Effects of Suxibuzone and Phenylbutazone on Development of Gastric Ulcers in Horses

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Suxibuzone (SBZ), a non-steroidal anti-inflammatory pro-drug, is systemically metabolized to phenylbutazone (PBZ), thereby bypassing local effects on gastric mucosa. Gastric ulcer scores in horses administered SBZ or PBZ as top-dress formulations were not significantly different compared with untreated controls. Thus, SBZ is no safer than PBZ in causing gastric ulceration when administered at recommended doses. Authors’ addresses: Equine Health Studies Program, Department of Veterinary Clinical Sciences, Louisiana State University, School of Veterinary Medicine, Baton Rouge, Louisiana 70803 (Andrews); East Tennessee Clinical Research, Rockwood, Tennessee 37854 (Reinemeyer); and Dechra Pharmaceuticals PLC, 11 Yeomanry Road, Battlefield Enterprise Park, Shrewsbury, Shropshire SY1 3EH, United Kingdom (Longhofer); e-mail: fandrews@lsu.edu (Andrews). © 2009 AAEP.

1. Introduction
Phenylbutazone (PBZ) and its derivative compound suxibuzone (SBZ) are commonly used to treat pain and inflammation in horses because of their analgesic and anti-inflammatory properties and history of safe use.1,2 These agents are usually given orally because of safety and practical considerations and both are available as top-dress formulations.

Gastric ulcers from PBZ administration are the result of both local and systemic mechanisms.3 Systemic toxicity seems to result from vasoconstriction related to prostaglandin inhibition or from toxic effects to the endothelium and local defenses (e.g., decreased mucin production).4 The local mechanism is related to rapid uptake by and direct damage to mucosal cells. Therefore, formulations of PBZ that avoid local irritation, such as enterically coated or pro-drug formulations, are generally considered to be better tolerated.3

Suxibuzone is a pro-drug that is systemically metabolized to PBZ, thereby bypassing local toxic effects on gastric mucosa. Consequently, SBZ should be at least as safe as PBZ regarding formation of gastric ulcers.3 This study compares the ulcerogenicity of top-dress formulations containing either PBZ or SBZ.

2. Materials and Methods
Twenty healthy adult light breed horses (10 mares and 10 geldings), selected from the resident facility herd and ranging in age from 3 to 14 yr, were used in this study. Horses were acclimated to the test facility for 14 days and housed individually in stall. All horses were found to have normal parameters and to be healthy as determined by physical examination during the acclimation period. Horses were fed a commercial “sweet” feed and hay divided twice daily. Treatments (SBZ or PBZ) were top-dressed
on the feed. Non-medicated water was available ad libitum.

On day −8, after acclimation, all horses received omeprazole pastea (4.0 mg/kg, PO, q 24 h) for 8 days to reduce ulcer number and severity scores to ≤1 before initiation of SBZ or PBZ treatment. On day 0, before SBZ or PBZ administration, gastroscopy was performed under xylazine (200 mg, IV) using a 3-m gastroscope. Non-glandular mucosa, glandular mucosa, and margo plicatus were examined, and mucosa was assigned ulcer number and severity scores using a standardized scoring system for horses. After gastroscopy, horses were ranked according to gastric ulcer scores. Each three consecutively ranked horses formed a replicate, with each horse in the replicate randomly assigned to either one of the two treatment groups or untreated control group.

The two study formulations were commercial products obtained from commercial sources. Formulations were packaged in individual sachets containing 1.0 g PBZ or 1.5 g SBZ for top-dress application. Horses were administered medications per label directions. Horses assigned to PBZ were administered two sachets q 12 h on day 0, one sachet q 12 h on days 1–4, and one sachet once daily (in the evening) thereafter. Horses assigned to SBZ were given two sachets q 12 h on days 0 and 1, one sachet q 12 h on days 2–4, 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 was −2.6 mg/kg PBZ and 3.5 mg/kg SBZ. Treatment began with the evening feeding on day 0 and continued through the evening feeding on day 14. Nothing was added to the grain in the control group. Gastroscopy was again performed on day 15 after an overnight fast, and gastric ulcer number and severity scores were assigned. The investigator (F.M.A.) that performed the gastroscopy was masked to the treatments received.

The horse was considered the experimental unit in the statistical analysis. The effect of treatment on gastric scoring (i.e., number and severity of lesions) was assessed using the GLIMMIX procedure in SAS, which is appropriate for ordinal data. Treatment was included as the only fixed effect and evaluated using two-sided tests at α = 0.05. If the effect of treatment was statistically significant, treatment groups were compared in a pairwise fashion.

### 3. 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) within the final study population. All horses readily ate the treated feed, and there were no obvious adverse reactions to treatment, and no horses were removed after the study began.

Gastric number/severity scores were 0/0 on the day before the study started (day −1) with the exception of one horse randomly assigned to the PBZ group (scores 1/1). The gastric scores at the end of treatment (day 15) had increased somewhat over pretreatment levels but were similar across treatments (Table 1). Scores were somewhat higher in the nonglandular stomach than in the glandular stomach, but none were significantly different among groups. Within the nonglandular stomach, scores as high as 4 were present across all three groups, including the controls. The median scores for the SBZ group were slightly higher than those for the PBZ group, but these differences did not approach statistical significance. The SBZ scores were similar to those of the controls, suggesting no effect related to treatment (Table 1).

### 4. Discussion

Treatment with SBZ had no obvious protective effect against gastric ulceration compared with equivalent PBZ therapy. This is not surprising given that PBZ has relatively low toxicity when given at recommended dosages to healthy, mature horses. SBZ protection is more likely to be observed when these drugs are administered at higher dosages or to young or debilitated animals. For example, 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 within the PBZ group, and one horse in this group had signs of overt toxicity (e.g., soft feces, marked anorexia, and hypona-

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**Table 1. Comparison of Median (Range) Ulcer Scores by Location Across Study Groups**

<table>
<thead>
<tr>
<th>Score Type</th>
<th>Control</th>
<th>PBZ</th>
<th>SBZ</th>
<th>p Value*</th>
</tr>
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<tr>
<td>Nonglandular number</td>
<td>1.0</td>
<td>0</td>
<td>2.0</td>
<td>0.68</td>
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<td>Range (0–4)</td>
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<tr>
<td>Nonglandular severity</td>
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<td>2.0</td>
<td>0.35</td>
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<td></td>
<td>(0–4)</td>
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<td></td>
</tr>
<tr>
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<td>0.5</td>
<td>0.67</td>
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<tr>
<td>Range (0–1)</td>
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<td>(0–3)</td>
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<tr>
<td>Glandular severity</td>
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<td>0.5</td>
<td>0.76</td>
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<tr>
<td>Range (0–1)</td>
<td></td>
<td>(0–2)</td>
<td>(0–2)</td>
<td></td>
</tr>
</tbody>
</table>

*p value for the effect of treatment.*

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tremia).3,6 Daily maintenance dosages of PBZ at ~2.6 mg/kg were administered to horses in this study versus dosages of 5.25–10.5 mg/kg/d in previous studies.3,6

In conclusion, the findings of this study suggest that both top-dress formulations were readily consumed and that neither formulation resulted in excess gastric ulceration when administered per label recommendations. Furthermore, no protective effect on gastric mucosa was seen for SBZ compared with PBZ. In this study, there was no attempt to correlate gastric ulcer formation and plasma levels for either drug. However, adverse responses in man and horses are dose dependent, but there is no correlation between plasma phenylbutazone concentrations and adverse responses on the gastrointestinal tract.7,8

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References and Footnotes

aGastroGard, Merial, Decatur, GA 30030.
bKarl Storz, Endoscopy, Goleta, CA 93117.
cEquipalazone; Dechra Veterinary Products, Harlescott, Shrewsbury, Shropshire, SY1 3TB, UK.
dDanilon Equidos; Janssen Animal Health, High Wycombe, Buckinghamshire, HP12 4EG, UK.