

EQUINE GASTRIC ULCER SYNDROME

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Introduction

Equine gastric ulcer syndrome (EGUS) is a disease complex in foals and horses that is associated with injury to the mucosa of the oesophagus, stomach, and duodenum. Gastric ulceration is highly prevalent both in foals and in mature horses. Horses turned out to pasture and exercised lightly typically have normal stomachs whereas horses kept in box stalls and trained intensively have a high prevalence of gastric ulcers. EGUS can have a profound impact on condition and performance.

One endoscopic study (Murray, 1989) revealed a 51% prevalence of gastric lesions in asymptomatic foals. The majority of these lesions were in the squamous epithelial mucosa. In another study the same author (Murray, 1989) found that 100 on 187 horses had no outward signs of illness but the other 87 horses had clinical signs of gastrointestinal disease. Of the 87 horses with clinical signs, 92% had gastric lesions. But even in the 100 horses with no signs of illness, 52% had gastric lesions. Gastric lesions were significantly more severe in the horses with gastrointestinal signs than in the normal horses. Prevalence of gastric ulceration of 80-90% and 60% have been reported in racing and show horses respectively (Hammond, 1986, Vatisstas 1994, Murray 1996). A recent study also showed that progressive training was correlated with worsening of lesions (Murray, 1996).

Anatomy of the stomach of the horse: functional considerations

The stomach of the horse is very small (8 - 15 liter) compared to the rest of the gastrointestinal system. The cardia is the entrance of the stomach, the outlet is formed by the pylorus. Because the equine stomach is strongly U-shaped the cardia and the pylorus are close to each other. The first part of the equine stomach is the saccus caecus, separated by the margo plicatus from the corpus ventriculi that ends in the antrum pyloricum. The upper compartment of the stomach is lined with a nonglandular squamous mucosa that is similar to that lining the oesophagus. It appears that the majority of the squamous mucosa in the normal horse rarely comes in contact with ingesta since the line of gastric fill comes up to about the level of the lower oesophageal sphincter. 80% of equine gastric ulcers occur in this compartment, primary because it has limited intrinsic resistance to hydrochloric acid and pepsin. The margo plicatus is the border between the squamous and the glandular epithelium. The lower compartment is lined with glandular

and mucus-secreting tissue. Only 20% of equine gastric ulcers occur in this compartment of the stomach because of its many intrinsic protective properties. The glandular mucosa that is present as a narrow stripe just adjacent to the margo plicatus is the cardiac gland region. In the horse very little is known about the function of this glandular portion of the mucosa. In swine one study has shown that its primary secretion is sodium bicarbonate. Also somatostatin-immunoreactive cells can be found within this region. Among other functions somatostatin plays an important role in endogenous control of gastric acid secretion through its sampling of intragastric pH and modulation of gastrin release by G-cells. This systems appears to be in place in the horse, as indicated by a study showing a direct correlation between pH and plasma gastrin concentration (Baker, 1993).

The fundic gland region lines the bottom of the stomach along the greater curvature and up the sides to where the junction with the cardiac gland mucosa occurs. Of the glandular part of the stomach, the fundic region is the largest portion. It is the site of the classic “gastric glands” that include parietal cells which secrete HCl and zymogen cells which secrete pepsinogen into the gastric lumen, and enterochromaffin-like (ECL) cells which may secrete histamine that in turn provokes the parietal cells to secrete acid by stimulation of histamine-2 receptors on their cell surface. Equine ECL cells also produce serotonin, an agent involved in control of gastric blood flow and secretion. Gastric gland also contain mucus and bicarbonate secreting cells which are important in maintaining mucosal defence against acid, pepsin and other potentially corrosive agents.

The pyloric gland region, which lines the gastric antrum, is the major source of the acid secretagogue, gastrin, produced by G-cells. This region of the equine stomach is also rich in somatostatin producing D-cells and serotonin-producing ECL cells.

The horse stomach continues to secrete acid, to a variable degree, also during the fasted state. Foals already secrete HCl from the age of 2 days; the pH of gastric fluid can vary between 1-7. A low pH is correlated to a high plasma gastrin concentration: a situation which can predispose to stomach ulcers.

Adult horses produces about 1.5 liter of stomach-fluid/hour; the acid secretion varies between 4-60 mmol HCl/hour. The pH of the stomach content varies between 1.5 - 7 dependent on the region. A nearly neutral pH is measured in the dorsal part of the stomach (saccus caecus) close by the lower oesophageal sphincter, while more acid pH's are measured close by the margo plicatus (3.0 -6.0) and in the glandular part (1.5 - 4.0). Emptying of the stomach takes 30 minutes for a liquid meal, while complete emptying after a hay-meal can take 24 hours. Stomach and duodenum motility (is not transit) is suppressed by alfa-2 and opiate based analgesics, endotoxin, anticholinergics and prostaglandin E. Conversely, bethanechol, a direct cholinergic agonist, and the indirect cholinergic cisapride enhance motility.

Pathogenesis

Peptic lesions produced when HCl and pepsin secreted by the stomach damage the mucosa of the oesophagus, stomach or duodenum. The prevalence is high especially in animals at risk, such as foals with a disorder and performance horses. The predominant factor in peptic injury to alimentary mucosa is HCl, and there is a variable degree of inherent susceptibility to HCl injury in the oesophagus, stomach and duodenum. The oesophagus and the dorsal portion of the equine stomach are lined with stratified squamous epithelial mucosa, which has minimal resistance to peptic injury: the primary barriers to HCl are intercellular tight junctions and intercellular secretion of bicarbonate ion. These weak barriers to HCl are located in the superficial epithelial layers, and cells deeper in the epithelium actually transport H⁺ intracellularly, leading to death of these cells when exposed to HCl.

Protection of the oesophageal mucosa is dependent on the lower oesophageal sphincter to prevent reflux of gastric contents into the oesophagus, flow of saliva to wash away gastric contents that may have entered the oesophagus, and salivary mucins that form a thin, protective layer on the mucosal surface.

Protection of the equine gastric squamous mucosa is dependent upon limited exposure to acidic gastric secretions, because there is no surface barrier to HCl and the epithelium has limited properties to prevent peptic injury.

The equine glandular epithelium has evolved elaborate mechanisms to protect itself from peptic injury: mucus/bicarbonate barrier, prostaglandins, mucosal blood flow and cellular restitution. Mucosal blood flow is probably the most important element of gastric mucosal protection and is essential in supplying the epithelium with nutrients and oxygen and for disposal of hydrogen ions and noxious agents permeating the mucosa.

The duodenum may have some inherent characteristics that protects it from injury by HCl; there are numerous submucosal glands that secrete mucoprotective mucins. Motility patterns of the duodenum promote progressive aborad movement of gastric effluent. The predominant protective characteristics for the duodenum are probably extrinsic involving secretion of water, sodium, chloride and bicarbonate from the pancreas that can dilute and neutralise HCl.

It is not surprising that the prevalence of peptic lesions in foals and horses is greatest in the gastric squamous epithelial mucosa, because this epithelium has minimal intrinsic resistance to HCl, yet it exists in a potentially highly acidic environment. The predominant mechanism of mucosal injury is excessive exposure to HCl: other factors that contribute are pepsin, and possibly bile acids. Studies using pH electrodes in horses have revealed that gastric pH typically is less than 2.0 during feed deprivation, but there are intermittent periods of spontaneous alkalinisation. Recently it has been shown that duodenogastric reflux is a common occurrence in the equine stomach, and that duodenal contents appear to account for much of the nonparietal secretions measured during pentagastrin infusion in horses. The role of bile acids in equine gastric mucosal injury is unknown but mild but enterogastric reflux has been shown to occur. The pH of reflux is typically 6 to 7 and , therefore, low pH does not appear to be a factor in injury to the mucosa in these cases.

When horses had free access to Timothy grass hay pH was often greater than 6. This probably reflects neutralisation of gastric acid by salivary bicarbonate and absorption of acidic gastric secretions by ingested hay. Consequently there are periods throughout a day when horses are not eating during which gastric acidity can be high.

Periods of prolonged high gastric acidity (pH < 2.0) were created in horses using a protocol of alternating 24 h periods of feed deprivation with free choice Timothy hay, which consistently resulted in erosion and ulceration, often severe, in the gastric squamous epithelial mucosa in horses.

Erosions, sometimes bleeding were seen after 48 h cumulative feed deprivation and ulcers were consistently seen after 96 h. Concurrent administration of the histamine type 2 receptor antagonist ranitidine during feed deprivation minimised the area of lesions. Imposed feed deprivation in the management of colic cases, as a pre-operative measure or for other reasons, results often in erosion and ulceration of the gastric squamous mucosa. Feeding practices and management of horses can influence gastric acidity and peptic injury to the gastric squamous mucosa. Changing horses from pasture to stall confinement with free choice hay for 7 days resulted in erosion and ulceration of the gastric squamous mucosa (Murray, 1996).

Feeding grain and pelleted feed was associated with significantly greater post prandial serum gastrin concentrations compared to feeding only coastal bermuda hay, and while gastric acidity was not measured in that study, such high serum gastrin concentrations should lead to increased HCl secretion in the stomach.

The effects of different feeds on gastric acidity and peptic injury have not been extensively investigated. In one report (Andrews, 1998), feeding alfalfa hay and grain resulted in higher gastric pH and lesser peptic injury to the gastric squamous mucosa than bromegrass hay. The authors speculated that the higher protein content and other constituents of the alfalfa might better buffer HCl.

Factors that may contribute to nutritional influences on peptic injury include the eating behaviour of the horse (grazing vs. meal feeding), natural constituents of pasture grasses, cured hay and different feeds, and the individual's physiological responses to feeds. Exercise and training appear to influence peptic injury in horses. The prevalence of gastric lesions in racehorses actively training was 70-90%, and increasing training activity was associated with increasing gastric lesion severity (Hammond, 1986, Murray, 1989, Vatisas, 1994, Murray, 1996, Orsini, 1997). The prevalence of gastric lesions in horses competing in 3-day-events was 75%.

It is well documented that strenuous training is associated with a high prevalence and incidence of gastric lesions in the horse. However the inter-related effects of feed constituents, feeding management and eating behaviour, and the effects of exercise on gastric physiology on peptic injury have not been differentiated. In a study examining the effects of treadmill exercise on development of gastric lesions, horses exercised at maximal intensity had significantly greater number and severity of gastric squamous mucosal lesions than horses maximally exercised at only a trot. The horses were managed identically so that the intensity of exercise was the differentiating factor between the two

groups. Possible influences of exercise include HCl secretory patterns, gastric emptying and mucosal blood flow.

In foals nursing is associated with an increase in pH and gastric pH becomes highly acidic when foals remain recumbent and do not suck for more than 2 hours.

Whereas peptic injury to the squamous mucosa is a matter of excessive exposure to HCl and pepsin, the causes of gastric glandular mucosal erosion and ulceration are less straightforward. In the feed deprivation model lesions in the gastric glandular mucosa were never induced and in the simulated race training model of increasing gastric acidity, only few lesions were seen.

Administration of non steroidal anti-inflammatory drugs (NSAIDs) is a well known cause of ulceration of gastric glandular and squamous mucosa in foals and horses: injury results from impairment in mucosal blood flow and the mucus-bicarbonate barrier.

The majority of equine duodenal lesions occurs in foals but with much less frequency than gastric lesions. In foals, many duodenal lesions appear to be primarily associated with enteritis. The competence of duodenal mucosal defences, interaction of gastrointestinal peptides and the possible influence of pathogenic agents are likely to contribute to duodenal ulcer disease in foals.

Clinical Symptoms

Two age-related clinical syndromes have been described, one in foals (age < 9 months) and the other in yearlings and mature horses (age > 9 months). Although the pathogenesis is similar in foals and mature horses, the syndromes frequently have different inciting causes and may produce different clinical signs.

Clinical syndromes of gastric ulceration in foals

EGUS in foals occurs from age 2 days-9 months. Four distinct clinical syndromes have been described in foals and include silent (subclinical) ulcers, active (clinical) ulcers, perforating ulcers with diffuse peritonitis and pyloric strictures from healing ulcers, which may produce gastric outflow obstruction.

Clinically inapparent or 'silent' gastric ulceration occurs in foals and is probably the most common syndrome. These foals show no apparent clinical signs. Ulcerations are commonly found in the squamous mucosa along the greater curvature adjacent to the margo plicatus, but can be found in the glandular mucosa. 'Silent' squamous ulcers are commonly seen in foal less than 4 months old, whereas 'silent' glandular ulcers are usually seen in similar aged foals with a concurrent medical problem. Glandular gastric ulcers are thought to be stress-induced. 'Silent' ulcers may resolve without treatment and are found as incidental finding at necropsy, however they can produce clinical signs that may be life-threatening.

Clinical ulcers producing clinical signs, usually occur in foals age < 270 days. These ulcers occur primarily in the nonglandular squamous mucosa along the greater or lesser curvature adjacent to the margo plicatus or in the glandular mucosa. When gastric ulcers in nonclinical foals become larger, more diffuse and coalesce, clinical signs are precipitated. The most frequent clinical symptoms are diarrhoea and poor appetite, however poor growth, rough hair coat, potbellied appearance, bruxism, dorsal recumbency, excessive salivation, interrupted suckling, and colic may also be seen in these foals. In advanced cases, foals may be sensitive to abdominal palpation just caudal to the xyphoid process and exhibit severe signs of colic and tend to roll and to lie in dorsal recumbency. The later signs are most probably associated with gastric distention and gastro-oesophageal reflux.

Perforating gastric ulcers are infrequent in foals. These ulcers can occur in the squamous mucosa and glandular mucosa of the stomach or in the duodenum and the severity cannot be predicted by their endoscopic appearance. Perforating ulcers occur most frequently in the squamous mucosa and may lead to diffuse peritonitis, which is almost always fatal. frequently, clinical signs in these foals are absent until just prior to rupture. Once gastric rupture has occurred, initially foals show profound depression, a wide base stance and later show tachycardia, abdominal distention, colic, prolonged capillary refill time, cyanotic mucous membranes and death. A severe metabolic acidosis may be seen in foals with septic peritonitis. Early detection of foals with clinical signs suggestive of gastric ulcers is essential and surgical correction in some cases decreases mortality. In other cases, prophylactic treatment in the high-risk foal can prevent gastric rupture.

Pyloric or duodenal ulcers are rare in foals, but when healed can produce stricture and gastric outflow obstruction. Ulcers in these regions occur in foals from age 2 days to 1 year, but are most often seen age 3 - 5 months.

No clinical signs may be seen in foals with pyloric or duodenal ulceration, but if clinical signs develop they are usually associated with a gastric outflow obstruction. Typical signs of gastric outflow obstruction include drooling of milk, bruxism, post prandial colic, excess salivation, scant faeces, and low volume diarrhoea. These foals may have gastro-oesophageal reflux, cholangitis, severe gastric ulceration, erosive oesophagitis and aspiration pneumonia. In severe cases, duodenal strictures and outflow obstruction may be associated with dehydration and a systemic hypochloremic metabolic alkalosis.

Clinical syndromes of gastric ulceration in yearlings and mature horses

Clinical syndromes of gastric ulceration in yearlings and mature horses are less well recognised than in foals, but may be more economically important. Two clinical syndromes are recognised and include 'silent' or nonclinical ulcers and clinical ulcers. However, duodenal ulcers, duodenal stricture, erosive oesophagitis and gastric rupture occur infrequently. In both of these syndromes, gastric ulcers occur primarily in the squamous mucosa adjacent to the margo plicatus along the greater and lesser curvatures.

Glandular ulcers are less frequent compared to foals, and are usually associated with administration of NSAIDs. Mild multifocal gastric ulcers in the squamous mucosa are usually seen in yearlings and 2-year-olds in training without apparent clinical consequence. In 2 surveys of over 200 young horses (age 6 months to 1.5 years), nonglandular ulcers were seen in 90% of these horses. These young horses were handled daily, halter-broken and housed in box stalls. Very few of these horses had clinical signs of gastric ulceration, although the ulcers were severe in some of the horses. Frequently, gastric ulcers in this age group are not associated with clinical signs, but when these horses are put into training or stressed by concurrent disease or given NSAIDs, gastric ulcers become diffuse and involve the deeper tissue layers, which can lead to clinical signs. Clinical signs in horses with EGUS include acute and recurrent colic, poor body condition, partial anorexia, poor appetite, poor performance and attitude changes. However, ulcers can occur secondary to disorders that cause diarrhoea. Gastric ulcers are consistently more severe in horses with clinical signs when compared to horses not showing clinical signs. Gastric ulcers can be the primary cause of colic or may be secondary to other gastrointestinal problems. Often there is no correlation between gastric ulcer severity as viewed through an endoscope and clinical signs in these horses.

Diagnosis

A presumptive diagnosis of these clinical syndromes relies on recognition of clinical signs, while a definitive diagnosis is based on endoscopic examination of the stomach. Food and water have to be withheld for minimum 6 hours. Sedation and a twitch are necessary during most examinations. A 3 m gastroendoscope is passed from the nostril into the stomach. The stomach has to be insufflated with air and a water jet pump can be used to remove feed material adhering to the wall of the stomach.

An adequate scoring system to describe the lesions is interesting to compare the effects of various agents on gastric ulcer healing and to compare the results of studies done by different investigators. A scoring system for gastric ulcers in the horse was published by MacAllister et al. in 1997.

This system uses a lesion number score and a lesion severity score for both parts of the stomach.

Glandular and non glandular portions of the stomach are graded separately.

Lesion number score	Description
0	No lesions
1	1 - 2 localised lesions

2	3 - 5 localised lesions
3	6-10 lesions
4	> 10 lesions or diffuse (or very large) lesions
Lesion severity score	
0	No lesion
1	Appears superficial (only mucosa missing)
2	Deeper structures involved (greater depth than No. 1)
3	Multiple lesions and variable severity (1,2 an/or 4)
4	Same as 2 and has active appearance (active=hyperaemic
and/or	darkened lesion crater)
5	Same as 4 plus active haemorrhage or adherent blood clot

Other diagnostics may help ascertain the severity of the ulcers and include fecal occult blood or gastric blood, contrast radiography, abdominal ultrasound and abdominocentesis. However, once these examinations are indicative of the disease, clinical evolution is often progressed to a severe state.

Treatment

The goals of EGUS treatment are to eliminate clinical signs, promote ulcer healing, prevent ulcer recurrence, prevent complications and reduce the cost and duration of treatment. Many products from human medicine are available for the control and treatment of acid-related diseases. These include compounds to buffer gastric acid such as antacids, gastric mucosal protectants such as sucralfate and bismuth compounds and compounds to inhibit gastric acid secretion such as histamine H2 receptor antagonists, proton pump inhibitors and synthetic prostaglandin.

Antacids

Antacids are basic compounds that neutralise acid in the gastric lumen and are one of the oldest forms of peptic ulcer therapy. Most are mixtures of magnesium hydroxide and aluminium hydroxide.

These products have only short-lived effect on the gastric pH in horses. Based on data from several studies in horses it appears that in a clinical situation, it would be difficult to administer antacids in adequate doses or frequently enough to anticipate having a prolonged clinical effect or adequate positive effect on ulcer healing. There is insufficient data available on the effects of antacids on gastric ulcer healing in horses. However many equine practitioners believe that administration often relieves clinical signs associated with EGUS.

Bismuth compounds

These compounds have little substantial acid-neutralising capacity. Their beneficial effects have been ascribed to gastric cell protection (enhanced secretion of mucus and bicarbonate, inhibition of pepsin activity, and accumulation of bismuth subcitrate preferentially in the craters of gastric ulcers). Although these compounds are often used in the treatment of equine diarrhoea, there is little information on their effects on equine gastric ulcers. When a compound containing 26.25 g bismuthsubsalicylate was administered to five normal mature horses, there was no significant change in gastric pH.

Sucralfate

Sucralfate is an hydroxy aluminium salt of sucrose octasulphate. At a pH<4 this complex forms a sticky viscid gel. This gel adheres to epithelial cells and, with more affinity, to the base of ulcer craters. Once the gel is established and adhered to the ulcer crater it is difficult to wash out. This binding to ulcer craters is thought to represent the main therapeutic action.

There is a scarcity of data available on its use in horses. Based on the lack of efficacy on stratified squamous ulcers, sucralfate is not recommended as sole therapy in the treatment of EGUS involving only the nonglandular portion of the stomach. The effect of sucralfate on duodenal or glandular gastric ulcers in horses has not been studied.

Histamine H₂ receptor antagonists

Histamine H₂ receptor antagonists were the first drugs reported to be used in the treatment of EGUS. Their primary effect is a dose dependent inhibition of gastric acid secretion. These compounds are highly selective with little or no effect on histamine H₁ receptors. Commonly available H₂ receptor antagonists include cimetidine, ranitidine, nizatidine and famotidine. The potency of these is significantly different. Although there is ample evidence that the histamine H₂ receptor antagonists have significant effect on intragastric pH in horses and foals, scientific evidence that these compounds enhance ulcer healing in horses is lacking.

Proton pump inhibitors

These agents are potent and highly specific inhibitors of gastric acid secretion and possess a novel mechanism of action: the inhibition of hydrogen-potassium adenosine triphosphatase (H⁺, K⁺-ATPase). This enzyme is the hydrogen ion pump in gastric parietal cells and is believed to be the terminal step in the acid secretory pathway.

Omeprazole and lansoprazole are the currently available proton pump inhibitors. Omeprazole, the first to be developed, has been shown to decrease gastric acid secretion in horses and lots of other species. It has a prolonged antisecretory effect, allowing for once-daily dosing and has been shown to have significantly greater effect than placebo on healing of NSAIDs induced gastric ulcers in horses. Healing is time and dose dependent. Studies on the effects of orally administered omeprazole on equine gastric acid secretion indicate that 3-5 days may be necessary for omeprazole to reach steady state and maximum antisecretory effects. Acutely symptomatic or painful horses/foals may require initial parenteral administration of omeprazole or a histamine H₂ receptor antagonist for more rapid effect.

Pectin-lecithin complex

Pectin-lecithin complex is a mucosal protective agent which is commercially available in the form of a dietetic supplement. In one report a clinical trial in a small group of horses revealed a highly significant reduction in the nonglandular gastric mucosal lesions and a significantly reduction in the glandular mucosal lesions.

Synthetic prostaglandin

Prostaglandins inhibit the secretion of gastric acid, stimulate the secretion of mucus and bicarbonate, and provide cytoprotection for the gastric mucosa. In 5 fasting, normal mature horses, oral administration of a synthetic prostaglandin analogue resulted in a maximum mean gastric pH 5 at 4 h and remained above basal for the 8 h test period. Complications of prostaglandin treatment include diarrhoea, abdominal pain and abortion. There is insufficient data to recommend the use of prostaglandin for the treatment of gastric ulcers in horses at this time.

Prevention

Negative factors have to be eliminated. Fresh food available (day and night) seems to be very important especially when in box stalls. Training has to be very progressive. Recurrent fasting, pain and long term treatment with NSAIDs are risk factors. Good observation and preventative treatment should prevent ulcers or allow to recognize them at an early stage.

Recent information on gastric ulcer prophylaxis in the critically ill neonates suggested that this is no longer appropriate. Prophylactic treatment of critically ill neonates for gastric ulceration has been standard therapy for years. This was due to evidence of

clinically 'silent' ulcers and concern over catastrophic rupture of unrecognized ulcers. Early treatment of sepsis in these neonates, sufficient oxygenation, improved monitoring, institution of enteral feedings and improved nursing all may contribute to the reduction in clinically relevant gastric ulcers. It appears that the use of histamine type 2 receptor antagonists and proton pump inhibitors may not be beneficial in the neonatal foal.

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