Intragastric pH in critically ill neonatal foals and the effect of ranitidine

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Objective—To characterize intragastric pH profiles in critically ill foals and determine whether administration of ranitidine altered pH profiles.

Design—Prospective observational study.

Animals—23 hospitalized neonatal foals ≤ 4 days of age.

Procedure—Intragastric pH was measured continuously for up to 24 hours by use of an indwelling electrode and continuous data recording system. In 21 foals, ranitidine was administered IV.

Results—10 foals had predominantly or exclusively alkaline profiles, 10 had profiles typical of those reported for healthy foals, with periods of acidity (hourly mean pH < 5.0 at least once), and 3 had atypical profiles with periods of acidity. All 10 foals that had intragastric pH profiles typical of healthy foals survived, whereas only 2 foals with alkaline profiles survived, and none of the foals with atypical profiles survived. The effects of ranitidine administration could not be assessed in 13 foals because of a high baseline intragastric pH. In 7 of the remaining 9, ranitidine administration resulted in an alkalinizing response, but this response was often of blunted duration. Ranitidine administration did not appear to alter the intragastric pH profile in the remaining 2 foals.

Conclusions and Clinical Relevance—Results suggested that hospitalized critically ill foals often have intragastric pH profiles different from those reported for healthy foals and may respond differently to ranitidine administration than do healthy foals. Many critically ill foals have continuously alkaline intragastric pH profiles, questioning the need for prophylactic administration of ranitidine in all critically ill foals. (*J Am Vet Med Assoc* 2001;218:907–911)

Equine gastric ulcer syndrome is a common disease complex associated with ulceration of the esophageal, gastric, or duodenal mucosa in foals and adult horses.[1] Lesions in horses with gastric ulcer syndrome vary widely with respect to severity, anatomic distribution, and cause. Major intrinsic factors involved in promoting ulcer formation are hydrochloric acid, bile acids, and pepsin. Major intrinsic factors involved in suppressing ulcer formation by promoting mucosal protection are mucus-bicarbonate production, mucosal blood flow, mucosal prostaglandin E_2 production, epidermal growth factor, gastric afferent innervation, epithelial cell restitution, and gastroduodenal motility.[2,3] In humans, extrinsic factors involved in ulcer formation include nonsteroidal anti-inflammatory drugs, *Helicobacter pylori* infection, stress, changes in diet, and gastrointestinal tract disorders, especially disorders resulting in delayed gastric emptying.[3] In human neonates, physiologic stress such as that associated with a major illness is of particular importance.[4] Many factors important for ulcer formation in human beings are also believed to be important in horses, but to date an infectious agent such as *H pylori* has not been identified in horses or foals with gastric ulcer syndrome.[2,5]

Gastric ulcer syndrome is of major clinical and economic importance in foals and adult horses.[1,2,6-11] Prevalence in foals has been reported to be as high as 25 to 57%.[12] Clinical signs attributable to gastric ulcer syndrome are variable and range from none to anorexia, colic, bruxism, and ptyalism, but neonatal foals with gastric ulceration rarely demonstrate the classic clinical signs seen in older foals, even up to the point of perforation. Consequently, many neonatal foals are treated prophylactically with **histamine$_2$ (H_2)** receptor antagonists whenever they become sick in an effort to prevent gastric ulceration. Unfortunately, information regarding efficacy of this class of drugs in sick neonatal foals is not currently available, and the response to antiulcer medications in sick human neonates is influenced by several factors, including CNS disease, delayed gastric emptying, small intestinal ileus, and alterations in drug pharmacokinetics.[13,14]

Measurement of the intragastric pH is the most common method for monitoring the potential for gastric ulceration and the response to treatment.[15-17] Intragastric pH is commonly monitored continuously in human patients, allowing physicians to determine how pH responds to meals, body position, and various anti-ulcer medications such as H_2-receptor antagonists and proton pump inhibitors.[16] Intragastric pH has been monitored continuously in healthy foals. In 1 study,[18] median 8-hour pH was 4.1 at 1 day of age, 3.4 at 2 days of age, and 2.3 at 7 days of age, with little change at 8 weeks and 3 months of age. In another study,[19] mean hourly pH did not vary with age from 2 to 6 days of age. Intragastric pH ranged from 0.8 to 6.0 without any obvious diurnal variation. There was, however, a marked alkalinizing effect of milk ingestion, and intragastric pH was lowest during periods of sleep.[19] Results of these studies suggest that sick neonatal foals in which milk intake may be infrequent and the volume of milk ingested may be low may have prolonged periods with low intragastric pH.

Histamine$_2$-receptor antagonists inhibit gastric acid secretion by competing with H_2 receptors on parietal cells.[20] They have been reported to inhibit acid produc-

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tion in adult horses and are widely used in foals and adult horses for prophylaxis and treatment of gastric ulcer syndrome.[21-26] As in humans, the aim is to maintain intragastric pH ≥ 4.0.[3] In healthy neonatal foals, IV administration of ranitidine (2 mg/kg [0.9 mg/lb] of body weight) maintained intragastric pH ≥ 4.0 for 4 hours, and oral administration of ranitidine (6.6 mg/kg [3 mg/lb]) was effective for 7 hours.[19] However, it is unclear whether ranitidine will have the same effects in sick neonatal foals. The purposes of the study reported here were to characterize intragastric pH profiles in hospitalized critically ill neonatal foals and determine whether administration of ranitidine altered pH profiles.

Materials And Methods

The experimental protocol was approved by the University of Florida Institutional Animal Care and Use Committee and the Veterinary Medical Teaching Hospital's Clinical Research Review Committee.

Foals—Twenty-three foals ≤ 5 days old at time of admission examined at the Alec P. and Louise H. Courtelis Equine Teaching Hospital at the University of Florida between November 1997 and April 1999 were included in the study. All foals had required placement of an indwelling nasogastric tube; permission of the owner and attending clinician for inclusion in the study was obtained.

Twenty-one foals received ranitidine hydrochloride (2 mg/kg [0.9 mg/lb], IV, q 8 h) during the study. Four of these had received ranitidine prior to inclusion in the study. One foal did not receive ranitidine during the study, and a second foal received ranitidine orally (6.6 mg/kg [3 mg/lb], q 8 h). Endoscopy of the gastric mucosa was not routinely performed. Data recorded from each foal's medical record included age, breed, sex, primary diseases, duration of gestation, body weight, modified sepsis score,[27] medications administered, whether the foal was predominantly recumbent or ambulatory, time of ranitidine administration, feeding schedule, results of bacterial culture of blood samples obtained at admission, outcome, and necropsy results, if applicable. Foals were considered premature if gestation was < 320 days.

Treatment—All foals were treated with parenteral fluids for replacement of fluid losses and maintenance. Oxygen was administered if necessary, and foals were treated with potassium penicillin G (22,000 to 44,000 U/kg [10,000 to 20,000 U/lb], IV, q 6 h) and amikacin sulfate (20 to 21 mg/kg [9.1 to 9.5 mg/lb], IV, q 24 h). Artificial tear ointment or triple antibiotic ophthalmic ointment was administered every 4 to 6 hours. Other therapeutic medications administered to individual foals included plasma, flunixin meglumine, magnesium sulfate, dimethyl sulfoxide, mannitol, dopamine, dobutamine, doxapram hydrochloride, metronidazole, diazepam, phenobarbital, oxytetracycline, atropine 1% ophthalmic ointment, and partial or total parenteral nutrition. Mechanical ventilation was performed in 5 foals.

Foals were fed mare's milk or a commercial milk replacer[a] at a rate of 10 to 25% of body weight daily, divided into feedings administered via a nasogastric tube every 1 to 2 hours. The feeding protocol was modified as necessary; some foals were fed colostrum initially, and others were fed at a more conservative rate. In 5 foals, enteral feedings were not initiated or were discontinued because of nasogastric reflux or abdominal distention. All predominantly recumbent foals were kept on well-padded beds and turned every 1 to 2 hours.

Measurement of intragastric pH—Prior to placement of the nasogastric tube in each foal, a disposable antimony pH electrode[b] that had been calibrated was placed in the lumen of the nasogastric tube so that the electrode tip protruded 3 to 4 cm beyond the end of the tube. The nasogastric tube was then inserted so that milk would pass into it. The electrode was considered to be in the proper place if gastric fluid could be aspirated from the nasogastric tube, the electrode indicated a pH < 3.5, or abdominal radiography indicated that the tip of the nasogastric tube was located within gastric fluid. The electrode was connected to a data recording system[c] that was attached to the foal's back with a harness if the foal was ambulatory or secured to the foal's torso with adhesive tape if the foal was predominantly recumbent.

The data recording system automatically recorded pH every 4 seconds. An attempt was made to measure intragastric pH continuously for 24 hours in each foal. In 15 foals, however, pH was recorded for < 24 hours because of premature dislodgement of the nasogastric tube or electrode, euthanasia, or death. However, pH was measured continuously for a minimum of 6 hours in all foals, and mean duration of recording was 17.4 hours. In all foals, pH recording was initiated within 29 hours after admission (mean, 6.6 hours; range, 1.5 to 29 hours). When recording was finished, data were loaded onto a personal computer, using specialized software,[d] for analysis. For each hour of recording, mean pH and percentage of time pH was ≥ 4 were calculated.

Results

The 23 foals consisted of 13 males and 10 females. There were 20 Thoroughbreds, 1 Paint, 1 Shire, and 1 Quarter Horse. Duration of gestation ranged from 273 to 380 days. Sixteen foals were 1 day old at the time of admission; the others were 2 to 4 days old. The most common reasons for admission were sepsis (11 foals), prematurity (7), and **hypoxic ischemic encephalomyelopathy** (**HIE**; 13). Two foals died, and 7 were euthanatized. The remaining 14 foals were discharged from the hospital, but 2 of these foals died or were euthanatized shortly after discharge because of the primary disease process or associated complications. Necropsy did not reveal gastric or duodenal ulceration in any of the foals that died or were euthanatized.

Intragastric pH profiles varied widely among individuals. Mean hourly pH ranged from 1.3 to 8, and hourly percentage of time pH was ≥ 4 ranged from 0 to 100%. Ten foals (43%) had an intragastric pH profile that was predominantly or exclusively alkaline; hourly mean pH was never < 5.0 in these foals, and the intragastric pH did not seem to change in response to administration of ranitidine (**Fig 1**). Ten foals (43%) had profiles similar to those recorded for healthy foals, with periods of acidity (hourly mean pH < 5.0 at least once; **Fig 2**). Three foals had periods of acidity but had atypical intragastric pH profiles. One of these foals initially had an acid pH but developed an alkaline pH after receiving ranitidine, and pH remained alkaline for the remainder of the recording period (22 hours after ranitidine administration). A second foal had an intragastric pH that remained in the range of 3.5 to 6.0 throughout the recording period. The third foal had a pH of 3 initially; pH increased to 6 for 15 minutes after ranitidine administration, decreased to 4, and then gradually increased to 7 during the subsequent 5 hours and remained alkaline for the remainder of the recording period. Although an increase in intragastric pH was evident after feeding in some foals, periods between

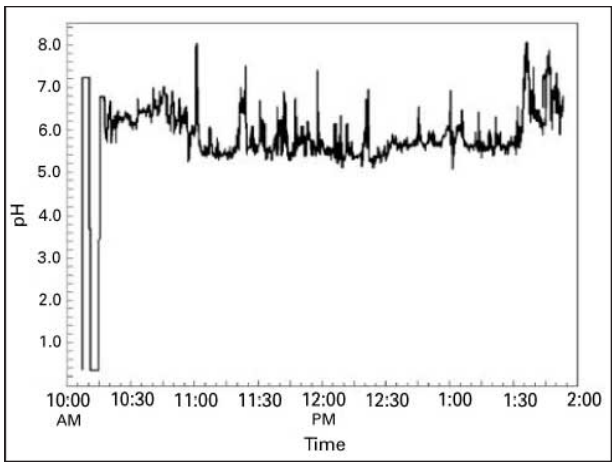

Figure 1—A selected portion of the intragastric pH profile from a foal with sepsis. Notice that pH was never < 5.2. Arrow indicates time of IV ranitidine administration. Mare's milk was administered via nasogastric tube at 11:00 AM and 12:35 and 2:00 PM.

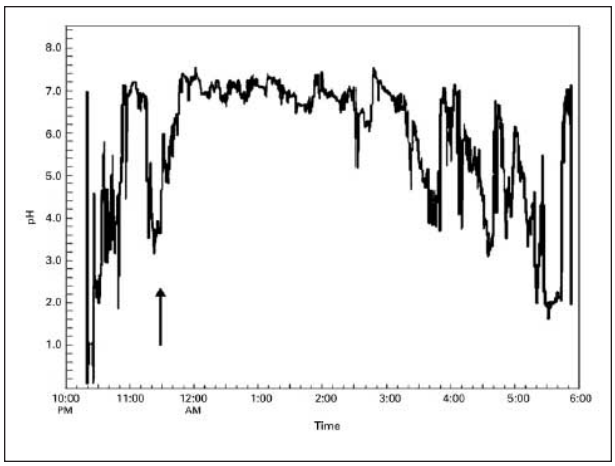

Figure 3—A selected portion of the intragastric pH profile from a foal with hypoxic ischemic encephalomyelopathy. Arrow indicates time of IV administration of ranitidine hydrochloride. Notice the alkalinizing response following ranitidine administration.

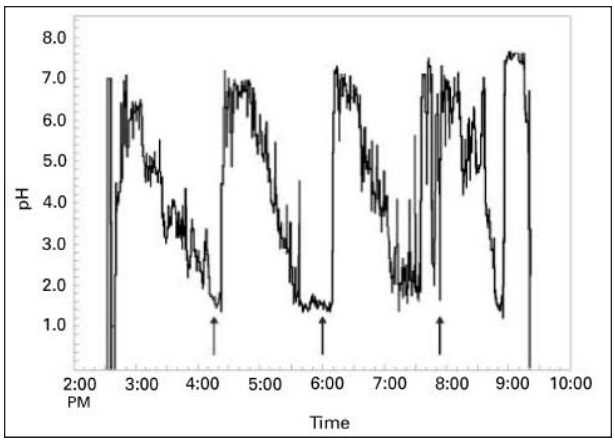

Figure 2—A selected portion of the intragastric pH profile from a foal with hypoxic ischemic encephalomyelopathy. Arrows indicate times when mare's milk was administered through a nasogastric tube. Ranitidine hydrochloride was administered IV at 2:00 PM.

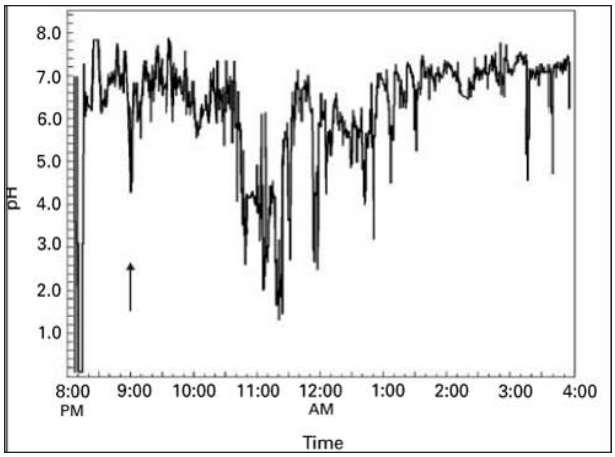

Figure 4—A selected portion of the intragastric pH profile from a foal with sepsis. Arrow indicates time of IV administration of ranitidine hydrochloride. High intragastric pH prior to ranitidine administration precluded any assessment of drug effects.

feedings were not always associated with an acidic intragastric pH.

All 10 foals that had intragastric pH profiles typical of healthy foals survived, whereas only 2 of the 10 foals with alkaline profiles survived, and none of the foals with atypical profiles survived. Six of 7 premature foals had an alkaline profile; the seventh had an atypical profile. Four premature foals were also septic, but none had HIE, and none survived. Eleven of 13 foals with HIE survived. Of these, 9 had a profile typical of healthy foals, 3 (all of which were also septic) had persistent intragastric alkalinity, and 1 had an atypical profile. Only 4 of 11 septic foals survived, and only 2 of these 11 foals had a normal pH profile.

In 7 foals, an alkalinizing response that could be directly attributed to ranitidine administration was seen (**Fig 3**). However, duration of this response was variable, lasting < 1 hour in 3 foals. High intragastric pH prior to administration of ranitidine precluded assessment of drug effects in 13 foals (**Fig 4**). Two foals had a profile typical of healthy foals independent of ranitidine administration (**Fig 5**).

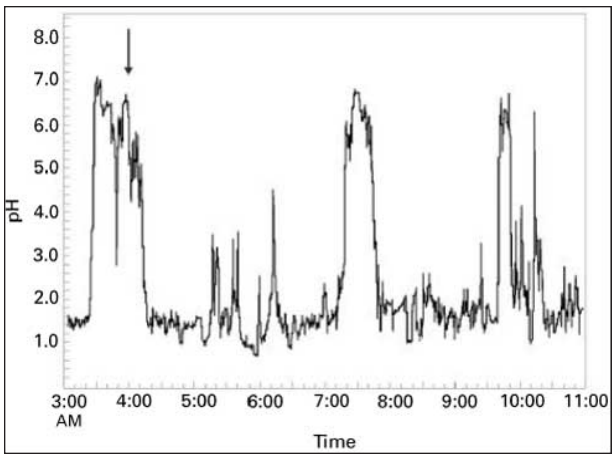

Figure 5—A selected portion of the intragastric pH profile from a foal with hypoxic ischemic encephalomyelopathy. Arrow indicates time of IV administration of ranitidine hydrochloride. Intragastric pH appeared to be independent of ranitidine administration.

Discussion

Methods for measuring intragastric pH previously reported for clinically normal foals[19] were easily adapted for use in clinically ill foals in the present study. Inherent difficulties with the use of hospitalized patients were encountered, most notably the wide variations in duration of gestation, diseases, and treatment regimens. In most foals, ranitidine was given IV to eliminate variations in drug uptake associated with decreased gastrointestinal tract motility and absorption and alterations in bile flow.

Compared with profiles reported for clinically normal foals,[19] intragastric pH profiles for foals in the present study were more alkaline overall and displayed more individual variation. A specific cause of the continuously alkaline intragastric pH profiles in 10 of these foals is not apparent. One possible explanation is that these foals had ileus with enterogastric reflux resulting in dilution of the normally acidic gastric contents by the more alkaline duodenal fluid. Some foals with continuously alkaline pH profiles had findings consistent with ileus, including gastric reflux, abdominal distention, minimal borborygmi or passage of feces, and ultrasonographic findings of gastric distention or dilated poorly motile small intestine loops.

Central nervous system disease is a common finding in foals admitted to neonatal intensive care units, and the most common CNS disease in neonatal foals is HIE. Many of the foals in the present study with HIE were examined because of an inability to suckle appropriately. Hypoxic ischemic encephalomyelopathy has been associated with periparturient asphyxia, which can also result in ischemic damage to other organs, most notably the renal system and gastrointestinal tract.[28] Gastrointestinal tract ischemia and subsequent reperfusion injury could result in a myriad of effects, including decreased motility and alterations in mucosal protection, blood flow, or acid production. Of the 13 foals with HIE in the present study, 9 had an intragastric pH profile typical of healthy foals, and 11 survived. One of the 2 foals that died was also septic and had an alkaline profile; the other had an atypical profile and enterocolitis. These results, therefore, suggest that foals with uncomplicated HIE will likely have intragastric pH profiles similar to those seen in clinically normal foals.

Six of the 7 premature foals in the present study had continuously alkaline intragastric pH profiles, and decreased or absent gastric acid production could possibly explain this alkalinity. The remaining premature foal had a period of acidity but never had an acid pH after administration of the first dose of ranitidine. However, 4 of the 7 premature foals were also septic, and none of them survived. Thus, the premature foals represented a severely ill segment of the population, and multiple factors may have contributed to the intragastric alkalinity. Premature human infants are capable of gastric acid production as early as 28 weeks of gestation.[14] In contrast, the ontogeny of gastric acid production in foals is not known.

In the present study, a consistent increase in intragastric pH in response to ranitidine administration was not evident. In some foals, a distinct increase in pH was evident following ranitidine administration, even though the pretreatment hourly mean pH was > 4.0. In some foals exhibiting a treatment response, however, the increase in pH was of much shorter duration than that reported for clinically normal foals. This shortened or absent response is similar to that reported for critically ill human neonates, particularly those with CNS injury or severe illness in which intragastric pH is poorly controlled during continuous infusion or bolus IV administration of ranitidine.[13,29] Differences in response to ranitidine in severely ill individuals may be related to a number of factors, including a delay in gastric emptying, which would likely result in decreased or erratic drug absorption from the small intestine following oral administration.[20] The use of a continuous infusion of ranitidine in children did not improve pH control, compared with that seen with bolus dosing, but it did decrease the variability.[13] In preterm infants, however, a prolonged response to ranitidine administration can be seen.[14] This may account for the prolonged period of alkalinity following ranitidine administration in the 1 premature foal that had an acidic pH prior to treatment and the continuously alkaline profile in 2 premature foals that had received ranitidine prior to recording.

Plasma ranitidine concentrations were not measured in the present study. Therefore, it was not possible to determine what role, if any, individual variations in ranitidine pharmacokinetics may have played in the response to ranitidine administration. For foals with an alkaline pH prior to ranitidine administration, a treatment effect would not be expected, because administration of ranitidine to clinically normal foals causes an increase in intragastric pH only to 6 to 8.[19] In addition, in the 4 foals that received ranitidine before inclusion in the study, a prolonged drug response may have occurred. For foals with an acidic pH prior to ranitidine administration, however, the lack of treatment effect is more difficult to explain. Potentially, like many critically ill human neonates, these foals may simply require a higher dosage than healthy foals to attain a similar effect.

In the present study, foals that were able to produce acid, as indicated by at least 1 hourly mean pH < 5.0, had a higher survival rate (10/13) than did foals that had predominantly or exclusively alkaline profiles (2/10). This difference raises the issue of the potential protective effect of an acidic intragastric pH against intestinal bacterial colonization and subsequent translocation in neonates. In critically ill children, intragastric pH < 7.3 at the time of admission to a pediatric intensive care unit was associated with a higher survival rate than was an intragastric pH ≥ 7.3.[30] In neonatal rabbits challenge exposed with *Enterobacter cloacae* via gavage, intragastric acidity was associated with decreased rates of intestinal colonization and bacterial translocation to the mesenteric lymph nodes, spleen, and liver.[31] In a clinical trial involving critically ill human neonates, treatment with ranitidine resulted in increases in intragastric pH and gastric bacterial colonization but did not increase the risk of infection.[32]

Although necropsy did not reveal ulcers in any of the foals in the present study that died or were eutha-

natized, gastric ulceration with and without perforation has been seen in similar foals. Gastric acid is only 1 factor contributing to gastric ulceration, and ulceration could likely occur in the absence of intragastric acidity. Nevertheless, results of the present study raise questions regarding the efficacy of ranitidine in critically ill foals. In addition, the need for constant intragastric alkalinity is controversial, because intragastric acidity may protect against bacterial translocation in young foals.

[a]Mare's Milk Plus, Buckeye Feed Mills, Dalton, Ohio.
[b]Zinectics 24, Synectics Medical, Shoreview, Minn.
[c]Digitrapper MD, Synectics Medical, Shoreview, Minn.
[d]EsopHagram, Synectics Medical, Shoreview, Minn.

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