**Diuretics**

The **loop diuretics** are the single most effective agents available to decrease circulating blood volume and reduce signs of congestion. They act via inhibition of the Na+/K+/2 Cl– cotransporter in the thick ascending loop of Henle. This leads to increased renal sodium and chloride excretion, with subsequent free water loss. Furosemide is the most widely used loop diuretic. When administered IV, it also directly reduces pulmonary capillary wedge pressure (before onset of diuresis) via local prostaglandin synthesis, which has a vasodilatory effect. The onset of action after IV administration is 5 min, with peak effects occurring at 30 min and lasting ∼2 hr. The onset of action after oral administration is 60 min, with peak effects seen at 1–2 hr and lasting ∼6 hr.

Emergency therapy of pulmonary edema often requires high doses of IV or IM furosemide (2–8 mg/kg for dogs; 2–4 mg/kg for cats), repeated at 30- to 60-min intervals until clinical signs of congestion are controlled. Because of the concern for hypotension, azotemia, and significant electrolyte disturbances with overzealous furosemide administration, tapering to the lowest effective dosage that controls signs of CHF is recommended once the animal is stable. Mild azotemia and electrolyte and acid-base disturbances (hyponatremia, hypokalemia, and a hypochloremic metabolic alkalosis) are not uncommon and are generally tolerated as long as the animal is eating and drinking. Oral doses used to manage chronic CHF may vary significantly between animals; the lowest possible dosage should be used. In dogs, CHF is often initially controlled at dosages of 1–2 mg/kg, sid-bid while cats are more sensitive to the development of adverse effects and generally require lower dosages (0.5–2 mg/kg every 12–48 hr). Use of furosemide or other diuretics as sole therapy in longterm management of CHF increases RAAS activation; thus, combination with an ACE inhibitor is recommended.

Furosemide resistance, typically defined by persistent signs of congestion despite dosages of 2–4 mg/kg, PO, tid, may develop in advanced cases of CHF. There are many causes of diuretic resistance, including decreased delivery of the drug to the nephron, activation of the RAAS (which counteracts the effects of diuresis), and hypertrophy of the distal convoluted tubular cells with consequent increases in ion transport in this region of the nephron. GI edema secondary to right-sided CHF may decrease absorption of orally administered diuretics and contribute to diuretic resistance. Animals with resistance to chronic high doses of oral furosemide may thus have an improved diuretic response from SC administration of the drug or from addition of other diuretic agents (“diuretic stacking”).

Adverse effects seen with furosemide administration are generally related to dehydration from volume depletion and electrolyte and acid-base abnormalities. Less common adverse effects include vomiting, pancreatitis, and idiosyncratic deafness with rapid IV administration. Animals with preexisting renal disease are more likely to develop adverse effects, and furosemide therapy should be reduced or temporarily withdrawn accordingly. Renal values should be monitored frequently when starting diuretic therapy (on initiation and at least 1 wk later) and should be reassessed every 3–6 mo during chronic administration. Some animals may remain mild to moderately azotemic, which is generally tolerated provided they are eating and drinking adequately.

Additional loop diuretics include torsemide and bumetanide. While there is less experience with these agents, they may prove useful in the management of refractory heart failure in which furosemide resistance has been documented, or when furosemide is not tolerated. Torsemide has a longer duration of action than furosemide and has ancillary aldosterone-blocking effects. Both torsemide and bumetanide are significantly more potent than oral furosemide, but they have not been evaluated extensively for use in veterinary medicine. Anecdotally, starting doses of both agents are approximately one-tenth that of furosemide.

**Thiazide diuretics** (eg, hydrochlorothiazide, chlorothiazide) decrease sodium resorption via inhibition of the Na+/Cl– cotransporter in the distal convoluted tubule. This results in increased sodium and water delivery to the collecting ducts and subsequent increased hydrogen and potassium excretion. While the thiazides are relatively weak diuretics, they do exert a synergistic effect when administered with loop diuretics and can cause profound electrolyte abnormalities (particularly hypokalemia) and dehydration if not used judiciously. Hydrochlorothiazide is more commonly used, with a recommended dosage of 1–4 mg/kg, PO, sid-bid. It is combined with the potassium-sparing diuretic spironolactone (*see* below) in the product aldactazide, which may also be dosed at 1–4 mg/kg, PO, sid-bid. Many animals do not tolerate dosages at the higher end of this range, and the lowest effective dosage should be used. Chlorothiazide is dosed at 20–40 mg/kg, PO, sid-bid. Thiazide diuretics are generally reserved for those cases in which resistance to furosemide has developed.

**Potassium-sparing diuretics** are the weakest of the diuretic class, exhibiting little to sometimes undetectable diuretic effect at standard dosages, especially when used alone. Drugs in this class include the aldosterone inhibitors spironolactone and eplerenone, and those that block sodium resorption at the distal tubules, triamterene and amilaride. Spironolactone at sub-diuretic dosages of 0.3–1 mg/kg, sid is advocated by some cardiologists for use in dogs with subclinical DCM or early myocardial failure for its theoretical benefit in blunting the aldosterone-mediated remodeling and fibrosis of the myocardium and vasculature. A large-scale clinical trial in people with heart failure demonstrated significant improvement in morbidity and mortality in patients administered spironolactone versus placebo, in addition to standard heart failure therapy. Eplerenone has demonstrated a myocardial protective effect in dogs with experimentally induced heart failure, although no clinical benefit of aldosterone blockade has been proved in veterinary patients with naturally occurring cardiac disease. A clinical trial using spironolactone in cats with hypertrophic cardiomyopathy (HCM) revealed no decrease in cardiac remodeling or improvement in diastolic function after 4 mo. Furthermore, severe ulcerative facial dermatitis occurred in approximately one-third of the cats receiving spironolactone. Consequently, use of spironolactone as a prophylactic antiremodeling agent in cats is not recommended.

Spironolactone is generally reserved for dogs and cats that are refractory to standard diuretic dosages, those with ascites, or those in which clinically significant hypokalemia has developed. It is dosed at 1–3 mg/kg, PO, sid-bid. Future studies may validate its use in certain cardiac disease entities. Eplerenone, triamterene, and amiloride are not routinely used in the management of cardiac disease in veterinary medicine.

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