Gastrointestinal ulceration and erosion (GUE) is an important problem in dogs but is less common in cats. Stress (i.e., an event causing substantial hypoperfusion or anoxia of the gastric mucosa) and drug therapy (especially with nonsteroidal antiinflammatory drugs [NSAIDs] and dexamethasone) are especially common causes of GUE in dogs. Prednisolone at commonly administered dosages is rarely ulcerogenic unless there is concurrent gastric hypoxia or hypoperfusion, severe spinal disease, or concurrent use of NSAIDs. Stress ulceration may be due to hypotensive shock, systemic inflammatory response syndrome, severe life-threatening illness, or extreme exertion. Marked hyperacidity (e.g., gastrinoma, mast cell tumor) may cause GUE but more commonly causes duodenal lesions. Hepatic failure, tumors, and, to a lesser extent, foreign bodies may also cause GUE.

Gastrointestinal (GI) protectants are primarily indicated to heal existing gastric ulcers and erosions. Removing the cause of the ulceration or erosion markedly enhances efficacy, as does maintaining GI perfusion. Protectants are often poorly effective at preventing ulceration when the cause (e.g., NSAID use, poor gastric mucosal perfusion) persists. However, when there is a known cause of GUE that cannot be readily alleviated, these drugs are often given in the hope that they will at least retard, if not prevent, ulceration. See Table 161-1 for a list of commonly used GI protectants and dosages.

Proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) prevent GI ulceration caused by certain forms of stress (probably a combination of poor gastric mucosal blood flow, hypoxia, and possibly other factors) in dogs.1 There are no drugs that have shown efficacy in preventing GUE caused by the use of steroids (especially dexamethasone).2-4 Although PPIs are somewhat prophylactic against NSAID-induced GUE, they are not completely effective.5-9 There is no evidence that combination therapy (e.g., an H2RA plus sucralfate) is any more effective than administration of just one drug.

Drugs that decrease gastric acid secretion are not antiinetics (i.e., they have no effect on the medullary vomiting center or the chemoreceptor trigger zone); however, they can have an antisympathetic effect that lessens nausea. They may be used to stimulate appetite or to enhance the efficacy of true antiinetics. When they are used to manage existing ulcers or erosions, evidence of improvement (e.g., less nausea, less bleeding) is expected within 2 to 5 days of beginning therapy, assuming that the initiating cause has been treated or eliminated. If there is no evidence of improvement within that time, endoscopic evaluation and/or surgical removal may be considered.

KEY POINTS

- Histamine-2 receptor antagonists (H2RAs) are competitive inhibitors of gastric acid secretion; they lower gastric acid secretion but do not abolish it. They also diminish pepsin secretion.
- Ranitidine and nizatidine are H2RAs that purportedly have gastric prokinetic activity.
- Cimetidine inhibits hepatic P-450 cytochrome enzyme activity. It can be used therapeutically (e.g., to minimize acetaminophen toxicity) or can cause drug interactions by delaying hepatic metabolism of drugs given concomitantly.
- Proton pump inhibitors are noncompetitive inhibitors of gastric acid secretion. They inhibit gastric acid secretion to a greater extent than H2RAs. It can take 2 to 5 days for them to achieve maximal effectiveness when given orally, but these drugs still have reasonable effectiveness immediately after therapy is begun.
- Sucralfate is an unabsorbed drug that binds to ulcerated or eroded mucosa. It can adsorb other drugs, delaying or inhibiting their absorption.
- Misoprostol is a prostaglandin analog designed to prevent ulceration and erosion due to nonsteroidal antiinflammatory drug (NSAID) use. It is not as effective or reliable in preventing NSAID-induced ulceration in dogs as it is in humans.
- Orally administered antacids used to neutralize gastric acid have a short duration of action and should not be used to manage or prevent ulcers and erosions in veterinary medicine.

HISTAMINE-2 RECEPTOR ANTAGONISTS

The most commonly used H2RAs in dogs and cats are cimetidine, ranitidine, and famotidine. The H2RAs block the histamine receptor on the gastric parietal cell.10-12 They are competitive inhibitors of gastric acid secretion, which means that they do not decrease gastric acid secretion as well as the noncompetitive PPIs. Their maximal effect in decreasing gastric acid secretion occurs almost immediately upon initiation of therapy. Nizatidine and ranitidine reportedly have some gastric prokinetic activity, probably via antiacetylcholinesterase activity. However, one study failed to find ranitidine effective in preventing gastroesophageal reflux in anesthetized dogs.13

Cimetidine and ranitidine are the least potent H2RAs and famotidine the most potent, with nizatidine being intermediate. Famotidine has the longest duration of action. With oral administration, cimetidine absorption is delayed by food, but absorption of ranitidine, nizatidine, and famotidine is not. Famotidine, ranitidine, and cimetidine undergo substantial first-pass hepatic metabolism but nizatidine does not. Nizatidine is the most bioavailable and famotidine the least when administered orally. Cimetidine and ranitidine are metabolized extensively by the liver, but famotidine and nizatidine are excreted almost completely unchanged in the urine. It has been suggested that the dosage of cimetidine and famotidine be reduced in patients with renal failure; however, it is not known how important such a dosage reduction is.

Cimetidine markedly inhibits hepatic P-450 enzymes and has been used therapeutically to lessen the severity of acetaminophen intoxication. However, cimetidine also decreases metabolism of theophylline, lidocaine, metronidazole, and many other drugs, which results in higher blood levels that can cause toxicity in some cases. Ranitidine has less effect on these enzymes, and famotidine and nizatidine have almost no such effect. Cimetidine also decreases hepatic blood flow by about 20%.
A new H₂RA, lafutidine, seems unique in that it has additional mechanisms of action (i.e., nitric oxide–mediated and histamine-independent mechanisms). It has a mucosa-protective action that is mediated by capsaicin-sensitive sensory nerves. In one study it was more effective than lansoprazole in inhibiting gastric acid secretion. It also appears to have mild intestinal protective activity.

Adverse effects are uncommon with H₂RAs, with cimetidine, ranitidine, and famotidine (with the exception of bocytopenia in people, which has prompted some to recommend that these drugs not be used in people with a history of aspirin-induced bocytopenia). Famotidine administration can be associated with thrombocytopenia and anemia in uremic cats, but this effect could not be reproduced experimentally. Famotidine administration can be associated with thrombocytopenia in people, which has prompted some to recommend that it not be used in coagulopathic patients. Famotidine administration causes only transient increases in serum gastrin concentrations, which is important to recognize when testing for gastrinomas.

### PROTON PUMP INHIBITORS

Omeprazole is the PPI that has been most commonly used in veterinary medicine; there is more limited experience with lansoprazole, pantoprazole, esomeprazole, and dexlansoprazole. In people, lansoprazole has greater bioavailability than omeprazole (80% to 85% vs. 30% to 40%, respectively). Lansoprazole, esomeprazole, and pantoprazole can be given intravenously, an advantage in vomiting patients. Dexlansoprazole is administered orally and is formulated in a dual delayed-release system that produces the longest duration of effect of any PPI; it can be given with food.

The PPI drugs irreversibly inhibit hydrogen-potassium adenosine triphosphatase on the luminal side of the parietal cell, thus stopping secretion of hydrogen ions into the gastric lumen. Omeprazole (which is actually a prodrug) is susceptible to destruction by gastric acid, so it is administered as enteric-coated granules that are absorbed in the duodenum. Absorption is diminished by food; therefore this drug should be given on an empty stomach. Once absorbed, omeprazole undergoes first-pass hepatic metabolism, and the rest is selectively sequestered in the acidic environment of the parietal cells, where it is transformed to the active drug. Therefore it is best to administer omeprazole about 1 hour before feeding so as to maximize the acidity of the parietal cell and thereby increase the amount of omeprazole sequestered there.

Because of this complex pharmacologic pathway, it usually takes 2 to 5 days before maximal acid suppression from omeprazole occurs. However, the PPIs are more effective than the H₂RAs; in fact, the immediate effects of omeprazole were superior to those of high-dose famotidine when sedled dogs were treated. Furthermore, suppression of gastric acid secretion continues for a few days after cessation of PPI therapy because of the irreversible inhibition of the proton pump enzyme.

Historically, H₂RAs were typically administered to patients with uncomplicated GUE first and a PPI used only if the initial therapy failed; however, PPIs are increasingly becoming first-line therapy due to their superior efficacy in lessening gastric acid secretion. Animals with severe esophagitis or duodenal ulceration due to paraneoplastic hyperacidity (e.g., mast cell tumors or gastrinomas) generally should be treated with PPIs as first-line therapy. PPIs are relatively effective in lessening gastric acid reflux during anesthesia, but reflux still occurs in some dogs. In people, PPIs are superior to misoprostol for preventing duodenal but not gastric lesions due to NSAIDs. Adverse effects associated with PPIs are rare. Toxicologic studies have shown that pantoprazole is relatively safe in dogs. Diarrhea is reported in humans and dogs taking various PPIs. Omeprazole and esomeprazole inhibit hepatic P-450 enzymes. Omeprazole has thus decreased antiplatelet activity by clopidogrel and decreased clearance of diazepam in people (pantoprazole and lansoprazole appear to have fewer such interactions). Hypomagnesemia has been suggested as an adverse effect in people, and elevated liver enzyme levels have been

### Table 161-1 | Selected Gastrointestinal Protectants Used in Dogs and Cats

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Dosage</th>
<th>Special Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td>H₂-receptor antagonist</td>
<td>5-10 mg/kg IV, IM, SC, PO q6-8h</td>
<td>Potent inhibitor of hepatic P-450 enzymes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Can affect metabolism of toxins or other drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Decreases hepatic blood flow</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Food delays absorption</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>H₂-receptor antagonist</td>
<td>0.5-2 mg/kg IV or 1-4 mg/kg PO q8-12h</td>
<td>Has prokinetic activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5 mg/kg IV or 3.5 mg/kg PO q8-12h daily</td>
<td>Has minimal effect on hepatic enzyme function</td>
</tr>
<tr>
<td>Famotidine</td>
<td>H₂-receptor antagonist</td>
<td>0.5-1 mg/kg IV, IM, SC, PO q12-24h</td>
<td>Longest acting and most potent H₂-receptor antagonist</td>
</tr>
<tr>
<td>Nizatidine</td>
<td>H₂-receptor antagonist</td>
<td>2.5-5 mg/kg PO q24h</td>
<td>Exclusively eliminated by the kidneys</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>Proton pump inhibitor</td>
<td>1.0-2.0 mg/kg PO q12-24h</td>
<td>Inhibits hepatic P-450 enzymes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>May cause elevations in liver enzymes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sometimes causes diarrhea</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>Proton pump inhibitor</td>
<td>0.5-1 mg/kg IV q24h*</td>
<td>Anecdotal</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>Proton pump inhibitor</td>
<td>1 mg/kg IV q24h*</td>
<td>Anecdotal</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>Proton pump inhibitor</td>
<td>1 mg/kg IV q24h*</td>
<td>Anecdotal</td>
</tr>
<tr>
<td>Misoprostol</td>
<td>Prostaglandin analog</td>
<td>2-5 mcg/kg PO q6-12h</td>
<td>Can cause abortion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Often causes transient diarrhea</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>Local-acting barrier</td>
<td>0.25-1 g PO q6-12h</td>
<td>Adsorbs many other drugs, slowing their absorption</td>
</tr>
</tbody>
</table>

H₂, Histamine-2; IM, intramuscularly; IV, intravenously; PO, per os; SC, subcutaneously.

*Extrapolated dosage.
noted. A wide range of hypersensitivity reactions to PPIs (e.g., anaphylaxis, urticaria, angioedema, cutaneous vasculitis, cytopenias, interstitial nephritis) have been reported in people, but they tend to be rare.\textsuperscript{28} A markedly increased gastric pH can affect absorption of some drugs such as ketoconazole and digoxin. Currently there is interest in the antineoplastic\textsuperscript{29} and antiprotozoal activities\textsuperscript{30} of PPIs (pantoprazole and rabeprazole have strong activity against \textit{Giardia} and \textit{Trichomonas in vitro}), but few data are currently available on the clinical relevance of these findings.

**SUCCRALFATE**

Sucralfate is the octasulfate of sucrose combined with aluminum hydroxide.\textsuperscript{31} It is a locally acting drug that is administered orally as a tablet or a suspension. It becomes viscous and binds tightly to epithelial cells in the acidic environment of the stomach, especially to the base of erosions and ulcers, where it may remain for 6 hours. It serves as a physical barrier while adhered to the ulcer or erosion and thus protects the ulcer from pepsin and bile acids; it also stimulates local production of prostaglandins and binding to epidermal growth factor (which favors mucosal repair). Sucralfate has almost no adverse effects besides sometimes causing constipation, which can be useful in patients with diarrhea. Sucralfate can adsorb other drugs (e.g., enrofloxacin), which slows their systemic absorption. It should be given before antacid therapy to maximize efficacy and theoretically should not be given with enteral feedings because it may bind the fat-soluble vitamins. Sucralfate can only be given orally, which limits its usefulness in vomiting patients.

**PROSTAGLANDIN ANALOGS**

Misoprostol is a prostaglandin E\textsubscript{1} analog with both antacid and mucosal protective properties (it stimulates secretion of mucus and bicarbonate and increases gastric mucosal blood flow).\textsuperscript{32} The antisecretory effect on gastric acid is probably more important. Misoprostol acts directly on parietal cells to inhibit both nocturnal acid secretion and secretions in response to food, pentagastrin, and histamine. The drug is absorbed rapidly (in the absence of food) and undergoes first-pass metabolism in the liver to the active form. Misoprostol has a short half-life and must be given two to three times daily.

This drug was developed to prevent ulceration caused by NSAIDs. Its greater cost, need for frequent administration, and higher rate of adverse effects usually mean that it is administered only when other therapies for GUE have failed or when patients have difficulty tolerating NSAIDs that they must receive to maintain a good quality of life. It is not as clearly effective in protecting dogs receiving NSAIDs as has been reported in people. Adverse effects include diarrhea and uterine contraction (which can result in abortion in pregnant females). Diarrhea often subsides after 2 to 5 days.

**ANTACIDS**

Numerous drugs are administered orally to neutralize gastric acid. These drugs are generally not appropriate for treating or preventing GUE because they usually have a relatively short half-life compared with H\textsubscript{2}RAs and PPIs. Furthermore, each set of antacid drugs tends to have its own idiosyncrasies. For example, aluminum and magnesium compounds delay or prevent absorption of other drugs.

**FUTURE DRUG THERAPY**

Troxipide is a new gastric cytoprotective drug.\textsuperscript{33} It does not appear to affect gastric acid secretion but was more effective than ranitidine in a preclinical study in people with spontaneous gastritis. Data for dogs are lacking. Another new gastroprotectant that has been studied in people is irsogladine.\textsuperscript{34} It seems to protect the gastric mucosa through endogenous nitric oxide and increased cyclic adenosine monophosphate. Irsogladine appears to prevent reduced mucosal blood flow, suppress formation of reactive oxygen radicals, and enhance gap junctional intracellular communication. The drug is currently available only in Japan.

**POTENTIAL COMPLICATIONS OF INCREASED GASTRIC pH**

Gastric acid is a major defense mechanism that prevents many infectious agents from gaining access to the intestinal tract since few bacteria can withstand the low pH of the stomach. Hence, there is concern that a prolonged increase in gastric pH may result in complications. In critically ill humans,\textsuperscript{35,36} it has been hypothesized that patients receiving long-term acid-suppression therapy are at increased risk of bacterial pneumonia following an aspiration event. However, studies have failed to find any consistent risk. Similarly, human patients in such settings have not been found to have an increased risk of gastric carcinoid formation or rebound hyperacidity. There is an increased risk of \textit{Clostridium difficile} infection in some populations, but since dogs and cats are rarely adversely affected by this bacterium, the risk to them appears minimal.

**REFERENCES**