Comparison of adverse effects of phenylbutazone, flunixin meglumine, and ketoprofen in horses

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Summary: The relative toxicity of phenylbutazone, flunixin meglumine, and ketoprofen was studied in healthy adult horses. Sixteen horses were randomly assigned to receive 10 ml of physiologic saline solution, or ketoprofen (2.2 mg/kg of body weight), flunixin meglumine (1.1 mg/kg), or phenylbutazone (4.4 mg/kg) iv, every 8 hours, for 12 days. Results of CBC, serum biochemical analyses, and fecal occult blood tests were monitored. On day 13, all horses were euthanized and complete necropsy examinations were performed.

Mean CBC values remained within normal limits for all groups. Phenylbutazone-treated horses had a significant (P < 0.05) decrease in serum total protein and albumin concentrations. Mean values of all other serum biochemical assays were not different from those of the saline-treated group. Results of all fecal occult blood tests were negative. At necropsy, the glandular portion of the stomach was the area of the gastrointestinal tract most severely affected by phenylbutazone, flunixin meglumine, and ketoprofen. In the phenylbutazone-treated group, but not in the other groups, edema of the small intestine and erosions and ulcers of the large colon were observed. None of the horses treated with saline solution had lesions in the glandular portion of the stomach or in the intestine. Four horses (1/5 and 3/3 in the flunixin- and phenylbutazone-treated groups, respectively) developed renal crest necrosis. Horses in the saline- and ketoprofen-treated groups did not develop renal lesions. Under the conditions of this study and with total daily doses that exceeded the manufacturers’ recommended doses, the toxic potential of the 3 nonsteroidal anti-inflammatory drugs was greatest for phenylbutazone, least for flunixin meglumine, and least for ketoprofen in clinically normal adult horses.

Phenylbutazone, flunixin meglumine, and ketoprofen are classified with the group of compounds commonly referred to as nonsteroidal anti-inflammatory drugs (NSAID). The major categories of NSAID include salicylates (aspirin), propionic acids (ibuprofen, fenoprofen, ketoprofen, and naproxen), pyrazolone (phenylbutazone), anthranilic acids (meclofenamic acid), and aminonicotinic acids (flunixin meglumine). The NSAID are a diverse group of compounds that are antipyretic, anti-inflammatory, and analgesic agents. They share a basic mechanism of inhibiting cyclooxygenase, resulting in decreased production of prostaglandin.1,2

Phenylbutazone was introduced into veterinary medicine in the 1950s, and soon became the nonsteroidal anti-inflammatory drug of choice in equine medicine.3 Phenylbutazone is indicated for the treatment of various musculoskeletal disorders in horses. It is also reported to decrease the adverse effects, but not to increase the survival rate, of ponies when administered after endotoxin.4 In adult horses, previous treatment with phenylbutazone (2 mg/kg of body weight) attenuated the effects of endotoxin but was associated with a brief, early, significant increase in plasma thromboxane B2 concentration.5 Until the late 1970s, the toxic effects of phenylbutazone in horses were underestimated. In 1979, substantial adverse effects of phenylbutazone were reported in ponies receiving phenylbutazone at a dosage of 10 mg/kg, daily, for 7 to 14 days.6 After that report, numerous investigators have confirmed the potential of phenylbutazone to cause adverse reactions in ponies, foals, and adult horses.7-14 Chronic ulcerative colitis with protein-losing enteropathy also has been reported.15,16

Flunixin meglumine was introduced into veterinary medicine in the late 1970s. It is reportedly effective in the treatment of musculoskeletal disease17 and colic in horses.18 Flunixin meglumine also is reported to reduce the adverse effects of endotoxin in ponies19-21 and horses.21 Toxic effects of flunixin meglumine in foals include gastrointestinal tract ulceration and diarrhea.22,23 Ketoprofen is relatively new in veterinary medicine. It was approved for use in horses in 1990 and is recommended for alleviation of inflammation and pain associated with musculoskeletal disorders in horses. In addition to blocking the cyclooxygenase pathway, studies indicate ketop-

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profen also may affect the lipoygenase pathway in human lung preparations\textsuperscript{25} and inhibit 5-lipoxygenase derived from rabbit polymorphonuclear leukocytes.\textsuperscript{26} However, in guinea pig lung, prior incubation with ketoprofen failed to inhibit production of slow-reacting substance of anaphylaxis.\textsuperscript{26} Leukotriene C\textsubscript{4}, D\textsubscript{4}, and E\textsubscript{4} (products of the lipoygenase pathway) have subsequently been shown to collectively account for the biologic activity of slow-reacting substance of anaphylaxis.\textsuperscript{27} Data currently is not available on the effect of ketoprofen on the equine lipoygenase pathway. Although this drug has been used extensively in human beings, little is known about its use or toxic potential in horses.

Until the early 1980s, NSAID were considered to be nontoxic in horses. This is somewhat surprising, considering that toxic effects of phenylbutazone in laboratory animal species\textsuperscript{28} and in human beings\textsuperscript{29} were well documented prior to 1962. Since the early 1980s, there have been numerous reports of the adverse effects of NSAID in horses, including oral, gastric, and duodenal ulceration; colonic ulceration and necrosis; renal crescentic necrosis; and hematologic changes.\textsuperscript{6,16,23-24}

Although the toxic changes caused by NSAID are well documented, the comparative toxicity of these compounds has not been studied in horses. Consequently, equine practitioners do not have comparative data to guide them in their use of these compounds. The purpose of the study reported here was to compare the adverse effects of 3 NSAID, phenylbutazone, flunixin meglumine, and ketoprofen, when administered iv to clinically normal horses.

Materials and Methods

Horses—Sixteen mixed-breed horses (5 geldings and 11 mares), ranging in age from 4 to 12 years (mean ± sd; 6.71 ± 2.24 years) and in body weight from 366 to 487 kg (mean ± sd; 418 ± 33 kg), were given a physical examination to determine that they were in good health prior to entry into the study. Horses were housed individually in 3.7 × 3.7-m box stalls. Diet consisted of a 14% protein, mixed-grain ration fed at a rate of 0.5 kg/50 kg of body weight, divided twice daily, and of free-choice grass hay. All horses were allowed 1 week to adapt to the diet and environment before starting the study. During the first 2 days of the acclimation period, all horses were vaccinated for eastern and western equine encephalomyelitis, tetanus, influenza, and equine herpesvirus 1, and were dewormed with ivermectin paste at a dosage of 200 μg/kg.

Experimental design—Horses were randomly assigned\textsuperscript{a} to 1 of 4 treatment groups: saline (n = 3), ketoprofen (n = 5), flunixin meglumine (n = 5), and phenylbutazone (n = 3). Individuals perform-

\textsuperscript{a}Eexcel, Microsoft Corp, Redmond, Wash.

Experimental procedure—On the day before the study, grain and hay were withheld to facilitate gastric emptying. Water was not withheld until 2 hours prior to gastroendoscopy. In the authors' experience, the equine stomach empties more completely if water is not withheld during the first several hours of grain and hay withdrawal. On the day of the study (day 0), all horses were anesthetized with iv administration of xylazine and ketamine and were positioned in right lateral recumbency for gastroendoscopic examination. Examinations were done with anesthesia so that the horses could be rolled to facilitate examination of the gastric mucosa. A 9.5-mm × 200-cm videodendoscope\textsuperscript{b} was passed into the stomach, and the stomach was insufflated with air to enhance visualization of the gastric mucosa. The primary reason for initial gastroendoscopy was to eliminate the possibility of including horses in the study that had preexisting severe gastric disease. All gastric mucosal abnormalities were recorded and the size and severity was estimated for a later attempt at comparison with necropsy findings. Ulcer size and severity was estimated by the primary author by reviewing videotapes of each gastroscopic procedure. Severity scores were estimated as 0, no lesion; 1, inflammation only (mucosa intact); 2, superficial lesions (appeared to be only mucosa disrupted); 3, moderate lesions (appeared to have deeper tissue involvement); 4, deeper tissue involved and hemorrhage evident; and 5, appeared close to perforation.

Drug administration was initiated at 8 AM on day 1, and continued through 12 midnight on day 12. Physical examinations were completed daily on all horses and abnormalities were recorded. Anorexia was assessed at the time of physical examination and was scored as eating normally, mild anorexia (did not finish grain but ate hay normally), moderate anorexia (did not eat grain but ate hay), marked anorexia (picky at hay or grain but did not eat sufficient quantities), and severe anorexia (refused to eat grain or hay). In addition to daily physical examinations, all horses were checked every 4 hours for signs of adverse reaction to treatment.

On days 0, 8, and 13, blood samples were collected from all horses for CBC, serum biochemical analyses (sodium, potassium, chloride, calcium, glucose, urea nitrogen, creatinine, phosphorus, albumin, total protein, magnesium, and total bilirubin concentrations; and aspartate transaminase, alkaline phosphatase, lactate dehydrogenase, cre-
atine kinase, and γ glutamyltransferase activities, and fecal samples were submitted for occult blood determination. Urine was collected from mares (2/3, 3/5, 3/5, and 3/3 horses in the saline, ketoprofen, flunixin, and phenylbutazone-treated groups, respectively) by catheterization for urinalysis; fractional clearance of sodium, potassium, chloride, and phosphorus; and urinary γ glutamyltransferase/creatinine ratio. Laboratory samples were analyzed by the Clinical Pathology Laboratory, College of Veterinary Medicine, Oklahoma State University.

Physiologic saline solution (10 ml), ketoprofen, flunixin meglumine, and phenylbutazone were administered IV via an indwelling jugular vein catheter at 8 AM, 4 PM, and 12 AM daily for 12 days. The daily dosage of ketoprofen, flunixin meglumine, and phenylbutazone was 6.6 mg/kg, 3.3 mg/kg, and 13.2 mg/kg, divided every 8 hours, respectively. This dosage schedule resulted in administration of the drugs at the manufacturers' recommended total daily dosage each 8 hours. After each injection, IV catheters were flushed with heparinized physiologic saline solution.

On day 13, all horses were euthanized. Immediately after euthanasia, complete necropsy was performed on all horses and all gross lesions were recorded. Oral and gastric mucosal lesions were counted and measured. For measurement purposes, stomachs were opened along the greater curvature from the cardia to the pylorus. All oral and gastric mucosal lesions were measured with a ruler, with the stomach placed flat on an examination table. Severity of gastric lesions was determined histologically and scored from 0 to 5, with 0 = no lesion, 1 = erosions only, 2 = primarily erosions with some ulcers, 3 = primarily ulcers, 4 = ulcers with polymorphonuclear leukocyte infiltration, and 5 = ulcers with polymorphonuclear leukocyte infiltration and thrombus formation. Intestinal lesions were scored from 0 to 5, with 0 = no lesions; 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe lesions, and 5 = extensive involvement.

Statistical analysis—Statistical calculations were performed on a computer, using commercial software. Tabular data were analyzed by generating contingency tables and by use of χ² and Fisher's exact test. Lesions (areas and histologic scores) were compared by use of nonparametric methods; measurements were ranked and ANOVA, with t tests for comparisons, was performed on the ranked data. The CBC, serum biochemical, and physical examination data were evaluated with ANOVA for repeated measures. Direct comparisons between treatments were performed by use of a Fisher least significant difference test.

Statistical parameters were compared with their respective probability distributions to determine the probability (P) of a chance occurrence. Probabilities were considered to be significant when P values were < 0.05.

Results

On day-0 gastroendoscopic examination, 15 of the 16 horses had visible lesions in the nonglandular (stratified squamous) portion of the stomach. Most of the lesions were adjacent to the margo plicatus. Four of the 16 horses (1 horse in each treatment group) had visible lesions in the glandular portion of the stomach.

Clinically apparent abnormalities observed on scheduled physical examinations and on observations included mild anorexia in 1 of the 3 saline-treated horses; mild and marked anorexia (n = 1 each) in flunixin-treated horses; and mild, moderate, and severe anorexia (n = 1 each) in phenylbutazone-treated horses. None of the ketoprofen-treated horses developed anorexia during the study. Watery diarrhea and mild colic developed in 1 horse in the flunixin group on days 8 and 9. Diarrhea and colic resolved without treatment. Mean CBC values remained within normal limits for all groups. Serum biochemical analyses indicated a treatment effect on total protein and albumin concentrations. Compared with the saline group, treatment with phenylbutazone caused a significant decrease in total protein and albumin concentrations on days 8 and 13 (Table 1). Results of fecal occult blood determinations were negative in all horses throughout the study. Treatment effect was not evident in results of urinalysis, urinary fractional clearance of electrolytes, or urinary γ glutamyltransferase/creatinine in the 11 mares. Because of the limited number of horses from

<table>
<thead>
<tr>
<th>Day of sampling</th>
<th>Saline</th>
<th>Ketoprofen</th>
<th>Flunixin</th>
<th>Phenylbutazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum total protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7.4</td>
<td>7.4</td>
<td>7.2</td>
<td>7.2</td>
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<tr>
<td>8</td>
<td>7.5</td>
<td>(0.4)</td>
<td>(0.5)</td>
<td>(0.3)</td>
</tr>
<tr>
<td>12</td>
<td>7.4</td>
<td>7.2</td>
<td>6.4</td>
<td>5.2*</td>
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<tr>
<td>Albumin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2.7</td>
<td>2.8</td>
<td>2.8</td>
<td>3.1</td>
</tr>
<tr>
<td>8</td>
<td>3.1</td>
<td>2.9</td>
<td>2.7</td>
<td>2.2*</td>
</tr>
</tbody>
</table>

*Significant (P < 0.05) change, compared with saline value.
Table 2—Mean (± SEM) area and severity score for mucosal erosion/ulceration in the gastrointestinal tract of horses treated with physiologic saline solution or with various nonsteroidal anti-inflammatory drugs.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Saline (mm²)</th>
<th>Ketoprofen (mm²)</th>
<th>Flunixin (mm²)</th>
<th>Phenylbutazone (mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral lesions</td>
<td>0 (0)</td>
<td>4 (0)</td>
<td>81 (56)</td>
<td>462* (196)</td>
</tr>
<tr>
<td>Gastric (nonglandular)</td>
<td>482 (66)</td>
<td>601 (68)</td>
<td>1,068 (50)</td>
<td>190 (60)</td>
</tr>
<tr>
<td>lesions (mm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric (glandular)</td>
<td>0 (0)</td>
<td>421 (117)</td>
<td>771* (347)</td>
<td>1,212* (523)</td>
</tr>
<tr>
<td>lesions (mm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Largest glandular</td>
<td>0 (0)</td>
<td>102 (18)</td>
<td>322* (152)</td>
<td>386* (169)</td>
</tr>
<tr>
<td>lesion (mm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intestinal lesion score</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2.0* (1.5)</td>
</tr>
</tbody>
</table>

*Significantly (P < 0.05) different from values in the saline group.

Lesions in the glandular portion of the stomach were found in 4 of 16 horses (1 horse in each treatment group) on day 0 of the study. At necropsy, lesions were not visible in the glandular portion of the stomach of the saline-treated horse, and therefore, the lesions seen during day-0 gastroscopy were considered to have healed during the treatment period. The NSAID-treated horses that had endoscopically evident lesions of the glandular portion at day-0 gastroscopy developed numerous lesions in the glandular mucosa during the treatment period, and therefore, a comparison of results of day-0 endoscopy and necropsy examination for the glandular portion of the stomach failed to determine the status of the lesions seen endoscopically on day 0 in these 3 horses. Saline-treated horses did not develop glandular mucosal erosions or ulcers.

Histologically, erosions were observed in the glandular mucosa of 0 of 3, 5 of 5, 4 of 5, and 3 of 3 horses from the saline, ketoprofen, flunixin, and phenylbutazone groups, respectively, with data from all treated groups being significantly different from that of the saline group. Ulceration of the glandular mucosa was found in 0, 2, 4, and 3 horses of the saline, ketoprofen, flunixin, and phenylbutazone groups, respectively, with a significant difference detected between results from the saline group and those from the flunixin and phenylbutazone groups. The mean area (± SEM) of glandular mucosal ulcers/erosions was 0 ± 0, 421 ± 117, 771 ± 347, and 1212 ± 523 mm² for the saline, ketoprofen, flunixin, and phenylbutazone groups, respectively. Only the values for the phenylbutazone and flunixin groups were significantly different from those of the saline group (Fig 1).

Lesions in the nonglandular portion of the stomach were found in 15 of 16 horses at day 0 of the study. A subjective comparison of day-0 gastroscopy results and necropsy results indicated that most gastric lesions visible in the nonglandular portion of the stomach on day 0 remained the same or because more severe during drug treatment. Using the gastric lesion measurements obtained at necropsy, significant difference was not detected between treatment groups in the area of nonglandular mucosa with ulcers/erosions (Table 2).

Figure 1—Mean area of and mean severity score for lesions of the glandular portion of the stomach in horses treated with physiologic saline solution or with ketoprofen (KETO), flunixin meglumine (FLUN), or phenylbutazone (PBZ). * Denotes significantly (P < 0.05) different from saline values; bars indicate SEM.

Figure 2. which urine was sampled, however, the possibility of a treatment effect cannot be ruled out.

Oral erosions/ulcers were detected in 0 of 3, 2 of 5, 2 of 5, and 3 of 3 horses from the saline, ketoprofen, flunixin, and phenylbutazone groups, respectively. Although oral lesions were found predominantly on the tongue, 2 horses from the phenylbutazone group also had lesions on the mucosa of the upper and lower lips. Mean area (± SEM) of oral ulcers/erosions was 0 ± 0, 4 ± 3, 81 ± 56, and 482 ± 196 mm² in the saline, ketoprofen, flunixin, and phenylbutazone groups, respectively. Only values from the phenylbutazone group were significantly different from those of the saline group (Table 2).

Lesions in the nonglandular portion of the stomach were found in 15 of 16 horses at day 0 of the study. A subjective comparison of day-0 gastroscopy results and necropsy results indicated that most gastric lesions visible in the nonglandular portion of the stomach on day 0 remained the same or because more severe during drug treatment. Using the gastric lesion measurements obtained at necropsy, significant difference was not detected between treatment groups in the area of nonglandular mucosa with ulcers/erosions (Table 2). Because of the high prevalence of lesions in the nonglandular portion of the stomach at day 0 of the study, accurate assessment of the effects of the NSAID on this area was not possible.

Lesions in the glandular portion of the stomach were found in 4 of 16 horses (1 horse in each treatment group) on day 0 of the study. At necropsy, lesions were not visible in the glandular portion of the stomach of the saline-treated horse, and therefore, the lesions seen during day-0 gastroscopy were considered to have healed during the treatment period. The NSAID-treated horses that had endoscopically evident lesions of the glandular portion at day-0 gastroscopy developed numerous lesions in the glandular mucosa during the treatment period, and therefore, a comparison of results of day-0 endoscopy and necropsy examination for the glandular portion of the stomach failed to determine the status of the lesions seen endoscopically on day 0 in these 3 horses. Saline-treated horses did not develop glandular mucosal erosions or ulcers.

Histologically, erosions were observed in the glandular mucosa of 0 of 3, 5 of 5, 4 of 5, and 3 of 3 horses from the saline, ketoprofen, flunixin, and phenylbutazone groups, respectively, with data from all treated groups being significantly different from that of the saline group. Ulceration of the glandular mucosa was found in 0, 2, 4, and 3 horses of the saline, ketoprofen, flunixin, and phenylbutazone groups, respectively, with a significant difference detected between results from the saline group and those from the flunixin and phenylbutazone groups. The mean area (± SEM) of glandular mucosal ulcers/erosions was 0 ± 0, 421 ± 117, 771 ± 347, and 1212 ± 523 mm² for the saline, ketoprofen, flunixin, and phenylbutazone groups, respectively. Only the values for the phenylbutazone and flunixin groups were significantly different from those of the saline group (Fig 1).

Severity scores for the glandular mucosal lesions were 0 ± 0, 1.4 ± 0.25, 3.6 ± 0.93, and 4.7 ± 0.33 for the saline, ketoprofen, flunixin, and phenylbutazone groups, respectively. Ulcerations in the flunixin and phenylbutazone groups were significantly more severe than those in the saline group (Fig 1). The mean area of the largest glandular mucosal lesion was 0 ± 0, 102 ± 18, 322 ± 152, and 388 ± 169 for the saline, ketoprofen, flunixin, and phenylbutazone groups, respectively. Only the values for the flunixin and phenylbutazone groups were significantly different from those of the saline group (Table 2).

Intestinal lesions attributable to drug treatment were found in the phenylbutazone group only. Two of the horses in this group had small-intestinal submucosal edema. One horse had large-
intestinal erosions, and 1 had extensive large-intestinal ulceration with venous thrombosis.

Renal crest necrosis developed in 0 of 3, 0 of 5, 1 of 5, and 3 of 3 horses in the saline, ketoprofen, flunixin, and phenylbutazone groups, respectively. Necrotizing pneumonia was evident in 1 horse each from the flunixin and phenylbutazone groups. Mild hepatitis was evident histologically in 1 horse each from the saline and phenylbutazone groups and in 2 horses from the ketoprofen group. Hepatitis in the saline- and ketoprofen-treated horses consisted of mild periporal lymphocytic infiltrate, the cause of which was not known. The phenylbutazone-treated horse with hepatitis had a moderate granulomatus infiltrate. Although the cause of this lesion could not be determined with certainty, this horse had extensive large-intestinal ulceration, suggesting a possible relationship between the intestinal and hepatic lesions. Eosinophilic hepatitis attributable to parasite migration also was seen in 1 horse each from the saline and ketoprofen groups.

Discussion

The 94% prevalence of endoscopically evident gastric lesions on day 0 of this study was higher than expected. The reported frequency of gastric ulceration in clinically normal, mature Thoroughbred horses at necropsy is 66% (129/195); however, 80% of the horses euthanatized directly from training had gastric lesions, compared with only 52% of those retired from training for a month or more.31 Previous training or other pertinent history for the horses of the study reported here was unknown. Horses were purchased locally and may have been through training procedures, horse auctions, or other potentially stressful situations.

Six horses became mildly anorectic during the study. This was anticipated, because 1 of the clinical signs of toxicosis from NSAID is anorexia. The reason for anorexia in the salines treated horse, however, was unknown. One horse, in the flunixin group developed diarrhea and colic on days 8 and 9. The cause of the diarrhea and colic were not determined, and treatment was not necessary. Diarrhea and colic were reported to be manifestations of toxicosis from NSAID. The decrease in serum albumin and total protein concentrations in this study was consistent with findings from other studies in which phenylbutazone caused hypoproteinemia and hyperalbuninemia. Studies in which 51CrCl3 was administered IV in ponies given phenylbutazone at a dosage of 10 mg/kg indicated that the protein loss in phenylbutazone toxicosis is via gastroenteropathy, and that the site of protein loss was variable and included the stomach and intestine.9 Gastrointestinal protein loss was confirmed by evaluating the excreted radioactivity in the feces and in the gastrointestinal contents of ponies that were necropsied. Gastrointestinal protein loss also occurred without visible gastrointestinal tract ulceration.9 The mild decrease in total protein in the flunixin group in our study was also similar to the results of a previous study in foals that were given physiologic saline solution or flunixin meglumine at a dosage of 0.55, 1.1, 2.2, or 6.6 mg/kg IV daily for 5 days. Mean serum total protein decreased significantly in the 0.55- and 6.6-mg/kg groups by day 3 of the study; however, by day 6, although a trend for greater loss of protein in all treated groups was observed, differences between values for the saline-treated group and for the flunixin groups were not significant.29

Renal disease developed in the flunixin and phenylbutazone groups only, and consisted of renal crest necrosis. Only mares (because of ease of urinary catheterization) were monitored for changes in results of urinalysis, urinary fractional clearance of electrolytes, and urinary γ glutamyltransferase/creatinine. Therefore, although a treatment effect was not found for urinary indices, it cannot be definitively ruled out because of the small number of horses from which samples were obtained for each treatment group. In a previous study on the effects of phenylbutazone on urinary enzymes in horses, phenylbutazone, administered at a dosage of 8.8 mg/kg, once daily for 6 days, failed to increase the urinary ratios of alkaline phosphatase, lactate dehydrogenase, or γ glutamyltransferase.32 Renal crest (papillary) necrosis has been reported as a manifestation of nephropathy caused by NSAID in human beings33,34 and in horses.35-36 Renal papillary necrosis is attributed to impaired blood supply, particularly in the medulla of the kidneys.34 Renal prostaglandins exert little or no important control over basal renal blood flow and glomerular filtration rate in healthy animals or human beings.34,35,37 In response to renal hypoperfusion, however, the kidneys increase local production of prostaglandins, which act as autoregulators to increase renal perfusion.34,31 Inhibition of prostaglandin synthesis by NSAID results in decreased ability of the kidneys to autoregulate blood flow.34,35

Without concurrent dehydration, phenylbutazone administration did not result in renal papillary necrosis in horses.38 However, the renal crest necrosis that was found in 4 of 13 horses treated with NSAID in the study reported here was not associated with clinically apparent dehydration or other disease process. These 4 horses with renal crest necrosis were, on at least 1 day of the study, mildly anorectic. Because water consumption was not monitored, these horses could have voluntarily reduced water consumption during the study and may have been subclinically dehydrated.

The negative results for fecal occult blood tests were not unexpected in horses with lesions limited to the stomach. The test used in this study does not detect hemoglobin that has been extensively digested. In clinically normal ponies, intragastric administration of > 100 ml of blood was necessary
to cause a positive result with a similar test kit.39 We were surprised that the horse in the phenylbutazone group with severe large-colon lesions had negative results of occult blood tests. Little blood may have been lost from these lesions, or blood lost into the large colon may have been digested by resident bacterial flora.

Nonsteroidal anti-inflammatory drugs may damage gastric mucosa by the same mechanism that causes their beneficial effect on inflammation. Indomethacin and aspirin decrease gastric mucosal blood flow in dogs.40 Prostaglandins increase gastric mucosal blood flow and mucus production, and decrease gastric acid production.41 Prostaglandins also increase migration of basal cells toward the lumen to repair mucosal injury.42 Inhibition of prostaglandin synthesis therefore may create an environment conducive to gastrointestinal tract ulcer disease. In recent studies, however, phenylbutazone did not reduce gastric or intestinal mucosal prostaglandin concentrations in horses 48 hours after administration.13,14 In this study, gastric and intestinal lesions were postulated to have resulted from microvascular injury induced by phenylbutazone, rather than from a reduction in the mucosal prostaglandin concentrations.13,14 Administration of exogenous prostaglandin at a dosage of 8.3 µg/kg, twice daily, decreased the toxic effects of phenylbutazone (dosage, 8.8 mg/kg/d) on the gastrointestinal tract of ponies.5 The small number of horses used in the studies of Muescher et al12,13 or the sampling times may have caused the failure to detect a decrease in prostaglandin concentrations. Alternatively, the protective effect of prostaglandins on the gastrointestinal mucosa may be associated with a cytoprotective mechanism other than prostaglandin replacement.43

Treatment effect of NSAID on the nonglandular (stratified squamous) portion of the stomach was difficult to assess. Fifteen of the 16 horses had lesions in the nonglandular portion of the stomach at gastroscopy on day 0; the same number had nonglandular mucosal lesions at necropsy. Although the lesions appeared subjectively to remain the same or to become more severe during the study, accurate comparison of endoscopic pictures with necropsy specimens was difficult. In this study, therefore, accurate comparison of the effects of NSAID on the nonglandular mucosa was not possible. The flunixin group had the largest mean area of nonglandular mucosal lesions; however, results from the groups treated with NSAID were not significantly different from those in the saline group. The results of this study appeared to be consistent with those of other studies in which effects of NSAID were less evident or were not detected in nonglandular mucosa and were most severe in glandular mucosa.6,9,11,14 In a study by MacKay et al,11 nonglandular ulcers adjacent to the margo plicatus appeared histologically to be caused by parasites. Evidence of parasitic origin was not found in lesions of the nonglandular portion of the stomach in our study.

The glandular portion of the gastric mucosa was the area most affected by administration of NSAID in this study. Considering gastrointestinal protein loss, oral erosions/ulcers, mean size of the largest glandular lesion, mean area of glandular lesions, ulcer severity scores, and renal crest necrosis, the toxic potential of the NSAID compared in this study was greatest for phenylbutazone, less for flunixin meglumine, and least for ketoprofen when these drugs were administered iv at a dosage of 4.4, 1.1, and 2.2 mg/kg, every 8 hours, respectively. A possible explanation for ketoprofen being the least ulcerogenic of the compounds tested is the ability of ketoprofen to at least partially block the production of some endproducts of the lipooxygenase pathway. These endproducts have been shown to be detrimental to the gastric mucosa.44

Necrotizing pneumonia was found in 2 of the horses treated with NSAID. This finding was unexpected and a cause for the pneumonia was not determined. In a study of phenylbutazone toxicosis, 4 of 8 horses had pulmonary vascular thrombosis at necropsy, and 1 of the 4 affected horses had pulmonary infarct.41 The potential of NSAID to enhance the development of pulmonary lesions in horses merits further study.

This study indicated that when phenylbutazone, flunixin meglumine, and ketoprofen were administered iv to clinically normal adult horses at dosages of 4.4, 1.1, and 2.2 mg/kg, every 8 hours, respectively, the toxic potential was greatest for phenylbutazone, less for flunixin meglumine, and least for ketoprofen. When use of these compounds is contemplated in clinical cases, the risk of adverse effects and the comparative toxic potential should be considered, along with the efficacy of the compound for the condition being treated.

References


