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Efficacy of Omeprazole Powder Paste or Enteric-Coated Formulation in Healing of Gastric Ulcers in Horses

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Background: GastroGard, an omeprazole powder paste formulation, is considered the standard treatment for gastric ulcers in horses and is highly effective. Gastrozol, an enteric-coated omeprazole formulation for horses, has recently become available, but efficacy data are controversial and sparse.

Objectives: To investigate the efficacy of GastroGard and Gastrozol at labeled doses (4 and 1 mg of omeprazole per kg bwt, respectively, PO q24h) in healing of gastric ulcers.

Animals: 40 horses; 9.5 ± 4.6 years; 491 ± 135 kg.

Methods: Prospective, randomized, blinded study. Horses with an ulcer score ≥1 (Equine Gastric Ulcer Council) were randomly divided into 2 groups and treated for 2 weeks each with GastroGard followed by Gastrozol (A) or vice versa (B). After 2 and 4 weeks, scoring was repeated and compared with baseline. Plasma omeprazole concentrations were measured on the first day of treatment after administration of GastroGard (n = 5) or Gastrozol (n = 5).

Results: Compared with baseline (squamous score (A) 1.65 ± 0.11, (B) 1.98 ± 0.11), ulcer scores at 2 weeks ((A) 0.89 ± 0.11, (B) 1.01 ± 0.11) and 4 weeks ((A) 1.10 ± 0.12, (B) 0.80 ± 0.12) had significantly decreased in both groups ($P < .001$), independent of treatment ($P = .7$). Plasma omeprazole concentrations were significantly higher after GastroGard compared with Gastrozol administration (AUC_{GG} = 2856 (1405-4576) ng/mL × h, AUC_{GZ} = 604 (430-1609) ng/mL × h; $P = .03$). The bioavailability for Gastrozol was 1.26 (95% CI 0.56–2.81) times higher than for GastroGard.

Conclusions and Clinical Importance: Both Gastrozol and GastroGard, combined with appropriate environmental changes, promote healing of gastric ulcers in horses. However, despite enteric coating of Gastrozol, plasma omeprazole concentrations after single labeled doses were significantly higher with GastroGard.

Key words: EGUS; Gastroenterology; GastroGard; Gastrozol.

Gastric ulcers are highly prevalent in performance horses and might be associated with attitude changes, poor appetite, weight loss, reduced performance, diarrhea, abdominal discomfort, or recurrent episodes of colic.[1,2] Prevalences are 90–100% for Thoroughbred racehorses in training and during active racing,[3,4] 93% in high-level endurance horses during the competition season,[5] and 44% in Standardbred racehorses.[6] Pleasure horses in Denmark and Poland have a prevalence of 40–53%.[7,8]

Omeprazole is highly effective for the treatment of gastric ulcers and the prevention of gastric ulcer recurrence.[9–11] GastroGard[a] (GG) contains omeprazole as an acid-labile, crystalline powder, which is rapidly degraded in the acid environment during its passage through the stomach. The fraction of omeprazole that remains intact is absorbed in the small intestine. Subsequently, it is transported via the blood stream to the basal side of the parietal cells where it exerts its effect. Despite the lack of acid protection, numerous studies have demonstrated that treatment of gastric ulcers with GG at the recommended dose of 4 mg/kg bwt is effective in healing of gastric ulcer lesions in horses.[10,12,13]

Omeprazole is used in an enteric-coated, encapsulated formulation in humans, which protects the agent during the passage through the acidic environment in the stomach. Once it reaches the alkaline environment of the small intestine, the acid-stable coating is degraded and the active ingredients are released.[14]

Abbreviations:

AUC	area under the curve
Cl	drug clearance
C_{max}	maximum plasma omeprazole concentration
C_{omep}	plasma omeprazole concentration
D	dose
EGUS	equine gastric ulcer syndrome
F	relative bioavailability
FUND	dorsal fundus
GG	GastroGard
GZ	Gastrozol
GLAND	glandular mucosa
LC	lesser curvature
MPGC	margo plicatus at the greater curvature
MPRT	margo plicatus at the right site
PYL	pylorus
T_{max}	time to maximal plasma omeprazole concentration

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Intragastric administration of enteric-coated omeprazole in an acetic acid solution at a dose of 1.5 mg/kg bwt to Thoroughbred racehorses with naturally occurring gastric ulcers resulted in complete ulcer healing in all animals after a treatment over 21 days.[14,15]

Gastrozol[b] (GZ) is an Australian paste formulation for horses, containing enteric-coated omeprazole labeled for treatment of gastric ulcers at a dose of 1 mg/kg bwt. There are only few studies investigating its efficacy in horses. GZ at the labeled dose of 1 mg/kg bwt is efficacious in healing and prevention of squamous gastric ulcers in Thoroughbred racehorses in training.[c,d] However, treatment with GZ does not result in a statistically equivalent increase of gastric pH compared with treatment with a powder paste formulation (Omoguard,[e] 4 mg/kg).[16] So far, the efficacy of GZ has not been compared with the efficacy of the well-established powder paste formulation GG at labeled doses.

The objectives of this study were to investigate the efficacy of GG and GZ at labeled doses in healing of gastric ulcers in horses. Our hypothesis was that both GZ at the recommended dose of 1 mg/kg bwt and GG at the recommended dose of 4 mg/kg bwt are effective for healing of gastric ulcers in horses.

Materials and Methods

Study Design

The study was designed as a prospective, randomized, blinded, controlled clinical trial. The study was conducted in accordance with the institutional animal welfare regulations and had been approved by the district veterinary office of the Canton of Zurich.

At the time of enrollment, a physical examination, gastroscopy, a complete blood count, and a biochemistry profile were performed. The same examinations were repeated on days 14 and 28.

Animals

Forty horses that were presented with gastric ulcers at the Equine Department of the Vetsuisse Faculty, University of Zurich, Switzerland were included in the study. All horses were client-owned animals and written owners' consent was obtained before inclusion of horses in the study. Inclusion criteria were age >1 year and a gastric ulcer score of ≥1/4 on a 5-point (0–4) scoring system (Equine Gastric Ulcer Council score[17,18]). Exclusion criteria were administration of antiulcer medication within 28 days before the commencement of the study.

Treatment

Horses were randomly allocated to group A or group B (n = 20 each). Randomization was performed using computer software.[f] Horses in group A were treated with the omeprazole powder paste formulation (GG, 4 mg/kg bwt, PO, q24h) for 14 days first, immediately followed by treatment with the enteric-coated omeprazole formulation (GZ, 1 mg/kg bwt, PO, q24h) for an additional 14 days. Conversely, horses in group B were treated with GZ for the first 14 days and with GG for the following 14 days.

Veterinarians not involved in the diagnostic procedures and follow-up examinations performed the allocation to treatment groups, prepared and supplied the medication, and discussed the treatment regimen with the owners. Treatment was initiated on the day after the initial examination.

After examination and allocation to treatment groups, the horses remained occasionally at the clinic for refeeding and were then discharged from the clinic into the care of their owners between examinations. The duration of hospitalization was recorded for each time point. Treatment was started on the day after gastroscopy. The owners were instructed to administer the medication 30–60 minutes before the morning meal directly into the mouth and to feed hay, straw, and carrots at their discretion, but no concentrated carbohydrate-rich feed. If the horses were emaciated, the owners were allowed to add an appropriate amount of corn pellets (≤0.5 kg/100 kg bwt) or vegetable oil (0.5 dL/100 kg bwt) to the meal. It was recommended that horses not be in active training and to perform light exercise only during the study period. Horses were allowed to be turned out on pasture. The owners were instructed to keep a diary throughout the study period where they recorded the general condition of the horse, information on feeding (including exact amounts of the different feed materials measured by scales), use and athletic performance, and any concurrent medication on each day. Owners were also asked about any technical difficulties they encountered while administering the drugs.

Endoscopic Examination and Gastric Ulcer Scoring

Before gastroscopy, food was withheld for at least 12 hours, while water was offered ad libitum. One horse was fasted for 6 hours. This horse had been previously fasted after showing signs of colic and was enrolled in the study after recurring colic during refeeding of a small amount of hay. Horses were sedated with xylazine[g] (0.5 mg/kg bwt IV) or detomidine[h] (10–20 μg/kg bwt IV) for the endoscopic examination. Using a 3 m videoendoscope[i] (VQ-8303, Olympus), the stomach was insufflated with air and feed adhering to the wall of the stomach was removed using a water jet pump attached to the biopsy port. A systematic examination of the stomach was conducted by an operator blinded to group assignment and treatment, following a standardized protocol. The examination included visualization of the margo plicatus at the greater curvature (MPGC), the margo plicatus at the right site (MPRT), the lesser curvature (LC), the dorsal fundus (FUND), the pylorus (PYL), and the glandular region (GLAND). Still images and video recordings of each region were digitally stored and all files were coded for blinding. The recordings were then graded by 4 independent, blinded observers using the Equine Gastric Ulcer Council scoring system.[17,18]

The scores ranged from 0 to 4, corresponding to the following findings: 0, intact epithelium; 1, intact mucosa, evidence of hyperkeratosis or hyperemia; 2, small, single, or multifocal lesions; 3, large, single or multifocal lesions or extensive superficial lesions; 4, extensive lesions with areas of apparent deep ulceration. An individual score was given to each segment of the squamous (MPGC, MPRT, LC, FUND) and of the glandular region (PYL, GLAND) of the stomach. The segmental scores were then averaged to obtain a *squamous score* (mean of the 4 squamous segments), a *glandular score* (mean of the 2 glandular segments), and a *composite score* (mean of all 6 segments). Furthermore, the *maximal squamous score* and the *maximal glandular score* were extracted for each horse at each time point, defined as the maximal score assigned to the squamous and the glandular region, respectively.

Measurement of Serum Omeprazole Concentrations

Five horses from each group were randomly selected to measure plasma omeprazole concentrations after oral administration

of the respective omeprazole formulation at labeled doses on the first day of treatment. Food was withheld for 12 hours before omeprazole administration. Venous blood samples were collected into lithium heparin tubes 5 minutes before and 30, 45, and 60 minutes after omeprazole administration. One hour after treatment, the horses were fed hay and additional blood samples were collected 2, 3, 4, 5, and 6 hours after omeprazole administration. Samples were centrifuged at 1,228 × *g* for 11 minutes, and plasma was harvested and stored at −80°C until further analysis. Plasma omeprazole concentrations were measured by liquid chromatography—mass spectrometry/mass spectrometry in a commercial laboratory.[j]

Statistical Analysis

Data were analyzed using commercial statistical software.[k,l] The level of significance was set at $P = .05$ for all tests. Population characteristics (age, weight, sex) were compared between groups using unpaired *t*-tests and Fisher's exact test. Days until discharge from the clinic were compared between groups using the Mann-Whitney rank sum test. Data on management and feeding were compared between groups using Fisher's exact test and the Mann-Whitney rank sum test. Two-way repeated-measures (mixed model) ANOVA was used to assess the influence of factors time (ie, baseline, 2-week follow-up, 4-week follow-up) and group (ie, A, B) on mean squamous scores, mean glandular scores, composite scores, maximum squamous scores, and maximum glandular scores. Also, two-way repeated-measures (two-factor repetition) ANOVA was conducted on the pooled patient population to assess the influence of time (ie, baseline, 2-week follow-up, 4-week follow-up) and gastric regions (ie, squamous, glandular) on mean and maximum scores. When the F-test indicated significant differences, all pairwise comparison testing was performed using the Holm-Sidak posthoc test. Homogeneity of variances was assessed by graphical display of the data and validity of the normality assumption was confirmed by assessment of normal probability plots of the residuals.

The proportion of horses in each group in which the mean regional scores, composite scores, and maximum scores had improved between baseline and follow-up examinations was compared using Fisher's exact test. Similarly, the proportional improvement of squamous scores versus glandular scores between baseline and follow-up examinations was compared.

Data for plasma omeprazole concentration (C_{omep}) were not normally distributed and displayed heterogeneous variance. Therefore, data were log transformed and analyzed using a two-way repeated-measures (mixed model) ANOVA to detect differences between the two formulations (ie, GG versus GZ). Furthermore, the area under the concentration-time curve (AUC) was calculated for each treatment and maximal plasma omeprazole concentration (C_{max}) and time to maximal plasma omeprazole concentration (T_{max}) were extracted from the data. The AUC, C_{max}, and T_{max} were compared between treatments with a Mann-Whitney *U*-test. Finally, the relative bioavailability (F) of GZ compared with GG was calculated, taking into consideration the orally administered doses (D_{GZ}, 1 mg/kg; D_{GG}, 4 mg/kg) and assuming that drug clearance (Cl) was equal for both formulations. Since $AUC = F \times D/Cl$,[19] the bioavailability ratio was calculated as $F_{GZ}/F_{GG} = 4 \times AUC_{GZ}/AUC_{GG}$ and reported as mean ratio and 95% confidence interval (CI).

Results

Forty horses were included in the study. The 20 horses assigned to *group A* had a mean (SD) age of 9.6 years (± 4.6 years) and a body weight of 511 kg (± 116 kg). The group was composed of 7 females and 13 castrated males of various breeds (13 Warmblood horses, 1 Freiberger horse, 1 Shetland pony, 1 Icelandic horse, 2 Thoroughbred horses, 1 Standardbred horse, 1 Quarter horse). Clinical signs included single episodes of mild colic (7), recurrent colic (10), weight loss (5), poor performance (4), depression (3), prolonged episodes spent in sternal or lateral recumbency (6), teeth grinding (3), and yawning (5). The 20 horses assigned to *group B* had a mean (SD) age of 9.4 years (± 4.8 years) and a body weight of 474 kg (± 151 kg). The group was composed of 6 females, 12 castrated males, and 2 males of various breeds (9 Warmblood horses, 2 Freiberger horses, 2 Shetland ponies, 1 Icelandic horse, 1 Standardbred horse, 1 Arabian horse, 1 Friesian horse, 1 Haflinger horse, 1 Dartmoor pony, 1 Shire horse/Trakehner mix). Clinical signs included single episodes of mild colic (7), recurrent colic (9), weight loss (1), poor performance (2), depression (4), prolonged episodes spent in sternal or lateral recumbency (4), teeth grinding (1), and yawning (4). Randomization was considered successful as there were no differences in age ($P = .89$), body weight ($P = .39$), and sex ($P = 1.0$) between groups. The mean duration until discharge of the horses from the hospital was not different between the groups (Table S1).

In none of the horses and at neither of the time points abnormalities were detected on physical examinations. Because of insufficient owner compliance, the first follow-up examination was conducted on day 15 (instead of day 14) in 2 horses and on day 16 in 1 horse. The second follow-up examination (scheduled on day 28) was conducted on day 26 in 1 horse, on day 30 in 1 horse, and on day 31 in 3 horses. Two horses (5%) did not complete the study period, including 1 horse in group A and 1 horse in group B. One of the horses was not presented to the second follow-up examination for an unknown reason and the other horse underwent diagnostic laparotomy because of recurrent colic. These horses were included in only the statistical analysis of the first 14 days.

Questionnaires were completed for 39/40 (97.5%) horses. One horse had been treated once with omeprazole 3 days before the beginning of the study. Because the questionnaires were returned after completion of the study, this horse was not excluded. With the exception of 1 horse (group B), all horses were taken out of active training and performed only light exercise during the study period. In general, the diet was predominantly roughage with supplemental corn pellets or (rarely) vegetable oil added to the diet as dictated by the horses' level of activity and body condition and by the owners' preference. The majority of horses had access to pasture during the study period. No differences were identified in the feeding regimen between horses in group A and group B (Table 1). Fourteen of the 40 horse owners (35%) complained about difficulties with handling of the paste applicator and administration of either GG (7 complaints) or GZ (7 complaints).

Table 1. Data on management and feeding provided by owner survey.

Variable	Unit	Group A n Median (Min–Max)	Group B n[c] Median (Min–Max)	*P* Value
Hay		20/20	19/19	1.00[a]
	g/kg/d	12.3 (8.5–32.5)	13.6 (5.1–25.1)	.88[b]
Straw		15/20	15/19	1.00[a]
	g/kg/d	2.1 (0–9.4)	2.0 (0–4.5)	.66[b]
Carrots		19/20	18/19	1.00[a]
	g/kg/d	0.82 (0–2.5)	0.79 (0–3.1)	.78[b]
Corn Pellets		7/20	5/19	.73[a]
	g/kg/d	0 (0–6.2)	0 (0–1.9)	.42[b]
Oil		2/20	0/19	.49[a]
	mL/kg	0.5	n/a	n/a
Pasture		17/20	17/19	1.00[a]
	min/d	35 (0–464)	42 (0–1234)	.47[b]

[a]Fisher's Exact Test.
[b]Mann-Whitney Rank Sum Test.
[c]Missing response (n = 1, Group B).

Mean regional, mean composite, and maximal ulcer scores at baseline and during follow-up examinations are summarized in Table 2. All scores were significantly lower both at the first and second follow-up examination, compared with baseline. Scores did not significantly change between the first and second follow-up examination and scores were not significantly different between groups (F-test: *P* value for factor "group" ranging from .3 to .7). Maximum scores (but not mean scores) were significantly higher in the squamous compared with the glandular mucosa at all time points ($P = .001$). Both squamous and glandular scores improved significantly between baseline and follow-up examinations.

The proportions of improvement versus no change or worsening between examinations of the mean squamous, glandular, composite, maximum squamous, and maximum glandular scores (Table 3) did not significantly differ between treatment groups, with the exception of a significantly higher proportion of improvement in composite score between baseline and the 4-week follow-up examination in group B compared with group A.

There was a greater proportion of improvement versus no change or worsening of mean squamous scores when compared with mean glandular scores (baseline versus 2-week, $P = .05$; baseline versus 4-week, $P = .006$). However, no significant differences were found between gastric regions for proportions of improvement in maximal scores (baseline versus 2-week, $P = .13$; baseline versus 4-week, $P = .1$).

Omeprazole was absorbed rapidly after oral administration, with the peak plasma concentration measured approximately 1 hour after administration (T_{max}) independent of the formulation used (Fig 1; Table 4). The plasma omeprazole concentrations were highly variable and C_{max} was not significantly different between formulations. However, plasma omeprazole concentrations over time and the AUC of the concentration–time curve were significantly higher when the powder paste formulation (GG) was administered at labeled doses (4 mg/kg) compared with the enteric-coated omeprazole formulation (GZ) administered at labeled doses (1 mg/kg). The relative bioavailability of GZ compared to GG, expressed as the mean F_{GZ}/F_{GG} ratio, was 1.26 (95% CI 0.56–2.81).

Table 2. Ulcer scores (mean ± SD) at admission and on the first and second follow-up examination. Groups A and B are listed separately, although no statistically significant differences were identified between groups ($P = .3$ to $.7$).

Variables	Baseline at Admission	2-week Follow-up	4-week Follow-up	*P* Value (All Pairwise Multiple Comparisons Between Examinations, Holm-Sidak Posthoc Test)
Squamous Score				
Group A	1.65 ± 0.11	0.89 ± 0.11	1.10 ± 0.12	Baseline versus 2 weeks: $P < .001$
Group B	1.98 ± 0.11	1.01 ± 0.11	0.80 ± 0.12	Baseline versus 4 weeks: $P < .001$
				2 weeks versus 4 weeks: $P = .98$
Glandular Score				
Group A	1.63 ± 0.13	1.25 ± 0.13	1.14 ± 0.13	Baseline versus 2 weeks: $P < .001$
Group B	1.46 ± 0.13	0.86 ± 0.13	0.98 ± 0.13	Baseline versus 4 weeks: $P < .001$
				2 weeks versus 4 weeks: $P = .96$
Composite Score				
Group A	1.66 ± 0.09	1.02 ± 0.09	1.13 ± 0.09	Baseline versus 2 weeks: $P < .001$
Group B	1.81 ± 0.09	0.98 ± 0.09	0.86 ± 0.09	Baseline versus 4 weeks: $P < .001$
				2 weeks versus 4 weeks: $P = .99$
Max. Squamous Score				
Group A	2.84 ± 0.14	1.76 ± 0.14	1.91 ± 0.15	Baseline versus 2 weeks: $P < .001$
Group B	2.81 ± 0.14	1.85 ± 0.14	1.40 ± 0.15	Baseline versus 4 weeks: $P < .001$
				2 weeks versus 4 weeks: $P = .30$
Max. Glandular Score				
Group A	2.16 ± 0.17	1.61 ± 0.17	1.41 ± 0.17	Baseline versus 2 weeks: $P < .001$
Group B	1.96 ± 0.17	1.26 ± 0.17	1.30 ± 0.17	Baseline versus 4 weeks: $P < .001$
				2 weeks versus 4 weeks: $P = .63$

Table 3. Ratio of the number of horses that showed improvement versus the number of horses that showed no change or worsening in their ulcer scores between baseline (admission), first and second follow-up examination in group A and group B.

Variables	Baseline–2 weeks	Baseline–4 weeks	2–4 weeks
Squamous Score			
Group A	18/2	15/4	9/10
Group B	17/3	19/0	11/8
P value	1.0	0.11	0.75
Glandular Score			
Group A	10/8	10/7	7/9
Group B	15/4	12/7	6/12
P value	0.08	1.0	0.73
Composite Score			
Group A	17/3	14/5	9/10
Group B	18/2	19/0	12/7
P value	1.0	0.046*	0.52
Max. Squamous Score			
Group A	17/3	16/3	7/12
Group B	16/4	17/2	11/9
P value	1.0	1.0	0.52
Max. Glandular Score			
Group A	12/8	14/5	7/12
Group B	14/6	12/7	7/12
P value	0.74	0.73	1.0

*Significant difference between groups in the proportion of horses in which scores had improved.

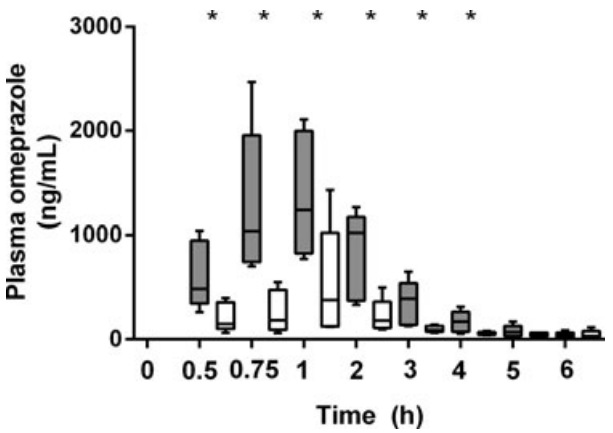

Figure 1. Plasma omeprazole concentrations after single oral administration of the omeprazole powder paste formulation (Gastrogard, 4 mg/kg bwt, gray boxes) and the enteric-coated omeprazole formulation (Gastrozol, 1 mg/kg bwt, white boxes), respectively, to 5 horses each. The box-and-whisker plots represent the median, the 25th and 75th percentile (box), and the lowest and highest measured concentrations (whiskers). The asterisks indicate significant differences between the 2 formulations at the respective time points.

Discussion

The results showed that both omeprazole as an enteric-coated formulation (GZ) at the labeled dose of 1 mg/kg PO q24h and omeprazole as powder paste formulation (GG) at the labeled dose of 4 mg/kg PO q24h promoted healing of gastric ulcers in the setting of this clinical study. However, the results also indicated that, at labeled doses, plasma omeprazole concentrations were significantly lower after administration of GZ compared with GG on the first day of treatment.

Table 4. Pharmacokinetic variables obtained after single oral administration of the omeprazole powder paste formulation (GastroGard, 4 mg/kg bwt) and the enteric-coated omeprazole formulation (Gastrozol, 1 mg/kg bwt) to 5 horses each.

Variables	Powder Paste Formulation (Gastrogard)	Enteric-Coated Formulation (Gastrozol)	*P* Value (Mann-Whitney *U*-test)
C_{max} (ng/mL)	1238 (785–2468)	375 (120–1428)	.06
T_{max} (min)	60 (45–60)	60 (60–120)	.19
AUC (ng/mL × h)	2856 (1405–4576)	604.4 (430–1609)	.03

Data are presented as median (range).

C_{max}, maximum plasma omeprazole concentration; T_{max}, time at which C_{max} was observed; AUC, area under the concentration-time curve.

Administration of enteric-coated omeprazole promotes healing of gastric ulcers in horses. However, results so far have been inconsistent, the protective efficacy of the enteric coating against degradation of the active ingredient is unknown, and the doses equivalent to those used for the powder paste formulations have not been well established.[14,15,20,21] Also, the efficacy of the commercially available enteric-coated formulation GZ has never been compared with that of the well-established powder paste formulation GG.

In our study, severity of ulcerations, both in the squamous and the glandular region of the stomach, as assessed by maximum and mean ulcer scores, improved significantly after 2 and 4 weeks of treatment compared with admission findings, independent of treatment course (Table 2). In the majority of horses, ulcer scores had improved 2 and 4 weeks after initiation of treatment, but—with 1 exception—the proportion of improved versus unchanged/worsened scores between examinations did not differ significantly between treatment groups (Table 3). Considering the family-wise error rate introduced when conducting multiple separate tests, the significant difference in proportions of improvement in the composite score between baseline and 4-week follow-up was not considered relevant.

Assessment of the changes in ulcer severity occurring between the first and the second follow-up examination is difficult, because the influence of residual drug effects from the first 2-week treatment course cannot be judged and remains unknown. However, during the first 2 weeks of the treatment course, all horses were treated with only one of the 2 formulations, allowing direct comparison of their efficacy during this time period. No significant differences were detected between treatments. Furthermore, there was no significant change in ulcer severity during the second 2 weeks of

treatment in either group (ie, no further improvement nor worsening with either of the formulations).

The effect size (ie, the actually observed differences in mean scores between groups) was low and ranged between 0.03 and 0.51. Considering the fact that the scoring system only allows integer scores, changes in scores of less than 1 might neither be clinically relevant nor applicable to an individual horse. Overall, the data suggest that both formulations used at labeled doses and combined with appropriate changes in management and feeding promote the healing of mild-to-moderate gastric ulcers in this clinical study setting.

Previous studies confirmed that intragastric administration of enteric-coated omeprazole formulations at a dose of 1.5 mg/kg bwt promoted the healing of gastric ulcers and inhibited basal and pentagastrin-stimulated acid output by 53% and 57%, respectively.[12,13] In addition, intragastric administration of enteric-coated omeprazole at doses of 0.7 mg/kg and 1.4 mg/kg inhibited basal acid output by 69 and 72%, respectively.[20,21] Inhibition of basal acid output even increased up to 92% if enteric-coated omeprazole was administered intragastrically at a dose of 5 mg/kg bwt.[14] There was no statistically significant difference in inhibition of basal and pentagastrin-stimulated acid output between horses that received a prototype paste formulation containing either enteric-coated omeprazole at a dose of 1.5 mg/kg bwt or omeprazole powder at a dose of 3 mg/kg bwt for 5 days.[14,15] In contrast to these results, a single dose of an enteric-coated omeprazole formulation (GZ, 1 mg/kg) did not result in a statistically equivalent increase in gastric pH compared to treatment with an omeprazole powder paste formulation (Omoguard[e] 4 mg/kg).[16] However, administration of enteric-coated omeprazole at a higher dose (GZ, 4 mg/kg) led to a statistically equivalent increase of gastric pH. All these findings support that omeprazole has a dose-dependent effect on gastric acid suppression that can be enhanced by the enteric coating of the active ingredient.

Comparison of treatment effects on squamous versus glandular mucosa revealed a slightly higher proportion of horses with improved mean (but not maximum) scores in the squamous gastric region when compared with the glandular region, although both squamous and glandular scores improved significantly from baseline to follow-up examinations. In agreement with our results, a previous study showed that the response of glandular gastric ulcers to administration of GZ at various doses (1 mg/kg, 2 mg/kg, and 4 mg/kg bwt) was inferior to the response of squamous gastric ulcers.[d] In addition, they could not detect a statistically significant change in mean glandular ulcer scores after treatment with GZ at the various doses over 28 days, which stands in contrast to our results.[d] Overall, the results of our study confirm a statistically significant effect of both omeprazole formulations on healing of gastric ulcers in both squamous and glandular gastric ulcers. However, they do not allow any definitive conclusions on preferential effects of omeprazole on either gastric region in horses.

Plasma omeprazole concentrations after administration of the omeprazole powder paste formulation were slightly lower, maximal concentrations occurred slightly later, but AUC was similar in this study compared with a previous study, in which the same formulation was administered to healthy horses at the same dose and in a similar setting.[13] However, omeprazole concentrations over time and the AUC after oral administration of the omeprazole powder paste formulation were significantly higher than after administration of the enteric-coated omeprazole formulation (Fig 1; Table 4).

The AUC reflects the body's exposure to a drug after administration of a single dose. Assuming linear kinetics, it is directly proportional to the amount of drug reaching the circulation (which is a function of oral drug dosage and bioavailability) and inversely proportional to drug clearance.[19] Therefore, the difference in AUC is most likely related to the different doses used for the 2 formulations. This would, however, mean that the enteric coating may not be very effective. In fact, the results indicate that the oral bioavailability of GZ is on average only 1.26 (95% CI 0.56–2.81) higher than that of GG, suggesting that the protective effect of the enteric coating is weak at best.

In 2 studies using the same horses, plasma omeprazole concentrations were measured in 8 horses after administration of enteric-coated omeprazole granules in gelatin capsules via nasogastric tube at a dose of 0.7 and 1.4 mg/kg bwt, respectively, once daily for 5 days. In both studies, the oral bioavailability of the enteric-coated omeprazole was low and ranged between 6 and 14%. Plasma omeprazole concentrations were very low both on day 1 and day 5 of the treatment course, with an AUC lower than the AUC found for the enteric-coated formulation in this study. With a reported terminal half-life between 0.5 and 8 hours[m] and a dosing interval of 24 hours, the calculated accumulation ratio for omeprazole ranges between 1.0 and 1.14,[22] supporting the finding of the above studies that considerable accumulation of omeprazole in plasma after repeated oral dosing does not occur. However, in both studies, cumulative antisecretory effects were observed and significant suppression of acid output was found on day 5 of the study period (ie, at the time when maximum gastric acid suppression is expected), despite low plasma drug concentrations.[20,21] Omeprazole's mechanism of action through irreversible binding to the H^+/K^+-ATPase enzyme system predicts that it might accumulate at the site of action and that therefore the plasma concentrations at steady state are not directly related to the amount of omeprazole that is bound to the enzyme.[m] Therefore, one could argue that high concentrations such as those found after single oral administration of GG in this study might not actually be necessary for successful treatment of mild-to-moderate gastric ulcers in horses, calling into question the use of a 4 mg/kg dose in affected horses.[20,21,23] Similarly, it would explain the apparent efficacy of the enteric-coated formulation, despite the lower dosage leading to lower plasma concentrations.

To minimize bias, the study was designed as a randomized, blinded clinical trial.[24] Randomization resulted in treatment groups that were balanced in regard to sex, age, severity of ulcer scores at the time of enrollment, and potential confounding effects, such as feeding, housing, and training during the study. However, because of the lack of a placebo control group, clear separation of drug effects from the influence of concurrent feeding and management changes in healing of gastric ulcers was not possible. Lack of a placebo control group must be considered the major limitation of this study. Horses included in the study were presented with clinical signs that were at least, in part, attributed to the presence of gastric ulcers. Reported risk factors for the development or recurrence of gastric ulcers in horses are intense or long-duration training,[3,4,25–30] stall confinement,[31] intermittent feeding regimens,[32–35] and diets high in grain concentration.[31,36] It has been previously shown that horses suffering from gastric ulcers that are treated with placebo failed to improve or showed signs of disease progression.[37,38] But it has been shown as well that feeding an alfalfa hay-grain diet led to a significant decrease of number and severity of nonglandular squamous gastric lesions compared with horses fed a bromegrass hay diet.[39] Therefore, it is recommended that the treatment of gastric ulcers in horses should be commenced immediately with effective pharmacologic agents, combined with preventative strategies aiming at a reduction of ulcer recurrence primarily involving environmental and nutritional management.[40,41] Because the study was conducted within the standard animal care guidelines of our hospital and had to be approved by the governmental animal welfare committee, ethical considerations and current clinical practice required that all horses included in the study were treated with antiulcer medication in addition to implementing appropriate management changes. GG, which has been extensively studied and is widely accepted as the antiulcer treatment of choice in horses, was considered an appropriate active control treatment. Because the efficacy of the enteric-coated omeprazole formulation GZ at labeled doses was largely unknown at the time of patient enrollment, all horses included in the study also had to be treated with GG for at least part of the study duration. Therefore, the study was designed as a crossover study without a washout period in between treatment courses. Nota bene, it was not a classical crossover design that allowed the effects of a treatment to wear off during a washout period,[42] because recurrence of gastric ulcers would not have been expected in all horses (considering the accompanying management changes) and was not desired with regard to the patient care guidelines and the ethical study approval. Because carry-over effects from the initial treatment had to be expected during the second 2-week treatment period, direct comparison of drug effects must be largely based on the initial 2-week treatment period (see above), while potential carry-over effects should be considered in the interpretation of the results of second treatment period.

Another limitation of the study was the fact that mostly mildly to moderately affected horses with average maximum squamous scores of 2.8 and relatively low mean regional and composite scores could be enrolled. However, the results must still be considered relevant because this corresponds to the average patient population seen in our hospital.

Finally, several deviations from the study protocol occurred after initial examination, randomization, and enrollment of the horses into the study. One horse was not taken out of training and a second horse was later reported to have been treated with one dose of omeprazole 3 days before inclusion into the study. Two horses did not complete the study period and were only included for the initial 14-day treatment period (for one of them, the questionnaire was not completed). However, applying the intention-to-treat principle to maintain prognostic balance generated from the original random treatment allocation, these horses were not removed from analyses.[43,44]

In conclusion, both omeprazole formulations used in this study, administered at the recommended oral doses of 4 mg/kg (GG) and 1 mg/kg (GZ) once daily and combined with appropriate changes in management and feeding, promote healing of mild-to-moderate gastric ulcers in horses. However, plasma omeprazole concentrations and AUC are significantly higher after GG administration. Further studies are needed, to compare the efficacy of both omeprazole formulations at different dosages and in horses with more severe gastric ulcerations, also taking into consideration the potential effects of management and feeding. Pharmacologic studies for comparison of the pharmacokinetic and pharmacodynamic properties of both formulations over a treatment course of several days would be of additional benefit.

Footnotes

[a] Merial Limited, Duluth, GA
[b] Axon Animal Health, Belrose, Australia
[c] Sykes BW, Sykes KM, Hallowell GD. A comparison of two doses of omeprazole in the prevention of squamous EGUS: A randomized, blinded study. J Vet Intern Med 2013;27:656 (abstract)
[d] Sykes BW, Sykes KM, Hallowell GD. A comparison of three doses of omeprazole in the treatment of gastric ulceration in thoroughbred racehorses. J Vet Intern Med 2013;27:652 (abstract).
[e] Nature Vet Pty Ltd, Glenorie, NSW, Australia
[f] www.graphpad.com/quickcalcs/index.cfm
[g] Xylazin Streuli ad us. vet., Streuli Pharma AG, Uznach, Switzerland
[h] Equisedan, Dr. E. Graeub AG, Bern, Switzerland
[i] Olympus, Volketswil, Switzerland
[j] Interlabor Belp, Belp, Switzerland

[k] GraphPad Prism v6.02, GraphPad Software, La Jolla, CA
[l] SigmaPlot v12.5, Systat Software, Inc, San Jose, CA
[m] Product Information, Merial Limited

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References

1. Murray MJ. Endoscopic appearance of gastric lesions in foals: 94 cases (1987–1988). J Am Vet Med Assoc 1989;195: 1135–1141.

2. Vatistas NJ, Snyder JR, Carlson G, et al. Epidemiological study of gastric ulceration in the Thoroughbred racehorse: 202 horses 1992–1993. Proc Am Ass Equine Pract 1994;40:125–126.

3. Murray MJ, Schusser GF, Pipers FS, et al. Factors associated with gastric lesions in Thoroughbred racehorses. Equine Vet J 1996;28:368–374.

4. Vatistas NJ, Snyder JR, Carlson G, et al. Cross-sectional study of gastric ulcers of the squamous mucosa in Thoroughbred racehorses. Equine Vet J 1999;29(Suppl):34–39.

5. Tamzali Y, Marguet C, Priymenko N, et al. Prevalence of gastric ulcer syndrome in high-level endurance horses. Equine Vet J 2011;43:141–144.

6. Dionne RM, Vrins A, Doucet MY, et al. Gastric ulcers in Standardbred racehorses: Prevalence, lesion description, and risk factors. J Vet Intern Med 2003;17:218–222.

7. Luthersson N, Nielsen KH, Harris P, Parkin TD. The prevalence and anatomical distribution of equine gastric ulceration syndrome (EGUS) in 201 horses in Denmark. Equine Vet J 2009;41:619–624.

8. Niedzwiedz A, Kubiak K, Nicpon J. Endoscopic findings of the stomach in pleasure horses in Poland. Acta Vet Scand 2013;55:45.

9. Vatistas NJ, Nieto JE, Snyder JR, et al. Clinical trial to determine the effect of omeprazole given once or twice daily on gastric ulceration. Equine Vet J 1999;29(Suppl):87–90.

10. Andrews FM, Sifferman RL, Bernard W, et al. Efficacy of omeprazole paste in the treatment and prevention of gastric ulcers in horses. Equine Vet J 1999;29(Suppl):81–86.

11. Wallmark B. Mechanism of action of omeprazole. Scand J Gastroenterol 1986;118(Suppl):11–17.

12. MacAllister CG, Sifferman RL, McClure SR, et al. Effects of omeprazole paste on healing of spontaneous gastric ulcers in horses and foals: A field trial. Equine Vet J 1999;29(Suppl):77–80.

13. Nieto JE, Spier S, Pipers FS, et al. Comparison of paste and suspension formulations of omeprazole in the healing of gastric ulcers in racehorses in active training. J Am Vet Med Assoc 2002;221:1139–1143.

14. Haven ML, Dave K, Burrow JA, et al. Comparison of the antisecretory effects of omeprazole when administered intravenously, as acid-stable granules and as an oral paste in horses. Equine Vet J 1999;29(Suppl):54–58.

15. Murray MJ, Haven ML, Eichorn ES, et al. Effects of omeprazole on healing of naturally-occurring gastric ulcers in thoroughbred racehorses. Equine Vet J 1997;29:425–429.

16. McConaghy FF, Hodgson DR, Perkins NR. Comparison of the effects of Omoguard and Gastroshield on gastric pH in fasted horses, and effects of differing doses of the generic omeprazole paste Gastrozol. Aust Equine Vet 2011;30:64–70.

17. Anonymous. Recommendations for the diagnosis and treatment of equine gastric ulcer syndrome (EGUS)—The Equine Gastric Ulcer Council. Equine Vet Educ 1999;11:262–272.

18. Bell RJ, Kingston JK, Mogg TD. A comparison of two scoring systems for endoscopic grading of gastric ulceration in horses. N Z Vet J 2007;55:19–22.

19. Toutain PL, Bousquet-Mélou A. Bioavailability and its assessment. J Vet Pharmacol Therap 2004;27:455–466.

20. Jenkins CC, Blackford JT, Andrews F, et al. Duration of antisecretory effects of oral omeprazole in horses with chronic gastric cannulae. Equine Vet J 1992;13(Suppl):89–92.

21. Andrews FM, Jenkins CC, Blackford JT, et al. Effect of oral omeprazole on basal and pentagastrin-stimulated gastric secretion in young female horses. Equine Vet J 1992;13(Suppl):80–83.

22. Toutain PL, Bousquet-Mélou A. Plasma terminal half-life. J Vet Pharmacol Therap 2004;27:427–439.

23. Murray MJ. Aetiopathogenesis and treatment of peptic ulcer in the horse: A comparative review. Equine Vet J 1992;13 (Suppl):63–74.

24. Kendall JM. Designing a research project: Randomised controlled trials and their principles. Emerg Med J 2003;20:164–168.

25. Vatistas NJ, Sifferman RL, Holste J, et al. Induction and maintenance of gastric ulceration in horses in simulated race training. Equine Vet J 1999;29(Suppl):40–44.

26. Hammond CJ, Mason DK, Watkins KL. Gastric ulceration in mature Thoroughbred horses. Equine Vet J 1986;18:284–287.

27. Lorenzo-Figueras M, Merritt AM. Effects of exercise on gastric volume and pH in the proximal portion of the stomach of horses. Am J Vet Res 2002;63:1481–1487.

28. Furr M, Taylor L, Kronfeld D. The effects of exercise training on serum gastrin responses in the horse. Cornell Vet 1994;84:41–45.

29. Vatistas NJ, Snyder JR, Carlson G, et al. Epidemiological study of gastric ulceration in the Thoroughbred race horse: 202 horses 1992–1993. Proc Am Assoc Equine Pract 1994;39:125–126.

30. Jonsson H, Egenvall A. Prevalence of gastric ulceration in Swedish Standardbreds in race training. Equine Vet J 2006;38:209–213.

31. Nadeau JA, Andrews FM, Patton CS, et al. Effects of hydrochloric, acetic, butyric, and propionic acids on pathogenesis of ulcers in the nonglandular portion of the stomach of horses. Am J Vet Res 2003;64:404–412.

32. Murray MJ, Schusser GF. Measurement of 24-h gastric pH using an indwelling pH electrode in horses unfed, fed and treated with ranitidine. Equine Vet J 1993;25:417–421.

33. Murray MJ. Equine model of inducing ulceration in alimentary squamous epithelial mucosa. Dig Dis Sci 1994;39:2530–2535.

34. Feige K, Furst A, Eser MW. Effects of housing, feeding and use on equine health with emphasis on respiratory and gastrointestinal diseases. Schweiz Arch Tierheilkd 2002;144:348–355.

35. Luthersson N, Nielsen KH, Harris P, Parkin TDH. Risk factors associated with equine gastric ulceration syndrome (EGUS) in 201 horses in Denmark. Equine Vet J 2009;41:625–630.

36. Andrews FM, Buchanan BR, Elliott SB, et al. In vitro effects of hydrochloric and lactic acids on bioelectric properties of equine gastric squamous mucosa. Equine Vet J 2008;40:301–305.

37. Lester GD, Smith RL, Robertson ID. Effects of treatment with omeprazole or ranitidine on gastric squamous ulceration in racing Thoroughbreds. J Am Vet Med Assoc 2005;227:1636–1639.

38. Vatistas NJ, Snyder JR, Nieto J, et al. Acceptability of a paste formulation and efficacy of high dose omeprazole in healing gastric ulcers in horses maintained in race training. Equine Vet J 1999;29(Suppl):71–76.

39. Nadeau JA, Andrews FM, Mathew AG, et al. Evaluation of diet as a cause of gastric ulcers in horses. Am J Vet Res 2000;61:784–790.

40. Reese RE, Andrews FM. Nutrition and dietary management of equine gastric ulcer syndrome. Vet Clin North Am Equine Pract 2009;25:79–92.

41. Videla R, Andrews FM. New perspectives in equine gastric ulcer syndrome. Vet Clin North Am Equine Pract 2009;25:283–301.

42. Sibbald B, Roberts C. Understanding controlled trials—Crossover trials. Br Med J 1998;316:1719.

43. Montori MV, Guyatt GH. Intention-to-treat principle. CMAJ 2003;165:1339–1341.

44. Gupta SK. Intention-to-treat concept: A review. Perspect Clin Res 2011;2:109–112.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Days until discharge from the hospital after gastroscopy.