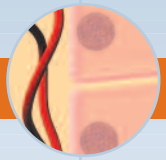

Disruption of the Gastric Mucosal Barrier in Dogs*

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ABSTRACT: The gastric mucosal barrier is a complex of interacting physical and chemical defense mechanisms that protect the gastric mucosa from erosions and ulcers. Several conditions can disrupt the gastric mucosal barrier, leading to gastric mucosal damage (e.g., gastritis, gastric erosions, ulcers). Causative factors include the use of NSAIDs or glucocorticoids, hepatic or renal disease, hypoadrenocorticism, shock, spinal cord disease, primary gastrointestinal disease, and neoplasia. This article reviews the normal physiology of the gastric mucosal barrier and the pathophysiologic factors that disrupt it.

The gastroduodenal lumen is a harsh environment composed of acid, pepsin, bile acids, and proteolytic enzymes. Although high luminal hydrochloric acid concentrations are obvious perpetrators of gastric epithelial damage, bile acids and proteolytic enzymes can injure the epithelial cells by degradation and dissolution of mucosal membrane lipids and induction of an inflammatory response and mucosal cell apoptosis.[1–3]

PHYSIOLOGY

Acid secretion by gastric parietal cells is modulated by cholinergic neurotransmission, endocrine secretion of the peptide hormone gastrin, and paracrine secretion of histamine and prostaglandins (PGs).[4–6] On the basolateral membrane of the parietal cell are receptors for three substances that stimulate acid secretion: gastrin, acetylcholine (muscarinic [M3] receptor), and histamine (H_2)[6–8] (Figure 1). These three primary secretogogues act synergistically to promote gastric acid secretion.[9] Gastrin is produced in the G cells of the gastric antrum, and its secretion is stimulated by ingestion of food and increased gastric luminal pH.[6–8,10] Acetylcholine is released from cholinergic nerve fibers in response to cephalic influences such as the site, smell, and taste of food and by gastric influences such as gastric distention.[6,8,10] When gastrin or acetylcholine bind to receptors on the basolateral surface of the parietal cell, they increase cytosolic calcium, which in turn stimulates protein kinase C, resulting in activation of the hydrogen ion (H^+)–potassium ion (K^+) ATPase pump on the apical surface.[5–7,9] Endocrine cells called *enterochromaffin-like cells* are in close proximity to parietal cells and have receptors for gastrin and acetylcholine as well as serve as a major source of histamine secretion.[5–7,10] Histamine, the most potent stimulator of acid secretion, is released from enterochromaffin-like cells and acts in a paracrine fashion to activate H_2 receptors on parietal cells. This results in activation of adenylyl cyclase, which

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*A companion article on the use of gastroprotectants starts on page 358.

increases intracellular cAMP.[4,7,9] cAMP activates protein kinase A to stimulate acid secretion by the H^+–K^+ ATPase pump.[4,7,8] At rest, H^+–K^+ ATPase remains intracellular within tubulovesicular structures in parietal cells. When H^+–K^+ ATPase is activated, these structures fuse with the apical membrane, thus inserting proton pumps into the membrane, where they exchange cytosolic hydrogen ions for luminal potassium ions.[4,7,8,11]

GASTRIC MUCOSAL BARRIER

The gastrointestinal (GI) mucosa uses several physical and chemical defense mechanisms to protect itself from the harsh luminal environment. Gastric mucosal cytoprotection is mediated by seven major factors that make up the gastric mucosal barrier: a hydrophobic mucus layer, mucosal bicarbonate secretion, epidermal growth factor, mucosal cell hydrophobicity, a high rate of mucosal blood flow, rapid epithelial cell turnover, and PG production[6,9,12] (Figure 2). The most superficial component of the gastric mucosal barrier is the mucus layer secreted by neck cells of the gastric glands and surface mucosal cells.[6,11,12] This mucus layer forms a water-insoluble, stable glycoprotein gel that adheres to mucosal surfaces and acts as a lubricant to prevent mechanical damage.[6,9] More important, this layer traps bicarbonate secreted by mucous neck cells, maintaining a gastric epithelial mucosal pH of 4 to 6 in contrast to a luminal pH of 1 to 2.[6,7,9,12,13] The mucus–bicarbonate layer, along with gastric epithelial cell tight junctions, protects the gastric epithelium from diffusion of free hydrogen ions from the gastric lumen back into the mucosal cells (i.e., back diffusion).[4,6,7,12] Salivary and gastric epidermal growth factor are found within the mucus layer and are thought to play an important role in both preventing and healing gastric mucosal damage.[14–17] Epidermal growth factor is believed to increase secretion of mucin glycoprotein, scavenge oxygen metabolites, and increase mucosal blood flow.[14–17]

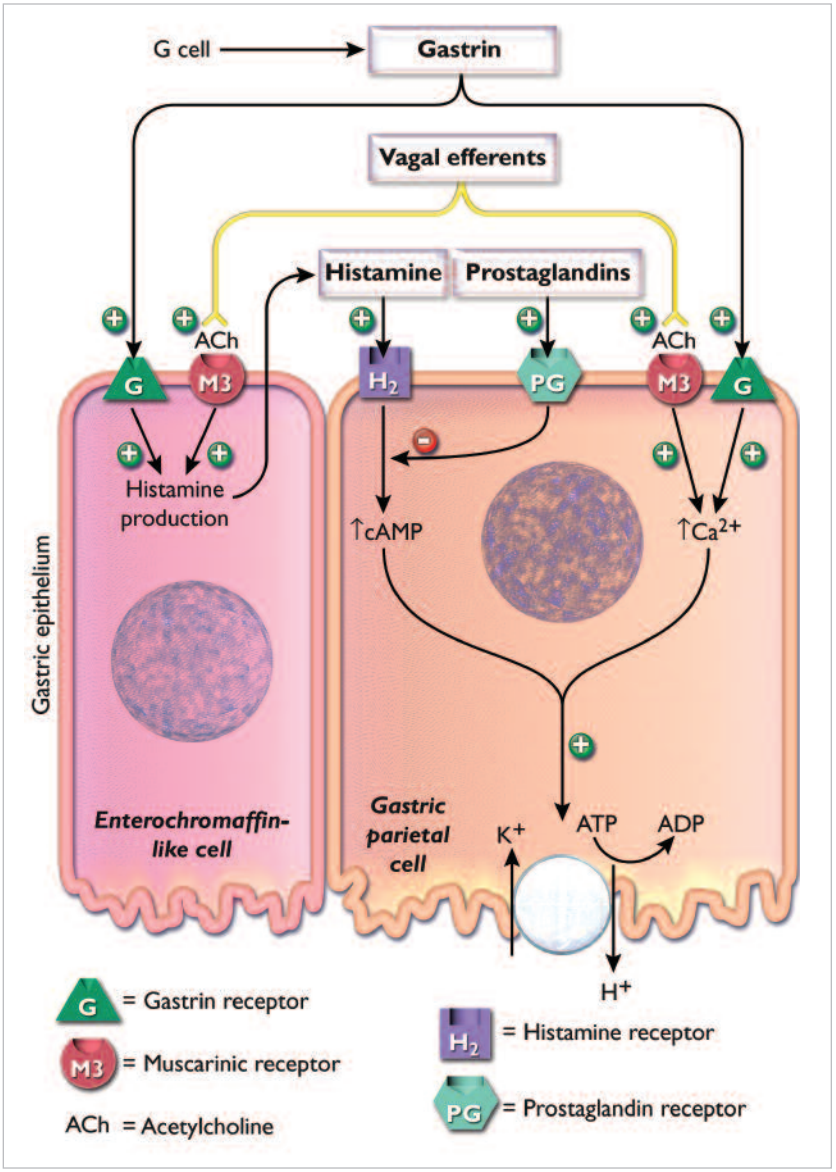

Illustration by Felecia Paras

Figure 1. Gastric acid secretion in the stomach. Gastrin is produced in the G cells of the gastric antrum. Enterochromaffin-like cells have receptors for gastrin and acetylcholine and are the major source of histamine secretion. By binding to receptors on the surface of the parietal cell, histamine increases cAMP, whereas gastrin and acetylcholine increase calcium, resulting in stimulation of acid secretion from the apical H^+–K^+ ATPase.

The next component of the gastric mucosal barrier is mucosal hydrophobicity. Cell membranes lining the stomach wall contain phospholipids, which, by virtue of their hydrophobicity, repel water-soluble luminal contents such as hydrogen and thereby prevent acid and pepsin back diffusion. The fourth defense mechanism is the high rate of mucosal blood flow supplied by a dense network of submucosal capillaries. This mucosal blood flow, which is reg-

Figure 2. Gastric mucosal barrier.

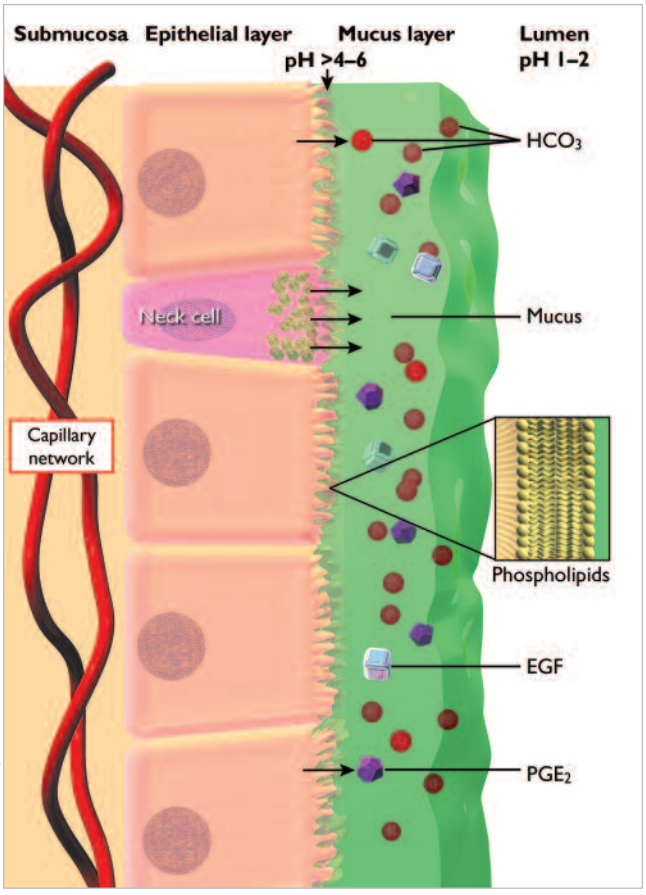

Illustration by Felecia Paras

Gastric mucosal cytoprotection is mediated by seven major factors that make up the gastric mucosal barrier: a hydrophobic mucus layer, mucosal bicarbonate (HCO_3) secretion, epidermal growth factor (EGF), mucosal cell hydrophobic phospholipids (PL), a high rate of mucosal blood flow, rapid epithelial cell turnover (adjacent image), and PG production (PGE_2).

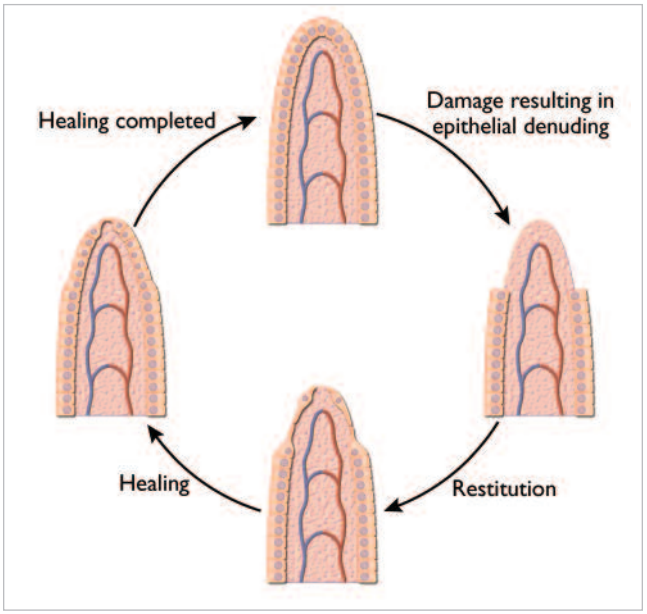

Illustration by Felecia Paras

Epithelial restitution is a process by which migrating epithelial cells extend lamellipodia over a region of damaged mucosa to rapidly heal the defect.

ulated largely by PGs, supplies oxygen and vital nutrients to the surface cells and is necessary to meet the high metabolic demand for production of gastric secretory products and cell renewal.[7,9,12] Gastric mucosal blood flow is also vital in the disposal or buffering of back-diffusing hydrogen ions by carrying bicarbonate to the mucosal surface.[6,18]

Another component of the gastric mucosal barrier is the ability of the gastric epithelium to continually and quickly repair injured cells; this is known as *epithelial restitution*.[6,9,12,19] Epithelial restitution involves a process by which migrating epithelial cells extend large lamellipodia over the damaged mucosa to quickly (<1 hour) seal small erosions and reestablish an intact epithelium, thereby preventing further damage to the mucosa.[6,7,12,19,20] (Figure 2).

The last and one of the most important elements of the gastric mucosal barrier is PGs, which are produced by gastric mucosal cells. PGs, particularly of the E and I group, protect the mucosa by increasing mucus and bicarbonate secretion, enhancing mucosal blood flow, stimulating epithelial cell growth, and inhibiting acid secretion.[7,6,12,21]

PATHOPHYSIOLOGY

A multitude of diseases and drugs can disrupt the integrity of the gastroduodenal mucosa and overwhelm mucosal protective mechanisms. When the integrity of the mucosal barrier is compromised, a cascade of pathologic events follows, contributing to further damage of the mucosal layer. First, the rate of back diffusion of gastric acid and pepsin increases, leading to inflammation and hemorrhage.[22,23] Endothelial and inflammatory cells, including neutrophils and mast cells, become activated and release histamine, leukotrienes, platelet-activating factor, proteolytic enzymes, and free radicals.[22] Histamine release causes further acid secretion, whereas other mediators promote vasodilation, venoconstriction, increased capillary permeability, edema, translocation of inflammatory cells, and capillary plugging. These events exacerbate the initial mucosal damage by reducing blood flow, leading to ischemia, impaired cell renewal, and reduced mucus and PG secretion.[22,24]

Causes of Canine Gastrointestinal Ulceration[12,22,25,26]

Drugs
- NSAIDs
- Corticosteroids

Metabolic disease
- Hepatic disease
- Renal disease
- Hypoadrenocorticism

Hypotension/ischemia
- Circulatory shock
- Thrombosis
- Anesthesia and/or surgery
- Volvulus

Neurologic disease
- Intervertebral disk disease

Trauma
- Foreign body
- Exercise-induced

Inflammatory disease
- Inflammatory bowel disease
- Pancreatitis

Infectious disease
- Bacterial enteritis
- Septic shock

Toxins
- Lead
- Corrosive compounds

Neoplasia
- Lymphosarcoma
- Gastric adenocarcinoma

Paraneoplastic
- Mast cell tumor
- Gastrinoma

CAUSES

A number of predisposing causes of gastric or duodenal ulcerative disease in dogs have been identified (see box on this page).[12,22,25,26] In a retrospective study[27] of 43 dogs with gastroduodenal ulceration, hepatic disease and NSAID use were the two most common factors associated with ulceration. Of the 23 dogs with a single predisposing cause, five had hepatic disease, four had received NSAID and/or corticosteroid therapy, and five had infiltrative (i.e., eosinophilic or plasmacytic/lymphocytic) gastroenteritis.[27] Eleven dogs, 10 of which had NSAID or corticosteroid therapy as one of the factors, had two predisposing factors.[27] Many dogs had three or more contributing problems, including disseminated intravascular coagulation (DIC), septicemia, major surgery, and severe trauma.[27] In a separate retrospective study[28] of 22 dogs with ulcerative disease, 16 showed marked liver pathology, three had mast cell neoplasia, and two had chronic renal failure. In a study[29] of 23 dogs and cats with spontaneous gastroduodenal perforation, four had hepatic disease, seven had received NSAID treatment, and nine had a history of corticosteroid administration.

NSAIDs

NSAIDs are one of the most common causes of GI ulceration in humans and dogs.[12] In human NSAID users, the prevalence of endoscopically detectable gastroduodenal erosions ranges from 14% to 60%, whereas the incidence of ulcers is 10% to 30%.[30–34] The incidence of GI complications associated with NSAID use in dogs is unknown; however, multiple studies[34–37] have illustrated gastric lesions in nearly all dogs administered aspirin. It has been estimated that, of the over 13 million human NSAID users in the United States, more than 100,000 are hospitalized and more than 16,500 die annually from NSAID-induced GI events.[33,38] Established risk factors in the development of NSAID ulcers in humans include advanced age, a history of a gastroduodenal ulceration or GI bleeding, concomitant use of corticosteroids or anticoagulants, administration of multiple or high-dose NSAIDs, and the presence of a serious systemic disorder.[38,39] In many studies[31] of human NSAID users, GI mucosal injury and the presence of clinical signs do not correlate well. In one report,[31] 58% of NSAID patients who experienced severe complications presented without warning symptoms. This problem may be exaggerated in veterinary medicine because many owners may not notice signs of mild GI disease in their pets.

Mucosal damage caused by NSAIDs is twofold: a direct topical effect on the gastric mucosa and a systemic effect mediated by cyclooxygenase (COX) inhibition of gastroprotective PGs.[12,30,32,34] Mucosal injury is initiated topically by the weakly acidic and lipid-soluble properties of aspirin and many other NSAIDs.[38,40] These weak acids remain in their nonionized lipophilic form in the acidic gastric lumen and freely diffuse across plasma membranes into surface epithelial cells. At cellular pH, they dissociate into the ionized form, releasing hydrogen ions that are trapped within the cell, leading to disruption of cellular function.[34,38,40,41] NSAIDs can also cause topical mucosal damage by decreasing the hydrophobicity of the mucus layer, allowing gastric acid and pepsin to injure the surface epithelium via back diffusion.[32,38,40] This effect of NSAIDs is partly due to a direct toxic effect on mucus-producing cells via uncoupling of mitochondrial oxidative phosphorylation.[41]

The second and more important component to NSAID-induced ulceration is the systemic effect through inhibition of COX-mediated PG (PGE_2, PGI_2) synthesis. This mechanism is not only responsible for the desired antiinflammatory action of NSAIDs but also central to the development of side effects via inhibition of PG-dependent gastroprotective mechanisms.[32,41,42] Inhibition of COX and therefore PG production leads to decreased mucosal blood flow, epithelial mucus production, bicarbonate secretion, and epithelial cell turnover.[38,40]

The two forms of COX, designated COX-1 and

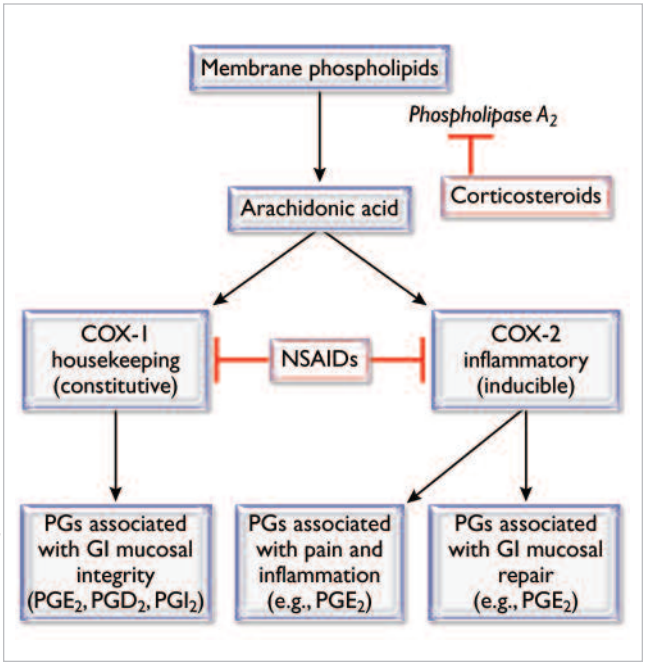

Illustration by Felecia Paras

Figure 3. PG synthesis through the classic COX pathway. NSAIDs block the pathway via inhibition of COX-1 and COX-2, whereas corticosteroids inhibit phospholipase A_2.

COX-2, play different roles in both GI tract protection and damage (Figure 3). COX-1 is constitutively expressed in normal GI tissue and is thought to be responsible for production of physiologic PGs (PGE_2, PGI_2, PGD_2) that have a protective effect on the gastric mucosa.[20,32,41,42] In contrast, COX-2, the inducible form, is expressed in many inflammatory cells and is implicated in the pathophysiologic production of PGs (e.g., PGE_2) that cause pain and inflammation.[20,32,33,40,43] Based on this traditional view of COX action, the clinical use of COX-2–specific inhibitors has gained much popularity in both human and veterinary medicine as a strategy to prevent NSAID-induced GI injury. However, emerging evidence suggests that the classic view of COX action described here may not be as simplistic as originally thought.

The classic hypothesis that NSAID-induced COX-1 inhibition is responsible for GI side effects has downplayed the role of COX-2 expression in the GI mucosa and its participation in the maintenance of gastric cytoprotection.[32,40,44] Although COX-1 is the predominant isoenzyme in normal gastric mucosa, increasing evidence shows that COX-2 is constitutively expressed in the GI tract and that its expression can be induced in damaged GI mucosa.[32] Studies[20,32,40,44] have demonstrated upregulation of COX-2 expression in the margins of healing gastric ulcers. Other studies[32] support the observation that selective inhibition of COX-1 alone may not be ulcerogenic and that simultaneous blockade of both COX-1 and COX-2 is necessary to induce lesions. Furthermore, selective COX-2 inhibitors have been shown to markedly aggravate gastric mucosal damage induced by ischemia–reperfusion.[20,32] It appears that COX-2 expression represents a second line of defense for the GI mucosa as well as an important mediator of mucosal repair. Thus COX-2 inhibitors may be contraindicated in cases of previously damaged mucosa.[32,44]

However, in multiple human studies[32,33,39,45] of low-risk patients, selective COX-2 inhibitors cause fewer GI side effects than do conventional NSAIDs. Results have not been as straightforward in veterinary patients. Multiple canine studies[39,46] have clearly shown a greater incidence of endoscopically visible but clinically silent gastroduodenal mucosal erosions after aspirin administration compared with placebo administration. However, no differences were detected among dogs administered carprofen (COX-2 selective), meloxicam (COX-2 selective), ketoprofen (COX-1 selective), etodolac (COX-1 selective), and a placebo.[39,46–48] In another study[34] evaluating the effects of buffered aspirin, carprofen, and etodolac in healthy dogs, those receiving aspirin had significantly higher lesion scores (hemorrhage, erosions, ulcerations) than those receiving a placebo.[47] However, there was no significant difference in median gastroduodenal lesion scores among dogs receiving a placebo, carprofen, or etodolac.[34] When adverse drug events data from the FDA's Center for Veterinary Medicine were examined, deracoxib (a COX-2–specific NSAID) had significantly more reports of GI effects (e.g., vomiting, melena, abdominal pain, peritonitis, GI perforation, GI ulceration) than did NSAIDs with less COX-2 selectivity.[49] Furthermore, in a recent retrospective study,[50] there were 29 cases of GI tract perforation in dogs receiving deracoxib. However, in this case series, several dogs were given higher-than-approved doses (55%) or had received other NSAIDs or corticosteroids (59%) closely associated with deracoxib.[50] It is clear that there are many unanswered questions in this field and that the role of both COX isoforms is more complex than initially anticipated. More research is needed in this area; meanwhile, caution should be exercised when regarding COX-2–selective inhibitors as "GI safe" drugs.[32]

An important factor complicating evaluation of the clinical safety of COX-2 versus COX-1 inhibition is that the COX-2 or COX-1 selectivity of NSAIDs is deter-

mined in vitro and may inadequately reflect in vivo drug effects at therapeutic doses.[40,41] The in vitro tests used to determine COX inhibition vary significantly among studies, making drug comparisons difficult. For example, with the use of a canine monocyte/macrophage cell line, carprofen was found to be only 1.75 times more active against COX-2 than COX-1, whereas in a separate enzymatic assay, carprofen inhibited canine COX-2 activity 100 times more than COX-1 activity.[51,52] In addition, there are important species differences in COX activity that make extrapolation across species unacceptable. For example, in a study[41] in which canine cell lines were used, carprofen showed high selectivity for COX-2, whereas etodolac and meloxicam were nonselective. This differs from a study[41] using human cell lines in which carprofen showed poor COX-2 selectivity and etodolac and meloxicam were more COX-2 selective.

Although COX inhibition clearly plays a key role in NSAID-induced mucosal injury, other mechanisms of mucosal damage have also been identified. Much attention has recently been focused on the role of neutrophil adherence and neutrophil-derived factors in mucosal injury.[38,53] Margination of circulating neutrophils, mediated by upregulation of adhesion molecules, is an early and critical event in the pathogenesis of NSAID-induced gastropathy.[54,55] Neutrophil adherence in response to NSAIDs may occur as a consequence of inhibition of endothelial PG synthesis; however, the exact mechanism is unclear.[53,56,57] Neutrophil adherence to the vascular endothelium can lead to obstruction of capillaries, resulting in reduction of mucosal blood flow and thereby predisposing the mucosa to injury through ischemia.[32,40,44,53] In rats, the severity of NSAID gastropathy was shown to be markedly reduced in those rendered neutropenic by pretreatment with antineutrophil serum or methotrexate.[32]

Another factor implicated in the pathogenesis of NSAID-induced lesions is lipid peroxidation mediated by release of oxygen-derived free radicals and proteases from activated neutrophils.[53,58,59] Lipid peroxidation and oxidation of critical cellular proteins destroy and damage cell membranes.[53] In experimental models of gastric ulceration in rodents, the degree of gastric mucosal damage induced by NSAIDs has been directly correlated with reactive oxygen species, such as hydroxyl radical, and the degree of lipid peroxidation.[53,59,60] Some of these studies[53,61–63] have also shown that prevention of lipid peroxidation by vitamin E or melatonin can protect the gastric mucosa against NSAID-induced damage. Additional clinical studies are needed to clarify the role of antioxidant therapy in preventing NSAID-induced gastric ulceration.

Lipoxygenase (LOX) inhibitors, such as tepoxalin, are relatively new NSAIDs in veterinary medicine. It is theorized that inhibition of COX enzymes with traditional NSAIDs could result in accumulation of substrates that may be shunted into other arachidonic acid metabolic pathways, such as the 5-LOX pathway.[64] Overproduction of 5-LOX products, such as leukotriene B_4, has been documented in the human gastric mucosa following treatment with NSAIDs.[64,65] Because leukotriene B_4 increases microvascular permeability and is a potent stimulus for chemotaxis, adhesion, and degranulation of neutrophils, it could contribute to gastric mucosal damage.[64,66,67]

Concurrent use of NSAIDs and glucocorticoids significantly increases the risk for GI ulceration and should be avoided.

Tepoxalin inhibits COX-1, COX-2, and LOX activity in dogs with chronic arthritis.[64] Therefore, it could theoretically suppress gastric mucosal injury induced by accumulated leukotriene. In short-term studies[67–69] in laboratory animals, tepoxalin lacked gastric ulcerogenic activity within its antiinflammatory therapeutic range, and pretreatment with tepoxalin was shown to have a preventive effect on gastric mucosal lesions induced by indomethacin.[69] Although these early studies are promising, an overall paucity of information on LOX inhibitors is available in the literature, and there have been no controlled clinical trials to evaluate the efficacy and safety of these drugs in dogs.

Corticosteroids

Corticosteroid use also predisposes the GI mucosa to injury. Although there is a clear clinical association between exogenous administration of corticosteroids and GI hemorrhage and ulceration in dogs, the exact mechanism is still poorly understood.[12,22,24,42,70] In humans, the direct GI toxicity of corticosteroids is less clear; however,

steroids have been shown to strongly potentiate NSAID-induced ulcers.[71–75] Corticosteroids can predispose the GI tract to damage by decreasing mucus production, altering the biochemical structure of mucus, decreasing epithelial cell turnover, and increasing acid output.[22,24,42,70,76] These effects may be partially mediated by inhibition of phospholipase A, resulting in reduced production of cytoprotective PGs.[22,42,70,77] Other deleterious effects of corticosteroids include retardation of healing and promotion of bacterial colonization of ulcers.[12,70,77]

Various canine studies have evaluated the cause-and-effect relationship between corticosteroid use and gastroduodenal ulceration. All dogs undergoing spinal surgery that were given a single dose of methylprednisolone sodium succinate (MPSS; 30 mg/kg) had positive results from fecal occult blood testing within 1 to 6 days after surgery, and 30% had evidence of gross GI tract bleeding.[77] Because spinal cord disease alone can cause GI mucosal injury, it is difficult to determine from this study the degree to which MPSS contributed to GI bleeding. However, in two studies,[24,76] administration of MPSS (30 mg/kg initially, then 15 mg/kg 2 and 6 hours later and q6h for 48 hours) or dexamethasone (2.2 mg/kg q12h for 8 days) alone resulted in the endoscopic appearance of gastric hemorrhage, positive results from fecal occult blood testing, and/or a drop in hematocrit in most dogs.[24,76] Collectively, these studies support the theory that corticosteroids alone can cause GI mucosal injury and hemorrhage.

Concurrent use of corticosteroids and NSAIDs greatly increases the risk for ulceration and should be avoided.[12,22,42] The effect of concurrent administration of meloxicam and dexamethasone on the gastroduodenal mucosa in healthy dogs has been evaluated via endoscopy.[42] Mucosal lesions were present after treatment in both the dexamethasone-only group and dexamethasone with meloxicam group, with the combination treatment group being more severely affected.[42] Because meloxicam is a COX-2–selective NSAID and therefore theoretically safer, other nonspecific NSAIDs would be expected to be even more detrimental when administered concurrently with corticosteroids.

Hepatic Disease

Hepatic disease, both acute and chronic, is frequently identified as a significant predisposing cause of gastric and duodenal ulceration. The pathogenesis is multifactorial and somewhat speculative, including increased gastric acid secretion and derangement in mucosal blood flow.[12,22,78] Increased gastric acid secretion in hepatic disease is partially due to decreased hepatic degradation of gastrin and histamine, resulting in increased blood levels of these secretogogues and thus increased acid secretion.[22,27] Compounding this is an increase in serum bile acid concentration, which stimulates gastrin secretion and can induce apoptosis of gastric epithelial cells.[12,78] Decreased GI mucosal blood flow occurs in chronic liver disease as a result of portal hypertension and thrombosis of gastric vessels.[22,78] In acute liver failure, reduced blood flow may also occur as a result of thrombosis secondary to DIC.[22,78] Mucus production and epithelial cell turnover are secondarily diminished because of poor mucosal blood flow.

Renal Disease

Renal disease predisposes dogs to gastric ulceration. The kidneys play an important role in the elimination of gastrin, with up to 40% of circulating gastrin filtered and excreted by the kidneys.[12,22,23,79] Therefore, decreased clearance of gastrin resulting in hypergastrinemia and increased gastric acid production has been proposed to be a central component in the pathogenesis of ulceration in renal disease.[22,23,27,80] Canine chronic renal disease has been shown to result in hypergastrinemia.[22,79] However, a recent study[80] suggested that gastrin hypersecretion, rather than decreased clearance, may also contribute to gastric ulceration in renal disease. Controversy surrounds the importance of gastric acid hypersecretion in the pathogenesis of uremic gastritis because not all studies can demonstrate gastric hyperacidity in association with uremic gastritis.[22,79,80] Another factor that has been implicated is decreased mucosal blood flow caused by diffuse vascular injury, resulting in compromise of the mucus–gel bicarbonate layer and impaired epithelial tight junctions.[22,79–81] High gastric ammonia levels, resulting from metabolism of increased urea that diffuses from interstitial fluids into the stomach, may contribute to the gastric epithelial damage induced by uremia.[12,22,27,80]

Hypoadrenocorticism

GI ulceration can occur secondary to hypoadrenocorticism.[82,83] Decreased gastric blood flow is the suspected underlying cause.[12,22] In rats, corticosteroid deficiency was shown to promote stress-induced gastric ulceration along with dilation of mucosal microvessels, decreased blood flow velocity in submucosal microvessels, and decreased arterial pressure.[84] Corticosteroid replacement

eliminated these effects, suggesting that the gastroprotective action of endogenous corticosteroids may be provided by maintenance of gastric blood flow.[84] Other studies[85–87] in rats have shown that corticosteroid deficiency induced by adrenalectomy or administration of corticosteroid-receptor antagonists potentiates formation of gastric erosions induced by various ulcerogenic stimuli (e.g., ethanol, aspirin, indomethacin, acetic acid). Corticosterone replacement before the onset of an ulcerogenic stimulus prevented or significantly decreased the erosion-potentiating effect, supporting a gastroprotective action of endogenous physiologic levels of corticosteroids.[85–87]

Stress Ulcers

GI ulceration has been identified as a complication in critically ill humans. Risk factors for upper GI bleeding and ulceration in these patients include hypotension, coagulopathy, sepsis, and respiratory failure requiring ventilation.[27,88,89] Other conditions associated with GI ulcers in critically ill patients include hypoadrenocorticism, shock, surgery, and trauma.[12,22,24,37] In this setting, ulcers are thought to form in response to the stress of critical illness and are often called *stress ulcers*.[22,88] The pathophysiology of stress ulcers remains controversial, although strong evidence suggests that hypoperfusion of the GI mucosa plays a major role.[22] Mucosal blood flow in critically ill patients is reduced by hypovolemia, hypotension, sympathetically mediated vasoconstriction due to high circulating levels of catecholamines, and the release of a variety of vasoactive agents, such as vasopressin and thromboxane.[12,22] Experimental studies[90,91] examining the effect of endotoxin in septic dogs showed a significant decrease in total gastric blood flow, resulting in mucosal ischemia in tissues following *Escherichia coli* infusion. Further mucosal damage is exacerbated by the release of histamine stimulated by catecholamines and stress-induced vagal activity.[22] The GI mucosa in these conditions may be damaged by oxygen-derived free radicals through reperfusion injury when blood returns to ischemic tissue.[22] No studies have specifically evaluated "stress ulceration" in dogs; however, there are multiple reports of GI ulcers in critically ill dogs with various underlying conditions, including sepsis, DIC, and hypoadrenocorticism, and in dogs undergoing major surgery.[27,83,92]

Neurologic Disease

In both human and veterinary medicine, GI hemorrhage and gastroduodenal ulceration have been reported after spinal cord injury.[24,70,76] GI bleeding is a substantial problem in canine neurosurgery patients, with a reported incidence of overt bleeding ranging from 14.8% to 20%.[77] The pathogenesis of ulcers after neurologic trauma is complex and not completely understood. Ulcers may develop in such patients from a combination of the systemic stress of critical illness, trauma, and surgery; hypovolemia and hypotension during neurosurgery; and an imbalance in autonomic innervation.[70,76,77] It is postulated that sympathetic–parasympathetic imbalance caused by spinal cord compression may cause paralytic vagotonia, resulting in hypersecretion of gastric acid and pepsin and bile reflux.[70,93] Furthermore, pain and surgical stress affect the hypophyseal–adrenal axis and cause increased secretion of endogenous catecholamines, which may decrease GI blood flow and motility.[70] Ulcers in patients with spinal cord injuries are potentiated by treatment with corticosteroids, which is a common therapy in these patients.[76]

No studies have specifically evaluated "stress ulceration" in dogs; however, there are multiple reports of GI ulcers in critically ill dogs.

Multiple studies[70,93] in the veterinary literature support a positive association between canine spinal disease and GI mucosal injury. In a prospective study,[70] endoscopic examination was used to determine the incidence of gastroduodenal ulceration in dogs with acute intervertebral disk disease and concurrent corticosteroid use. In this study, the prevalence of gastric mucosal lesions (e.g., hemorrhage, erosions, ulcers) was 76% at the time of surgical referral; however, two-thirds of the dogs had received corticosteroids or NSAIDs before admission.[70] Two of 22 dogs had ulcers at completion of the study (i.e., 5 to 6 days after surgery and therapy with corticosteroids).[70] A more recent study[93] examined the prevalence of subclinical gastroduodenal ulceration in dachshunds with intervertebral disk prolapse. Thirty dogs with myelographic confirmation of disk prolapse had gastroduodenoscopy performed at admission, fol-

lowed by steroid administration (i.e., methylprednisolone at 30 mg/kg IV) and surgical decompression. Six of 11 dogs (55%) that had not received any form of ulcerogenic drug (NSAID or corticosteroid) before admission had lesions at presentation ranging from submucosal hemorrhage to obvious ulceration.[93] This supports the view that ulcerogenic drugs are not the only factor involved in ulceration with spinal cord disease and that other factors such as autonomic dysfunction may play a more substantial role.[93] Follow-up endoscopy 3 and 4 days postoperatively revealed lesions ranging from mucosal hyperemia to submucosal hemorrhage, with an overall prevalence of gastroduodenal mucosal lesions of 76%.[93] These patients had multiple potential ulcerogenic factors, including spinal cord disease, steroid administration, and surgery; therefore, it is difficult to determine the extent to which individual factors were involved in mucosal injury.

Gastrointestinal Disease

Primary GI tract disease can also result in ulceration. Gastric foreign bodies cause gastritis and ulceration via direct irritation of the mucosa, distention of the antrum causing gastrin release and gastric acid secretion, and retention of gastric contents via obstruction of the pylorus.[22] Gastric neoplasia, pyloric stenosis, and motility disorders can also result in hyperacidity-induced gastritis.[22] Ulcers related to gastric dilatation-volvulus are thought to be associated with ischemia.[27] Ulceration has also been reported in dogs with inflammatory bowel disease.[25]

Neoplasia

Paraneoplastic disease is another cause of GI ulceration. Mast cell tumors, regardless of their size or appearance, can release significant amounts of histamine, resulting in hypersecretion of gastric acid and subsequent injury to the gastric and duodenal mucosa.[12,22,27] This complication of mast cell tumors is most evident with surgical manipulation or aggressive palpation due to massive mast cell degranulation and intense histamine release.[12] A less common paraneoplastic syndrome (i.e., Zollinger-Ellison syndrome) occurs with gastrinomas (i.e., small pancreatic tumors that secrete large amounts of gastrin), leading to excess secretion of gastric acid.[12,22,27] Patients with gastrinomas commonly suffer from severe gastroesophageal reflux, esophagitis, gastritis, and duodenitis.[12]

Exercise

Gastric ulceration and GI bleeding have been reported in human athletes and performance horses in association with severe physical exertion.[94] Sustained strenuous exercise has been found to increase the circulating cortisol concentration, which may impair mucosal integrity of the GI tract.[95] A study evaluating dogs participating in the Iditarod Sled Dog Race showed that 48.5% of these dogs had endoscopic gastric lesions, including ulcers, erosions, or mucosal hemorrhage, after completion of the race.[94] Many factors were speculated as causes, including high dietary fat leading to delayed gastric emptying and hyperacidity, mucosal disruption from bacterial pathogens or foreign bodies, exercise-induced visceral ischemia, increased cortisol levels, and physiologic stress.[94]

Helicobacter spp

In humans, *Helicobacter pylori* is clearly associated with gastric ulcers along with gastritis and gastric neoplasia.[96,97] However, a similar association has not been found in dogs. The prevalence of *Helicobacter* spp in dogs is high, with spiral bacteria identified in 41% to 100% of clinically healthy dogs.[97–102] The role of *Helicobacter* spp in the pathogenesis of gastric inflammation in dogs is not fully known. Some studies[97–99] have identified inflammation, glandular degeneration, and lymphoid follicle hyperplasia in some but not all colonized dogs. However, no significant association was found among infection and proinflammatory cytokine expression, the severity of histopathologic changes, the presence of gastritis, and differences in the pathogenicity of various *Helicobacter* spp.[97,103,104] Furthermore, there is no significant correlation with clinical signs, and no relationship with GI ulceration has been found in dogs.[98,102]

CONCLUSION

Gastric mucosal injury is common in veterinary patients because many regularly used drugs and common diseases can overwhelm mucosal defense mechanisms. To better recognize and treat gastric injury, it is important to understand both the physiology behind the normal gastric mucosal barrier and the pathophysiology associated with the factors that disrupt it.

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ARTICLE #1 CE TEST

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1. Which disease has not been associated with GI ulceration in dogs?

a. intervertebral disk disease
b. mast cell tumor
c. diabetes mellitus
d. inflammatory bowel disease

2. In the largest retrospective study of dogs with GI ulceration, which two predisposing factors were most common?

a. hepatic disease and NSAID use
b. renal disease and NSAID use
c. hepatic disease and mast cell tumors
d. intervertebral disk disease and hepatic disease

3. Which is not an established risk factor in the development of NSAID ulcers in humans?
a. advanced age
b. a history of GI bleeding
c. concomitant use of anticoagulants
d. concomitant use of antibiotics

4. Which mechanism is not suspected in the pathogenesis of ulcers in canine hepatic disease?
a. increased serum bile acid concentration, thereby stimulating gastric secretion
b. decreased mucosal blood flow secondary to thrombosis
c. increased blood levels of gastrin and histamine
d. increased susceptibility to *Helicobacter* infection

5. Which is not a major factor of the protective gastric mucosal barrier?
a. rapid epithelial cell turnover
b. mucosal hydrochloric acid secretion
c. high rate of blood flow
d. mucosal cell hydrophobicity

6. Which NSAID is properly matched with its COX selectivity?
a. carprofen: COX-1 selective
b. deracoxib: COX-1 selective
c. meloxicam: COX-2 selective
d. ketoprofen: COX-2 selective

7. Which is not thought to play a role in NSAID-induced mucosal damage?
a. hypergastrinemia due to decreased gastrin metabolism
b. uncoupling of oxidative phosphorylation in mitochondria
c. neutrophil adherence to the vascular endothelium
d. inhibition of COX-mediated PG synthesis

8. In two canine studies, the overall prevalence of gastric mucosal lesions in dogs with intervertebral disk disease was ___%.
a. 10
b. 24
c. 76
d. 90

9. Which is not a primary secretogogue of gastric acid secretion?
a. gastrin
b. histamine
c. acetylcholine
d. serotonin

10. Which is not theorized to play a role in corticosteroid-induced mucosal damage?
a. decreased mucus production
b. increased histamine production
c. increased acid output
d. decreased epithelial cell turnover