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THE USE AND MISUSE OF ANTIULCER DRUGS

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The increased understanding of ulcer pathogenesis and increased use of endoscopy have enhanced the awareness in veterinary medicine to the presence of gastrointestinal (GI) ulcer disease in small animals. Consequently, antiulcer drugs have become among the most commonly used drugs in veterinary medicine. Treatment options for GI ulcers include drugs which neutralize or inhibit gastric acid secretion or enhance mucosal defense mechanisms. The later drugs (cytoprotective agents) exert beneficial effects without changing the concentration of acid in the gastric lumen. Treatment also can be aimed not only to heal ulcers but in certain cases to prevent the occurrence.

Proper use of antiulcer drugs depends on knowledge of the predisposing causes of ulceration and the underlying mechanisms by which these conditions are thought to induce ulcer formation combined with a thorough knowledge of the pharmacologic properties of antiulcer drugs.

OVERVIEW OF ULCER PATHOGENESIS

Gastric mucosal integrity is maintained through mucosal defense and repair mechanisms balancing the effects of ulcerogenic factors, primarily acid and pepsin. When this balance is disturbed by either excessive acid production, impaired mucosal defense and repair, or both, gastric ulceration may occur. Gastric mucosal defense is the result of many separate and interacting components including mucus and bicarbonate secretion, mucosal hydrophobicity, intrinsic epithelial cell defenses (apical barrier, acid extrusion, antioxidant mechanisms), and mucosal blood flow. Repair processes include cell restitution, epithelial cell replication (growth factors), formation of granulation tissue, angiogenesis, and remodeling of the basement membrane. Both mucosal defense and repair mechanisms are stimulated by mucosal prosaglandins. Disruption of any superficial component (e.g. mucus-bicarbonate layer) of mucosal defense usually results in minimal gastric mucosal damage so long as the other components remain intact. Damage to the mucus layer and superficial epithelium (erosion), stimulates the production of mediators such as growth factors and prostaglandins which increase mucosal blood flow and stimulate cell restitution and replication leading to rapid healing. The inability of these compensatory components to overcome ulcerogenic factors leads to extension of the injury through the muscularis mucosae into the submucosa (ulceration).

CAUSES OF GI ULCERATION

A number of drugs and conditions have been recognized to be associated with GI ulceration. The majority of these factors predispose to ulcer formation by damaging mucosal defense mechanisms. Gastrinoma, mastocytosis, and head trauma are the only conditions in which hyperacidity is considered to be the primary underlying mechanism for ulcer formation.

Drugs are a common cause of gastric mucosal injury (hemorrhage, erosion, ulceration) in small animals. Of the different classes of drugs, the non-steroidal anti-inflammatory drugs (NSAIDs) are by far the most frequently incriminated. These drugs are commonly used in small animals for their anti-inflammatory, antipyretic and analgesic effects. As a group, their mechanisms of action and pharmacological effects are similar. However, their pharmacokinetic properties vary widely, resulting in markedly different disposition patterns. These differences account for their variable propensity for inducing gastric mucosal injury. Gastric ulceration in the dog has been reported with the use of aspirin, indomethacin, ibuprofen, carprofen, ketoprofen, meclofenamic acid, naproxen, flunixin meglumine, and piroxicam. Non-steroidal anti-inflammatory drugs appear to produce most of their damaging effects by inhibiting prostaglandin synthesis. These drugs inhibit the enzyme cyclooxygenase in the arachidonic acid pathway that leads to prostaglandin formation. Aspirin inhibits cyclooxygnase irreversibly, whereas other NSAIDs inhibit this enzyme in a reversible, concentration-dependent manner. This may explain why aspirin, in comparison to other NSAIDs, remains one of the most potent inhibitors of prostaglandin synthesis.

Two structurally related cyclooxygenase isoforms have now been identified: cyclooxygenase-1 and -2 (COX-1 and COX-2). COX-1 is found in most of the body's tissue including the stomach. COX-2, in contrast, is undetectable in most tissues under normal physiologic conditions. COX-2 is inducible through the action of cytokines and endotoxins. Thus it is found in high concentrations in sites of inflammation. Most available NSAIDs inhibit both COX-1 and COX-2, although the ratio of their selectivity for COX-1 and COX-2 varies widely. NSAIDs that would selectively inhibit COX-1 but not COX-2 could potentially decrease inflammation while having minimal gastroduodenal effects. Recently, a selective COX-2 inhibitor (minimal COX-1inhibition at therapeutic dosages), firocoxib, has been introduced.

The blockage of cyclooxygenase may also divert arachidonic acid metabolism toward synthesis of leukotrienes (lipoxygenase pathway) which have been implicated in the pathogenesis of NSAID-induced gastric mucosal injury. The NSAID tepoxalin inhibits both cyclooxygenase and lipooxygenase pathways. Development of gastric mucosal injury associated with the use of NSAIDs can also be partially attributed to topical mucosal effects, inhibition of mucus secretion, increased acid secretion, decreased mucosal blood flow, and reduced duodenal bicarbonate output. In addition NSAIDs may potentiate pepsinogen secretion. Overall, observations of NSAIDs gastrointestinal manifestations likely reflect the combined effects of all these mechanisms.

Corticosteroids are another group of anti-inflammatory drugs that have been associated with gastric mucosal damage. They may prevent prostaglandin synthesis by

inhibiting phospholipase, another enzyme in the arachidonic pathway necessary for the synthesis of prostaglandins. As opposed to the NSAIDs, corticosteroids are usually associated with gastric mucosal disturbances only when administered in the presence of other ulcerogenic factors. Concurrent administration of corticosteroids and NSAIDs is particularly damaging.

Gastric ulceration can occur from the inadvertent ingestion of a variety of toxic chemicals. Chemicals causing gastric ulceration include cleaning agents, floor finishes, and fertilizers. Ingested chemicals can cause gastric ulceration by disrupting cell structure and interfering with cell function. Some chemicals can solubilize cell lipids or denature cell proteins. Ingested chemicals may have effects on additional systems which can assist diagnosis.

Acute and chronic liver disease can cause GI ulceration. In both forms of liver disease, ulceration primarily appears to result from reduced mucosal blood flow. In acute liver disease, reduced blood flow is usually the result of thrombosis. The liver is rich in thromboplastin, which is released in acute, severe hepatic disease. Thromboplastin initiates the clotting cascade, causing thrombosis and the resultant reduction in gastric blood flow. In chronic liver disease, reduced blood flow occurs as a result of portal hypertension, microvascular shunting, and thrombosis and dysplasia of gastric vessels. Gastric mucosal prostaglandin production appears decreased in patients with chronic liver disease. Conflicting data exists regarding serum gastrin levels and acid secretion.

Gastric ulceration can be observed with renal failure. The pathogenesis is multifactorial involving decreased mucosal blood flow, impaired mucus and bicarbonate secretion, and acidosis. Decreased mucosal blood flow caused by diffuse vascular injury appears to be the most important factor. Acidosis reduces the delivery of bicarbonate to the gastric mucosa. Although hypergastrinemia is found with renal failure, a corresponding increase in gastric acid secretion has not been demonstrated. Ulceration secondary to renal failure appears to uncommon in dogs and cats.

Adenocarcinomas are the most common neoplasms associated with GI ulceration. Leiomyosarcomas can also be associated with ulceration and significant GI blood loss. On occasion GI lymphoma can be associated with ulceration. Ulceration related to these neoplasms occurs due to infiltration and breakdown of the mucosal barrier.

Gastroduodenal ulceration appears to be common in dogs with intervertebral disc prolapse. There is conflicting data whether the prevalence of ulceration is influenced by the administration of corticosteroids.

Stressful disorders including trauma, shock, sepsis, and burns can result in gastric ulceration. The major factors that are implicated are a decrease in mucosal blood flow, a reduction in mucus and bicarbonate secretion, and reduced mucosal turnover and repair. The reduction in mucosal blood flow is mediated by increased sympathetic activity and circulating catecholamines which leads to vasoconstriction. In sepsis, disseminated intravascular coagulation and mucosal thrombosis may further compromise mucosal blood flow. When blood flow returns to the ischemic tissues reperfusion injury may occur.

Inflammatory bowel disease, most notably eosinophilic gastritis/enteritis, can result in GI ulceration. Ulceration results from infiltration and breakdown of the mucosal barrier.

Dogs with hypoadrenocorticism can develop gastric erosions and ulcers, and at times significant gastric hemorrhage. The reasons for gastric mucosal injury are unclear but it appears basal levels of glucocorticoids may be necessary for gastric cytoprotection.

Gastrointestinal ulceration may be associated with hypersecretion of gastric acid. Secretion of excessive gastrin or histamine usually underlies the increased gastric acid secretion. Excessive gastrin is released from gastrinomas and other APUD tumors. Mastocytomas of all grades and sizes release large amounts of histamine. Head injuries may also be associated with increased gastric acid secretion and gastric ulceration. The acid hypersecretion probably results form stimulation of the oxyntic and G cells via vagal pathways originating in the CNS.

ANTIULCER DRUGS

Inhibitors of Gastric Acid Secretion

Gastric acid secretion by the oxyntic cell is regulated by an intricate interplay of neural (acetylcholine), hormonal (gastrin), and paracrine (histamine) mechanisms. Receptors for each of these secretagogues and the pathways to which these receptors are coupled have been identified on the oxyntic cell. The stimulatory effect of acetylcholine and gastrin is mediated by an increase in cytosolic calcium, whereas that of histamine is mediated by activation of adenylate cyclase and generation of cAMP. All the pathways converge on and modulate the activity of the luminal enzyme, H^+K^+-ATPase, the proton pump of the oxyntic cell. Potentiation (synergism) appears to occur between histamine and either acetylcholine or gastrin. Acetylcholine and gastrin also appear to stimulate the release of histamine from mucosal enterochromaffin-like (ECL) cells.

H_2-receptor antagonists are analogs of histamine which competitively inhibit acid secretion by eliminating the direct and synergistic influence of histamine on gastrin- and acetylcholine-stimulated acid secretion. Cimetidine (Tagamet®:dogs and cats 10 mg/kg q6-8h PO, IV), ranitidine (Zantac®: dogs 2 mg/kg q8-12h PO, IV; cats 3.5 mg/kg q12h PO, 2.5 mg.kg q12h) and famotidine (Pepcid®: dogs and cats 0.5 mg/kg q 12-24h PO, IV) are the most commonly used H_2-receptor antagonists in small animals. The H_2-receptor antagonists are remarkably safe. Cimetidine, and to a lesser extent ranitidine, reversibly bind to the cytochrome P-450 enzyme system and can interfere with the clearance of drugs metabolized by this route. This interaction is rarely of clinical significance except with drugs that have narrow therapeutic ranges such as

theophylline, diazepam, and propranolol. Adjustment of dosing is not necessary when there is hepatic dysfunction. The elimination half-life of H_2-receptor antagonists is increased in patients with moderate to severe renal failure and dosages should be reduced by 50%. Cimetidine can interfere with renal clearance of procainamide and its metabolite N-acetyl-procainamide elevating plasma concentrations by 50% in some cases. The increased intragastric pH associated with the effect of H_2-receptor antagonists may reduce absorption of drugs that require an acid medium for dissolution or absorption (e.g. ketoconazole, ampicillin). Despite differences in the potencies of the H_2-receptor antagonists, these drugs have been shown to be equally effective in promoting mucosal healing.

Proton pump inhibitors block the H^+K^+-ATPase at the apical border of the oxyntic cell. These drugs covalently bind to the H^+K^+-ATPase, irreversibly blocking acid secretion in response to all modes of stimulation, making them the most potent inhibitors of gastric acid secretion. A single daily dose is thought to result in virtual anacidity. Unlike H_2-receptor antagonists renal impairment has minimal or no effect on the pharmacokinetics of proton pump inhibitors making dosage adjustments unnecessary. In humans, increased (alkaline) gastric pH is associated with gastric gram-negative bacterial overgrowth which may predisopose ill patients to pneumonia. Proton pump inhibitors inhibit hepatic cytochrome P450 (most notably omeprazole) and sustained hypochlorhydria has the potential to result in hypergastrinemia, ECL cell hyperplasia, and the development of carcinoid tumors. Despite these concerns, clinically significant side effects have not been reported in dogs and cats. Proton pump inhibitors may diminish the absorption of drugs that require an acidic environment for dissolution of absorption. Omeprazole (1 mg/kg q12-24h PO), lansoprazole (1 mg/kg q24h PO, IV), and pantoprazole (1 mg/kg q24h IV) are proton pump inhibitors that have reported use in the dog.

Cytoprotective Agents

Sucralfate (Carafate: dogs 0.5 - 1.0 gm q 8-12 h, PO; 0.25 gm q8-12h, PO) is a complex salt of sucrose sulfate and aluminum hydroxide. The major drug actions of sucralfate that contribute to mucosal healing are related to stimulation of prostaglandin-dependent and prostaglandin-independent mucosal defense and reparative mechanisms and its antipeptic effects. In addition, sucralfate promotes mucosal healing by binding to damaged mucosa and providing a physical barrier to the back diffusion of acid and pepsin. Although, sucralfate is most effective in an acidic environment, it appears to work adequately at near-neutral intragastric pH. Since sucralfate may interferewith the absorption of other drugs (i.e. NSAIDS, H2-receptor antagonists, digoxin) it is advisable to separate the administration of sucralfate from other drugs. Like all aluminum containing drugs, sucralfate can cause constipation and hypophosphatemia.

Aluminum-containing antacid tablets (1 tablet q6h) effectively heal ulcers. Ulcer healing appears to mainly reside in the ability of aluminum-containing antacids to stimulate mucosal defense mechanisms, not in neutralizing gastric acid.. Aluminum-containing antacids also effectively bind pepsin. Drug interactions and side effects are similar to sucralfate.

Misoprostol (Cytotec®: 5 μg/kg q6-9h PO) is a synthetic prostaglandin E_1 analog which stimulates gastric mucosal defense mechanisms and at higher dosages also inhibits gastric acid secretion. It has been shown to be as effective as other antiulcer drugs in healing GI ulcers but its lack of a demonstrated advantage over H_2-receptor antagonists and side effects have prevented the use of misoprostol as initial antiulcer therapy. This drug has the potential to significantly reduce gastric mucosal injury when administered (2-5 mcg/kg) concurrently with nonsteriodal antiinflam-matory drugs (NSAID). A self-limiting secretory diarrhea is the most common side effect associated with this drug. Since misoprostol may induce abortion it should not be use in pregnant animals.

TREATMENT

Ulcer Healing

Treatment of small animals with GI ulceration is aimed at restoring the balance between ulcerogenic factors and mucosal defenses. Initially, therapy is directed at the initiating cause. Supportive care may also be indicated. Choice of drug therapy should be based on the confirmed or suspected underlying mechanism(s) involved in ulcer formation. Optimally, gastric acid suppression should be tailored to match the acid-related condition with consideration given to the extent and severity of that condition.

H_2-receptor antagonists, proton pump inhibitors, or sucralfate can be used to effectively treat ulcers caused by interference with mucosal defense mechanisms. The approach to reducing gastric acid secretion is based on evidence that a reduction in acid secretion heals ulcers in most patients. Hydrochloric acid is a major factor that interferes with mucosal healing and by suppressing its secretion the balance is tipped toward mucosal defenses allowing mucosal healing to occur. The choice of antiulcer therapy should be based on cost and owner convenience (dosage interval and duration of therapy). Based on studies in human patients, antiulcer therapy should be continued for 3-4 weeks with proton pump inhibitors and 6-8 weeks with the H_2-receptor antagonists and sucralfate. The concomitant use of a gastric acid inhibitors and sucralfate is discouraged due to cost, inconvenience, and no evidence supporting benefit from this combination therapy. The use of multiple drugs also increases the risk of clinically important metabolic drug interactions. Failure to treat for the prescribed period of time may result in ulcer relapse increasing morbidity for the patient and cost for the owner. Ideally, ulcer healing should be determined by endoscopic examination.

Proton pump inhibitors are the drug of choice where gastric hyperacidity (gastrinoma and mastocytosis) represents the primary cause of ulcer formation.

For refractory ulcers, owner compliance should first be investigated. The cost of medication may result in poor compliance. Prescribing a less expensive alternative drug treatment (e.g. alulminum-containing antacid tablet) that the owner will administer may be better than having an optimal (proton pump inhibitor), but more expensive drug not delivered. Continued use of a NSAID may also cause failure of ulcers to heal. Nonsteriodal antiinflammatory drug therapy should be discontinued for at least two weeks following the initiation of antiulcer therapy. Refractory ulcers should also prompt a search for a evidence of localized or systemic mast cell neoplasia or gastrin-producing tumor. Biopsies of refractory ulcers should also be considered to rule out the possibility of malignancy. If the above causes are excluded, treatment should be continued for a longer period of time. If an H_2-receptor antagonist or sucralfate were used initially, consider switching to a proton pump inhibitor. Proton pump inhibitors should not be given concurrently with an H_2-receptor antagonist. The H_2-receptor antagonist may prevent uptake of the proton pump inhibitor by the oxyntic cell.

A recent study evaluating both H_2-receptor antagonists (ranitidine, famotidine) and proton-pump inhibitors (omeprazole, pantoprazole) suggest that current recommended doses may not effectively suppress gastric acid secretion to allow for optimal treatment of acid-related diseases when assessed by criteria used for human patients. The optimal degree of gastric acid suppression has not been established in dogs and cats. This obviates the need for additional studies to determine potentially more efficacious doses for gastric acid inhibitors.

ULCER PROPHYLAXIS

NSAID-Induced Ulcers

Misoprostol (2-5 mcg/kg q 8 h) is the only antiulcer drug shown to reduce gastric mucosal injury when concurrently administered with NSAIDs in dogs. Because H_2-receptor antagonists and proton pump inhibitors have yet to be shown to be of benefit in preventing NSAID-induced gastric mucosal injury in dogs, it appeared likely that the efficacy of misoprostol was not related to inhibition of gastric acid secretion. However, recent studies in human patients have shown high dose H_2-receptor antagonists and proton pump inhibitors to be effective at preventing NSAID-related gastric ulcers. Because of cost, the use of misoprostol should be reserved for those patients with a previous history of gastric ulceration requiring chronic NASID therapy or in older debilitated patients in whom a NSAID-induced ulcer and associated complications would be life threatening.

Corticosteroid-Induced Ulcers

Although controversial, it appears that corticosteroids alone do not impart detectable risk for ulcer formation. For this reason, the concurrent administration of cytoprotective agents or gastric acid inhibitors in patients requiring corticosteroids therapy is not routinely recommended. Corticosteroids do appear to exacerbate NSAID-induced ulceration.

Stress Ulcers

Severely ill human patients especially those with burns, head injury, major trauma, sepsis, shock, respiratory failure or tetraplegia may develop GI ulcers. The pathogenesis of these ulcers is not completely understood, but acid and pepsin, decreased blood flow, mucosal ischemia and hypoperfusion and reprerfuion injury are known to play significant roles. Severe bleeding requiring aggressive hemodynamic support can result from stress ulceration. Although not well documented, a similar scenario probably exists in small animals. Prophylaxis is the best approach to stress ulceration. In human patients, this is best achieved by maintaining intragastric pH above 4, a pH below 4 is required to activate pepsinogen to its proteolytic form, pepsin. A pH > 6 is necessary to provide hemostasis with acute gastrointestinal bleeding. A pH > 6 allows sufficient platelet aggregation and prevents dissolution of blood clots. In human patients maintaining gastric pH > 4, and optimally 6, is best achieved by intravenous infusions of proton pump inhibitors. Concurrent use of prophylactic therapy should be limited to patients in which clinical findings support the probability that ulceration will occur. Optimal doses for the use of injectable proton pump inhibitors have yet to be determined in dogs and cats.