Comparison of paste and suspension formulations of omeprazole in the healing of gastric ulcers in racehorses in active training

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Objective—To compare effects of a commercially available omeprazole paste and a compounded omeprazole suspension on healing of gastric ulcers in Thoroughbred racehorses in active training.

Design—Randomized controlled trial.

Animals—32 horses with gastric ulcers.

Procedure—Horses were assigned to 2 groups on the basis of endoscopic gastric ulcer severity. Group-1 horses were treated with omeprazole suspension for 30 days and with omeprazole paste for an additional 30 days. Group-2 horses were treated with omeprazole paste for 30 days and omeprazole suspension for an additional 30 days. Serum omeprazole concentrations were measured in 4 additional healthy horses after administration of a single dose of each formulation. In all instances, omeprazole was administered at a dose of 4 mg/kg (1.8 mg/lb), PO.

Results—Ulcer severity scores on day 0 were not significantly different between groups. On day 30, ulcer severity score was significantly decreased, compared with day-0 score, in group-2 but not in group-1 horses. On day 60, ulcer severity score was significantly decreased, compared with day-0 and day-30 scores, in group-1 horses. In group-2 horses, ulcer severity score on day 60 was significantly lower than the day-0 score but was not significantly different from the day-30 score. Maximum observed serum omeprazole concentration and area under the concentration-time curve were significantly higher after administration of the paste versus the suspension formulation.

Conclusions and Clinical Relevance—Results suggest that although administration of the commercially available paste omeprazole formulation was effective in promoting healing of gastric ulcers in these horses, administration of the compounded omeprazole suspension was ineffective. (*J Am Vet Med Assoc* 2002; 221:1139–1143)

Gastric ulceration is common in performance horses,[1-3] and although many horses with ulcers do not have clinical signs, gastrointestinal tract disease and poor performance have been attributed to gastric ulceration in horses.[3,4] Gastric ulceration has been detected in up to 90% of racehorses in active training and in 50 to 60% of show horses.[1-3,5]

Several agents have been used for the treatment and prevention of gastric ulcers in horses. Of these, omeprazole, a substituted benzimidazole that selectively inhibits the proton pump in the gastric mucosa, is one of the more common. Omeprazole is a potent, highly specific inhibitor of gastric acid secretion.[6] It may be considered a pro-drug in that the administered form is converted into an active, sulphenamide form by protonation. The active form of omeprazole links irreversibly with the hydrogen-potassium ATPase enzyme in the secretory canaliculi of parietal cells.[7] Omeprazole has a prolonged antisecretory effect, allowing treatment once a day, instead of several times a day as with other antiulcer substances.[8] In horses, omeprazole has been proven to be highly effective for the treatment of gastric ulceration and the prevention of gastric ulcer recurrence, even in horses maintained in active training.[9-11]

Since the patent on omeprazole has expired in some countries, there has been an increased number of generic omeprazole-containing products on the market. In addition, although omeprazole is still protected by a patent in the United States, a number of pharmacies have been compounding suspension or paste formulations of omeprazole for use in veterinary medicine. Besides the legal implications involved, this practice raises questions about the therapeutic equivalence of these generic substitutes, as the omeprazole base is obtained from various countries without control of the Food and Drug Administration, and these preparations have not been evaluated in clinical trials.

Drug products are considered to be pharmaceutically equivalent if they contain the same active ingredients and are identical in strength or concentration, dosage form, and route of administration. Pharmaceutically equivalent drugs are considered to be bioequivalent when the rates and extents of bioavailability of the active ingredient in the 2 products are not significantly different under suitable test conditions.[6,12] The purpose of the study reported here was to compare the effects of a commercially available omeprazole paste[a] with those of a compounded liquid suspension of omeprazole[b] on healing of gastric ulcers in Thoroughbred racehorses maintained in active training and on recurrence of gastric ulcers following healing.

Materials and Methods

Experimental design—The study was designed as a blinded, prospective, crossover controlled trial. Thoroughbred

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racehorses residing in 2 barns at Golden Gate Park in Albany, California and receiving veterinary care from 1 of the authors (DCS) were eligible for inclusion in the study. Horses were included in the study if they were in active race training, did not have any concurrent medical problems, had not experienced any major alterations in training or feeding schedules during the preceding 14 days, and had not received any antiulcer medications in the preceding 28 days and if the owner or trainer provided informed consent. All horses were privately owned and managed with due regard to their welfare. Horses from only these 2 barns were selected for inclusion in the study in an attempt to limit variability in the management of enrolled horses.

At the time of enrollment in the study (ie, day 0), all horses were evaluated by means of gastric endoscopy. Prior to endoscopy, food and water were withheld for at least 6 hours. Horses were sedated with xylazine hydrochloride (0.5 mg/kg [0.23 mg/lb], IV) and lightly restrained for endoscopic examination. A 3-m videoendoscope[c] was used. The stomach was insufflated with air, and a water jet pump[d] attached to the biopsy port of the endoscope was used to remove feed material that adhered to the wall of the stomach. A systematic examination of the stomach, including the greater curvature, lesser curvature, and dorsal portion of the fundus, was then performed. Severity of gastric ulceration was graded by 2 of the authors (JEN, JRS), and a score from 0 to 6 was assigned. A score of 0 was assigned if the mucosa appeared grossly normal and no ulcers were visible. A score of 1 was assigned if there were nonerosive mucosal changes; hyperemia (reddening without any apparent mucosal defect) or yellowing (hyperkeratosis) may have been present. A score of 2 was assigned if mucosal erosions were apparent. A score of 3 was assigned if mild ulceration, characterized as multifocal or generalized areas of superficial ulceration with or without hyperemia and mild or moderate hyperkeratosis, was evident. A score of 4 was assigned if there was moderate ulceration, characterized as extensive superficial lesions or deeper focal lesions with or without some mucosal proliferation along lesion margins and active hemorrhage. A score of 5 was assigned if there was severe ulceration, characterized as deep multifocal ulcers or generalized ulceration with or without moderate mucosal proliferation along lesion margins and active hemorrhage. A score of 6 was assigned if there were extensive areas of deep ulceration with or without extensive mucosal proliferation along margins and active hemorrhage. Four photographs of the squamous portion of the stomach (greater curvature, right side, lesser curvature, dorsal aspect of the fundus) were obtained. If lesions were observed in the glandular portion of the stomach, photographs of these areas were also obtained. An individual score was given to each of the 4 portions of the squamous stomach (greater curvature, right side, lesser curvature, dorsal aspect of the fundus); the squamous ulcer severity score was defined as the mean of the lesion scores for the 4 squamous portions of the stomach.

Gastric endoscopy was performed on 44 horses. The 32 horses with the highest squamous ulcer severity scores were allocated according to ulcer severity into 2 groups of 16 horses each. For this allocation, horses were ranked from greatest to least squamous ulcer severity score and assigned alternately to the 2 groups. Only horses with a score > 2 were included in the study.

Horses in group 1 were treated for 30 days with a compounded omeprazole suspension[b] (pH 3.41; 4 mg/kg [1.8 mg/lb], PO, q 24 h) and were then treated with a commercially available omeprazole paste[a] (pH 8.43; 4 mg/kg, PO, q 24 h) for an additional 30 days. Horses in group 2 were treated with the commercially available omeprazole paste for the first 30 days and with the compounded omeprazole suspension for the subsequent 30 days.

Omeprazole was administered each day before the morning meal, and horses were observed several times each day. It was not possible to control the administration of other medications; however, the use of any concurrent medication was recorded. Omeprazole paste was provided to the trainers as a commercial paste formulation. Omeprazole suspension (67 mg/mL) was purchased in 1-L bottles, and daily individual doses (30 mL) were prepared for each horse to standardize the amount and facilitate administration. Horses were estimated to weigh 500 kg, and all horses received 2 g of omeprazole base/d with either the paste or the suspension formulation.

A physical examination was performed and blood was collected for a CBC[e] at the time of enrollment in the study (day 0); follow-up physical examinations and gastric endoscopy were performed on days 30 and 60. A questionnaire was administered to the trainers of the 32 horses included in the study. Questions solicited information about the horse's disposition and appetite, its overall and current performance, whether the horse had a history of colic or diarrhea, the number of days the horse was trained each week, whether the horse had any evidence of lameness, the names and dosages of any medications administered, and the amount and type of food consumed.

Determination of serum omeprazole concentrations— Four additional adult horses (2 males and 2 females) owned by the Center of Equine Health at the University of California were used to determine serum omeprazole concentrations after oral administration of the suspension and paste formulations. Horses were determined to be healthy on the basis of results of a physical examination, gastric endoscopy, serum biochemical profile, and CBC and were housed in stalls 1 week prior to the study. They were fed a mixture of alfalfa and oat hay twice a day and had free access to water and trace mineral salts. Food was withheld for 12 hours before omeprazole administration, and alfalfa hay was provided 1 hour after administration. Horses were weighed, and 2 were given omeprazole suspension, and the other 2 were given omeprazole paste at a dose of 4 mg/kg, PO. Jugular blood samples were collected by venipuncture into serum separator tubes[f] immediately before (time 0) and 30 and 45 minutes and 1, 2, 3, 4, 5, and 6 hours after omeprazole administration. Samples were centrifuged at 1,228 × *g* for 10 minutes, and serum was harvested and stored at –80°C until assayed. One week later, horses were subjected to the same protocol, with the only change being a crossover in the formulation of omeprazole administered.

Serum omeprazole concentrations were determined by means of ion trap mass spectrometry.[g] Standard software[h] was used for data acquisition and processing. Separations were accomplished on a reverse-phase, 4.6 × 150-mm, 3.5-µm particle size column,[i] preceded by a 4 × 4-mm, 5-µm particle guard column.[j] The initial mobile phase composition was 100mM NH_4CO_2H (9:1) and 10mM NH_4CO_2H (9:1) delivered at a flow rate of 1.0 mL/min. The 100mM NH_4CO_2H was held at 40% for 0.5 minutes, then ramped to 90% at 7.5 minutes and held for 3 minutes. At 11.51 minutes into the run, the mobile phase was switched to the initial conditions, and the flow rate was increased to 1.2 mL/min to rapidly re-equilibrate the column. The total run time was 15 minutes. Analyses were performed with full-scan mass spectrometry in positive ionization mode. Concentration of omeprazole in serum was calculated by means of linear regression analysis. The area under the plasma concentration-time curve was calculated with the trapezoidal method.[13]

Statistical methods—On day 0, squamous ulcer severity

scores of horses in the 2 groups were compared with a Mann-Whitney test. Repeated-measures ANOVA followed by the Bonferroni (Dunn) multiple comparison procedure was used to test for differences in regard to ulcer severity score within groups after 30 and 60 days of omeprazole administration. Prior to the analysis, data were tested for sphericity by using the Mauchly test of sphericity (P values, 0.56 and 0.78 for groups 1 and 2, respectively) with an epsilon estimated by the Huynh-Feldt method of 1.0 for both groups. To test for differences for pharmacokinetic results between groups, a student t-test was used. Standard statistical software[k] was used. Values of $P < 0.05$ were considered significant.

Results

Of the 44 horses initially examined, 41 (93%) had gastric ulceration (ie, gastric ulcer score > 2). Two of the remaining horses only had hyperkeratosis, and 1 had mucosal erosions. Four of the 41 (10%) horses with gastric ulceration had ulceration of the glandular portion of the stomach.

Most of the 32 horses included in the study raced every 2 to 3 weeks. Three ran in allowance or stake races, 7 ran in races valued between $18,000 and $50,000, 15 ran in races valued at < $16,000, and 7 ran in maiden races or did not race. Nine horses were retired because of musculoskeletal injuries or because they were claimed during the study. Horses were excluded from statistical analyses if results of gastric endoscopy performed on days 0, 30, and 60 were not available.

For all 32 horses, results of physical examinations and CBCs performed on day 0 were normal. Similarly, results of physical examinations performed on days 30 and 60 were also unremarkable. Questionnaires were completed by owners of 28 of the 32 (87.5%) horses. Mean number of days horses were trained each week was 5.5 days (range, 5 to 7 days). Temperament was reported as normal for 15 horses, nervous for 9 horses, and quiet for 4 horses. Performance was as expected for 19 horses and below expectations for 9. Phenylbutazone was administered intermittently to 5 horses, before racing to 7 horses, and once a week to 7 horses; the remaining 7 horses did not receive phenylbutazone. Horses were fed and watered in a similar, although not identical, manner. In general, the diet was predominantly hay (timothy or ryegrass, oat, or alfalfa) with supplemental grain added to the diet as dictated by the horse's level of activity and the trainer's preference. Horses were housed in individual box stalls with pine shavings for bedding. All but 1 of the horses had the medication administered directly in the mouth, and both products were easily administered. In 1 horse, the paste and suspension formulations of omeprazole were mixed with a small amount of grain for administration because of behavioral problems.

Mean ± SEM squamous ulcer severity scores on day 0 were 3.09 ± 0.81 for group-1 horses (suspension formulation for first 30 days and paste formulation for second 30 days) and 2.92 ± 0.59 for group-2 horses (paste formulation for first 30 days and suspension formulation for second 30 days). At day 30, ulcer severity score was not significantly decreased, compared with day-0 values, for horses in group 1 (2.06 ± 0.85; $P = 0.087$) but was significantly decreased for horses in group 2 (0.73 ± 0.68; $P < 0.001$). At day 60, ulcer severity score was significantly decreased (0.78 ± 0.76; $P = 0.006$ compared with day-0 score and 0.021 compared with day-30 score) in group-1 horses. In group-2 horses, ulcer severity score on day 60 (1.44 ± 0.68) was higher than score on day 30, although this difference was not significant ($P = 0.054$). Score on day 60 was still significantly ($P = 0.001$) lower than score on day 0.

Omeprazole was absorbed rapidly after oral administration, with peak serum concentrations measured 30 minutes after administration (**Fig 1**). Thirty, 45, and 60 minutes after drug administration, mean serum omeprazole concentration was significantly higher when the paste formulation was administered than when the suspension formulation was administered. In addition, values for maximum observed serum omeprazole concentration and area under the concentration-time curve obtained after administration of the paste formulation were significantly higher than values obtained after administration of the suspension formulation, although time to maximum observed serum omeprazole concentration was not significantly different between formulations (**Table 1**).

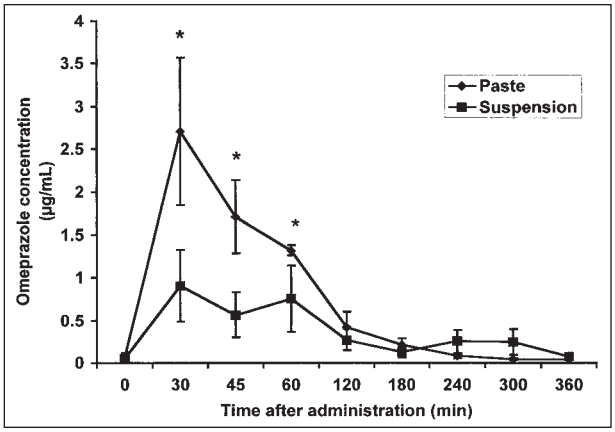

Figure 1—Mean serum omeprazole concentrations in 4 horses after administration of a commercially available paste formulation and a compounded suspension formulation at a dose of 4 mg/kg (1.8 mg/lb), PO. Error bars represent SD. *Significantly ($P < 0.05$) different from value obtained following administration of the suspension formulation.

Table 1—Pharmacokinetic values obtained after administration of a commercially available omeprazole paste formulation and a compounded omeprazole suspension formulation in 4 horses

Variable	Suspension	Paste
C_{max} (µg•mL^{-1})	1.13 ± 0.39	2.85 ± 0.76*
T_{max} (min)	105 ± 65.50	34 ± 3.75
AUC_{last} (µg•min•mL^{-1})	114.60 ± 34.05	184.30 ± 20.10*

Data are given as mean ± SD. Omeprazole was administered at a dose of 4 mg/kg (1.8 mg/lb), PO.

*Significantly ($P < 0.05$) different from value obtained following administration of the suspension formulation.

C_{max} = Maximum observed serum omeprazole concentration. T_{max} = Time at which maximum serum omeprazole concentration was observed. AUC_{last} = Area under the concentration-time curve, determined by the trapezoidal method.

Discussion

Results of the present study suggest that although administration of a commercially available paste omeprazole formulation at a dosage of 4 mg/kg, PO, every 24 hours was effective in promoting healing of gastric ulcers in Thoroughbred racehorses maintained in active training, administration of a compounded omeprazole suspension at the same dosage was ineffective. The suspension formulation did appear to provide some protection from recurrence of ulcers, in that in group-2 horses, mean squamous ulcer severity score on day 60, after administration of the suspension formulation for 30 days, was still significantly lower than the baseline (day-0) score.

We did not measure serum omeprazole concentrations in horses in active training in the present study; however, we did measure concentrations in 4 healthy horses after administration of each formulation. In these horses, maximum serum omeprazole concentration and area under the concentration-time curve were significantly higher when the paste formulation was administered than when the suspension formulation was administered. Omeprazole's effects on gastric acid secretion are long lasting, and the total amount of omeprazole reaching the circulation, which is proportional to the area under the concentration-time curve, is more important than the shape of the concentration-time curve or the specific concentration at any given time after drug administration.[6] Presumably, higher serum concentrations following administration of the paste formulation resulted in an improved healing response, compared with concentration following administration of the suspension formulation.

Omeprazole is a lipophilic weak base that degrades rapidly in acidic aqueous solutions.[14] In humans, to prevent acid degradation, omeprazole is administered as capsules containing enteric-coated acid-resistant granules, which allows for release of the drug in the alkaline environment of the small intestine. The gelatin capsule prevents premature dissolution of the acid-resistant enteric coating by water or saliva. Gastric acid dissolves the gelatin capsule, releasing the drug into the gastric lumen, but the enteric coating prevents dissolution of omeprazole in the acidic environment of the stomach. In the neutral or alkaline environment of the small intestine, the enteric coating dissolves and releases the drug, allowing it to be absorbed.[15] Because gastric acidity can protonate the drug before absorption and decrease penetration into parietal cells, alternative routes of administration (IV, IM, and per rectum) and administration concurrently with food have been evaluated in humans.[15-18] In horses, the antisecretory effects of omeprazole when administered IV as acid stable granules and as oral paste have also been evaluated.[19] When omeprazole is given with food, absorption is delayed.[20] Therefore, it has been recommended that omeprazole be administered before the morning meal, although time between drug administration and feeding did not affect absorption in a previous study.[6]

In 2 previous studies[17,21] involving horses, administration of encapsulated omeprazole orally or by nasogastric tube decreased gastric acid production and resulted in complete healing of gastric ulcers. In the present study, complete healing of the gastric ulcers was not observed following 30 days of omeprazole paste administration; however, there was a 75% reduction in the squamous ulcer severity score. The difference in results between the present study and these previous studies most likely is attributable to the fact that horses in the present study were maintained in active training. Administration of omeprazole paste (4 mg/kg) to horses has been shown to inhibit basal and pentagastrin-stimulated gastric acid secretion by more than 80%,[20] and omeprazole paste has been shown to enhance healing of spontaneous gastric ulcers in horses of various ages and breeds, even when horses were maintained in active race training.[9-11,22-24] When 2 paste formulations, 1 containing acid-stable omeprazole granules and the other containing uncoated omeprazole powder, were compared with similar doses of stable omeprazole granules administered by nasogastric tube, similar potency was observed.[17] Thus, it is possible that the paste vehicle provides omeprazole with some protection from intragastric degradation that the suspension vehicle does not. Furthermore, we measured the pH of the 2 products evaluated in the present study and found that the omeprazole suspension was slightly acidic (pH 3.41), whereas the omeprazole paste was alkaline (pH 8.43). Omeprazole is slightly soluble in water but is very soluble in alkaline solutions.[6] Because omeprazole degrades rapidly in aqueous solutions at lower pH values, acidic substances and solvents will have a deleterious effect on the stability of omeprazole and are not recommended for omeprazole formulations.[6] When human volunteers received a buffer solution followed by omeprazole mixed in water plus sodium bicarbonate (pH 9), the **maximum omeprazole concentration (C_{max})** and area under the omeprazole concentration-time curve were higher than when the same amount of drug was administered in water.[6] In addition, when administration of the buffered suspension was compared with administration of enteric-coated granules at the same dose, the C_{max} and area under the concentration-time curve were higher with the buffered suspension, and it was concluded that the same pharmacologic effects were achieved with both preparations.[6] Although we could not analyze the concentration of omeprazole in the suspension or paste formulation used in the present study, we assumed both products were manufactured with the concentration of omeprazole specified in the label. However, a recent study[1] of 10 compounded omeprazole products showed a wide variation in concentration of the active ingredient, with concentration ranging from 6 to 74% of the concentration indicated on the label. Although impractical in many situations, it is recommended that if compounded preparations are used, batches of the final product should be quality tested for strength, potency, contents, and stability.[25] The true reason for the difference between gastric ulcer scores when horses were given the omeprazole suspension or paste formulation was not determined in the present study. However, differences in the sources of omeprazole and partial inactivation of omeprazole by the suspension vehicle or by gastric contents following

administration of the suspension formulation may be partially responsible. It is also possible some of the omeprazole was lost during oral administration of the suspension. However, in the 4 horses used to examine omeprazole pharmacokinetics, care was taken to ensure that all medication was consumed and serum omeprazole concentration was still lower after administration of the suspension formulation than the paste formulation.

[a]Gastrogard, Merial Limited, Iselin, NJ.
[b]Omeprazole suspension, GaLar Pharmacy, St Matthews, SC.
[c]Fujinon, Wayne, NJ.
[d]The endopump, Fujinon, Wayne, NJ.
[e]Hematology Laboratory, Veterinary Medical Teaching Hospital, University of California, Davis, Calif.
[f]CORVAC, Sherwood-Davis & Geck, St Louis, Mo.
[g]ThermoFinnigan LLC, San Jose, Calif.
[h]Xcalibur, Novatia, Princeton, NJ.
[i]Zorbax SB-CN C_{18}, Agilent Technologies, Palo Alto, Calif.
[j]Hypersil BDS C_{18}, Agilent Technologies, Palo Alto, Calif.
[k]SPSS Inc, Chicago, Ill.
[l]Maye DE, Pipers F, Hurtig FS. Diminishing returns: compounded omeprazole products found to have little or no value. Merial Veterinary Bulletin GGD-1023-3.39-FBL.1-01.

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