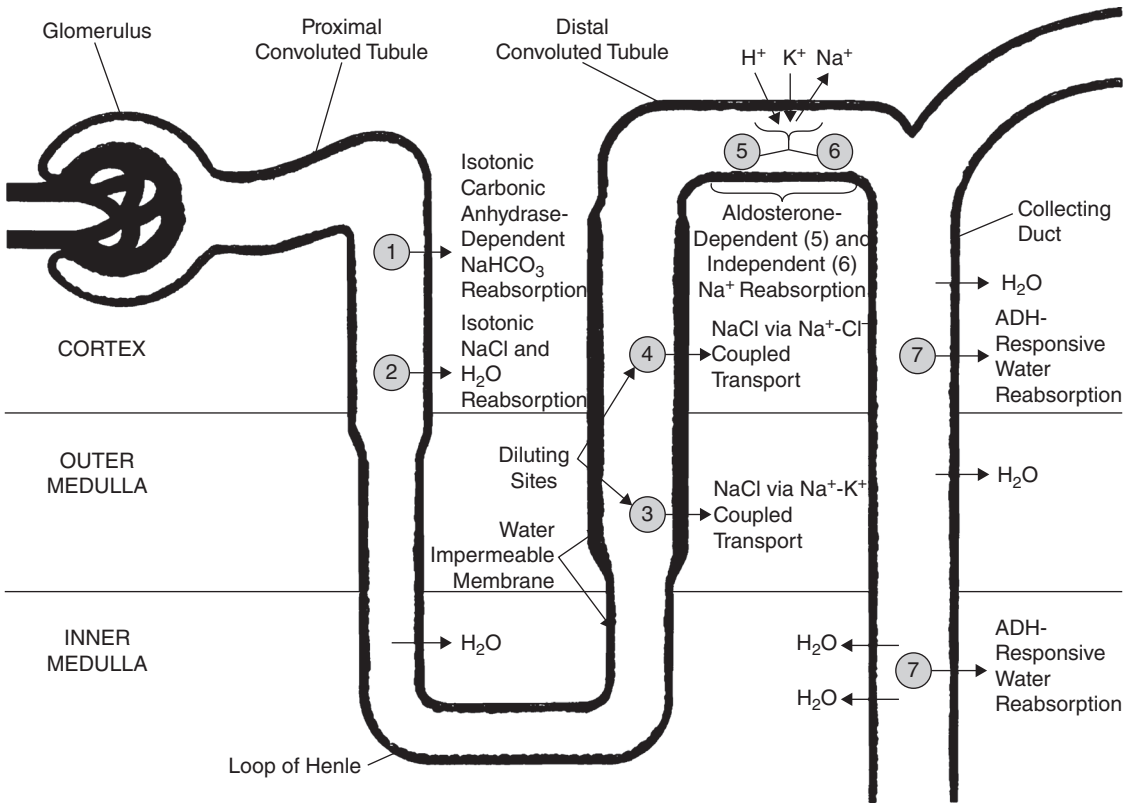

Figure 23.2 Functional processes for regulation of salt and water transport in a nephron. Source: Thier 1987. Reproduced with permission of Taylor & Francis.

ducts are relatively impermeable to water. In this case, sodium and chloride have been reabsorbed proximally to the collecting ducts, tubular fluid is hypoosmotic, and voided urine is dilute (Thier, 1987).

Renal reabsorption of sodium in the distal nephron is increased by aldosterone, a mineralocorticoid synthesized in the zona glomerulosa of the adrenal cortex. Aldosterone is produced and released in response to stimulation by angiotensin II, hyperkalemia, and by a decrease in dietary sodium intake. Adrenocorticotropic hormone (ACTH) and hyponatremia play permissive roles in promoting aldosterone secretion. Increased dietary sodium and atrial natriuretic peptide (ANP) decrease aldosterone production. ANP is a polypeptide released from atrial and ventricular myocytes in response to atrial distention associated with volume expansion. ANP causes vascular smooth muscle relaxation, inhibits production of aldosterone in the adrenal glands, and blocks the production of angiotensin II. Study results suggest that parathyroid hormone (PTH) is required for augmented ANP secretion in response to acute volume loading in rats. PTH may play an important role in the regulation of fluid homeostasis via control of ANP (Geiger et al., 1992).

In general, chloride is reabsorbed with sodium throughout the nephron. As previously noted, chloride is exchanged in a ratio of 1 Na^+ : 1 K^+ : 2 Cl^- in the thick ascending limb of Henle's loop during sodium reabsorption. Because the cotransporter in this exchange has a very high affinity for both Na^+ and K^+, luminal Cl^- concentration is normally the rate-limiting step in NaCl entry into the cell (Gregor and Velazquez, 1987). Additional active and passive processes contribute to proximal Cl^- reabsorption in the renal tubules. Chloride exchange for formate appears to occur via an anion exchanger in the luminal membrane. Low concentrations of filtered formate combine with H^+ to form formic acid (HF) in the tubular lumen. Because HF is uncharged, it moves freely into the tubular cell. Two additional mechanisms set the stage for conversion of HF back to formate and H^+. First, basolateral Na^+,K^+-ATPase pumps maintain a low intracellular sodium concentration, and this, in turn, allows for the continued exchange of Na^+-H^+ across the luminal membrane. As Na^+ is reabsorbed and H^+ is secreted, the interior of the cell is left with a lower [H^+] than the tubular lumen. Under these conditions HF is converted back to H^+ and formate, providing for continued chloride–formate exchange. Reabsorbed chloride is returned to the ECF across the basolateral membrane by selective Cl^- channels and a K^+-Cl^- cotransporter (Rose, 1994). Additional transport mechanisms in type B intercalated cells in the cortical collecting tubule may exchange bicarbonate for chloride. The favorable inward concentration gradient for chloride (lumen concentration greater than inside the cell) presumably provides the energy for bicarbonate secretion via this mechanism (Bastani et al., 1991).

Understanding the mechanisms for renal regulation of acid–base balance and electrolyte transport is increasingly dependent upon use of transgenic mice in which the function and regulation of key transporter proteins can be assessed (Cantone et al., 2006).

Disorders of Water, Sodium, and Chloride Balance

Types of Dehydration

Dehydration may be considered in three general categories: hypertonic, isotonic, and hypotonic. Pure water loss and loss of hypotonic fluid lead to hypertonic dehydration. As pure water is lost from the ECF, fluid shifts from the intracellular to the extracellular compartment in response to increased osmolality. The resulting proportionate distribution of volume loss results in fewer clinically detectable signs of volume depletion in the patient. Causes of dehydration associated with pure water deficit include hypodypsia due to neurological disease, diabetes insipidus, respiratory losses during exposure to elevated temperatures, fever, and inadequate access to water.

Loss of hypotonic fluid, as compared to pure water, results in a greater depletion of ECF volume since there is less osmotic drive to pull volume from the intracellular space. Hypotonic fluid losses are common and have been subclassified as extrarenal and renal. Extrarenal losses could include gastrointestinal (e.g., vomiting or diarrhea) or third-space loss (e.g., pancreatitis, peritonitis, as a result of surgery or cutaneous injury). Third spacing is a term used to describe extravasation of fluid from the vascular compartment into extravascular spaces. As tonicity of lost fluid approaches or exceeds normal plasma osmolality (about 300 mOsm/kg), disproportionate depletion of ECF causes more evident clinical signs of dehydration. Volume depletion would likely be the most clinically apparent in cases of hypertonic fluid loss.

Estimations of percent dehydration based on clinical signs are given in Table 23.5. Skin elasticity is a useful indicator of hydration status. However, age of the animal, body condition, and the technique used for evaluating elasticity may affect hydration assessment. With advancing age or cachexia, loss of fat and protein may account for decreased skin elasticity unrelated to hydration. Conversely, obese animals are likely to retain skin elasticity longer in the face of dehydration. Possibly as a result of variations in elastin content of skin, some species display smaller changes in elasticity for a given degree of dehydration. This may be clinically important in the horse. While dry mucous membranes can indicate dehydration, open-mouthed breathing associated with respiratory disease may cause misleading mucous membrane dryness. Degree of enopthalmos is considered a very useful parameter in assessment of dehydration in large animals.

Table 23.5 Physical findings in dehydration

Percent dehydration	Clinical signs
4 or less	History of fluid loss, mucous membranes still moist, evidence of thirst
5–6	Subtle loss of skin elasticity, slight delay in return of skin to normal position, hair coat dull, mucous membranes slightly dry but tongue still moist
7–8	Definite delay in return of skin to normal position, both mucous membranes and tongue may be dry, eyeballs may be soft and sunken, slight prolongation of capillary refill time
9–11	Tented skin does not return to normal position, definite prolongation of capillary refill time, eyes definitely sunken in orbits, all mucous membranes dry, may be signs of shock such as tachycardia, cool extremities, rapid and weak pulses
12–15	Definite signs of shock and circulatory collapse, death is imminent

For example, the measured gap between the eyeball and orbit has been included as a guideline for assessment of dehydration in neonatal calves. A gap less than 0.5 cm is correlated with 9–10% dehydration, and a gap greater than 0.5 cm suggests 11–12% loss of hydration (Naylor, 1996). A study in diarrheic calves evaluated several clinical and laboratory parameters to determine which were most useful in assessment of dehydration. Factors assessed included extent of enophthalmos, skin-tent duration on neck, thorax, and upper and lower eyelids, heart rate, mean central venous pressure, peripheral (extremities) and core temperatures, packed-cell volume, and hemoglobin and plasma protein concentration. The best predictors of degree of dehydration were extent of enophthalmos, skin elasticity on neck and thorax, and plasma protein concentration (Constable et al., 1998). Laboratory parameters such as hematocrit, plasma protein, and osmolality are often useful, but assessment should include consideration of possible preexisting derangements, such as anemia or hypoproteinemia, that could confound interpretation. If an accurate previous body weight is known, serial changes in weight are considered a very useful and accurate measurement in determining degree of dehydration.

Hypernatremia

As the most important and abundant ECF cation, sodium is essential for proper maintenance of membrane potentials, initiation of action potentials, and, according to strong ion difference theory, maintenance of acid–base balance. Plasma sodium concentration and plasma osmolality generally vary in parallel since sodium and its associated anions account for greater than 95% of plasma osmolality. Plasma sodium concentration reflects the ratio of body sodium ion concentration to TBW. Total body sodium content, however, is independent of plasma sodium concentration and may be increased, decreased, or unchanged in the presence of hyper- or hyponatremia.

Clinical signs associated with alterations in serum sodium are more related to the rapidity of change rather than to the magnitude of sodium increase or decrease. Hypernatremia (e.g., >155 mEq sodium/l in dogs) and ECF hypertonicity can be caused by a loss of pure water, a loss of hypotonic fluid (extrarenal or renal), or a gain of impermeable sodium-containing solute (Figure 23.3). Clinical signs of hypernatremia are usually observed in dogs and cats as sodium concentration approaches and exceeds 170 mEq/ml. The signs seen are related to the osmotic movement of water out of cells. Negative effects of cellular dehydration are most pronounced in the brain and lead to the characteristic neurological deficits associated with hypernatremia. These deficits include abnormal behavior and mentation, ataxia, seizures, and coma. The more rapidly water shifts out of brain cells, the greater the chance that decreased brain volume will lead to rupture of cerebral vessels and focal hemorrhage (Arieff and Guisado, 1976). If sodium concentration or concentration of sodium-containing impermeable solute increases slowly, the brain attempts to adapt to the hypertonic state by production of intracellular solutes (e.g., sugars, amino acids) known as "idiogenic" osmoles. Production of these osmotically active substances protects the cell by retaining intracellular volume and preventing cellular dehydration. In addition to neurological deficits, other clinical signs of hypernatremia include thirst, anorexia, lethargy, vomiting, and muscle weakness. If hypernatremia is related to hypotonic fluid loss, then clinical signs of dehydration (as previously described) may be present. If a gain of sodium has caused the hypernatremia, volume overload may be a problem, especially in patients with cardiac disease.

Restoration of ECF volume and tonicity is of primary importance in treatment of hypernatremia. Volume replacement must be accomplished slowly to avoid rapid shifts in plasma osmolality. In general, the rate of fluid administration is determined by the rate of onset of the hypernatremia. When treating chronic hypernatremia, the serum sodium concentration should drop at a rate that does not exceed 0.7 mEq/l/h (O'Brien, 1995). If plasma osmolality drops quickly, water may be attracted intracellularly by idiogenic osmoles, resulting in development of cerebral edema.

Patients with clinical hypernatremia are also often dehydrated, and need volume resuscitation. Custom fluid combinations can be designed to gradually bring down sodium while being able to give high rates of fluids to replace volume. In the case of pure-water loss, volume can be replaced with 5% dextrose in water over a 48- to

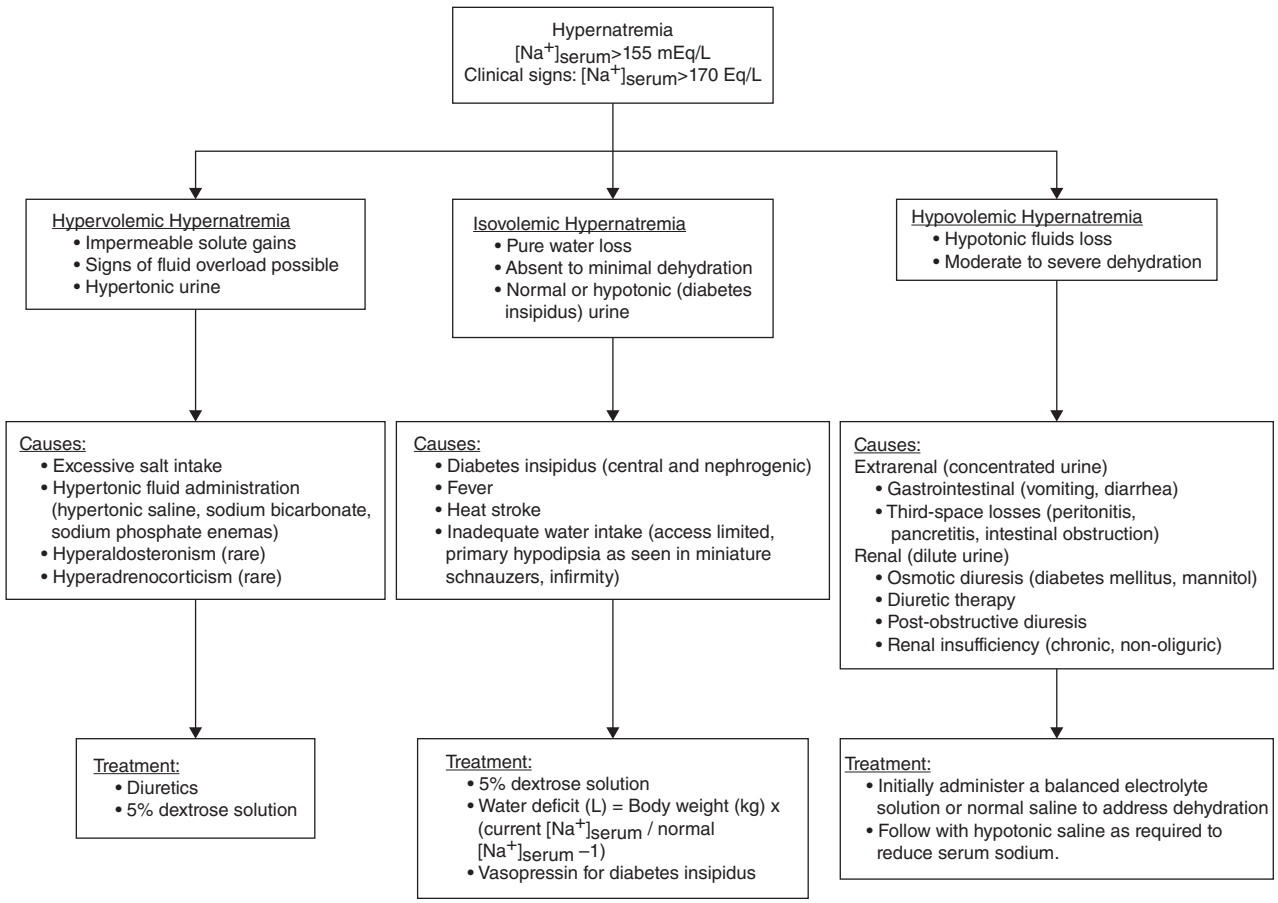

Figure 23.3 Summary of classification, causes, and treatment of hypernatremia. See text for additional details of treatment.

72-hour period. Since the dextrose ultimately enters cells and is metabolized, 5% dextrose administration is essentially replacement with pure water. Use of a 1 : 1 mixture of normal saline with 5% dextrose solution yields an isotonic solution of 2.5% dextrose, 0.45% saline that has also been utilized. This solution decreases plasma tonicity more slowly and decreases the chance for cerebral edema. Hypotonic fluid losses should generally be replaced with an isotonic crystalloid solution. If hypernatremia has resulted from addition of sodium or sodium-containing impermeable solute, then administration of 5% dextrose and water should be accomplished cautiously to avoid pulmonary edema. Diuretics may be useful in promoting saluresis (sodium excretion) as ECF volume is restored (Marks, 1998).

Evaluation and treatment of hypernatremia in critically ill cats was reviewed with emphasis on the importance of careful monitoring and early recognition of signs for positive therapeutic outcomes (Temol et al., 2004).

Hyponatremia

Causes of hyponatremia (<135–140 mEq sodium/l) are best categorized if two additional variables, osmolality and hydration, are also considered. As indicated in Figure 23.4, the more common causes of hyponatremia are accompanied by decreased plasma osmolality (<290 mOsm/kg) with or without volume depletion. If volume depletion exists with hyponatremia, then loss of body sodium has exceeded water loss. Physiological responses to hypovolemia lead to impaired water excretion and a relative dilution of the sodium remaining in body fluids. Hypovolemia causes decreased renal perfusion and GFR, leading to a decline in water excretion. Slower movement of filtrate through renal tubules enhances isosmotic reabsorption of salt and water in the proximal tubules and decreases presentation of tubular fluid at distal diluting sites. Additionally, hypovolemia prompts vasopressin release, further impairing water elimination. Finally, thirst related to hypovolemia results in consumption of low-sodium fluids that also dilute existing plasma sodium (DiBartola, 1992c).

Hyponatremia accompanied by hypervolemia and low plasma osmolality occurs in clinical disorders where there is a physiological perception of volume depletion by in vivo volume detectors. The physiological response

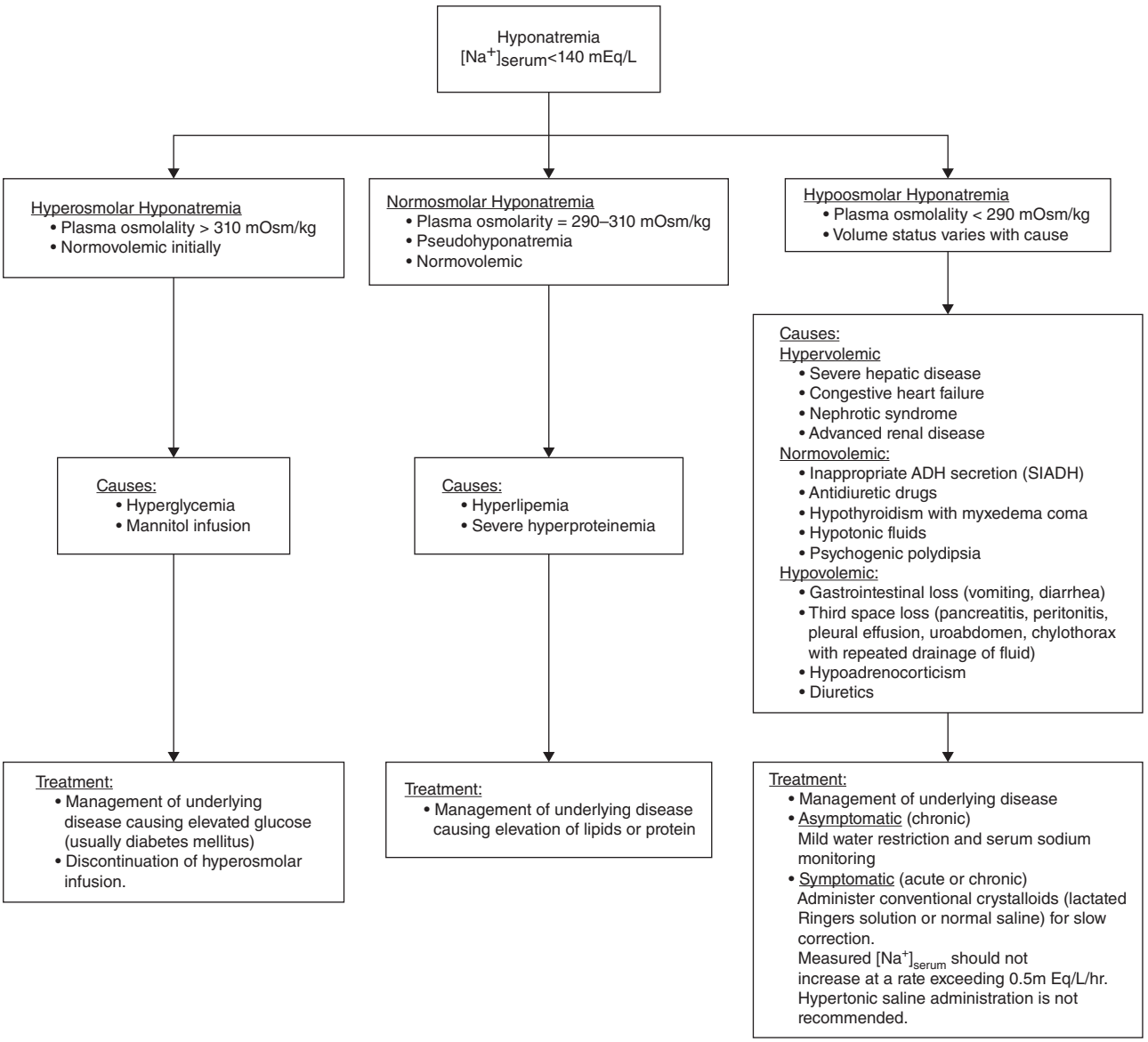

Figure 23.4 Summary of classification, causes, and treatment of hyponatremia. See text for additional details of treatment.

is volume expansion. For example, in congestive heart failure, decreased cardiac output is sensed as volume depletion by baroreceptors. Release of vasopressin impairs water excretion, leading to expanded vascular volume. Decreased effective circulating volume and decreased renal perfusion also lead to activation of the renin–angiotensin–aldosterone system. Enhanced renal retention of sodium contributes to expanded vascular volume. In cirrhosis and the nephrotic syndrome, hypoalbuminemia and decreased oncotic pressure may contribute to decreased effective circulating volume and, ultimately, vasopressin release and volume expansion. Other features of hepatic and renal disease also contribute to decreased circulating volume and/or impaired water excretion (DiBartola, 1992c).

Hyponatremia is relatively less common when associated with increased plasma osmolality. The most frequent cause of sodium decreases in the presence of increased plasma osmolality is the increased circulating glucose levels associated with diabetes mellitus. Each 100 mg/dl increase in glucose results in a measured decrease of serum sodium by 1.6 mEq/l (Katz, 1973). In response to the increased concentration of serum glucose, water shifts from the intracellular to the extracellular compartment, resulting in dilution of measured sodium. Serum osmolality remains high due to elevated glucose concentrations. Hyponatremia associated with normal plasma osmolality is referred to as pseudohyponatremia. The decreased sodium concentrations are spurious and are almost universally related to technical

difficulties in sodium measurement when plasma lipid or protein concentrations are high.

As with hypernatremia, clinical signs of hyponatremia are more severe if sodium concentration changes rapidly than if it changes over a more prolonged period of time. If sodium concentrations and plasma osmolality decrease quickly, water shifts out of the ECF and into cells. The central nervous system (CNS) is most affected by a rapid fluid shift, which, in hyponatremia, results in development of cerebral edema. If onset of hyponatremia is slow, the brain can adjust cell volume by decreasing intracellular osmolality and preventing influx of water from the ECF. Patients with chronic hyponatremia will also adjust intracellular osmolality to an extent that clinical signs may not be obvious even though sodium concentrations are quite low.

Treatment of hyponatremia varies with etiology of the disorder. The goals of therapy are to manage the underlying disease and, if necessary, to increase serum sodium and osmolality. Infusion with conventional crystalloid solutions (e.g., normal saline or lactated Ringer's solution) is reported to accomplish sodium and volume replacement in hyponatremic, hypovolemic patients (DiBartola, 1992c). Use of hypertonic saline solutions is not recommended since overly rapid correction of hyponatremia may do more harm than good. Chronic hyponatremia, in which the brain has adjusted to the decrease in osmolality and sodium, must be handled cautiously to avoid brain dehydration and injury, including osmotic demyelination syndrome. This syndrome, often occurring several days after correction of hyponatremia, results from areas of demyelination caused by treatment-induced increases in serum sodium concentration. Dogs with asymptomatic chronic hyponatremia are best treated by mild water restriction and monitoring of serum sodium. Chronic, symptomatic dogs should be treated such that the rate of increase of serum sodium does not exceed 10–12 mEq/l/day (0.5 mEq/l/h) (DiBartola, 1998). Again, the most important therapeutic goal in management of hyponatremia should be treatment of the underlying disease.

Hyperchloremia

Fluid loss associated with small bowel diarrhea often results in greater loss of HCO_3^- than chloride due to loss of alkaline pancreatic secretions and bile and HCO_3^- secretion in exchange for Cl^- in the ileum. The resulting hyperchloremic metabolic acidosis is characterized by a normal anion gap. Additional causes and treatment for hyperchloremic metabolic acidosis will be considered subsequently under the heading of metabolic acidosis. Please refer to the discussion of hypernatremia for treatment of hyperchloremia associated with loss of free water.

Hypochloremia

Hypochloremia may be seen in patients with fluid losses due to vomiting or excessive diuretic administration. Hypochloremic metabolic alkalosis may develop in these cases because an excess of chloride is lost, leading to decreased filtered Cl^- in the renal tubules. As previously noted, activity of the Na^+-K^+-$2Cl^-$ cotransporter in the luminal membrane of the macula densa cell is primarily determined by the availability of Cl^-. In hypochloremia, less Cl^- is delivered, resulting in less NaCl reabsorption, promotion of renin release leading to secondary hyperaldosteronism, and increased distal H^+ secretion. If further Na^+ reabsorption does occur, then Na^+ must be accompanied by an anion other than chloride, usually bicarbonate, or must be exchanged for a secreted cation, either H^+ or K^+. In addition, bicarbonate secretion in exchange for chloride, which is thought to occur in intercalated cells of the cortical collecting tubule, will decrease since this process is presumably driven by a favorable inward gradient for Cl^-. As luminal $[Cl^-]$ decreases, the gradient is dissipated and bicarbonate is retained in the system. All of the foregoing mechanisms promote retention of base and excretion of H^+, leading to a hypochloremic metabolic alkalosis (Rose, 1994). Treatment with chloride-replete fluid such as normal saline is usually adequate to resolve chloride-responsive alkalosis. Potassium depletion may also promote a metabolic alkalosis and should be addressed as needed by addition of potassium chloride to fluids.

Potassium

Homeostasis

As the major intracellular cation, potassium concentrations inside (145 mEq/l) and outside (3.5–5.5 mEq/l) the cell are maintained by the Na^+,K^+-ATPase pump. Under normal circumstances each pump actively transports three sodium ions out of and two potassium ions into the cell, but the ratio can change depending upon the circumstances. The ratio of intra- to extracellular concentration of potassium ($[K^+]_i/[K^+]_o$) is the major determinant of resting membrane potential. Resting membrane potential is crucial to normal membrane excitability associated with cardiac conduction, muscle contraction, and nerve impulse transmission.

The normal dietary intake of potassium is much more than the body requires. About 90% of this intake is excreted in the urine, with the remainder of what is not required eliminated in the stool. Plasma potassium concentration is determined by the movement of potassium into or out of cells. Two important factors stimulating the transport of potassium into cells are insulin and β-adrenergic stimulation (Clausen and Flatman, 1987).

Aldosterone is the primary determinant of potassium secretion across renal tubular epithelial surfaces.

Renal Regulation of Potassium Excretion

Most filtered potassium (60–80%) is reabsorbed in the proximal tubule. In the early proximal tubule, potassium enters the tubular cell at the luminal surface by active transport. The intracellular concentration of potassium is high, and the lumen of the tubule is negatively charged relative to the interior of the early proximal tubular cell. Potassium passively exits the basolateral membrane of the tubular cell down a favorable chemical concentration gradient. In the mid-to-late proximal tubule, the tubular lumen is relatively more positively charged than the tubular cell interior. This favors the passive reabsorption of potassium. Potassium again exits on the basolateral side of the tubular cell down a concentration gradient. Potassium reabsorption by intercalated cells in the distal nephron is similar to the process in the early proximal tubule and involves active transport at the luminal cell membrane followed by passive diffusion from the cell at the basolateral membrane. Tubular secretion of potassium is aldosterone mediated and occurs in the distal nephron (late distal tubule or connecting tubule of the collecting duct system) primarily in the "principal" cells of the collecting tubules. Additional information on mechanisms of collecting duct system reabsorption and secretion is given in Chapter 24 (Figure 24.2). Principal cells are rich in Na^+,K^+-ATPase and respond to aldosterone by increasing the number and activity of Na^+,K^+-ATPase pumps in the basolateral membrane. The increasing luminal membrane permeability to sodium causes greater lumen negativity relative to the tubular cell interior and increases luminal permeability to potassium. This facilitates potassium secretion into the tubule lumen. Aldosterone-stimulated Na^+,K^+-ATPase actively pumps potassium out of the peritubular fluid through the basolateral tubular cell membrane. Movement of potassium from the tubular cell through the luminal membrane and into the tubule lumen is favored by relative negativity of the lumen compared to the interior of the distal tubule cell (Black, 1993).

When plasma potassium concentration is low, secretion of potassium by the principal cells is reduced while hydrogen ion secretion may be increased. Active potassium reabsorption by intercalated cells in the distal nephron is also stimulated by a potassium deficit. An additional factor affecting the movement of potassium across tubular cells is related to tubular flow rate. A rapid flow of filtrate through the tubules maximizes the potassium concentration gradient between the tubular cell interior and the lumen of the tubule and enhances potassium excretion. A reduction of tubular flow slows secretion by allowing a relatively greater concentration of potassium to be maintained in the lumen of the distal tubule (DiBartola and Autran de Morais, 1992).

Disorders of Potassium Balance

Disorders of potassium balance have marked effects on excitable membranes. The difference between the resting membrane potential and the membrane potential required for depolarization (threshold potential) determines the excitability of a cell. Hypokalemia makes the resting membrane potential more negative, thereby hyperpolarizing the cell and increasing the difference between resting and threshold potentials. Hyperkalemia causes the resting membrane potential to become more positive, hypopolarizing the cell and causing hyperexcitability. In hyperkalemia, if the resting potential decreases to less than the threshold potential, the cell depolarizes but is incapable of repolarizing, resulting in loss of cell excitability (DiBartola and Autran de Morais, 1992). In cardiac muscle this results in diastolic arrest; in vascular smooth muscle hyperkalemia causes vasoconstriction.

Changes in pH affect the distribution of potassium between the ICF and the ECF. When acidosis is present, potassium moves out of cells in exchange for hydrogen, which moves intracellularly. In the distal tubule more hydrogen, and relatively less potassium, may be exchanged for sodium at the luminal membrane, leading to decreased potassium excretion. Based on these general principles, a clinical rule of thumb predicts that each 0.1 unit decrease in pH will be accompanied by a 0.6 mEq/l increase in serum potassium concentration.

Conversely, in alkalosis potassium tends to move into cells in exchange for extracellular movement of hydrogen. Hypokalemia has been thought to promote alkalosis because less potassium is available to be exchanged for sodium in the distal tubule. Instead, sodium exchanges for hydrogen at the luminal membrane, leading ultimately to reclamation of bicarbonate and increased systemic pH. At the same time that systemic pH is increasing, secreted hydrogen ions exchanged for sodium cause the urine pH to decline.

Although the principles outlined above are commonly stated and widely applied clinically, it is not clear that these explanations are adequate. In acidosis, the effect of pH changes on potassium translocation varies with the nature of the acid anion, blood pH and HCO_3^- concentration, osmolality, hormonal activity, and liver and renal function (DiBartola and Autran de Morais, 1992). Although changes in serum potassium have been documented during acute mineral acidosis caused by HCl or NH_4Cl (Adrogue and Madias, 1981), acute metabolic acidosis caused by organic acids did not increase serum potassium as predicted (Oster et al., 1980; Adrogue and Madias, 1981). In certain conditions (e.g., diabetic

ketoacidosis), hyperkalemia may be more directly associated with hyperosmolality and insulin deficiency than with the acidosis itself. In lactic acidosis, increased serum potassium concentration may be the result of release of intracellular potassium caused by cell breakdown associated with decreased peripheral perfusion (Black, 1993). Metabolic acidosis associated with both mineral and organic acids may directly or indirectly stimulate aldosterone secretion. The effects of aldosterone facilitate excretion of the acid load and, presumably, potassium, although one study failed to show any changes in serum potassium concentration (Perez et al., 1980).

Early studies of the effects of hypokalemia on acid–base balance may have overlooked the key role of chloride depletion in causing metabolic alkalosis (DiBartola and Autran de Morais, 1992). When pure potassium depletion is created iatrogenically in rats, metabolic alkalosis results. However, in dogs, potassium deficit with normal chloride levels leads to metabolic acidosis due, presumably, to a distal renal tubular acidification defect (Garella et al., 1979).

Hyperkalemia

Total body potassium may be normal, decreased, or increased with hyperkalemia. Clinical signs of hyperkalemia (>7.5 mEq/l) are generally associated with changes in membrane excitability and are more severe if the increase in potassium has been rapid. Muscle weakness, twitching, and irritability may occur. Electrocardiographically determined cardiac effects may include extrasystoles, intraventricular conduction blocks, high-peaked T waves, altered QT interval, widened QRS interval, decreased amplitude or disappearance of P waves, depressed ST segment, ventricular asystole, or fibrillation.

Causes of hyperkalemia are summarized in Table 23.6. The more common causes are related to decreased urinary potassium excretion. Pseudohyperkalemia related to hemolysis can occur in species that have high red cell potassium concentrations similar to humans. Dogs, sheep, and cattle can be divided into two groups based on Na^+,K^+-ATPase activity in red cell membranes. Those animals with high activity and high intracellular potassium concentrations are at risk for hyperkalemia caused by hemolysis. Animals with genetically determined low activity and low intracellular concentrations of potassium are unlikely to suffer from pseudohyperkalemia since the concentration of potassium in red cells resembles the concentration in the ECF (DiBartola and Autran de Morais, 1992).

The effects of several different drugs may impact serum potassium concentration. Since potassium uptake by cells is mediated in part by catecholamines at β receptors, beta blockers decrease intracellular potassium movement and increase ECF potassium concentrations.

Table 23.6 Causes of hyperkalemia. Source: Adapted from DiBartola, 1992a. Reproduced with permission of Elsevier.

Decreased excretion
Urethral obstruction
Ruptured bladder
Anuric or oliguric renal failure
Hypoadrenocorticism
Gastrointestinal diseases (e.g., trichuriasis, salmonellosis, perforated duodenal ulcers)
Chylothorax with repeated drainage of the pleural effusion
Drugs
ACE inhibitors (e.g., captopril, enalapril)
Potassium-containing drugs (e.g., potassium chloride)
Potassium-sparing diuretics (e.g., spironolactone, amiloride, triamterene)
Nonsteroidal antiinflammatory agents
Heparin
Translocation from the intracellular to extracellular fluid
Acute mineral acidosis (e.g., HCl or NH_4Cl administration)
Insulin deficiency (e.g., diabetic ketoacidosis)
Ischemia reperfusion
Drugs (e.g., propranolol)
Acute tumor lysis syndrome
Hyperkalemic periodic paralysis (rare)
Increased intake (rare)
Pseudohyperkalemia
Thrombocytosis
Hemolysis

Angiotensin-converting enzyme (ACE) inhibitors may cause hyperkalemia by interfering with angiotensin II–mediated aldosterone secretion. Prostaglandin inhibitors, heparin, and selected potassium-sparing diuretics (e.g., spironolactone) increase serum potassium by decreasing the secretion of aldosterone or by blocking its activity. In many cases drugs alone may not have a marked effect on serum potassium concentration but if combined with a potassium load or decreased renal function may cause clinically significant hyperkalemia.

Treatment of hyperkalemia varies with the severity of the condition in terms of magnitude and rapidity of onset. Emergency treatment is indicated if potassium rises quickly and exceeds 6.0–8.0 mEq/l (Phillips and Polzin, 1998). Serum potassium concentrations less than these do not typically induce life-threatening cardiotoxicity and can usually be managed with administration of potassium-free fluids. More aggressive treatment is necessary if electrocardiographic signs suggest toxicity. Additional measures that may be taken in treatment of severe hyperkalemia are summarized in Table 23.7. Some are directed toward increasing movement of potassium from the extracellular to the intracellular compartment (i.e., glucose, insulin, and sodium bicarbonate), while others are intended to decrease potassium from the ECF by enhanced renal excretion (e.g., diuretics) or decreased gastrointestinal absorption (i.e., orally

Table 23.7 Therapeutic considerations in the management of severe hyperkalemia

Establish venous access and administer potassium-deficient fluids
Discontinue potassium intake, including drugs that may promote hyperkalemia
Administer the following as needed:
$NaHCO_3$ (0.5–1 mEq/kg, slowly IV) if animal is acidotic
Calcium gluconate (10% solution; 0.5–1 ml/kg slowly IV up to 10 ml maximum)
Glucose (20% solution; 0.5–1.0 g/kg IV)
Insulin (0.5 IU/kg) and glucose (20% solution; l g/kg; half given IV bolus and the remainder infused over 2 hours)
Potassium-wasting diuretics (furosemide, chlorothiazide, hydrochlorothiazide)
Sodium polystyrene (20 g with 100 ml 20% sorbitol) per os or 50 g in 100–200 ml tap water (retention enema)
Peritoneal dialysis (last resort)

administered potassium-binding resins such as sodium polystyrene sulfonate).

Therapy with calcium gluconate is included as part of the emergency treatment of hyperkalemia because changes in membrane excitability associated with alterations in potassium may be exacerbated by abnormalities in ionized calcium. Ionized calcium affects the threshold potential of a membrane and, when calcium is decreased, brings threshold closer to resting membrane potential, resulting in greater membrane excitability. An increase in ionized calcium has an opposing effect on membrane excitability by increasing the threshold potential and making depolarization more difficult. Hence, hypocalcemia exacerbates hyperkalemia while hypercalcemia counteracts hyperkalemia.

Hypokalemia

Since 97% of total body potassium is intracellular, depletion can occur with no change in plasma potassium concentration or even with an increase if acidosis is present. Clinical signs of hypokalemia (<2.5–3.0 mEq/l) can include weakness of skeletal and respiratory muscles and loss of intestinal smooth muscle tone. As in hyperkalemia, cardiac changes occur as potassium concentration changes. Supraventricular and ventricular arrhythmias are most commonly observed in animals. ECG hallmarks of hypokalemia in humans are flattened or inverted T waves, depressed S-T segment, and the appearance of U waves. Prolongation of the QT interval and U waves have been reported in dogs but are not as consistently seen as they are in humans. Hypokalemia is increasingly recognized as an important clinical problem in cats, especially in association with chronic renal failure and geriatric animals (Phillips and Polzin, 1998). Feline hypokalemic polymyopathy syndrome, characterized by generalized muscle weakness associated with

Table 23.8 Causes of hypokalemia. Source: Adapted from DiBartola, 1992a. Reproduced with permission of Elsevier.

Increased loss
Gastrointestinal (FEK <4–6%)
Persistent vomiting of stomach contents
Diarrhea
Urinary (FEK >4–6%)
Chronic renal failure in cats
Diet-induced hypokalemic nephropathy in cats
Renal tubular acidosis
Postobstructive diuresis
Excess circulating mineralocorticoid
Hyperadrenocorticism
Primary hyperaldosteronism (hyperplastic or neoplastic)
Diuretics (loop acting, thiazides and osmotic)
Antibiotics (penicillins, amphotericin B, aminoglycosides)
Translocation from extracellular fluid to intracellular
Alkalemia
Overadministration of insulin and glucose-containing fluids
Hyperthyroidism
Hypokalemic periodic paralysis
Possible complication of hypothermia
Decreased intake
Unlikely as sole cause

hypokalemia, is often manifest in cats as ventroflexion of the head and a stiff, stilted gait.

Increased loss associated with the gastrointestinal or the urinary system is a common cause of hypokalemia, as indicated in Table 23.8. Differentiating gastrointestinal from urinary causes of hypokalemia is largely accomplished by clinical signs and physical exam, but fractional potassium excretion rates (FE_K) may also be useful. Fractional potassium excretion can be calculated using the following formula:

$$FE_K = \left(U_K/S_K\right) / \left(U_{CR}/S_{CR}\right) \times 100$$

where U indicates the urine concentration of potassium (K^+) or creatinine (CR), and S indicates the serum concentration.

Treatment of hypokalemia is indicated if significant potassium loss is expected based on history and clinical signs (e.g., vomiting, diarrhea, overzealous use of diuretics) or if clinical signs of hypokalemia are present. Appropriate potassium administration is often required with prolonged fluid therapy. If feasible, oral potassium supplementation is most desirable since this is the safest route of administration. If intravenous potassium supplementation is warranted, the amount administered should be based on clinical status of the animal and measured serum potassium values. Table 23.9 provides approximate potassium dosages for treatment of hypokalemia in small animals. Alternatively, a rule of thumb may be applied in which 20 mEq/l of potassium is supplemented with careful monitoring of changes in serum potassium. An important caution regarding the administration of intravenous potassium is not to exceed a rate

Table 23.9 Potassium supplementation in treatment of hypokalemia

Serum potassium concentration (mEq/l)	Supplement fluids (mEq/l)[a]
3.5 to 4.5	20
3.0 to 3.5	30
2.5 to 3.0	40
2.0 to 2.5	60
<2.0	80

[a]Quantity of potassium to add per liter of fluid. Do not exceed administration rate of 0.5 mEq K^+/kg/h.

of 0.5 mEq/kg/h. Parenteral potassium administration should always be monitored to ensure that rate of potassium addition does not exceed rate of potassium movement into cells.

Principles of Acid–Base Metabolism

Homeostasis

Blood pH is highly regulated and is normally maintained between 7.38 and 7.42. Pulmonary and renal functions are necessary for precise regulation of pH of all body fluids, blood, and extravascular tissues. An acid is defined by Bronsted and Lowry as a substance that can supply H^+ (protons), and a base is defined as a substance that can accept H^+. In aqueous solutions, H^+ are hydrated; therefore, H_3O^+ is considered an acid and is implied by the symbol H^+. Blood pH is the negative logarithm of the hydrogen ion concentration. Although hydrogen ion concentration cannot be measured directly, hydrogen ion activity is measured chemically using a pH electrode. In body fluids, the difference between activity of hydrogen ions and concentration of hydrogen ions is negligible; hence hydrogen ion concentration and pH are commonly referred to in acid–base discussions. The hydrogen ion concentration of blood at pH 7.4 is 40 nmol/l (nanoequivalents per liter) and is therefore approximately a millionfold lower than the blood concentration of electrolytes such as sodium and potassium. Appropriate hydrogen ion concentration is critical in order to maintain body proteins in configurations required for enzymatic and structural function. An increase in hydrogen ion concentration with a decrease in blood pH is termed acidemia and can be caused by pathophysiological processes that cause accumulation of acids in the body. As the concentration of hydrogen ions decreases, and blood pH increases, alkalemia occurs and can be associated with pathophysiological processes that cause accumulation of alkali in the body. The disordered processes leading to acidemia and alkalemia are termed acidosis and alkalosis, respectively.

On a daily basis, an excess of acid (70–100 mEq) is generated in the body as a result of dietary intake and intermediary metabolism. Catabolism of carbohydrate, fat, and protein account for most of this as a result of: oxidation of sulfur-containing amino acids to sulfuric acid; oxidation of phosphoproteins to phosphoric acid; incomplete oxidation of fats and carbohydrates to organic acid; production of lactate/lactic acid during anaerobic glycolysis; and conversion of carbon dioxide and water produced in the tricarboxylic acid cycle to carbonic acid. Buffers throughout the body minimize changes in blood pH associated with alterations of acid–base balance. The most effective physiological buffers have pK_a values between 6.1 and 8.4, with buffering capacity being maximal within one pH unit of the pK_a. Important extracellular buffers include bicarbonate, inorganic phosphates, and plasma proteins.

Most extracellular buffering occurs as a result of the bicarbonate–carbonic acid buffer pair (pKa = 6.1). Equilibrium of this buffer pair is indicated with the following:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

The hydration of CO_2 is a rapid reaction in the presence of the enzyme carbonic anhydrase, which is found primarily in red blood cells and renal tubular cells. The dissociation of any acid, in this case carbonic acid, can be described utilizing the concept that the velocity of a reaction is proportional to the product of the concentration of the reactants. In the case of the bicarbonate buffer system, the carbonic anhydrase–catalyzed hydration of CO_2 to form H_2CO_3 reaches equilibrium almost instantaneously, with the number of dissolved CO_2 molecules far exceeding the number of carbonic acid molecules. By defining dissociation constants and rearranging, the useful Henderson–Hasselbalch form of the dissociation equilibrium equation can be derived:

$$pH = pKa + \log \left[HCO_3^-\right] / \left[H_2CO_3\right]$$

Gaseous CO_2 produced in the tissues, primarily via the tricarboxylic acid cycle, is soluble in water; the concentration of dissolved CO_2 in body fluids can be related to the partial pressure of CO_2 in the gas phase, PCO_2, by the following expression:

$$\left[\text{dissolved } CO_2\right] = 0.03 \times P_{CO_2}$$

Hence the clinically useful form of this equation for the bicarbonate–carbonic acid buffer system becomes

$$pH = 6.1 + \log \left[HCO_3^-\right] / (0.03 \times P_{CO_2})$$

The bicarbonate–carbonic acid system is the most physiologically important extracellular buffer system because it is present in relatively high concentrations in the blood and because it can effectively buffer by rapid regulation of PCO_2 through alveolar ventilation. As carbonic acid is

formed from the buffering of excess H^+ by HCO_3^-, this drives the dissociation equation of carbonic acid to the left, causing an increase in PCO_2. An increase in ventilation enhances CO_2 excretion and lowers the PCO_2.

Intracellular buffers also contribute to maintenance of body pH. The primary intracellular buffers are proteins, organic and inorganic phosphates, and, in the red cell, hemoglobin. Hemoglobin is an especially important buffer for carbonic acid since the primary extracellular buffer, the bicarbonate system, cannot buffer this acid. Bone also acts as a tissue-based buffer by exchanging surface Na^+ and K^+ for H^+ under conditions of acid load. Additionally, dissolution of bone mineral results in release of buffer compounds into the ECF.

Regulation of Hydrogen Ion, Carbon Dioxide, and Bicarbonate

Pulmonary and renal control of dissolved CO_2 and bicarbonate concentrations, respectively, is responsible for maintenance of body pH. The "tail" of the Henderson–Hasselbalch equation for the bicarbonate system (i.e., HCO_3^-/dissolved CO_2) provides a simplistic but useful means to consider pulmonary and renal adjustments during simple acid–base disturbances. Under normal physiological conditions, the ratio of HCO_3^- to dissolved CO_2 is 20 : 1. This ratio can be disturbed by addition or loss of CO_2 or bicarbonate to the system. Table 23.10 depicts changes in the tail of the bicarbonate–carbonic acid dissociation equation that might occur during simple acid–base disturbances. The respiratory component of acid–base regulation (the denominator of the tail, or dissolved CO_2) involves changes in respiratory rate and volume prompted by changes in PCO_2. Initiation of these processes requires only minutes.

The renal component of acid–base regulation (the numerator of the tail, or HCO_3^-) involves selective absorption of bicarbonate and secretion of H^+. During periods of acidosis, relatively more H^+ are secreted, while relatively more K^+, Na^+, and HCO_3^- are retained. During alkalosis, K^+ is secreted, while relatively more H^+ and less Na^+ and HCO_3^- are retained. This process requires hours to days to produce an effect. The kidney regulates acid–base balance by maintaining the appropriate HCO_3^- in the plasma. The kidney accomplishes this by reclaiming virtually all filtered HCO_3^- and excreting an amount of acid that equals the amount of ingested or endogenously generated nonvolatile acid. In the proximal tubule of the kidney, cytoplasmic carbonic anhydrase catalyzes the formation of H^+ and bicarbonate from cellular carbon dioxide and water, controlling the rate of hydrogen secretion and bicarbonate reabsorption. In the luminal membrane, carbonic anhydrase converts carbonic acid to carbon dioxide and water, increasing net bicarbonate reabsorption (Figure 23.5A). In the distal nephron, intercalated cells specialized for hydrogen secretion contain large quantities of carbonic anhydrase, again yielding hydrogen and bicarbonate. In this case, secreted H^+ serves to titrate buffers in the urine (phosphate buffering is shown in Figure 23.5B) and lower urinary pH. As titratable acidity of the urine reaches a maximum, another adaptation, increased ammonia (NH_3) production by tubular cells, contributes to excretion of acid loads. Figure 23.5C, shows production of freely

Table 23.10 Examples of changes in the "tail" of the Henderson–Hasselbalch equation occurring during simple acid–base disturbances

Respiratory acidosis (↓ CO_2 elimination) associated with inadequate ventilation:

$$\frac{20HCO_3^-}{1CO_2}\ (\text{Normal}) + 2CO_2\ (\downarrow \text{Ventilation}) \rightarrow \frac{20HCO_3^-}{3CO_2}\ (\text{Uncompensated}) + 40HCO_3^-\ (\text{Renal production}) \rightarrow \frac{60HCO_3^-}{3CO_2}\ (\text{Compensated}) = \frac{20}{1}$$

Respiratory alkalosis (↑ CO_2 elimination) associated with hyperventilation:

$$\frac{20HCO_3^-}{1CO_2}\ (\text{Normal}) - 0.5CO_2\ (\uparrow \text{Ventilation}) \rightarrow \frac{20HCO_3^-}{0.5CO_2}\ (\text{Uncompensated}) - 10HCO_3^-\ (\text{Renal excretion}) \rightarrow \frac{10HCO_3^-}{0.5CO_2}\ (\text{Compensated}) = \frac{20}{1}$$

Metabolic acidosis (bicarbonate deficit) associated with diarrhea:

$$\frac{20HCO_3^-}{1CO_2}\ (\text{Normal}) - 10HCO_3^-\ (\text{Loss in feces}) \rightarrow \frac{10HCO_3^-}{2CO_2}\ (\text{Uncompensated}) - 0.5CO_2\ (\text{Eliminated by } \uparrow \text{ ventilation}) \rightarrow \frac{10HCO_3^-}{0.5CO_2}\ (\text{Compensated}) = \frac{20}{1}$$

Metabolic alkalosis (bicarbonate excess) associated with administration of alkali:

$$\frac{20HCO_3^-}{1CO_2}\ (\text{Normal}) + 20HCO_3^-\ (\text{Alkali administration}) \rightarrow \frac{40HCO_3^-}{1CO_2}\ (\text{Uncompensated}) - 1CO_2\ (\text{Eliminated by } \downarrow \text{ ventilation}) \rightarrow \frac{40HCO_3^-}{2CO_2}\ (\text{Compensated}) = \frac{20}{1}$$

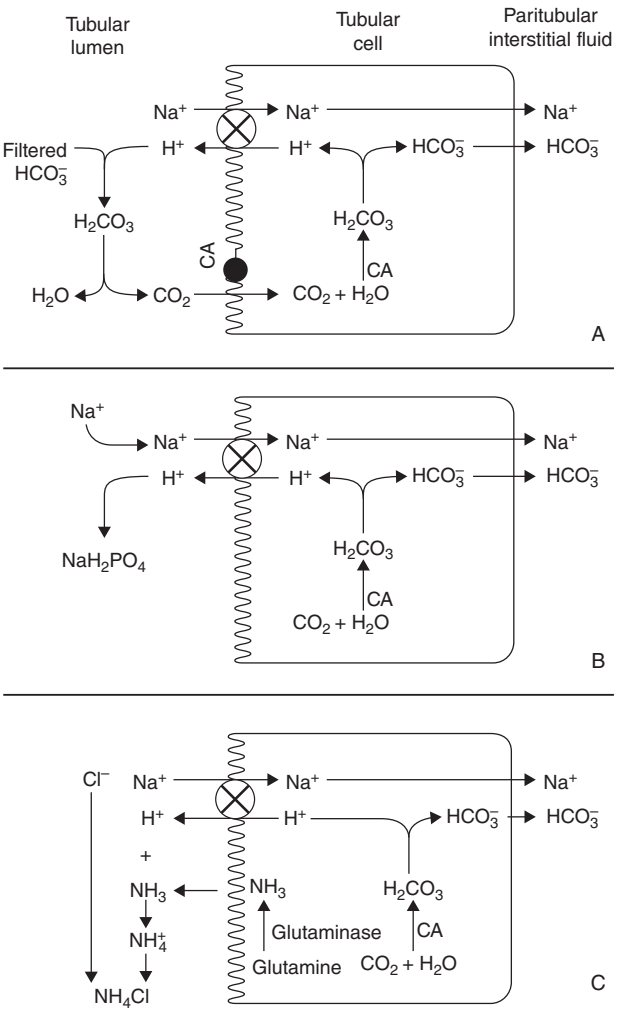

Figure 23.5 Renal mechanisms for H^+ excretion. See text for explanation of each panel.

diffusable NH_3 from glutamine moving into the tubular lumen, where it combines with H^+ to form ammonium (NH_4^+). Ammonium, in turn, combines with chloride for excretion as ammonium chloride. While this is an oversimplification of the physiological events, it is acceptable to consider ammonium chloride as a flexible mechanism for H^+ secretion based on the ability of the kidney to generate ammonia.

Assessment of Acid–Base Disturbances

Disorders of acid–base equilibrium can result from a primary disturbance in pulmonary regulation of the concentration of H_2CO_3 in body fluids via changes in alveolar ventilation and P_{CO_2} levels, from metabolic changes in concentration of bicarbonate, or from a combination of these mechanisms.

The partial pressure of CO_2 (P_{CO_2}) is generally accepted as the best measure of respiratory disturbances. Assessment of P_{CO_2} depends upon availability of a blood gas analyzer and proper arterial sample collection. A blood gas analysis provides three measured parameters (pH, P_{CO_2}, P_{O_2}) and typically two calculated values (actual bicarbonate and base excess). Acidemia and alkalemia (using pH), eucapnia, hypercapnia or hypocapnia (using P_{CO_2}), and hypoxemia (using P_{O_2} if the sample is arterial) may be directly assessed. In-house blood gas and electrolyte analyzers have become much more common in practice, making assessment of these parameters practical and economical. Results obtained with one handheld analyzer appropriate for in-house testing were similar to those obtained from a standard chemistry analyzer with the exception of sodium concentration in canine samples and hematocrit in equine samples (Looney et al., 1998).

Actual bicarbonate values are useful in assessment of nonrespiratory disorders, but these values will vary with compensatory changes in alveolar ventilation and P_{CO_2}. Bicarbonate values are derived using the Henderson–Hasselbalch equation and measured values for pH and P_{CO_2}. Plasma bicarbonate values may also be estimated by measurement of total CO_2. Total CO_2 combines measurement of both the numerator and the denominator of the tail of the Henderson–Hasselbalch equation ($[HCO_3^-]/[H_2CO_3]$) by converting both to measurable CO_2. Total CO_2 and plasma bicarbonate are used interchangeably in reporting plasma bicarbonate concentrations even though total CO_2 is actually plasma bicarbonate plus 1.1–1.3 mEq of H_2CO_3. As compared to actual plasma bicarbonate, standard bicarbonate is defined as the concentration of bicarbonate after fully oxygenated whole blood has been equilibrated with CO_2 at a P_{CO_2} of 40 mmHg at 38°C; this measurement eliminates the influence of respiration on plasma HCO_3^-.

Standard base excess (BE) is the concentration of titratable base of ECF; this value may be calculated using a Siggaard–Anderson alignment nomogram that interrelates BE and total CO_2 and HCO_3^- when pH and P_{CO_2} are measured. Because this calculation is based on a constant oxygen saturation, error may be introduced by inclusion of air bubbles in a poorly handled blood sample. In veterinary medicine, error may also be inherent because the nomogram is based on human blood and excludes the effects of plasma protein and electrolytes on acid–base equilibrium. BE is useful because it accounts for the effects of CO_2 on carbonic acid equilibrium and identifies nonrespiratory causes of acid–base derangement. Base deficit is defined as the negative of base excess (Bailey and Pablo, 1998).

Anion Gap

Further analysis, beyond pH, P_{CO_2}, HCO_3^-, and BE, may be useful in assessment of complex acid–base

disturbances. The anion gap (AG) is defined as the difference between the quantity of unmeasured cations (UCs) and unmeasured anions (UAs) in the blood. Major UAs include phosphates, sulfates, and organic acids (e.g., lactate, citrate, ketones), with chloride and bicarbonate being the measured anions. Major UCs include calcium and magnesium, with sodium and potassium being the measured cations. Calculation of the AG according to the following equations reflects the law of electroneutrality, according to which total cations must equal total anions (DiBartola, 1992d).

$$[Na^+] + [K^+] + [UC] = [Cl^-] + [HCO_3^-] + [UA]$$

$$\text{Anion gap} = UC - UA = ([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-])$$

The normal AG varies with the species but is approximately 13–24 mEq/l in dogs and cats. AG is most often used to identify causes of metabolic acidosis. In organic acidoses, HCO_3^- buffers hydrogen ions that are generated from dissociation of organic acid (e.g., lactic acid). In theory, the measured $[HCO_3^-]$ should decrease as the concentration of the UA (the organic acid) increases. As long as $[Cl^-]$ remains unchanged (normochloremic metabolic acidosis), the gap will increase proportionately with the increase in acid. Several factors that may confound this simple relationship include the following: (i) other buffers besides HCO_3^- also respond to the influx of organic acid; (ii) the volume of distribution of HCO_3^- may be different from that of the acid; and (iii) the patient's AG baseline (prior to the presenting illness) is often not known. Hence the AG is useful but not fully predictable.

Increased AG often occurs in lactic acidosis, diabetic ketoacidosis, azotemic renal failure (due to increased phosphates and sulfates), and poisoning (ethylene glycol, salicylate). Constable et al. (1997) demonstrated a useful correlation between AG and serum creatinine concentration in calves with experimentally induced diarrhea and adult cattle with abomasal volvulus. Although the AG was not a useful predictor of all anion-associated changes (e.g., no correlation was found between AG and blood lactate levels), the AG could alert clinicians to the potential presence of uremic acidosis.

A normal AG usually occurs in metabolic acidosis related to diarrhea, renal tubular acidosis, excessive use of carbonic anhydrase inhibitors, or ammonium chloride administration and in iatrogenic expansion acidosis caused by excessive normal saline administration. The two most common causes of a decreased AG are hypoalbuminemia or dilution of plasma proteins caused by infusion of crystalloid solutions. In both cases the gap decreases as a result of a decreased concentration of net negative charges associated with plasma proteins. Each 1.0 g/dl decrease in albumin is associated with an approximately 2.4 mEq/l decrease in the AG (Gabow, 1985).

Nontraditional (Stewart's) Acid–Base Analysis

An understanding of the traditional interrelationships between H^+, CO_2, and HCO_3^- is adequate to explain the behavior of aqueous solutions; however, it does not account for the effects of plasma proteins and electrolytes, particularly sodium and chloride, on acid–base status in biological systems. Stewart described a new approach to understanding acid–base physiology based on three fundamental concepts of electrolyte chemistry (Stewart, 1978, 1983). First, electroneutrality must always be maintained. Hence, as with the concept of the AG, the sum of all positive charges must equal the sum of all negative charges. Second, mass must be conserved even though it may change in form within a solution. Finally, the dissociation or ionization of a substance in water is determined by its dissociation constant. Weak electrolytes relevant to acid–base physiology include proteins, water, and CO_2. In contrast, sodium and chloride are considered strong electrolytes because they are fully dissociated in water. Evaluation of acid–base status using the Stewart approach requires assessment of independent, or primary, variables; dependent, or unknown, variables; and dissociation constants of all variables. Values of independent variables are controlled externally and cannot be changed by processes occurring within the solution. Independent variables dictate the acid–base status of a solution.

The independent variables controlling acid–base status in biological solutions are strong ion difference (SID), PCO_2, and total weak acid concentration (A_{TOT}). The first variable, SID, is the sum of the strong cation concentrations minus the sum of the strong anion concentrations:

$$SID = ([Na^+] + [K^+]) - ([Cl^-] + [\text{lactate}^-] + [\text{ketoacid}])$$

Unless lactic acidosis or ketoacidosis is suspected in a given case, these terms may be eliminated from the equation since their values would be quite small. Likewise, $[K^+]$ is often dropped from the equation since it contributes a relatively small number to the total cation population. If PCO_2 and A_{TOT} remain constant, increases in SID suggest nonrespiratory alkalosis and decreases suggest nonrespiratory acidosis. Mean normal SID values are derived by each laboratory based on their reference population, and these values vary across species. The second independent variable, PCO_2, is an indication of the amount of CO_2 dissolved in plasma. As in traditional acid–base theory, an increase in PCO_2 shifts the dissociation equation for carbonic acid to the right, increasing the $[H^+]$ and making the solution more acidic. The final independent variable, $[A_{TOT}]$, is accounted for by plasma proteins (95%), primarily albumin, and inorganic phosphates (5%). A_{TOT} has

been calculated for horses (Constable, 1997) using the formula

$$[A_{TOT}]\ (mEq/l) = 2.25\ [albumin]\ (g/dl) + 1.4\ [globulin]\ (g/dl) + 0.59\ [phosphate]\ (mg/dl)$$

These three independent variables influence several dependent, or unknown, variables. Dependent variables are affected by processes occurring within the solution and do not change unless independent variables change. Values for dependent variables are thus the result, not the cause, of events in solution. Dependent variables include $[H^+]$, $[HCO_3^-]$, carbonate ion concentration ($[CO_3^{2-}]$), $[OH^-]$, concentration of dissociated weak acids ($[A^-]$), and concentration of nondissociated weak acids ([AH]). Values of dependent variables are not affected by the values of other dependent variables. Because the values for $[CO_3^{2-}]$ and $[OH^-]$ are so small, they are not measured or evaluated in a clinical setting. The variables for dissociated and nondissociated weak acids reflect the dynamic relationship between acid–base balance and protein ionization. The ability of proteins to function as enzymes, cell membrane pumps, ion channels, receptors, etc., depends upon their state of ionization, and this is directly affected by changes in independent variables (PCO_2, SID, and A_{TOT}). Likewise, the ratio of ionized to unionized calcium depends upon protein binding, which changes with alterations of A_{TOT} and pH.

Independent variables are controlled via respiration (PCO_2) and renal function (SID). As in traditional acid–base theory, rate and depth of respiration control retention or elimination of CO_2, which may lead to respiratory acidosis or alkalosis, respectively. Control of SID is primarily accomplished by the kidney with a smaller contribution from the gastrointestinal tract. Changes in SID via the kidneys are achieved much more slowly than respiratory changes and are on the order of hours to days. The kidney regulates SID by differential reabsorption of Na^+ and Cl^-. Since Na^+ reabsorption is strongly related to renal regulation of ECF volume, net Cl^- excretion relative to net Na^+ excretion is the primary mechanism for renal regulation of acid–base balance. Control of PCO_2 and SID is the primary determinant of acid–base balance because there is no evidence that the body alters the third independent variable, protein concentration $[A_{TOT}]$, in order to regulate acid–base balance.

In summary, the most important premise of Stewart's approach is that concentrations of HCO_3^- and H^+ are dependent on concentrations of primary, or independent, variables, notably CO_2, Na^+, and Cl^-. The complex equations derived by Stewart address the changes induced by independent variables and quantitate each potential influence by solving for the dependent variables. Much simplified versions of Stewart's formula have been adopted on a limited basis by clinicians who value Stewart's theories and believe that they provide a more complete picture of acid–base derangements. Table 23.11 summarizes the equations being applied for nontraditional analysis of nonrespiratory acid–base status (Russell et al., 1996). In brief, increases in SID suggest nonrespiratory alkalosis, whereas decreases suggest nonrespiratory acidosis. Negative values for Δ albumin suggest hyperproteinemic acidosis, whereas positive values reflect hypoproteinemic alkalosis. Negative values for Δ phosphorus suggest hyperphosphatemic acidosis. Negative changes in free water point to dilutional acidosis, and positive values suggest concentration alkalosis. Positive values for Δ chloride suggest hypochloremic alkalosis, and negative values suggest hyperchloremic acidosis.

Table 23.11 Formulas for quantitative analysis of nonrespiratory acid–base status

I. Estimation of [SID] (all values expressed as mEq/l)
   $[SID\ approx.] = [Na^+_{mean\ normal}] - [Cl^-_{corrected}]$
   $[Cl^-_{corrected}] = [Cl^-_{patient}] \times ([Na^+_{mean\ normal}] / [Na^+_{patient}])$
II. Alterations in acid–base balance
   A. Changes in acid–base balance due to weak acids
      Δ albumin (mEq/l) = $3.7 \times ([alb_{mean\ normal}]\ (mg/dl) - [alb_{patient}]\ (mg/dl))$
      Δ phosphorus:
      $[phos_{adjusted}]\ (mg/dl) = [phos_{mean\ normal}]\ (mg/dl) - [phos_{patient}]\ (mg/dl)$
      $phos_{adj}\ (mg/dl) \times 0.3229 = phos\ (mmol/l)$
      effective phos (mEq/l) = 1.8 × phos (mmol/l)
   B. Changes in acid–base balance due to alterations in [SID] (all values expressed in mEq/l)
      Δ free water = $z([Na^+_{patient}] - [Na^+_{mean\ normal}])$
      where $z = [SID] / [Na^+_{mean\ normal}]$
      Δ chloride = $[Cl^-_{mean\ normal}] - [Cl^-_{corrected}]$
      Δ unmeasured anions (UA) = BE − (Δ free water + Δ Cl^- + Δ phos + Δ albumin)

BE, base excess; SID, strong ion difference; UA, unmeasured anions.

While most clinicians still favor the traditional approach to evaluation of acid–base balance, modified applications of Stewart's theories broaden this scope and lend useful quantitative insights into the complexities of acid–base disturbances (Constable, 1999).

Disorders of Acid–Base Metabolism

Disorders of acid–base equilibrium can result from a primary disturbance in pulmonary regulation of the concentration of CO_2, from metabolic changes in strong ions and, dependently, bicarbonate, or from a combination of these mechanisms. An acid–base disturbance is considered simple if it is limited to a primary disturbance and an appropriate secondary or compensatory response. Primary disturbances and expected compensatory responses are modeled using the tail of the Henderson–Hasselbalch equation in Table 23.10 and summarized in Table 23.12. Mixed acid–base disturbances are suspected

Table 23.12 Characteristics of primary acid–base disturbances. Source: Adapted from Rose, 1994.

Disorder	pH	[H+]	Primary disturbance	Compensatory response
Metabolic acidosis	↓	↑	↓ [HCO_3^-], ↓ [SID]	↓ PCO_2
Metabolic alkalosis	↑	↓	↑ [HCO_3^-], ↑ [SID]	↑PCO_2
Respiratory acidosis	↓	↑	↑ PCO_2	↑ [HCO_3^-], ↑ [SID]
Respiratory alkalosis	↑	↓	↓ PCO_2	↓ [HCO_3^-], ↓ [SID]

SID, strong ion difference.

when the compensatory response to a primary disorder is not as expected or when the pH is changing in a direction opposite that predicted by the primary disorder. Mixed acid–base disturbances are characterized by two or more primary disturbances in the same patient.

Metabolic (Nonrespiratory) Acidosis

Metabolic acidosis may be characterized by a decrease in plasma HCO_3^- concentration, decreased pH, increased concentration of strong anions (such as chloride, lactic acid, or ketoacids), and decreased plasma sodium concentration associated with renal disease or diarrhea. The clinical signs most commonly associated with metabolic acidosis are hyperpnea and CNS depression. Laboratory analysis of blood and urine reveals a lowered urine and blood pH, decreased serum HCO_3^- (<20 mEq/l), decreased [SID], and a variable serum PCO_2 depending upon the degree of respiratory compensation. Figure 23.6 summarizes causes of metabolic acidosis and provides general principles of treatment. Metabolic acidosis is the most common acid–base disorder in dogs, cats, and horses, and causes may be usefully subdivided into those conditions that increase the AG and those that do not.

Loss of Na^+ and HCO_3^- associated with diarrhea is the most common cause of normal AG (hyperchloremic) metabolic acidosis. Intestinal secretions replete in Na^+ and HCO_3^- may also be sequestered in lower obstructive bowel disease and paralytic ileus. Hypoadrenocorticism may also present with a nongap metabolic acidosis, but these patients usually have hypochloremia as a result of impaired water excretion, lack of aldosterone, and poor renal function.

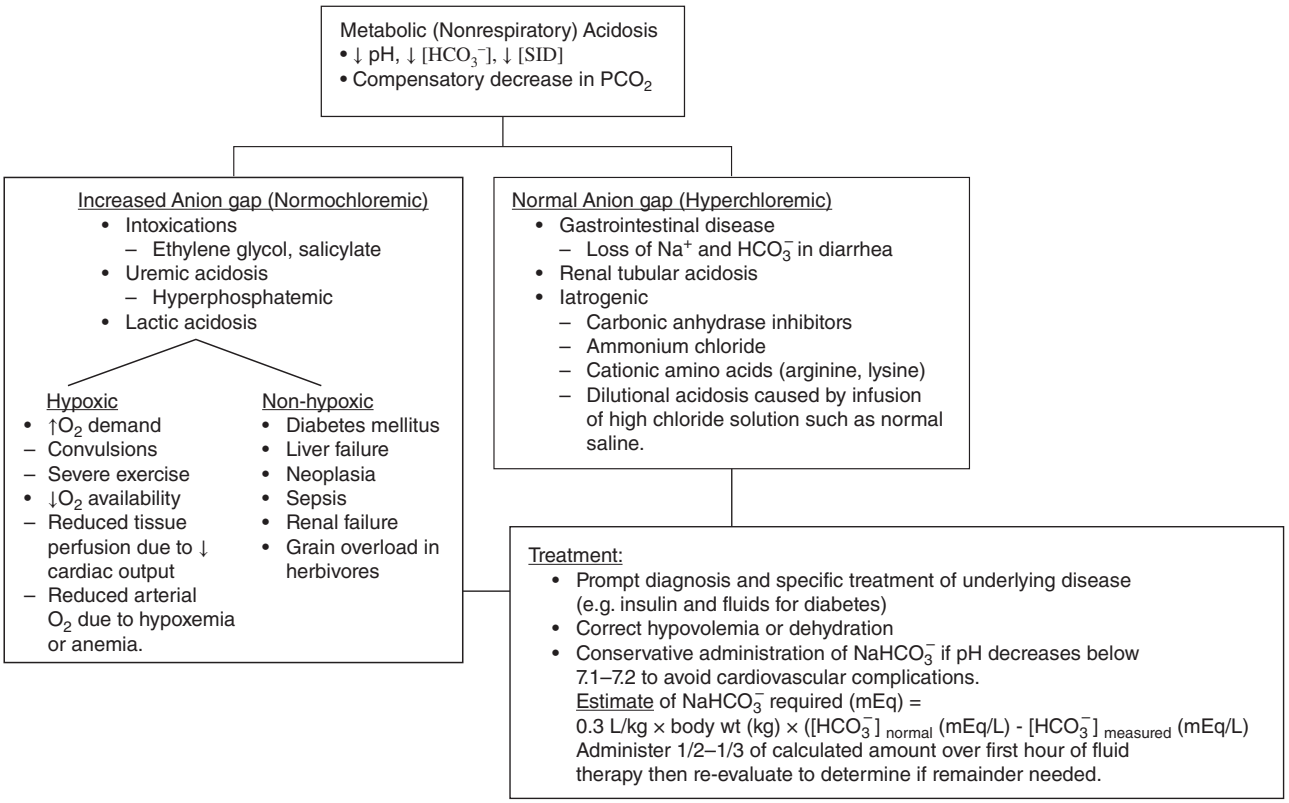

Figure 23.6 Causes of metabolic acidosis and general treatment principles.

Lactic Acidosis

Production of lactic acid and accumulation of lactate, an unmeasured anion, decrease the [SID], resulting in a high AG metabolic acidosis. Lactic acid is the final product of anaerobic glycolysis in eukaryotic cells and is formed by the action of lactate dehydrogenase (LDH) on pyruvic acid with NADH as a cofactor.

$$CH_3COO^- + NADH + H^+CH_3CHOHCOO^- + NAD^+(\text{pyruvate})\text{LDH}(\text{lactate})$$

The direction of the LDH reaction depends upon the relative intracellular concentrations of pyruvate and lactate and on the ratio of reduced (NADH) to oxidized (NAD^+) nicotinamide adenine dinucleotide cofactor. Newly produced lactic acid is partially buffered by HCO_3^-, resulting in rapid generation of sodium lactate, which dissociates to lactate and sodium ions. Under aerobic conditions in the liver and the kidney, lactate is converted back to pyruvate, and pyruvate is metabolized through the tricarboxylic acid (TCA) cycle to yield HCO_3^-, CO_2, and H_2O. Alternatively, hepatic uptake of lactate and conversion to pyruvate can feed gluconeogenesis, a process that also regenerates HCO_3^-. In either case, the net result of aerobic lactate metabolism is production of alkalinizing equivalents in the form of HCO_3^-:

Conversion via the TCA cycle

$$\text{lactate}^- + 3O_2 \rightarrow HCO_3^- + 2CO_2 + 2H_2O$$

Conversion via gluconeogenesis

$$2\ \text{lactate}^- + 2H_2O + 2CO_2 \rightarrow 2HCO_3^- + \text{glucose}$$

If the ratio of NADH/NAD^+ in the cell shifts toward accumulation of NADH (e.g., in exercising muscle or poorly oxygenated tissues), more lactic acid accumulates, decreasing cellular pH. In the case of poorly oxygenated tissues, inability to oxidize NADH via the respiratory chain blocks oxidative phosphorylation and production of ATP. ATP depletion in lactic acidosis causes leaky ATP-dependent K^+ channels, leading to hyperpolarized membranes and decreased Ca^{++} influx via voltage-dependent Ca^{++} channels. Decreased intracellular Ca^{++} produces smooth muscle relaxation, vasodilation, and a potential decline in systemic blood pressure (Landry and Oliver, 1992).

Causes of the two types of lactic acidosis, hypoxic (type A) and nonhypoxic (type B), are listed in Figure 23.6. (Only L-lactate is metabolized by animals; hence the discussion that follows refers only to L-lactic acidosis and not D-lactic acidosis, a condition described in humans and associated with small bowel resection or short bowel syndrome.) Reduced tissue perfusion and hypoxia caused by cardiac arrest/cardiopulmonary resuscitation, shock, hypovolemia, left ventricular failure, low cardiac output, and acute pulmonary edema limit oxygen availability and force cells into anaerobic glycolysis. As NADH accumulates, the LDH reaction is pushed to the right, resulting in lactic acid accumulation. Successful management of most of these conditions involves returning tissue perfusion and oxygenation to normal, often with the aid of parenteral fluid administration. Reversal of circulatory failure decreases further lactate accumulation and, if the liver is well perfused, will result in conversion of accumulated lactate to HCO_3^-.

Administration of $NaHCO_3^-$ to animals suffering from lactic acidosis is controversial. Benefits could include improved tissue perfusion related to reversal of acidemia-induced vasodilation and an increase in [SID] (associated with Na^+ administration). Potential risks include overshoot metabolic alkalosis caused by the cumulative effect of $NaHCO_3^-$ administration and metabolism of the accumulated lactate into HCO_3^-. A study in rats (Halperin et al., 1996) concluded that $NaHCO_3^-$ therapy extended the period of survival during acute, hypoxic L-lactic acidosis. Hypoxia was induced in anesthetized, paralyzed rats ventilated with a lowered (5.5%) oxygen concentration, which was sufficient to cause a severe degree of L-lactic acidosis. Survival in rats receiving $NaHCO_3^-$ was close to twofold longer than in rats receiving no sodium bicarbonate or NaCl only. The rate of $NaHCO_3^-$ infusion was titrated to equal the rate of L-lactic acid appearance in the ECF of control hypoxic rats. Part of the benefit of alkali treatment was hypothesized to be increased anaerobic glycolysis, causing enhanced ATP and L-lactic acid production and a decreased oxygen consumption. Despite continued accumulation of L-lactic acid and a decrease in cardiac output that was greater than in control rats, availability of ATP for vital organs was considered critical to prolonged survival in alkali-treated animals. While results using this controlled model are not directly clinically applicable, they suggest that continued consideration of the advantages and disadvantages of alkali supplementation in L-lactic acidosis may be merited. Many clinicians favor a conservative therapeutic approach in which small amounts of $NaHCO_3^-$ are administered to keep the arterial pH above 7.1–7.2 and to avoid progressive decline in cardiovascular function (Rose, 1994). In the absence of severely elevated concentrations of lactate, and in the presence of a well-perfused liver, the use of lactate-containing alkalinizing solutions is effective for volume restoration. Alternatives to lactate-containing solutions include $NaHCO_3^-$, sodium gluconate, and sodium acetate.

Ketoacidosis and Other Causes

Metabolic acidosis associated with ketonemia and ketonuria occurs when the rate of formation of ketone bodies is greater than the rate of their use. This occurs most often in two conditions, diabetes mellitus and starvation. Excess acetyl coenzyme A (CoA) derived

from fatty acid or pyruvate oxidation is diverted, primarily in the liver, to production of ketone bodies (acetoacetate, β-hydroxybutyrate, acetone). Ketones can be transported in the blood and utilized as an energy source by peripheral tissues. In diabetes the lack of insulin increases lipolysis, and an excess of glucagon indirectly increases fatty acetyl CoA entry into hepatic mitochondria for conversion to ketones. An elevation of ketones in the blood results in acidemia because the carboxyl group of the ketone body has a pK_a of about 4. At physiological pH the ketoacid is fully dissociated, losing a proton (H^+), which lowers blood pH. Addition of an unmeasured anion, the ketoacid, decreases the [SID] driving an acidosis. Ketoacidosis is often complicated by dehydration associated with osmotic (glucose-driven) diuresis. The use of alkali to treat diabetic ketoacidosis is controversial and not generally recommended. Rehydration (usually with normal saline) and administration of insulin is the treatment of choice since circulating ketoacids will subsequently be metabolized to HCO_3^- and move plasma pH toward normal.

Renal failure typically produces a normochloremic, high-AG metabolic acidosis due to accumulation of phosphates, sulfates, and other organic anions, altered handling of chloride, and an inability to excrete the daily dietary acid load. Enhanced generation of ammonia by the renal tubular cells allows the kidney to respond, up to a point, to the chronic retention of fixed acid. Use of alkali to treat metabolic acidosis associated with renal failure is controversial. Three reasons cited in support of treatment are that treatment (i) spares depletion of bone serving as a H^+ buffer, (ii) prevents the potentially catabolic effects of acidosis on muscle protein, and (iii) limits complement-mediated tubulointerstitial damage that may occur in concert with increased ammoniagenesis. Oral administration of $NaHCO_3^-$ (0.5–1.0 mEq/kg/day) with the goal of maintaining plasma HCO_3^- at 15 mEq/l may be effective if the associated sodium load does not encourage fluid retention.

Metabolic (Nonrespiratory) Alkalosis

Metabolic alkalosis is characterized by an excess of HCO_3^- caused by a deficit of H^+ in the ECF. This state may be caused by excessive vomiting (especially from gastrointestinal obstruction), excessive alkaline therapy, or use of diuretics that can create iatrogenic metabolic alkalosis, or excessive loss of potassium caused by hyperadrenocorticism or administration of large quantities of K^+-free solutions. Clinical signs of metabolic alkalosis are depressed breathing (slow and shallow), nervous excitement, including tetany, and even convulsions and muscular hypertonicity. Respiratory compensation is not as effective as respiratory compensation for metabolic acidosis.

Values for serum electrolytes usually reveal elevated [HCO_3^-], lowered [Cl^-], and variable [Na^+]. There is usually a low serum [K^+] in this condition. A relationship exists between K^+ loss and metabolic alkalosis in that each can result in the other (positive feedback). In ruminants the situation is much more complex, and unlike in small animals, metabolic alkalosis is much more common. Compensation for metabolic alkalosis requires the kidneys to excrete HCO_3^- and retain H^+. Therapy for metabolic alkalosis involves treatment of the underlying disease and, potentially, use of acidifying solutions such as NaCl (0.9%), NH_4Cl (1.9%) (NH_3^+ is conjugated to urea in the liver, which frees H^+ and Cl^-), and Ringer's solution, which supplies Na^+, K^+, Ca^{++}, and Cl^-.

Respiratory Acidosis

Respiratory acidosis (Table 23.13) involves retention of CO_2 as a consequence of alveolar hypoventilation. The fall in pH is predictable from the Henderson–Hasselbalch equation. Impaired respiration can be

Table 23.13 Causes of respiratory acidosis. Source: Adapted from DiBartola, 1992a. Reproduced with permission of Elsevier.

Inadequate mechanical ventilation
Airway obstruction
Respiratory center depression
Neurologic disease
Drugs (e.g., anesthetic agents, narcotics, sedatives)
Cardiopulmonary arrest
Neuromuscular defects
Myasthenia gravis
Tetanus
Botulism
Polyradiculoneuritis
Polymyositis
Tick paralysis
Hypokalemic periodic paralysis in Burmese cats
Hypokalemic myopathy in cats
Drugs (e.g., succinylcholine, pancuronium, aminoglycosides with anesthetics, organophosphates)
Restrictive defects
Diaphragmatic hernia
Pneumothorax
Pleural effusion
Hemothorax
Chest wall trauma
Pulmonary fibrosis
Pyothorax
Chylothorax
Pulmonary disease
Respiratory distress syndrome
Pneumonia
Severe pulmonary edema
Diffuse metastatic disease
Smoke inhalation
Pulmonary thromboembolism
Chronic obstructive pulmonary disease
Pulmonary fibrosis

caused by pneumonia, pulmonary edema, emphysema, pneumothorax, respiratory muscle paralysis, morphine, barbiturate, or anesthetic poisoning, airway occlusion, or, most commonly, hypoventilation during positive pressure ventilation (iatrogenic). Clinical signs include respiratory distress and CNS depression with progressive disorientation, weakness, and finally coma (CO_2 narcosis). Cyanosis is often present in the advanced stages. Laboratory analysis of blood and urine will show a decreased urine pH, decreased blood pH, increased serum HCO_3^- (from tissue buffers and renal reabsorption of HCO_3^-), and a decrease in serum Cl^- because of renal excretion. Hypoventilation results in CO_2 retention, an excess of H_2CO_3, and thereby an excess of H^+. The compensatory mechanism is for the kidneys to conserve HCO_3^- and excrete H^+. The most important treatment for this condition is proper ventilation of the animal. Use of alkalinizing solutions may aid in cases of lung disease when ventilation alone will not correct the condition. Whenever possible, therapy should be directed at removal of the causative factor.

Respiratory Alkalosis

Causes of respiratory alkalosis are indicated in Table 23.14. The most common cause of this disease in animals is overactive positive pressure ventilation during anesthesia (iatrogenic). Other causes include fever, stimulation of respiratory centers by encephalitis, salicylate intoxication, a deficiency of O_2 (hypoxia), heat prostration, or conditions causing chronic hyperventilation (excessive blowing off of CO_2). Clinical signs include hyperpnea (with or without panting), hyperactive tendon reflexes, and CNS stimulation with or without convulsions. Laboratory analysis reveals increased urine pH, increased blood pH, and decreased serum HCO_3^-. Serum Cl^- is usually normal to slightly increased, and pathogenesis of the condition relates to excessive blowing off of CO_2. Compensation occurs by renal excretion of HCO_3^- and retention of H^+. Treatment for this condition should involve correcting the hyperventilation, when feasible, and use of the same acidifying solutions used for metabolic alkalosis. Underlying etiological factor(s) must be eliminated.

Table 23.14 Causes of respiratory alkalosis. Source: Adapted from DiBartola, 1992a. Reproduced with permission of Elsevier.

Overzealous mechanical ventilation
Hypoxemia (stimulation of peripheral chemoreceptors by decreased oxygen delivery):
Right-to-left shunts
Decreased Po_2 (e.g., high altitude)
Congestive heart failure
Severe anemia
Hypotension
Pulmonary diseases resulting in ventilation–perfusion mismatching:
Pneumonia
Pulmonary embolism
Pulmonary fibrosis
Pulmonary edema
Pulmonary disease resulting in stimulation of nociceptive receptors independent of hypoxemia:
Pneumonia
Pulmonary embolism
Interstitial lung disease
Pulmonary edema
CNS-mediated hypocapnia with direct stimulation of medullary respiratory center:
Liver disease
Gram-negative sepsis
Drugs (e.g., salicylate intoxication, progesterone, xanthines)
Recovery from metabolic acidosis
Central neurological disease
Heat stroke

Mixed Acid–Base Disturbances

The preceding discussion of acidosis and alkalosis has purposely dealt with idealized, single etiological processes in the genesis of acid–base abnormalities. Such states rarely exist in real life. Mixed disturbances usually occur, and treatment will often convert one type of acid–base disturbance into another. Proper therapy must include careful appraisal of repeated laboratory determinations and close observation of the clinical situation. Using these techniques, mixed disturbances can be identified, evaluated, and managed successfully. Examples of potential causes of mixed respiratory and metabolic disorders are noted in Table 23.15.

Practical Aspects of Fluid Therapy

Diagnosis and Monitoring

When fluid therapy is under consideration, the practitioner must ask the following six questions: (i) When should fluid therapy be instituted? (ii) What kind(s) of solution(s) should be used? (iii) How much fluid should be administered? (iv) How fast should the solution be given? (v) What route of administration should be used? (vi) How will the success of the therapy be evaluated? The answers to these questions are individual in nature and are critically dependent on a knowledge and understanding of normal homeostatic mechanisms. They are also dependent on the history of the patient, a basic understanding of how a particular disease affects water and electrolyte balance, and a correct diagnosis.

The purpose of fluid and electrolyte therapy is to correct dehydration or overhydration and electrolyte imbalance and/or acid–base imbalance. It may also be indicated to correct a condition of acidosis or alkalosis,

Table 23.15 Examples of potential causes of mixed respiratory and metabolic disorders. Source: Adapted from DiBartola, 1992a. Reproduced with permission of Elsevier.

Respiratory acidosis and metabolic acidosis
Hypoadrenocorticism-like syndrome in dogs with gastrointestinal disease
Cardiopulmonary arrest
Severe pulmonary edema
Thoracic trauma with hypovolemic shock
Low-cardiac-output heart failure with pulmonary edema
Advanced septic shock
Gastric dilatation volvulus
Acute tumor lysis syndrome
Respiratory acidosis and metabolic alkalosis
Pulmonary edema and diuretics
Gastric dilatation volvulus
Respiratory alkalosis and metabolic acidosis
Hypoadrenocorticism-like syndrome in dogs with gastrointestinal disease
Septic shock
Salicylate toxicity
Heat stroke
Gastric dilatation volvulus
Liver disease (renal tubular acidosis and impaired metabolism of lactate)
Lactic acidosis with excessive hyperventilation
Pulmonary edema
Parvovirus gastroenteritis and septicemia
Severe exercise
Acute tumor lysis syndrome
Cardiopulmonary resuscitation
Respiratory alkalosis and metabolic alkalosis
Gastric dilatation volvulus
Hyperadrenocorticism with pulmonary thromboembolism
Ventilator-induced mixed alkalosis (too rapid correction of abnormal arterial P_{CO_2})
Congestive heart failure and diuretics
Hepatic disease and diuretics
Vomiting or hypoproteinemia
Parvovirus gastroenteritis and septicemia

treat shock, give parenteral nourishment, or even stimulate organ function (i.e., the kidneys). Causes of fluid, electrolyte, and/or protein loss include situations wherein substances are not available because of lack of supply or condition of the animal; for example, an animal with a fractured mandible may be unable to take in food or liquid, or an animal with a CNS disturbance may be unable to eat or drink because of the primary disease state. Other causes of fluid, electrolyte, and/or protein imbalances may involve excessive elimination.

The following information must be acquired by questioning the owner, observation of the patient, and/or clinical examination: duration and frequency of vomiting and/or diarrhea, consistency of stools, frequency of urination, color of urine, presence and character of thirst, fluid and dietary intake, dryness or elasticity (turgor) of the skin, nature and color of the mucous membranes and sclera, presence of excessive salivation or panting, odor of the breath, and weight loss or gain.

In combination with clinical signs, laboratory examination of the blood provides a rational basis for estimating patient fluid and electrolyte needs and monitoring treatment success. Measurements should include hematocrit, plasma protein, blood gases (P_{O_2}, P_{CO_2}, base excess, HCO_3^-, or total CO_2) and electrolytes (Na^+, K^+, Cl^-), blood urea nitrogen, and creatinine. Because red blood cells and plasma protein are largely limited to the vascular space, the concentration of both tends to increase with dehydration. It is best to assess both hematocrit and plasma protein since results of one or the other test alone can be misleading if preillness values are out of the normal range. For example, preexisting anemia, hypoproteinemia, or physiological events such as splenic contraction can confound interpretation of either parameter if considered alone.

Collection, measurement, and analysis of urine are important for proper care of the critically ill patient. Urinalysis should include tests for specific gravity, glucose, acetone, pH, and albumin and microscopic sediment examination. During a state of dehydration, if the kidneys are functioning normally, specific gravity will increase and urine volume will decrease. If the specific gravity of urine is unchanged or lowered and the animal shows clinical signs of dehydration, the kidneys are probably not functioning properly, and more sophisticated renal function tests must be employed. Specific gravity of urine should be monitored during the treatment period. A decrease in this parameter indicates that hydration is taking place. If the animal has not yet received treatment with a solution containing glucose and it is found in the urine, diabetic acidosis is possibly the cause of dehydration. The urine glucose should also be monitored during treatment. If the animal is receiving glucose and the urine glucose reaches $^+3$ or $^+4$, the dosage must be lowered. Acetone in the urine is a frequent finding during dehydration and/or carbohydrate starvation. If the pH of the urine in species with normally acid urine tests alkaline, a diagnosis of alkalosis may be indicated if no kidney or urinary tract disease is present. The presence of urinary albumin and sediment may be an indication of renal disease. If the kidneys are functioning properly, they can adjust markedly to insult. However, in the presence of renal impairment, therapy must be specific or the treatment may be fatal.

Diligent assessment of clinical signs and laboratory parameters is essential to successful diagnosis and monitoring of fluid and electrolyte imbalances. Useful parameters are summarized in Table 23.16.

Fluid Volume and Type

A standard approach to estimating fluid volume needs should be used. Replacement of adequate volume is often the single most important key to improved clinical status

Table 23.16 Parameters to be monitored during fluid therapy. Source: Adapted from DiBartola, 1992a. Reproduced with permission of Elsevier.

Normal bronchovesicular lung sounds on auscultation
Packed-cell volume
Total protein
Electrolytes: Na^+, Cl^-, Ca^{2+}, HCO_3^-
Arterial pH
Arterial PCO_2
Urine output
Body weight
Hemodynamics
Central venous pressure
Pulmonary capillary wedge pressures
Mean arterial pressure
Mean pulmonary arterial pressure

of animals with multiple fluid and electrolyte disturbances. Volume replacement should have three specific aims: correct existing deficits, satisfy maintenance needs, and replace continuing loss. Initial volume deficits are addressed by administration of replacement fluids. Calculation of the amount of fluid needed is based on clinical and laboratory assessment of percent of dehydration. See Table 23.5 for a summary of signs correlated to degree of dehydration. The volume needed to address the initial deficit is estimated according to the following equation:

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

Clinicians working with both small and large animals should become comfortable with the large differences in volume that will be required to address deficits in different animals. For example, the replacement volume needed to address an 8% fluid deficit in a dehydrated mare weighing 500 kg is 100 times greater than that needed for a similarly dehydrated cat weighing 5 kg. Forty liters of fluid would initially be administered to the mare versus 400 ml to the cat. In general, the composition of replacement fluids should reflect the composition of the volume of fluid lost. For example, if the volume deficit is related to loss of electrolyte-rich gastrointestinal fluid, then a balanced replacement solution containing Na^+, K^+, Cl^-, and bicarbonate equivalents would likely be selected. Table 23.17 details the compositions of commonly utilized replacement fluids.

Table 23.17 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	2780	0	0	0	0	0	50	0
	7.5% saline	—	2566	1283	0	1283	0	0	0	0
	8.4% $NaHCO_3$	—	2000	1000	0	0	0	0	0	1000
	14.9% KCl	—	4000	0	2000	2000	0	0	0	0

BES, balanced electrolyte solution.

In addition to replacing existing deficits, maintenance fluid needs must be calculated. Maintenance fluids are needed when a patient does not voluntarily ingest sufficient food and water to replace normal losses occurring via urine, feces, respiratory tract, and skin. The average resting animal at standard conditions of humidity and temperature has a rather constant rate of water turnover. For practical purposes, 40–65 ml/kg/24 h (30 ml/lb/day is often used as a rule of thumb) for mature animals and 130 ml/kg/24 h for immature animals serve as average water turnovers for all mammalian species. Based on these assumptions, an average mature dog weighing 20 kg requires about 1.3 l for a daily maintenance supply of water, while a horse weighing 450 kg would require about 29 l/day. Maintenance needs may be modified under conditions of severe stress or fever, extreme environmental conditions, or in the presence of various disease processes. Older animals may need more or less maintenance volume depending upon the presence of polyuria or compromised cardiovascular function, respectively. Administration of various drugs (e.g., glucocorticoids, diuretics) will also affect maintenance needs. The electrolyte composition of fluids used for maintenance differs from that of replacement fluids used to address initial deficits. Because of the composition of fluid lost daily in urine and as insensible loss from the skin and respiratory tract, maintenance fluids are typically lower in sodium (approximately 40 mEq/l) and higher in potassium (approximately 10–16 mEq/l) than replacement fluids. Table 23.17 details the composition of both commercial maintenance fluids and maintenance fluids that can be prepared using other commonly available fluid components. In veterinary medicine, in contrast to human medicine, patients are less often transitioned from replacement to maintenance fluids. Consequently, veterinary hospitals do not typically stock commercially available maintenance fluid.

If the animal being treated continues to lose water during the treatment period (e.g., due to continued vomiting, diarrhea, polyuria) this additional amount must be estimated and added to the replacement and maintenance volumes. The volume required to replace continued loss is based on clinical observation (e.g., frequency of defecation, character and volume of feces in the case of diarrhea). Like the volume used to address the initial deficit, the type of fluid selected to replace continuing loss should, in general, resemble the fluid lost. More often than not, balanced electrolyte solutions such as lactated Ringer's are chosen.

Application of the principles outlined above may be appreciated using the following case example. A 2-year-old, 20-kg mixed-breed dog presents with a chief complaint of diarrhea of 2 days' duration. A physical exam reveals a loss of skin elasticity and a definite delay in return of skin to normal position when tented. Both mucous membranes and tongue are dry and the eyeballs feel soft and slightly sunken. Capillary refill time is slightly prolonged. Based on these clinical signs, dehydration is assessed at 8%. The dog is continuing to pass semi-fluid stools every 2–3 hours, resulting in an estimated ongoing loss of 150 ml/day. The owner reports that the dog is not eating or drinking. Calculation of the volume of fluid to be administered to this dog over the next 24 hours would include

Replacement of initial deficit:	20 kg × 0.08 =	1.6 l
Maintenance needs:	65 ml/kg/day × 20 kg =	1.3 l
Continued loss:		0.15 l
Total estimated fluid needs:		3.05 l

This volume is considered an estimate because it is based on clinical signs and average maintenance losses. Despite the importance of good data collection and appropriate application of fluid therapy principles, at some level adjusting volume is dependent upon a "guess and reassess" process driven by diligent and thorough patient observation (Roussel, 1990).

Rates and Routes of Administration

The rate of fluid and/or electrolyte replacement should parallel the severity of dehydration and electrolyte or acid–base imbalance. Fluids should be administered rapidly at first and then at decreasing rates until the condition is corrected. The rate of infusion is slowed after the first hours of administration to align with a daily administration rate of 200 ml/kg/day or about 8 ml/kg/h. Rates of about 15 ml/kg/h are cited and Cornelius et al. (1978) have shown that rates of 90 ml/kg/h are tolerated in moderately dehydrated, unanesthetized normal dogs. These rates of fluid administration are not recommended for ill animals (e.g., cardiac, renal or other dysfunction) as heart failure can occur with overly aggressive fluid administration. No deaths occurred in the Cornelius study, but clinical signs of severe overhydration were evident in dogs given fluids at 360 ml/kg/h. At 90 ml/kg/h pulmonary artery wedge pressures and central venous pressures were increased in dogs with normally functioning hearts. A seriously ill dog, with compromised cardiac muscle contractility, could be injured by infusion rates that result in acute volume overload. If central venous pressures are being monitored, the infusion rate can be individually adjusted for each patient. This technique is simple and inexpensive. The attending veterinarian should monitor this parameter in the critically ill patient and adjust the rate of fluid administration according to individual needs.

Infusion rates of 50 ml/kg/h have been tolerated in severely dehydrated cases but this is considered aggressive. Less severe cases could be aggressively

managed with initial rates of 15–30 ml/kg/h but lower rates are often used. In all cases the rate of infusion should be slowed after the first hour of administration and should be slowed considerably if no urine flow is established. After 4 or more hours of fluid administration without urine flow, the rate of administration should be 2 ml/kg/h or less. Every attempt must be made to establish renal function if no urine flow is detected after 2 hours of fluid administration. To accurately monitor urine flow, all critically ill animals should have a urinary bladder catheter in place.

Common sense and clinical judgment must be exercised. If an animal is severely dehydrated and in shock, it is difficult to administer fluids too fast during the initial stages of treatment. If, however, an animal is almost normally hydrated and the aim is only to maintain hydration, the rate should be slowed considerably. The importance of renal function has been repeatedly emphasized and is typically assessed by measurement of blood urea nitrogen, creatinine, and urine specific gravity.

The route of fluid administration depends on the type of illness being dealt with and the severity of the condition, degree of dehydration, condition of the patient, type of electrolyte imbalance, organic functions of the patient, and time and equipment available. Probably the easiest, most physiological, and most overlooked route of administration of fluid and electrolytes is oral or nasogastric. The oral route is the least dangerous, since the solution can be administered without strict attention to tonicity, volume, and asepsis. Oral replacement of electrolytes by using combinations of electrolyte salts, glycine, and dextrose has been especially successful (Hamm and Hicks, 1975). Proper technique for oral fluid administration should preclude complications associated with fluid aspiration or administration of excessive amounts of air. A relatively unused route of administration that might be considered, especially in very young animals, is per rectum. Warm water, K^+, Na^+, and Cl^- are well absorbed via this route. It may be difficult, however, to get the animal to retain material given in this manner, especially in the presence of gastrointestinal disease. Rectal infusion of fluids in birds has been suggested as an effective alternative route to intravenous, intraosseous, oral, or subcutaneous (Ephrati and Lemeij, 1997).

The most commonly used and perhaps most practical routes of fluid and electrolyte administration are the parenteral routes: intravenous (IV), subcutaneous (SC), intraperitoneal (IP), or intraosseous (IO). The IV route is the most versatile. Severe disturbances of fluid and electrolyte balance demand it. Nearly all the toxicity of solutions administered in this manner is more related to rate than volume or composition. No indications for hypotonic solutions have been found, but indications for isotonic and hypertonic solutions exist, and some of these have been discussed previously. Some of the problems associated with IV administration include those associated with maintenance and asepsis of indwelling catheters, clotting, and hematomas, as well as the location of a vein on very small or very ill animals. Obviously, the fluids administered and equipment used must be sterile. Large volumes of fluid administered too rapidly may overload the circulatory system, causing pulmonary edema and even death, especially in severely ill or toxic cases. This is the preferred route for blood, blood plasma, and plasma volume expanders.

Subcutaneous administration of fluid is referred to as hypodermoclysis. This technique is convenient for correction of mild to moderate deficits in small animals. Fluids are absorbed more slowly than by the IV route, but if the animal is not in critical condition, this is of no real consequence. Only isotonic solutions should be used in this manner. Dextrose of any tonicity or any solutions lacking electrolytes in isotonic levels are contraindicated because they may produce an initial rapid diffusion of major extracellular electrolytes to the area. This can result in severe reactions, including death, especially if the animal is already in shock. Hypodermoclysis is extremely valuable in very young or very small animals. If the animal is difficult to restrain long enough for a prolonged IV infusion, this is a useful technique. When edema is present, absorption will not occur, and this route of administration is contraindicated. If the animal is chilled by a cold environment or a cold fluid is injected, absorption by this route will be delayed, and it is recommended that fluids be prewarmed to body temperature when feasible. Administration of fluids in one anatomical location should be limited to amounts that are readily absorbed (approximately 10–12 ml/kg) (Greco, 1998). Fluid should be deposited dorsally along the area bordered by the scapulae anteriorly and the iliac crests posteriorly. Hypodermoclysis is not commonly used as a route of administration in large animals.

IP infusion of fluids has the same restrictions as those for hypodermoclysis. The technique may predispose to peritonitis, so aseptic procedures must be used. The fluids are mobilized faster than in SC administration, but this route is potentially more hazardous (puncture of abdominal organs). Nevertheless, this is a good route for electrolyte and water absorption. Plasma and a large percentage of red blood cells administered using this technique are rapidly absorbed. In large animals it can be a very practical method of treatment, since a large quantity of fluid can be administered rapidly with few adverse effects. Perhaps the greatest application of this technique is with peritoneal lavage.

Intraosseous fluids are administered through a catheter placed into bone. This route may be chosen if vascular access is limited or cannot be performed in adequate time due to very small patient size, cardiac arrest,

Table 23.18 Indications, dosages, administration, and side effects associated with use of selected colloids in dogs. Source: Modified from Rudloff and Kirby, 1998. Other sources for information in table include Mathews, 1998 and Hughes, 2000.

Type of colloid	Indications	Dosage and administration	Side effects and contraindications
Plasma	Coagulopathies; disseminated intravascular coagulation; low antithrombin; acute hypoalbuminemia.	20–30 ml/kg/day administered: (a) continuously over 24 h, (b) as a 2–4 h infusion, (c) 6–10 ml/kg in 1-h infusions every 8 h, or (d) until plasma albumin is over 2.0 g/dl. Approximately 22.5 ml/kg of plasma needed to increase patient albumin by 5 g/l.	Rapid volume expansion may be detrimental to patients with oliguric or anuric renal failure or congestive heart failure.
Dextran 40	Rapid, short-term intravascular volume resuscitation from hypovolemic shock; rapid improvement of microcirculatory flow by lowering blood viscosity; prophylaxis of deep vein thrombosis and pulmonary emboli.	10–20 ml/kg/day IV bolus to effect; with distributive shock due to SIRS dextran can be followed by a CRI of hetastarch to maintain MAP of at least 80 mm Hg.	*See* plasma. Dilutional effect on serum coagulation factors in addition to possible direct effects on these factors. Contraindicated in patients with severe coagulopathies. Sludging of RBCs in microcirculation in dehydrated patients may occur if sufficient crystalloids are not administered. Anaphylaxis reported in humans. AKI has been reported.
Dextran 70	Rapid, intravascular volume resuscitation from hypovolemic, traumatic, or hemorrhagic shock.	*See* dextran 40.	*See* dextran 40. Dextran 70 is thought to impair coagulation more than dextran 40. No AKI reported.
Hetastarch (hydroxyethyl starch or HES)	Rapid, intravascular volume resuscitation from all forms of shock; small-volume resuscitation; volume replacement and maintenance in SIRS patients.	10–40 ml/kg/day IV bolus to effect; with cardiogenic shock, pulmonary contusions, or head injury, 5 ml/kg boluses are administered to effect, using the smallest volume possible to maintain MAP of 80 mm Hg.	*See* dextran 40. Anaphylaxis has not been reported with hetastarch, but pruritus possibly associated with deposits of HES in cutaneous nerves has been reported in up to 33% of patients treated with long-term infusions. AKI may be a concern.
Pentastarch (PEN)	Rapid, intravascular volume resuscitation from hypovolemic, traumatic, or hemorrhagic shock.	10–25 ml/kg/day; terminal half-life shorter than HES.	*See* dextran 40. Anaphylaxis and AKI have not been reported.
Vetstarch	Treatment and prophylaxis of hypovolemia. Not a substitute for red blood cells or coagulation factors in plasma	Up to 20 ml/kg/day in small animal patients; infuse initial 10–20 ml slowly and observe for possible anaphylactoid reactions.	See dextran 40.

AKI, acute kidney injury; CRI, constant-rate infusion; MAP, mean arterial pressure; SIRS, systemic inflammatory response syndrome.

hypovolemic shock, or patient anatomy (Mazzaferro, 2009).

Products for Fluid Therapy

Major categories of parenteral fluids include crystalloids, colloids, blood replacements, and nutritional solutions. Blood replacement products (whole blood, blood components, and red blood cell substitutes) and nutritional solutions (amino acids and fat emulsions) are considered elsewhere. The composition and characteristics of selected crystalloid solutions and additives used to spike parenteral solutions are listed in Table 23.17. Types and recommended dosages of synthetic colloids are listed in Table 23.18.

Crystalloids

As detailed in Table 23.17, crystalloid solutions are polyionic but differ in the amount of each ion and in tonicity. As discussed previously, the tonicity of

parenteral fluids partially dictates distribution of volume into interstitial and intracellular spaces. Fluids that most closely resemble the ECF are isotonic, high in sodium, and low in potassium and may be acidifying or alkalinizing. These replacement fluids, also referred to as balanced electrolyte solutions (BES), may be given in large volumes at a rapid rate to patients in shock in an attempt to reestablish effective perfusion without severely altering electrolyte concentrations. Alkalinizing solutions depend upon metabolism of various substrates (e.g., lactate, acetate, gluconate) to alkalinizing equivalents in order to reduce acidemia. Lactate and acetate are metabolized in the liver and muscle, respectively, while gluconate is metabolized widely in the body. Perfusion and function of the liver are required for generation of alkalinizing equivalents from the most commonly used replacement fluid, lactated Ringer's solution. A large percentage of veterinary patients that require fluid therapy suffer from nonrespiratory acidosis and are treated with alkalinizing balanced electrolyte solutions. These fluids are generally indicated for animals suffering from diarrhea, vomiting (assuming vomitus contains bile), renal disease, trauma, and shock and those requiring pre- and postsurgical support. To avoid calcium precipitation, calcium-containing balanced electrolyte solutions, such as lactated Ringer's solution, should not be coadministered through the same port with whole blood or sodium bicarbonate.

Normal saline and Ringer's solution are considered acidifying solutions and are used to treat the relatively small percentage of small-animal patients that present with metabolic alkalosis. Both solutions are high in chloride and promote renal excretion of bicarbonate. Normal saline is also commonly used in treatment of patients with electrolyte disorders such as hyperkalemia or hypercalcemia in which absence of electrolytes in parenteral fluids is desirable. Assuming appropriate insulin therapy is instituted, normal saline is also considered the fluid of choice for treatment of diabetic ketoacidosis.

Colloids

The critical distribution of water between plasma and interstitial fluid is maintained in part by the colloid osmotic pressure (COP) of plasma protein. COP includes the osmotic pressure exerted by plasma proteins and their associated electrolyte molecules. This force draws water into capillaries and balances the hydrostatic pressure driving water out (see Starling relationships described in Section Fluid and Electrolyte Distribution). Although the basic concept of Starling relationships is straightforward, in vivo application of these concepts is complicated by the heterogeneity of Starling forces within different tissues and the complexity of transvascular fluid dynamics. Despite these caveats, it is practical to say that the balance between intravascular COP and capillary hydrostatic pressure drives net fluid extravasation and forms the basis for intravenous colloid therapy.

Therapeutic colloids may be of two types: natural and synthetic. Natural colloids include whole blood, plasma, and albumin. Synthetic colloids, include dextran 40, dextran 70, hetastarch, pentastarch, and oxypolygelatin. Therapeutic colloid solutions contain large particles and are retained within the vascular space more readily than crystalloids. As a result, smaller volumes of colloids cause greater volume expansion than crystalloids do. Initial tissue perfusion has been found to be better after volume expansion with colloids or combinations of colloids and crystalloids than with crystalloids alone (Funk and Baldinger, 1995). The duration of this effect varies and is dependent upon many variables, including the species of animal, dose, specific colloid formulation, preinfusion intravascular volume status, and microvascular permeability (Hughes, 2000).

The osmotic effect of colloid solutions is related to the number of particles rather than the size of particles in a solution. However, heterogeneity of particle size causes considerable complexity in the pharmacokinetics of these solutions. Synthetic colloids contain molecules that vary in molecular weight more than the molecules in a solution of a natural colloid such as albumin. After synthetic colloids are administered, the smaller molecules pass rapidly into the urine and are eliminated or move to the interstitium, negating their ability to attract water into the vasculature. Larger molecules remain in the circulation to exert COP until they are hydrolyzed by amylase or removed by the monocyte phagocytic system. Because of differences in particle behavior and in pharmacokinetic study design (e.g., duration of study, volume status of study subjects, volumes and rates of colloid administration), specific half-lives reported for colloids may vary considerably (Mathews, 1998). Such variation may pose therapeutic problems since actual duration of action of colloids may not coincide with manufacturer estimates of the same.

Indications for colloid use include perfusion deficits, hypooncotic states, deficiency of blood components, and diseases that lead to systemic inflammatory response syndrome (SIRS). SIRS is a generalized inflammatory process with evidence of decreased organ perfusion. Sepsis may be the source of SIRS but other conditions may also result in generalized systemic pathophysiology (e.g., heat stroke, acute pancreatitis, and neoplasia). Hallmarks of SIRS include alterations in temperature, heart rate, respiratory rate, P_{CO_2}, and white blood cell count. Peripheral vasculature dilates, capillary permeability increases, and plasma proteins leak from affected vessels. The resulting hypoalbuminemia leads to a reduction in COP, loss of vascular volume, and hypoperfusion

of tissues. High-molecular-weight colloids administered to SIRS patients are retained more effectively in leaky vessels and force retention of volume. Approximately 20–24% of crystalloid remains within the vasculature 1 hour after infusion into normal animals compared with 100% of the volume of infused colloid. Hence, colloids may initially expand the volume of the intravascular space approximately fourfold more than crystalloids (Hughes, 2000).

Colloids are often included in fluid regimens for small-volume resuscitation (e.g., during traumatic, hypovolemic, or cardiogenic shock), improvement of microcirculatory flow and capillary integrity (e.g., SIRS), and management of ongoing hemorrhage. While colloids are useful in reestablishing vascular integrity, replenishment of interstitial and intracellular fluid deficits depends upon appropriate use of colloids and crystalloids in combination. Colloid administration typically reduces the required amount of crystalloid fluid by as much as 40–60% (Rudloff and Kirby, 1998). Care must be taken to adjust amounts and rates of all fluids administered to prevent intravascular volume overload and subsequent interstitial edema. Monitoring of colloid therapy ideally includes direct measurement of COP with a membrane osmometer in addition to measurement of traditional indices of perfusion and hydration.

Problems associated with colloid therapy may include dilutional effects caused by expansion of the intravascular space. Packed-cell volume, albumin concentration, serum potassium concentration, and amount of circulating coagulation factors typically decline following administration of synthetic colloids. Rapid volume expansion may be of greatest concern in patients with oliguric or anuric renal failure or congestive heart failure. Precipitation of acute renal failure (now more commonly referred to as acute kidney injury) has been reported in humans with dextran 40 (Ferraboli et al., 1997) and is also of concern in veterinary patients (Hayes et al., 2016). Impairment of coagulation as a result of dilution of coagulation factors is another clinically important potential side effect (Gauthier et al., 2015). Adverse effects and lack of outcomes advantages of resuscitation using colloids as compared to crystalloid solutions has been shown in humans and is of concern in veterinary patients (Cazzolli and Prittie, 2015). Anaphylactic or anaphylactoid reactions associated with colloids have been reported in humans. Concern has also been raised over the effects of selected colloids on reticuloendothelial function (Hughes, 2000). Because cats are more likely to show signs of allergic reactions, especially when synthetic colloids are administered quickly, only small volumes infused at slow rates (5 ml/kg increments given over 5–10 minutes, repeated to effect up to 20 ml/kg) are recommended for use in this species.

Table 23.18 lists indications, dosages, and administration details for colloids used to treat dogs. Albumin (66,000–69,000 daltons) accounts for 80% of the COP of the only natural colloid listed, plasma. Each gram of albumin can retain as much as 18 ml of fluid in the intravascular space, assuming infused albumin does not leak from damaged vessels. The intravascular half-life of albumin in plasma is approximately 16 hours (Mathews, 1998). The three major categories of synthetic colloids are dextrans, hydroxyethyl starches, and gelatins. Dextrans are prepared from a macromolecular polysaccharide produced by bacterial fermentation of sucrose. Because these products represent a range of molecules with different molecular weights, they are described by a weight average molecular weight (MWw). MWw is defined as the sum of the number of molecules at each molecular weight times their mass divided by the total weight of the molecules. Dextran 70 (MWw = 70,000 daltons) was used in the past as a 6% solution in either 0.9% saline or 5.0% dextrose but is no longer readily available. Hydroxyethyl starches are derived from plant amylopectin and are modified by hydroxyethylation to reduce hydrolysis by amylase. Hetastarch (Hespan®) has a MWw of 100,000–300,000 daltons and is available as a 6% (6 g/dl) solution in 0.9% saline. Vetstarch (Voluven®)(6% hydroxyethyl starch 130/0.4 in 0.9% sodium chloride) is increasingly preferred due to fewer side effects. Pentastarch has a narrower range of molecular weights and a shorter duration of action than hetastarch. In the United States pentastarch is only approved for leukapheresis, while in Canada it is approved as a plasma volume expander. In 2013, the FDA announced a boxed warning on increased mortality, renal injury, and risk of bleeding with use of hydroxyethyl starch solutions in some settings with human patients.

Hypertonic Solutions

For several decades, resuscitation of experimental and clinical animals suffering from shock has been attempted using hypertonic saline (HSS), and studies have generally supported the benefits of HSS for transient restoration of cardiovascular function. Although a full understanding of the mechanism of action has been elusive, there is agreement that the primary benefits of HSS infusion result from plasma volume expansion. High circulating concentrations of sodium attract water into the vasculature from the interstitial and intracellular spaces and help to restore capillary flow and tissue perfusion. Cardiac output has been reported to increase as a result of increased preload, decreased afterload related to systemic and pulmonary vasodilation (Constable et al., 1995), increased adrenergic activity through release of catecholamines, and improved oxygen delivery to the heart (Tobias et al., 1993). Positive inotropy has also been reported but this remains a controversial point (Cambier

et al., 1997). In vitro studies have shown that, at least during the initial treatment period, negative inotropy may predominate (Constable et al., 1994). All of the above effects are short lived (peak occurs within approximately 1 hour) but resuscitative benefits may be prolonged by combination of HSS with colloids such as dextran 70. Ideally, rapid recovery of cardiovascular parameters occurs with administration of smaller volumes of HSS or HSS plus dextran (HSD) compared to crystalloids, thus decreasing the risk of edema related to volume overload. In addition to primary volume expansion, HSS is thought to invoke a lung vagal reflex important to circulatory control during hypovolemia. How much this reflex contributes to the cardiovascular effects of HSS infusion remains controversial. HSS may also have immunomodulatory effects that protect organs from oxidative injury and enhance cell-mediated immunity (Coimbra et al., 1996).

HSS use is indicated in the treatment of shock associated with hemorrhage (Bauer et al., 1993), trauma (Schertel et al., 1996), gastric-dilatation volvulus (Schertel et al., 1997), acute pancreatitis (Horton et al., 1989), burns (Horton et al., 1990), and sepsis (Fantoni et al., 1999; Maciel et al., 1998). The evidence for use of HSS in the first three of these is most compelling, with fewer studies unequivocally demonstrating advantage under specific study conditions associated with the other disorders. HSS has also been utilized in treatment of head injury since, like mannitol, HSS draws interstitial and intracellular water away from edematous tissues and into the vasculature (Prough and Zornow, 1998). Regardless of the indication, HSS effects are transient, necessitating combination with crystalloids or colloids to achieve long-term resuscitative goals. Effects of HSS should be monitored by improvement in cardiovascular parameters correlated with increased perfusion as well as by assessment of mean arterial blood pressure, electrocardiogram, and electrolytes. Monitoring is aimed at preventing volume overload and electrolyte imbalances that may occur as a result of therapy.

HSS use is contraindicated in hypernatremic patients or those with increased plasma osmolality. Use in dehydrated animals is controversial since these patients frequently suffer from increases in both parameters. Studies that support HSS use in the presence of dehydration include those in which resuscitation with HSD of hypovolemic, diarrheic calves found this method to be at least as effective as others (Constable et al., 1996; Walker et al., 1998). In animals suffering from shock related to trauma and hemorrhage, two additional problems, hypokalemia and increased risk of rehemorrhaging, may be of concern. Rehemorrhage – bleeding caused by breakdown of clots in areas where hemorrhage has previously occurred – may be related to the sudden increase in cardiac output and arterial blood pressure associated with HSS resuscitation (Schertel and Tobias, 2000). HSS may also dilute circulating coagulation factors and affect platelet function. As with colloids, these concerns may only be of practical significance if the patient suffers from preexisting coagulopathies or thrombocytopenia. Using a swine model of hemorrhagic shock, Dubick et al. (1993) demonstrated that the combination of 7.5% NaCl/6% dextran 70 did not significantly affect various measures of coagulation and platelet aggregation in their model. Studies continue to address the pros and cons of HSS use in various animal models and in clinical patients (Krausz, 1995). Variation across species lines, differences in physiological circumstances of each study, and different views of cost versus benefit ratios may account for differing conclusions on the overall value of HSS treatment.

HSS is administered most effectively in combination with colloids or crystalloids in order to optimize resuscitative effects; 5% HSS, at a dose of 6–10 ml/kg, and 7–7.5% HSS, at a dose of 4–8 ml/kg, are administered at a rate of 1 ml/kg/min. Similar dosages may be used for HSD. More rapid administration rates may invoke a vagal-mediated hypotension, decreased heart rate, bronchoconstriction, and rapid, shallow breathing. To prepare 7% saline in 6% dextran 70, 33.0 g of anhydrous sodium chloride is added to a 500 ml bag of 6% dextran 70 in 0.9% saline. Half of the sodium chloride crystals are placed into the barrel of a 35 ml syringe and an adequate volume of dextran 70 solution is drawn into the syringe to dissolve the crystals. This solution is filtered through a 0.22 μm filter and is injected back into the bag of dextran 70. The procedure is repeated a second time to dissolve the remaining half of the sodium chloride (Schertel and Tobias, 2000). Although a reported advantage of HSS is presumed sterility due to hypertonicity, St. Jean et al. (1997) have demonstrated the ability of bacteria to adapt and survive in the hypertonic environment of HSS. Hence, aseptic technique consistent with handling of all intravenous fluids should be followed.

Blood Substitutes

The term *oxygen carrier* (or *oxygen therapeutic*) has replaced the terms *blood substitute* and *red blood cell substitute* because it more appropriately describes the common oxygen-carrying role of these agents, which have some but not all of the functions of blood (Wohl and Cotter, 1995; Awasthi, 2005). Two types of products have been developed for use as oxygen carriers—perfluorocarbons (PFCs) and hemoglobin-based oxygen carriers (HBOCs). Neither of these two types of products are currently readily available.

Perfluorochemicals

Perfluorochemicals are comprised of carbon and fluoride, are chemically inert, and are insoluble in water.

They were originally developed as hydraulic fluids and transformer coolants but are used as oxygen carriers because of their ability to dissolve oxygen and carbon dioxide. PFCs have a high oxygen solubility and are emulsified with a surfactant for intravenous administration. Unemulsified PFCs can dissolve 40–56 ml of oxygen per 100 ml of liquid while emulsified PFC dissolves 5–8 ml O_2/100 ml. The oxygen content of PFC has a linear dependence on PO_2 and in order to transport physiological quantities of oxygen a very high oxygen tension is needed. This factor limits the use of PFCs as oxygen carriers to situations where high oxygen tension can be maintained (e.g., surgery). PFCs have a short intravascular half-life, can activate the complement cascade, and have a slow elimination (Rentko, 1992; Wohl and Cotter, 1995).

Fluosal-DA is a 20% (by weight) emulsion previously licensed by the FDA for use in humans during coronary angioplasty surgery. PFC can also be potentially used during tumor radiation therapy, vascular surgery, extracorporeal organ perfusion, peritoneal lavage, and carbon monoxide poisoning (Rentko, 1992; Wohl and Cotter, 1995).

The half-life of perfluorochemicals depends upon the molecular size and structure of the agent. PFCs are expired in the lungs after phagocytosis by fixed macrophages, primarily in the liver and spleen (Wohl and Cotter, 1995).

Hemoglobin-Based Oxygen Carriers

Hemoglobin-based oxygen carriers (HBOCs) are useful for replacing red blood cells in anemic humans and animals. These products contain purified hemoglobin, removed from red blood cells and suspended in solution, and are especially useful when compatible red blood cells are not available. These solutions can pass through microcirculation more readily than red blood cells making them ideal for treating severe anemia or hypovolemia due to acute hemorrhage or poor blood flow distribution (Callan and Rentko, 2003; Lichtenberger, 2004).

HBOCs are developed from animal or human hemoglobin. Hemoglobin is an iron-containing protein composed of a tetramer of two α-chains and two β-chains with a heme molecule within the folds of each chain. When hemoglobin is administered, it breaks down into its constituent chains and has toxic effects (Awasthi, 2005). The dissociation is also associated with a short circulation half-life (Rentko, 1992). Small-sized, modified hemoglobin chains tend to extravasate, sequester nitric oxide, and cause vasoconstriction (Awasthi, 2005).

Cross-linking, glutaraldehyde polymerization, or polyethylene glycolation of hemoglobin prevents dissociation, improves the circulation half-life, and increases the size of the molecule to reduce extravasation (Rentko, 1992; Awasthi, 2005). The amount of cross-linking, polymerization, or polymer-linking also affects the viscosity of HBOC solutions. HBOCs cause an increase in plasma hemoglobin concentration and act as colloids to cause volume expansion (Wohl and Cotter, 1995; Awasthi, 2005).

Encapsulation is another technique used to stabilize hemoglobin. Hemoglobin can be encapsulated in nonantigenic phospholipids (liposomes), which prevents glomerular filtration and increases the half-life compared to free hemoglobin. Initial problems associated with encapsulated hemoglobin are related to reticuloendothelial stimulation, contamination with endotoxins, and rapid clearance (Rentko, 1992; Awasthi, 2005).

The only commercially available HBOC approved by the FDA for use in veterinary species is Oxyglobin® (OPK Biotech LLC, Cambridge, MA). Oxyglobin (hemoglobin glutamer-200 [bovine]), approved for use in the United States for treatment of anemia in dogs, is given as a single dose (10–30 ml/kg, 1.3–3.9 g/kg) administered at a rate no greater than 10 ml/kg/h (Hamilton et al., 2001; Callan and Rentko, 2003). This product is a purified and chemically modified bovine hemoglobin, which is stable at room temperature, has a shelf-life of 3 years, and has a similar oxygen-carrying capacity as endogenous hemoglobin (Senior, 1998; Callan and Rentko, 2003; Awasthi, 2005). The hemoglobin is polymerized to glutaraldehyde and is reconstituted in a modified lactated Ringer's solution (Hamilton et al., 2001; Lichtenberger, 2004). Oxyglobin does not need to be cross-matched and does not have the potential to transmit disease (Lichtenberger, 2004); therefore, it may be useful in emergencies when there is not time to cross-match or prepare blood products (Lanevschi and Wardrop, 2001).

The product has an osmolality of 300 mOsm/kg, lower viscosity than whole blood, hemoglobin concentration of 13 g/dl, colloidal oncotic pressure of 20–25 mm Hg, and a half-life of around 36 hours (30–40 hours) (Rentko, 1992; Senior, 1998; Callan and Rentko, 2003; Lichtenberger, 2004). It has a pH of 7.8 and expands the intravascular space by at least its own volume (Lichtenberger, 2004). Oxyglobin is not associated with renal toxicity, and there is no clinical evidence of allergic reaction with repeated doses (Rentko, 1992). Hamilton et al. (2001) demonstrated that multiple administrations of Oxyglobin (nine administrations over 50 weeks) in eight splenectomized dogs produced neither adverse physiological effects nor adverse pathological effects. Although most dogs produced Oxyglobin-specific IgG antibodies, no anaphylactic or anaphylactoid reactions were noted and the development of IgG antibodies did not affect the oxygen-carrying capacity (Senior, 1998; Hamilton et al., 2001).

The oxygen affinity of Oxyglobin is dependent on chloride ion concentration rather than the concentration of 2,3-diphosphoglycerate (2,3-DPG) (Lichtenberger, 2004). In humans and dogs the oxygen affinity

of hemoglobin is determined by the interaction of hemoglobin and 2,3-DPG in red blood cells (Rentko, 1992). The levels of 2,3-DPG decrease in blood stored over 1 week, which leads to increased oxygen binding and decreased delivery of oxygen to the tissues. Compared to canine blood, Oxyglobin has a lower oxygen affinity enhancing oxygen delivery to tissues (Lichtenberger, 2004). One gram of hemoglobin from Oxyglobin can deliver the same amount of oxygen to tissues as 3–4 grams of red blood cell hemoglobin (Callan and Rentko, 2003).

Twenty-four hours after being opened, the product must be discarded due to the production of methemoglobin and to avoid bacterial contamination (Callan and Rentko, 2003; Lichtenberger, 2004). Oxyglobin is stored in its deoxygenated state and becomes oxygenated when it passes through the lungs (Senior, 1998). The primary effects of Oxyglobin last about 24 hours, and 90–95% percent of Oxyglobin is eliminated in 5–9 days (Senior, 1998; Callan and Rentko, 2003; Lichtenberger, 2004).

The volume of distribution, plasma clearance, and terminal elimination half-life of Oxyglobin are dose dependent, and administration of this product increases plasma hemoglobin concentrations. Medications should not be added to the bag, and fluids and drugs should not be administered through the same infusion set as Oxyglobin (Callan and Rentko, 2003).

Hemopure® (hemoglobin glutamer-250 [bovine]) (OPK Biotech LLC, Cambridge, MA) is a glutaraldehyde-polymerized bovine hemoglobin similar to Oxyglobin approved in South Africa for use in humans (Callan and Rentko, 2003; Awasthi, 2005). Hemopure can transport oxygen, needs no refrigeration, is compatible with all blood types, has a long shelf life, and has a minimized risk of disease transmission (Fitzpatrick et al., 2005). Fitzpatrick et al. (2005) demonstrated in laboratory studies that Hemopure reversed anaerobic metabolism in the treatment of hemorrhagic shock without end-organ damage. The decreased urine output noted in animals given Hemopure in laboratory studies has been attributed to the smaller volumes needed to resuscitate the animals and has not been associated with long-term decreased renal function (Fitzpatrick et al., 2005). Animal studies with Hemopure have demonstrated that it can carry oxygen more efficiently than red blood cells on a per-gram basis (Hamilton et al., 2001).

PolyHeme® (Northfield Laboratories, Evanston, IL) is a glutaraldehyde-polymerized human hemoglobin-based product (Awasthi, 2005).

Hemospan® (MP4 or MPEG-Hb) (Sangart, San Diego, CA) is a polyethylene glycolated hemoglobin (Awasthi, 2005; Björkholm et al., 2005). MP4 is very viscous, made from stroma-free human hemoglobin, has a high oxygen affinity, and is reported to not cause vasoconstriction (Awasthi, 2005; Björkholm et al., 2005). Based on in vitro and animal studies, the lack of vasoconstriction (i.e., avoidance of engaging autoregulatory vasoconstriction) is thought to be related to increased molecular size and oxygen affinity, which lead to a decreased diffusive oxygen transfer in the plasma space (Björkholm et al., 2005).

Cross-linking or polymerization stabilizes the structure of HBOCs so that there is almost no urinary excretion. Some modified hemoglobin may still be deposited in renal tubules. Other sites of deposition for HBOCs are lymph, liver, and spleen. HBOCs use fixed macrophages in their metabolism, which may impair macrophage phagocytic ability (Wohl and Cotter, 1995).

Adverse Effects

One of the shortcomings of early HBOCs was nephrotoxicity associated with contamination with red blood cell stromal elements. Current HBOCs are ultrapurified to prevent contamination (Callan and Rentko, 2003).

HBOCs should be used cautiously in euvolemic or hypervolemic patients to avoid volume overload related to the colloidal effects of HBOCs. Cats and small mammals appear to be more predisposed to pulmonary edema following volume overload (Lichtenberger, 2004). Circulatory overload is dependent on rate of infusion and is most marked in dogs receiving greater than 10 ml/kg/h and cats receiving more than 5 ml/kg/h (Wohl and Cotter, 1995; Callan and Rentko, 2003). Because HBOCs are colloids, they should be used cautiously in patients with preexisting cardiopulmonary disease (Callan and Rentko, 2003).

Ischemia–reperfusion injury is common to all HBOCs and occurs due to production of free radicals by hemoglobin and its oxidation products (Awasthi, 2005). HBOCs can provide oxygen and iron as electron donors leading to oxygen radical production and tissue damage (Wohl and Cotter, 1995).

Anaphylactic reactions are a possibility (though not documented in clinical or research cases) with repeated administration of heterologous HBOCs (Wohl and Cotter, 1995; Callan and Rentko, 2003; Awasthi, 2005). If hypersensitivity occurs, infusion of the HBOC should be discontinued, and appropriate resuscitation measures should be implemented (e.g., crystalloids, epinephrine).

Adverse effects of HBOCs in dogs, cats, and small mammals are discoloration of mucous membranes, sclera, and urine (Wohl and Cotter, 1995; Callan and Rentko, 2003; Lichtenberger, 2004). In bird species no discoloration of urine or mucous membranes is noted. Measurements of colorimetric lab tests are affected for 24–72 hours after Oxyglobin administration (Lichtenberger, 2004).

Hypertension can also be an adverse effect of hemoglobin solutions. HBOCs have a pressor effect

that is attributed to sequestration, or scavenging, of nitric oxide following extravasation, but other mechanisms may be involved including endothelin release and sensitization of peripheral α-adrenergic receptors (Callan and Rentko, 2003; Fitzpatrick et al., 2005). Polymerization or polyethylene glycolation of hemoglobin decreases extravasation but does not completely eliminate its pressor effect (Awasthi, 2005; Fitzpatrick et al., 2005).

It is beyond the scope of this chapter to compare treatments for hemorrhagic shock, but much has been written on the topic, including therapy with blood substitutes. In a study comparing autologous/shed blood, hemoglobin-based oxygen carrier/Oxyglobin, crystalloid/saline, colloid/Hespan (6% hetastarch), and vasopressin in a canine hemorrhagic shock model (50–55% total blood loss with a mean arterial pressure of 45–50 mmHg as a clinical criterion), all resuscitation modalities except vasopressin restored microvascular and systemic function changes close to prehemorrhagic values. Autologous blood was the only treatment that restored oxygenation changes to prehemorrhagic levels (Cheung et al., 2007).

Special Topics

Horses

Horses present some special problems in acid–base management. In cases of severe diarrhea, shock, and intestinal obstruction, the horse seems predisposed to severe metabolic acidosis (Waterman, 1977). Electrolyte disorders common in horses with acute abdominal disease have been reviewed (Borer and Corley, 2006a,b). Respiratory acidosis is a very common sequel to closed-circuit inhalation anesthesia in the horse. An abnormally low concentration of Na^+ is a common problem in dehydrated horses. Severe hypokalemia, with blood K^+ values less than 2.5–3 mEq/l, may require treatment with solutions high in K^+. Dangerous hyperkalemia, with blood levels greater than approximately 7 mEq/l, may be associated with acidosis in foals. Prompt correction of the acidosis will usually correct the hyperkalemia.

Cattle

Ruminants also present special fluid and electrolyte management problems. When a diagnosis of abomasal disease is coupled with an obvious fluid balance disorder, hypochloremia, hypokalemia, and alkalosis are usually present. These should be confirmed by appropriate laboratory tests. Grain overloading will result in severe dehydration and metabolic acidosis. Calf diarrhea also results in severe dehydration and metabolic acidosis, with dangerous hyperkalemia in some cases. If hyperkalemia exists, one must guard against administration of even more K^+. When dealing with herbivores, it is important to remember that normal feed contains high levels of K^+. When these animals are anorexic, they frequently become K^+ depleted. The best way to replace K^+ deficits is by consumption of hay or grass, but K^+ must be added parenterally when the situation dictates. A wide variety of electrolyte mixtures containing K^+ are available for oral administration.

Intravenous administration of 5% dextrose alone or with isotonic sodium bicarbonate to hypernatremic, diarrheic calves has been preliminarily observed to provide benefit (Abutarbush and Petrie, 2007). Despite the fact that the average reduction rate of serum sodium concentration in these calves (n = 5) was about four times that recommended, no complications were reported in this small cohort. Further studies are needed to determine how this approach compares with other therapies.

Anesthetic and Surgical Effects

General anesthesia may exert several effects on water, electrolyte, and acid–base balance. Almost all general anesthetics induce some degree of Ca^{++} channel blockade, resulting in some degree of vasodilation and myocardial depression. The end effect can be a reduction in cardiac output and/or alterations in organ blood flow. Arterial pressures are frequently lowered in a dose-dependent manner, and GFR may be affected. The commonly used inhalation anesthetic agents (halothane, enflurane, and isoflurane) all cause direct systemic vasodilation. Narcotics and some muscle relaxants also can cause vasodilation. As a result of the vasodilation, fluid requirements may be increased during the course of the surgical procedure to maintain adequate blood pressure and cardiac output. After recovery from the general anesthetic, when vascular tone is normalized, the patient may be volume overloaded and hypertensive. Fluid loss may also increase during general anesthesia as a result of tracheal intubation and/or artificial ventilation. Normal mechanisms for the humidification of inspired air are bypassed, and the cold, dry gases from the anesthesia machine can cause a considerable amount of fluid loss. Open body cavities allow for evaporative losses. Third spacing may occur with extravasation of fluid from the vascular to the extravascular, extracellular spaces. If extravasated fluid is replaced to maintain adequate circulatory volumes, the patient with inadequate cardiac reserve or poor renal function may suffer fluid overload and congestive heart failure when postoperative redistribution of the fluid back into the circulation occurs (Gold, 1992).

Surgical injury can result in significant reductions in serum albumin, total proteins, and total lymphocyte

counts. These decreases are typically greater following abdominal surgery. The decreases have been found to be primarily caused by the volume of IV fluids frequently required for resuscitation and to compensate for blood loss.

Acknowledgment

Dr. Claire Fellman, Department of Clinical Sciences, Cummings School of Veterinary Medicine, Tufts University provided expert peer review of this chapter.

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24

Diuretics and Renal Pharmacology

Butch Kukanich and Deborah T. Kochevar

This chapter presents the physiological basis for fluid and electrolyte balance, including discussion of selected renal mechanisms for regulation of water, sodium, chloride, potassium, hydrogen, and bicarbonate. In this chapter these concepts will be extended in order to understand the mechanism of action, therapeutic uses, and side effects of diuretic agents and renal pharmacology. Diuretic agents are used to mobilize tissue fluid, most often in the treatment of edema of cardiac, renal, or hepatic origin. The history of diuretics dates back to consumption by Paleolithic humans of caffeine-containing plants. Besides xanthine derivatives such as caffeine, osmotic diuretics were clinically important prior to the 20th century. The use of mercurial diuretics, now therapeutically obsolete, began in the early 1900s and was followed by introduction of the first modern diuretic, acetazolamide, in the mid-1950s. By the late 1950s and early 1960s the formulary of modern diuretics included chlorothiazide, furosemide, and potassium-sparing diuretics (Morrison, 1997). These drugs and their relatives constitute the mainstays of diuretic treatment. Finally, the renin–angiotensin–aldosterone system will be discussed, which can be activated by different mechanisms resulting in local and systemic effects including vascular and renal effects.

Renal Physiology

Nephron Function

Knowledge of renal anatomy and physiology is essential to understanding the mechanism of action of diuretic drugs. Although a thorough review of these topics is beyond the scope of this text, a brief overview of nephron function is provided. The basic functional unit of the kidney is the nephron, which consists of a filtering apparatus, the glomerulus, connected to an extended tubular structure that reabsorbs and conditions the glomerular ultrafiltrate to produce urine. Each kidney is composed of thousands of nephron units. Figures 24.1 and 24.2 are drawings of single nephron units, indicating the broad subdivisions of nephron segments and the sites of action of diuretic agents. This diagram provides the simplest nomenclature for nephron segments. As knowledge of the function and epithelial morphology of each segment has increased, the tubular portion of the nephron has been subdivided into approximately 14 shorter segments referred to by a standardized nomenclature (Kriz and Kaissling, 1992).

Blood flow through the kidney goes from the renal artery into smaller arteries until it reaches the afferent arteriole (Figure 24.1). The afferent arteriole becomes the glomerular capillaries (where glomerular filtration occurs) then the efferent arterioles. The efferent arterioles carry blood into the peritubular capillaries, which surround the renal tubules and is where the majority of the glomerular filtrate (water, electrolytes, glucose, etc.) is reabsorbed.

Formation of urine starts in the glomerulus, where a portion of plasma water is filtered through fenestrated glomerular capillary endothelial cells, a basement membrane, and, finally, filtration slit diaphragms formed by the visceral epithelial cells that cover the basement membrane on its urinary space side. The filtrate collects in Bowman's space, a double-walled invagination that surrounds the glomerular capillaries. From Bowman's capsule the filtered fluid passes into the proximal tubule and begins its passage through the renal tubular system. Small solutes (e.g., sodium, chloride, glucose) are actively filtered with plasma water while larger elements, such as protein, blood cells, and macromolecules, are retained within the glomerular capillaries. The rate of filtration in each nephron is a function of hydrostatic pressure in the glomerular capillaries, hydrostatic pressure from the ultrafiltrate in Bowman's space, mean colloid osmotic pressure in the glomerular capillaries, colloid osmotic pressure of the ultrafiltrate in Bowman's space, and the properties of the filtering membrane. Hydrostatic pressures are the pressures of the fluid against the surface membrane; in the glomerular capillaries, hydrostatic pressure is determined by capillary blood pressure and in

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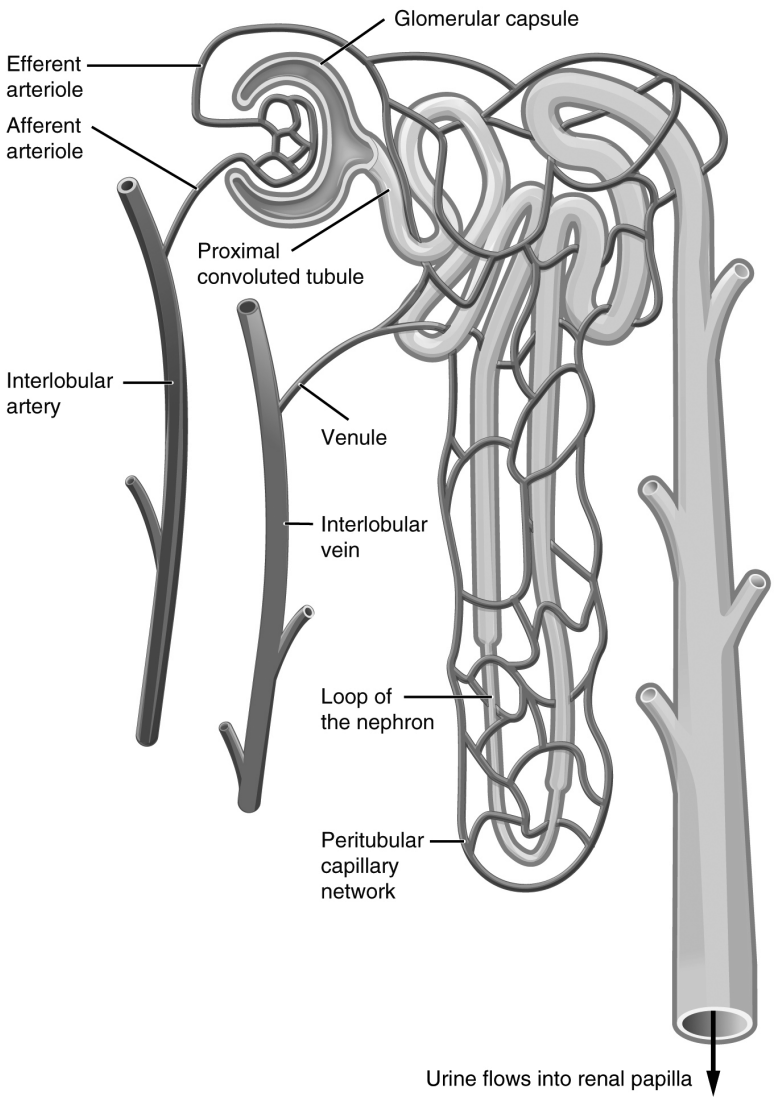

Figure 24.1 Anatomy of the nephron and associated structure. Source: http://cnx.org/contents/14fb4ad7-39a1-4eee-ab6e-3ef2482e3e22@7.30. Used under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/.

the Bowman's space by the pressure of the ultrafiltrate. The primary constituent of the glomerular capillary colloid osmotic pressure is albumin in the plasma and there is little colloidal osmotic pressure in normal urine produced by healthy glomeruli. The colloid osmotic pressure in the plasma is higher than the glomerular filtrate, resulting in an opposing force to filtration. The net filtration pressure (Figure 24.3) is determined by the following relationship:

Net filtration pressure = (blood hydrostatic pressure)
– (blood colloid osmotic pressure)
– (ultrafiltrate hydrostatic pressure)

Changes in glomerular capillary hydrostatic pressure (e.g., hyper- or hypotension), blood colloid osmotic pressure (e.g., hypoalbuminemia), and ultrafiltrate hydrostatic pressure (e.g., albuminuria) can have profound effects on glomerular filtration.

Ultrafiltrate from the glomerulus enters the proximal tubule from Bowman's capsule. By the time urine exits the distal tubule and collecting duct, better than 99% of ultrafiltrate volume will be reabsorbed. Figure 24.4 summarizes the characteristics of reabsorption in broad sections of the renal tubules.

The proximal convoluted tubule (PCT) reabsorbs the majority of sodium (~60% that enters the nephron) by various transporters and water passively follows and is eventually absorbed into the peritubular capillaries by osmosis. Nearly 100% of the glucose, amino acids, and other substances such as vitamins are also reabsorbed in the PCT by various transporters. Animals with hyperglycemia (e.g., diabetes mellitus) may have large amounts of glucose in the nephron, which exceeds the transport capacity of the active transporters to reabsorb from the nephron and glycosuria can occur. Approximately 90% of bicarbonate is reabsorbed in the PCT through the activity of the enzyme carbonic anhydrase (CA) (Figure 24.5).

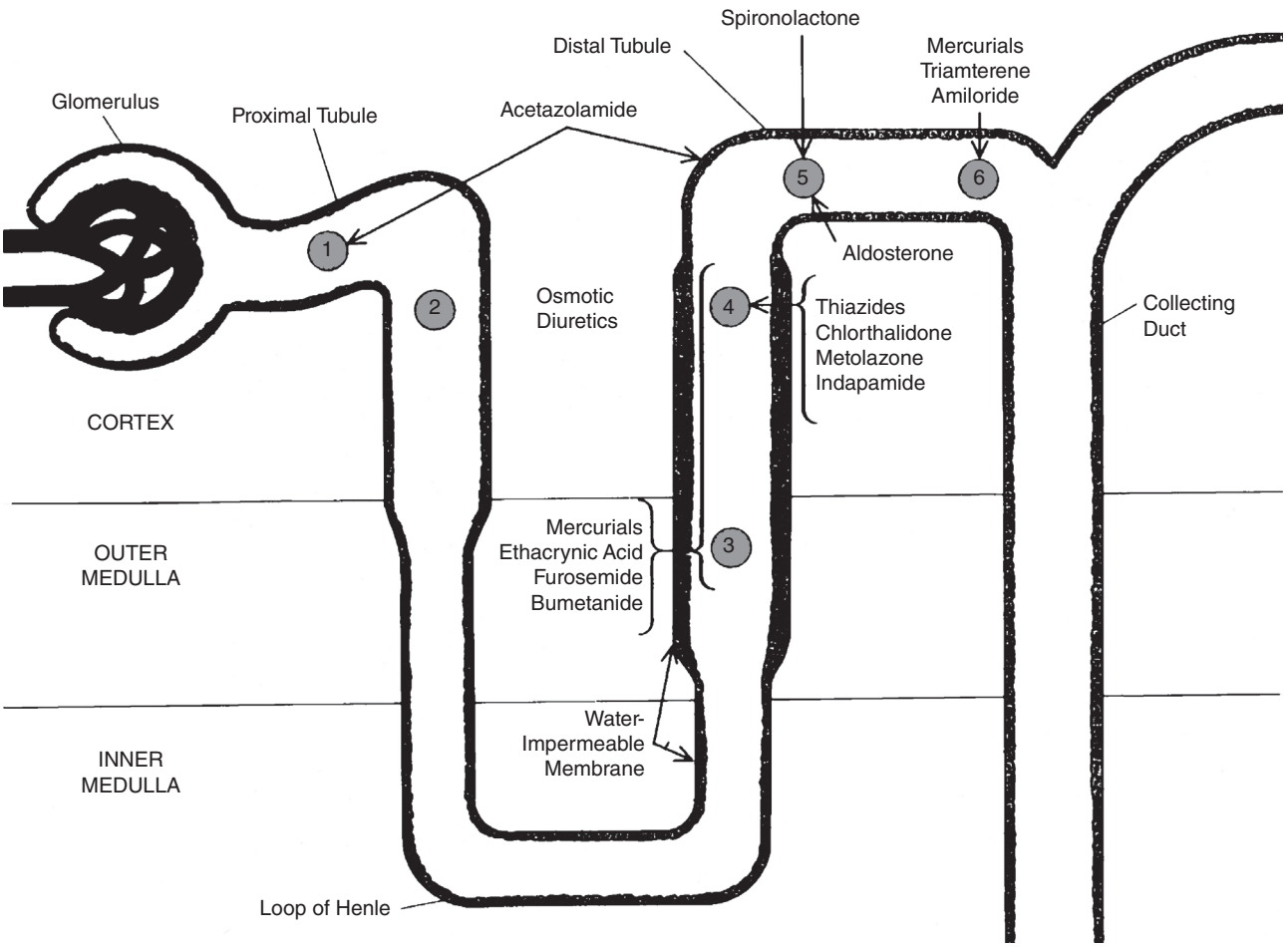

Figure 24.2 Locations within the nephron where diuretic agents exert their effects.

In the nephron bicarbonate combines with a hydrogen ion to produce carbonic acid. Carbonic acid is converted to water and carbon dioxide by CA and carbon dioxide freely diffuses into the PCT cell. Carbon dioxide in the PCT cell then combines with water to form carbonic acid, catalyzed by CA, and the carbonic acid dissociates into bicarbonate and a hydrogen ion effectively transporting bicarbonate from the nephron into the PCT cell. Bicarbonate is then cotransported with sodium to the interstitial fluid where it can diffuse into the peritubular capillaries. Carbonic anhydrase inhibitors (e.g., acetazolamide, methazolamide) exert their primary effects in the PCT, but also have effects on the distal convoluted tubule (DCT).

The Loop of Henle consists of a thick descending loop, thin descending loop, thin ascending loop, and thick ascending loop. Water pores (aquaporins) are present in the thin descending loop that allow water to osmotically move out of the nephron into the interstitial space, which is hyperosmolar (up to four times osmolarity as the original nephron contents). Reabsorption of sodium, potassium, and chloride from the nephron into the renal tubule cell by the sodium-potassium-2-chloride ($Na^+/K^+/2Cl^-$) cotransporter occurs in the thick ascending loop. Sodium is then transported from the cell to the interstitial fluid by the sodium/potassium ATPase and chloride follows sodium through chloride channels to the interstitial fluid (Figure 24.6). The thick ascending loop is impermeable to water. The high osmolarity of the interstitial fluid is thus maintained by the net movement of sodium and chloride from the nephron to the interstitial fluid, which transports a large portion of the sodium and chloride (~35% of the original ultrafiltrate) (Figure 24.7).

The thick ascending limb of the loop of Henle is of particular importance since this is the site of action of the most effective diuretic drugs (i.e., loop diuretics, furosemide). Approximately 25% of filtered solutes are reabsorbed in the loop of Henle, and most of this reabsorption occurs in the thick ascending limb. The thick ascending loop connects with the distal convoluted tubule to make a critical contact with the afferent arteriole through a cluster of specialized epithelial cells, referred to as the macula densa, which monitors the sodium and tubular flow rates and is discussed in more

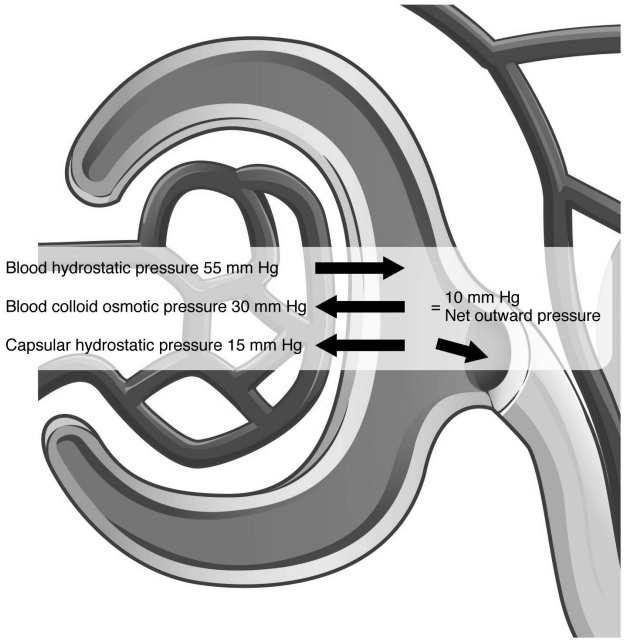

Figure 24.3 The glomerular net filtration pressure. Source: http://cnx.org/contents/14fb4ad7-39a1-4eee-ab6e-3ef2482e3e22@7.30. Used under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/.

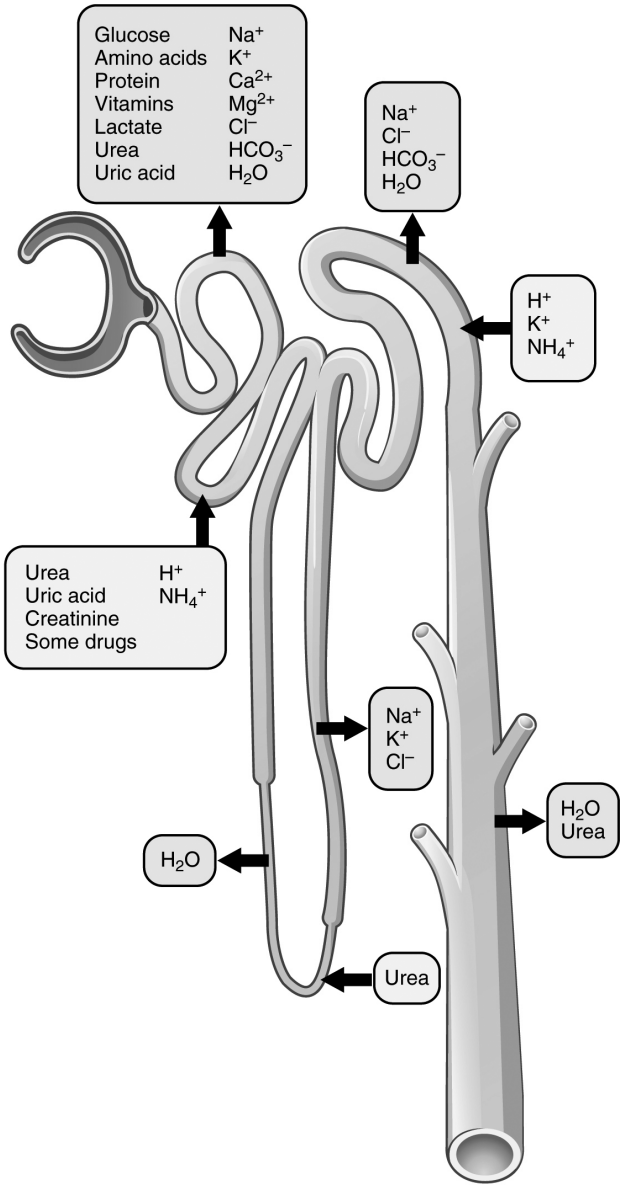

Figure 24.4 Nephron ion and water movement. Source: http://cnx.org/contents/14fb4ad7-39a1-4eee-ab6e-3ef2482e3e22@7.30. Used under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/.

detail in Section Renin–Angiotensin–Aldosterone System (Figure 24.8). Water, sodium, chloride, bicarbonate, and calcium are reabsorbed in the DCT. Sodium/chloride symporters transport sodium and chloride from the nephron into the DCT cells and are sensitive to the thiazide diuretics (Figure 24.9). Aldosterone enhances sodium and water reabsorption in the DCT and collecting duct by increasing the amount of sodium/potassium ATPase transporters moving sodium out of the nephron and chloride follows along with water. Spironolactone, an aldosterone antagonist, is a diuretic that exerts its effects in the DCT and the collecting duct. Parathyroid hormone (PTH) receptors on the DCT when bound by PTH insert calcium channels on the luminal surface to enhance recovery of calcium from the tubules.

The collecting duct produces the final effects on urine volume based on plasma osmolarity. More water is reabsorbed if the plasma osmolarity is high (e.g., dehydration) and more water is lost if the plasma osmolarity is low (e.g., overhydration). Two main cell types are present in the collecting duct, the principal cells and intercalated cells. The principal cells possess channels for the recovery or loss of sodium and potassium and the intercalated cells secrete or absorb acid and bicarbonate. Intercalated cells are important factors in regulating urine (and plasma) pH through absorption of bicarbonate and excretion of hydrogen ions. Antidiuretic hormone (ADH, arginine vasopressin, or specifically in swine lysine vasopressin) is released from the posterior pituitary gland when plasma osmolarity increases with an effect of increasing water reabsorption in the collecting duct through aquaporins (water channels). Antidiuretic hormone stimulates aquaporin channels to be inserted on the apical side (tubular side) of the principal cells, resulting in water movement from the nephron into the principal cells due to an osmotic gradient. Different aquaporin channels on the basolateral cell membrane allow water movement from the cell into the interstitial space by osmotic movement. The water than diffuses into the peritubular capillaries and reenters the circulation. Alcohol (ethanol) consumption decreases ADH resulting in a diuretic effect,

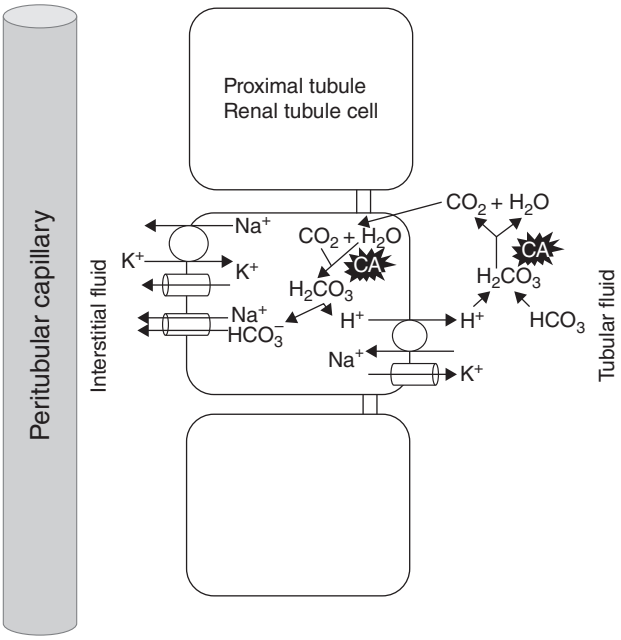

Figure 24.5 Reabsorption of bicarbonate from the proximal convoluted tubule, the primary location of carbonic anhydrase inhibitor effects.

which is observed in animals treated for ethylene glycol toxicity. Aldosterone also produces an effect on the collecting duct, resulting in increased sodium reabsorption from the collecting duct by sodium/potassium channels and sodium/potassium ATPases. Water passively follows sodium, resulting in a net increased reabsorption of sodium and water and net excretion of potassium. Spironolactone administration results in inhibition of aldosterone leading to loss of sodium and water and retention of potassium from the collecting duct and is often referred as a "potassium-sparing" diuretic.

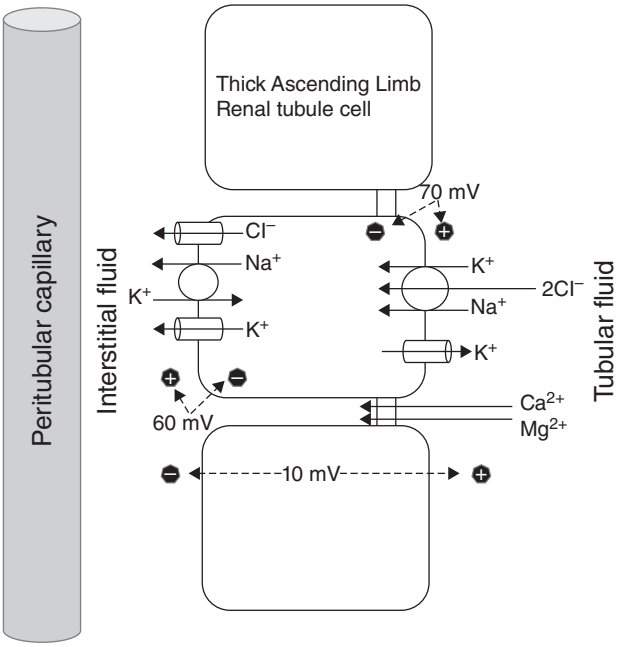

Figure 24.6 Ion movement in the thick ascending loop, the primary location of furosemide effects.

Factors Regulating Renal Function

Renin–Angiotensin–Aldosterone System

The macula densa is located at the junction of the thick ascending limb and distal convoluted tubule and sits between the afferent and efferent arterioles. Together with the juxtaglomerular cells, which produce renin, these components form the juxtaglomerular apparatus (Figure 24.8). Increased reabsorption of Na and Cl detected by the macular densa results in inhibition of renin release into the efferent arteriole by the juxtaglomerular cells through activation of adenosine (A_1) receptors. Conversely, decreased reabsorption of Na and Cl detected by the macular densa stimulates renin release into the efferent arterial through prostaglandins (PGE_2, PGI_2). Renin release is also enhanced when low blood pressure is detected by intrarenal baroreceptors, triggering the release of prostaglandins (PGE_2, PGI_2). Renin release can also be stimulated by an extrarenal mechanism, sympathetic nerve stimulation of β_1 receptors on the juxtaglomerular cells.

Renin release from the juxtaglomerular cells results in a cascade of events known as the renin–angiotensin–aldosterone system (RAAS) (Figure 24.10). Renin converts angiotensinogen, which is released from the liver, to angiotensin I (ATI). Angiotensin I is converted to angiotensin II (ATII) by angiotensin converting enzymes (ACE) located in the lungs. Angiotensin II is a vasoconstrictor, which binds to AT receptors in the vasculature resulting in increased vascular tone and increased blood pressure. Angiotensin II also stimulates the release of aldosterone from the adrenal cortex, which enhances sodium and subsequently water reabsorption in the distal convoluted tubule and collecting ducts, increasing circulating blood volume and blood pressure.

ATII increases vascular tone by multiple mechanisms. ATII produces direct vasoconstriction through AT receptors, resulting in the rapid pressor response. Peripheral sympathetic neurotransmission is enhanced by ATII, resulting in increased release of norepinephrine from nerve terminals. Centrally mediated enhanced sympathetic outflow is also stimulated by ATII. ATII also stimulates catecholamine release from the adrenal medulla.

ATII has affects on renal function. ATII stimulates Na^+/K^+ exchange in the PCT, which increases the reabsorption of Na^+, Cl^-, and $HCO3^+$ (Figure 24.5). The expression of the Na^+/glucose transporter in the PCT

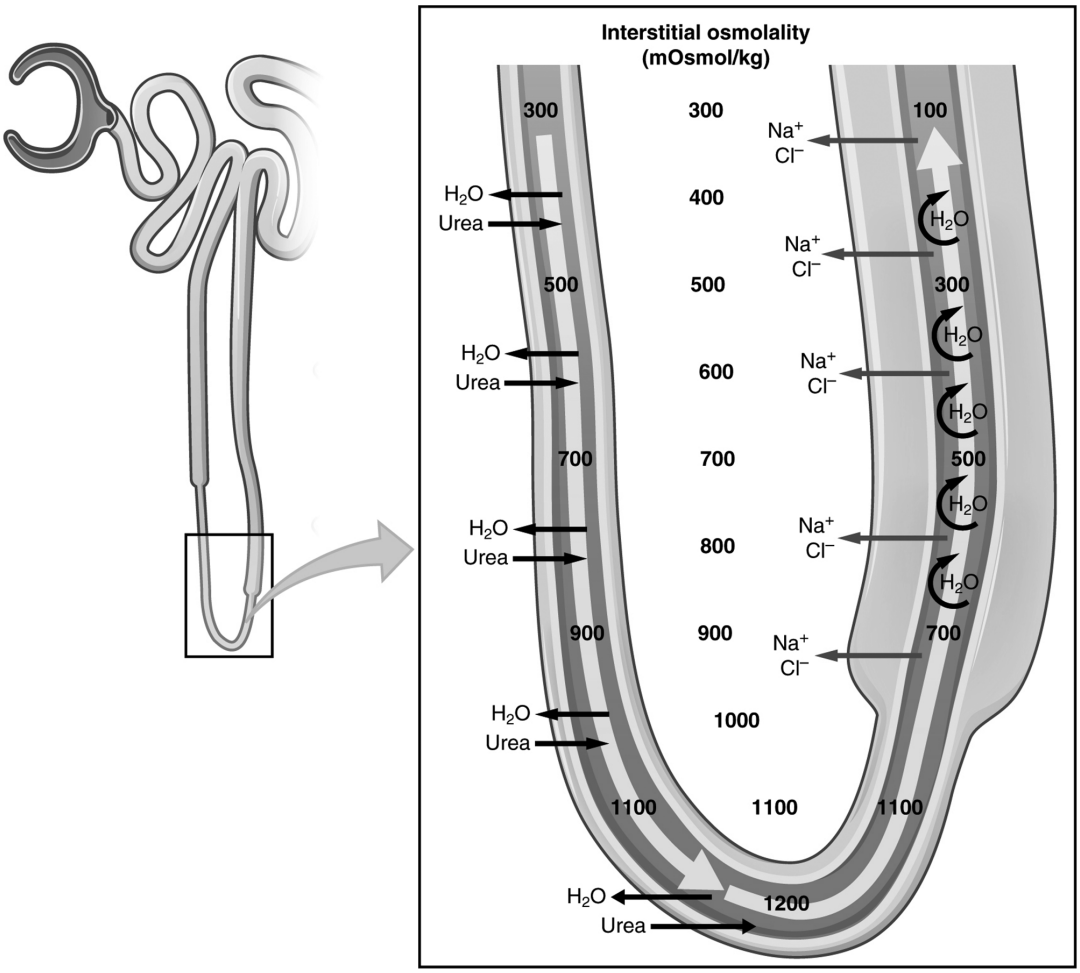

Figure 24.7 The loop of Henle countercurrent multiplier system and osmolality of the interstitial fluid and tubular fluid. Source: http://cnx.org/contents/14fb4ad7-39a1-4eee-ab6e-3ef2482e3e22@7.30. Used under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/.

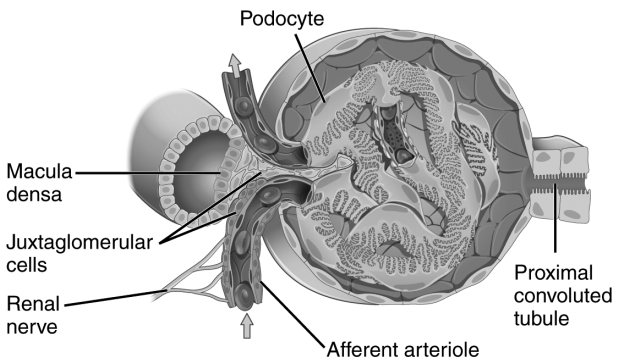

Figure 24.8 Anatomy of the glomerulus, macula densa, juxtaglomerular cells and renal vasculature. Source: http://cnx.org/contents/14fb4ad7-39a1-4eee-ab6e-3ef2482e3e22@7.30. Used under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/.

is increased with low concentrations of ATII. The activity of $Na^+/K^+/2Cl^-$ transporter in the thick ascending limb is also enhanced. ATII stimulates the release of aldosterone, which acts at the DCT and collecting ducts to enhance retention of Na^+ and water while increasing elimination of K^+. The vasoconstriction induced by ATII in most cases decreases GFR by affecting the afferent arteriole greater than the efferent arterial. However, during renal hypotension ATII affects the efferent arterial to a greater extent than the afferent, resulting in increased GFR. Administration of ACE inhibitors during renal hypotension increases the risk of acute renal failure.

The RAAS production of ATII is also associated with altered cardiovascular structures. Increased cardiac afterload, due to increased vascular tone, and increased preload, due to aldosterone-mediated sodium and water retention, contribute to cardiac remodeling and hypertrophy. Direct effects of ATII on cardiac myocytes, vascular smooth muscle, and fibroblasts also result

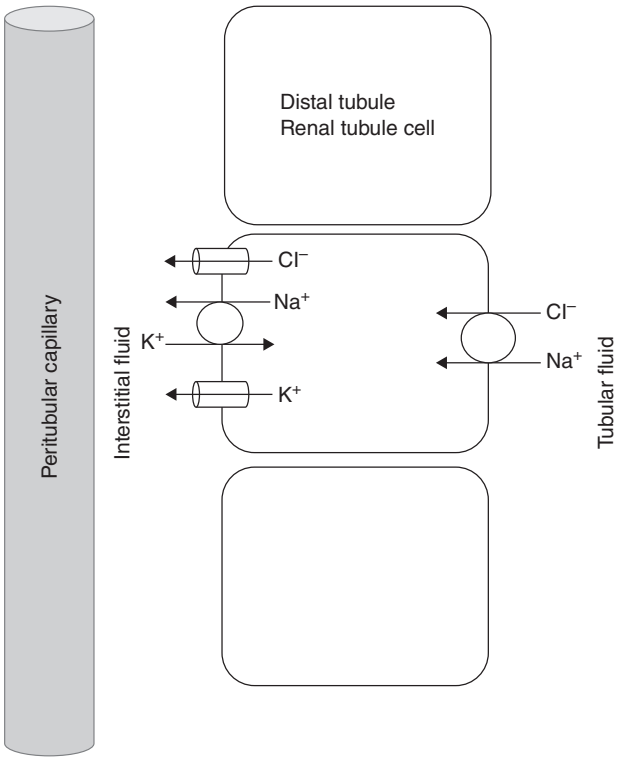

Figure 24.9 Ion movement in the distal convoluted tubule, the primary location of thiazide diuretic effects.

in cardiac hypertrophy and remodeling and vascular remodeling resulting in increased vascular wall thickness and decreased vascular compliance.

Renin release is modulated by feedback inhibition. Angiotensin II stimulates AT receptors on the juxtaglomerular cells decreasing the release of renin and is known as the short negative feedback loop. Increases in blood pressure due to ATII vasoconstriction results in decreased sympathetic tone and subsequently β_1 receptor stimulation. Increases in afferent arterial pressures decrease renin release and is termed the long loop negative feedback.

The RAAS is classically described as an endocrine system response as described above in this section, but locally active and alternative pathways for angiotensin synthesis are present. ACE is present throughout the vascular system in endothelial cells and circulating renin can be stored in the endothelial cells, which can subsequently locally activate the RAAS (Mompeón et al., 2015). Addition tissues (brain, vasculature, heart, adrenal glands, etc.) can produce renin, AT, or ACE that affect local tissue function and structure (Bader and Ganten, 2008). There are also other enzymes that can contribute to the metabolism of angiotensinogen to ATI and ATII. Chymases are enzymes implicated in production of ATII from angiotensin in tissues that can be refractory to ACE inhibitor therapy. There appears to be species-specific

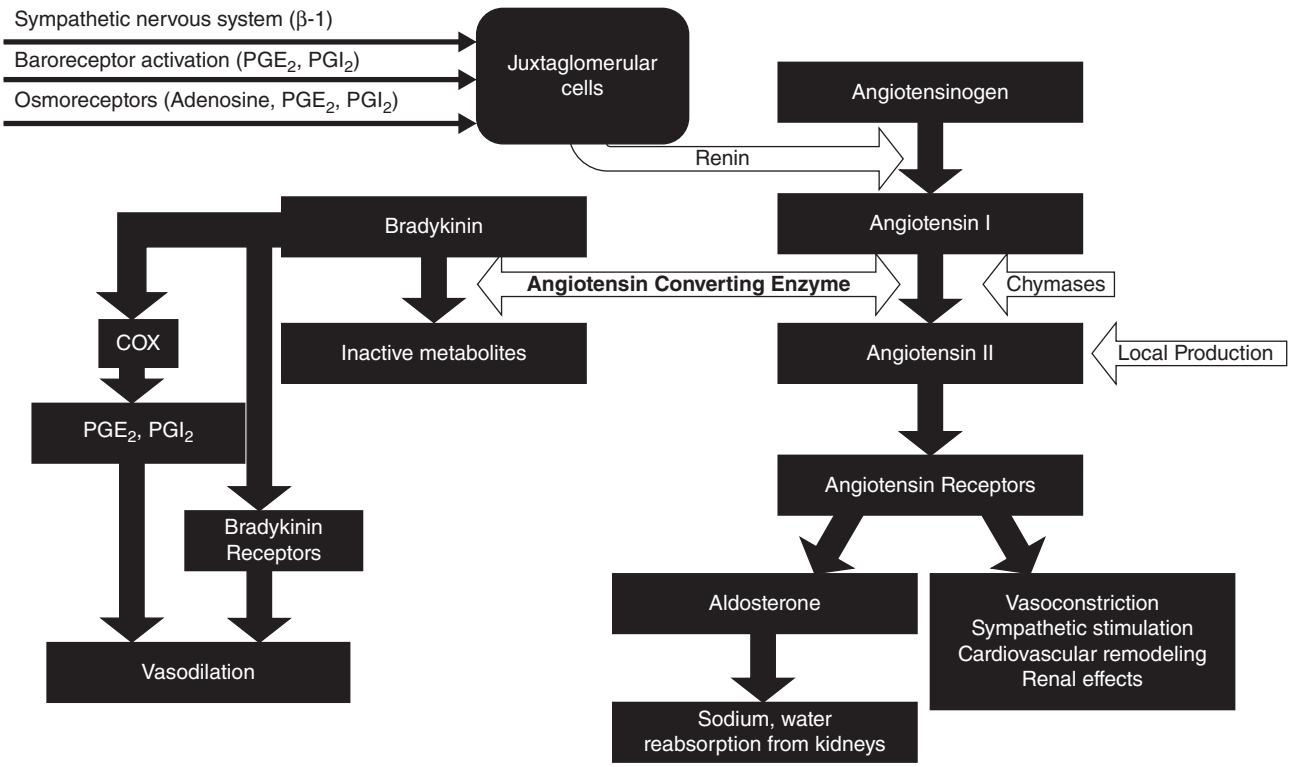

Figure 24.10 Schematic of the renin–angiotensin–aldosterone system.

differences and the overall contribution to ATII formation appears much less than ACE (Aramaki et al., 2003; Campbell, 2012).

Sympathetic Nervous System

The kidneys are innervated by the sympathetic nervous system. Adrenergic α_1-receptor activation results in vasoconstriction of the afferent arterial resulting in decreased blood flow, decreased hydrostatic pressure in the glomerulus, and decreased glomerular filtration rate. Sympathetic β_1 receptors are also located on the macula densa, which stimulate renin release and activation of the RAAS.

Antidiuretic Hormone

Osmoreceptors are specialized cells in the hypothalamus that are sensitive to changes in blood osmolarity (primarily influenced by sodium ion concentration). If blood osmolarity increases, typically due to sodium ingestion or water deprivation), ADH is released from the posterior pituitary with its primary effects on the collecting duct cells to increase water reabsorption from the tubular fluid by inserting aquaporins on the apical (lumen) side of the cells. ADH release is controlled by a negative feedback loop in which low blood osmolarity detected by the osmoreceptors inhibits the release of ADH. Diabetes insipidus is a disease characterized by insufficient production of ADH, resulting in blood hyperosmolarity. Ethanol, which is used in the management of ethylene glycol toxicity, inhibits the release of ADH, which can cause diuresis. ADH is also known as vasopressin as high concentrations result in vasoconstriction.

Cyclooxygenase

Cylcooxygenase (COX) exists as at least two distinct enzymes (COX1, COX2) and is described in detail in Chapter 20. Both COX isoforms are constitutively expressed in the kidneys, but COX2 expression can be induced to produce substantial local effects within the kidneys during periods of hypotension or decreased blood flow. Eicosanoids, products of COX, can exert prominent roles in renal physiology during certain conditions including hypotension (cardiac disease, vasodilation), hypovolemia (dehydration, hemorrhage), and hyponatremia. COXs produce a variety of eicosanoids, including prostaglandin E_2 (PGE_2), prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), prostacyclin (PGI_2), and thromboxane ($TBXA_2$) with resultant effects in the kidney. The eicosanoids can produce afferent arteriole vasodilation (PGE_2, PGI_2) locally antagonizing the effects of systemic vasoconstriction such as sympathetic stimulation, ATII, and vasopressin. Eicosanoids enhance renin release (PGE_2, PGI_2), but renin release is not solely dependent on prostaglandins. Eicosanoids enhance elimination of sodium and water (PGE_2, PGI_2, $PGF_{2\alpha}$) through inhibition of Na^+/K^+ ATPase activity and aquaporin activity. Prostaglandins (PGE_2, PGI2) also produce local vasodilation to maintain medullary blood flow during states of systemic vasoconstriction. Therefore it is not surprising that COX inhibitors can have profound renal effects, with renal adverse effects of nonsteroidal antiinflammatory drugs being the second most common organ system affected with adverse effects.

Renal Epithelial Transport

The presence of anion and cation transporters is essential for most highly protein-bound diuretic drugs to gain access to their site of action, the lumen of the renal tubule. Loop and thiazide diuretics and carbonic anhydrase inhibitors are secreted through the organic acid pathway, and amiloride and triamterene via an organic base transporter (Brater, 1998). Renal insufficiency accompanied by reduced creatinine clearance decreases delivery of diuretic drugs to their secretory site and hence to their site of action. Accumulation of endogenous organic acids during chronic renal failure may result in competition with diuretics for transport at proximal tubule secretion sites (Brater, 1993). Other transporters, including the p-glycoprotein efflux pump, breast cancer resistance protein (BRCP), multidrug and toxin extrusion proteins (MATE1, MATE2-K), and multidrug resistance proteins (MRP2, MRP4), are located in the proximal tubule that contribute to transport of drug into the urine functioning as a mechanism of drug clearance (2013).

Principles of Diuretic Use

Overview

The current therapeutic goal of diuretic use is increased excretion of sodium followed by water. The degree of sodium loss in the urine (referred to as natriuresis or, in combination with chloride, saluresis) varies with the mechanism of action of the drug. All except osmotic diuretics inhibit specific enzymes, transport proteins, hormone receptors, or ion channels that function, directly or indirectly, in renal tubular sodium reabsorption. Although saluresis is the primary clinical goal, diuretics also alter elimination of other ions to varying degrees (e.g., K^+, H^+, Ca^{2+}, Mg^{2+}, Cl^-, HCO_3^-, phosphates) and may affect renal hemodynamics. Diuretic-induced depletion of circulating blood volume may lead to adverse effects such as electrolyte imbalances and dehydration if therapy is not well monitored. Older animals and those with cardiac or renal disease are also at increased risk for adverse effects if diuretic-induced hypovolemia goes untreated. Because these groups are also the primary target groups for diuretic use, rational

Table 24.1 The effect of diuretics on water and electrolyte elimination

	H_20	Na^+	K^+	Cl^-	Mg^{2+}	Ca^{2+}	HCO_3^-	H_2PO_4	H^+
Carbonic anhydrase inhibitors	+	+	++	0–+	+/–	0	++	++	–
Osmotic diuretics	++	++	+	+	++	+	+	+	?
Loop diuretics ($Na^+K^+2Cl^-$ symport)	++	++	++	++	++	++	0–+	0–+	+
Thiazide diuretics (Na^+/Cl^- symport)	+	+	++	+	+	-(chronic)	0–+	0–+	+
K^+-sparing (Na^+ channel)	+	+	–	+	–	–	+	0	–
Aldosterone antagonists	+	+	–	+	0	?	+	?	–

++, large increase in elimination; +, increase in elimination; 0, little to no change in elimination; – decreased elimination; +/– variable effect; ? effect unknown.

use of diuretic drugs is essential. Table 24.1 summarizes selected features of diuretic drugs most commonly used in veterinary medicine.

Edema Formation

The most common indication for diuretic use is removal of tissue edema. Understanding the physiological principles underlying edema formation depends upon an understanding of net capillary filtration. Similar to net filtration pressure in the glomeruli, net capillary filtration, or fluid flux out of a capillary, is dependent upon the plasma colloidal osmotic pressure retaining fluid, and hydrostatic pressure in the arterial capillary forcing fluid out of the capillary through fenestrations and pores. Since the arterial capillary hydrostatic pressure is greater than the plasma colloidal osmotic pressure in most tissues, a small amount of fluid moves from the vasculature into the interstitial space. However, on the venous capillary side, plasma osmotic pressure is greater than the venous hydrostatic pressure and fluid is reabsorbed from the interstitial space into the venous capillary in most tissues, resulting in little net fluid loss into the interstitial space. The lymphatics contribute to fluid absorption from the interstitial space, ensuring no accumulation of fluid in the interstitial space in healthy tissues.

If the fluid movement out of the capillaries exceeds absorption of fluid by venous capillaries and lymphatics, edema results. There can be numerous causes of edema including: lymphatic obstruction (i.e., neoplasia), decreased plasma osmotic pressure (i.e., hypoalbuminemia), and increased venous hydrostatic pressure (i.e., decreased cardiac contractility, excessive intravascular fluid volume). Additionally, the loss of capillary integrity (i.e., inflammation, neurogenic) can result in tissue edema and noncardiogenic pulmonary edema due to head trauma, seizures, and electrocution that occur as a result of poorly understood mechanisms. Therefore the cause of the edema should be identified prior to any therapy, including diuretics.

Congestive heart failure (CHF) is a complex pathophysiological process that begins with decreased cardiac output. The decreased cardiac output and decreased renal blood flow leads to activation of the renin–angiotensin–aldosterone system followed by renal retention of salt and water. High baroreceptor activity causes increased peripheral vascular resistance and increased ADH, which lead to further salt and water retention by the kidneys. Increased central venous pressure caused by increased left ventricular end-diastolic pressures cause increased capillary hydrostatic pressure. All of these factors lead to greater fluid flux out of vessels, resulting in edema related to cardiac disease.

Inhibitors of Carbonic Anhydrase

Chemistry/Formulations

This class of drugs was discovered as a result of the observation that sulfanilamide chemotherapeutic agents were capable of causing metabolic acidosis by inhibition of carbonic anhydrase (CA). Screening of sulfanilamides resulted in identification of compounds whose predominant mechanism of action was CA inhibition. These drugs have been used sparingly in veterinary medicine as diuretics and are more commonly used for ophthalmic purposes as topical formulations. The prototype drug in this class, acetazolamide (Diamox®, Dazamide®), is available in tablets (125 and 250 mg), extended-release capsules (500 mg), and injectable (500 mg per vial). Other CA inhibitors include preparations for oral use, dichlorphenamide (Daranide®) and methazolamide (Neptazane®), and a topical drug, dorzolamide (Trusopt®), for ophthalmic use.

Mechanisms and Sites of Action

Renal Mechanisms

Drugs in this class are active in the CA-rich segments of the nephron, in particular the proximal tubule. Noncompetitive, reversible inhibition of CA located in the luminal and basolateral membranes (type IV CA) as well as in the cytoplasm (type II CA) results in decreased

formation of carbonic acid from CO_2 and H_2O (see Figure 24.5 and equation below):

$$HCO_3^- + H^+ \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$$

Reduction in the amount of carbonic acid yields fewer H^+ within proximal tubular cells. Because H^+ is normally exchanged for Na^+ from the tubular lumen by the Na^+/H^+ antiporter (also referred to as a Na^+/H^+ exchanger or NHE), less Na^+ is reabsorbed and more is available to combine with urinary HCO_3^-. The NHE maintains a low proton concentration in the cell so that $H_2CO_3^-$ ionizes spontaneously to form H^+ and HCO_3^-. This, in turn, creates an electrochemical gradient for HCO_3^- across the basolateral membrane that drives movement of HCO_3^- into the interstitial space. Diuresis is established when water is excreted with sodium bicarbonate that accumulates due lack of CA activity. As sodium bicarbonate is trapped in the urine and eliminated, less HCO_3^- is returned to plasma, and a systemic acidosis eventually develops. As a result of the systemic acidosis, H^+ becomes available, Na^+ reabsorption is reestablished, and diuresis decreases. Continual use of CA inhibitors is therefore self-limiting in terms of diuretic action. Diuresis induced by CA inhibitors is mild due to incomplete inhibition of CA, redundancy of Na^+ transporting systems in the proximal tubule, and rescue of Na^+ by reabsorption later in the distal tubule. Because intracellular K^+ can, to some extent, substitute for H^+ in the Na^+ reabsorption step, CA inhibitors cause enhanced K^+ excretion. As more Na^+ is presented to the distal tubule, the potential for K^+ wasting increases. CA inhibitors also decrease secretion of titratable acids and ammonia in the collecting duct (Jackson, 1996). For this reason, and due to the increased excretion of sodium bicarbonate, urine pH increases despite the decreasing systemic pH associated with CA inhibitor induced acidosis. This class of drugs has little, if any, effect on excretion of Ca^{2+} and Mg^{2+} but does enhance phosphate elimination.

Extrarenal Actions

Other actions of CA inhibitors are related to the wide distribution of CA in body tissues including the eye, gastric mucosa, pancreas, central nervous system (CNS), and red blood cells. The most important therapeutic consequence is associated with CA inhibition in the eye. The ciliary processes of the eye mediate the formation of aqueous humor, which contains an abundance of osmotically active HCO_3^-. This process is CA dependent and, when inhibited, leads to a decreased rate of formation of aqueous humor and subsequent reduction in intraocular pressure. Although not therapeutically relevant in veterinary medicine, CA inhibition in the CNS has been associated with anticonvulsant actions attributed to this class of drugs.

Absorption and Elimination

Limited information is available regarding pharmacokinetics of CA inhibitors in animals. The pharmacokinetics of acetazolamide in dogs administered an extended release product produced an approximately 7-hour half-life with a T_{MAX} at 3 hours (Li et al., 2014). Acetazolamide gains access to the renal tubules via the organic acid secretion pathway. A dose of 22 mg/kg is reported to have an onset of action of 30 minutes, maximal effects in 2–4 hours, and a duration of action of 4–6 hours in small animals (Roberts, 1985). Oral absorption of drugs in this class is appears to be good in dogs. The oral bioavailability of acetazolamide is 25% in horses, with a terminal half-life of 7 hours (Alberts et al., 2000). Acetazolamide is eliminated primarily through the kidneys. The pharmacokinetics of methazolamide has not been reported in dogs, cats, or horses.

Toxicity, Adverse Effects, Contraindications, and Drug Interactions

Although CA inhibitors are sulfonamide derivatives, side effects commonly associated with sulfonamides are not reported or expected (Trepanier, 2004). CNS drowsiness and disorientation may occur as a result of inhibition of CA in the CNS. Because CA inhibitors decrease ammonia excretion, the severity of preexisting hepatic disease may be worsened and hepatic encephalopathy can be induced. Use is also contraindicated in patients with certain electrolyte disturbances (due to K^+ and Na^+ wasting) and those with metabolic or respiratory acidosis. Use in patients with severe pulmonary disease who cannot respond to drug-induced metabolic acidosis with respiratory compensation is also contraindicated. Because CA inhibitors alkalinize the urine, calcium phosphate calculi formation is enhanced, and excretion of weak organic bases is reduced. Rare blood dyscrasias associated with CA inhibitors have also been reported in the human, but not in the veterinary literature.

Therapeutic Uses

The primary indication for use of CA inhibitors is to inhibit production of aqueous humor and reduce intraocular pressure. Topical application of dorzolamide (q 8–12 h) produced similar reductions in intraocular pressure compared to oral methazolamide (5 mg/kg q 12 h) or the combination of topical and oral therapy (Gelatt and MacKay, 2001). The topical CA inhibitors therapy is preferred due to equivalent efficacy, lower potential for adverse effects, and lower cost than systemic administration. Acetazolamide (5–10 mg/kg PO q 8 h) and methazolamide (5 mg/kg PO q 12 h given two to three times daily) have been used previously in dogs for

management of glaucoma. CA inhibitors have been administered to patients with hydrocephalus for short-term medical management, often in combination with furosemide, but long-term management with diuretics, in people, is often not successful (Thomas, 2010).

In human medicine, CA inhibitors have been used as an adjunctive therapy for epilepsy and in management of acute mountain (high-altitude) sickness. In both human and veterinary medicine, the use of CA inhibitors as diuretics has limited effectiveness due to the rapid development of tolerance. Theoretically, acetazolamide could be used to manage metabolic alkalosis, but this is not a typical clinical practice in veterinary medicine.

Osmotic Diuretics

Chemistry/Formulations

Osmotic diuretics contain simple solutes of low molecular weight that are typically freely filtered by the glomerulus, undergo limited tubular reabsorption, and are pharmacologically inert. They increase serum and tubular fluid osmolarity resulting in fluid shifts. The most common osmotic diuretic is mannitol, a six-carbon non-metabolized polyalcohol with a molecular weight of 182. Other agents include glycerin, isosorbide, urea, and hypertonic saline solutions. Because mannitol is the most commonly used osmotic diuretic in both human and veterinary medicine, subsequent discussion will focus primarily on this drug. Concentrated mannitol (15–25%) may crystallize at cooler temperatures, in which case the drug can often be resolubilized by warming the solution. Prior to administration, the solution should be cooled and any remaining crystals removed using an in-line intravenous (IV) filter. There are no veterinary-approved mannitol formulations available. For IV use in animals, the human formulations are used. Human products (Osmitrol®, Resectisol®) range from 5% (275 mOsm/l) to 25% (1375 mOsm/l) and are available for IV administration.

Mechanisms and Sites of Action

Hyperosmolar solutions exert part of their effects by establishing an osmotic gradient between plasma and extravascular fluid compartments resulting in fluid movement into the plasma. Acute effects of this gradient include decreases in hematocrit, blood viscosity, plasma sodium, plasma pH, and, to some degree, the volume of solid organs. Hence, parenchymal dehydration and acute hemodilution are theoretically related as long as the osmotically active particles are effectively separated by a relatively solute-impermeable barrier.

Renal Mechanisms

Initially, osmotic diuretics were thought to act primarily at the level of the proximal tubule by limiting the movement of water from the lumen into the interstitial space. Water retained in the tubular lumen diluted concentrations of sodium and other ions, reduced ion reabsorption, and promoted diuresis. It is now held that osmotic diuretics, in particular mannitol, have effects throughout the length of the tubule, with the most prominent action occurring in the loop of Henle. Sodium reabsorption is markedly reduced in the descending and thin limbs of the loop of Henle, as determined by studies in dogs and rats. Sodium load to the thick ascending limb of the loop of Henle and to the distal tubule is consequently increased, but the nephron fails to recapture the increased loads of salt and water. As demonstrated in the dog, sodium reabsorption is also thought to be directly inhibited in medullary collecting ducts (Better et al., 1997).

Other reported renal effects of mannitol include increases in cortical and medullary blood flow due to a decrease in renal vascular resistance, impairment of urinary concentration, reduction in medullary tonicity (also known as medullary washout), an increase in GFR during renal hypoperfusion (may vary according to species), and an increase in urinary excretion of other electrolytes (e.g., K^+, Ca^{2+}, Mg^{2+}, phosphate, bicarbonate) (Better et al., 1997). Mannitol may also prompt the release of atrial natriuretic factor and vasodilatory prostaglandins and inhibition of renin release.

Extrarenal Mechanisms

The actions of mannitol extend beyond the renal effects and include changes in blood rheology, direct transient effects on vascular tone, and increases in cardiac output. In addition to decreasing the hematocrit by hemodilution, mannitol decreases the volume, rigidity, and cohesiveness of red blood cell membranes. The combination of reduced viscosity and reduced mechanical resistance presumably leads to enhanced blood flow. Mannitol-induced increases in cardiac output are thought to be related to reduced peripheral resistance and reduced afterload, a transient increase in preload, and mild positive inotropy. Mannitol may also exert a cytoprotective effect by acting as an oxygen-free radical scavenger (Paczynski, 1997).

Absorption and Elimination

Mannitol is not metabolized and is handled as an inert substance by the body. Studies in dogs and humans indicate that mannitol distribution and elimination follow a two-compartment model (Cloyd et al., 1986; Rudehill et al., 1993). The distribution half-life of intravenously administered mannitol is measured in minutes. Elimination half-life is dose dependent and ranges from 0.5 to

1.5 hours for doses between 0.25 and 1.5 g/kg. Mannitol is eliminated rapidly by the kidneys unless renal function is impaired. As a result, penetration of mannitol into tissues is limited by rapidly falling plasma concentrations. Mannitol is administered intravenously in a slow bolus over 15–30 minutes. Glycerin and isosorbide are administered orally. Of the available osmotic diuretics, only glycerin is eliminated by biotransformation.

Adverse Effects and Drug Interactions

Acute Adverse Effects

Pulse pressure and mean arterial blood pressure usually increase transiently with mannitol administration. However, acute hypotensive, hyponatremic effects of mannitol administration have been reported, especially subsequent to rapid infusion in dehydrated individuals. The mechanism for this acute vasodilatory effect is not well understood, but the problem can largely be prevented by appropriate rates of administration (0.25–1.5 g/kg over 15–30 min). Acute hyponatremia may account for the nausea and vomiting that are sometimes observed with mannitol infusion. Rapid expansion of plasma volume related to attraction of fluid into the vascular compartment may precipitate CHF or pulmonary edema in certain patient populations. However, because the drug is cleared rapidly this problem is not common unless renal function is impaired or underlying cardiac disease is present.

Dehydration and Electrolyte Disturbances

Because the ratio of the volume of fluid eliminated in urine to the volume of mannitol administered is high, care should be taken to avoid hypertonic dehydration. Circulating plasma volume tends to be preserved as hypertonic dehydration develops, making it harder to clinically detect that a problem exists. The presence of dehydration and significant hypernatremia should be closely monitored using body weight, urine output, and other clinical parameters. In addition to hypertonic dehydration, loss of other electrolytes, including potassium, phosphate, and magnesium, can lead to clinically significant cardiac arrhythmias and neuromuscular complications.

Hyperosmolar State and Osmotic Compensation

The phenomenon of osmotic compensation occurs when cells respond to prolonged treatment with a hyperosmolar agent by increasing the presence of intracellular, idiogenic osmoles. Compensation is thought to occur rapidly when the osmolality of plasma is increased by 25 mOsm/kg or more above normal. Newly generated, osmotically active intracellular particles counteract the dehydrating effect of hyperosmolar plasma. Osmotic compensation can limit therapeutic effectiveness by decreasing the osmotic gradient from tissue to plasma. Increased intracellular osmolarity may also promote conditions, especially in the brain, where iatrogenic edema may occur. The risk of edema formation is increased if a hyperosmolar state is reversed rapidly, leaving the intracellular osmoles as the most osmotically active site. To prevent this complication, the duration of return of plasma to normal osmolality should be approximately equal to the duration of the hyperosmolar state.

Contraindications

The use of mannitol in patients with ongoing intracranial hemorrhage, anuric renal failure, severe dehydration, or pulmonary congestion or edema is contraindicated. Adequate fluid therapy should be administered to dehydrated animals prior to administration of mannitol. Mannitol should not be added to whole-blood products unless at least 20 mEq/l of sodium chloride is added to the solution; otherwise, pseudoagglutination may occur.

Therapeutic Uses

Mannitol is used in the prophylaxis and treatment of renal failure, for the reduction of intracranial and intraocular pressure, and with other diuretics to mobilize edema. For reasons already discussed, short-term use of mannitol is most effective to prevent adverse effects and decreased therapeutic efficacy.

Prophylaxis of Acute Renal Failure

Anuric patients should not be routinely treated with mannitol, although a small (0.25–0.5 g/kg), single test dose may be used to try and induce diuresis. Administration of mannitol to patients with renal dysfunction must be done cautiously to prevent problems associated with decreased elimination and prolonged hyperosmolarity. Acute renal failure (ARF) may be caused extrinsically (pre- and postrenal failure) or intrinsically, often associated with acute renal tubular necrosis (ATN). Mannitol has been found to be effective in limiting the decrease in GFR caused by ATN if administered before the ischemic insult or exposure to nephrotoxins. Protection of tubules from necrosis may be due to dilution of nephrotoxic substances, reduction of swelling of tubular elements, or removal of tubular casts that are obstructing urine flow. In human medicine, mannitol has been shown to be clearly beneficial in the preservation of kidneys for transplant and for decreasing the incidence of posttransplant ARF. Fewer data are available to support the general value of mannitol for treatment of ARF outside the area of transplantation (Better et al., 1997). In vascular and open-heart surgery, prophylactic mannitol maintains urine flow but not GFR. Some evidence suggests

that mannitol administration in patients with established ATN may increase the conversion of oliguric to nonoliguric patients (Levinsky and Bernard, 1988).

Reduction of Intracranial Pressure

Osmotherapy has been used for decades to decrease intracranial pressure (ICP). Reduction in ICP is rapid and usually appears within minutes of completion of administration, with maximum effects within the hour. Several theories have been formulated to account for the effectiveness of mannitol in reducing ICP. The osmotic theory holds that brain shrinkage occurs as a result of osmotically driven movement of fluid from tissue and into the vascular compartment. Sensitive, high-resolution imaging methods seem to support the significance of osmotically induced changes in brain water content (Betz et al., 1989). The hemodynamic theory of ICP reduction states that cerebral blood volume is decreased as a result of decreased blood viscosity and increased cerebral perfusion pressure, both of which act to enhance oxygen delivery to the brain. Increased oxygen delivery to the brain is thought to trigger a compensatory reduction in vascular caliber and secondarily a reduction in cerebral blood volume. Detractors of this idea suggest that mannitol is just as likely to decrease blood viscosity as a result of hemoconcentration secondary to hypertonic dehydration. While attention to fluid replacement should prevent dehydration, it has recently been suggested that alternative agents, such as hypertonic saline, are safer and equally effective at reducing ICP (Raslan and Bhardwaj, 2007). Hypertonic saline has been shown to establish a strong transendothelial osmotic gradient but without the tendency to reduce intravascular volume (Prough and Zornow, 1998). Finally, the diuretic theory of ICP reduction suggests that mannitol-induced decreases in central venous pressure translate directly to decreases in ICP due to the valveless communication between the central venous system and the jugular drainage system. This effect may be more important in sustaining, rather than inducing, a decrease in ICP (Paczynski, 1997). Regardless of the theory, mannitol has been used for temporary reduction of ICP in patients with a variety of intracranial lesions as well as those with spinal cord trauma and edema. Evidence of ongoing intracranial hemorrhage is considered a contraindication for mannitol administration. Rebound increases in intracranial pressure have been observed with mannitol in 10–20% of human patients (Node and Nakazawa, 1990) and may be due in part to mannitol movement through the blood–brain barrier (Raslan and Bhardwaj, 2007).

Other Uses

Osmotic diuretics have also been used successfully to control intraocular pressure during acute glaucoma attacks and to reduce intraocular pressure before or after ophthalmic surgery. Decreases in intraocular pressure occur by loss of intraocular water to hyperosmolar plasma. As the vitreous shrinks, the lens moves posteriorly and the iridocorneal angle opens, improving drainage from the eye. The duration of action depends upon the degree to which the osmotic diuretic is excluded from ocular fluids. Mannitol is reported to increase retinal oxygen tension and is used at a dose of 1–2 g/kg at a rate of 1 ml/kg/min to reduce intraocular pressure in dogs. Although still useful for decreasing intraocular pressure due to glaucoma, other therapies including topical carbonic anhydrase inhibitors (i.e., dorzolamide), β_1 antagonists (i.e., timolol), and prostaglandin analogues (i.e., latanoprost) are the preferred therapies.

Inhibitors of $Na^+/K^+/2Cl^-$ Symport (Loop or High-Ceiling Diuretics)

Drugs belonging to this class are among the most effective and the most commonly prescribed diuretics, and all share a common mechanism of action. By blocking a key sodium transport mechanism in the thick ascending limb of the loop of Henle (hence the name loop diuretic), these drugs inhibit reabsorption of up to 25% of the filtered sodium load. Nephron segments distal to the thick ascending limb (TAL) are incapable of reabsorbing the additional solute, leading to a marked (or high-ceiling) natriuresis and diuresis. Because furosemide (Salix®, Disal®) is by far the most commonly used diuretic in veterinary medicine, the remaining discussion will focus primarily on this drug (also referred to as frusemide). Other drugs in this class include ethacrynic acid (Edecrin®), bumetanide (Bumex®), and the most recent addition approved in the United States, torsemide (Demadex®).

Chemistry/Formulations

Except for ethacrynic acid, the structurally diverse drugs in this class are sulfonamide derivatives; however, they are not subject to the same adverse effects as sulfonamide antimicrobials. Furosemide is light sensitive and stable under alkaline conditions; the veterinary injectable preparations (Salix or generic; 50 mg/ml) have a light yellow color, whereas the human injectable (Lasix®; 10 mg/ml) should not be used if it appears yellow. A wide range of veterinary preparations of furosemide are available, including oral tablets approved for use in dogs and cats (12.5 mg, 50 mg), oral solution approved for use in dogs (10 mg/ml), large-animal boluses approved for use in cattle (2 g/bolus), and injectable (5%) approved for use in dogs, cats, horses not intended for food, and cattle.

Milk and slaughter withdrawal time for both oral and injectable formulations for cattle is 48 hours. Bumetanide (Bumex® is supplied in 0.5, 1, and 2 mg tablets and as a 0.25 mg/ml parenteral injection. Bumetanide is approximately 40 to 50 times more potent than furosemide in the dog. Torsemide (also torasemide) (Demadex) is supplied as 5, 10, 20, and 100 mg tablets and in 2 or 5 ml ampules containing 10 mg/ml for intravenous administration. Torsemide dosage in the dog has been estimated at approximately one-tenth the human dose but the drug has not been well studied in dogs and cats (Kittleson and Kienle, 2007).

Mechanisms and Sites of Action

Renal Effects

Drugs in this class block the Na^+-K^+-$2Cl^-$ symporter in the TAL by binding to the Cl^- binding site of the transporter protein (Figure 24.6). All of these drugs must be actively secreted into the tubular lumen by an organic acid pathway in order to reach and inhibit the luminal symporter. A high degree of protein binding (>95%) limits glomerular filtration of furosemide and other loop diuretics, making tubular secretion essential.

The mechanism involved in Na^+ reabsorption in the TAL depends upon Na^+/K^+ ATPase activity in the basal membrane of tubular cells, creating an electrochemical gradient. The low intracellular sodium concentration induced by the Na^+/K^+ATPase drives the absorption of sodium, along with potassium and chloride, from the tubular fluid by $Na^+/K^+/2Cl^-$ symporter located in the luminal membrane. Recycling of the potassium back into the tubular fluid is accomplished by the potassium channels on the luminal membrane. Chloride channels on the basolateral side efflux chloride from the intracellular compartment. Basolateral Cl^- conductance and luminal K^+ conductance determine membrane voltage. The polarity of K^+ and Cl^- conductances results in a lumen-positive transepithelial voltage. This voltage drives cations (Ca^{2+} and Mg^{2+}) between tubular cells via the paracellular shunt pathway. When loop diuretics block the $Na^+/K^+/2Cl^-$ symporter, Cl^- concentrations in the cell fall, the cell becomes hyperpolarized, transepithelial voltage is disrupted, and paracellular cation reabsorption is blocked (Bleich and Gregor, 1997). Because renin-producing cells in the area of the macula densa generate part of their membrane voltage via Cl^- channels, the new Cl^- equilibrium also depolarizes these cells and enhances the secretion of renin.

Loop diuretics interfere with establishment of a hypertonic medullary interstitium (due to impaired sodium reabsorption) and disrupt the countercurrent mechanism. Hence, these drugs block the kidney's ability to concentrate and dilute urine appropriately. Inhibitors of the $Na^+/K^+/2Cl^-$ symporter also inhibit Ca^{2+} and Mg^{2+} reabsorption in the TAL by disruption of the transepithelial potential difference. Some loop diuretics, notably furosemide, also have weak carbonic anhydrase-inhibiting activity that leads to enhanced urinary excretion of HCO_3^- and phosphate. All $Na^+/K^+/2Cl^-$ symporter inhibitors increase the urinary excretion of K^+ and H^+ by presenting a greater load of Na^+ to the distal tubule. Sodium is reabsorbed while K^+ and H^+ are excreted.

Nonsteroidal antiinflammatory drugs (NSAIDs) inhibit the diuretic, natriuretic, and chloruretic responses to furosemide. Furosemide enhances production of prostaglandin E2 (PGE_2), which in turn inhibits chloride and sodium reabsorption in the TAL. In the presence of NSAIDs, PGE_2 production is blocked, and furosemide-induced diuresis is decreased (Kirchner, 1987). In the absence of volume depletion, loop diuretics generally increase and redistribute total renal blood flow. The mechanism for this effect is thought to be related to prostaglandins, and the effect is diminished or blocked in the presence of NSAIDs (Data et al., 1978). Furosemide-induced hemodynamic changes correlate with an increase in urinary excretion of PGE_2.

Extrarenal Effects

Furosemide causes extrarenal hemodynamic effects that include increased venous compliance and decreased right atrial pressure, decreased pulmonary artery pressure, decreased pulmonary artery wedge pressure, and decreased pulmonary blood volume (Hinchcliff and Muir, 1991). Prostaglandins are thought to account for the acute increase in systemic venous capacitance and subsequent decrease in left ventricular filling pressure. All of these effects are dependent upon the presence of a functional kidney and the uninhibited production of prostaglandins. In the isolated rabbit heart, furosemide has also been reported to exert a mild negative inotropic effect that is prostaglandin dependent (Feldman et al., 1987). Similarly, prostaglandins are important for furosemide's effects in horses since phenylbutazone decreased its diuretic and vascular responses (Hinchcliff et al., 1995).

Inhaled furosemide in humans has been shown to protect against the early response to inhaled allergens and to prevent exercise-induced bronchoconstriction (Bianco et al., 1988, 1989). Furosemide may prevent bronchoconstriction in part by inhibiting release of inflammatory mediators from lung cells (Anderson et al., 1991). Pulmonary gas exchange is reportedly improved by furosemide in experimental pulmonary edema. Furosemide also reduces the rate of pulmonary transvascular fluid filtration through a reduction in pulmonary vein pressure (Demling and Will, 1978).

Absorption and Elimination

Furosemide is approximately 77% bioavailable in dogs and has an elimination half-life of about 1 hour following an IV dose of 5 mg/kg (Hirai et al., 1992). The absorption of orally administered furosemide takes place mainly in the upper parts of the canine gastrointestinal tract, decreasing rapidly across the jejunum. Peak diuretic effects of an IV dosage of furosemide in the dog are reported at approximately 30 minutes and following oral dosing at about 1–2 hours. The rate of urinary furosemide excretion, more so than the concentration of plasma furosemide, has been found to closely correlate with diuretic response in dogs. As in humans, the relation between the natriuretic response and the concentration of diuretic in the urine (at the site of action) is represented by a typical sigmoidal concentration–response curve. The shape of the curve suggests that a threshold quantity of drug must be achieved at the site of action in order to elicit a response and that a maximal dose can be identified that yields a maximal response. Beyond that maximal dose, the curve plateaus, and limited additional benefits are derived from dose increases (Brater, 1998; Hirai et al., 1992). Because intermittent doses produce a brief effect in dogs and higher doses do not produce a greater effect, the use of a constant-rate infusion (CRI) has been explored. In dogs, a loading dose of 0.66 mg/kg is followed by a CRI of 0.66 mg/kg/h × 8 hours. This results in greater natriuresis, calciuresis, and diuresis than with intermittent treatment (Adin et al., 2003).

Elimination half-life of IV furosemide in the horse is similar to that in the dog and, in the absence of renal impairment, is slightly less than 1 hour. Furosemide is typically administered IV or IM three to four times daily to horses. A study comparing oral and IV administration of the drug determined that systemic availability of furosemide given orally is poor, erratic, and variable among horses. Median systemic bioavailability was low and, at a dose of 1 mg/kg PO, diuresis was not induced (Johansson et al., 2004). In a study comparing CRI to intermittent administration of furosemide in the horse, CRI of the drug produced more uniform urine flow, decreased fluctuations in plasma volume, and suppressed renal concentrating ability throughout the study. Although potassium, calcium, and chloride excretion were higher with CRI than intermittent administration, CRI was preferred if profound diuresis was required in the horse (Johansson et al., 2003).

In humans and other animals, including the dog and horse, approximately 50–60% of a furosemide dose is excreted unchanged in the urine, and the remaining drug is conjugated to glucuronic acid in either the kidney, the liver, or other extrahepatic site (Brater, 1998; Dyke et al., 1998).

Plasma half-life in patients with renal insufficiency is prolonged, and dosage adjustments should be made. Binding of furosemide to excessive amounts of albumin (>4 g/l) in the urine decreases the amount of unbound, active drug and diminishes the diuretic response. In human patients with nephrotic syndrome, doses of two to three times normal are recommended to provide sufficient amounts of active drug to block the $Na^+/K^+/2Cl^-$ symporter.

In humans, bumetanide and torsemide are metabolized in large part by the liver, and so dosage generally does not need to be adjusted for renal disease. Bumetanide's potency in the dog is, in part, explained by limited biotransformation. In addition, renal uptake of bumetanide is greater than furosemide and the drug has a more marked effect on sodium transport in the ascending limb of the Loop of Henle. Approximately 67% of bumetanide in dogs is eliminated unchanged in the urine and feces (Schwartz, 1981). Oral bioavailability of these drugs is much more predictable than that of furosemide and in humans ranges from 80 to 100% (Brater, 1998).

Toxicity, Adverse Effects, Contraindications, and Drug Interactions

Most adverse effects of furosemide administration are related to abnormalities of fluid and electrolyte balance. Extracellular volume depletion and hyponatremia may lead to reduced blood pressure and diminished organ perfusion. Most at risk for adverse effects related to volume depletion are patients with renal disease (may decrease GFR, increase prerenal azotemia, and, possibly, cause tubular necrosis), cardiac disease (stroke volume and cardiac output may decrease), and hepatic disease (precipitation of hepatic encephalopathy). As noted previously, $Na^+/K^+/2Cl^-$ symporter inhibitors deliver an increased load of Na^+ to the distal tubules, resulting in a renin–angiotensin–aldosterone-driven increase in excretion of K^+ and H^+ in exchange for Na^+. Hypochloremic alkalosis and hypokalemia may result. Risk factors for cardiac dysrhythmias related to diuretic-induced hypokalemia include inadequate dietary intake of K^+, concurrent administration of cardiac glycosides, and additional electrolyte imbalances. A common cause of anorexia in CHF patients is digitalis toxicity, and risk of arrhythmias is increased in these patients if hypokalemia is present. Deficiencies in Mg^{2+} and Ca^{2+} may also be caused by diuretic-enhanced excretion of these substances. Serum electrolyte levels should be monitored in patients receiving ongoing diuretic therapy, especially if risk factors exist related to appetite, diuretic dosage, or severity of disease.

Ototoxicity, which is usually transient, has been described primarily with ethacrynic acid and less often with all other loop diuretics. In veterinary medicine,

ototoxicity may be of greatest concern in treatment of cats with high-dose IV regimens. Other adverse effects reported with use of loop diuretics include gastrointestinal disturbances, bone marrow depression, and hyperglycemia. Hyperglycemia may be related to impairment of proinsulin-to-insulin conversion associated with diuretic-induced decreases in K^+ levels. Patients hypersensitive to sulfonamides may also be hypersensitive to furosemide since this drug contains a sulfonamide moiety. Diuretic-induced depletion of water-soluble vitamins may occur, and supplementation of B-complex vitamins has been recommended for animals receiving continuous diuretic therapy (Keene and Rush, 1995).

Loop diuretics are contraindicated in animals with severe fluid and electrolyte disturbances or anuria that does not respond to test doses of diuretics.

Drug interactions may occur when furosemide is administered with theophylline/aminophylline (enhanced effects due to theophylline-induced diuresis), aminoglycosides or cisplatin (enhanced ototoxicity and, if volume depleted, nephrotoxicity), digitalis glycosides (diuretic-induced hypokalemia may increase risk of arrhythmias), aspirin or other anticoagulants (anticoagulant activity increased), neuromuscular blockers (alteration in extent of muscle relaxation), corticosteroids (enhanced potassium wasting), insulin (alteration of insulin requirements associated with hyperglycemic effects), lithium and propranolol (increased plasma levels), probenecid (competition for secretion of diuretic into tubular lumen leading to decreased diuretic effect), NSAIDs (as previously described, decreased diuretic effects), and thiazides (synergistic diuretic activity).

Therapeutic Uses

Furosemide is used in small animals for treatment of edema of cardiac, hepatic, or renal origin. In general, the dose of drug in dogs (1–3 mg/kg every 8–24 hours PO for chronic use; 2–5 mg/kg every 4–6 hours IV, IM, SC) is higher than that used in cats (1–2 mg/kg every 12 hours up to 4 mg/kg every 8–12 hours IV, IM, SC, PO) (Ware, 1998). Furosemide is also used to establish diuresis in renal failure and to promote excretion of other substances, including elevated electrolytes such as Ca^{2+} and K^+. In large animals, furosemide has been used to treat edema in cattle and edema and exercise-induced pulmonary hemorrhage (EIPH) in horses. A general dose of 0.5–1 mg/kg twice daily or as needed to control edema has been recommended in large animals (Reef and McGuirk, 1996). Benefits of furosemide use for treatment of EIPH remain controversial (see Section Exercise-Induced Pulmonary Hemorrhage). Specific state guidelines should be consulted for details of furosemide use (dose, frequency, allowable levels) in racing animals.

Diuretic effects of orally administered torsemide (0.3 mg/kg) and furosemide (3 mg/kg) were compared in dogs and cats (Uechi et al., 2003). Both furosemide and torsemide increased urine volume but the effects of furosemide peaked at 2–3 hours and dissipated by 6 hours while the effects of torsemide peaked at 2–4 hours but persisted for 12 hours in normal dogs, dogs with mitral regurgitation, and cats with experimentally induced left ventricular concentric hypertrophy. It was noted that torsemide decreased urine potassium excretion in study dogs with mitral regurgitation. In a previous study, the ratio of sodium to potassium excretion was found to be 20:1 for torsemide and 10:1 for furosemide (Ghys et al., 1985).

Renal Insufficiency

Decreased GFR and decreased delivery of drug to the tubular site of action and site of elimination in renal insufficiency results in decreased efficacy and increased half-life of furosemide. A sufficiently high dose of drug must be administered to attain an effective amount of drug at the site of action. For the dog, furosemide doses starting at 2 mg/kg IV and increasing in 2 mg/kg increments every hour for 3 hours may be used to try and induce diuresis in severe renal insufficiency. Once a maximal dosage is reached (approximately 6–8 mg/kg), exceeding this amount is not advantageous based on the sigmoidal shape of the fractional sodium excretion curve. In all cases, fluid deficits should be addressed prior to furosemide therapy.

Cardiogenic or Pulmonary Edema

Furosemide has been widely used to reduce extracellular volume and minimize venous and pulmonary congestion in chronic and acute CHF. In humans, beneficial effects in congestive heart failure are noted prior to induction of diuresis suggesting vascular effects are important components of furosemide benefits in patients with pulmonary edema. Human patients with CHF do not require large dosages since furosemide is adequately delivered to the tubular fluid. However, because renal responsiveness to loop diuretics appears to be decreased in these patients, increased frequency of administration has been recommended (Brater, 1998). Diuretics have traditionally been considered front-line therapy for the treatment of chronic CHF in small animals, and furosemide is reported to be the most frequently used drug for this purpose (Goodwin and Hamlin, 1993; Watson and Church, 1995). Despite the popularity of furosemide, human studies have revealed that CHF patients controlled on loop diuretics alone deteriorate more quickly than those treated concurrently with either angiotensin-converting enzyme (ACE) inhibitors or digoxin. Use of furosemide alone is thought to enhance early activation of the renin–angiotensin–aldosterone

system, with detrimental effects on long-term prognosis (Swedberg et al., 1990). Current recommendations include furosemide for treatment of more advanced stages of heart failure in patients already receiving ACE inhibitors, digoxin, or both. Furosemide remains a drug of choice for treatment of acute cardiogenic pulmonary edema. Within the context of severity and chronicity of disease, the lowest effective dosage and frequency of furosemide administration should be determined by observation of clinical signs and consideration of owner observations.

Exercise-Induced Pulmonary Hemorrhage

Exercise-induced pulmonary hemorrhage, or bleeding from the lungs as a consequence of intense exercise, occurs in horses engaged in a variety of athletic activities. The problem has been best studied in racing horses, particularly Thoroughbreds. A consensus statement on EIPH has been released by the American College of Veterinary Internal Medicine (Hinchcliff et al.,2015).

In most studies, furosemide has been found to reduce right atrial, pulmonary arterial, and pulmonary wedge pressures in exercising horses. Some studies suggest that changes in pulmonary pressures caused by furosemide are due to reduction in plasma and blood volume and not to direct effects of the drug on the pulmonary vasculature. Furosemide produces a rapid reduction in blood and plasma volume, which has been shown in the horse to be essential for subsequent reduction in pulmonary pressures (Hinchcliff et al., 1996). Furthermore, administration of polyionic fluids in an amount equal to the volume lost in urine restores furosemide-induced decreases in right atrial pressure and blood volume in the horse (Rivas and Hinchcliff, 1997). Furosemide administration 4 hours prior to exercise has been found to significantly decrease pulmonary capillary hypertension, which is thought to correlate with decreased risk of EIPH. Administration of the drug at shorter intervals prior to exercise did not result in more effective attenuation of exercise-induced pulmonary capillary hypertension (Magid et al., 2000). Combination of furosemide with either clenbuterol (Manohar et al., 2000) or pentoxifylline (Manohar, 2001) have not been found to enhance the pulmonary hemodynamic efficacy of furosemide in EIPH.

Data from additional studies leave open the question of direct effects of furosemide on pulmonary pressures and mechanics in EIPH. In one study horses treated with NSAIDs (phenylbutazone and flunixin) prior to administration of furosemide followed by exercise did not show reductions in pulmonary and right atrial pressures (Olsen et al., 1992). In a subsequent study these effects could not be reproduced (Manohar, 1994). Differences in the studies may be related to drug dosages, time of administration, amount of diuresis, and degree of cyclooxygenase inhibition. While it is accepted that NSAIDs decrease the diuretic and vascular responses to furosemide, it is as yet unresolved whether these drugs mitigate furosemide-induced reductions in pulmonary and right atrial pressures. It is also not clear whether the magnitude of reduction of pulmonary capillary transmural pressure with furosemide is sufficient to prevent capillary rupture in exercising horses (Soma and Uboh, 1998). This is consistent with clinical observations that furosemide reduces, but does not completely eliminate, pulmonary hemorrhage in exercising horses.

Administration of furosemide to racing animals is thought to enhance their performance, although this conclusion remains somewhat controversial. Use of furosemide in racing Thoroughbreds, Quarter Horses, and Standardbreds is estimated at 74.3, 19, and 22.5%, respectively (Hinchcliff, 1999). A cross-sectional study concluded that Thoroughbreds receiving furosemide raced faster, earned more money, and were more likely to win or finish in the top three positions than unmedicated horses (Gross et al., 1999). Early studies showed increases in racing times when EIPH was diagnosed and a subsequent improvement of racing times upon administration of furosemide (Soma et al., 1985). Treadmill studies have not consistently shown furosemide-induced changes in maximal O_2 consumption, time to fatigue, or the speed at which fatigue occurred in exercising horses (Hinchcliff et al., 1993). However, in these and later studies, the loss of weight associated with furosemide administration did reduce carbon dioxide production, the respiratory exchange ratio, and plasma lactate. Furosemide-induced gains in performance were reversed by addition of a weight equal to the weight of the volume lost. These results suggest that performance benefits associated with furosemide administration to EIPH horses may be unrelated to reduction in hemorrhage and more related to changes in body weight (Soma and Uboh, 1998). Based on human studies, this interpretation should not be extended to circumstances in which the race distance is long and exertion prolonged. In these cases, the detrimental effects of dehydration would rapidly offset the advantage of running under reduced weight.

A final issue related to use of furosemide in racing animals involves the regulation of administration of furosemide and other drugs to equine athletes. The control of drugs in racing animal is discussed in more detail in Chapter 57. Doses of 250–500 mg furosemide per horse (0.5–1.0 mg/kg) administered IV no later than 4 hours prior to post time are permitted for medication of horses with EIPH in most jurisdictions in the United States. Specific regulations at a given track should be consulted. The regulation of furosemide administration according to track rules has been approached in a variety of ways. Some jurisdictions use a combination of urine

specific gravity of 1.015 or 1.010 and a plasma concentration of greater than 60 or 100 ng/ml as an indication of a violation of the rules. The combination of these two parameters, low specific gravity and high plasma concentration, will suggest that an irregularity related to dose, time, or route of furosemide administration occurred (Soma and Uboh, 1998). By considering both urine specific gravity and plasma furosemide concentration, the probability of misclassifying horses as being in violation of regulatory concentrations is reduced (Chu et al., 2001).

Widespread use of furosemide in racing animals also presents problems related to screening of urine for presence of regulated substances. The urinary concentration of coadministered drugs may be diluted as a function of furosemide-enhanced diuresis. Urinary excretion rates of some drugs, especially those that are water-soluble acids, may be altered as a result of furosemide competition for the organic anion tubular secretion pathway. Furosemide has been shown to decrease the urinary concentration of phenylbutazone through both of these mechanisms. In comparison, the excretion rate of other agents, notably fentanyl, procaine, and methylphenidate, is increased by furosemide. Faster clearance of these substances may make it more difficult to detect illegal use prior to a race (Hinchcliff and Muir, 1991).

Other Uses

Furosemide has been shown to decrease pulmonary resistance and increase dynamic compliance in ponies with chronic obstructive pulmonary disease. In this case, the rapidity of the response and the finding that the response could be blocked by NSAIDs suggested a cyclooxygenase-mediated event rather than an effect dependent upon loss of body fluid (Broadstone et al., 1991). Immediate changes in pulmonary pressures in other species (e.g., dogs with pulmonary edema) are thought to be related to direct effects of furosemide on the pulmonary vasculature. Similar to use in small animals, furosemide is indicated for treatment of CHF and associated pulmonary edema by decreasing cardiac preload and plasma volume. Furosemide is also recommended to increase urine flow in acute renal failure in horses.

Inhibitors of Na^+/Cl^- Symport (Thiazide and Thiazide-Like Diuretics)

Chemistry/Formulations

Thiazide diuretics are benzothiadiazines or analogs and are derivatives of CA-inhibiting sulfonamides. Compared to carbonic anhydrase inhibitors which promote the elimination of sodium bicarbonate, thiazides promote renal excretion of sodium chloride producing a true saluretic effect. Two of the first thiazides synthesized, and the two drugs most commonly used in veterinary medicine, are chlorothiazide (Diuril®, human-approved 250 and 500 mg tablets, 50 mg/ml suspension, and 500 mg/vial injectable available) and hydrochlorothiazide (Hydrozide®, veterinary-approved 25 mg/ml injectable; HydroDiuril®, human-approved 25, 50, and 100 mg tablets and 10 mg/ml oral suspension). Both drugs are derivatives of benzothiadiazine and are water soluble. Hydrozide® is the only veterinary-approved product for use in cattle and has a 72-hour milk withholding time for lactating dairy cattle; no meat withholding time has been reported. Newer generation, more lipid-soluble benzothiadiazine derivatives include cyclothiazide and methychlothiazide.

Nonbenzothiadiazine derivatives have thiazide-like effects, and these drugs also promote excretion of sodium with chloride. Quinazolinone derivatives are in this class and include metolazone and chlorthalidone. These drugs are not commonly used in veterinary medicine but are examples of thiazide-like diuretics.

Mechanisms and Sites of Action

The primary site of action of thiazides is the distal convoluted tubule, with some secondary activity, possibly CA-related, in the proximal tubule. In the distal tubule, Na/Cl reabsorption is mediated by an electroneutral cotransport (symport) system (Figure 24.9). The driving force for Cl^- entry is the transmembrane Na^+ gradient established by the activity of basolateral Na^+/K^+-ATPase. The apical (luminal) Na/Cl cotransporter is reversibly inhibited by thiazides. Basolateral movement of Cl^- out of the cell is mediated by a Cl^- channel and K^+ by a K^+ channel. The lumen-negative transepithelial potential generated by the polarity of K^+ and Cl^- exit may drive anion reabsorption via a paracellular shunt pathway. Ca^+ reabsorption is enhanced by thiazides, by increasing distal tubule Na^+/Ca^{2+} exchange (antiporter) on the basolateral membrane due to low intracellular sodium. Because 90% of filtered Na^+ is reabsorbed prior to the distal tubule, the peak diuresis caused by thiazides is moderate compared to loop diuretics. Like loop diuretics, thiazides enhance excretion of K^+ by increasing the delivery of Na^+ to the distal tubule.

Absorption and Elimination

Thiazide and thiazide-like diuretics are absorbed slowly and incompletely from the gastrointestinal tract. Most drugs in this class are highly protein bound and undergo renal excretion (chlorothiazide and hydrochlorothiazide)

or by a combination of renal and biliary routes (thiazide-like drugs). Hydrochlorothiazide is less protein bound (40%) than others in the class and partitions and accumulates in red blood cells (Velazquez et al., 1995). All drugs in this class gain access to the lumen of the renal tubule via an organic acid secretory pathway. Hence effectiveness of these drugs is decreased if renal blood flow diminishes.

Toxicity, Adverse Effects, Contraindications, and Drug Interactions

Similar to loop diuretics, most problems associated with administration of thiazides are related to fluid and electrolyte disturbances. Potassium wasting, especially with concurrent use of digitalis, increases the risk of cardiac arrhythmias. Low K^+ may secondarily affect conversion of proinsulin to insulin, leading to hyperglycemia. Enhanced calcium reabsorption can lead to hypercalcemia, and mild magnesuria may cause magnesium deficiency. Depletion of extracellular volume, hyponatremia, hypochloremia, and hypochloremic metabolic alkalosis may occur as adverse effects with prolonged or aggressive thiazide use. Because thiazides block solute reabsorption at nephron sites involved in dilution of urine, these agents increase the risk of hyponatremia under conditions of increased consumption of hypotonic fluids. CNS and gastrointestinal effects may occur but are not common.

Although thiazides contain sulfur, they do not induce reactions similar to sulfa antimicrobials (Trepanier, 2004). Patients with severe renal disease, hypovolemia, or electrolyte disturbances are poor candidates for thiazide therapy. Impaired hepatic function that may be worsened by volume contraction (leading to hepatic encephalopathy) is a contraindication for thiazide use. Diabetic patients are at risk for thiazide-induced derangements of glucose and insulin.

Drug interactions may include decreased effects of anticoagulants and insulin and increased effects of some anesthetics, diazoxide, digitalis glycosides, lithium, loop diuretics, and vitamin D. Combination therapy using low-dose thiazides with antihypertensives (e.g., ACE inhibitors) is currently considered to be an effective alternative strategy for management of human hypertension (Neutel et al., 1996). At low doses, adverse effects of thiazides are decreased, making their use in combination regimens particularly appealing.

Thiazides are reported to prolong the half-life of quinidine. In the face of thiazide-induced hypokalemia, an elevated plasma quinidine level increases the risk of polymorphic ventricular tachycardia (torsades de pointes), a condition that can deteriorate into ventricular fibrillation (Jackson, 1996). NSAIDs may reduce the effectiveness of thiazides and loop diuretics (Brater, 1998).

Therapeutic Uses

Thiazides may be used to treat edema of cardiac, hepatic, or renal origin. Typical oral dosages in the dog and cat are 20–40 mg/kg every 12 hours (chlorothiazide) and 2–4 mg/kg every 12 hours (hydrochlorothiazide). Effects of both chlorothiazide and hydrochlorothiazide peak at 4 hours and last up to 12 hours, with hydrochlorothiazide typically having a longer duration (12 hours) than chlorothiazide (6–12 hours). Cattle may be treated for udder edema with hydrochlorothiazide (125–250 mg IV or IM once or twice daily). Oral chlorothiazide (not a veterinary-approved product) at a dose of 4–8 mg/kg once or twice daily has been substituted for injectable hydrochlorothiazide following the first or second day of parenteral treatment.

Thiazides have previously been used in veterinary medicine in management of the early stages of CHF. As mentioned previously, early use of loop and thiazide diuretics in CHF activates aldosterone-mediated mechanisms that eventually lead to cardiac deterioration. For this and other reasons, the use of thiazides in treatment of CHF is not common in veterinary medicine. In general, furosemide is more commonly used in veterinary medicine to treat edema, whether it be cardiac, hepatic, or renal in origin. In human medicine, thiazides are commonly used in the management of hypertension. Because thiazides increase reabsorption of calcium, they may also be beneficial in treatment of calcium nephrolithiasis in humans and animals.

Thiazides are used effectively to reduce the volume of urine in patients with nephrogenic diabetes insipidus. Diuretic-induced volume contraction leads to increased proximal tubule reabsorption and a decrease in urine volume of 30–50%. Although dosages are individualized in these patients, starting ranges of 10–20 mg/kg twice daily (chlorothiazide) or 2.75–5.5 mg/kg (hydrochlorothiazide) twice daily have been suggested (Nichols and Thompson, 1995).

Inhibitors of Renal Epithelial Sodium Channels (K^+-Sparing Diuretics)

Chemistry/Formulations

The two relevant drugs in this class, triamterene (Dyrenium®) and amiloride (Midamor®), both belong to the class of cyclic amidine diuretics. Triamterene is a pteridine ring with amino groups at the 2, 4, and 7 positions. It was originally synthesized as a folic acid antagonist. Amiloride consists of a substituted pyrazine ring with a carbonylguanidinium side chain. A number of analogs of this basic structure have been synthesized and have been useful tools in elucidating mechanisms

of sodium transport. Both triamterene and amiloride are organic bases and are secreted into the proximal tubule by an organic base transport system. Although neither of these drugs is used with frequency in veterinary medicine, triamterene is the more commonly used and hence will be the focus of these discussions. No parenteral forms of the drug are available; oral preparations are available in 50 and 100 mg capsules.

Mechanisms and Sites of Action

Triamterene and amiloride cause a mild increase in excretion of NaCl and a retention of K^+. Both drugs slightly augment diuresis and are used in combination with loop diuretics or thiazides to decrease K^+ excretion (hence the term K^+-sparing). Both drugs act at the late distal tubule (or connecting tubule) and collecting duct to block the electrogenic transport of Na^+. As with other diuretics, the basolateral Na^+/K^+-ATPase creates an electrochemical gradient that drives events at the luminal surface of the tubular cell. In this case, the principal cells of the connecting tubule contain a Na^+ channel in their luminal membrane that provides a pathway for entry of Na^+ and sets up a lumen-negative transepithelial potential. The transepithelial voltage is the key force involved in driving K^+ out of the principal cell and into the tubular lumen. Blockade of Na^+ channels by triamterene or amiloride hyperpolarizes the luminal membrane, reduces the lumen–negative potential difference, and decreases the excretion of K^+, H^+, Ca^{2+}, and Mg^{2+}. It has been speculated that effects of both of these drugs may also be mediated by inhibition of a Na^+/H^+ antiport located in the late distal tubule and collecting duct. Additional, direct effects on Mg^{2+} excretion may also occur.

Triamterene has been shown to exert cardiac effects that are not secondary to alterations in renal function. Early studies documented a prolongation of the cardiac action potential duration and functional refractory period and an increase in myocardial contractile force. Triamterene has also been shown to decrease digitalis-induced K^+ loss from the heart and increase the dose of digitalis necessary to induce toxic effects in dogs (Palmer and Kleyman, 1995; Netzer et al., 1995). Neither triamterene nor amiloride has been shown to affect renal hemodynamics or glomerular filtration rates, and neither acts as an aldosterone antagonist.

Absorption and Elimination

Both amiloride and triamterene are administered orally; triamterene is up to 70% bioavailable, but neither drug has been extensively evaluated in most veterinary species. Amiloride is renally excreted. The pharmacokinetics of triamterene are complex. The parent drug is converted in the liver to an active metabolite, 4-hydroxytriamterene sulfate, which is actively secreted into the renal tubules. Hence renal or hepatic disease could impair elimination of triamterene. The peak onset of action of triamterene is 6–8 hours, with effects persisting up to 12–16 hours.

Toxicity, Adverse Effects, Contraindications, and Drug Interactions

The most important potential adverse effect of these drugs is hyperkalemia. The presence of diseases or circumstances that may increase the risk of hyperkalemia (e.g., renal failure, coadministration of other drugs with K^+-sparing properties, including ACE inhibitors and K^+ supplements and NSAIDs) should be noted and these patients treated with other diuretic combinations. Triamterene may decrease GFR and, in combination with NSAIDs, has been shown to increase the likelihood of hyperkalemia and renal dysfunction. Triamterene-induced renal casts may be responsible for increased risk of interstitial nephritis and renal stones. Both triamterene and amiloride may induce hypersensitivity reactions that include rash and photosensitivity in humans. CNS, gastrointestinal, and hematological side effects have also been reported. As with most other diuretics, use in patients with severe hepatic disease or renal disease is contraindicated. In human patients with hepatic disease, the mild folic acid antagonism inherent in triamterene may increase the risk of megaloblastosis.

Therapeutic Use

Because these drugs have relatively weak diuretic properties, they are clinically important primarily because of their K^+-sparing properties in combination with loop and thiazide diuretics. Both have been used in this capacity for treatment of edema associated with CHF, liver cirrhosis, nephrotic syndrome, steroid-induced edema, and idiopathic edema. Triamterene is administered at a dose of 2–4 mg/kg/day orally to dogs with food to avoid gastrointestinal side effects.

Antagonists of Mineralocorticoid Receptors (Aldosterone Antagonists and K^+-Sparing Diuretics)

Chemistry/Formulations

Spironolactone is a 17-spirolactone and along with eplerenone are the only aldosterone antagonists approved in the United States. Canrenone, an active metabolite of spironolactone, and potassium canrenoate are closely related structurally and are available in other countries. All of these drugs share a four-ring, steroid

structure similar to the mineralocorticoid aldosterone. Spironolactone is available as a human-approved oral preparation (Aldactone®) in 25, 50, and 100 mg tablets and eplerenone is available in 25 and 50 mg tablets.

Mechanisms and Sites of Action

Aldosterone is a steroid hormone that binds to mineralocorticoid receptors (MRs) located in the cytoplasm of target cells. The inactive MR complex is bound to heat shock protein 90 (HSP90), a protective chaperon protein, and is incapable of binding to target DNA sequences. Upon binding of aldosterone, HSP90 dissociates from the receptor–hormone complex, allowing movement of the activated receptor into the nucleus. The complex binds to target sequences of DNA referred to as mineralocorticoid-response elements (also termed hormone-responsive elements) that regulate transcription of downstream, mineralocorticoid-responsive genes. Protein products of these responsive genes, aldosterone-induced proteins (AIPs), cause Na^+ reabsorption and increase excretion of K^+ and H^+ in the late distal tubule and collecting duct. AIPs are thought to have multiple effects, including activation, redistribution, and de novo synthesis of Na^+ channels and Na^+/K^+-ATPase, changes in permeability of tight junctions, and increased mitochondrial production of ATP. These effects combine to cause an increase in Na^+ conductance of the luminal membrane and increased Na^+ pump activity in the basolateral membrane. As a result, Na and Cl transport is increased across tubular epithelial cells, and the lumen-negative transepithelial voltage is increased. Secretion of K^+ and H^+ into the tubular lumen increases with increasing voltages.

Aldosterone antagonists act by binding to the MR and facilitating the release of HSP90 from the steroid-binding subunit of the receptor. The unprotected MR complex is thought to be inactivated by proteases. In the absence of activated MRs, gene transcription is not induced, AIPs are not produced, and the physiological effects of aldosterone are blocked.

In addition to antagonism of aldosterone, spironolactone is thought to act in a manner similar to calcium channel blockers to cause direct vasodilation. By binding to plasma membrane sites, spironolactone may inhibit inward slow calcium channels and depress contractions dependent on release of calcium from the sarcoplasmic reticulum. Aldosterone antagonists have also been shown to increase nitric oxide vasodilation and circulating levels of atrial natriuretic peptide as evaluated in the dog. Spironolactone may produce antiarrhythmic effects by blocking the ether-a-go-go protein on the cardiac potassium ion channels (Gómez et al., 2005). Hence direct and aldosterone-mediated effects of the drug may contribute to its usefulness in treatment of cardiac disease (Endou and Hosoyamada, 1995).

Absorption and Elimination

In humans, spironolactone is absorbed moderately well (60–90%), is highly protein-bound, and is extensively biotransformed in the liver, exhibiting a first-pass effect. An active metabolite, canrenone, has a longer half-life than the parent drug and extends the biological effects of spironolactone to about 16 hours in humans. Spironolactone has approximately 60% oral bioavailability in dogs (Karim et al., 1976) and exhibits near proportional drug exposure (canrenone) from 0.7 to 8 mg/kg PO (Guyonnet et al., 2010). Peak diuresis occurs as late as 2–3 days after initiation of therapy. Aldosterone antagonists do not require secretion into the renal tubule to induce diuresis. Greater effects of aldosterone antagonists are expected as the concentration of aldosterone increases and conversely if low concentrations of aldosterone are present, less effects are expected.

Toxicity, Adverse Effects, Contraindications, and Drug Interactions

Hyperkalemia, dehydration, and hyponatremia are the most common side effects of aldosterone antagonists. When used alone, these drugs can also cause hyperchloremic metabolic acidosis. In humans, sexual side effects limit the use of spironolactone in some patients due to effects on progesterone and androgen receptors. This lack of receptor specificity drives continued efforts to identify a more-MR-specific antagonist for use in human medicine.

As previously noted, combination of any K^+-sparing diuretic, including spironolactone, with ACE inhibitors must be accomplished cautiously to avoid hyperkalemia. This is a clinically significant scenario that merits patient monitoring of plasma K^+ concentrations. Spironolactone may decrease oral bioavailability of digoxin due to increased p-glycoprotein expression (Ghanem et al., 2006), but may decrease digoxin renal clearance; therefore, therapeutic drug monitoring of digoxin is recommended when administered concurrently with spironolactone (O'Brien et al., 1985). The presence of spironolactone in plasma may also confound therapeutic drug monitoring of digoxin if a cross-reactive antidigoxin antibody is used in the assay. Aspirin apparently blocks spironolactone-induced natriuresis (Endou and Hosoyamada, 1995).

Therapeutic Uses

The effectiveness of aldosterone antagonists in promoting diuresis is largely dependent upon elevated concentrations of endogenous aldosterone. Aldosterone secretion increases upon activation of the renin–angiotensin–aldosterone system, which, in turn, responds to reductions in serum sodium, effective blood

volume, and cardiac output, and decreases in serum K^+. Secondary hyperaldosteronism and edema are associated with cardiac failure, hepatic cirrhosis, nephrotic syndrome, and severe ascites. Spironolactone is used in veterinary medicine at a dose of 2–4 mg/kg/day orally in management of refractory edema associated with these conditions and has been used in the management of hepatic cirrhosis. In both human and veterinary medicine, aldosterone antagonists are commonly administered with a thiazide or loop diuretic to increase peak diuresis and to spare K^+.

Elevated aldosterone levels have been shown to be a useful prognostic indicator in heart failure, with higher levels correlated with a poorer prognosis. Activation of the renin–angiotensin–aldosterone system in arterial hypertension is thought to lead to remodeling of the myocardial collagen network with progressive cardiac interstitial fibrosis. As fibrosis increases, diastolic function deteriorates and pathological cardiac hypertrophy occurs. When aldosterone-mediated effects are blocked by spironolactone, progression of myocardial failure is presumably slowed. A clinical study in humans supported this contention by showing significant delays in progression of CHF in patients treated with spironolactone (Pitt et al., 1999). No comprehensive study has been published to verify this effect in veterinary patients. Diuretic efficacy of spironolactone was not demonstrated in a study combining the drug with furosemide in greyhound dogs (Riordan and Estrada, 2005).

A newer drug, eplerenone, reduced mortality in a human study of heart failure due to myocardial infarction (Weir and McMurray, 2005), and the drug has also been shown to have cardioprotective effects in animal models of myocardial failure (McMahon, 2003). Despite the potential side effect of hyperkalemia associated with coadministration of aldosterone-antagonists and ACE inhibitors, this combination with appropriate dosages has been deemed effective in management of CHF. Addition of furosemide, which enhances elimination of K^+, may decrease the risk of hyperkalemia. Patient monitoring for K^+ derangements is critical to safe implementation of this approach. In veterinary medicine, spironolactone may be useful in patients with CHF secondary to chronic valvular heart disease or dilated cardiomyopathy that become unresponsive to therapy with ACE inhibitors, digoxin, and furosemide.

Methylxanthines

Overview

Methylxanthines (aminophylline and theophylline) are primarily used for bronchodilator effects and are discussed in more detail in Chapter 48. Methylxanthines are adenosine receptor antagonists at lower dosages and higher dosage produce phosphodiesterase inhibitor effects. They produce weak diuresis and natriuresis. The mechanism of diuresis appears in part due to vasodilation of the renal afferent arterial increasing glomerular filtration rate. However adenosine receptors in the proximal convoluted tubule stimulate fluid and bicarbonate transport as well as Na^+/glucose and Na^+/phosphate symport (Rieg et al., 2005). Although not a primary choice as a diuretic, low-dose aminophylline has demonstrated efficacy as an adjunct in human pediatric patients that are refractory to furosemide diuresis (2005; 2012). The clinical utility in veterinary medicine has not been reported, but use of aminophylline as a diuretic adjunct in furosemide-resistant patients is an area that requires further research prior to recommended use in animals.

New and Experimental Agents

Aquaretics

Vasopressin (or arginine vasopressin, AVP) regulates water and solute excretion in the kidney by binding to V2 receptors in the principal cells of the renal collecting duct system. As one of three G-protein-coupled AVP receptor subtypes (V1a, V1b, V2), V2 receptors mediate the antidiuretic effects of AVP. V2 receptor antagonists, so-called aquaretic agents, promote solute-free water excretion. These antagonists hold considerable promise for treatment of edematous states associated with heart failure, liver cirrhosis, nephrotic syndrome, and syndrome of inappropriate secretion of antidiuretic hormone (Verbalis, 2006). While peptide derivatives of AVP have been found to have intrinsic antidiuretic properties, several nonpeptide antagonists are currently approved, including conivaptan and tolvaptan. These drugs typically increase urine volume and decrease urine osmolality and body weight without affecting urinary sodium excretion (Orita and Nakahama, 1998; Serradeil-Le Gal, 1998; Palm et al., 2006). Tolvaptan administered to healthy dogs dose dependently (0.3–10 mg/kg PO) increased urine volume and decreased urine osmolality, without increasing urinary sodium excretion (Miyazaki et al., 2007). Similar effects were observed in dogs with experimentally induced heart failure. In the healthy and CHF-induced experimental dogs, tolvaptan did not increase sympathetic or renin–angiotensin–aldosterone systems, but did increase AVP concentrations. No effects were observed on glomerular filtration rates, renal blood flow, or peripheral vascular resistance. No published clinical trials of tolvaptan in naturally occurring cardiac disease in dogs or cats are available. Conivaptan was shown to improve impaired cardiovascular parameters induced

by intravenous infusion of AVP in a dog model, suggesting possible clinical usefulness (Yatsu et al., 2002).

Although vasopressin antagonists represent a promising area of drug development for induction of aquaresis, drugs that interfere with secretion of AVP from the neurohypophysis and drugs that directly inhibit water channels in the collecting ducts are also of interest. Aquaporin-CD, the water channel of the principal cell of the cortical and medullary collecting duct, has been cloned and provides an attractive site for drugs intended to inhibit diuresis.

Neutral Endopeptidase Inhibitors

Neutral endopeptidase (NEP) is an enzyme that rapidly degrades atrial natriuretic factor, the cardiac peptide hormone that increases sodium and water excretion, inhibits the renin–angiotensin–aldosterone system, and produces vasodilation. NEP inhibitors have been investigated for their possible usefulness in increasing circulating concentrations of atrial natriuretic factor and therefore increasing the fractional excretion of sodium. An experimental NEP inhibitor, ecadotril, has been investigated in induced heart failure in dogs (Solter et al., 2000; Mishima et al., 2002) and been shown to attenuate progression of disease. NEP inhibitors have been shown in dogs to enhance the actions of furosemide and prevent the furosemide-induced activation of the renin–angiotensin–aldosterone system (Kittleson and Kienle, 2007).

Dopamine Receptor Agonists

Dopaminergic receptor 1 (DA_1) and dopaminergic receptor 2 (DA_2) have both been considered targets for low–dose dopamine therapy of low output renal failure in dogs and humans. Efficacy of low-dose dopamine has been questioned and concerns have been raised over renal morbidity and gastrointestinal side effects. It has been noted that although dopamine increases renal perfusion and urine output, increases in creatinine clearance are not sufficient to achieve therapeutic efficacy in management of renal failure. In comparison, DA_1 selective agonists may be more effective at increasing renal blood flow, inducing diuresis and natriuresis, and increasing glomerular filtration rate. This is particularly true in cats, a species that does not respond well to the renal effects of dopamine. Fenoldopam, a selective DA_1 agonist, has been investigated in both dogs and cats. In cats, fenoldopam at a dose of 0.5 μg/kg/min induced diuresis in a delayed manner, by 6 hours postadministration, increased urine output, sodium excretion, fractional clearance of sodium, and elimination of creatinine (Simmons et al., 2006).

Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Antagonists

Chemistry/Formulations

Numerous angiotensin converting enzyme (ACE) inhibitors are approved for use in humans and animals. Captopril was the first ACE inhibitor marketed and is available in oral dosage from 12.5 to 100 mg tablets and in combination with hydrochlorothiazide. Enalapril maleate is a prodrug ester approved for use in dogs and in humans and is available in tablets ranging from 1 to 20 mg and as a 1 mg/mL oral solution. Enalaprilat is the active drug and is available as an injection (1.25 mg/mL), but rarely used in veterinary medicine. Benazepril hydrochloride is available as 5–40 mg tablets and is approved in some countries for use in dogs and cats. Imidapril and ramipril are also approved for use in some countries for dogs. Although numerous other ACE inhibitors are available, they are less commonly used.

Angiotensin receptor antagonists, also known as angiotensin receptor blockers (ARBs) are approved for use in humans. Losartan, telmisartan, valsartan, and irbesartan, available for oral administration, have rarely been used in dogs and cats, but may see increasing use in veterinary medicine.

Mechanisms and Sites of Action

The action of ACE inhibitors is to decrease the metabolism of angiotensin I (ATI) to angiotensin II (ATII), which produces profound physiological effects, as described in Section Renin–Angiotensin–Aldosterone System (Figure 24.10). ACE also inactivates bradykinin, therefore ACE inhibitors increase bradykinin and subsequently prostaglandins both of which may provide additional benefits. The efficacy of the different ACE inhibitors are similar in humans, but differences in pharmacokinetics and individual sensitivity to adverse effects are the primary differences for ACE inhibitor selection for specific patients.

Angiotensin receptor blockers are selective antagonists of the angiotensin receptor type 1 (AT_1). Although they are considered reversible antagonists, their (or their active metabolite) antagonism cannot be overcome with higher concentrations of ATII. The ARBs are specific for inhibiting ATII in contrast to ACE inhibitors that can additional effects such as decreased bradykinin metabolism.

The ACE inhibitors decrease ATII formation while the ARBs directly inhibit ATII binding to AT receptors, decreasing ATII effects including direct vasoconstriction, rapid and slow pressor responses, vasopressin and aldosterone release, sympathetic nervous system tone,

enhanced release of norepinephrine, and adrenal catecholamine release. Although ACE inhibitors and ARBs are expected to have minimal blood pressure effects in healthy animals, animals with high concentrations of renin and ATII can have profound effects. In humans, ACE inhibitors and ARBs are usually started at a low dose and increased over time to minimize acute hypotension. However, hypotension is much less of a problem in dogs and cats as, in general, the ACE inhibitors and ARBs are relatively low-efficacy vasodilatory drugs.

Absorption and Elimination

Most ACE inhibitors are formulated as a prodrugs to enhance oral bioavailability. The exception is captopril, which is an active drug. The oral bioavailability of most ACE inhibitors in dogs and cats are low, but sufficient for clinically relevant effects. In contrast, the oral bioavailability of enalapril in horses is very low and enalapril is not an effective PO drug in horses (Gardner et al., 2004). Additionally, when benazepril, ramipril, quinapril, and perindopril were administered PO to horses only benazepril produced reasonable effects in horses (Afonso et al., 2013). The oral bioavailability of enalapril and benazepril are not affected by feeding, but the oral bioavailability of captopril, imidapril, and ramipril are decreased by administration with food. Enalapril, benazepril, imidapril, and ramipril are prodrugs metabolized to the active metabolites enalaprilat, benazeprilat, imidaprilat, and ramiprilat. Enalaprilat and captopril are primarily eliminated unchanged in the urine while benazeprilat, ramiprilat, and imidaprilat are approximately equally eliminated in the urine and bile. Therefore animals with decreased renal function will have decreased elimination of captopril and enalaprilat, which could lead to exaggerated and adverse effects if dosages are not adjusted. Thus benazepril, ramipril, and imiapril are preferred in animals with decreased renal function. The doses of ACE inhibitors are: enalapril 0.25–0.5 mg/kg PO q 12–24 h; benazepril 0.25–0.5 mg/kg PO q 12–24 h; imidapril 0.25 mg/kg PO q 24 h; and ramipril 0.125–0.25 mg/kg PO q 24 h.

The pharmacokinetics of the oral ARBs losartan, telmisartan, valsartan, and irbesartan have been reported in dogs, but not in cats (Huang et al., 2005; Baek et al., 2013). In cats, telmisartan produced greater and longer lasting effects than losartan and irbesartan. However, limited dosage ranges were assessed and the pharmacokinetics, including oral bioavailability and half-life, are unknown; therefore, it is unclear if telmisartan is a better choice in cats or if the dosages of losartan and irbesartan were inappropriate (Jenkins et ., 2015). The oral bioavailability of losartan in dogs is relatively low, 23–33%, but the absolute oral bioavailability of the other ARBs have not been reported (Christ et ., 1994). In humans, the oral bioavailability of most ARBs is <50%. In humans, losartan is metabolized to an active metabolite, E-3174, which is more potent than losartan, but minimal amounts of the metabolite are produced in dogs (Suzuki et al., 2001). Metabolism of losartan has not been reported in cats. Despite the lack of the active metabolite in dogs, effects of losartan against exogenous ATII were profound, but of short duration. In humans, ARBs are primarily eliminated by hepatic metabolism and biliary secretion with changes in renal function having minimal effects on their pharmacokinetics. Food markedly decreases the oral absorption of telmisartan and valsartan but not losartan and irbesartan in humans. The effect of food on the pharmacokinetics of ARBs in dogs has not been extensively evaluated, therefore it would be prudent to administer to fasted animals until further data are available.

Toxicity, Adverse Effects, Contraindications, and Drug Interactions

Angiotensin converting enzyme inhibitors in dogs are cats are, overall, well tolerated. Acute renal failure is an adverse effect with ACE inhibitors and ARBs that warrant close monitoring. Renal adverse effects may be more severe and rapidly progressive in animals treated with enalapril or captopril as drug accumulation occurs once renal dysfunction starts, but renal adverse effects can occur with any ACE inhibitor. Renal failure risks are increased in animals with renal hypotension as ATII vasoconstriction of the efferent arteriole maintains renal blood pressure, but is blocked by ACE inhibitors and ARBs. In contrast, animals with renal hypertension and proteinuria can have therapeutic benefits of ACE inhibitors and ARBs. Animals that are dehydrated and hyponatremic are at higher risk for renal failure. Serum creatinine should be routinely monitored for development or worsening of azotemia, initially within a week of initiating therapy and then periodically throughout therapy. If azotemia is detected, decreasing the dose of concurrent diuretics (decreasing dehydration and hyponatremia) may be appropriate in addition to decreasing or discontinuing ACE inhibitor or ARB therapy.

Hyperkalemia due to ACE inhibitors and ARBs in animals is rare unless combined with potassium-sparing diuretics or renal failure. The RAAS is important for the development of normal kidney anatomy in utero and exposure to ACE inhibitors and ARBs result in numerous birth defects and should be avoided in pregnant animals and neonates. Although hypotension can occur with ACE inhibitors and ARBs, it is uncommon in animals unless the animal is dehydrated or receiving other vasodilators. In humans, coughing and angioedema is a common adverse effect due to enhanced bradykinin from ACE inhibitors, but not ARBs; however, coughing and

angioedema are rarely or not reported adverse effect in animals.

There is the potential for drug interactions with ACE inhibitors and ARBs in dogs and cats. The risk of renal adverse effects appears to increase and the antihypertensive effects diminished when combined with NSAIDs that affect prostaglandin formation (KuKanich et al., 2012). Concurrent administration of vasodilators with ACE inhibitors are expected to produce exaggerated vasodilatory effects, which could result in systemic hypotension in addition to renal hypotension, increasing the risk of renal toxicity. The concurrent use of diuretics can lead to hyponatremia and dehydration, which increases the risk of renal toxicity. Likewise, the concurrent use of nephrotoxic drugs, including but not limited to aminoglycosides, amphotericin B, and cisplatin, increases the risk of renal toxicity. Combination of ACE inhibitors with potassium sparing diuretics, including spironolactone, increases the risk of hyperkalemia. In humans, ACE inhibitors decrease the clearance of digoxin, but this interaction has not been reported in animals.

Therapeutic Uses

Angiotensin converting enzyme inhibitors are commonly administered to dogs with chronic heart disease. Although ACE inhibitors are used in cats with hypertrophic cardiomyopathy, there are less data available demonstrating therapeutic benefits. However, numerous laboratory studies and clinical trials are available in dogs demonstrating the benefit of ACE inhibitors in dogs with chronic heart disease (dilated cardiomyopathy and chronic valvular diseases) often combined with other therapeutics, including diuretics (primarily furosemide and spironolactone), digoxin, and pimobendan (Chapter 21), as appropriate (Lefebvre et al., 2007). The most important clinical effects for clients are improved quality of life and increased survival times when affected dogs with symptomatic heart disease are treated with ACE inhibitors in combination with appropriate concurrent therapeutics. Dogs treated chronically had greater decreases in pulmonary edema, respiratory effort and coughing, and improved appetite, exercise tolerance/ mobility/ activity, attitude, and general demeanor with the addition of ACE inhibitors. Despite the clinical improvement, specific physiological measurements such as cardiac output, stroke volume, pulmonary arterial pressures, and systemic vascular resistant are often unaffected. The data are more equivocal with dogs exhibiting asymptomatic/ subclinical heart disease and routine use of ACE inhibitors in these dogs are not currently recommended. There are no studies reporting the efficacy of ARBs in dogs or cats with naturally occurring chronic heart disease, but the availability of cost-effective ARBs will likely increase their use in veterinary medicine.

ACE inhibitors are also administered to dogs and cats for the treatment of proteinuria and glomerular diseases (Brown et al., 2013; King et al., 2006). Dogs with a urine protein to creatinine ratio (UPC) exceeding 0.5 are recommended to be treated with an ACE inhibitor. Clinical trials have demonstrated efficacy of enalapril in decreasing proteinuria in dogs with glomerular disease and delayed the onset of azotemia (Brown et al., 2013). Although studies demonstrating the efficacy of benazepril on dogs with proteinuria are lacking, benazepril is often administered to dogs with elevated UPC and glomerular disease. An advantage of benazepril is that its pharmacokinetics are minimally affected by renal dysfunction, compared to enalapril which is significantly altered. There are no reports of ARBs used for the management of naturally occurring proteinuria and glomerular disease in dogs, but with the availability of cost-effective ARBs they will likely be used more commonly. In cats, benazepril has been recommended for the management of chronic kidney disease (CKD) with elevated UPC (King et al., 2006). Benazepril significantly decreased UPC and maintained plasma protein concentrations compared to placebo in cats. However, there was no significant difference in survival time and need for parenteral fluids/ euthanasia/ death due to renal failure, but there was large variability. Similarly, telmisartan significantly decreased UPC in cats with CKD (Sent et al., 2015).

ACE inhibitors as a sole treatment for hypertension in dogs and cats have a low efficacy and most often do not provide a clinically desired effect. Vasodilators such as amlodipine (Chapter 21) are often administered concurrently with ACE inhibitors to achieve clinically desired decreases in blood pressure.

References and Additional Reading

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