

The pharmacologic spectrum of furosemide

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Abstract

Objective: To review the clinical spectrum and mechanisms of action of furosemide in human and small animal veterinary patients.

Data sources: Review of human and veterinary literature.

Data synthesis: Furosemide is used primarily for its properties as a loop diuretic; however, it has many other actions that may be clinically applicable. Furosemide has a vasodilatory effect that precedes diuresis that may confer its immediate benefit in patients with volume overload. Furosemide can be inhaled to relieve dyspnea in patients with bronchospasm. Furosemide also shows promise as an adjunct to antiseizure therapy to help control epilepsy, status epilepticus, and acute ischemic damage related to seizures. It has activity as an antioxidant, iodine depletive, and may increase thoracic lymph duct flow. Reported furosemide side effects include altered drug metabolism, electrolyte depletion, ototoxicity, mucociliary impairment, endocrine and exocrine pancreatic effects, delayed wound healing, sulfonamide toxicity, and thyroid binding interference. It is worthwhile to consider the implications of these effects when using furosemide either alone or in combination with other drugs.

Conclusions: Despite the research in animal models that demonstrates a wide spectrum of pharmacologic activity, furosemide has not been widely recognized or used clinically in veterinary medicine except as a loop diuretic.

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Introduction

Furosemide is well known as a sulfamoylbenzoic acid loop diuretic that inhibits the renal $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$ co-transporter (NKCC) in the luminal membrane of the ascending loop of Henle. However, furosemide has effects in multiple organ systems, not just the kidney. There is renewed interest in its clinical use following the discovery of furosemide-inhibited NKCCs in non-renal tissues. Furosemide also demonstrates pharmacologic activity that appears to be unrelated to this co-transporter. To date, many of the mechanisms of furosemide's effects have not been fully established.

Pharmacology

Furosemide has diuretic properties in all mammalian species.¹ It is administered to remove excess body fluid in patients with volume overload. Classified as a high

ceiling loop diuretic for its rapid onset and short duration of action, it inhibits the NKCC on the luminal side of the thick ascending loop of Henle. Furosemide is active from inside the tubular lumen, as are all other diuretics except spironolactone.^{2,3} The degree of diuresis is determined by the amount of furosemide that reaches the renal tubular lumen, not the plasma concentration.² Adequate urinary levels must be sustained for maximal diuresis.⁴ Inhibition of this co-transporter results in increased renal excretion of water, sodium, chloride, potassium, calcium, magnesium, ammonium, hydrogen ion, and possibly phosphate.^{2,5}

There are two isoforms of NKCC. NKCC1 has been identified in the mammalian kidney, heart, vascular endothelium, lung, brain, skeletal muscle, stomach, colon, red blood cells, smooth muscle, epithelia, fibroblasts, and neurons.⁶ NKCC2 is specific to the luminal (apical) membrane of the thick ascending limb of the loop of Henle in the kidney.^{6–9} The two isoforms have molecular weights between 120–190 kDa and 50–60% amino acid sequence homology.⁷ NKCC1 is the larger of the two co-transporters, with an additional 80 amino acids at the amino terminus.⁶ The variation between these receptors is responsible for differing

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co-transporter ion affinities and inhibition responses.⁷ NKCC1, the secretory co-transporter, is located in the basolateral cellular membrane, and NKCC2, the absorptive co-transporter, is in the apical cellular membrane.^{6,10}

Characteristics of all NKCCs are: (1) ion translocation depends upon on simultaneous occupation of all three ion-binding sites on the same side of the membrane; (2) electroneutrality in binding with 1 sodium, 1 potassium, and 2 chloride ions (NH_4^+ can substitute for K^+ in acidic conditions); (3) an ion flux driving force supplied in part by the inward sodium gradient maintained by the sodium-potassium-ATPase pump elsewhere in the cell membrane; (4) the ability to create a chloride gradient (this acts as a driving force for chloride secreting epithelial cells); (5) chloride delivery as the rate-limiting step; (6) the potential for competition at the second chloride-binding site by loop diuretics that results in co-transport inhibition.⁷ NKCC is electrically silent, as co-transport is not driven by transmembrane voltage and does not generate a membrane current.⁶

Loop diuretics inhibit NKCC and the K^+-2Cl^- co-transporter (KCC) in a dose-dependent manner, with a higher affinity and potency against the NKCC. KCC shares 25% amino acid homology with NKCC⁶ and has four identified isoforms.^{10,11} KCCs have been found in cells of normal brain, heart, kidney, liver, spleen, stomach, colon, red blood cells, epithelia, and in Ehrlich ascites tumor cells.⁶ The two co-transporters differ in their response to loop diuretics. NKCCs show a greater inhibition by bumetanide than furosemide, while KCCs have greater inhibition by furosemide than bumetanide.⁶

The sustained delivery of furosemide depends on both glomerular filtration rate and active secretion of furosemide by renal tubular cells.¹² Furosemide is 90–95% protein bound and the free furosemide concentration in plasma is inversely proportional to the plasma albumin concentration.¹³ Only the free furosemide is filtered at the glomerulus and available to the receptors at the luminal membrane.

Paradoxically, however, sustained furosemide delivery to the renal tubule, and therefore maximal diuretic effect, are not improved with low plasma albumin concentration.¹² Protein binding is necessary to trap a significant percentage of circulating furosemide in the vascular compartment, enhancing delivery to proximal tubular cells over time through sustained secretion.³ With marked hypoalbuminemia (plasma albumin $<2\text{g/dL}$), even though free furosemide levels are initially high in both the plasma and ultrafiltrate, the effect is not sustained and much of the free furosemide is excreted unchanged in the urine. This decreases the total diuretic effect. Diuretic efficacy in humans with

marked hypoalbuminemia can be increased by co-administration of furosemide and albumin, with most protocols mixing 40 mg furosemide with at least 6.25 g albumin before administration.²

Only a small amount of plasma furosemide is metabolized via hepatic conjugation with glucuronic acid.¹⁴ Half of the delivered furosemide is excreted unchanged in the urine and 20–50% is inactivated by renal glucuronidation.^{2,14} Thus, the kidney is the major site of action, metabolism, and excretion of furosemide.¹⁵

Heart failure, renal failure, cirrhosis, or hypoalbuminemia with reduced renal blood flow and/or proteinuria may require higher doses to achieve therapeutic levels due to a reduction of free drug entry into the tubular lumen. This effect may be opposed by the prolonged half-life in renal patients, reported to increase up to 3-fold due to reduced glomerular filtration rate. Proteinuria may also reduce the diuretic response due to intratubular drug binding to the protein.² Another concern in human cardiac patients is the co-administration of furosemide and other protein-bound drugs, such as warfarin, that compete for the same albumin-binding site.¹⁶ The clinical significance of protein-binding displacement with furosemide administration is not known, but may be an important consideration.¹⁷

Furosemide, a weak organic acid, is actively secreted by renal organic anion transporters (OAT).^{15,18} Movement from the basolateral to the luminal membrane in the proximal tubule is mediated by OAT3 and to a lesser extent OAT1. Human OAT1 has been localized at the S_2 segment of the proximal tubule, while human OAT3 is found at the S_1 , S_2 , and S_3 proximal tubule segments.¹⁸ There are interspecies differences in OAT1 expression between humans and rats¹⁹ that has led to speculation of other potential differences still to be determined.

Co-administration and retention of organic acids reduces proximal tubular secretion of furosemide due to OAT binding site competition.^{15,17,20} Renal failure patients may show limited diuretic excretion in part due to retention of hippurate, an organic anion that competes for secretion. OAT transporters are also responsible for movement of non-steroidal anti-inflammatories,¹⁷ H_2 receptor antagonists, antivirals, some antineoplastic drugs, prostaglandins, angiotensin-converting enzyme inhibitors, and β -lactam antibiotics.¹⁸ The effect of co-administration of these agents on furosemide transport is unknown.

Oral absorption in humans is approximately 50% with a range among individuals of 10–100% that makes dosing difficult to calculate and necessitates titration to desired effect.⁴ An increased bioavailability of furosemide with oral co-administration of ascorbic

acid in canine studies is attributed to potential decreased gastric first-pass metabolism, increased renal tubular reabsorption, or an increase in the unionized fraction present at receptor sites.²¹ The current recommendation for human patients is to administer oral furosemide until the desired clinical effect is achieved, or to add a diuretic agent acting at another receptor site when approaching the upper dosage range limits of furosemide.⁵

Furosemide acts differently in different species. Canine patients show increased sodium excretion as compared with potassium, and must be monitored more closely for development of secondary hyponatremia.⁵ Canine salivary and diuresis will occur over a broad therapeutic range, starting at 0.625 mg/kg as compared with cats at 1.25 mg/kg. Despite having a narrower therapeutic range, cats have increased diuretic sensitivity, showing stronger and more rapid salivary and diuresis as compared with dogs.²² A reported upper limit to feline dosing tolerance is 10 mg/kg intramuscular (IM), with lethargy and decreased appetite noted for 24–48 hours following administration of higher doses. Dogs are reported to show apathy, staggering and decreased blood pressure, suggesting a dosing tolerance, at 50 mg/kg IM. The decrease in blood pressure following furosemide injection in anesthetized cats given 25 mg/kg IM is more dramatic than the similar effect in dogs at 50 mg/kg IM.¹ Rats are reported to be less sensitive¹; an important fact because many studies are performed in murine models.

Route of administration is an important consideration in determining therapeutic effect. The half-life of furosemide in humans is 1.5–2 hours and a maximal natriuretic response is defined as excretion of about 20% of filtered sodium. Owing to bioavailability, the maximal oral dose is usually twice the intravenous (IV) dose, although dosages can be doubled up to 5 times until adequate diuresis is achieved.³ Intestinal absorption delay may reduce urinary excretion to suboptimal drug levels; absorption delay may be the result of decreased intestinal perfusion, increased intestinal motility, and/or mucosal edema. IV administration in dogs results in a 1–2 hour half-life, with potential for rebound sodium and water retention that can be attributed to neurohumoral activation. Constant rate of infusion (CRI) has been shown in humans and dogs to cause more diuresis, natriuresis, and calciuresis, with less kaliuresis as compared to intermittent bolus delivery.⁵

Loop Diuretic Properties

Furosemide reduces symptomatic volume overload secondary to moderate and severe heart failure in all mammalian species²³ and improves exercise tolerance

in humans.²⁴ Increasing sodium and water excretion results in reduced circulating volume, reducing preload, and edema formation. A debate in human medicine exists concerning the beneficial effects *versus* potential complications in long-term administration for chronic heart failure. Increased hospitalization rates and death from worsening chronic heart failure are reported to be higher with long-term furosemide administration.²⁴ There is no proof of causation between increased mortality and furosemide dose, as patients with more severe illness and diuretic resistance related to chronicity of administration require higher doses. Morbidity associated with higher doses is reported secondary to volume contraction, hypotension, electrolyte abnormalities, neuroendocrine activation,²⁴ and diuretic resistance.²⁵ Chronic administration is associated with distal tubule hypertrophy²⁵ and collecting duct overexpression of NKCC.^{26,27} Current canine research is exploring co-administration with brain natriuretic peptide to enhance furosemide's effects, with the goal of increasing glomerular filtration without aldosterone activation.²³ Furosemide, administered for volume overload due to acute myocardial decompensation, should not be the sole agent given to chronic heart failure patients.²⁴ Administration of a single agent that reduces vascular volume results in short-term improvement. Over time, this reduction may result in a reduction of effective circulating volume, contributing to the progression of cardiac disease. Agents that support other components of cardiac output should also be utilized. At this time, furosemide is recommended only for patients with acute or chronic decompensation with clinical evidence of volume overload. Thus, it should be considered as an adjunct to primary therapy in all congestive heart failure patients.

Protection Against Renal Ischemia

Furosemide administration in animal studies protects the kidney from ischemic damage.² Renal oxygen consumption has been positively correlated to tubular sodium reabsorption²⁸ and glomerular filtration rate.²⁹ Sodium is actively transported out of the cells into the interstitium by the Na⁺-K⁺-ATPase-dependent pump on the basolateral membrane. Reducing sodium reabsorption results in a proportional decrease in renal oxygen consumption.³⁰ Loop diuretic administration decreases renal tubular cell metabolic demand by blocking the NKCC transporter and thus turning off the need for ATPase pump activity. This reduces renal tubular oxygen demand and helps to maintain the balance between oxygen delivery (DO₂) and oxygen demand (VO₂) in the high-risk medullary and juxtamedullary regions. Under normal circumstances these

tissues are relatively hypoxic due to low blood flow, oxygen requirements for concentrating mechanisms in the medulla, and a countercurrent effect in the vasa recta. NKCC2 activity is normally reduced in renal ischemic conditions by a locally produced, non-prostaglandin, cytochrome p450 arachidonic acid metabolite. Furosemide, through inhibition of NKCC2, increasing renal blood flow, and decreasing tubular sodium reabsorption may be useful in preserving cell viability by protecting ischemic kidneys under conditions of inadequate perfusion.²⁹

A recent study in human postoperative mechanically ventilated patients with normal renal function confirmed this renal-protective effect.²⁹ Furosemide was administered at 0.5 mg/kg IV loading dosage, then infused at 0.5 mg/kg/hr for three 30-minute periods. Despite a 12% decrease in both cardiac output and glomerular filtration rate, there were no significant changes in mean arterial pressure, heart rate, renal blood flow, or renal vascular resistance. Urine flow and fractional sodium excretion increased by 10–15-fold. Renal oxygen consumption and tubular sodium reabsorption were reduced.²⁹ Reduction in renal oxygen demand may be clinically important to protect against further damage in conditions of ischemic renal insufficiency. Unfortunately, rat studies indicate this protective effect does not occur with co-administration of furosemide and contrast media, a cause of human nephropathy.³⁰

Despite its proposed benefits, the administration of furosemide to humans with acute renal failure is controversial. Many conclude it does not appear to shorten the duration of renal failure nor demonstrate effectiveness in prevention or treatment of toxic or ischemic renal failure.^{31,32} A prospective, multicenter, multinational human study in 1743 acute renal failure patients has shown no association between diuretic usage and increased risk of mortality.³³ Although increasing tubular flow rates may help flush out tubular casts and ameliorate intratubular obstruction, it may worsen cast formation in myeloma and light chain nephropathy. Patients with renal insufficiency and nephrotic syndrome show a decreased responsiveness to furosemide due to decreased renal diuretic delivery, decreased peritubular diuretic uptake, enhanced renal metabolism to inactive glucuronide, and decreased free diuretic.¹⁵ Unfortunately, these are the patients that would most benefit from protection from further renal damage. Recommendations for treatment of human patients with acute renal failure include furosemide to increase urine output in oliguric or anuric patients; a result of its diuretic properties to relieve or prevent fluid overload. Controversy exists as to the presence of any clinical benefit from its ability to preserve renal

blood flow and oxygen concentration, with no documented evidence of improved overall outcome. Despite the controversy, furosemide remains the diuretic of choice for treatment of volume overload in patients with oliguria or anuria.³

Most recently, furosemide has been evaluated for its effects on genes that control angiogenesis. Rats were evaluated to determine which genes were expressed or down-regulated under conditions of ischemia-reperfusion. Furosemide administration at 30 µg/kg/min initiated before ischemia and continued for 6 hours of reperfusion showed enhanced expression of genes that may help to restore renal vascularity and perfusion. Although the study did not evaluate renal function, the study raises the possibility of a molecular mechanism of renal protection.³⁴

Vasodilator Properties

Administration of furosemide causes vasodilation and a decrease in total peripheral vascular resistance.^{35–38} It also causes renal venodilation and a transient increase in glomerular filtration rate that may be due to vasodilatory prostaglandins.^{4,29} This intrarenal effect may or may not occur in dogs.^{39,40} Furosemide is also used clinically and in a research setting to interrupt tubuloglomerular feedback,⁴¹ the macula densa response to sodium chloride elevations.

It may be the significant non-diuretic effect of furosemide (rapid vasodilation) that contributes to immediate symptomatic improvement of volume overload.^{36,42} Diuretics have been used since the 1960s in the treatment of acute cardiogenic pulmonary edema.^{25,35} Furosemide is documented in human and veterinary cardiac patients to reduce pulmonary congestion and left ventricular filling pressures.^{42,43} The vasodilation that precedes diuresis appears to be due to venous pulmonary dilation and an increase in peripheral vascular capacitance. Preload is reduced before a measurable increase in urinary output. There are studies that indicate that these effects are preserved in anephric patients at a furosemide dosage of 2 mg/kg IV.^{44,45} In contrast, the literature also reports a requirement for renal involvement, with no dilation occurring in anephrics.^{46,47} Both *in vitro* and *in vivo* studies report an indirect, immediate venodilator effect, with significant variability in different vascular beds, including those affecting renal blood flow.^{37,38,48,49} The debate continues concerning the magnitude, mechanism of action, and clinical significance of this vasodilatory effect in various species and tissues.

Species and age variations have been discovered relating to the magnitude of vasodilation. Based on these differences, some researchers are doubtful that

in vitro results will have human therapeutic relevance beyond that of relief of dyspnea. High concentrations of furosemide in one study were found to exert a weak direct relaxant effect on isolated human resistance arteries, as compared with a more pronounced effect in guinea pigs, and especially rats.⁵⁰ Guinea pig studies in isolated pulmonary artery relaxation illustrated an age-related effect with the greatest relaxation response in the adult, a lesser effect in the newborn, and the fetus showing the least relaxation.⁵¹ There is concern furosemide may not reach *in vivo* therapeutic levels in the vascular compartment as it is 95% protein bound and not concentrated locally as it is in the kidney.⁵⁰ There may also be varying responsiveness in different vascular beds.³⁷

The acute hemodynamic response after systemic administration is believed to be a direct relaxant effect.^{36,38,50} Furosemide-induced vasoactivity has been measured immediately after IV and within 15 minutes after oral administration.^{13,38} Some studies suggest an indirect response, in which furosemide stimulates production of a secondary agent with vasodilatory properties.^{37,52} There may be a balance of direct and indirect effects, with a variation based on the model, type of patient, species, or other variables. Venodilation has been shown at clinically relevant concentrations. Arterial dilation has been reported not to occur, or only to occur at suprathreshold doses.⁴³ Veins appear to have a higher concentration of NKCC1 as compared with arteries, potentially explaining the variation in co-transporter inhibition and the predominately venodilatory effect.^{36,43,50} However, more potent co-transporter inhibitors such as bumetanide do not cause more potent vasodilation.³⁶

Other potential mechanisms reported include vascular structural changes, weak angiotensin receptor blocking,³⁷ prostaglandin release,⁴³ competitive thromboxane A₂ contraction inhibition,⁵³ renin-aldosterone-angiotensin activation,³⁶ sympathetic stimulation,³⁵ and/or co-factor presence.⁵⁴ Plasma renin elevation secondary to prostaglandins is documented within minutes of furosemide administration irrespective of venodilation or arterial constriction.⁵⁵ Plasma renin levels, but not venodilation, increase in a dose-dependent manner. It is possible that the vasodilatory prostaglandin release is either a direct or indirect *in vivo* endothelial compensation to angiotensin II-mediated contraction.⁵² The acute venodilator effect appears to be blocked by non-steroidal anti-inflammatory drugs in human patients with chronic heart failure, supporting some form of cyclooxygenase mediation.³⁷ Concentration-dependent arterial resistance vessel dilation *in vitro* has been reported as independent of membrane potential, prostaglandin release, or intact endothelium, suggesting

a relation to cellular calcium metabolism or sensitivity.⁵⁰ A study in bovine aortic endothelial cells suggested a dilatory response secondary to enhanced synthesis and release of endothelium-derived kinins that then trigger cytosolic calcium release and the formation of the vasodilators nitric oxide and prostaglandin I₂.⁴⁷ However, other studies suggest that the vasodilatory response does not appear to be related to nitric oxide or prostaglandin I₂ production.^{36,56,57} Studies in human vascular preparations show a vasodilator effect in the absence of functional endothelium, indicating a response not related to kinins or prostaglandins.⁵³

Changes in blood viscosity induced by furosemide may also play a role in the vasodilatory response. A feline femoral artery study suggested that diuresis causes an increase in shear stress that triggers endothelium-mediated vasodilation. A human study explored this idea in healthy *versus* elderly hypertensive patients by giving members of each group a CRI of 0.5 mg/min until their hematocrit increased 2%. Only the healthy patients experienced secondary carotid vasodilation, suggesting that chronic endothelial or arterial wall alterations may also be variables to consider.⁵⁸

The potential for furosemide-induced vasoactivity is a concern in chronic cardiac patients. A worsening of myocardial perfusion may follow the initial benefit related to relief of acute pulmonary edema. A reduction in circulating volume is contraindicated in patients who are not volume overloaded.³⁵ Acute heart failure results in a reduction in stroke volume that activates sympathetic maintenance of systemic arterial pressure.⁵⁹ Chronic heart failure patients may not exhibit predictable vasodilation in response to furosemide and the risks of increasing myocardial oxygen demand or reducing renal blood flow and glomerular filtration rate make chronic administration potentially harmful.²³ If volume overload does occur in these patients, their response to acute administration of furosemide is influenced by their preexisting renin-angiotensin-aldosterone system activation.⁵⁹ This suggests that chronic use of furosemide may blunt its effectiveness when it is needed in the acute setting of volume overload.

Furosemide has been suggested to promote hemodynamic deterioration in human chronic cardiac failure patients. In heart failure studies, plasma norepinephrine is measured as an indicator of neuroendocrine stimulation, an initial physiologic response to maintain effective circulating volume. The degree of renin-angiotensin-aldosterone stimulation is measured using plasma renin and plasma aldosterone levels. With furosemide dosages of 1.3 mg/kg IV, transient elevations of plasma renin, norepinephrine, and arginine vasopressin have been measured in human chronic heart failure patients within the first 20 minutes of

administration. Although all values returned to baseline over a maximum of 4 hours, this stimulation of the neurohumoral axis may contribute to cardiac dysfunction.⁵⁹ Diuresis, in the absence of pulmonary edema, may reduce circulating blood volume and renal blood flow, further stimulating the renin–angiotensin–aldosterone system. Use without maintenance of vascular volume is contraindicated, especially in cardiac patients. Additionally, chronic heart patients should also receive an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. Current recommendations for use of furosemide in acute and chronic heart failure depend on the degree of edema. At this time, furosemide has not been validated as safe or efficacious for long-term administration in the absence of volume overload.

Furosemide is currently being studied as an adjunct therapy for acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Mechanically ventilated dogs given a CRI of 0.2 mg/kg/hr showed significantly improved lung injury scores, increased pulmonary gas exchange, and decreased intrapulmonary shunt fraction in a research model of ARDS.⁴⁵ In another study of ALI, administration of furosemide with albumin compared with furosemide alone was shown to significantly improve oxygenation, hemodynamic stability, and provide a greater net fluid balance.⁶⁰ Unfortunately, this study was not powered sufficiently to evaluate clinical endpoints, such as mortality or duration of mechanical ventilation. The concentration of albumin has been suggested to be the main cofactor required to facilitate the furosemide-induced *in vitro* endothelium-independent vasodilation.⁶¹ Rabbit studies, however, showed that furosemide's attenuation of the vascular smooth muscle relaxation was weakened by the presence of albumin.⁶² It has been suggested that the inconsistency and variability of *in vitro* studies may relate to the difficulty with completely removing albumin from tissue preparations.⁶¹

Canine studies have repeatedly demonstrated furosemide-induced dilation in gastrointestinal vascular beds that has an unknown clinical significance.^{48,49} This effect is believed to be related to prostaglandin production, because the effect is blocked by prostaglandin synthetase inhibitors.⁴⁸ With an onset of 24–30 seconds, maximal dilation of gastric vasculature occurred at 36 seconds, duodenum at 66 seconds, small intestines at 78–84 seconds, and large intestines at 90 seconds.⁴⁸ Oxygen consumption was not altered, despite maximal blood flow elevations of 60% in the stomach and duodenum and 80% in the small and large intestines.⁴⁸ Elevations in blood flow did not appear dependent on perfusion pressure, as no quantitative change to mean abdominal aortic pressure was identified.^{48,49} An

increase in canine biliary secretion and pancreatic blood flow (with no appreciable increase in pancreatic exocrine secretion) was initiated at a dosage of 2.4 mg/kg IV. It is suggested that this is not due to a direct effect on the pancreas, but a consequence of increased circulation through the superior pancreaticoduodenal artery.⁴⁹ A conflicting study reported a reduction of blood flow to all pancreatic regions, which did not appear to impact endocrine function.⁶³ Hepatic, splenic, and renal arterial blood flows appeared to be unchanged.⁴⁸ The clinical relevance of these studies is unknown, especially under pathologic conditions.

Furosemide is administered in humans for chronic heart failure, acute pulmonary edema, and hypertension.³⁶ Despite suggestions that venodilation provides the acute benefit of furosemide administration, there are currently no double-blind, placebo-controlled trials studying these hemodynamic effects. The mechanism of action remains unknown, and yet furosemide shows promise in many other areas of critical care, such as in ALI and ARDS.

Bronchial Antispasmodic Properties

Inhaled furosemide attenuates or prevents bronchospasm, stimulates bronchodilation, alleviates the sensation of dyspnea,^{64,65} and inhibits allergen-induced, exercise-induced,⁶⁶ and adenosine-induced bronchoconstriction.⁶⁷ Administration results in a 14% rise in forced expiratory volume over 1 second in human asthmatic patients.⁶⁶ Doubling the inhaled dose from 15 to 30 mg resulted in a longer duration of action, but no measurable difference in degree of protective effect in patients with chronic obstructive pulmonary disease or exercise-induced asthma.^{64,66} An inhalation study in healthy, anesthetized cats showed a blunted behavioral reaction to airway occlusion without an alteration in inhaled noxious stimulus response for 3 hours after administration.⁶⁸ Anesthetized rat studies report inhibition of pulmonary irritant receptors and activation of pulmonary stretch receptors at end-expiratory volume.⁶⁹ Canine studies have also demonstrated inhibition of laryngeal irritant receptors in anesthetized animals.⁶⁵ Human studies examining furosemide's effect on attenuation of allergic rhinitis symptoms report results that vary from no effect⁷⁰ to a protective effect on nasal mucosa reactivity.⁷¹ The nasal variability may be the result of a more rapid rate of mucosal absorption and a shortened exposure time or the result of a weaker benefit masked by the ability to induce more severe symptoms in nasal rhinitis volunteers as compared with asthmatics.⁷⁰

One suggested mechanism for the benefit of inhaled furosemide in asthma is based on ionic alterations in

airway epithelium sensory receptors and/or modulation of pulmonary vagal afferent nerve stimulation.^{65,68,69} NKCC1 is expressed on sensory neurons, with the potential for furosemide-induced chloride alterations inhibiting sensory nerve activation.^{72,73} Inhaled furosemide may also relieve dyspnea by mimicking the effects of large tidal volumes that relieve air hunger in humans.⁷⁴ Other postulated mechanisms for beneficial human asthmatic effects include induction of relaxant prostaglandins, inflammatory cell mediator production blockade, alterations of airway epithelial ion exchange, or production of local inhibitory prostaglandins.^{67,75,76} Damaged epithelium may also have a different pharmacokinetic profile than healthy tissues.⁷⁶ Diuretics with greater potency against NKCC1 have been less effective than furosemide in blocking the asthmatic response.^{67,77} Despite the current findings, studies supporting nebulized furosemide are limited by small sample sizes and conflicting results. At this time it is not routinely used in human asthmatics. If proven clinically, this effect could be beneficial in veterinary patients with asthma, chronic bronchitis, lower airway diseases and pulmonary edema secondary to left heart failure.

Parenteral furosemide has also shown some bronchodilatory action. Studies examining cats are lacking, and potentially clinically significant given their increased airway responsiveness in pathologic condition when compared with other species. Feline hyperreactivity may be explained by the extension of smooth muscle toward the distal airways.⁷⁸ Bronchial response differences have been discovered between species and even stage of life. An *in vitro* study of guinea-pig tracheal and bronchial response found significant differences between adults, newborns, and fetuses with the equivalent of 1 mg/kg IV application. Airway segment relaxation was greatest in the fetus, lesser in the newborn, and least in adults.⁵¹ Canine tracheal epithelial sheets are more effected by serosal than luminal application due to a basolateral linked sodium chloride entry process; the canine tracheal epithelium actively secretes chloride and alterations of this transcellular pathway led to a decline in tissue conductance.⁷⁹ Anatomic, physiologic, and stage of life differences in pulmonary responsiveness may provide further applications or further contraindications of furosemide.

Anticonvulsant Properties

Furosemide has anticonvulsant properties^{80–82} that avoid the common side effects of generalized neuronal suppression associated with antiepileptic drugs.⁸³ One study in humans undergoing surgery for medically intractable epilepsy showed that administration of

furosemide (0.18–0.45 mg/kg IV) significantly suppressed both spontaneous epileptic spikes and electrical stimulation-evoked epileptiform discharges in all subjects, with complete blockage in some.⁸³ It has been shown in laboratory models to suppress different forms of epileptiform activity.^{81,84} Furosemide is believed to increase the minimal current required to elicit ictal discharges, increasing the threshold and possibly decreasing the ability of brain cortical tissues to maintain and propagate seizure activity.⁸³ It may represent an important adjunctive therapeutic agent in specific circumstances, such as status epilepticus.⁸² A human epidemiological study has also reported that past or present furosemide use is considered protective against development of a first unprovoked seizure in older adults, regardless of therapeutic indication.^{80,83}

Non-synaptic modulation may play a critical role in controlling different manifestations of epileptogenicity.^{83,85} Furosemide is lipid soluble, protein bound, and crosses the blood–brain barrier under normal circumstances and with an enhanced rate in status epilepticus.^{84,86} The nervous system NKCC isoform is NKCC1. It is believed to be responsible for maintaining neuronal intracellular chloride in pyramidal and non-pyramidal neurons. It is also involved in astrocyte and oligodendrocyte potassium uptake and intracellular sodium maintenance.⁷ NKCC1 is an important component to activity-evoked cell volume changes in glial cells that lead to further spontaneous evoked potentials.^{83,86} There is a transient NKCC1 down-regulation 12 hours after human focal cerebral ischemic reperfusion believed to be a compensatory mechanism against neuronal excitotoxicity.⁷ Furosemide administration may be neuroprotective of further cell swelling and secondary damage.

Four isoforms of the furosemide-sensitive KCC have been identified.¹¹ KCC2 is neuron-specific through the cortex, hippocampus, and cerebellum.⁸² Its main function is chloride movement into the extracellular space under normal physiologic conditions and does not appear to be involved in cell volume regulation.⁸⁷ The KCC2 found in oligodendrocytes is involved in extracellular volume regulation under normal and pathologic conditions.^{6,11,85} KCC2 accumulates intracellular chloride, potentially providing the chloride gradient for hyperpolarization and inhibition of γ -aminobutyric acid (GABA) receptors.^{6,87} Furosemide blockade of KCC is also neuroprotective, improving outcomes in rat anoxia studies.¹¹

Furosemide inhibits seizure-induced (also called activity-evoked) cell swelling through inhibition of NKCC and KCC that are responsible for maintaining chloride concentrations.^{11,82,83} With the hyperactivity of pathologic condition, such as status epilepticus, there is

an activity-dependent cell swelling and elevation of extracellular potassium believed to predispose to additional epileptiform activity. Furosemide modulates ionic perturbations, neuronal excitability, and extracellular volume changes independent of its diuretic effect.^{81–83} It alters the extracellular electrical field interactions involved in neuronal hypersynchrony and changes the ionic gradients that have indirect and direct effects on neuronal discharge.^{82,88} Multiple studies have shown no blood pressure alterations⁸⁸ and brain histopathology does not show a significant change in extracellular space volume.^{81,83}

Ischemic damage and increased neuronal activity result in a stimulus-induced elevation of extracellular potassium that is considered to be proconvulsant.^{81,83} Elevation of extracellular potassium results in glutamate release and astrocyte swelling.⁷ Furosemide plays a significant role in potassium redistribution from the extracellular space.^{7,81,83,89} High extracellular potassium activates the NKCC1 co-transporter, moving sodium, potassium, and chloride back into the cells.⁸² This NKCC1-related potassium scavenging does not occur unless extracellular potassium is elevated.⁹⁰ KCC2 is also believed to have a high affinity for extracellular potassium, contributing to the removal of excess potassium.⁸⁷ The beneficial effect of reducing elevation of extracellular potassium may be a species-specific response, as astrocyte culture studies showed a 50% reduction in potassium in rats and no reduction in mice,⁹¹ or a dose-dependent response as the same researchers achieved a reduction in mice cultures exposed to double the dose.⁹⁰

Conflicting experimental evidence also surrounds the use of furosemide to reduce choroid plexus cerebrospinal fluid (CSF) production, alter CSF ionic composition, and/or lower intracranial pressure.⁹² NKCC1 is present on the choroid plexus epithelium, suggesting inhibition may reduce CSF production or alter CSF ionic content.^{7,44} Human OAT1 and OAT3 have been discovered in the cytoplasmic membrane and cytoplasm of human choroid plexus cells but their significance is unknown.¹⁹ Human dosages varying from 5 to 50 mg/kg have been reported to reduce CSF production.^{92,93} One study reported an initial CSF reduction of 50% within 30 minutes in cats administered either 50 mg/kg IV or a comparable dosage administered intraventricularly. The rate of CSF production continued to decrease for 1.5 hours and a reduction of CSF potassium was observed. The study concluded with washing of the choroid plexus and demonstrating a return to baseline production after 1 hour.⁹⁴ Nephrectomized, normocapnic dogs are reported to have no changes in CSF composition at 2.5 mg/kg IV or 0.125 mg/kg instilled into the lateral cerebral ventricles.⁹⁵ High dosages of

furosemide (50 and 400 mg/kg IV) did not significantly alter ionic composition in nephrectomized dogs, but CSF production was reduced.⁴⁴ Dogs given 0.25 mg/kg intraventricularly had a reduction in CSF chloride.⁹⁵ Although the CSF alterations do not relate to its antiepileptic effects,⁸⁶ furosemide's ability to reduce CSF production and thus improve cerebral blood flow under pathologic conditions warrants further examination.

Current proposed mechanisms for reduction of intracranial pressure include a reduction in normal and edematous brain water by reducing ion penetration across either an intact or altered blood–brain barrier. Of concern is a reported feline study where 1 mg/kg furosemide reduced mean arterial pressure by 10% causing decreased edema by reducing cerebral perfusion pressure and tissue pressure gradients.⁹² Care should be taken to monitor for the development of hypotension that would contraindicate the use of furosemide.⁹³

Furosemide is more effective at reducing elevations in intracranial pressure when it is administered at a 1 mg/kg IV dosage 15 minutes after an IV mannitol infusion.⁹³ A canine study reported a reduction in maximum intracranial pressure due to a synergism between furosemide and mannitol. Anesthetized dogs received 0.7 mg/kg IV furosemide 15 minutes after receiving 1 gm/kg IV mannitol. Together they produced a greater (62.4% as compared with 56.6% for mannitol alone) and longer duration (5 hours *versus* 2 hours for mannitol alone) of intracranial pressure reduction.⁹²

Transcranial Doppler ultrasound, a non-invasive evaluation of intracerebral blood flow, has been used to evaluate furosemide's effect on cerebral vascular resistance. Healthy dogs given 1 mg/kg IV showed no significant vascular resistance changes.⁹⁶ Clinical and experimental studies are conflicting, with potential variations based on species and alterations in normal *versus* edematous brain tissues. Current recommendations include furosemide administration as a component of elevated intracranial pressure therapy, despite inconsistent findings.⁹³

Antioxidant Properties

Furosemide has direct *in vitro*⁹⁷ and *in vivo*³¹ antioxidant properties and may reduce elimination of other free radical scavengers.⁹⁸ It has been shown *in vitro* to have dose-dependent antioxidant effects.³¹ Furosemide provides partial protection against free radical damage in rats when administered during the course of oxidative damage.⁹⁷ Dosages as low as 0.1 mg/kg/day intraperitoneally for 6 days before oxidative damage have been shown to be protective. The mechanism may be

direct free radical scavenging, ion channel modification, membrane fluidity changes, or induction of or reduced elimination of another free radical scavenger.³¹

Iodine Depletive Properties

Furosemide administration results in total body iodine depletion^{99,100} by reducing the reabsorption of filtered iodide in the thick ascending loop of Henle. Administration of furosemide may be useful for the treatment of toxic ingestion of iodine compounds. Furosemide is also under study as a therapeutic adjunct to radioiodine treatment for human thyrotoxicosis to reduce radioactive doses and provide more efficacious therapy.^{99,101} By reducing total body iodine content before therapy, patients showed increased uptake of administered radioiodine. Administration of 40 mg/day oral furosemide for 5 days was more effective than 14 days of a low-iodine diet.⁹⁹ Furosemide was also shown to enhance human elimination of radioiodine after ablation treatment, reducing radiation burden and shortening hospital stays.¹⁰⁰ There are no studies in veterinary patients receiving radioactive iodine therapy. The iodine-depletive effect of furosemide is also important to neonates because iodine is a requirement for neonatal growth and development. Furosemide administration should be avoided in lactating animals, as it reduces iodide delivery into the milk.¹⁰²

Effect on Thoracic Duct Lymph Flow

Furosemide increases lymph flow through the canine thoracic duct. Following dosages of 8–10 mg/kg, thoracic duct lymph flow increases significantly within 6 minutes, persisting at maximal flow for 20 minutes. This effect is not dependent on renal function based on the mean lymph flow increase in intact dogs and in dogs with bilateral ureteral ligation and nephrectomy.¹⁰³ Canine studies also report an increase in intestinal, but not hepatic, lymph flow.⁴⁸

Effect on Neoplastic Effusions

An Ehrlich ascites tumor is a research cell line derived from a mouse mammary carcinoma. It is a transplantable, poorly differentiated malignant tumor line used in the examination of neoplastic cell responses, ascitic fluid production, and responses to ascitic fluid. These cells contain NKCC and KCC,⁶ with known furosemide responses such as altered chloride fluxes,¹⁰⁴ and changes in cell volume.¹⁰⁵ Furosemide is known to decrease ascitic transudate from some neoplasms¹⁰⁶; it is possible that the presence of these receptors in certain neoplastic tissues may explain this effect.

Adverse Effects of Furosemide

Electrolyte alterations

Fluid and electrolyte alterations represent the most common adverse effect of furosemide. Patients should be monitored for hypovolemia, hyponatremia, hypokalemia, hypocalcemia, hypomagnesemia, and hyperglycemia. Neonates and patients with disease processes that prolong the serum half-life of furosemide are more likely to develop these alterations. Furosemide's impairment of sodium and chloride reabsorption decreases the medullary osmolal gradient, which limits antidiuretic hormone's ability to increase water reabsorption. Dogs have an increased incidence of secondary hyponatremia, rather than hypokalemia, as compared with other species.¹⁰⁷ Furosemide administration results in elevated levels of sodium, chloride, and water delivered to the distal collecting ducts, resulting in enhanced renal secretion of potassium and hydrogen. This may result in a hypokalemic, hypochloremic metabolic alkalosis in some patients.¹⁰⁸ Although rarely clinically significant, potassium supplementation may be required, especially in patients with a pro-arrhythmic condition such as preexisting hypokalemia.

Patients may require thiamine supplementation due to a flow-dependent, non-specific increase in urinary excretion of thiamine,^{2,108} the significance of which has not been examined in clinical veterinary patients.

A furosemide-induced reduction of divalent cation reabsorption may be useful in treating toxic ingestions of bromide, fluoride, or iodide.

Hypocalcemia

Furosemide increases urinary calcium excretion, but clinical secondary hypocalcemia is not usually recognized with routine use because calcium is actively reabsorbed in the distal convoluted tubule.³ There are compensatory mechanisms to prevent calcium loss that include solute-induced up-regulation of calcium channels and calcium-binding proteins in the distal convoluted tubule¹⁰⁹ and enhanced intestinal calcium absorption, without alteration in serum vitamin D levels.¹¹⁰ Calciuresis can be induced by a combination of furosemide with 0.9% saline administration, so furosemide is an adjunct to other therapies that are described for hypercalcemia. Chronic heart failure patients should be monitored for potential osteopenia, secondary hyperparathyroidism, and nephrocalcinosis due to secondary hyperaldosteronism.¹¹¹

Hypomagnesemia

Furosemide is associated with increased urinary magnesium excretion and impaired magnesium

reabsorption.^{26,108} A reduction in magnesium concentration of any etiology may lead to excessive calcium accumulation, reported in humans to potentially cause perivascular and/or interstitial fibrosis that may result in abnormal vasomotor reactivity, arrhythmias, and/or ventricular dysfunction.¹⁰⁸

Alterations in drug metabolism

Furosemide decreases human patient sensitivity to aspirin therapy, potentially due to competition for the same OAT site,¹¹² production of local vasodilators, protein binding competition, or renin-angiotensin activation.¹¹³ Furosemide diuresis in dogs is attenuated by aspirin, but the degree of this effect is variable as reported studies are not consistent regarding administration of fluid therapy and anesthetic agents that could have impaired renal autoregulation.¹¹³ Low-dose aspirin is administered to human and feline cardiac patients to prevent pathologic clot formation. Unfortunately, low- and high-dose aspirin therapy for 1 week has also been shown to inhibit the beneficial furosemide-induced acute venodilation in humans with CHF.³⁷ Administration of both non-steroidal COX-1 and COX-2 inhibitors in humans blunts the furosemide diuretic response¹⁷; however, furosemide kinetics and actions have shown no clinically significant alterations with coadministration of meloxicam in healthy or compensated cardiac failure humans,¹¹⁴ perhaps making this the non-steroidal anti-inflammatory drug of choice with concomitant furosemide administration.

Parenteral furosemide has also been reported to decrease, then increase, thiopurine methyltransferase levels in canine red blood cells¹¹⁵ potentially altering metabolism of thiopurine medications such as azathioprine.

Mucociliary impairment

Parenteral administration for resolution of positive fluid balance in mechanically ventilated patients may result in alteration of mucociliary clearance through mucosal dehydration, systemic dehydration, or altered membrane ionic concentrations. Conflicting studies report no effect *versus* impairment of mucociliary function for up to 4 hours after furosemide administration.¹¹⁶

Ototoxicity

Furosemide may cause dose-dependent, usually transient deafness, via endolymph electrolyte alterations.^{2,117} Canine dosages of 20 mg/kg IV have been reported to cause ototoxicity while cats may exhibit signs at much lower doses due to the increased sensitivity of this species. Potentiators of ototoxicity include renal insufficiency, hypoalbuminemia, neonates, high dosages, or the presence of other ototoxic or nephro-

toxic drugs. Current recommendations for human patients at risk for ototoxicity include lower dosing, slower administration, or use of an alternative agent.¹¹⁷

Pancreatic effects

Parenteral furosemide is reported in humans in rare instances to cause nausea and acute pancreatitis. Induction of acute pancreatitis may be related to its sulfonamide structure, or potentially direct stimulation of pancreatic secretion.¹¹⁸ Furosemide is reported to alter insulin and anti-hyperglycemic agent requirements, potentially resulting in hyperglycemia. Oral and IV administration have been shown to directly inhibit insulin, but not somatostatin, secretion in humans and canines.¹¹⁹ This effect appears species-specific as murine pancreatic β -cell studies show furosemide-stimulated calcium uptake and increased insulin release attributed to decreased total outward chloride transport via inhibition of a NKCC.¹²⁰ The suggested modes of action in canine models include prostaglandin E-mediated alterations or pancreatic β -cell alterations secondary to hypokalemia.¹¹⁹ Two conflicting studies demonstrated both increased⁴⁹ and decreased pancreatic blood flow with furosemide⁶³; however, neither study showed any difference in endocrine secretion. Furosemide's effect on glucose-induced insulin release appears to be dose-dependent, with insulin release reduced at low concentrations, increased at high concentrations, and no effect at intermediate concentrations.^{119,120} However, it has been suggested aberrations related to diuretic administration occur only in those with previous abnormal glucose tolerance.⁶³

Delayed wound healing

Furosemide has been used to alter chloride ion concentrations in studies focused on the pharmacologic alteration of ionic electric currents and their effect on the rate of wound healing.^{121,122} A 2005 study of rat corneal lacerations found that topical furosemide (1 mM) to wounded corneas resulted in a 36% reduction in wound edge size with a 29% slower healing rate. Altered wound currents are thought to directly correlate with *in vivo* wound healing rate.¹²¹ No published reports on alteration of wound healing rates in veterinary or human patients receiving parenteral or oral furosemide therapy were identified.

Reproductive effects

Furosemide is used in a research setting as an inhibitor of rat oxytocin-induced myometrial contractions by unknown mechanisms.⁵⁴ NKCC1-deficient mice show significant male and female infertility.¹⁰ The implication for reproductive safety in reproductive or pregnant animals and humans receiving furosemide is unreported.

Human pediatric physicians warn against using furosemide in the first few days of life, as it displaces bilirubin, potentially increasing the severity or incidence of neurotoxicity in patients with neonatal jaundice.¹²³

Sulfonamide toxicity/side effects

Cross-allergy sulfonamide hypersensitivity has been reported rarely in humans with an incidence of <0.5%.¹²⁴ There is no reported cross-reactivity with other sulfonamide compounds in dogs, presumably due to furosemide's lack of the primary arylamine structure.¹²⁵ Reported veterinary side effects include skin reactions¹²⁶ (bullous skin lesions),² hematologic effects (anemia, leukopenia), weakness, gastrointestinal disturbances,¹ and restlessness.⁵ Human reported side effects also include rare interstitial nephritis and anxiety.² Subsequent administration of furosemide in human patients after non-anaphylactic-type reactions has been successful without recurring reaction.¹²⁴ Approximately one-third of human patients receiving chronic furosemide therapy may experience a subclinical haptenic immunologic reaction.¹²⁷

Thyroid binding interference

Care must be taken interpreting thyroid function tests in patients receiving either short- or long-term furosemide. Furosemide interferes with thyroid function tests via competitive binding with serum thyroxine (T_4) and serum triiodothyronine (T_3) for thyroxine-binding globulin (TBG) and albumin.^{128,129} This low affinity reversible binding is proportional to plasma drug concentration.^{130,131} Patients may potentially be misdiagnosed with hypothyroidism and receive unwarranted treatment especially if serum T_4 alone is measured.

Protein binding provides a thyroid hormone circulating buffer pool, extending the half-life of T_4 and T_3 , and providing a T_4 plasma reserve. Protein-binding interference results in a greater concentration of unbound free hormone, which shortens the circulating half-life. This results in a transient increase in free serum thyroid hormone levels, leading to a potential for feedback modification to the hypothalamus and anterior pituitary ultimately reducing thyroid stimulating hormone (TSH) secretion.¹²⁸ The resultant laboratory profile can be mistaken for that of the hypothyroid patient.

On thyroid panels, the furosemide patient may initially show a decrease in serum T_4 despite increased free T_4 (f T_4) concentrations.¹²⁹ Continued administration may result in decreased serum T_4 , increased f T_4 , and normal TSH levels.¹²⁶ Dogs have been reported to show a similar response to acute administration, with a decreased serum T_4 and increased f T_4 .¹³² If only T_4 and TSH levels are evaluated, the canine patient may be

incorrectly diagnosed as hypothyroid or sick euthyroid, a condition associated with illness and a reduction in T_4 with normal TSH levels.¹³¹

This interference is magnified in hypoalbuminemic states as T_4 , T_3 , and furosemide are extensively and competitively albumin bound. Careful interpretation must also occur with hepatic insufficiency as albumin and TBG are produced by the liver.¹²⁸ Human *in vitro* tests have suggested that furosemide may have no effect at usual therapeutic doses. However, single large dosages given to human renal failure patients resulted in a 26% increase in f T_4 within 4 hours.¹³⁰

Some authors have also recommended cessation of treatment with furosemide for 7–10 days before thyroid testing.¹²⁹ An alternative includes performing a complete thyroid panel on furosemide patients, including T_4 , f T_4 , and TSH levels to accurately assess thyroid function. A thyroid panel showing decreased serum T_4 with normal to increased serum f T_4 and TSH is consistent with impaired plasma protein binding.¹³¹

Conclusion

Furosemide inhibits NKCC and KCC, resulting in a wide range of therapeutic effects and research implications. Furosemide is widely used in veterinary medicine as a loop diuretic, reducing the symptoms of volume overload in renal and cardiac disease. The acute improvement of clinical symptoms may be the result of vasodilation and relief of dyspnea before diuresis.

Animal models and current human research support anecdotal reports of antiseizure properties and use in status epilepticus in veterinary patients. Other effects of furosemide include its activity as an antioxidant and as an iodine depletive, and its effects on thoracic lymph duct flow.

Side effects include altered drug metabolism, electrolyte depletion, ototoxicity, mucociliary impairment, endocrine and exocrine pancreatic effects, delayed wound healing, sulfonamide toxicity, and thyroid binding interference. It is worthwhile to consider the implications of these effects when administering furosemide.

References

1. Klatt P, Muschaweck R, Bossaller W, et al. Method of collecting urine and comparative investigation of quantities excreted by cats and dogs after administration of furosemide. *Am J Vet Res* 1975; 36(7):919–923.
2. Chasse R. Diuretics, erythropoietin, and other medications used in renal failure. In: Chernow B. ed. *The Pharmacologic Approach to the Critically Ill Patient*. Baltimore: Williams & Wilkins; 1983, pp. 632–639.
3. Brater DC. Diuretic therapy. *N Engl J Med* 1998; 339(6):387–395.
4. Péron JM, Bureau C, Gonzalez L, et al. Treatment of hepatorenal syndrome as defined by the international ascites club by albumin

- and furosemide infusion according to central venous pressure: a prospective pilot study. *Am J Gastroenterol* 2005; 100(12):2702–2707.
5. Adin DB, Taylor AW, Hill RC, et al. Intermittent bolus injection versus continuous infusion of furosemide in normal adult greyhound dogs. *J Vet Intern Med* 2003; 17(5):632–636.
 6. Russell JM. Sodium–potassium–chloride cotransport. *Physiol Rev* 2000; 80(1):211–276.
 7. Chen H, Sun D. The role of Na–K–Cl co-transporter in cerebral ischemia. *Neurol Res* 2005; 27(3):280–286.
 8. Gagnon E, Bergeron MJ, Brunet GM, et al. Molecular mechanisms of Cl[–] transport by the renal Na(+)-K(+)-Cl(–) cotransporter. *J Biol Chem* 2004; 279(7):5648–5654.
 9. Iwamoto LM, Fujiwara N, Nakamura KT, et al. Na–K–2Cl cotransporter inhibition impairs human lung cellular proliferation. *Am J Physiol Lung Cell Mol Physiol* 2004; 287(3):L510–L514.
 10. Delpire E, Mount DB. Human and murine phenotypes associated with defects in cation-chloride cotransport. *Annu Rev Physiol* 2004; 64(4):803–843.
 11. Malek SA, Coderre E, Stys PK. Aberrant chloride transport contributes to anoxic/ischemic white matter injury. *J Neurosci* 2003; 23(9):3826–3836.
 12. McClellan JM, Goldstein RE, Erb HN, et al. Effects of administration of fluids and diuretics on glomerular filtration rate, renal blood flow, and urine output in healthy awake cats. *Am J Vet Res* 2006; 67(4):715–722.
 13. Sjöström PA, Kron BG, Odland BG. Determinants of furosemide delivery to its site of action. *Clin Nephrol* 1995; 43(Suppl. 1):S38–S41.
 14. Vree TB, van der Ven AJ. Clinical consequences of the biphasic elimination kinetics for the diuretic effect of furosemide and its acyl glucuronide in humans. *J Pharm Pharmacol* 1999; 51(3):239–248.
 15. Wilcox CS. New insights into diuretic use in patients with chronic renal disease. *J Am Soc Nephrol* 2002; 13(3):798–805.
 16. Mizuma T, Benet LZ, Lin ET. Interactions of human serum albumin with furosemide glucuronide: a role of albumin in isomerization, hydrolysis, reversible binding and irreversible binding of a 1-O-acyl glucuronide metabolite. *Biopharm Drug Dispos* 1999; 20(3):131–136.
 17. Trepanier LA. Potential interactions between non-steroidal anti-inflammatory drugs and other drugs. *J Vet Emerg Crit Care* 2005; 15(4):248–253.
 18. Hasannejad H, Takeda M, Taki K, et al. Interactions of human organic anion transporters with diuretics. *J Pharmacol Exp Ther* 2004; 308(3):1021–1029.
 19. Alebouyeh M, Takeda M, Onozato ML, et al. Expression of human organic anion transporters in the choroid plexus and their interactions with neurotransmitter metabolites. *J Pharmacol Sci* 2003; 93(4):430–436.
 20. Odland B. Relationship between tubular secretion of furosemide and its saluretic effect. *J Pharmacol Exp Ther* 1979; 208(3):515–521.
 21. Lee MG, Chiou WL. Mechanism of ascorbic acid enhancement of the bioavailability and diuretic effect of furosemide. *Drug Metab Dispos* 1998; 26(5):401–407.
 22. Friedman PA, Roch-Ramel F. Hemodynamic and natriuretic effects of bumetanide and furosemide in the cat. *J Pharmacol Exp Ther* 1977; 203(1):82–91.
 23. Cataliotti A, Boerrigter G, Costello-Boerrigter LC, et al. Brain natriuretic peptide enhances renal actions of furosemide and suppresses furosemide-induced aldosterone activation in experimental heart failure. *Circulation* 2004; 109(13):1680–1685.
 24. Singh A, Blackwell J, Neher J. Clinical inquiries. Does furosemide decrease morbidity or mortality for patients with diastolic or systolic dysfunction? *J Fam Pract* 2005; 54(4):370–372.
 25. Ravnan SL, Deedwania PC. The rational use of diuretics in heart failure. *Curr Cardiol Rep* 2003; 5(3):237–242.
 26. Na KY, Oh YK, Han JS, et al. Upregulation of Na⁺ transporter abundances in response to chronic thiazide or loop diuretic treatment in rats. *Am J Physiol Renal Physiol* 2003; 284(1):F133–F143.
 27. Buffin-Meyer B, Younes-Ibrahim M, El Mernissi G, et al. Differential regulation of collecting duct Na⁺, K⁺-ATPase and K⁺ excretion by furosemide and piretanide: role of bradykinin. *J Am Soc Nephrol* 2004; 15(4):876–884.
 28. Maril N, Margalit R, Mispelger J, et al. Sodium magnetic resonance imaging of diuresis: spatial and kinetic response. *Magn Reson Med* 2005; 53(3):545–552.
 29. Sward K, Valsson F, Sellgren J, et al. Differential effects of human atrial natriuretic peptide and furosemide on glomerular filtration rate and renal oxygen consumption in humans. *Intensive Care Med* 2005; 31(1):79–85.
 30. Liss P, Nygren A, Ulfendahl HR, et al. Effect of furosemide or mannitol before injection of a non-ionic contrast medium on intrarenal oxygen tension. *Adv Exp Med Biol* 1999; 471:353–359.
 31. Lahet JJ, Lenfant F, Courderot-Masuyer C, et al. In vivo and in vitro antioxidant properties of furosemide. *Life Sci* 2003; 73(8):1075–1082.
 32. Lameire N, Van Biesen W, Vanholder R. Acute renal failure. *Lancet* 2005; 365(9457):417–430.
 33. Uchino S, Doig GS, Bellomo R, et al. Diuretics and mortality in acute renal failure. *Crit Care Med* 2004; 32(8):1669–1677.
 34. Aravindan N, Shaw A. Effect of furosemide infusion on renal hemodynamics and angiogenesis gene expression in acute renal ischemia/reperfusion. *Ren Fail* 2006; 28(1):25–35.
 35. Gammage M. Treatment of acute pulmonary oedema: diuresis or vasodilation? *Lancet* 1998; 351(9100):382–383.
 36. Stanke F, Devillier P, Breant D, et al. Frusemide inhibits angiotensin II-induced contraction on human vascular smooth muscle. *Br J Clin Pharmacol* 1998; 46(6):571–575.
 37. Jhund PS, Davie AP, McMurray JJ. Aspirin inhibits the acute venodilator response to furosemide in patients with chronic heart failure. *J Am Coll Cardiol* 2001; 37(5):1234–1238.
 38. Greenberg S, McGowan C, Xie J, et al. Selective pulmonary and venous smooth muscle relaxation by furosemide: a comparison with morphine. *J Pharmacol Exp Ther* 1994; 270(3):1077–1085.
 39. Carriere S, Desrosiers M, Friberg J, et al. The effect of furosemide on the intrarenal blood flow distribution in the dog. *Can J Physiol Pharmacol* 1972; 50(8):774–783.
 40. Data JL, Rane A, Gerkens J, et al. The influence of indomethacin on the pharmacokinetics, diuretic response, and hemodynamics of furosemide in the dog. *J Pharmacol Exp Ther* 1978; 206(2):431–438.
 41. Wronski T, Seeliger E, Persson PB, et al. The step response: a method to characterize mechanisms of renal blood flow autoregulation. *Am J Physiol Renal Physiol* 2003; 285(4):F758–F764.
 42. Biddle TL, Yu PN. Effect of furosemide on hemodynamics and lung water in acute pulmonary edema secondary to myocardial infarction. *Am J Cardiol* 1979; 43(1):86–90.
 43. Pickkers P, Dormans TP, Russel FG, et al. Direct vascular effects of furosemide in humans. *Circulation* 1997; 96(6):1847–1852.
 44. Javaheri S, Corbett W, Adams JM, et al. Acute respiratory acidosis: large-dose furosemide and cerebrospinal fluid ions. *J Appl Physiol* 1994; 76(6):2651–2655.
 45. Reising CA, Chendrasekhar A, Wall PL, et al. Continuous dose furosemide as a therapeutic approach to acute respiratory distress syndrome (ARDS). *J Surg Res* 1999; 82(1):56–60.
 46. Johnston GD, Hiatt WR, Nies AS, et al. Factors modifying the early non-diuretic vascular effects of furosemide in man. The possible role of renal prostaglandins. *Circ Res* 1983; 53(5):630–635.
 47. Wiemer G, Fink E, Linz W, et al. Furosemide enhances the release of endothelial kinins, nitric oxide and prostacyclin. *J Pharmacol Exp Ther* 1994; 271(3):1611–1615.
 48. Wallach S, Charbon GA, Beijer HJ, et al. Furosemide vasodilates the canine gastrointestinal tract. *J Clin Pharmacol* 1982; 22(8–9):348–358.
 49. Wallach S, Charbon GA, Beijer HJ, et al. Effect of furosemide on biliary secretion, pancreatic blood flow, and pancreatic exocrine secretion. *J Clin Pharmacol* 1983; 23(10):401–413.
 50. Pickkers P, Russel FG, Thien T, et al. Only weak vasorelaxant properties of loop diuretics in isolated resistance arteries from man, rat and guinea pig. *Eur J Pharmacol* 2003; 466(3):281–287.

51. Stevens EL, Uyehara CF, Southgate WM, et al. Furosemide differentially relaxes airway and vascular smooth muscle in fetal, newborn, and adult guinea pigs. *Am Rev Respir Dis* 1992; 146(5 Part 1):1192–1197.
52. Johnston GD, Nicholls DP, Leahey WJ. The dose-response characteristics of the acute non-diuretic peripheral vascular effects of frusemide in normal subject. *Br J Clin Pharmacol* 1984; 18(1):75–81.
53. Stanke-Labesque F, Cracowski JL, Bedouch P, et al. Furosemide inhibits thromboxane A₂-induced contraction in isolated human internal mammary artery and saphenous vein. *J Cardiovasc Pharmacol* 2000; 35(4):531–537.
54. Mozhayeva MG, Bagrov YaYu. The inhibitory effects of frusemide on Ca²⁺ influx pathways associated with oxytocin-induced contractions of rat myometrium. *Gen Physiol Biophys* 1995; 14(5):427–426.
55. Datar S, McCauley FA, Wilson TW. Testing the “redirection hypothesis” of prostaglandin metabolism in the kidney. *Prostaglandins* 1987; 33(2):275–285.
56. Pourageaud F, Bappel-Gozalbes C, Marthan R, et al. Role of EDHF in the vasodilatory effect of loop diuretics in guinea-pig mesenteric resistance arteries. *Br J Pharmacol* 2000; 131(6):1211–1219.
57. Corboz MR, Ballard ST, Inglis SK, et al. Dilatory effect of furosemide on rat tracheal arterioles and venules. *Am J Respir Crit Care Med* 1997; 156(2 Part 1):478–483.
58. Fazio M, Bardelli M, Cominotto F, et al. Haemoconcentration, shear-stress increase and carotid artery diameter regulation after furosemide administration in older hypertensives. *Exp Gerontol* 2001; 36(3):571–581.
59. Francis GS, Siegel RM, Goldsmith SR, et al. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. *Ann Intern Med* 1985; 103(1):1–6.
60. Martin GS, Moss M, Wheeler AP, et al. A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury. *Crit Care Med* 2005; 33(8):1681–1687.
61. Abrahams Z, Pang MY, Lam EK, et al. What is the plasma cofactor required by diuretics for direct vascular relaxant effect in vitro? *J Hypertens* 1998; 16(6):801–809.
62. Andreassen F, Christensen JH. The effect of furosemide on vascular smooth muscle is influenced by plasma protein. *Pharmacol Toxicol* 1988; 65(3):324–326.
63. Holland SD, Williamson HE. Acute effects of high ceiling diuretics on pancreatic blood flow and function. *J Pharmacol Exp Ther* 1984; 229(2):440–446.
64. Ong KC, Kor AC, Chong WF, et al. Effects of inhaled furosemide on exertional dyspnea in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 169(9):1028–1033.
65. Nishino T, Ide T, Sudo T, et al. Inhaled furosemide greatly alleviates the sensation of experimentally induced dyspnea. *Am J Respir Crit Care Med* 2000; 161(6):1963–1967.
66. Novembre E, Frongia G, Lombardi E, et al. The preventative effect and duration of action of two doses of inhaled furosemide on exercise-induced asthma in children. *J Allergy Clin Immunol* 1995; 96(6 Part 1):906–909.
67. Polosa R, Rajakulasingam K, Prosperini G, et al. Relative potencies and time course of changes in adenosine 5'-monophosphate airway responsiveness with inhaled furosemide and bumetanide in asthma. *J Allergy Clin Immunol* 1993; 92(2):288–297.
68. Nehashi S, Nishino T, Ide T. Inhaled furosemide inhibits behavioral response to airway occlusion in anesthetized cats. *Anesthesiology* 2001; 95(5):1234–1237.
69. Sudo T, Hayashi F, Nishino T. Responses of tracheobronchial receptors to inhaled furosemide in anesthetized rats. *Am J Respir Crit Care Med* 2000; 162(3 Part 1):971–975.
70. Prat J, Mullol J, Ramis I, et al. Release of chemical mediators and inflammatory cell influx during early allergic reaction in the nose: effect of furosemide. *J Allergy Clin Immunol* 1993; 92(2):248–254.
71. Nucera E, Schiavino D, Milani A, et al. Effect of pre-treatment with inhaled furosemide on allergen nasal challenge. *Am J Rhinol* 1998; 12(5):359–361.
72. Willis EF, Clough GF, Church MK. Investigation into the mechanisms by which nedocromil sodium, frusemide, and bumetanide inhibit the histamine-induced itch and flare response in human skin in vivo. *Clin Exp Allergy* 2004; 34(3):450–455.
73. Granados-Soto V, Arguelles CF, Alvarez-Leefmans FJ. Peripheral and central antinociceptive actions of Na⁺-K⁺-2Cl⁻ cotransporter blockers on formalin-induced nociception in rats. *Pain* 2005; 114(2):231–238.
74. Moosavi SH, Binks AP, Lansing RW, et al. Effect of inhaled furosemide on air hunger induced in healthy humans. *Respir Physiol Neurobiol* 2007; 156(1):1–8.
75. Yen ZS, Chen SC. Best evidence topic report. Nebulized furosemide in acute adult asthma. *Emerg Med J* 2005; 22(9):654–655.
76. Polosa R, Rajakulasingam K, Prosperini G, et al. Inhaled loop diuretics and basal airway responsiveness in man: evidence of a role for cyclo-oxygenase products. *Eur Respir J* 1995; 8(4):593–599.
77. Foresi A, Pelucchi A, Mastropasqua B, et al. Effect of inhaled furosemide and torasemide on bronchial response to ultrasonically nebulized distilled water in asthmatic subjects. *Am Rev Respir Dis* 1992; 146(2):364–368.
78. Padrid P. Chronic lower airway disease in the dog and cat. *Probl Vet Med* 1992; 4(2):320–344.
79. Widdicombe JH, Nathanson IT, Highland E. Effect of “loop” diuretics on ion transport by dog tracheal epithelium. *Am J Physiol* 1983; 245(5 Part 1):C388–C396.
80. Hesdorffer DC, Stables JP, Hauser WA, et al. Are certain diuretics also anticonvulsants? *Ann Neurol* 2001; 50(4):458–462.
81. Gutschmidt KU, Stenkamp K, Buchheim K, et al. Anticonvulsant actions of furosemide in vitro. *Neuroscience* 1999; 91(4):1471–1481.
82. Schwartzkroin PA, Baraban SC, Hochman DW. Osmolarity, ionic flux, and changes in brain excitability. *Epilepsy Res* 1998; 32(1–2):275–285.
83. Haglund MM, Hochman DW. Furosemide and mannitol suppression of epileptic activity in the human brain. *J Neurophysiol* 2005; 94(2):907–918.
84. Holtkamp M, Matzen J, Buchheim K, et al. Furosemide terminates limbic status epilepticus in freely moving rats. *Epilepsia* 2003; 44(9):1141–1144.
85. Hochman DW, Baraban SC, Owens JW, et al. Dissociation of synchronization and excitability in furosemide blockade of epileptiform activity. *Science* 1995; 270(5233):99–102.
86. Stringer JL, Pan E. Effect of seizures and diuretics on the osmolality of the cerebrospinal fluid. *Brain Res* 1997; 745(1–2):328–330.
87. Jarolimek W, Lewen A, Misgeld U. A furosemide-sensitive K⁺-Cl⁻ cotransporter counteracts intracellular Cl⁻ accumulation and depletion in cultured rat midbrain neurons. *J Neurosci* 1999; 19(12):4695–4704.
88. Read SJ, Smith MI, Benham CD, et al. Furosemide inhibits regenerative cortical spreading depression in anesthetized cats. *Cephalalgia* 1997; 17(8):826–832.
89. Barbaro NM, Takahashi DK, Baraban SC. A potential role for astrocytes in mediating the antiepileptic actions of furosemide in vitro. *Neuroscience* 2004; 128(3):655–663.
90. Walz W, Hertz L. Intense furosemide-sensitive potassium accumulation in astrocytes in the presence of pathologically high extracellular potassium levels. *J Cereb Blood Flow Metab* 1984; 4(2):301–304.
91. Walz W, Kimelberg HK. Differences in cation transport properties of primary astrocyte cultures from mouse and rat brain. *Brain Res* 1985; 340(2):333–340.
92. Pollay M, Fullenwider C, Roberts PA, et al. Effect of mannitol and furosemide on blood-brain osmotic gradient and intracranial pressure. *J Neurosurg* 1983; 59(6):945–950.
93. Barbosa AP, Cabral SA. New therapies for intracranial hypertension. *J Pediatr (Rio J)* 2003; 79(Suppl. 2):S139–S148.
94. Melby JM, Miner LC, Reed DJ. Effect of acetazolamide and furosemide on the production and composition of cerebrospinal fluid from the cat choroid plexus. *Can J Physiol Pharmacol* 1982; 60(3):405–409.

95. Johnson DC, Frankel HM, Kazemi H. Effect of furosemide on cerebrospinal fluid composition. *Respir Physiol* 1984; 56(3):301–308.
96. Seo M, Choi H, Lee K, et al. Transcranial Doppler ultrasound analysis of resistive index in rostral and cerebral arteries in dogs. *J Vet Sci* 2005; 6(1):61–66.
97. Kang MY, Tsuchiya M, Packer L, et al. In vitro study on antioxidant potential of various drugs used in the perioperative period. *Acta Anaesthesiol Scand* 1998; 42(1):4–12.
98. Reyes AJ. The increase in serum uric acid concentration caused by diuretics might be beneficial in heart failure. *Eur J Heart Fail* 2005; 7(4):461–467.
99. Kapucu LO, Azizoglu F, Ayvaz G, et al. Effects of diuretics on iodine uptake in non-toxic goiter: comparison with low-iodine diet. *Eur J Nucl Mol Imaging* 2003; 30(9):1270–1272.
100. Seabold JE, Ben-Haim S, Pettit WA, et al. Diuretic-enhanced I-131 clearance after ablation therapy for differentiated thyroid cancer. *Radiology* 1993; 187(3):839–842.
101. Hamburger JI. Diuretic augmentation of I-131 uptake in inoperable thyroid cancer. *N Engl J Med* 1969; 280(20):1091–1094.
102. Rillema JA, Hill MA. Prolactin regulation of the pendrin-iodide transporter in the mammary gland. *Am J Physiol Endocrinol Metab* 2003; 284(1):E25–E28.
103. Szwed JJ, Kleit SA, Hamburger RJ. Effect of furosemide and chlorothiazide on the thoracic duct lymph flow in the dog. *J Lab Clin Med* 1972; 79(5):693–700.
104. la Cour M, Baekgaard A, Zeuthen T. Antibodies against a furosemide binding protein from ehrlich ascites tumour cells inhibit Na⁺, K⁺, Cl⁻ co-transport in frog retinal pigment epithelium. *Acta Ophthalmol Scand* 1997; 75(4):405–408.
105. Geck P, Heinz E, Pfeiffer B. Influence of high ceiling diuretics on ion fluxes and cell volume of ehrlich ascites tumour cells. *Scand Audiol Suppl* 1981; 14(Suppl.):25–37.
106. Razis DV, Athanasiou A, Dadiotis L. Diuretics in malignant effusions and edemas of generalized cancer. *J Med* 1976; 7(6):449–461.
107. Plumb DC. *Veterinary Drug Handbook*. Furosemide, 4th edn. Minnesota: Blackwell Publishing; 2002, pp. 394–397.
108. Weber KT. Furosemide in the long-term management of heart failure: the good, the bad, and the uncertain. *J Am Coll Cardiol* 2004; 44(6):1308–1310.
109. Lee CT, Chen HC, Lai LW, et al. Effects of furosemide on renal calcium handling. *Am J Physiol Renal Physiol* 2007; 293(4):F1231–F1237.
110. Bushinsky DA, Favus MJ, Langman CB, et al. Mechanism of chronic hypercalciuria with furosemide: increased calcium absorption. *Am J Physiol* 1986; 251(1 Pt 2):F17–F24.
111. Law PH, Sun Y, Bhattacharya SK, et al. Diuretics and bone loss in rats with aldosteronism. *J Am Coll Cardiol* 2005; 46(1):142–146.
112. Bartoli E, Arras S, Faedda R, et al. Blunting of furosemide diuresis by aspirin in man. *J Clin Pharmacol* 1980; 20(7):452–458.
113. Berg KJ, Loew D. Inhibition of furosemide-induced natriuresis by acetylsalicylic acid in dogs. *Scand J Clin Lab Invest* 1977; 37(2):125–131.
114. Müller FO, Middle MV, Schall R, et al. An evaluation of the interaction of meloxicam with frusemide in patients with compensated chronic cardiac failure. *Br J Clin Pharmacol* 1997; 44(4):393–398.
115. Kidd LB, Salavaggione OE, Szumlanski CL, et al. Thiopurine methyltransferase activity in red blood cells of dogs. *J Vet Intern Med* 2004; 18(2):214–218.
116. Kondo CS, Macchionne M, Nakagawa NK, et al. Effects of intravenous furosemide on mucociliary transport and rheologic properties of patients under mechanical ventilation. *Crit Care* 2002; 6(1):81–87.
117. Cook DJ, Tudball CF. Potentators and bolus intravenous furosemide. *Lancet* 2001; 358(9290):1373–1374.
118. Scarpelli DG. Toxicology of the pancreas. *Toxicol Appl Pharmacol* 1989; 101(3):543–554.
119. Hermansen K, Schmitz O, Arnfred J, et al. Effects of furosemide and indapamide upon pancreatic insulin and somatostatin secretion in vitro. *Diabetes Res* 1986; 3(4):221–223.
120. Sandstrom P, Sehlin J. Furosemide reduces insulin release by inhibition of Cl⁻ and Ca²⁺ fluxes in beta-cells. *Am J Physiol* 1988; 255(5 Part 1):E591–E596.
121. Reid B, Song B, McCaig CD, et al. Wound healing in rat cornea: the role of electric currents. *FASEB J* 2005; 19(3):379–386.
122. Patarca R, Candia OA, Reinach PS. Mode of inhibition of active chloride transport in the frog cornea by furosemide. *Am J Physiol* 1983; 245(6):F660–F669.
123. Shankaran S, Poland RL. The displacement of bilirubin from albumin by furosemide. *J Pediatr* 1997; 90(4):642–646.
124. Earl G, Davenport J, Narula J. Furosemide challenge in patients with heart failure and adverse reactions to sulfa-containing diuretics. *Ann Intern Med* 2003; 138(4):358–359.
125. Trepanier LA. Idiosyncratic toxicity associated with potentiated sulfonamides in the dog. *J Vet Pharmacol Ther* 2004; 27(3):129–138.
126. Ochoa PG, Arribas MT, Mena JM, et al. Cutaneous adverse reaction to furosemide treatment: new clinical finding. *Can Vet J* 2006; 47(6):576–578.
127. Sommers SC, Higgins TE, Kimelblatt BJ. Chronic aortitis following furosemide therapy. *Arch Pathol Lab Med* 1984; 108(4):293–294.
128. Lim CF, Loidl NM, Kennedy JA, et al. Drug effects on triiodothyronine uptake by rat anterior pituitary cells in vitro. *Exp Clin Endocrinol Diabetes* 1996; 104(2):151–157.
129. Gulikers KP, Panciera DL. Influence of various medications on canine thyroid function. *Comp Contin Edu Pract Vet* 2002; 24(7):511–523.
130. Stockigt JR, Lim CF, Barlow JW, et al. Interaction of furosemide with serum thyroxine-binding sites: in vivo and in vitro studies and comparison with other inhibitors. *J Clin Endocrinol Metab* 1985; 60(5):1025–1031.
131. Surks MI, Sievert R. Drugs and thyroid function. *N Engl J Med* 1995; 333(25):1688–1694.
132. Daminet S, Ferguson DC. Influence of drugs on thyroid function in dogs. *J Vet Intern Med* 2003; 17(4):463–472.