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Gastric Ulcer Prophylaxis in the Critically Ill Equine Neonate (6-Nov-2001)

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Introduction

Gastric ulcer disease has been recognized in foals and adult horses. It is a complex disease and lesions vary in anatomic distribution, severity and cause. In the neonatal foal (<30 days of age) gastric ulcers and mucosal desquamation have been documented in clinically normal foals [1-4]. Due to this finding many clinicians feel it is necessary to treat critically ill neonates prophylactically with anti-ulcer medications, probably due to early reports of catastrophic rupture of unrecognized gastric ulcers in neonates being treated for other problems. Recently the pathophysiologic mechanism of gastric ulcer development has been described as an imbalance between protective and aggressive factors [5,6]. The cornerstone of treatment for gastric ulcer disease remains suppression of gastric acid, although in the clinically ill neonate prophylactic treatment to suppress gastric acid production may not be beneficial. This section contains old information on gastric ulcer disease in foals, but provides new concepts in gastric ulcer disease in the critically ill neonatal foal. Gastric ulcer disease in the neonate may very well be a distinct clinical entity, with a different underlying pathophysiology from gastric ulcer disease in the older foal.

Clinical Manifestation

Gastric ulcer disease in foals can be divided into 4 clinical syndromes as reported by Becht and Byars in 1986 [7]. These 4 syndromes are subclinical or silent ulcers, clinical or active ulcers, perforating ulcers and ulcers associated with gastric or duodenal obstruction [7]. The subclinical or silent ulcers are usually incidental findings at necropsy and most heal without treatment or apparent clinical problems [7]. A majority of these lesions are located in the squamous mucosa along the greater curvature and have been documented in up to 50% of young foals [1-4,7]. It appears that foals <30 days are the most susceptible to the mild ulcers and these lesions may occur in association with desquamation or "shedding" of the squamous epithelium [1-4,7]. Superficial ulcers in the gastric glandular mucosa have also been observed and these also heal without treatment or clinical incidence [1-4,7].

Clinically active gastric ulcers can occur in either the squamous or glandular portions of the stomach, but often occur in both areas [1-4,7]. These can be primary or secondary to an underlying problem. Clinical signs include diarrhea, abdominal pain, restlessness, rolling, lying in dorsal recumbency, excessive salivation and bruxism [1-4,7]. In the neonatal foal, the only clinical signs present may be depression or partial anorexia until a more catastrophic event occurs, such as perforation or stricture. A perforating ulcer results in diffuse peritonitis, profound depression, cardiovascular collapse, tachypnea, abdominal pain, tachycardia, injected toxic mucous membranes and abdominal distension [1-4,7]. The final syndrome is associated with lesions in the gastric mucosa extending from pylorus into proximal duodenum. These ulcers result in stricturing of the pylorus or proximal duodenum and are most commonly a sequela of healing ulcers [1-4,7]. These foals are usually older (>1 month of age) and will have a greater volume of reflux [1-4,7]. Bruxism and ptyalism are also more prominent.

Pathogenesis

Originally the pathophysiologic mechanism of gastric ulcer development was thought to be increased gastric acid production. More recently, ulcer formation has been ascribed to an imbalance between protective and aggressive factors [5,8,9]. These protective factors are responsible for maintaining a healthy gastro-intestinal tract and include maintenance of adequate mucosal blood flow, adequate mucous and bicarbonate production, prostaglandin E2 production, epithelial growth factor, gastric afferent innervation, epithelial cell restitution and gastroduodenal motility [5,6,8,9]. Probably the most important factor is maintenance of mucosa blood flow, which is responsible for supplying the epithelium with nutrients and oxygen and providing a route for disposal of hydrogen ions and agents that may be noxious to the mucosa [5,6,8,9]. Hypoxia, nitric oxide, prostaglandins and gastric afferent innervation can all influence mucosal blood flow [5,6,8,9]. The aggressive factors include gastric acid, bile salts, pepsin and various degradative enzymes [5,6,8,9]. These factors can either directly injure the

mucosa or cause damage indirectly by increasing the secretion of another more noxious agent. Few specific causes have been found for gastric ulcer disease in adults and foals. Excessive administration of non-steroidal antiinflammatories (NSAIDs) can result in ulceration of the glandular and squamous epithelium due to an inhibition of prostaglandin production which leads to a decrease in mucosal blood flow and an increase in acid production [5,6,8]. NSAIDs can also impair the healing of lesions [5,6,8]. In the critically ill neonate the focus on the etiology of gastric ulcers has shifted from an excessive amount of intraluminal gastric acid to gastric mucosal ischemia [10]. Shock, sepsis or trauma can result in gastric mucosal ischemia, allowing for the disruption of epithelial cell integrity and permitting damage by aggressive factors or providing an local environment favorable to the establishment of bacteria colonization including gram negative organisms or *Candida* [9,10]. Impairment of mucosal blood flow may also result in reperfusion injury, which could result in the formation of gastric ulcers [9,10]. In the sick neonatal foal (<7 days of age) a wide variability in the intragastric pH has been documented depending on the type of disease, severity and milk intake [11].

Diagnosis

The most sensitive and specific method for diagnosing gastric ulcers is visualization by endoscopic examination [3].

Gastroscopy enables one to assess the extent and severity of the lesions. In the neonate, gas used to insufflate the stomach should be removed at the end of the procedure to prevent colic. The aforementioned clinical signs may help to build a suspicion for gastric ulcers in foals. Other diagnostics may help ascertain the severity of the ulcers and include fecal occult blood or gastric blood, contrast radiography, abdominal ultrasound and abdominocentesis [3].

The presence of a very brown gastric reflux fluid may indicate the presence of bleeding ulcers. A positive fecal occult blood could also indicate bleeding ulcers although a positive result is unlikely due to degradation of hemoglobin by the colonic bacteria [3].

Contrast radiography is useful if delayed gastric emptying is suspected. If a stricture has developed in the outflow tract of the stomach a delay in complete emptying of barium from the stomach (>2 hours) may be noted [3]. Abdominal ultrasound may be useful to visualize free abdominal fluid and gastric or small intestinal distension if a perforation is suspected [3].

Abdominocentesis may also help confirm a perforation by revealing an inflammatory reaction or bacteria in the abdominal cavity [3].

Treatment

Traditional therapy includes mucosal adherents, histamine type 2 receptor antagonists, proton pump inhibitors and antacids [12].

The most widely used mucosal adherent is sucralfate which is a hydroxy aluminum salt of sucrose. The main therapeutic action of sucralfate is to bind to the negatively charged particles in the ulcer crater [12,13]. At a pH <2 sucralfate is converted to a sticky viscous gel, which adheres to the ulcer crater and remains adhered for 6 hours [12]. In the presence of a higher pH, the sucralfate remains in a suspension, but is still effective by inhibiting peptic activity by adsorbing pepsin and buffering hydrogen ions [12]. Other important actions of sucralfate not requiring a gel state include stimulating prostaglandin E, which helps maintain mucosal blood flow, increasing bicarbonate secretion, stimulating mucous secretion and binding of epidermal growth factor [12]. In 1993 Borne and others looked at the effect of sucralfate in subclinical ulcers in 6-7 month old foals. A majority of the ulcers were located in the squamous gastric mucosa and the results of the study revealed that after 14 days of treatment the sucralfate ulcer healing was not enhanced [13]. Sucralfate may be more beneficial in lesions of the glandular mucosa.

The histamine type 2 receptor antagonists include cimetidine, ranitidine and famotidine. These compounds block the interaction of histamine with the histamine type 2 receptor on the parietal cell resulting in inhibition of gastric acid secretion [11,12,14]. These agents cause a dose dependent inhibition of gastric acid secretion [12]. In clinically normal neonatal foals, intravenous and oral administration of ranitidine increased intragastric pH [14]. This study also documented that clinically normal neonatal foals have a highly acidic gastric fluid that was influenced by sucking [14]. Conversely, in critically ill neonatal foals the intragastric pH was variable and a limited response to ranitidine administration was noted [11]. This suggests that, at in critically ill neonatal foals, the development of gastric ulcers may not be due to increased intraluminal gastric acid.

The most commonly used proton pump inhibitor is omeprazole. This drug inhibits the secretion of hydrogen ion at the parietal cell by irreversibly binding to the hydrogen-potassium adenosine triphosphate proton pump of the cell [12,15]. In foals (4 - 12 weeks of age) with lesions in the stratified squamous mucosa, a majority of the lesions were healed after daily administration of omeprazole for 28 days [15]. To date no work has been done in neonatal foals (<30 days of age).

Antacids have been used to neutralize acid but their effects are short-lived and thus need to be administered frequently [12,16]. Bismuth compounds provide cytoprotection although in adults no significant change in gastric pH has been noted [12,16]. Table 1 summarizes the therapeutic agents for treating gastric ulcers in foal.

Table 1. Therapeutic agents for treating gastric ulcers in foals.		
Mucosal Protectants		
Sucralfate	10 - 20 mg/kg	P.O. Q6 - 8hr
Histamine Type 2 Receptor Antagonists		
Cimetadine	10 - 20 mg/kg	P.O. Q4hr
	6.6 mg/kg	I.V. Q4hr
Ranitidine	5 - 10 mg/kg	P.O. Q6hr - 12hr
	0.8 - 2.2 mg/kg	I.V. Q6hr
Proton-pump Inhibitors		
Omeprazole	4 mg/kg	P.O. Q24hr
	1-2 mg/kg	P.O. Q24hrs (prophylaxis)
Antacids		
Milk of Magnesia	2 - 4 oz/kg	P.O. Q12 -24hr
Maalox	240 ml	P.O. Q4hrs

Prophylactic treatment of critically ill neonates for gastric ulcers has been standard therapy for years, due to the evidence of clinically silent "ulcers" and concern over catastrophic rupture of unrecognized ulcers. There are several reasons why this may not be the most appropriate approach. The human medical literature has reported an increased incidence of nosocomial pneumonia and systemic sepsis associated with a high gastric pH [17-19,21,23]. Those patients in the intensive care units treated prophylactically with histamine type 2 receptor antagonists were more likely to develop pneumonia during ventilation therapy and gastric colonization with potentially pathogenic bacteria or yeast [17,21]. It appears that an acid environment is protective against bacterial colonization and translocation of bacteria [17-19,21]. Another point against gastric ulcer prophylaxis in the critically ill neonate, as stated earlier, is that the pathogenesis in this specific group may not involve intraluminal gastric acid, but instead maybe involve hypoxic/ischemic insult to the gastric mucosa [10]. A recent report revealed that gastric ulcer disease in equine neonatal intensive care unit patients is independent of pharmacological prophylaxis [22]. Table 2 depicts that in the years when gastric ulcer prophylaxis was standard (1989-1996) compared to the years when prophylaxis was not standard (1997-1999) there was no statistically detectable difference between these two populations [22].

Additionally, despite decreased treatment, the incidence of gastric ulcers found in these foals at necropsy had decreased [22]. Similarly in a human intensive care unit, the incidence of stress ulcers had decreased independent of the use of prophylaxis [10,23]. A reason for the decrease in both of these situations may be due to an improvement in the management of patients in the critical care unit. Early treatment of sepsis, 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. These therapies are standard in the treatment of gastric ulcer disease in the older foal and have been demonstrated to be efficacious. The medical literature has reported that in some instances sucralfate may be most beneficial. In a rat model sucralfate reduced the rate of bacterial translocation during hemorrhagic shock [24,25]. Sucralfate may also prohibit the generation of acute gastric mucosal injury and progression to ulcer formation induced by ischemia-reperfusion [25]. In a human medical intensive care unit, airway colonization by new pathogens occurred more frequently in patients receiving agents that increased gastric pH

than in those receiving sucralfate, suggesting again that maintaining the gastric acid barrier, if present, is important in the management of some critically ill patients [17,23].

In pediatric patients risk factors for the development of upper gastrointestinal tract bleeding has been identified and include burn patients, head trauma patients and patients receiving drugs known to compromise gastrointestinal integrity [10,19]. In the critically ill neonatal foal such factors have not been identified, although those treated routinely with NSAIDS may be more likely to develop gastric lesions. Prophylactic treatment for gastric ulcer in critically ill neonates may not be necessary and careful consideration should be given prior to their administration.

Table 2. Ulcer prophylaxis in the Neonatal Intensive Care Unit. Results are from a retrospective study evaluating the presence or absence of gastric ulceration in foals dying or euthanized due to critical illness in the neonatal period and subjected to complete post-mortem examination. Medical records were searched for record of treatment with anti-ulcer medication.				
Results				
Years	Treated and Gastric Ulcers	Treated and No Gastric Ulcers	Not Treated and Gastric Ulcers	Not Treated and No Gastric Ulcers
1989-1996 (n = 90)	18 (20%)	21 (23.3%)	11 (12.2%)	40 (44.4%)
1997-1999 (n = 51)	1 (2.0%)	2 (3.9%)	7 (13.7%)	41 (80.3%)
Total (n = 141)	19 (13.4%)	23 (16.3%)	18 (12.7%)	81 (57.4%)

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