Effects of large doses of phenylbutazone administration to horses

Robert J. MacKay, BVSc; T. W. French, DVM; Hai T. Nguyen, VMD, MS; I. G. Mayhew, BVSc, PhD

SUMMARY

The effects of large doses of phenylbutazone were evaluated in clinically normal horses. The drug was given to 4 groups of 2 horses each at the rate of 30 mg/kg of body weight, orally, or 30, 15, or 8 mg/kg iv daily for up to 2 weeks. All horses became anorectic and depressed after 2 to 4 phenylbutazone treatments, and the horses given 15 or 30 mg/kg died on or between days 4 and 7 of treatment. A decrease in total blood neutrophil count occurred in all horses, and was associated with toxic left shift in horses given the 2 larger dosage schedules. The horses also had progressive increases in serum urea nitrogen, creatinine, and phosphorus concentrations, accompanied by decreasing serum calcium concentrations. There was a progressive decrease in total serum protein in all 8 horses. Gastrointestinal ulcerations, renal papillary necrosis, and vascular thromboses were the predominant postmortem findings.

Phenylbutazone (PBZ) was first synthesized in 1946, and was introduced into human and veterinary medicine shortly thereafter. It remains the most widely used and arguably the most effective anti-inflammatory agent available for the equine species.

Phenylbutazone is classified, with other compounds of diverse chemical structure but similar biologic actions, as a nonsteroidal anti-inflammatory drug (NSAID). Although its exact mode of action is unknown, PBZ, in common with other NSAID, is thought to diminish the inflammatory response by interfering with the synthesis of prostaglandins in damaged tissues. The well-known analgesic and antipyretic properties of PBZ in horses and other animals reflect these effects on inflammation of bone, joints, and other soft tissues.

Although PBZ has been used extensively and successfully for the management of painful rheumatic diseases of human beings, the occurrence of undesirable side effects has limited its use in recent years. It has been estimated that between 10% and 45% of human beings treated with PBZ develop clinical signs of toxicosis. Although these complications are usually mild and reversible, many fatalities directly attributable to the drug have been reported. Some of the reported side effects were fluid retention and edema, skin rashes, nausea and vomiting, systemic hypersensitivity reactions, oral and gastrointestinal ulceration and bleeding, various renal disorders, hepatitis, and bone marrow depression. In veterinary literature, there are scattered reports of PBZ toxicosis in dogs and cats.

Recommendations for PBZ dosages in horses vary slightly among different manufacturers. The maximum daily dose and duration of therapy suggested for one brand is 8.8 mg/kg of body weight for 2 days. Another manufacturer recommends a maximum of 2 g (4.4 mg/kg) of their product daily for 5 days, continued (if necessary) by oral therapy. The maximum oral dose for 450-kg horses is generally 4 g, with reevaluation of treatment after 5 days. Such doses are apparently well tolerated. Several horses were given daily oral treatments of 2 g of PBZ for periods of 32 days, 6 months, and up to 3 years without developing clinical or hematologic abnormalities. In another study, 2 ponies were given the drug iv at a dosage rate of 6.6 mg/kg for 1 day, followed by 4 mg/kg for 6 days without any adverse effects. However, in 4 of 6 horses given PBZ iv at a dosage of 8 mg/kg daily, there were marked decreases in plasma protein values by the 13th day of treatment. The occurrence of fever, anorexia, diarrhea, and death in horses was attributed to the use of PBZ at recommended dosage levels (not specified) at an equine hospital in Switzerland. At the same clinic, 3 horses became anorectic and developed leukopenia after each was given 2 g of the drug orally twice daily for an unspecified period. Three other horses were given daily doses of 7.5 mg of PBZ/kg iv and 2 became depressed, anorectic, and febrile. One of these horses died after 8 treatments. Each of the 3 horses became profoundly neutropenic (< 2,000 cells/mm<sup>3</sup>) and had abnormal liver function tests during treatment. Neutrophil counts increased rapidly to > 10,000 cells/mm<sup>3</sup> after medication was stopped.

In case reports lacking substantive documentation, PBZ usage in the horse has also been linked to low PCV and hemoglobin concentration, hypoplastic anemia, intestinal ulceration resulting in fatal hemorrhage in a foal and colic in adult horses, acute depression and shock in

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*Phenylbutazone injection, 200 mg/ml, Med-Tech Inc, Elwood, Kan.*

*Butazolidin, Jensen-Salsbury, Division of Richardson-Merrell Inc, Kansas City Mo.*
ponies, epistaxis, and depressant or tranquilizing effects. There have been limited investigations into the effects of higher (> 8.8 mg/kg daily) doses of PBZ in the equine species. One horse died after administration of 16 g orally (per day) for 4 days. Postmortem examination revealed intestinal ulcers, but other tissues were too autolyzed for examination. During the same investigation, intestinal, gastric, and oral ulcers were found in a horse that was euthanized after administration of 8 g of PBZ daily for 9 days. There was also necrotizing phlebitis of portal vessels in this horse, and in another that had been given 2- g doses daily for 32 days. In another study, 8 ponies were given PBZ orally at a rate of 8.1 to 14.6 mg/kg daily. All, but one, developed clinical signs of toxicosis, and 3 ponies died after 10 to 14 days of treatment. The most consistent serum biochemical abnormality was an approximately 25% decrease in serum protein values. Lingual ulcers, diarrhea, and ventral edema were seen in all ponies. At necropsy, there were ulcers of the large colon in each pony, and gastric ulceration was found in 1 pony.

Materials and Methods

Experiment 1—Two clinically normal horses, a mature Thoroughbred mare and her 10-month-old colt, were used. Each of the horses was given 30 mg of PBZ/kg of body weight, orally, once daily until death. Phenylbutazone (1 g) tablets (6 for the foal and 12 for the mare) were crushed and mixed with 60 ml of molasses for dosing by syringe.

Clinicopathologic examination—The horses were observed for clinical signs twice daily during the study. Samples of blood were withdrawn from the jugular veins daily and were allowed to clot. Serum was harvested and stored at -20 C for a maximum of 2 weeks before determination of sorbitol dehydrogenase (SDH) and γ-glutamyl transferase (GGT) activities, and up to 3 months for the remaining biochemical determinations.

Postmortem examination—Within 2 hours of death, a complete necropsy examination was performed. Representative tissues were removed and fixed in 10% buffered formalin. After fixation, the tissues were embedded in paraffin, sectioned at 6 μm, and stained with hematoxylin and eosin for light microscopic examination.

Experiment 2—Seven mature mares (ages 7 to 22) of various breeds were used. The horses were kept in stalls and monitored for 4 to 7 days before the experiment. Six of the horses were assigned to 3 treatment groups of 2 horses each, and the other horse served as a control. The treatment groups were given single daily IV PBZ injections (20%) of 30, 15, or 8 mg/kg and the control horse was given a volume of PBZ solvent mixture equal to that contained in 30 mg of aqueous PBZ solution/kg. Treatments were given over 3 minutes via a 100-cm polyethylene catheter sutured into a jugular vein. Those horses in extremis or surviving 14 days were euthanized with an overdose of sodium pentobarbital.

Clinicopathologic examination—Horses were observed as in experiment 1, and serum samples were collected daily. In addition, 3-ml samples of blood were withdrawn into vacuum tubes containing disodium EDTA for daily WBC and platelet counts and PCV and plasma protein determinations. Blood was smeared on glass slides, air-dried, fixed in anhydrous methanol, and stained with Wright-Giemsa stain for later examination. Urine samples were obtained periodically by clean urethral catheterization for routine urinalysis. Rectal fecal samples were collected daily and tested for the presence of occult blood, using a standard reagent tablet (Hematest®). Samples of bone marrow were aspirated from the sternum before and during treatment, via a 13-gauge needle and stylet. The aspirates were smeared on glass slides, air-dried, fixed in methanol, and stained with Wright-Giemsa stain for later examination. Postmortem examination was performed as in experiment 1.

Results

Clinical signs (experiments 1 and 2)—Horse 9 (8 mg/kg, IV) died from complications of a ruptured cecum after 4 treatments following signs of colic for 2 days. Hematologic and serum biochemical data from this horse are not presented; however, summaries of clinical and postmortem examinations are included.

All horses given PBZ orally or IV became acutely anorectic and depressed on day 2, 3, or 4 (ie, after 2, 3, or 4 treatments). With the exception of horse 8 (8 mg/kg, IV), clinical deterioration continued until death or euthanasia was performed in extremis on or between days 4 and 7. Horse 8 was intermittently anorectic and slightly depressed between days 3 and 10, but appeared clinically normal thereafter. A striking 'brick-red' discoloration of oral mucous membranes was noticed in the horses given 30 mg/kg orally or IV. In addition, numerous large oral and lingual ulcerations developed in the mare and foal treated orally. Diarrhea occurred in horses 2, 4 (30 mg/kg), 6, and 7 (15 mg/kg). Other clinical signs varied widely among individual horses (Table 1).

Hematologic results (experiment 2)—Hematologic examinations were performed on the first days of the experiment and on the day of spontaneous death or euthanasia (Table 2). In each horse, trends indicated by these results were supported by additional examinations (data not shown) made on intervening days.

Profound, progressive neutropenia and toxic left shift occurred in horses given daily doses of 30 mg/kg and 15 mg/kg (Table 2). These changes could be detected within 12 hours of the first treatment in the horses at the highest dosage level (horses 4 and 5). Horse 8 (8 mg/kg) did not develop a consistent neutropenia, although mature neutrophil counts of < 3,000 cells/mm³ were recorded on 7 of 14 treatment days compared with that on 0 of 6 pretreatment days.

The WBC changes were accompanied by an increasing PCV in horses 4 through 7 (those given 30 and 15 mg/kg). The PCV of horse 8 did not change significantly during the experiment.

Platelet counts decreased during PBZ treatment in all horses, except horse 8 (8 mg/kg), but remained within the limits of normal ranges.

Bone marrow aspirates (experiment 2)—The results of the examination of bone marrow aspirates are shown in Table 3. Three of the 4 horses in the 2 higher dosage groups had a lower myeloid/erythroid (M/E) ratio after treatment compared with that before treatment. This was largely due to a relative decrease in the number of mature neutrophils in posttreatment samples. A posttreat-

W. A. Butler, Columbus, Ohio.

Ames Co, Division of Miles Laboratories Inc, Elkhart, Ind.
TABLE 1—Experimental design and summary of major clinical signs and tests for fecal occult blood

<table>
<thead>
<tr>
<th>Horse No.</th>
<th>Dose (mg/kg/day)</th>
<th>Anorexia and depression</th>
<th>Tongue ulcers</th>
<th>Red mucous membranes</th>
<th>Dyspnea</th>
<th>Diarrhea</th>
<th>Dementia, thrashing</th>
<th>Colic</th>
<th>Fecal occult blood</th>
<th>No. treatment days before death</th>
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<tbody>
<tr>
<td>1</td>
<td>30 PO</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>30 PO</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>Control</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>30 IV</td>
<td>(2)</td>
<td>(3)</td>
<td>(2)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>30 IV</td>
<td>(3)</td>
<td>(3)</td>
<td>(3)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>15 IV</td>
<td>(2)</td>
<td>(3)</td>
<td>(3)</td>
<td>+</td>
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<td>5</td>
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<tr>
<td>7</td>
<td>15 IV</td>
<td>(2)</td>
<td>(2)</td>
<td>(2)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>7</td>
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<tr>
<td>8</td>
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<tr>
<td>9</td>
<td>8 IV</td>
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<td></td>
<td></td>
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</tr>
</tbody>
</table>

No. in parentheses are the day the clinical sign was first recorded. PO = per os. + = Clinical signs present; - = no clinical signs present.

TABLE 2—Hematologic results on pretreatment day (day 0) and on day of spontaneous death

<table>
<thead>
<tr>
<th>Horse No.</th>
<th>Day</th>
<th>PCV (mg/dl)</th>
<th>WBC</th>
<th>Myelocytes</th>
<th>Metamyelocytes</th>
<th>Band neutrophils</th>
<th>Segmented neutrophils</th>
<th>Lymphocytes</th>
<th>Monocytes</th>
<th>Eosinophils</th>
<th>Basophils</th>
<th>Platelets</th>
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<tr>
<td>3*</td>
<td>0</td>
<td>36</td>
<td>12,109</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8,107</td>
<td>1,936</td>
<td>847</td>
<td>1,210</td>
<td>0</td>
<td>222</td>
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<tr>
<td>4</td>
<td>0</td>
<td>33</td>
<td>9,550</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6,463</td>
<td>3,995</td>
<td>0</td>
<td>1,292</td>
<td>0</td>
<td>250</td>
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<tr>
<td>5</td>
<td>0</td>
<td>52</td>
<td>3,400</td>
<td>646</td>
<td>612</td>
<td>748</td>
<td>5,930</td>
<td>2,390</td>
<td>443</td>
<td>863</td>
<td>863</td>
<td>300</td>
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<tr>
<td>6</td>
<td>0</td>
<td>43</td>
<td>8,850</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>220</td>
<td>1,320</td>
<td>476</td>
<td>0</td>
<td>0</td>
<td>160</td>
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<td>7</td>
<td>0</td>
<td>31</td>
<td>8,250</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4,785</td>
<td>1,898</td>
<td>412</td>
<td>1,073</td>
<td>82</td>
<td>215</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>41</td>
<td>7,550</td>
<td>255</td>
<td>900</td>
<td>3,075</td>
<td>1,575</td>
<td>1,425</td>
<td>300</td>
<td>0</td>
<td>0</td>
<td>117.5</td>
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<tr>
<td>9</td>
<td>0</td>
<td>34</td>
<td>11,150</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>7,805</td>
<td>2,788</td>
<td>223</td>
<td>334</td>
<td>0</td>
<td>245</td>
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<tr>
<td>10</td>
<td>0</td>
<td>61</td>
<td>2,300</td>
<td>138</td>
<td>276</td>
<td>644</td>
<td>92</td>
<td>1,150</td>
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<td>160</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
<td>39</td>
<td>10,150</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6,596</td>
<td>2,233</td>
<td>609</td>
<td>710</td>
<td>0</td>
<td>222.5</td>
</tr>
<tr>
<td>12</td>
<td>14</td>
<td>44</td>
<td>6,150</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1,907</td>
<td>3,382</td>
<td>492</td>
<td>369</td>
<td>207.5</td>
<td>0</td>
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</table>

* Control.

TABLE 3—Analyses of bone marrow aspirates

<table>
<thead>
<tr>
<th>Horse No.</th>
<th>M:E (%)</th>
<th>Mature neutrophils (%)</th>
<th>Day</th>
<th>Mature neutrophils (%)</th>
<th>Comment</th>
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<tr>
<td>3*</td>
<td>0.62</td>
<td>16.8</td>
<td>14</td>
<td>0.60</td>
<td>15.8</td>
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<tr>
<td>4</td>
<td>0.41</td>
<td>11.8</td>
<td>3</td>
<td>0.31</td>
<td>2.0</td>
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<tr>
<td>5</td>
<td>0.69</td>
<td>19.2</td>
<td>3</td>
<td>0.27</td>
<td>0.6</td>
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<tr>
<td>6</td>
<td>0.85</td>
<td>18.5</td>
<td>4</td>
<td>1.50</td>
<td>1.7</td>
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<tr>
<td>7</td>
<td>0.87</td>
<td>21.4</td>
<td>4</td>
<td>0.36</td>
<td>0.9</td>
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<tr>
<td>8</td>
<td>0.69</td>
<td>19.4</td>
<td>14</td>
<td>1.35</td>
<td>28.0</td>
</tr>
</tbody>
</table>

* Control.

Horse aspirate from horse 6 also had a relative decrease in mature neutrophils, but the M:E ratio actually increased due to a higher proportion of neutrophil precursors. Slight cytoplasmic basophilia of neutrophil precursors was the only evidence of toxicosis in posttreatment samples from these horses. In horse 8, the M:E ratio doubled due to a uniform increase in cells of the neutrophil series. The morphologic features and abundance of cells of the erythroid and megakaryocytic series did not appear to change significantly in any horse.

Serum biochemical results (experiments 1 and 2)—A summary of serum biochemical analyses from the first and last days of each experiment are shown in Table 4. The most consistent alterations occurred in horses on the 2 higher dosage schedules (IV or orally). There were progressive increases in serum urea nitrogen (SUN), creatinine, and phosphorus concentrations, accompanied by decreasing serum calcium concentrations. The changes in electrolyte concentrations could be detected by the 2nd treatment day. Similar changes were not seen in horse 8, which was given 8 mg/kg daily.

There was a progressive decrease in total serum protein (TP) concentration in all the PBZ-treated horses. In the horses in the 2 higher IV dosage groups, the decrease in TP occurred in the face of an increasing PCV. The change in TP was most marked in horse 8 (8 mg/kg) in which the TP decreased from 7.1 g/dl to 4.0 g/dl after 14 days. Albumin and globulin were affected almost equally.

Moderate elevations in serum alkaline phosphatase (ALP) activity occurred in horses given 15 mg/kg and 30 mg/kg daily. However, other enzyme activities and serum bilirubin concentrations did not change significantly during treatment.

Urinalyses—The results of 6 urinalyses performed before and during treatment of horse 8 were unremarkable. In the horses given the higher doses, trace-to-slight proteinuria (0 to 30 mg/dl) was the only abnormality detectable by the use of multireagent dipsticks (N-Multistix®). Examination of urinary sediments was unremarkable, with
the exception of moderate hematuria and pyuria in horse 2 on days 5 and 7. Tubular casts were not seen. The specific gravities of urine samples were not determined.

**Necropsy results**—The results of gross and histologic postmortem examinations are summarized in Table 5. Although some of the more spectacular necropsy findings were unique to individual horses (eg, diaphragmatic hernia in horse 5, colonic infarction in horse 6), a number of qualitatively similar changes occurred in most or all of the treated horses. Gastric mucosal damage was found in 4 of 6 horses. The lesions were present only in the glandular mucosa, and ranged from microscopic erosions to 2-to 4-cm ulcerations extending into the submucosa. Intestinal mucosal erosions or ulcerations were detected histologically in 6 horses in the small and/or large intestine. Intestinal ulcers were apparent grossly in horses 4, 7, and 8. Other more variable findings were submucosal edema, inflammatory infiltrates in the lamina propria and submucosa, and thrombosis and proliferation of vessels adjacent to large ulcerations.

Morphologic abnormalities were detected in the kidneys of all PBZ-treated horses. The severity of renal lesions appeared to be dose related. Focal segments of renal papillary necrosis were evident grossly as discrete 0.2 to 1 cm brownish-green, wedge-shaped discolorations under the renal crest in one or more papillae in 4 of 6 horses in the higher dosage groups. Histologically, these areas appeared as coagulation necrosis with loss of cellular definition. Evidence of inflammation in adjacent viable tissues was not seen. In addition, there was swelling, necrosis, and sloughing of tubular epithelial cells, most prominent in medullary collecting tubules, and medullary interstitial edema. These lesions were present but mild in horses 8 and 9 (8 mg/kg). Degenerative changes in proximal tubular cells, tubular casts, and lymphocytic cortical infiltrates were inconsistently present.

All livers were grossly normal and hepatocellular changes were mild or absent. However, clumps of bacilli were seen in portal veins and adjacent sinusoids in horse 7. In addition there was partial thrombosis and necrosis of portal venules noticed in some liver sections in horse 1. There was also pulmonary arterial thrombosis and infarction of a section of lung in this horse. Lesser thrombi were seen in the pulmonary vasculature of 3 other horses (No. 4, 6, and 9). These thrombi were not occlusive and did not appear to be associated with major lung lesions.

**Control horse**—The results of clinical and laboratory examinations of the control horse were within normal limits during the experiment. Abnormalities were not found during postmortem examination.

**Discussion**

Phenylbutazone has a narrow therapeutic index in horses. All 6 horses given daily doses of 15 mg/kg or 30 mg/kg died or were euthanatized in extremis within 8 days of beginning treatment. Marked lesions and histologic changes were also demonstrated in a horse given 8 mg/kg daily. The doses of PBZ used in this experiment were all well in excess of manufacturers recommendations for both amount of drug and duration of therapy. However, because of a general belief among veterinarians in the safety and the dose-dependent analgesic effect of the drug, recommended dose schedules are frequently exceeded. Daily doses of 6 to 8 g of PBZ (approx 13.2 to 17.6 mg/kg) for several days or more are not uncommon.

The finding of oral, gastric, and intestinal mucosal erosions and ulcerations is consistent with previous reports of PBZ toxicity in horses. It is not known precisely how PBZ damages mucosal cells. Proposed mechanisms have included alteration of the mucous layer in the stomach, interference with a protective effect of prostaglandins, and decreased replacement of desquamated mucosal cells. Gastrointestinal lesions were produced by oral and iv administration in horses in this study, but too few animals were used to determine whether the drug was more ulcerogenic when given orally, as has been suggested for aspirin in human beings. Severe lingual ulceration occurred only in horses treated orally in our study, suggesting a mainly local irritant effect of the drug. The development of oral lesions could probably have been avoided if the PBZ had been delivered directly into the pharynx (eg, by balling gun) or stomach.
Serum leakage into the intestinal lumen through damaged gastrointestinal mucosae probably accounted for most of the decrease in serum protein in our horses. Random urinalyses failed to indicate heavy protein loss in the urine. Using $^{61}$Cr-labeled plasma albumin, previous workers have demonstrated increased fecal losses of protein in ponies given large doses of PBZ (10.0 mg/kg/day). 14 Hemodilution and decreased serum protein as a result of increased sodium and $H_2O$ retention occur commonly in human beings taking PBZ. 24 Such an effect was unlikely in our study, however, because all but 1 horse had an increasing PCV and clinical evidence of dehydration. It is of interest that hematologic evidence of protein loss did not correlate well with the presence of detectable amounts of fecal occult blood.

There was a striking uniformity in the occurrence and distribution of renal lesions in horses given 15 or 30 mg of PBZ/kg daily. In addition to grossly obvious renal papillary necrosis (seen in 4 of 6 horses), there was a consistent pattern of medullary interstitial edema and tubular epithelial cell necrosis predominantly affecting collecting tubules. Some degree of clinical renal failure was associated with the lesions in these horses as indicated by progressive increases in $SUN$, serum creatinine, and phosphorus concentrations and decreases in serum calcium. Similar biochemical changes were seen in ponies treated orally with high dosage levels of PBZ, but the results of postmortem examination of the kidneys were not reported. 13 The renal tubular changes in the horses given 8 mg/kg daily were mild, and in horse 8, were not associated with obvious serum biochemical abnormalities.

In rats, PBZ has been shown to cause renal papillary necrosis acutely, 25 and after long-term administration. 26 Renal tubular degeneration and necrosis were noticed in a dog 26 and several cats 16 that died after administration of large doses of PBZ. A comparable clinical and pathologic syndrome known as analgesic nephropathy often follows abuse of a variety of NSAID drugs in human beings. 27 Phenacetin and phenacetin-aspirin combinations are most frequently incriminated, but PBZ has been associated with renal papillary necrosis in several case reports. 29 The focal accumulations of lymphocytes in the renal cortices of horses 5 and 6 may represent an early phase in the development of cortical interstitial inflammation and scarring which, in addition to renal papillary necrosis, are the characteristic changes in chronic analgesic nephropathies of human beings and laboratory animals. 30 It is interesting that renal lesions were produced so readily in our experimental horses when the use of massive doses of a variety of NSAID has failed to produce a consistent model for analgesic nephropathy in various animals. 31

Renal papillary necrosis has been described in horses treated with PBZ or other NSAID. 32 The lesions were sometimes associated with severe renal disease, and in other cases were considered an incidental finding. It is not clear why the renal papilla is susceptible to NSAID, but both direct toxic effects 33 and ischemia secondary to vascular effects 34 have been proposed to explain the distribution of lesions in analgesic nephropathies. Loss of maximal concentrating ability and sterile pyuria occur as a consequence of the tubular-interstitial inflammation and necrosis characteristic of analgesic nephropathies of human beings and experimental animals. 27 As in the present study, proteinuria is usually mild to moderate.
The occurrence of neutropenia and toxic left shift in horses given PBZ is in general agreement with observations of previous investigators who reported the development of reversible neutropenia (< 2,000 cells/mm³) in horses given daily doses of 4 g orally or 7.5 mg/kg IV. Only those horses given 15 or 30 mg/kg became consistently neutropenic. The mechanism of this profound neutropenia is difficult to determine. It is apparent from examination of peripheral blood and bone marrow aspirates that there was severe depletion of circulating and bone marrow pools of mature neutrophils. Possible explanations are suppression of granulopoiesis, as has been suggested previously in similarly affected dogs, and/or increased loss (destruction, consumption, or sequestration) of circulating neutrophils. The rapid (< 12 hours) onset of neutropenia in horses 4 and 5 (30 mg/kg) and the lack of serious toxic changes in bone marrow aspirates indicate that bone marrow suppression was probably not the only cause of neutropenia. In addition to direct toxic effects of the drug, increased bacterial endotoxin absorption through damaged intestinal mucosa may have contributed to the WBC picture. The effects of neutrophils in the horses in this study appeared to be dose-related and are probably not comparable with the idiosyncratic occurrence of aplastic anemia or agranulocytosis in human beings given PBZ occasionally.

Local thrombophlebitis in horses injected with PBZ occurs commonly. The drug may also have thrombotic effects at sites distant to administration, as was shown by the presence of necrotizing thrombophlebitis of portal venules and pulmonary arterial thrombosis in horse 1 (treated orally), colonic vein thrombosis in horse 6 (treated IV), and partial pulmonary vascular thrombosis in 3 horses treated IV. Necrotizing phlebitis of the portal veins has been reported previously in 2 horses given PBZ orally, probably reflecting the higher portal venous concentration when the drug is given orally, rather than IV.

Generally, there was little or no morphologic evidence for hepatotoxicity, and the liver-specific enzyme (SDH, GGT) activities did not increase appreciably during the study. The observed increases in ALP may have originated, at least in part, from damaged intestinal mucosa, lysed neutrophils, or other extrahaematopoetic tissues.

Despite the evidence presented in the present report, there is little doubt that PBZ at recommended doses is well tolerated by the equine species. However, such variables as errors in body weight estimation, the possibility of drug interactions, or individual or breed variations in drug metabolism, and the presence of preexisting disease states, may render a given animal susceptible to PBZ toxicity even at prescribed doses. It has been well shown in animal models of aspirin nephropathy that a state of hydropenia (dehydration) must exist for expression of the nephrotic potential of the drug. Also, many NSAID cause gastrointestinal side effects that are more severe in arthritic human beings and animals than in healthy individuals. Rats with adjuvant-induced arthritis were more susceptible to the gastrointestinal effects of PBZ than were healthy controls. Such considerations may be relevant to the analgesic management of severely painful, immobilizing conditions of horses such as laminitis, pleuritis, and septic arthritis in which large doses of PBZ are commonly used, and hydration may be poor. Careful clinical and laboratory monitoring of PBZ-treated horses is advisable if serious toxic effects are to be avoided, especially when large doses are used in stressed or dehydrated patients.

Further work in this area is necessary before definitive recommendations about additional label warnings can be made.

References