

## Effects of Intravenously Administrated Omeprazole on Gastric Juice pH and Gastric Ulcer Scores in Adult Horses

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The study was performed to evaluate the efficacy of omeprazole powder in sterile water, administered intravenously, on gastric juice pH in adult horses with naturally occurring gastric ulcers. Omeprazole (0.5 mg/kg, IV) was administered once daily for 5 days to 6 adult horses with gastric ulcers. Gastric juice was aspirated through the biopsy channel of an endoscope and pH was measured before and 1 hour after administration of omeprazole on day 1, and then before and after administration of omeprazole on day 5. Gastric ulcer scores were recorded on day 1 before administration of omeprazole and on day 5, 23 hours after the 4th daily dose. Gastric juice pH and ulcer scores were compared between the times. When compared with the pre-injection value ( $2.01 \pm 0.42$ ), mean  $\pm$  SD gastric juice pH was significantly higher when measured 1 hour after administration of the initial dose ( $4.35 \pm 2.31$ ), and before ( $5.27 \pm 1.74$ ) and 1 hour after ( $7.00 \pm 0.25$ ) administration of omeprazole on day 5. Nonglandular gastric ulcer number score significantly decreased from a mean  $\pm$  SD of  $3.2 \pm 0.80$  to  $2.0 \pm 1.1$ , but nonglandular gastric ulcer severity score remained the same. Few glandular ulcers were seen in the study, and scores did not change. Because of its potent and long duration of action on gastric juice pH, this intravenous formulation of omeprazole may show promise for treatment of equine gastric ulcer syndrome (EGUS) in horses with dysphagia, gastric reflux, or other conditions that restrict oral intake of omeprazole paste.<sup>a</sup> Aspiration of gastric juice and measurement of pH can be of use to determine whether the desired pH  $> 4.0$  has been reached after omeprazole treatment.

**Key words:** Equine; Equine Gastric Ulcer Syndrome; Gastroenterology; Stomach.

### Introduction

Omeprazole is a substituted benzimidazole that decreases gastric acid secretion and increases gastric juice pH by blocking the H<sup>+</sup>, K<sup>+</sup> ATPase (proton pump) in the secretory membrane of the parietal cell.<sup>1</sup> This drug is also classified as a proton-pump inhibitor. Gastric juice pH ( $< 4.0$ ), long periods of no feed intake and environmental stress are presumed causes of gastric ulcers in man and horses.<sup>2–5</sup> In vitro studies in horses have revealed that nonglandular stomach mucosa when exposed to HCl at pH  $\leq 4.0$  have significantly decreased tissue sodium transport and resistance, with histopathologic evidence of cell swelling.<sup>3,4</sup> Furthermore, healing rates of esophageal, gastric, and duodenal ulcers in people strongly correlate with control of gastric juice pH by proton-pump inhibitors.<sup>6</sup> Also, a similar correlation was observed after 8 weeks of treatment with proton-pump inhibitors in human patients with erosive esophagitis (gastroesophageal reflux disease [GERD]) and healing rates and duration of intragastric pH  $> 4.0$  ( $r = 0.87$ ;  $P < .05$ ).<sup>7</sup> Because gastric ulcer disease in the squamous region of horse stomach has been likened to GERD in people, and inhibition of gastric acid secretion and maintenance of the gastric juice pH above 4.0 is the

mainstay of treatment for gastric ulcer disease in humans and equine gastric ulcer syndrome (EGUS).<sup>8–10</sup>

Omeprazole paste<sup>a</sup> increases gastric juice pH and is effective in the treatment and prevention of EGUS, but this formulation can only be administered PO.<sup>11,12</sup> However, administration of oral medications in horses with gastric reflux or dysphagia is contraindicated, so an intravenous formulation of omeprazole would be helpful to increase gastric juice pH in horses with these conditions.

The purpose of this study was to determine the effect of intravenously administered omeprazole<sup>b</sup> on gastric juice pH and gastric ulcer score. Results of this study will aid in the evaluation of this formulation for treatment of EGUS in horses that cannot receive the oral paste formulation, or that require aggressive treatment to prevent gastric rupture secondary to severe gastric ulceration.

### Materials and Methods

#### Animals and Study Design

Six healthy adult mixed-breed Quarter Horse mares (mean: 8.2 years of age; range 4–12 years of age) with a mean weight  $\pm$  SD of  $432 \pm 29$  kg were used in the study. The mares were part of the University of Tennessee reproduction teaching herd housed at the university farm in a pasture environment. Before entering the study, the horses had normal physical examinations and were dewormed 1 month before starting the study. The horses were vaccinated, as part of a regular scheduled maintenance program, 6 months before starting the study. Two weeks before the beginning of the study, the horses were transported to the veterinary teaching hospital, where they were housed individually in stalls measuring  $3.7 \times 3.7$  m, and horses were fed brome grass hay ad libitum and grain<sup>c</sup> (1 kg, twice daily). The mares were chosen because of temperament and handling to facilitate passing of the endoscope and were not prescreened based on ulcer score. All procedures performed in this study were approved by the Institutional Animal Care and Use Committee at the University of Tennessee (IACUC #1402).

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**Table 1.** Mean  $\pm$  SD gastric juice pH value and gastric ulcer scores in 6 horses before and after omeprazole (0.5 mg/kg, IV, once daily for 5 days) administration.

Parameter	pH	NG Number Score	NG Severity Score	G Number Score	G Severity Score
Day 1, Before OME	2.01 $\pm$ 0.42 <sup>a</sup>	3.2 $\pm$ 0.8	1.5 $\pm$ 0.5	0.3 $\pm$ 0.5	0.3 $\pm$ 0.5
Day 1, 1 hour after OME	4.35 $\pm$ 2.31 <sup>b</sup>	—	—	—	—
Day 5, Before OME	5.27 $\pm$ 1.74 <sup>b</sup>	2.0 $\pm$ 1.1*	1.8 $\pm$ 1.0	0	0
Day 5, 1 hour after OME	7.00 $\pm$ 0.25 <sup>c</sup>	—	—	—	—

OME, omeprazole; NG, nonglandular mucosa of the stomach; G, glandular mucosa of the stomach.

<sup>a,b,c</sup> Values with different superscripts are significantly different from each other ( $P < .05$ ).

\* Values denote significant ( $P < .05$ ) difference when compared with control value.

Each horse served as its own control. Omeprazole (0.5 mg/kg), sterile powder<sup>b</sup> reconstituted with sterile water, was administered intravenously between 8 AM and 10 AM each morning for 5 consecutive days, via 18-gauge, 1.5-inch needle.

### Endoscopic Examination and Gastric Ulcer Scoring

Horses were evaluated on days 1 and 5 of the study after feed and water were removed for 12 and 4 hours, respectively. Horses were restrained in stocks and sedated with detomidine<sup>d</sup> (5 mg, IV), 15 minutes before each endoscopic procedure. A 3-m gastroscop<sup>e</sup> was then introduced into the fundic portion of the stomach, and gastric juice was aspirated through the biopsy channel under suction. The horses underwent endoscopy, and gastric juice was collected before and 1 hour after omeprazole administration on days 1 and 5, so that each horse underwent endoscopy twice, 1 hour apart, on these 2 days. The horses were muzzled and not allowed access to feed or water during the period between endoscopic procedures.

During each endoscopic procedure, gastric juice was collected and the stomach insufflated using an air compressor attached to the biopsy canal. The stomach was given a gastric ulcer score on days 1 and 5, only during the first endoscopic procedure, using a previously published gastric ulcer scoring system.<sup>13</sup>

### Measurement of Gastric Juice pH

Gastric juice was collected in a covered glass bottle from the endoscope biopsy channel. The pH was measured immediately after collection using a portable pH meter<sup>f</sup> with attached probe. The pH meter was calibrated using standard pH 4.0 and 7.0 solutions before the beginning of each collection period.

### Statistical Analysis

Values for gastric juice pH and gastric ulcer score before and after treatment on days 1 and 5 were compared statistically using a statistical analysis program.<sup>g</sup> Results are presented as mean  $\pm$  SD values. Statistical difference for gastric juice pH values and gastric ulcer scores was determined using a mixed analysis of variance (ANOVA) blocked on horse (with repeated measures for pH) and statistical significance was considered when  $P < .05$ .

### Results

Horses were clinically normal during the study period. No adverse responses to omeprazole, the gastroscopic procedure, or aspiration of the gastric juice were detected. Mean body weight did not change significantly during the study period (bwt).

Gastric juice pH was low in all horses before omeprazole administration and varied from 1.54 to

2.65. On day 1, mean  $\pm$  SD gastric juice pH significantly increased from 2.01  $\pm$  0.42 before omeprazole administration to 4.35  $\pm$  2.31, 1 hour after omeprazole administration (Table 1). However, only 3 of 6 horses had gastric juice pH values of  $>4.0$ . On day 5, gastric juice pH was 5.27  $\pm$  1.74 before omeprazole was administered (23 hours after the 4th daily dose was given) and only 5 of 6 horses had a gastric juice pH of  $>4.0$  (Table 1). One hour after the 5th daily omeprazole dose, mean gastric juice pH significantly increased to 7.00  $\pm$  0.25 and all horses had gastric juice pH of  $>4.0$ .

Mean  $\pm$  SD nonglandular gastric ulcer number score significantly decreased from 3.2  $\pm$  0.8 on day 1 to 2.0  $\pm$  1.1 on day 5 (Table 1). The nonglandular gastric ulcer severity score did not change between day 1 (1.5  $\pm$  0.5) and day 5 (1.8  $\pm$  1.0). Two horses in this study had glandular ulcers and both healed during the study period, but there was no significant difference in glandular ulcer scores during the study period.

### Discussion

Gastric juice pH was variable but low (mean 2.01  $\pm$  0.42; range 1.54–2.64) in all of the horses before omeprazole administration. After omeprazole administration, there was considerable variation in pH (range, 1.65–6.77) between horses. Considerable inter-horse variation has been reported in basal and posttreatment gastric juice pH measurements in horses.<sup>11,14</sup> However, although variability in gastric juice pH measurements exists among horses, there appears to be good intra-individual reproducibility for recordings repeated in the same horse.<sup>11,14</sup> Also, repeated sampling of gastric juice may lead to altered gastric juice pH results. However, a previous report in horses where gastric juice samples were taken from horses at 0.5, 2, 4, 8, 18, 24, 36, 42, 48, 60, and 72 hours revealed minimal variability in gastric juice pH measurements within the same horse over these multiple sampling periods, and these data are similar to data reported on horses in this study.<sup>15</sup>

Omeprazole given intravenously (0.5 mg/kg bwt) resulted in a significant increase in gastric juice pH in horses in this study. One hour after the first dose, mean gastric juice pH increased to greater than 4.0 in 3 of 6 horses. Gastric juice pH values obtained before and after a single intravenous dose of omeprazole in horses in this

study were similar to previous reports in the literature in horses with gastric cannulae.<sup>14,16</sup> In those studies, gastric juice pH values increased from a mean of 2.6 to a mean of 5.7, 30 minutes after the first omeprazole dose (0.5 mg/kg, IV), and only 4 of 7 horses had a gastric juice pH > 4.0. The onset of action of this intravenous formulation of omeprazole was rapid and potent. Omeprazole has a potent inhibitory effect on gastric acid secretion that results from strong binding of the inhibitory molecule of omeprazole to the H<sup>+</sup>, K<sup>+</sup> ATPase enzyme (proton pump) in the gastric parietal cell.<sup>17-19</sup> Omeprazole accumulates in the acidic secretory canaliculi of the gastric parietal cell because of its weak base properties (pKa = 4.0). Once inside the canaliculi, the omeprazole molecule is rapidly transformed into its active form and binds to the H<sup>+</sup>, K<sup>+</sup> ATPase enzyme, which is in close proximity.

However, another explanation for the increase in gastric juice pH in these horses after omeprazole administration could have been related to the effect of the sedative agent, detomidine, on gastric emptying. Alpha-2 agonists, detomidine (0.01 mg/kg, IV) and to a lesser extent xylazine (0.5 and 1.0 mg/kg, IV), have been shown to delay solid and liquid phase gastric emptying in horses,<sup>20,21</sup> which could have raised gastric juice pH by increasing the amount of bicarbonate-rich duodenal reflux present in the stomach during the second endoscopic examination. Furthermore, other alpha-2 agonists clonidine, guafacine, and B-HT 920 have been shown to decrease gastric secretion in rats.<sup>22</sup> However, the effect of sedation on gastric juice pH seems less likely because results in the horses studied here were similar to those reported in nonsedated and sedated horses administered omeprazole intravenously,<sup>14</sup> subcutaneously,<sup>15</sup> and intramuscularly.<sup>23</sup> Also, during the second endoscopic procedure, the volume of gastric juice in the stomach by visual examination did not appear to be increased compared with the first endoscopic procedure. However, the volume was only estimated by visual examination and no quantitative measurements were done. Small changes in gastric fluid may not have contributed to the increase in gastric juice pH seen in the stomach of these horses, but the amount of duodenal reflux did not contribute to a noticeable increase in gastric juice pH, because gastric juice pH data were similar to previous studies. Therefore, from these results, we concluded that sedation with detomidine may have altered gastric juice volume but had little effect on gastric juice pH in the horses in this study. However, including a parallel control group or another measurement of gastric juice pH 1 hour after sedation, before treatment, may have been helpful to confirm the effects of sedation on gastric juice pH, but neither was included in this study.

Although there was a significant increase in mean gastric juice pH > 4.0 after a single intravenous dose in the study reported here, 3 of 6 horses had gastric juice pH of >4.0, which is considered important in ulcer healing.<sup>8,9,24</sup> Omeprazole's ability to inhibit gastric acid secretion and increase gastric juice pH is dose and time dependent and varies among horses. The 3 horses that

had lower gastric juice pH values after administration of omeprazole in this study also had the lowest gastric pH before treatment. Thus, horses with lower initial gastric juice pH may require a higher dose of omeprazole to acutely decrease gastric secretion and increase gastric juice pH above 4.0. Aspiration of gastric juice in horses 1 hour after administration of omeprazole (0.5 mg/kg, IV) is potentially a useful tool to identify horses that require a higher dose of omeprazole. If it is determined that the initial dosage is too low for an individual horse, then additional omeprazole could be administered to increase gastric juice pH above 4.0 in that horse. Alternatively, all horses could be given a 1.0 mg/kg loading dose of omeprazole with the aim of raising gastric juice pH values above 4.0 in all horses; however, this was not measured in the study presented here but is a reasonable expectation because a previous report revealed that intravenous administration of omeprazole at 0.25, 0.5, and 1.0 mg/kg, IV doses resulted in a dose-dependent inhibition of gastric acid secretion and increase in gastric juice pH.<sup>h</sup> In the same study, a dose of omeprazole (1.0 mg/kg, IV) resulted in all horses having a gastric juice pH of >4.0, with the mean pH being 7.5.

Collection of gastric juice before omeprazole was administered on day 5 also provided an opportunity to assess the effects of this drug 23 hours after administration (on day 4). When measured at this time point, gastric juice pH values were significantly higher than day 1 pre-administration values (mean pH of 5.4). This long duration of action is similar to previous reports in the literature in which pH increased to 5.5 and 5.7 in horses 22 hours after the 4th oral (4.0 mg/kg) or intravenous (0.5 mg/kg) omeprazole dose was administered, respectively.<sup>11,14</sup> Omeprazole has a cumulative inhibitory effect on gastric acid secretion in horses during the first days of repeated daily administration.<sup>14</sup> According to previous reports, the steady state of this inhibitory effect is reached after 5 daily doses in horses. In the study reported here, there was a marked inhibitory effect on gastric acid secretion after the 5th daily dose compared with 1 hour after the first dose. The long duration of effect suggests that this intravenous formulation of omeprazole is effective in increasing gastric juice pH above 4.0 when administered once daily. Results also indicate that the dosage of 0.5 mg/kg, IV, given once daily may be sufficient to induce steady-state gastric acid inhibition by the 5th day in horses. Use of a higher dose or more frequent administration of omeprazole may shorten the time required for steady-state gastric acid inhibition to be achieved. In humans, steady state can be reached in only 3 days if a 0.5 mg/kg, IV, once daily dosage is administered.<sup>19</sup>

Mean nonglandular gastric ulcer number score significantly decreased from 3.2 to 2.0, during the 5-day study period. These results are not surprising because intravenous administration of omeprazole results in a rapid increase in gastric juice pH, which sets up a permissive environment to allow ulcers to begin to heal. However, although the gastric ulcer number score was decreased in these horses, continued treatment

is necessary to achieve gastric ulcer healing. It has been shown that 14 to 28 days of omeprazole administration, PO, is required to achieve significant gastric ulcer healing in horses.<sup>11,12</sup> It has also been demonstrated in another study that gastric ulcer healing is dose dependent in horses; a significant decrease in nonglandular ulcer scores was detected when a higher dosage of omeprazole (1.0 mg/kg, PO, once daily) was administered for 14 days instead of a placebo.<sup>1</sup> Gastric ulcer healing did not differ significantly between horses that received omeprazole or placebo after 14 days, but these groups differed significantly after 28 days of treatment. Unfortunately, there is no current data on the effects of intravenously administered omeprazole on gastric ulcer healing in horses, and extrapolation from oral data may not be appropriate; however, human data suggest that the greater area under the plasma concentration curve (AUC) translates into better healing rates in GERD and gastric ulcers.<sup>24</sup> However, AUC was not measured in the horses in this study.

Only 2 horses had observed ulcers in the glandular mucosa on day 1 before omeprazole treatment. The glandular gastric ulcers were not present on the 5th day of the study. Ulcers in the glandular mucosa have been shown to heal more rapidly after omeprazole treatment at low doses (0.25 mg/kg, IV) when compared with placebo.<sup>1</sup> However, because of the small number of glandular ulcers seen in this study, conclusions regarding healing of these ulcers should be interpreted with caution.

Intravenous administration of omeprazole may be useful for the treatment of EGUS in horses with restricted oral intake because of gastric reflux, such as duodenitis-proximal jejunitis (DPJ), postoperative ileus, dysphagia, or facial bone fractures. Recently, Dukti et al.<sup>1</sup> showed that horses with DPJ had a higher prevalence of gastric ulceration (68%) compared with horses with large colon impactions (32%) or large colon volvulus (14%). Thus, parenteral administration of omeprazole may be indicated in some horses with diagnosed DPJ.

In conclusion, intravenous administration of omeprazole (0.5 mg/kg), after reconstitution of powdered drug with sterile water, causes a rapid increase in gastric juice pH that is maintained for 23 hours, after the 4th daily dose. However, interhorse variation in gastric juice pH after omeprazole (0.05 mg/kg, IV) administration was detected in this study, which suggests that an intravenous loading dose (1.0 mg/kg) should be considered to rapidly increase gastric juice pH above 4.0 in treated horses. A maintenance intravenous dose of omeprazole (0.5 mg/kg) may be sufficient to keep gastric juice pH above 4.0 for 24 hours, and this sustained increase in gastric pH may be necessary to facilitate nonglandular gastric ulcer healing. However, this compounded intravenous formulation of omeprazole should only be used in horses with restricted oral intake that cannot receive the current Food and Drug Administration (FDA)-approved omeprazole paste,<sup>a</sup> or in horses with severe gastric ulceration that are at risk of gastric perforation.

## Footnotes

- <sup>a</sup> Omeprazole paste, GastroGard, Merial Limited, Duluth, GA  
<sup>b</sup> Omeprazole for IV administration, Omeprazole Sterile Powder, Premier Pharmacy Labs Inc, Weeki Wachee, FL  
<sup>c</sup> Grain, Co-op Supreme, Knoxville Co-op Inc, Knoxville, TN  
<sup>d</sup> Dormosedan (detomidine), Pfizer Animal Health Inc, Exton, PA  
<sup>e</sup> Gastroscope, ETM-Endotech, München, Germany  
<sup>f</sup> AP62, Accumet AP61 portable pH meter, Fischer Scientific, Pittsburgh, PA  
<sup>g</sup> Statistical analysis program, SAS 9.1 for Windows, Cary, NC  
<sup>h</sup> Blackford JT, Jenkins CC, Andrews FM, et al. The dose effect of intravenous omeprazole on inhibiting gastric acid secretion in horses. Proc Am Coll Vet Int Med 13th Annual Forum 1995, San Diego, CA (abstract)  
<sup>i</sup> MacAllister CG, Andrews FM, Hardin L, et al. The effects of PO administered omeprazole on healing of flunixin-induced gastric ulcers in young horses. Proc Am Coll Vet Int Med 14th Annual Forum 1996, San Antonio, TX (abstract)  
<sup>j</sup> Dukti SA, Perkins S, Murphy J, et al. Prevalence of gastric ulceration in 100 horses presenting to a referral hospital for abdominal pain. Proc International Colic Res Symp 8th Symp 2005, Quebec City, Canada (abstract)

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