Effects of treatment with omeprazole or ranitidine on gastric squamous ulceration in racing Thoroughbreds

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EQUINE

Objective—To compare the effects of oral administration of omeprazole and ranitidine on gastric squamous ulceration in Thoroughbreds in race training.

Design—Modified crossover study.

Animals—60 Thoroughbreds in race training with gastric squamous mucosal ulceration.

Procedure—Horses were randomly allocated into 3 groups. Group 1 received no treatment for 28 days followed by administration of omeprazole (4 mg/kg [1.8 mg/lb], PO, once daily) for 28 days; group 2 received omeprazole (4 mg/kg, PO, once daily) for 28 days followed by no treatment for 28 days; and group 3 received ranitidine (6.6 mg/kg [3.0 mg/lb], PO, q 8 h) for 28 days followed by administration of omeprazole (4 mg/kg, PO, once daily) for 28 days. Ulceration was assessed endoscopically at days 0, 28, 42, and 56. Lesions were scored from 0 (no ulceration) to 3 (severe ulceration).

Results—After the initial 28 days of treatment, the decrease in ulcer severity was significantly greater after omeprazole treatment than after ranitidine treatment. Ulcer severity decreased significantly in group 3 horses after 14 days of treatment with omeprazole. Discontinuation of omeprazole resulted in worsening of ulcer scores; however, ulcer scores at completion of the study were less than at day 0. Horses that received omeprazole after 28 days of ranitidine treatment had a further reduction in ulcer severity.

Conclusions and Clinical Relevance—Omeprazole was more effective than ranitidine in healing gastric squamous ulcers in Thoroughbreds in race training. Improvement was detected by 14 days and persisted in most of the group 2 horses for at least 28 days after omeprazole treatment was discontinued. (*J Am Vet Med Assoc* 2005;227:1636–1639)

The reported point prevalence of gastric squamous mucosal ulceration in horses varies from 55% to 100%.[1–4] The prevalence appears to be influenced by a range of factors that includes type and intensity of activity, feeding practices, and type of housing. Thoroughbreds and Standardbreds in race training are at greatest risk for ulceration, with reported frequencies commonly from 80% to 95%.[1,4–6] The observation of greatest prevalence among this population of horses has prompted estimation of risk factors for ulceration. Putative risk factors include feeding a high-concentrate diet, stall confinement, intense exercise and racing, and stress. Given the difficulty in reducing many of these factors, the administration of antacid drugs has become the mainstay of ulcer treatment and prevention.

The primary pharmacologic agents used in the management of gastric squamous mucosal ulceration include **histamine type 2 receptor antagonists (H_2RAs)** and **proton pump inhibitors (PPIs)**. The most commonly used H_2RAs in equine practice are cimetidine and ranitidine. The PPI best characterized in horses is omeprazole. Data directly contrasting the efficacy of H_2RAs and PPIs in horses are limited to a crossover study[7] in racing Thoroughbreds comparing cimetidine and omeprazole. Administration of both agents resulted in a decrease in ulcer severity, but a significant decrease in ulcer severity was recorded only for horses treated with omeprazole. Ulcer severity increased when treatment of horses was changed from omeprazole to cimetidine, and conversely, ulcer severity decreased when treatment was changed from cimetidine to omeprazole. Results of an endoscopic study[4] in Thoroughbreds and Standardbreds in training indicated that horses that received a proprietary omeprazole formulation, but not H_2RAs, were significantly less likely to have moderate or severe squamous mucosal ulceration than those that had received no treatment in the 2 weeks prior to examination.

Registered preparations of omeprazole and ranitidine are commonly administered to horses in Australia. The rules of Thoroughbred racing in Australia permit horses to race after administration of either preparation, although the medications cannot be administered on the day of racing. The products differ in terms of dosing frequency and cost, with omeprazole being more expensive than ranitidine; however, omeprazole is administered once daily, compared with 3 times daily administration for ranitidine. Given these differences, a direct comparison of efficacy under natural conditions is warranted. The purpose of the study reported here was to compare the effects of oral administration of omeprazole and ranitidine on gastric squamous ulceration in Thoroughbreds in race training.

Materials and Methods

Horses—The study was approved by the Murdoch University Animal Ethics Committee (Approval number 959/02) and included informed owner consent. Thoroughbred racehorses in active race training were initially screened for gastric squamous ulcer disease. Horses were included in the study if they had an ulcer score ≥ 1, were anticipated by the trainer to remain in race training for a minimum of 56 days, and had not received antiulcerative medication within 2 weeks of the beginning of the study. Horses were randomly allocated to 1 of 3 groups. Horses in group 1 (n = 20) received no treatment for 28 days followed by administration of omeprazole

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paste[a]; horses in group 2 (n = 20) received omeprazole paste for 28 days, followed by 28 days of no treatment; and horses in group 3 (n = 20) received ranitidine paste[b] for 28 days followed by 28 days of omeprazole paste. All horses that completed the study remained in training during the entire study.

Medications—Body weight was approximated at 500 kg (1,100 lb) for all horses. Horses received ranitidine hydrochloride (3,300 mg [6.6 mg/kg {3.0 mg/lb}], PO, 3 times daily) or omeprazole (1,983 mg [4 mg/kg {1.8 mg/lb}], PO, once daily). Both medications were administered 30 to 60 minutes prior to morning meal feeding. The second dose of ranitidine was also given 30 to 60 minutes prior to afternoon meal feeding; however, the third dose of ranitidine was given independently of meal feeding.

Procedure—Gastroscopy was performed on days 0, 28, 42, and 56 of the study. The procedure was performed after food had been withheld for a minimum of 10 hours. Water intake was not restricted. Horses were sedated with a combination of xylazine hydrochloride (200 mg [0.4 mg/kg {0.18 mg/lb}], IV) and butorphanol tartrate (5 mg [0.01 mg/kg {0.0045 mg/lb}], IV). The squamous mucosa was examined in its entirety by use of a 3-m videoendoscope.[c] Examinations were recorded on videotape; ulcers were scored at a later time.

Ulcer scoring—After completion of the trial, the videotape recordings were reviewed; the reviewer was unaware of treatment group allocation. The squamous mucosa was scored by use of a 0 to 3 scale, as described by others[4] as follows: 0, intact epithelium with no apparent mucosal changes or squamous hyperkeratosis; 1, small single or multifocal lesions; 2, large single or multifocal lesions or extensive superficial lesions; and 3, extensive lesions with apparent deep ulceration. Lesions within cardiac gland mucosa or glandular mucosa were not graded.

Statistical analyses—Statistical analyses were performed by use of a commercial statistical software package.[d] Differences in ulcer scores among the 3 groups of horses were evaluated by use of the Kruskal-Wallis test or the Wilcoxon signed rank test as appropriate. Results are given as mean ± SEM. A value of $P < 0.05$ was considered significant.

Results

One hundred eighteen horses from 8 training stables were initially screened via gastroscopy. Ulceration was detected in 72.2% of horses. There was large variation in point prevalence among stables, ranging from 22% to 92%. There were significant ($P < 0.001$) differences in ulcer scores among stables, but these differences in ulcer severity were not significant ($P = 0.652$) when the comparison was restricted to horses enrolled in the study. Most (55.2%) horses enrolled in the study were geldings; 3.4% were sexually intact males, and 41.4% were females. Mean age of horses was 3.3 ± 0.1 years. There were no significant effects of sex or age on ulcer score among the entire population of horses that were initially screened or among horses with ulcers that were included in the study.

There was attrition across all groups; 19 horses (32%) did not complete the 56-day trial, including 6 horses in group 1, 8 horses in group 2, and 5 horses in group 3. Among horses that were removed from the study, most (17/19) were removed during the second 28-day period. Musculoskeletal injury (fracture, dorsal metacarpal disease, or tendonitis) and exercise-induced pulmonary disease were the primary reasons for removal from the study.

On day 0, the mean ulcer score ranged from 1.6 for horses in groups 1 and 3 to 2.1 for horses in group 2 (**Table 1**). The ulcer score did vary significantly ($P = 0.018$) among the 3 groups of horses on day 0. Horses in group 2 had significantly worse squamous mucosal ulceration than horses in groups 1 or 3. There was no significant difference in ulcer scores between groups 1 and 3 on day 0 (**Table 2**).

Table 1—Mean ± SEM (95% confidence intervals) ulcer scores in Thoroughbred racehorses receiving no treatment for 28 days followed by administration of omeprazole paste (4 mg/kg [1.8 mg/lb], PO, once daily) for 28 days (group 1); receiving omeprazole paste (4 mg/kg, PO, once daily) for 28 days followed by no treatment for 28 days (group 2); or receiving ranitidine paste (6.6 mg/kg [3.0 mg/lb], PO, q 8 h) for 28 days followed by omeprazole paste (4 mg/kg, PO, once daily) for 28 days (group 3).

Group	Day 0	Day 28	Day 42	Day 56
1	1.6 ± 0.2[a] (1.2, 1.9)	1.7 ± 0.2[a] (1.3, 2.2)	0.3 ± 0.2[b] (0.0, 0.8)	0.3 ± 0.2[b] (0.0, 0.8)
No. of horses	20	19	14	14
2	2.1 ± 0.2[a] (1.8, 2.5)	0.3 ± 0.1[b] (0.1, 0.6)	0.6 ± 0.3[b] (0.0, 1.2)	0.8 ± 0.3[a,b] (0.1, 1.5)
No. of horses	20	20	12	12
3	1.6 ± 0.2[a] (1.2, 1.9)	0.8 ± 0.3[a,b] (0.4, 1.3)	0.2 ± 0.1[b] (0.0, 0.5)	0.3 ± 0.2[b] (0.0, 0.8)
No. of horses	20	19	15	15

[a,b]Within a row, values with different superscript letters are significantly ($P < 0.05$) different.

Table 2—Mean ± SEM (95% confidence intervals) change in ulcer scores in Thoroughbred racehorses receiving no treatment for 28 days followed by administration of omeprazole paste (4 mg/kg, PO, once daily) for 28 days (group 1); receiving omeprazole paste (4 mg/kg, PO, once daily) for 28 days followed by no treatment for 28 days (group 2); or receiving ranitidine paste (6.6 mg/kg, PO, q 8 h) for 28 days followed by omeprazole paste (4 mg/kg, PO, once daily) for 28 days (group 3).

Group	Day 0	Change in score (Day 0–28)	Change in score (Day 28–42)	Change in score (Day 42–56)	Change in score (Day 28–56)
1	1.6 ± 0.2[a] (1.2, 1.9)	–0.2 ± 0.2[a] (–0.6, 0.2)	1.4 ± 0.3[a] (0.8, 2.0)	–0.1 ± 0.2 (–0.5, 0.3)	1.6 ± 0.3[a] (1.0, 2.2)
2	2.1 ± 0.2[b] (1.8, 2.5)	1.8 ± 0.2[b] (1.4, 2.2)	–0.2 ± 0.2[b] (–0.8, 0.3)	–0.4 ± 0.3 (–1.0, 0.2)	–0.5 ± 0.2[b] (–1.1, 0.0)
3	1.6 ± 0.2[a] (1.2, 1.9)	0.7 ± 0.2[c] (0.2, 1.2)	0.6 ± 0.3[b] (0.0, 1.1)	0.1 ± 0.3 (–0.5, 0.7)	0.6 ± 0.2[c] (0.1, 1.1)
P value	0.009	< 0.001	0.002	0.243	< 0.001

[a–c]Within a column, values with different superscript letters are significantly ($P < 0.05$) different. A positive value indicates improvement in ulcer severity, and a negative value indicates worsening in ulcer severity.

There was a significant difference in ulcer scores among groups after the initial 28 days of treatment. The decrease in ulcer severity, compared with baseline (day 0) measurements, was significantly greater in horses receiving omeprazole paste than in those receiving ranitidine (Table 2). Both medications caused a significant decrease in ulcer scores, when compared with the untreated group, which worsened slightly, but not significantly, during the initial 28-day period.

Examination of data between day 28 and day 56 revealed significant differences among groups. Consistent with the initial response recorded in group 2, the treatment of group 1 horses with omeprazole paste from day 28 to 56 resulted in a significant decrease in ulcer score (1.7 ± 0.2 to 0.3 ± 0.2). A significant decrease in ulcer severity was detected after 14 days of treatment and was sustained during the remainder of the treatment period.

Withdrawal of omeprazole after 28 days of treatment (group 2) resulted in worsening of the mean ulcer score from 0.3 ± 0.1 to 0.6 ± 0.3 by 14 days and to 0.8 ± 0.3 by 28 days. The degree of ulceration was less than that at day 0 (2.1 ± 0.2); however, this difference was not significant ($P = 0.062$).

Ulcer severity decreased in horses that received omeprazole paste after 28 days of ranitidine treatment (group 3) such that after 14 and 28 days of omeprazole treatment, the ulcer score was significantly less than that at day 0.

Discussion

In the study reported here, the overall prevalence of gastric squamous ulcer disease was slightly lower than expected, based on results of other studies[1–4,6] in racing Thoroughbreds. There was a large variation in point prevalence among stables. Unfortunately, further investigation of the factors responsible for this unexpected variability could not be investigated because of the small numbers of stables included in the study. There were substantial differences in housing of horses that could, in combination with various other management factors, provide the basis for future investigation of risk factors. There was moderate attrition of horses throughout the study, primarily attributable to acquired musculoskeletal disease or exercise-induced pulmonary hemorrhage. The impact to the study was lessened by the timing and distribution of the affected horses. Most horses were removed from the study during the final 28-day treatment period, and removal of horses was similar among groups.

Compared with no treatment, improvement in ulcer severity as reflected by a significant decrease in ulcer score was detected after ranitidine or omeprazole treatment. The decrease in ulcer scores was significantly greater in horses that had received omeprazole. Despite random allocation to treatment groups, horses allocated to group 2 had significantly higher ulcer scores than those in groups 1 or 3 at the onset of the study. Consequently, the high ulcer scores detected on day 0 may have influenced the magnitude of the change in ulcer scores after treatment. The decrease in ulcer scores in group 2 horses was similar to the change in group 1 horses after 28 days of treatment with omeprazole paste.

There is evidence that gastric acidity is a key factor in the initiation and propagation of gastric squamous ulceration in horses. This statement is supported principally by the observation that ulceration can be reversed in most horses through administration of treatments that increase intragastric pH, either through pharmacologic blockade of acid secretion or neutralization of contents with alkalinizing solutions.[4,8–11] Histamine type 2 receptor antagonists and PPIs effectively decrease acid output and increase intragastric pH in clinically normal horses and foals.[12–21] In our study, the enhanced efficacy of PPIs, compared with H_2RAs, was expected on the basis of the mechanism of action of these drugs. Histamine provides the most important stimulus for acid secretion from gastric parietal cells and is released primarily from enterochromaffin-like cells in response to gastrin, acetylcholine, and β-adrenergic agonists.[22] Blockade of histamine binding to histamine type 2 receptors on parietal cells with ranitidine, cimetidine, or famotidine has a negative effect on acid secretion.[22] Gastrin and acetylcholine act primarily through enterochromaffin-like cell-mediated release of histamine to stimulate acid secretion, but both have additional direct secretagogue effects on parietal cells through activation of cholecystokinin B and muscarinic type 3 receptors, respectively.[22] This permits limited acid secretion to continue in the face of H_2RA treatment. In contrast, PPIs irreversibly bind parietal cell H^+-K^+-ATPase, the proton pump responsible for H^+ secretion, thereby preventing acid secretion irrespective of secretagogue activity.

Administration of omeprazole to horses in race training has advantages, compared with ranitidine, in terms of frequency of administration and therefore owner or trainer compliance. Bioavailability of H_2RAs is poor and varies among horses (approx 27% for ranitidine in adult horses and from 7% to 22% for cimetidine).[23,24] Furthermore, the duration of acid suppression after administration of H_2RAs is short, from 2 to 8 hours. This has led to the general recommendation to treat horses 3 times daily, ideally every 8 hours. In contrast, omeprazole as a commercial paste formulation is well absorbed and, at recommended doses, will suppress acid production for approximately 24 hours.[18] This permits once-daily administration.

The recommended duration for ulcer treatment is typically between 21 and 28 days. Our results indicated that ulcers healed significantly within 14 days of beginning omeprazole treatment. Unfortunately, experimental design precluded evaluation of ulcer scores after 14 days of treatment with ranitidine. Although the ulcer score after 28 days of treatment with ranitidine (0.8 ± 0.3) was not significantly different from the ulcer score on day 0 (1.6 ± 0.2; $P = 0.12$), the decrease in ulcer severity was significantly better than in the untreated group, which worsened slightly during the same period. This latter finding supports a role for ranitidine in ulcer reduction in horses maintained in race training, although the drug has reduced efficacy, compared with omeprazole. Orsini et al[4] concluded that H_2RA treatment was no more effective than no treatment in predicting ulcer severity in a large group of racing Thoroughbreds and Standardbreds, but H_2RA

type, dosage, or frequency of administration varied across the population studied. Nieto et al[7] investigated cimetidine and omeprazole by use of a crossover design, but did not report significant improvement after treatment with cimetidine, although there was a decrease in ulcer score. Any improvement in endoscopic ulcer score after treatment with cimetidine was further enhanced when treatment of horses was changed to omeprazole paste.[7] These studies focused on drug efficacy with respect to ulcer severity. The role of H_2RAs and PPIs in the relief of ulcer pain is another factor that should be considered when deciding on an appropriate treatment for horses in work. Trainers would occasionally report subjective improvement in appetite, behavior, and performance despite minimal endoscopic improvement. Unfortunately, these observations were based on trainer assessment and, as such, were not suitable for statistical analyses. The nature of the treatments used in our study precluded blind administration, thereby creating a likely bias.

In humans, withdrawal of H_2RA or PPI treatment may coincide with worsening of gastroesophageal reflux disease associated with high concentrations of gastrin, which tends to increase during administration of antisecretory treatment. Whether any clinical implications exist in the treatment of human beings is not known. In the study reported here, withdrawal of omeprazole was associated with only subtle worsening of ulcer scores during the following 28 days such that ulcer scores as evaluated endoscopically 28 days after omeprazole treatment was discontinued were less than baseline or ulcer scores recorded before treatment. This indicated that clinically relevant gastric acid hypersecretion after omeprazole treatment was discontinued did not occur at the dosage administered or for that duration of treatment.

Data derived from this and other studies indicate that commercial omeprazole paste, administered to horses once daily at an approximate dose of 4 mg/kg, PO, is more effective than H_2RAs in healing gastric squamous mucosal ulcers in Thoroughbreds maintained in race training.[7] Of further interest was the persistence of improvement in endoscopic ulcer score in group 2 horses for at least 28 days after omeprazole treatment was discontinued.

a. GastroShield, Merial Australia Pty Ltd, Paramatta, Australia. Available in the United States as GastroGard, Merial, Duluth, Ga.
b. Ulcerguard, Ranvet Pty Ltd, Beaconsfield, Australia. Available in the United States as Zantac, Glaxo Inc, Research Triangle Park, NC.
c. VES EV G300, Xion, Germany.
d. JMP 5.1, SAS Institute, Cary, NC.

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