

Evaluation of the analgesic effects of phenylbutazone administered at a high or low dosage in horses with chronic lameness

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Objective—To compare analgesic effects of phenylbutazone administered at a dosage of 4.4 mg/kg/d (2 mg/lb/d) or 8.8 mg/kg/d (4 mg/lb/d) in horses with chronic lameness.

Design—Controlled crossover study.

Animals—9 horses with chronic forelimb lameness.

Procedure—Horses were treated IV with phenylbutazone (4.4 mg/kg/d or 8.8 mg/kg/d) or saline (0.9% NaCl) solution once daily for 4 days. All horses received all 3 treatments with a minimum of 14 days between treatments. Mean peak vertical force (mPVF) was measured and clinical lameness scores were assigned before initiation of each treatment and 6, 12, and 24 hours after the final dose for each treatment.

Results—Compared with values obtained after administration of saline solution, mPVF was significantly increased at all posttreatment evaluation times when phenylbutazone was administered. Clinical lameness scores were significantly decreased 6 and 12 hours after administration of the final dose when phenylbutazone was administered at the low or high dosage but were significantly decreased 24 hours after treatment only when phenylbutazone was administered at the high dosage. No significant differences in mPVF and clinical lameness scores were found at any time when phenylbutazone was administered at the low versus high dosage.

Conclusions and Clinical Relevance—Results suggest that the high dosage of phenylbutazone was not associated with greater analgesic effects, in terms of mPVF or lameness score, than was the low dosage. Considering that toxicity of phenylbutazone is related to dosage, the higher dosage may not be beneficial in chronically lame horses. (*J Am Vet Med Assoc* 2005; 226:414–417)

Phenylbutazone is a nonsteroidal anti-inflammatory drug commonly used for its analgesic effects in horses with musculoskeletal disorders. The recommended dosage range is 2.2 to 8.8 mg/kg (1 to 4 mg/lb)

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once or twice daily. However, numerous studies document toxicoses in ponies,¹ foals,² and horses^{3–7} when phenylbutazone is administered long-term at dosages > 4.4 mg/kg (2 mg/lb). These toxicoses are thought to result from nonselective inhibition of both branches of the cyclooxygenase enzyme system.

Nonselective inhibition of the cyclooxygenase enzyme system ultimately results in suppression of prostaglandin formation. Prostaglandins are responsible not only for the vascular changes and hyperalgesia associated with inflammation but also for a variety of physiologic actions, including gastric mucosal blood flow, gastric hydrogen ion secretion, and renal blood flow. Suppressing prostaglandin formation induces desirable anti-inflammatory effects but may inhibit protective physiologic mechanisms. Toxicoses associated with phenylbutazone administration in horses include inappetence, signs of depression, weight loss, renal papillary necrosis, oral and gastrointestinal tract ulcers, colic, diarrhea, protein-losing enteropathy, hypovolemia, and endotoxic shock.^{8–11}

Despite the potential for toxicoses, phenylbutazone is commonly administered at dosages > 4.4 mg/kg/d on the basis of the assumption that a higher dosage is associated with greater efficacy.^{4,7,12} Although a relationship does exist between dosage and plasma concentration,^{13,14} few studies^{13,15} have demonstrated a linear relationship between plasma concentration and therapeutic efficacy. In fact, pharmacokinetic-pharmacodynamic modeling of the effects of phenylbutazone would seem to predict otherwise. In a study¹⁴ involving 5 horses with experimentally induced arthritis of the carpal joints, phenylbutazone was predicted to have no therapeutic effects when administered at doses < 1 mg/kg (0.45 mg/lb) and maximum therapeutic effect when administered at doses of approximately 2 mg/kg (0.9 mg/lb). The authors suggested that administration of higher doses would not increase the therapeutic effect, although it might increase the duration of effect.¹⁴ However, their results were derived from pharmacokinetic-pharmacodynamic modeling and were not verified in live horses. Thus, whether administration of phenylbutazone at higher dosages is associated with sufficiently greater efficacy to warrant the higher risk of toxicoses is still unclear.

In lame horses, the therapeutic efficacy of phenylbutazone can be measured as a change in the severity of lameness. Severity of lameness is traditionally evaluated in horses by observing the gait and assigning a clinical lameness score. However, lameness scores can vary among clinicians.¹⁶ Therefore, objective methods, such as force plate analysis and kinematic evaluation of the gait, have been developed.^{17–21} In lame horses, mean peak vertical force (mPVF) has been found to be inversely proportional to the degree of lameness,^{19,20}

making force plate analysis an excellent method for studying the pharmacodynamic effects of analgesic drugs in horses with musculoskeletal disease.²¹

The purpose of the study reported here was to compare analgesic effects of phenylbutazone administered IV at a dosage of 4.4 mg/kg/d or 8.8 mg/kg/d in horses with chronic lameness. Analgesic effects were evaluated by measuring mPVF and assigning lameness scores.

Materials and Methods

Animals—Nine horses (7 geldings and 2 mares) of Quarter Horse-type breeding ranging in age from 6 to 18 years (mean \pm SD, 12 \pm 3.7 years) and weighing between 443 and 583 kg (975 and 1,283 lb; mean \pm SD, 522 \pm 45 kg [1,148 \pm 99 lb]) were used in the study. All horses had chronic lameness associated with naturally acquired conditions and had been lame for at least 2 months prior to enrollment in the study. Horses were in good health other than the lameness.

In all horses, the underlying cause of the lameness had been determined on the basis of results of clinical examinations, regional nerve blocks, and radiography. All horses had navicular syndrome, and 4 horses had concurrent abnormalities consisting of proximal sesamoiditis (1 horse), dystrophic mineralization of the distal portion of the deep digital flexor tendon (1), chronic fracture of the medial aspect of the navicular bone (1), and mild degenerative joint disease of the proximal and distal interphalangeal joints (1).

Severity of the lameness in all horses was determined to be stable by determining peak vertical force and clinically observing the gait on 2 occasions 10 days apart. Horses were acclimated to their diet and surroundings for a minimum of 14 days prior to commencement of the study. During the acclimatization period, horses were dewormed with ivermectin paste. Horses were housed in a paddock, fed grassy alfalfa hay and water ad libitum, and observed at least twice daily to monitor health. The Oklahoma State University Institutional Animal Care and Use Committee approved the study protocol.

Study design—The study was designed as a controlled crossover study. Horses were ranked from lowest to highest mPVF obtained 1 day prior to initiation of the study and were assigned to 3 replicates on the basis of these ranks, with 3 horses in each replicate. Horses in each replicate were randomly assigned to receive phenylbutazone at a dosage of 8.8 mg/kg, IV, every 24 hours (high dosage); phenylbutazone at a dosage of 4.4 mg/kg, IV, every 24 hours (low dosage); or physiologic saline (0.9% NaCl) solution (15 mL, IV, every 24 hours). Treatments were administered in the morning for 4 days via an indwelling catheter placed in a jugular vein. Lameness scores were assigned and mPVF was measured 6, 12, and 24 hours after the fourth dose was administered.

Horses were rotated through all 3 treatments by use of a 3 \times 3-Latin square design. A minimum 14-day washout period was allowed between treatments.

Measurement of mPVF—For each horse, peak vertical forces were recorded from the forelimb determined by results of physical examination to be more severely affected. All subsequent evaluations were of the same limb. For measurement of peak vertical forces, horses were trotted by a handler along a 15.24-m walkway containing a centrally positioned force plate.^a Forward velocity was recorded with a phototiming switch system^b with the 2 photoelectric cells placed 3 m apart. A run was considered successful when the selected forelimb contacted the surface of the force plate while the horse was trotting at a speed of 2.5 to 2.9 m/s. Each horse was trotted across the force plate until measurements were recorded from 6 successful runs. Peak vertical force for each run was calculated with specialized software.^c Data were normalized to body weight obtained just prior to force plate evaluation. The least square mean of the peak vertical force for the 6 successful runs was then calculated.

Assignment of clinical lameness scores—Clinical lameness scores were assigned prior to initiation of the study and then prior to force plate evaluations 6, 12, and 24 hours after the fourth dose of each treatment was administered. Severity of lameness was scored from 0 to 5 on the basis of guidelines from the American Association of Equine Practitioners.²² A single individual (CGM) who was unaware of the treatment each horse had received assigned all clinical lameness scores.

Data analysis—Primary endpoints were mPVF and clinical lameness score prior to the initiation of treatment and 6, 12, and 24 hours after the fourth dose of each treatment. Horse and sequence were included as random effects in the model. The intrahorse variance structure was modeled with repeated-measures techniques. An autoregressive covariance structure was found to best fit the data. Planned comparisons of the 3 treatments were performed by use of least squares methods. Standard software was used for all analyses^d; values of $P < 0.05$ were considered significant.

Results

Peak vertical force—Mean peak vertical force was significantly higher 6, 12, and 24 hours after the fourth dose when phenylbutazone was administered than when saline solution was administered (Table 1). There were no significant differences in values for mPVF when horses were administered phenylbutazone at the high versus the low dosage.

Clinical lameness scores—Clinical lameness scores were significantly lower 6 and 12 hours after the

Table 1—Mean peak vertical force expressed as a percentage of body weight before (time 0) and 6, 12, and 24 hours after administration of phenylbutazone at a high dosage (8.8 mg/kg [4 mg/lb], IV, q 24 h), phenylbutazone at a low dosage (4.4 mg/kg [2 mg/lb], IV, q 24 h), or saline (0.9% NaCl) solution (15 mL, IV, q 24 h) for 4 days in 9 horses with chronic forelimb lameness.

Treatment	Time (h)			
	0	6	12	24
Phenylbutazone				
High dosage	76.44 \pm 2.35 ^a	84.20 \pm 3.43 ^a	83.80 \pm 3.67 ^a	84.70 \pm 4.15 ^a
Low dosage	75.45 \pm 2.53 ^a	84.37 \pm 2.65 ^a	85.29 \pm 2.71 ^a	82.19 \pm 3.50 ^a
Saline solution	74.92 \pm 2.33 ^a	75.78 \pm 2.99 ^b	76.76 \pm 2.34 ^b	77.12 \pm 2.68 ^b

Values were obtained from force plate analyses of the more severely affected forelimb in each horse; data are given as least squares mean \pm SEM.
^{a,b}In each column, values with different superscripts were significantly ($P < 0.05$) different.

Table 2— Mean clinical lameness scores before (time 0) and 6, 12, and 24 hours after administration of phenylbutazone or saline solution for 4 days in 9 horses with chronic forelimb lameness.

Treatment	Time (h)			
	0	6	12	24
Phenylbutazone				
High dosage	3.1 ± 0.3 ^a	2.5 ± 0.2 ^a	2.3 ± 0.4 ^a	2.5 ± 0.4 ^a
Low dosage	3.2 ± 0.2 ^a	2.4 ± 0.4 ^a	2.3 ± 0.4 ^a	2.7 ± 0.4 ^{a,b}
Saline solution	3.4 ± 0.2 ^a	3.1 ± 0.2 ^b	3.1 ± 0.2 ^b	3.2 ± 0.2 ^b
<i>See Table 1 for key.</i>				

fourth dose when phenylbutazone was administered at the low or high dosage, compared with scores recorded after administration of saline solution (Table 2). However, a significant difference was detected 24 hours after the fourth dose only when phenylbutazone was administered at the high dosage. There were no significant differences in clinical lameness scores at any time when horses were administered phenylbutazone at the high versus the low dosage.

Discussion

Results of the present study demonstrate that the analgesic effects of phenylbutazone can be quantified in lame horses through measurement of mPVF. The significant increases in mPVF at all measurement times following administration of phenylbutazone, compared with administration of saline solution, indicated that under the conditions of this study, phenylbutazone had a measurable effect for at least 24 hours. Analyses of clinical lameness scores yielded similar results, except that improvement was not identified 24 hours after the fourth dose when horses were given phenylbutazone at the low dosage.

In the present study, we did not find any significant differences in regard to mPVF and clinical lameness scores between values obtained when horses were given phenylbutazone at the high dosage and values obtained when they were given phenylbutazone at the low dosage. These findings agree with results of a previous study¹⁴ of the pharmacokinetic-pharmacodynamic effects of phenylbutazone in which maximal effects of phenylbutazone were predicted to be obtained at a dose of 2 mg/kg. This study predicted that although there would not be any increase in analgesia with higher doses, there would be dose-dependent increases in duration of effect, with a predicted duration of effect of about 16 hours when phenylbutazone was administered at a dose of 4 mg/kg, IV. In the present study, significant analgesic effects lasted at least 24 hours, suggesting that the true duration of effect was longer than that predicted by the pharmacokinetic-pharmacodynamic model following administration for multiple days. This may indicate that a systemic steady state is established following accumulation of drug in inflamed tissues²³⁻²⁵ or may result from irreversible receptor binding.²⁴ Our findings may also be related to the fact that at least 98% of phenylbutazone is bound to plasma proteins following administration at therapeutic doses.¹³ Therapeutic plasma concentrations may result in saturation of plasma proteins and maximal inhibition of the cyclooxygenase enzyme system. This saturation would prevent development of greater anal-

gesic effects despite administration of larger doses. However, larger doses will increase the half-life of the drug allowing for a longer duration of effect. Accumulation of the drug with multiple dosing may lead to a greater potential for toxicoses.

Age and breeding may influence the pharmacokinetics of phenylbutazone in horses,¹ but any potential intrahorse variability in the present study was minimized by the use of a crossover design. The discrepancy in results obtained for clinical lameness scores and mPVF 24 hours after administration of phenylbutazone at the low dosage likely was a reflection of the variability that can occur with subjective lameness evaluation methods. Alternatively, it may suggest that the high dose of phenylbutazone had a duration of analgesic effect substantially > 24 hours, whereas the efficacy of the low dose may have been diminishing by 24 hours. This is possible considering the dose-related half-life of phenylbutazone, with higher dosages associated with longer half-lives.¹³ However, in another crossover study²¹ involving 12 horses, mPVF and clinical lameness scores were comparable at all times following administration of phenylbutazone at the same dosages. In that study, assignment of half-point scores was permitted, which may have allowed for a more accurate assessment of lameness severity.

The low phenylbutazone dosage in the present study was selected on the basis of its documented safe use in horses.^{8,26} In contrast, the high dosage has been implicated in phenylbutazone toxicosis in horses,^{4,7,10} especially with long-term use or if cofactors for toxicosis, such as water deprivation,¹¹ are present. Because we wanted to avoid induction of toxicosis in the present study, treatment administration was limited to 4 days.

Horses with naturally occurring chronic lameness were used in the present study. Unpublished results of force plate analyses for these horses indicated that the severity of lameness was stable, with no significant interday variation in mPVF. Therefore, each horse acted as its own control in the present study.

Results from this study have implications for recommended dosages of phenylbutazone in horses. In particular, our results would suggest that there is no benefit in administering phenylbutazone at dosages higher than 4.4 mg/kg/d, IV, in horses with navicular syndrome. Further studies are required to determine the minimum effective dose of phenylbutazone and to determine the duration of effect following single- and multiple-day dosing.

a. Multicomponent force plate, model 9287BA, Kistler Instrument Corp, Amherst, NY.

- b. Phototiming switch system, model 49-551A, Tandy Corp, Fort Worth, Tex.
- c. Bioware 3.0, Kistler Instrument Corp, Amherst, NY.
- d. PROC MIXED, SAS, version 8.1, SAS Institute Inc, Cary, NC.

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