The Use of Gastroprotectants in Treating Gastric Ulceration in Dogs*

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ABSTRACT: Disruption of the gastric mucosal barrier occurs secondary to a vast array of drugs and diseases, leading to the development of inflammatory, erosive, and ultimately ulcerative lesions. Gastroprotectants such as histamine (H_2)-receptor antagonists, proton pump inhibitors, sucralfate, misoprostol, antacids, and bismuth subsalicylate decrease gastric acidity and/or promote mucosal protective mechanisms and, therefore, are used both to prevent mucosal damage and to treat ulcerations. This article reviews the various gastroprotectant medications, including their mechanisms of action, means of administration, side effects, and efficacy in various disease states.

Gastroprotectants are among the most commonly used drugs in veterinary medicine because the gastrointestinal (GI) tract can be injured secondary to a plethora of diseases and administration of various drugs. Many drugs have been developed to decrease intraluminal acidity and/or promote mucosal protective defense mechanisms to prevent and treat ulcerative disorders. These drugs include histamine (H_2)-receptor antagonists, proton pump inhibitors (PPIs), sucralfate, misoprostol, antacids, and bismuth subsalicylate (Table 1). Although a vast amount of information pertaining to these agents exists in the human literature, clinical trials in dogs are quite limited. Therefore, to provide a comprehensive review, much of the information in this article is based on human and experimental animal studies.

*A companion article on disruption of the gastric mucosal barrier starts on page 340.

H₂-RECEPTOR ANTAGONISTS

H_2-receptor antagonists (H_2-RAs) are analogues of histamine that competitively and reversibly inhibit the binding of histamine to H_2 receptors on the gastric parietal cell.[1–3] H_2-RAs are highly selective for H_2 receptors without action on H_1 or H_3 receptors.[4,5] By blocking histamine action on H_2 receptors, H_2-RAs reduce intracellular cAMP concentrations and thereby the secretion of acid by gastric parietal cells.[6] H_2-RAs also render the cell less responsive to stimulation by acetylcholine and gastrin through two mechanisms[2,4,5]: First, histamine released from enterochromaffin-like cells following stimulation by gastrin or acetylcholine is prevented from binding to the parietal cell H_2 receptor.[4,5] Second, decreased intracellular cAMP levels secondary to H_2 blockage prevent gastrin- and acetylcholine-mediated increases in protein kinase activity in the gastric parietal cells, which are necessary for these agents to promote acid secretion.[4,5]

Four H_2-RAs are available: cimetidine, ranitidine, famotidine, and nizatidine. These drugs

Table 1. Dosages, Mechanisms of Action, and Notable Points Regarding Various Gastrointestinal Protectants.[1,10,37,51,55,56,87,96]

Drug	Dosage	Mechanism of Action	Comments
Cimetidine	5–10 mg/kg PO, SC, IM, or IV q6–8h	Decreases HCl secretion by inhibition of histamine binding to H_2 receptors (H_2 antagonist)	Inhibits the hepatic cytochrome P-450 system Decreases hepatic blood flow
Ranitidine	2 mg/kg PO, SC, or IV q8–12h	Decreases HCl secretion (H_2 antagonist)	Prokinetic effect mediated through acetylcholinesterase inhibition
Nizatidine	5 mg/kg PO q12–24h	Decreases HCl secretion (H_2 antagonist)	Prokinetic effect mediated through acetylcholinesterase inhibition
Famotidine	0.5–1 mg/kg PO, SC, or IV q12–24h	Decreases HCl secretion (H_2 antagonist)	No appreciable cytochrome P-450 binding
Omeprazole	0.7–2 mg/kg PO q24h or 20 mg/dog in dogs >44 lb (20 kg) or 10 mg/dog in dogs <44 lb (20 kg)	Inhibits gastric acid secretion by binding to and blocking the H^+-K^+ ATPase enzyme (proton pump)	Inhibits cytochrome P-450 enzymes Provides superior intragastric pH control
Sucralfate	0.5–1 g PO q8h	Binds to ulcers, forming a protective barrier Stimulates local formation of PGs and epidermal growth factor	Works best in an acidic environment but is effective at a near neutral pH
Misoprostol	2–5 µg/kg PO q8–12h	Synthetic PGE_1 analogue Inhibits acid secretion and increases bicarbonate secretion, mucus production, and mucosal blood flow	Primarily used in NSAID-induced ulcer prevention
Antacids	0.5–1 ml/kg PO q2–4h	Neutralize HCl	Aluminum- or magnesium-containing antacids are most efficacious Duration of action is only 2–3 hr
Bismuth subsalicylate	0.25 ml/kg (4.375 mg/kg) PO q6–8h Also available as a 262-mg tablet	Absorbs toxins and coats ulcers Stimulates PG, mucus, and bicarbonate secretion Mild antimicrobial actions Inhibitory effect on intestinal PGs and chloride secretion	May cause blackening of stool Radiopaque Should be used carefully in cats because of salicylate toxicosis

differ in their potency, duration of action, prokinetic effects, and tendency to interact with other drugs. The order of potency of gastric acid inhibitors is[7–13]:

Famotidine > Ranitidine = Nizatidine > Cimetidine

Cimetidine was the first H_2-RA used in dogs. Acid inhibition after cimetidine administration in dogs peaks at 75% within 1.5 hours, and the effect of the drug is negligible after 5 hours.[3] This relatively short biologic effect necessitates administration of the drug at least every 8 hours.[3,9] Cimetidine inhibits the hepatic cytochrome P-450 system and can therefore interfere with the clearance of drugs metabolized by this system.[1,6,9,10] Cimetidine also decreases hepatic blood flow, which may decrease the clearance of flow-limited drugs.[3,14] Cimetidine prolongs the half-life of a number of drugs, including warfarin, theophylline, phenytoin, lidocaine, quinidine, propranolol, metoprolol, tricyclic antidepressants, benzodiazepines, calcium channel blockers, sulfonylureas, and metronidazole.[4,10,15–19] Furthermore, cimetidine, along with the other H_2-RAs, can also interfere with absorption of drugs that require an

acidic environment for absorption.[18] For example, absorption of ketoconazole, a weak base, is delayed with elevated gastric pH.

Ranitidine inhibits acid secretion to a greater extent than does cimetidine in dogs and has a longer duration of action, necessitating only twice-daily dosing.[3,11,20] However, in a recent study[21] of dogs treated with ranitidine at 2 mg/kg IV bid, no significant difference was found in median 24-hour intragastric pH compared with dogs given saline solution. Because ranitidine binds less avidly than cimetidine to the cytochrome P-450 system, resulting in less inhibition of these enzymes, it is associated with fewer drug interactions than is cimetidine.[1,3,4,6,10] Ranitidine has a prokinetic effect on the GI tract mediated through acetylcholinesterase inhibition.[22–25]

Famotidine, the most potent H_2-RA, has a longer duration of action than does cimetidine or ranitidine and thus requires only once-daily dosing.[2,9,26] A recent study[21] in healthy dogs found that after 6 days of intravenous administration of famotidine, intragastric pH was maintained at greater than 4 for 48.4% of the time.

reduced.[6] Therefore, dose reduction is indicated in patients with moderate to severe renal insufficiency.[4,6,10]

To treat ulcer disease in humans, standard doses of H_2-RAs are effective in healing approximately 75% to 90% of uncomplicated NSAID-related ulcers after discontinuation of the offending drug.[4,31–33] If NSAID therapy is not discontinued, H_2-RAs are not as effective in ulcer healing.[4,31,32] The duration of treatment in humans is generally 4 to 8 weeks for uncomplicated ulcers and 6 to 12 months for complicated or recurring ulcers.[34–36] Because of the lack of such information in dogs, treatment times need to be extrapolated from human studies.

A plethora of large trials in human medicine have examined the effect of H_2-RAs in the prevention of NSAID-induced ulcers.[34,37] In pooled analysis of five randomized human trials, standard doses of H_2-RAs significantly reduced the risk of NSAID-induced duodenal ulcers but were ineffective in preventing NSAID-induced gastric ulceration.[31,33,34,38–41] However, separate data from multiple randomized human trials[32,34,40] suggest

Clinical studies evaluating the efficacy of H_2-RAs in veterinary patients are lacking.

Famotidine has no appreciable binding to the cytochrome P-450 enzyme system; therefore, concurrent use with other medications is not a concern.[6,9,26]

Nizatidine, like ranitidine, has anticholinesterase activity, resulting in a prokinetic effect.[22,23] Its use may be beneficial in dogs requiring acid inhibition that have concurrent gastric motility abnormalities. Like famotidine, nizatidine does not inhibit hepatic microsomal enzymes.[6,13]

H_2-RAs have an outstanding safety profile. There is limited documentation regarding side effects in the veterinary literature; however, rare adverse events have been noted in humans. Rapid intravenous infusion of cimetidine, ranitidine, and possibly famotidine can cause bradycardia, likely through a blockade of cardiac H_2 receptors.[27–29] Thus these drugs should be given slowly over 15 to 30 minutes.[4,6,27] Other rare side effects noted in humans include reversible increases in liver enzymes and blood dyscrasias such as thrombocytopenia, anemia, and leukopenia.[4,18] In addition, H_2-RAs are eliminated by a combination of hepatic metabolism, glomerular filtration, and renal tubular secretion.[4,6,13,30] In renal failure, the half-life is increased and total body clearance is

that high- or double-dose H_2-RAs are effective against both NSAID-induced duodenal and gastric ulcers.

Clinical studies evaluating the efficacy of H_2-RAs in veterinary patients are lacking. In experimental studies in dogs,[42,43] various H_2-RAs were shown to effectively reduce maximal acid output by 50% to 70%. In multiple studies[44–46] of aspirin-induced gastric mucosal injury, pretreatment with cimetidine or ranitidine prevented mucosal damage in a dose-related manner; however, another study[47] disputed these findings, showing no difference in gastric lesions in dogs treated with cimetidine.[44–47] In a study[48] examining the gastroprotective effect of H_2-RAs in dogs undergoing spinal surgery, there was no difference in the risk of occult or gross GI tract bleeding in dogs treated with cimetidine compared with controls. The lack of effectiveness of cimetidine in this study might be explained by the observation that there is no evidence to suggest that increased hydrochloric acid (HCl) production is central to the pathogenesis of GI tract bleeding in dogs undergoing spinal surgery.[48] In addition, most dogs in this study had hematochezia, not melena, suggesting lower GI bleeding for which H_2-RAs would not be protective.
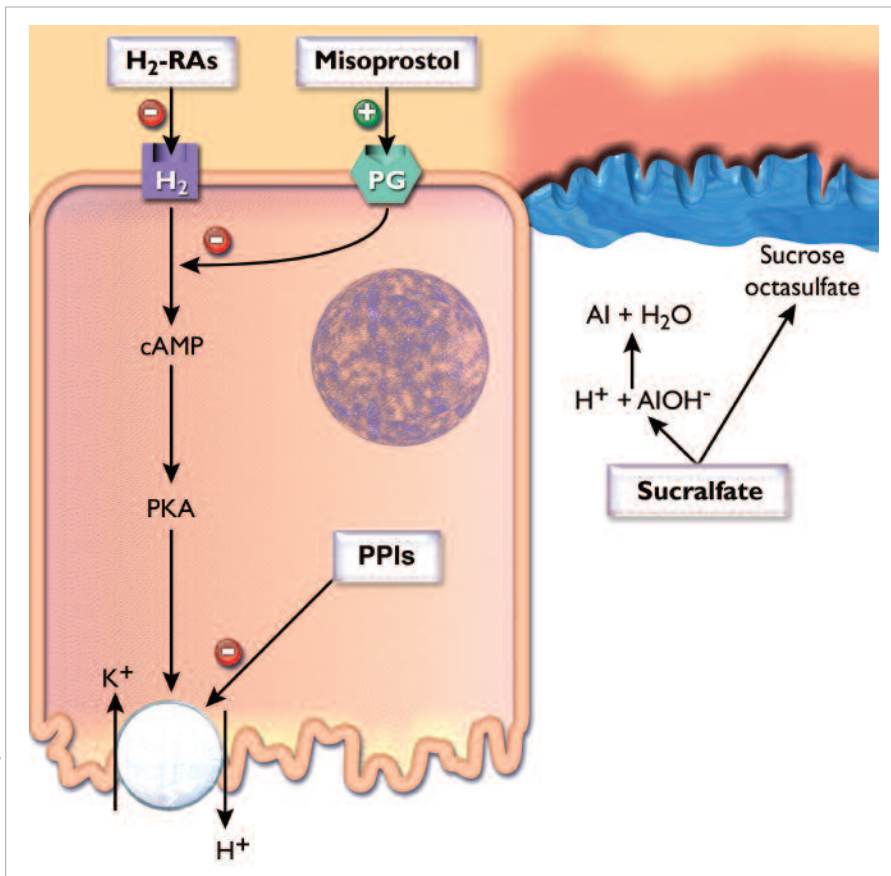
Figure 1. Mechanism of gastroprotection for H$_2$-RAs, misoprostol/PG, PPIs, antacids, and sucralfate. (*PKA* = protein kinase A)

Illustration by Felecia Paras

PROTON PUMP INHIBITORS

PPIs are among the most widely sold drugs worldwide because of their outstanding efficacy and safety. Five PPIs are available for clinical use: omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole.[4,49] In general, the pharmacology of these drugs is quite similar. All of the PPIs are metabolized primarily by the hepatic cytochrome P-450 system.[50–51] However, studies[52] using human liver microsomal preparations suggest that lansoprazole and pantoprazole are the most potent in vitro cytochrome P-450 inhibitory enzymes. All PPIs are available for oral administration, but only pantoprazole and lansoprazole are available in intravenous formulations. Notable differences in pharmacology in humans are that esomeprazole has a somewhat higher potency and rabeprazole has a more rapid onset of action.[53]

PPIs are substituted benzimidazoles, which act as prodrugs. They are systemically absorbed in the alkaline environment of the duodenum.[1,4,54] At physiologic pH, PPIs, which are weak bases, are unprotonated and therefore diffuse readily into cells. Only in acidic compartments, such as within the parietal cell canaliculus, are the prodrugs protonated, trapped, and converted to their active forms.[1,3,4,55–58] Because this acidic compartment is unique to the gastric parietal cell, PPIs have no effect on other proton pumps.[3,51,56] Within the parietal cell, PPIs rapidly undergo molecular conversion into their active form, a thiophilic sulfonamide cation, which covalently binds to the hydrogen ion (H$^+$)–potassium ion (K$^+$) ATPase enzyme, blocking its activity.[4,51,55,58–61] H$^+$–K$^+$ ATPase catalyzes the exchange of cytosolic hydrogen ions for luminal potassium ions and is referred to as a *proton pump*.[51,56] By blocking this pump, which represents the final step in acid secretion, PPIs profoundly and irreversibly inhibit gastric acid secretion[1–3,54,56,58] (Figure 1).

Omeprazole has recently been reported to have an antioxidant effect independent of its antisecretory activity. By scavenging hydroxyl free radicals in these studies,[62–65] omeprazole was able to prevent oxidative damage to membrane lipids and proteins. This effect may represent another mechanism of mucosal cytoprotection induced by PPIs.[62–64,66]

The potential side effects of long-term therapy (>3 months) with PPIs are controversial, and little information is available on adverse effects in veterinary patients. Because an acidic environment promotes absorption of food-borne minerals, including iron, calcium, phosphorus, magnesium, and zinc, and is necessary for releasing vitamin B$_{12}$ from food, mineral and vitamin deficiencies are possible but have not been reported in human or veterinary patients.[4] Because gastric acid is an important barrier to bacterial colonization of the GI tract, increases in gastric bacterial counts occur with long-term omeprazole therapy.[4,59] Although patients receiving omeprazole may have an increased risk for enteric infections, large case-controlled studies[1,4] in humans using omeprazole for

longer than 1 year showed no association with clinical enteric infections. Periodic production of an acidic environment during PPI therapy may keep bacterial overgrowth from becoming a clinically significant problem.[10,59] Early studies[67,68] in humans on ventilatory support demonstrated an increased incidence of nosocomial pneumonia in patients receiving PPIs. However, more recent studies[67,69,70] have found no significant difference in ventilator-associated pneumonia with various GI protectants.

Another consequence of PPI-induced inhibition of acid secretion is increased gastrin levels due to alteration

proton pumps are actively secreting at the canalicular surface. However, a large reserve of additional proton pumps is postprandially recruited to the apical membrane from intracellular vesicles. Thus PPIs should be administered 1 hour before a meal so that the peak serum concentration coincides with the maximal activity of proton pump secretion.[4,49] In the first 24 hours of therapy with omeprazole in humans and dogs, gastric acid output is reduced by only approximately 30% because not all proton pumps can be inactivated with one dose.[49,56,74] Up to 3 to 5 days are required before gas-

> *The use of PPIs in veterinary medicine is still in its infancy; therefore, information on their clinical use is based primarily on the human literature.*

of the feedback loop that regulates gastrin secretion. The primary physiologic function of gastrin secretion from gastric chief cells is to stimulate parietal cells to secrete HCl and enterochromaffin-like cells to secrete histamine.[59] In turn, increased intragastric acidity stimulates antral D cells to release somatostatin, which binds to receptors on G cells, inhibiting further gastrin synthesis and secretion.[4,59] Acid suppression by PPIs interrupts this negative feedback cycle, resulting in a two- to fourfold rise in gastrin levels.[4,51,71,72] Gastrin has growth-promoting trophic properties for the gastric mucosa and can lead to reversible hyperplasia of the gastric mucosa in rats and humans.[1,4,51,55,56,59,71,72] In rats, but not humans, long-term administration of PPIs can result in the development of gastric carcinoid tumors.[1,4,59,71,72] The clinical significance of hypergastrinemia in veterinary patients is unknown.

Because omeprazole is a weak base and is unstable in an acidic environment, it is supplied as an enteric-coated capsule to prevent inactivation in the stomach and allow absorption in the alkaline environment of the small intestine.[1,4,50,55,56] When a patient requires a smaller dose, it is recommended to divide the contents of the capsule and repackage the enteric-coated granules into new capsules to avoid degradation by gastric acid.[51,55,56] Alternatively, omeprazole may be administered to dogs as a suspension prepared by mixing the granules of one 20-mg capsule with 10 ml of 8.4% sodium bicarbonate ($NaHCO_3$) to make a 2-mg/ml solution.[21,73]

PPIs are capable of inhibiting $H^+–K^+$ ATPase only when it is present on the apical membrane of the parietal cell. In the fasting state, only approximately 10% of

tric acid production is nearly completely inhibited.[2,4,56,60,61,74,75] Because of this delay in gastric acid suppression, H_2-RAs can be used concurrently with PPIs for the first few days of treatment.[2] However, in a recent canine study,[21] omeprazole and pantoprazole use resulted in an increased gastric pH (>3) after only 2 days of administration. Although PPIs have a short serum half-life of 1.5 hours, their duration of acid inhibition is prolonged because they irreversibly inactivate the proton pump, and synthesis of new $H^+–K^+$ ATPase pump molecules takes 36 to 96 hours.[4,49,55,74,75]

Omeprazole is highly protein bound (98%) and undergoes hepatic metabolism by cytochrome P-450 enzymes to inactive metabolites, which are excreted as sulfate conjugates in urine.[1,50,55] Dose adjustments in dogs with renal or mild to moderate hepatic disease are not needed but are recommended in patients with severe liver disease.[4,55] Omeprazole inhibits hepatic microsomal cytochrome P-450 enzymes to an extent similar to that of cimetidine; therefore, the potential for drug interactions must be considered.[1,3,50,51,55] Drug interactions in humans have been reported with warfarin sulfate, diazepam, and phenytoin.[4,55] In addition, PPIs increase gastric pH, possibly altering absorption of drugs with a bioavailability dependent on intragastric acidity, such as ketoconazole, ampicillin esters, iron salts, and digoxin.[4,10,55]

The use of PPIs in veterinary medicine is still in its infancy; therefore, information on their clinical use is based primarily on the human literature. In humans, PPIs provide superior control of intragastric pH over a 24-hour period compared with H_2-RAs and effect greater relief of clinical signs and healing of mucosal

damage.[49] PPIs are most useful in treating diseases in which profound inhibition of acid secretion is necessary, such as gastroduodenal ulceration due to paraneoplastic production of secretogogues (mastocytomas or gastrinomas).[1–3,10] In addition, PPIs are useful in controlling bleeding from GI ulcers. Increased intragastric pH is a key factor in controlling bleeding ulcers. Both HCl and pepsin alter coagulation by interfering with the coagulation system, fibrinogen polymerization, and platelet aggregation.[76] A reduction of intraluminal gastric acidity to a pH greater than 4 is effective in preventing GI ulcer bleeding, but a pH of greater than 6 is necessary to control actively bleeding ulcers.[4,76] This higher pH is necessary because platelet aggregation is inhibited below a pH of 5.9.[77] With intravenous administration of PPIs, an intragastric pH greater than 4 is achieved for 24 hours in the vast majority of humans, and a pH greater than 6 is achieved intermittently.[76,77] To attain an intragastric pH greater than 6 for prolonged periods, a constant-rate infusion of PPI after a high-dose bolus is necessary.[77]

The use of PPIs in healing and preventing NSAID-induced ulcers has also been widely evaluated in human studies. Both H_2-RAs and PPIs are efficacious in healing NSAID-induced ulcers in humans when NSAID use is discontinued.[4] H_2-RAs are not effective when NSAID therapy is not discontinued, whereas PPIs are

tributed to the lack of statistical significance. In addition, more than 75% of dogs in this study had mucosal lesions at the time of surgical referral before omeprazole administration. The use of PPIs in veterinary patients requires further study.

SUCRALFATE

Sucralfate is a sulfated disaccharide–aluminum hydroxide complex. After oral administration, sucralfate dissociates in the acid environment of the stomach into its primary components—aluminum hydroxide and sucrose octasulfate.[1,87,88] The latter undergoes polymerization to form a viscous paste-like complex with a strong negative charge that binds electrostatically to positively charged proteins in the base of ulcers or erosions for up to 6 hours.[1,2,4,48,51,87] This insoluble complex forms a barrier that protects the ulcer from further damage by preventing back diffusion of hydrogen ions, inactivating pepsin, and absorbing gastric-damaging bile acids refluxed from the duodenum.[1,2,51,87]

The cytoprotective effects of sucralfate are further augmented by its ability to stimulate formation of local mediators, such as prostaglandins (PGs) and growth factors, that protect the gastric mucosa.[1,51,89] PG release enhances mucosal blood flow and increases secretion of mucus and bicarbonate, thereby accelerating ulcer healing.[3,51,87] Sucralfate is also thought to bind salivary and

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Sucralfate works best in an acidic environment; however, it is effective at acidic to near-neutral pH and can therefore be used concurrently with antisecretory drugs, such as H_2-RAs or PPIs.

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effective.[31–34,38,78] PPIs are also superior to H_2-RAs in preventing NSAID-induced ulcers in humans.[33,41,51,79]

There are limited studies on the use of PPIs in dogs. In one study,[80] omeprazole decreased the degree of gastritis associated with aspirin therapy, whereas cimetidine did not. In a recent study[81] of racing sled dogs, omeprazole use led to a significant reduction in the severity of exercise-induced gastric lesions. This is not unexpected in light of multiple equine studies showing that omeprazole is effective both in healing and preventing gastric ulcers in racehorses.[82–85] In a study[86] evaluating the efficacy of omeprazole in reducing the incidence of gastric lesions in dogs receiving corticosteroids for acute intervertebral disk disease, a trend toward improvement in mucosal lesions was noted in the omeprazole group. Small numbers of dogs in each group may have con-

gastric epidermal growth factor, resulting in its accumulation in ulcer beds, thus enhancing mucosal repair.[90,91]

Sucralfate works best in an acidic environment; however, it is effective at acidic to near-neutral pH and can therefore be used concurrently with antisecretory drugs, such as H_2-RAs or PPIs.[1,2,10,51] However, no synergistic or additional therapeutic effect has been proven in animals or humans via coadministration of sucralfate with an antisecretory agent.[1,51] Sucralfate is minimally absorbed after oral administration and thus is quite safe.[1,88] The only known side effect of sucralfate is constipation secondary to aluminum hydroxide.[4,10,88] Sucralfate may bind to and interfere with absorption of concurrently administered drugs, such as fluoroquinolones, theophylline, tetracycline, and digoxin.[1,4,10,51] In general, sucralfate should not be administered within 2 hours of other medications.[1,2]

In humans, sucralfate has been shown to be more effective in treating duodenal ulcers than gastric ulcers.[4,33,51] In a study[92] of humans with NSAID-induced mucosal lesions, sucralfate was superior to a placebo, similar to ranitidine, but significantly less effective than omeprazole in ulcer healing. The use of sucralfate to prevent NSAID-induced ulceration in humans has been disappointing. Although initial studies showed some benefit with short-term aspirin use, long-term studies have failed to show significant benefit compared with a placebo.[77,92] Therefore, sucralfate cannot be recommended as a prophylactic agent to prevent NSAID-induced gastropathy in humans.[38]

In a study[48] examining the efficacy of multiple gastroprotectants in dogs undergoing spinal surgery, dogs treated with sucralfate showed no difference in occult or gross GI tract bleeding compared with controls. However, hematochezia occurred more frequently than melena during this study, suggesting that the colon was a more common injury site than was the small intestine; thus sucralfate would not be expected to be as clinically beneficial.[48]

MISOPROSTOL

Misoprostol, a synthetic analogue of PGE_1, is a gastric cytoprotective agent with both acid-inhibitory and mucosal-protective properties. Its cytoprotective effect is mediated by increasing bicarbonate secretion, mucus production, and mucosal blood flow, which increases the oxygen and nutrient supply to the healing mucosa, ultimately increasing epithelialization.[1,2,93] In addition, misoprostol decreases intracellular cAMP levels, leading to decreased activity of the luminal $H^+ - K^+$ ATPase pump.[1,3,4] This results in a modest decrease in gastric acid secretion.[1,2,4,93]

Following oral administration, misoprostol is rapidly absorbed and undergoes significant hepatic first-pass metabolism to the active form, a free acid.[1,4] The free acid undergoes further hepatic biotransformation before excretion in the urine.[1] Because the serum half-life is less than 30 minutes, misoprostol must be given three to four times per day.[4] Dose reduction is not needed in patients with renal insufficiency.[4] Misoprostol may stimulate intestinal motility and secretion, leading to diarrhea, abdominal discomfort, and nausea.[1,3,10,93,94] In humans, these GI side effects limit widespread use of the drug. Misoprostol also stimulates uterine contractions and therefore should not be used during pregnancy or handled by pregnant women.[3,4,51]

The primary indication for misoprostol is prevention of NSAID-induced ulcers.[1,10] NSAID-induced gastric mucosal injury is mainly attributed to reduction of endogenous PGE (i.e., PGE_2) synthesis through inhibition of cyclooxygenase. By replacing PGE_2, misoprostol provides a specific strategy to prevent mucosal injury.[2] Misoprostol prevents NSAID-induced gastroduodenal ulcers and reduces the incidence of life-threatening ulcer complications.[32,39,78,94] In three prospective studies[95–97] of dogs given aspirin, misoprostol prevented endoscopically detectable gastric lesions or hemorrhage.[41] Although one of these studies[95] found that dosing twice daily was as effective as three times daily, human studies[33,39,41] have repeatedly shown a dose-dependent protective effect against both duodenal and gastric ulcers.

Misoprostol is not particularly effective in healing existing NSAID-induced ulcers.[87] In most comparative studies[51] in humans, healing rates associated with the use of H_2-RAs, sucralfate, and PPIs are higher than those associated with misoprostol use.

Multiple studies[86,98] have shown a high prevalence of gastroduodenal ulceration in dogs with intervertebral disk disease undergoing spinal surgery and corticosteroid treatment. In two separate studies,[48,86] misoprostol administration in this setting had no effect on the incidence of gastric hemorrhage. In rodents, but not humans, misoprostol has demonstrated some efficacy in preventing corticosteroid-induced GI tract bleeding.[48,51] To date, no studies have specifically evaluated the role of misoprostol on corticosteroid-induced GI damage in small animals.

ANTACIDS

Antacids have been used for centuries and were the mainstay treatment of acid–peptic disorders until the introduction of H_2-RAs and PPIs. Antacids are weak bases that transiently neutralize gastric HCl in the gastric lumen.[1,3,4,87] Although their principal mechanism of

> *Of all the available GI protectants, PPIs provide superior control of intragastric pH and the greatest efficacy in treating ulcers.*

action is reduction of gastric acidity, they may also promote mucosal defense mechanisms by stimulating mucosal PG production, decreasing pepsin activity, and binding to bile acids in the stomach.[4,51,87]

Antacids vary in the cations and anions they contain, each with different buffering capacity and unique side effects. Common cations of antacids include aluminum, calcium, magnesium, and sodium. Aluminum- or magnesium-containing antacids are the most efficacious.[1] Antacids containing magnesium hydroxide or aluminum hydroxide neutralize hydrogen chloride, forming magnesium chloride or aluminum chloride and water. Aluminum-containing antacids have the added benefit of inactivating pepsin, binding bile acids, and inducing local PG synthesis.[1,10,99] The most common side effects of aluminum- and magnesium-containing antacids are constipation and diarrhea, respectively. Therefore, these compounds are commonly administered together in proprietary formulations to minimize the impact on bowel function. Both magnesium and aluminum are absorbed and excreted by the kidneys; therefore, patients with renal insufficiency should not be given these agents on a long-term basis.[4] A possible sequela to prolonged use of aluminum-containing antacids is hypophosphatemia due to interaction with dietary phosphorus, resulting in reduced intestinal absorption.

Sodium- and calcium-containing antacids, although equally efficacious, can cause more side effects than do other antacids. $NaHCO_3$ reacts rapidly with HCl, pro-

for use in small animals.[87] Although antacids have been shown to be as effective as H_2-RAs in reducing gastric acidity, their duration of action is only 2 to 3 hours.[1,10] Therefore, they must be administered at least six times per day for maximum therapeutic benefit. Noncompliance with the frequent dosing regimen required with antacid use may result in increased total daily acid secretion or "acid rebound," which may exacerbate the initial condition.[3,87] Acid rebound occurs because of loss of the normal inhibitory influence of acid pH on gastrin release.[1] The resultant hypergastrinemia can stimulate acid secretion when the antacid effects are gone. Hypergastrinemia also occurs with H_2-RA and PPI use, but their longer duration of action leaves little time for hypergastrinemia to stimulate acid secretion.[3] Because antacids increase intragastric pH, they may interfere with the rate of dissolution, absorption, and bioavailability of concurrently administered drugs (e.g., digoxin, tetracyclines, fluoroquinolones, H_2-RAs) and iron supplements.[1,4,87] In general, concurrent administration of antacids and other drugs should be avoided.[1,10]

BISMUTH SUBSALICYLATE

Bismuth subsalicylate has several beneficial actions in the GI tract. In the stomach, it dissociates into bismuth and salicylate. Bismuth absorbs toxins and coats ulcers and erosions, creating a protective layer against acid and pepcin.[4] It may also stimulate PG, mucus, and bicarbonate secretion.[4,51] Bismuth has mild antimicrobial actions

Because of compliance issues, antacids are rarely the drug of choice to treat ulcer disease in dogs.

ducing carbon dioxide (CO_2) and sodium chloride. CO_2 formation results in gastric distention and belching.[4] Unreacted bicarbonate can be absorbed systemically, leading to metabolic alkalosis. This complication is more likely to occur when $NaHCO_3$ is given in high doses or to patients with renal insufficiency.[4] Systemic absorption of sodium can exacerbate fluid retention in patients with heart failure, hypertension, and renal insufficiency. Because of such potentially serious sequelae, the use of $NaHCO_3$ as an antacid should be avoided.[1] Calcium carbonate is less soluble than $NaHCO_3$ and reacts more slowly with HCl to form CO_2 and calcium chloride but can cause gastric distention and metabolic alkalosis.[4]

The use of antacids in veterinary medicine has significant limitations.[87] No specific doses have been defined

and binds enterotoxins, accounting for much of its benefit in treating diarrhea.[1,4] The salicylate component has an inhibitory effect on intestinal PGs and chloride secretion, thereby decreasing intestinal secretions and stool frequency.[1,4,51] Bismuth subsalicylate is also used in combination therapy for *Helicobacter* infection.[100–103]

In humans, bismuth is minimally absorbed, with over 99% of the compound excreted in the feces.[4] Conversely, salicylate is rapidly absorbed and undergoes hepatic metabolism followed by renal excretion.[1,4] High doses of bismuth subsalicylate may lead to salicylate toxicosis in humans and likely dogs.[4] The drug should be used only for limited periods of time and should be avoided in patients with renal disease.[4] Bismuth subsalicylate may cause blackening of the feces, which should not be con-

fused with GI bleeding.[1,4] It is also notable that the compound is radiopaque and may confuse radiographic studies of the GI tract.[1]

SUMMARY

GI ulcers are a serious sequela to a number of clinically important disease states in companion animals and can be associated with the use of NSAIDs and corticosteroids. Therefore, gastroprotectants are widely used in companion animals. Despite this, there is little information on the pharmacokinetics and pharmacodynamics of these drugs in veterinary patients. Clinical experience suggests that H$_2$-RAs, PPIs, sucralfate, and misoprostol are well tolerated in veterinary patients, and some limited prospective studies have suggested that they are efficacious in preventing GI ulceration. If we rely on information from humans and animal models, some generalizations on the use of gastroprotectants can be made. H$_2$-RAs are effective in healing uncomplicated ulcers and in preventing NSAID-induced duodenal ulcers. However, PPI use results in superior control of intragastric pH and is thus more effective in both preventing and treating ulcers, especially when NSAID use is continued. Sucralfate use is most appropriate in the treatment rather than prevention of ulcers and may be better in the treatment of duodenal ulcers. Misoprostol is primarily indicated in the prevention of NSAID-induced ulcers and is less effective in treating existing ulcers. Because of compliance issues, antacids are rarely the drug of choice to treat ulcer disease in dogs. Bismuth subsalicylate, although primarily indicated to control secretory diarrhea, can be used as one component in treating *Helicobacter* infection or mild inflammatory gastritis. More veterinary studies are needed to further evaluate the efficacy and appropriate use of gastroprotectants in dogs.

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ARTICLE #2 CE TEST CE

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1. **Which H₂-RA is the most potent and requires the least frequent administration?**
   a. famotidine
   b. cimetidine
   c. ranitidine
   d. nizatidine

2. **Which drug reportedly has antioxidant properties?**
   a. omeprazole
   b. misoprostol
   c. sucralfate
   d. anticholinergics

3. **Which statement regarding omeprazole is incorrect?**
   a. It is supplied in enteric-coated capsules because it is unstable in acidic environments.
   b. It inhibits hepatic cytochrome P-450 enzymes to an extent similar to that of cimetidine.
   c. It has been effectively administered as a suspension with bicarbonate.
   d. Its long-term use is strongly associated with significant bacterial overgrowth.

4. Which statement regarding PPIs is incorrect?
  a. Pantoprazole and lansoprazole are available in intravenous formulations.
  b. It takes 3 to 5 days for maximal inhibition of gastric acid production with oral PPIs.
  c. PPIs are effective in healing ulcers only when NSAID use is discontinued.
  d. PPIs are converted within the parietal cell to an active form, a thiophilic sulfonamide.

5. Which gastroprotectant can cause blackening of the stool?
  a. famotidine
  b. bismuth subsalicylate
  c. misoprostol
  d. omeprazole

6. Which statement regarding antacids is correct?
  a. Because their duration of action is 8 to 12 hours, they can be given two or three times per day.
  b. The side effects of aluminum- and magnesium-containing antacids are diarrhea and constipation, respectively.
  c. Antacids decrease gastric acidity via inhibition of gastric histamine receptors.
  d. Both sodium- and calcium-containing antacids can cause metabolic alkalosis.

7. Which GI protectant has been associated with diarrhea, abdominal discomfort, and nausea?
  a. cimetidine
  b. sucralfate
  c. misoprostol
  d. antacids

8. Which statement regarding sucralfate is correct?
  a. It may interfere with absorption of concurrently administered drugs.
  b. The most common and often limiting side effect is diarrhea.
  c. Because it is renally excreted, the dose should be reduced in patients with renal disease.
  d. Because it is effective only at an acidic pH, it should not be used with concurrent antisecretory drugs.

9. Which H_2-RA inhibits the hepatic cytochrome P-450 system to the greatest extent?
  a. famotidine
  b. cimetidine
  c. ranitidine
  d. nizatidine

10. Which H_2-RAs have a prokinetic effect?
  a. ranitidine and famotidine
  b. famotidine and cimetidine
  c. nizatidine and cimetidine
  d. ranitidine and nizatidine