

Effects of Top-Dress Formulations of Suxibuzone and Phenylbutazone on Development of Gastric Ulcers in Horses*

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CLINICAL RELEVANCE

Eighteen mature, healthy horses were divided into three groups (six per group) receiving either no treatment, 15 consecutive days of phenylbutazone (PBZ), or 15 consecutive days of suxibuzone (SBZ) at recommended label doses. Horses underwent endoscopy before and after the treatment period and were assigned gastric ulcer scores. Gastric ulcer number and severity scores were similar across treatment groups. These findings suggest that when administered at the recommended label dose for 15 days, neither PBZ nor SBZ causes an increase in the number or severity of gastric ulcers over what would be expected with traditional stabling and intermittent feeding patterns. Also, PBZ-treated horses did not have more severe gastric ulcers than SBZ-treated horses, indicating that SBZ does not appear to offer an advantage over PBZ in preventing gastric ulcers when used at recommended label doses. However, ulcers in other regions of the gastrointestinal tract (e.g., right dorsal colon, duodenum) were not evaluated in horses in this study.

INTRODUCTION

Because of their analgesic and antiinflammatory properties, NSAIDs are commonly used to treat pain and inflammation in horses. The most commonly used NSAIDs are phenylbuta-

zone (PBZ) and derivative compounds such as suxibuzone (SBZ).^{1,2} These NSAIDs are usually given orally because of safety and practical considerations,² with several preparations marketed for horses as top-dress formulations.

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Gastric ulceration is one of the recognized adverse events associated with PBZ administration in horses. However, this event has primarily been reported when PBZ was given at higher dosages than currently recommended. For example, Collins and Tyler³ observed clinical toxicity only in horses receiving PBZ at dosages >8.8 mg/kg/day. Pathophysiologic changes in these horses included ulcerative colitis, protein-losing enteropathy, and ulcers of the stomach

avoid local irritation, such as enterically coated or prodrug formulations, are generally considered to be better tolerated.¹³

SBZ is a prodrug that is systemically metabolized to PBZ, thereby bypassing local effects on the gastric mucosa. Consequently, SBZ should be at least as safe as PBZ regarding formation of gastric ulcers.¹³ The purpose of this study was to evaluate whether top-dress formulations containing either PBZ or SBZ cause

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and mouth. The 262 horses receiving dosages of ≤ 8.8 mg/kg/day for a maximum of 4 days or 2.2 to 4.4 mg/kg/day for prolonged periods showed no consistent evidence of toxicity.³ Similar signs of toxicity have been reported in ponies given 10 to 12 mg/kg/day for longer than 7 days.⁴⁻⁷ Ulceration also seemed to be more common if horses were deprived of water.⁸ Ulceration is much less common in healthy adult horses given PBZ at the currently recommended doses.^{2,9} However, long-term use (>15 days) at therapeutic doses has been associated with ulcer formation in various regions of the gastrointestinal tract.^{2,9,10}

Gastric ulcers from PBZ administration are the result of both systemic and local mechanisms.⁵ Systemic toxicity appears to result from vasoconstriction related to prostaglandin inhibition or from toxic effects on the endothelium and local defenses (e.g., decreased mucin production).⁹ The local mechanism is related to rapid uptake and trapping of PBZ inside the superficial mucosal cells, which leads to cell damage.^{11,12} Therefore, forms of PBZ that

gastric ulcers when fed to healthy, mature horses. We hypothesized that neither PBZ nor SBZ would cause gastric ulcers when fed to horses at therapeutic doses.

■ MATERIALS AND METHODS

Twenty adult horses (10 mares and 10 geldings) from a resident facility herd were selected for possible inclusion in this study. These horses were typical light saddle breeds, including quarter horse and Tennessee walking horse, and grade horses. Ages ranged from 3 to 14 years at the start of the acclimation period, and body weights ranged from 294 to 467 kg on the day before the trial began.

Candidate horses were acclimated to the test facility for at least 14 days under conditions similar to those expected during the study. Horses were housed individually in similar stalls and exposed to ambient conditions that were monitored continually but not controlled. All horses were fed a commercial "sweet" feed (Co-Op 11% Sweet Horse Feed Coarse, Tennessee Farmers Cooperative, LaVergne, TN) consisting of a mixture

of extruded pellets, cracked corn, and hulled oats. Each horse was offered a daily quantity of feed equal to approximately 0.5% of its body weight. The feed was divided into two similar portions that were offered morning and evening. Because treatments were top-dressed on the feed, any unconsumed feed was collected before the next feeding, and the residual portion was weighed and recorded. Each horse was also offered a quantity of grass hay equal to 2% of its body weight (similarly divided into morning and evening portions). Nonmedicated water was supplied by a local utility and was available ad libitum.

Before the start of the acclimation period, all candidate horses not recently treated with an anthelmintic were given an ivermectin-praziquantel deworming preparation (Equimax Paste, Pfizer Animal Health) to remove existing parasites. The treatment protocol is outlined in Table 1. All horses received omeprazole (GastroGard Paste, Merial, Ltd.; 4.0 mg/kg PO q24h) daily for 8 days before study drugs were administered so that treatment could be initiated with low or zero gastric ulcer scores.

Clinical health observations were made by study investigators or a trained technician daily during the acclimation period. On the final day of acclimation, food was withheld in the morning in anticipation of gastroscopy, and all horses

TABLE 1. Description of Days and Treatments Given

<i>Day</i>	<i>Event</i>
Days -14 to -1	Acclimation period
Days -8 to -1	Omeprazole treatment
Day -1	Gastroscopy performed, gastric ulcer scores assigned, and horses enrolled in the study
Days 0 to 14	Treatments administered as a top-dress formulation
Day 15	Gastroscopy performed and gastric ulcer scores assigned; study ended

were examined by a veterinarian to evaluate general health. After administration of xylazine (200 mg IV) for sedation, gastroscopy was performed using a 3-m gastroscope (Karl Storz, Goleta, CA) attached to a 300-W xenon light source. Once the endoscope entered the stomach, the stomach was insufflated with air to provide better visualization of the nonglandular and glandular mucosae. A stream of water was used to remove excess debris from the mucosa. The nonglandular mucosa, glandular mucosa, and margo plicatus were examined, and the mucosa was assigned ulcer number and severity scores using a standard-

TABLE 2. Scoring System for Number and Severity of Gastric Ulcers*

<i>Score</i>	<i>Number</i>	<i>Severity</i>
0	0	No lesions
1	1-2 localized lesions	Superficial (mucosa only) lesions
2	3-5 localized lesions	Deeper structures involved (i.e., deeper than score 1)
3	5-10 localized lesions	Multiple lesions with severity ranging from 1 to 4
4	>10 lesions or very large/diffuse lesions	Same as score 2, but lesions appear more active (hyperemia and/or darkened centers)
5	N/A	Same as score 4 plus active hemorrhage or adherent clots

*Number and severity scores were assigned independently.
N/A = not applicable.

ized system (Table 2).¹⁴ In some of the horses, residual gastric juice was aspirated from the stomach to provide better visualization of the glandular mucosa. Also, the pyloric sphincter, a common site for NSAID-induced glandular ulcers, was observed in all but one horse.

A horse was considered eligible for participation in the study if it was cooperative and healthy (based on physical examination and clinical observation) and if initial gastric ulcer number and severity scores were <2. Horses could be removed after study initiation if they developed serious adverse reactions, injury, or illness; were given unauthorized concomitant medications; died; or became uncooperative.

This study was conducted according to Good Clinical Practice, Guidance GL9, International Cooperation on Harmonization of Technical

Masking was achieved through separation of duties, so that clinical investigators and test facility personnel responsible for making clinical health observations and assigning gastric ulcer scores remained masked to the treatments assigned to each horse. Dosage administrators and personnel responsible for randomization, allocation, and statistical analysis had knowledge of treatment assignments.

The two study formulations were commercial products obtained from commercial sources. Formulations were packaged in individual sachets containing 1.0 g of phenylbutazone (Equipalazone, Dechra Veterinary Products) or 1.5 g of suxibuzone (Danilon Equidos, Janssen Animal Health) for top-dress application. Both medications were given according to UK label recommendations. Thus, horses assigned to PBZ

There were no obvious adverse reactions to treatment, and no horses were removed after the study began.

Requirements for Registration of Veterinary Medicinal Products (VICH), June 2000.¹⁵ Due regard for animal welfare was considered at all times, and accepted standards of clinical research and documentation were employed.

Study Procedures

This study was a controlled, masked clinical trial conducted at a single site. Horses were ranked according to the number of ulcers and severity scores assigned on initial gastroscopy. Horses with identical ulcer scores were ranked secondarily by ascending identification number. Every three consecutively ranked horses formed a replicate, with each horse in the replicate randomly assigned to either one of the two treatment groups or the control group. Randomization followed the SAS PLAN procedure (SAS Institute, Cary, NC).

were given two sachets twice daily on day 0, one sachet twice daily on days 1 to 4, and one sachet once daily (in the evening) thereafter. Horses assigned to SBZ were given two sachets twice daily on days 0 and 1, one sachet twice daily on days 2 to 4, and one sachet daily (in the evening) thereafter. Whole sachets were used for each dose regardless of the horse's weight. The daily maintenance dosages (i.e., after day 4) associated with these treatments were approximately 2.6 mg/kg of PBZ and 3.5 mg/kg of SBZ.

Treatment began with the evening feeding on day 0 and continued through the evening feeding on day 14. The top-dress products were deposited directly onto the preweighed grain ration. Nothing was added to the grain fed to the control group. Each horse was allowed 60 minutes to consume its meal, after which the remaining grain (if any) was collected.

TABLE 3. Comparison of Day 15 Ulcer Scores by Location across Study Groups*

Score Type	Control	Phenylbutazone	Suxibuzone	P Value [†]
Nonglandular number (individual scores)	1.0 (0, 2, 4, 0, 1, 1)	1.0 (4, 2, 0, 0, 0, 0)	2.0 (2, 2, 2, 0, 0, 2)	.68
Nonglandular severity (individual scores)	1.5 (0, 1, 2, 0, 2, 2)	0.0 (1, 4, 0, 0, 0, 0)	2.0 (4, 2, 4, 0, 0, 2)	.35
Glandular number (individual scores)	0.0 [‡] (1, 0, 0, 0, 1)	1.0 (0, 2, 2, 3, 0, 0)	0.5 (3, 0, 0, 1, 0, 1)	.67
Glandular severity (individual scores)	0.0 [‡] (1, 0, 0, 0, 1)	0.5 (0, 2, 1, 2, 0, 0)	0.5 (2, 0, 0, 1, 0, 1)	.76

*Median (individual horse scores).

[†]P value for the effect of treatment.

[‡]The glandular mucosa was not observed in one horse, and thus no score was given.

Clinical health status was evaluated twice daily throughout the study period. Physical examination and gastroscopy were repeated on day 15 (i.e., the day after treatment ended), and the number and severity of lesions were again scored. This second round of scoring comprised the outcome variable used in subsequent analyses.

Data Analysis

Each horse was considered an experimental unit in the statistical analysis. The effect of treatment on gastric scoring (i.e., number and severity of lesions) was assessed using the SAS GLIMMIX procedure, which is appropriate for ordinal data. Treatment was included as the only fixed effect and evaluated using two-sided tests at $\alpha = .05$. If the effect of treatment was statistically significant, treatment groups were compared in a pair-wise fashion.

RESULTS

One gelding was excluded because of a fractious temperament, and one mare was excluded because of an ulceration score of 2, leaving 18 horses (six triplicates) in the final study population. All horses readily ate the treated feed, with

more than 99% consumed on average. The upper and lower limits of SBZ doses administered to the horses were 3.0 g and 1.5 g, respectively. The upper and lower limits of the PBZ doses administered were 2.0 g and 1.0 g, respectively. There were no obvious adverse reactions to treatment, and no horses were removed after the study began. Abnormal health observations were recorded for several horses, but these were mostly mild to moderate upper respiratory signs (e.g., cough, ocular discharge) that did not appear to be related to treatment; these signs were observed in all treatment groups.

The nonglandular mucosa was visualized in all horses. Approximately 90% of the glandular mucosa and pyloric sphincter was visualized in all but one of the horses during the second endoscopic examination. Feed material obscured the glandular mucosa in that horse (Table 3), for which no glandular gastric ulcer number or severity score was assigned.

Median gastric ulcer number and severity scores after treatment are listed in Table 3. After omeprazole treatment and before starting PBZ and SBZ treatment (day -1), all horses had a gastric ulcer number and severity score of 0, except for one horse with a number and

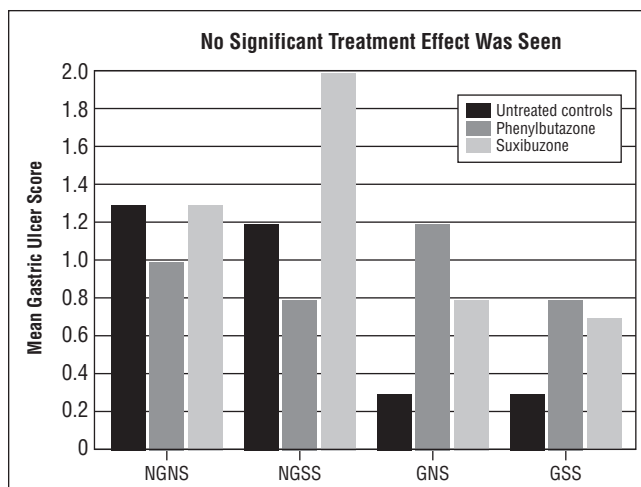


Figure 1. Mean gastric ulcer scores in untreated control horses, phenylbutazone-treated horses, and suxibuzone-treated horses after 15 days of treatment at recommended label doses. There was no significant difference between any of the ulcers scores and no treatment effect. (NGNS = nonglandular number score; NGSS = nonglandular severity score; GNS = glandular number score; GSS = glandular severity score)

severity score of 1 (which was randomly assigned to the PBZ group). Mean and median gastric ulcer numbers and severity scores increased in all groups by day 15 of the trial, but a significant treatment effect was not seen (Table 3 and Figure 1). Mean gastric ulcer number and severity scores were increased in the nonglandular stomach compared with the glandular stomach (Figure 1) and had increased above pretreatment levels in all groups. There was no significant treatment effect in the horses in this study (Table 3). Normal stomachs were observed in all treated and untreated groups in this study (Figure 2). Also, untreated control horses and PBZ- and SBZ-treated horses had gastric ulcers in the nonglandular (Figure 3) and glandular (Figure 4) mucosae.

DISCUSSION

Daily treatment with either PBZ or SBZ for 15 consecutive days did not result in signifi-

cantly different gastric ulcer number or severity scores. Gastric ulcer number and severity scores significantly increased from baseline among all groups, including controls. These data suggest that stress from stall confinement and twice-daily feeding patterns, rather than administration of PBZ or SBZ, increased gastric ulcer number and severity. The stress of stall confinement and feeding patterns compared with grazing free-choice on pasture has been documented to cause and increase the severity of gastric ulcers in horses.^{16,17}

Previous research suggests that NSAIDs cause ulcers primarily in the glandular portion of the equine stomach.^{9,13,16} In the current study, ulcer scores were

higher for the nonglandular portions of the stomach, supporting the conclusion that factors such as stress and diet were primarily responsible.¹⁰ Gastric ulcer scores of ≤ 1 in these horses at the first endoscopic examination most likely reflected omeprazole administration during the acclimation period. Omeprazole paste, a parietal cell proton-pump inhibitor, has been shown to heal gastric ulcers in horses.¹⁸ As in previous research,¹⁹ omeprazole treatment was used in this study so that treatment could be initiated with low to 0 baseline gastric ulcer scores.

Horses treated with SBZ did not have fewer gastric ulcers compared with horses treated with the equivalent doses of PBZ. This is not surprising given that PBZ has relatively low toxicity when given at recommended dosages to healthy, mature horses.^{2,9} The advantage of SBZ over PBZ in causing fewer and less severe gastric ulcers would likely be seen in horses if these drugs



Figure 2. Normal stomach showing nonglandular and glandular mucosae and margo plicatus at the lesser curvature in a horse treated with phenylbutazone (horse #375).

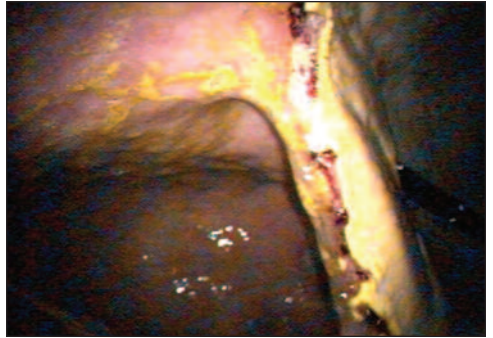


Figure 3. Gastric ulcers present on the lesser curvature of the nonglandular stomach in a horse receiving suxibuzone as a top-dress preparation (horse #371).

were administered at doses above recommended therapeutic levels or to young, dehydrated, or debilitated horses. For example, Monreal and associates¹³ reported that all five horses given more than twice the recommended dosage of PBZ had gastric ulcers compared with only two of five treated with the equivalent dose of SBZ. Ulcers were significantly larger and deeper in the PBZ group, and one horse in this group had signs of overt toxicity (e.g., soft feces, marked anorexia, hyponatremia).^{13,20} Daily maintenance doses of PBZ at approximately 2.6 mg/kg were administered to horses in the current study versus dosages of 5.25 to 10.5 mg/kg/day in the previous studies.^{13,20}

CONCLUSION

The findings here showed that both SBZ and PBZ top-dress formulations were readily consumed and that neither formulation—given at recommended doses—caused gastric ulcers over what would be expected in mature horses housed in stalls and fed hay and grain twice daily. Furthermore, SBZ treatment did not have an advantage over PBZ in causing fewer or less severe gastric ulcers in the healthy horses in this study. However, it must be emphasized that long-term use (>15 days) of these



Figure 4. Gastric ulcers present in the glandular stomach in a horse receiving suxibuzone orally (horse #209).

and other NSAIDs, even at recommended label doses, may have produced higher gastric ulcer scores compared with untreated controls. Also, NSAIDs used in this study may have caused ulcers in other regions of the gastrointestinal tract, including the duodenum and colon, but these areas were not evaluated in this study.

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