

NEWER CONCEPTS IN GASTROINTESTINAL THERAPEUTICS IN SMALL ANIMALS

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Gastrointestinal (GI) disorders are among the most common reasons that small animal patients are presented to veterinarians. As a result, a number of drugs have been made available for the treatment of gastrointestinal signs (vomiting, diarrhea, inappetance). Certain of these drugs are in combination preparations that, although they may alleviate the clinical signs of a GI problem, may not effect primary treatment for a particular disorder. Veterinary education should continue to stress the importance of pursuing a definitive diagnosis whenever possible as well as prescribing a specific treatment.

This paper discusses two of the newer drugs available for use in veterinary clinical practice for treatment of gastrointestinal disorders in dogs and cats. They are metoclopramide (Reglan[®]), a prokinetic agent, and cimetidine (Tagamet[®]), an H₂ - receptor blocker. These drugs offer primary therapy for disorders that previously were difficult to treat effectively. Specific indications for their use are discussed.

Metoclopramide

Metoclopramide (Reglan[®] - A.H. Robins) is a drug recently marketed in the United States with the unique gastrointestinal actions of both depressing the emetic center and stimulating motility of the stomach and proximal small intestine to promote more effective aboral movement. Specifically, metoclopramide increases gastric antral contractions, promotes relaxation of the pylorus, increases tone at the gastroesophageal junction and reduces small bowel transit time. Metoclopramide has been found to be especially useful in treatment of gastric motility disorders and other problems characterized by chronic intermittent vomiting in dogs and cats.

Clinical Pharmacology

Metoclopramide acts both centrally and peripherally. It antagonizes the effect of the inhibitory neurotransmitter dopamine in the central nervous system and other organ systems. Peripherally metoclopramide stimulates release of acetylcholine and sensitizes gastric smooth muscle to acetylcholine stimulation.¹ Metoclopramide also has an effect on the medullary chemoreceptor trigger zone which makes it useful as an antiemetic agent.¹ Metoclopramide has no effect on gastric, biliary or pancreatic secretion.

Clinical Applications

Several clinical applications for use of metoclopramide in dogs and cats have been identified. These include gastric motility disorders, gastroesophageal reflux, as an aid to diagnostic endoscopy and radiology and as treatment for nausea and vomiting caused by various disorders.^{2,3}

Gastric motility disorders are being recognized with increasing frequency in veterinary medicine. Gastric stasis, characterized by abdominal discomfort, periodic bloating, borborygmus, nausea and vomiting may be associated with a number of clinical states that include inflammatory disorders (e.g. gastritis), gastric ulcers, gastroesophageal reflux, infiltrative lesions (e.g. neoplasia), hypokalemia and chronic gastric dilatation.² Short-term continued vomiting that is observed in some cases after apparent recovery from viral enteritis may be due to gastric motility abnormalities. Transient (3 to 14 days) gastric hypomotility may also occur after gastric or abdominal surgery. Motility disorders with no organic cause may be best classified as idiopathic. For any of the disorders listed the primary cause should be treated, and metoclopramide may be a valuable short-term adjunct to therapy in these cases. Metoclopramide alternatively may be used as the primary treatment on a long-term basis for idiopathic motility disorders.³

The primary clinical signs of gastric motility disorders seem to most commonly be cyclical in nature and include vomiting, inappetance and gastric distention. Vomiting often occurs 6 to 12 hours after eating and is characterized by a consistency of undigested or only partially digested food. On some days the patient remains active and alert but on others listlessness and inappetance are noted. Loud abdominal gurgling sounds may be described by the owner. Abdominal discomfort may also accompany conditions resulting from gastric emptying disorders.

Metoclopramide also has been useful in treatment of dogs that have chronic vomiting characterized by episodes occurring routinely in the early morning and containing bile fluid. This problem has been most frequently observed in small breeds of dogs. A single dose at bedtime to stimulate upper gastrointestinal smooth muscle activity and decrease duodenal-gastric reflux of bile often alleviates early morning nausea and vomiting in these dogs. Certainly, many patients with this history are presented to veterinarians who until now have had little to offer in alleviating this problem. Many clients perceive even mild intermittent bloating and vomiting as significant problems and after proper therapy they frequently comment on the improved quality of life they feel their pets are experiencing.

Metoclopramide has been useful in management of pyloric stenosis either as an aid to diagnosis (i.e. good response to therapy) or as treatment when a client declines the option of surgery. Metoclopramide's antiemetic action has proven quite effective in management of chemotherapy-induced vomiting. Treatment with metoclopramide 30 to 60 minutes prior to chemotherapy and for 1 to 3 days afterward consistently reduces chemotherapy-related nausea and vomiting in people as well as animals. Large breed dogs with intermittent gastric dilatation (without volvulus) and attendant nausea, belching and vomiting respond well. Metoclopramide may be necessary on a long-term basis in some of these cases in conjunction with dietary management. Finally, metoclopramide given prior to endoscopic examination may facilitate passage of the endoscope through the pylorus to the duodenum as a result of its effect of facilitating relaxation of the pylorus.

Dosage

The dosage of metoclopramide that has previously been recommended is 0.5 to 1.0 mg/kg BID to QID. I have had success using the following dosage range:

Less than 10 lbs (4.5 kg) - 2.5 mg per dose,
10 to 40 lbs (4.5 to 18 kg) - 5 mg per dose,
Greater than 40 lbs (18 kg) - 10 mg per dose (maximum dose needed)

Metoclopramide is given 20 to 30 minutes before meals and again at bedtime. Animals that require chronic medication may need only 1 to 2 doses daily. Because of its short half-life, the drug is not effective when given by intravenous or intramuscular bolus injection for purposes other than when only one treatment would be administered (i.e. pre-endoscopy or radiologic contrast study). Subcutaneous administration into fat may be of benefit when oral therapy is contraindicated and an intravenous line is not available.² Metoclopramide can be administered in intravenous fluids as a constant infusion for treatment of severe vomiting associated with viral (e.g. parvovirus) or bacterial enteritis. The calculated total daily dose is 1.0 to 2.0 mg/kg per 24 hours in a continuous infusion.²

Metoclopramide is supplied in 10 mg tablets and as a cherry flavored liquid containing 5 mg/ml. Injectable metoclopramide is available in 2 ml single dose vials and in 10 ml and 30 ml multiple dose vials (5 mg/ml).

Side effects

Some adverse effects may occur if metoclopramide is given in the usual therapeutic doses. Clients should be apprised of these before the medication is prescribed. These effects are uncommon.

Motor restlessness and hyperactivity may occur and when observed these usually begin 20 to 30 minutes after a dose and last 4 to 5 hours. Alternatively, drowsiness and depression occasionally occur. Side effects are infrequent in cats but clients have reported disorientation, frenzied behavior and hiding tendencies associated with the medication. These side effects are reversible but generally do not subside when lower doses are given. Unless side effects are infrequent, the use of metoclopramide should be discontinued if adverse reactions are seen.

Metoclopramide should not be given in combination with phenothiazines or to epileptic patients.^{1,2} Patients on combination therapy which includes metoclopramide should be observed for abnormal behavior. This usually resolves if the metoclopramide is discontinued. Metoclopramide should not be given to patients with intestinal obstruction (e.g. foreign body, intussusception).

Cimetidine

Cimetidine (Tagamet[®] - Smith Kline & French) is a potent histamine H₂ - receptor antagonist that is effective in reducing gastric acid secretion. In recent years, cimetidine has been the world's best-selling drug and in human medicine has been used primarily for treatment of gastric and duodenal ulcers. Several indications for use in small animals have been identified.

Clinical Pharmacology

Cimetidine is effective in reducing gastric acid secretion by blocking the histamine receptor (H_2 -receptor) of the parietal cell. Primary agonists of gastric acid secretion by the parietal cells include the neurotransmitter acetylcholine, the gastrointestinal hormone gastrin and the biogenic amine histamine.⁵ Gastrin acts to stimulate maximal acid secretion when the H_2 - receptor is occupied by histamine and in the presence of acetylcholine. If all parietal cell receptor sites (i.e. for gastrin, acetylcholine, and histamine) are occupied, and then one site is blocked (i.e. atropine blocking acetylcholine or cimetidine, the H_2 - receptor antagonist, blocking histamine), stimulation through the other receptors will result in less than maximal response.⁵ Because there are currently no anti-gastrin drugs available and because anticholinergics can have adverse effects in vomiting patients, use of H_2 - receptor antagonists is the safest and currently most effective means of controlling gastric acid secretion when a decrease in luminal gastric acid levels would be beneficial to the patient.

Gastric Mucosal Barrier

Most clinical indications for the use of an H_2 - receptor antagonist involve conditions or use of drugs that potentially can damage the protective gastric mucosal barrier. The gastric mucosal barrier consists of two parts, the mucous layer lining the surface of the epithelial cells and the mucosal cells that comprise the epithelial membrane.⁵ This barrier is extremely resistant to gastric acid and accounts for the ability of the gastric lining to withstand the effects of a gastric luminal pH which is often as low as one.

Damage to the mucosal barrier allows for back diffusion of luminal acid into the mucosa, which potentially can lead to a series of events including direct damage to the mucosa and destruction of the subepithelium. Mast cells present in the submucosa and lamina propria degranulate and release histamine on contact with acid. The release of histamine stimulates further parietal cell secretion of hydrochloric acid as well as local inflammation and edema.⁵ Gastric acid alone is not a cause of gastric ulcers; however, it is recognized as essential for the pathogenesis of gastric ulceration after initiation of damage of the gastric mucosal barrier has occurred, allowing for initiation of back diffusion of gastric acid. Normally in the presence of an intact mucosal barrier there is a minimal slow back diffusion of acid that occurs into the mucosa that is of no clinical significance. This small amount of acid is removed by the gastric microcirculation.

Clinical Applications

Cimetidine therapy may be indicated for any condition which causes or potentiates damage of the gastric mucosal barrier. Table 1 lists potential causes of gastric ulcers in small animals. Clinicians must be able to recognize signs of gastric and duodenal erosions and ulcerations as early in their course as possible. Clinical signs include nausea, vomiting, melena, abdominal pain and inappetance. Hematemesis is a serious clinical sign that warrants early diagnostic pursuit. A careful history regarding any recent drug administration and careful investigation for underlying disorders should be undertaken as early as possible.

Table 1 Causes of Gastric Ulcers in Small Animals

Drugs

Aspirin
Phenylbutazone
Indomethacin
Flunixin meglumine
Hypertonic solutions

Stress factors

Shock
Trauma
Severe illness

Neurologic disease

(corticosteroids given in conjunction increase incidence)

Metabolic disease

Renal failure
Liver disease
Adrenocortical insufficiency

Gastric hyperacidity

Mast cell tumor
Systemic mastocytosis
Zollinger - Ellison Syndrome (gastrinoma)

Bile reflux

(gastric mucosa is not protective against bile)

Factors such as shock, trauma, hypotension, neurologic disease and severe illness may alter gastric microcirculation with a resultant decrease in mucosal cell turnover. Superficial mucosal erosions or focal ischemic necrosis may occur.⁵ In some cases these changes are significant enough to cause vomiting and melena. Treatment for the primary disorder may need to be accompanied by H₂ - receptor antagonist therapy to decrease gastric acid levels and thereby facilitate healing of the gastric mucosa.

An association between neurologic disease and gastric lesions has been recognized in both man and animals. Gastric ulcers associated with spinal cord lesions are thought to result from a combination of stress-related factors and an imbalance in the sympathetic and parasympathetic nervous innervation to the stomach that results in altered mucosal blood flow and mucosal ischemia.^{5,6} Parasympathetic overdrive further stimulates an increase in gastric acid and enzyme secretions. Glucocorticoids which are both released endogenously and administered exogenously in these situations can decrease gastric mucous production and increase gastrin levels and gastric acid production, leading to further compromise of the gastric mucosal barrier.^{5,6} Cimetidine therapy should be instituted early in the course of a neurologic disorder when corticosteroids are part of the therapeutic regimen. A decreased incidence of gastric discomfort (decreased abdominal pain on palpation) and vomiting observed on a clinical basis has been noted. Usually cimetidine therapy can be discontinued 1 to 3 days after discontinuation of corticosteroids.

Metabolic disorders including renal failure and liver disease may cause gastric erosions or ulcers. Decompensated renal failure patients are often presented with the primary complaint of vomiting, listlessness and anorexia. Biochemical profiles support primary renal disease (elevated BUN, creatinine and phosphorus levels in conjunction with low urine specific gravity). Patients with significantly reduced renal function have been shown to have hypergastrinemia secondary to decreased renal clearance of gastrin.⁷ Increased gastrin results in increased release of hydrochloric acid. Damage to the gastric mucosal barrier from circulating uremic toxins and altered gastric blood flow patterns in conjunction with increased luminal hydrochloric acid results in gastric mucosal erosions (uremic gastritis). Vomiting which may include partially digested blood is observed. Primary treatment of vomiting in the uremic patient should include cimetidine to decrease gastric acid levels. Gastrin levels will not be decreased; however, the hyperacidity that results from the effects of hypergastrinemia will be decreased. If vomiting is severe, other antiemetic therapy (e.g. chlorpromazine) may need to be given in conjunction with cimetidine initially to help alleviate nausea-related discomfort. Some patients with liver disease may also be noted to have hematemesis or melena secondary to gastric lesions. These lesions probably occur because of altered gastric microcirculation and decreased metabolism of gastrin by the liver. Cimetidine dosage in renal and liver disease patients should be altered as a reflection of decreased clearance of the drug by these organs. Cimetidine therapy is usually discontinued 2 to 3 weeks after vomiting and melena resolve in these cases.

Other indications for H₂ - receptor antagonist therapy (Table 2) include mast cell tumor cases that show evidence of gastric and/or duodenal ulceration, occasional cases of exocrine pancreatic insufficiency and acute acetaminophen toxicosis. Some mast cell tumor patients develop gastric or duodenal lesions secondary to the effects of hyperhistaminemia resulting from degranulation of

Table 2 Clinical Applications of Cimetidine Therapy in Small Animals

Gastric erosions/ulcers due to:

- stress
- gastric ischemia (secondary to shock, metabolic disorders such as adrenocortical insufficiency)
- iatrogenic (drug administration, ingestion of toxic compounds)

Neurologic disease

- with accompanying g.i. signs (vomiting and/or melena)
- initiate therapy if high dose corticosteroids are used in primary treatment regimen

Gastroesophageal reflux disorders

Esophagitis

Bile acid reflux

(duodenal - gastric reflux)

Renal failure

- primary treatment of uremic gastritis

Liver disease

- if hematemesis and/or melena occur in conjunction

Mast cell tumor disorders

Exocrine pancreatic insufficiency

Acetaminophen toxicity

mast cells. Patients with even small isolated skin tumors may be affected. Careful routine examination of mast cell tumor patients for evidence of GI bleeding is extremely important. Perforated ulcers with ensuing peritonitis have occurred secondary to mast cell hyperhistaminemia.

The majority of exocrine pancreatic insufficiency (EPI) cases respond quite well to digestive enzyme replacement therapy. However, occasionally excessive amounts of enzymes are destroyed by gastric acid before they are able to reach the duodenum to aid in digestion. Patients known to have EPI that do not respond adequately (as judged by resolution of diarrhea and improved weight gain) may benefit from cimetidine therapy used to lessen destruction of pancreatic enzymes in the stomach. In these cases cimetidine is administered 30 minutes before feeding and the response is often dramatic (i.e. immediate resolution of diarrhea).

Recent evidence has shown that cimetidine may decrease the toxicity of high-dose acetaminophen by preventing formation of its hepatotoxic oxidative metabolites.⁸ While cimetidine does inhibit hepatic microsomal oxidative drug metabolism it has no effect on hepatic conjugation. Hepatic conjugation is responsible for a major proportion of acetaminophen metabolism yielding nontoxic metabolites that are subsequently cleared from the body. However, the small proportion that is oxidatively metabolized assumes major importance because the severely hepatotoxic acetaminophen metabolites are formed via this pathway.⁸ Thus cimetidine's effect of inhibiting hepatic oxidative metabolism appears to be of value as adjunctive treatment of currently recommended use of acetylcysteine (Mucomyst[®]) and vitamin C for acetaminophen overdose. Known history of acetaminophen ingestion is most helpful so that cimetidine can be administered as early as possible after ingestion.

Dosage

The recommended dose of cimetidine is 5mg/kg TID. For treatment of uremic gastropathy an initial intravenous dose of 10mg/kg is followed by 5mg/kg given intravenously BID.^{6,7} Dosage is reduced to 5mg/kg BID in patients with liver disease as well.

Cimetidine is supplied as tablets (200mg, 300mg, 400mg) and injectable liquid (300mg/2ml in single dose and 8ml multiple dose vials). An oral liquid is also available (300mg/5ml).

References

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