

Effectiveness of administration of phenylbutazone alone or concurrent administration of phenylbutazone and flunixin meglumine to alleviate lameness in horses

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Objective—To determine the effectiveness of administering multiple doses of phenylbutazone alone or a combination of phenylbutazone and flunixin meglumine to alleviate lameness in horses.

Animals—29 adult horses with naturally occurring forelimb and hind limb lameness.

Procedures—Lameness evaluations were performed by use of kinematic evaluation while horses were trotting on a treadmill. Lameness evaluations were performed before and 12 hours after administration of 2 nonsteroidal anti-inflammatory drug (NSAID) treatment regimens. Phenylbutazone paste was administered at approximately 2.2 mg/kg, PO, every 12 hours for 5 days, or phenylbutazone paste was administered at approximately 2.2 mg/kg, PO, every 12 hours for 5 days in combination with flunixin meglumine administered at 1.1 mg/kg, IV, every 12 hours for 5 days.

Results—Alleviation of lameness was greater after administration of the combination of NSAIDs than after oral administration of phenylbutazone alone. Improvement in horses after a combination of NSAIDs did not completely mask lameness. Five horses did not improve after either NSAID treatment regimen. All posttreatment plasma concentrations of NSAIDs were less than those currently allowed by the United States Equestrian Federation Inc for a single NSAID. One horse administered the combination NSAID regimen died of acute necrotizing colitis during the study.

Conclusions and Clinical Relevance—Administration of a combination of NSAIDs at the dosages and intervals used in the study reported here alleviated the lameness condition more effectively than did oral administration of phenylbutazone alone. This may attract use of combinations of NSAIDs to increase performance despite potential toxic adverse effects. (*Am J Vet Res* 2008;69:167–173)

Phenylbutazone and flunixin meglumine are the 2 NSAIDs most commonly used in horses to reduce inflammation and pain associated with lameness. There is little controversy concerning their use for this purpose. However, they are also sometimes administered before or during competitions, and sometimes more than 1 NSAID is administered at the same time (ie, stacking). Bodies that govern equine events may allow administration of phenylbutazone or flunixin meglumine before or during competition, but testing blood and urine samples is necessary to screen for high concentrations or for evidence of stacking. For example, the Equine Drugs and Medications Committee of the USEF allows use of phenylbutazone or flunixin meglu-

ABBREVIATIONS

| | |
|-------|---|
| NSAID | Nonsteroidal anti-inflammatory drug |
| USEF | United States Equestrian Federation Inc |
| A1 | Amplitude of vertical movement attributed to lameness |
| A2 | Amplitude of normal vertical displacement |
| TBxB2 | Thromboxane-B ₂ |

mine before sanctioned events when they are used at recommended dosages and administration is discontinued at least 12 hours before competition.¹ When owners and trainers adhere to these guidelines, it is unlikely that concentrations of NSAIDs in blood or urine will be above allowable limits. Moreover, the USEF typically allows up to 2 NSAIDs to be in found in blood and urine samples. An exception is made for concurrent use of phenylbutazone and flunixin meglumine, and when both are found above threshold detection limits in blood or urine samples, the owner, trainer, and horse may be penalized.

Usage of NSAIDs is restricted partially to protect horses from potential toxic effects. Restriction may also be important to prevent injury to a horse that is enabled

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to perform because of a masking effect of drug-induced pain relief when it otherwise could not. Also, integrity of the competition should be protected by providing a level field for all entrants. However, there is scant objective evidence that a combination treatment with phenylbutazone and flunixin meglumine allows horses with lameness to perform as if they were sound such that veterinary inspection is compromised or that it reduces lameness more effectively than oral administration of phenylbutazone alone. An adjustable heart-shaped bar shoe has been used to induce lameness, and heart rate was used as a measure of pain.^a In that study, administration of a single dose of phenylbutazone (4.4 mg/kg, IV) and flunixin meglumine (1.1 mg/kg, IV) was not more effective than administration of phenylbutazone (4.4 mg/kg, IV) alone. However, competitors commonly administer NSAIDs as a series, and it is not unusual for some to administer the drugs before and sometimes even during an extended competitive event.^b

The purpose of the study reported here was to objectively determine whether a multiple-dose combination of phenylbutazone and flunixin meglumine would alleviate lameness in horses more effectively than administration of phenylbutazone alone. We also wanted to evaluate the effectiveness of a multiple-dose combination of phenylbutazone and flunixin meglumine to alleviate lameness such that a horse may be considered sound. The hypotheses tested were that administration of a combination of phenylbutazone and flunixin meglumine would alleviate lameness more effectively than would administration of phenylbutazone alone and to such an extent that lameness could be completely alleviated or masked.

Materials and Methods

Animals—Twenty-nine horses (20 geldings and 9 mares) 2 years of age or older (range, 2 to 18 years) that weighed between 325 and 533 kg were used in the study. Horses were Quarter Horse, Thoroughbred, or mixed-breed horses. Horses used in the study were residents at a local Thoroughbred retirement center, part of the University of Missouri Teaching Herd, or privately owned by employees of the University of Missouri Veterinary Medical Teaching Hospital.

All horses had a preexisting, naturally occurring, verifiable lameness of the forelimbs or hind limbs of at least 4 months' duration. Twenty-three horses had osteoarthritis of a single joint (14 forelimbs and 9 hind limbs), 1 had osteoarthritis of 2 joints (both in the forelimbs), 4 had navicular disease, and 1 had generalized physitis. Diagnosis was made on the basis of results of physical examination; subjective lameness evaluation; radiography; and, in some cases, regional nerve or joint blocks. By use of subjective lameness evaluation and the American Association of Equine Practitioners lameness scale,² all horses were judged to have lameness with a severity of grades 1 to 3. The study design was reviewed and accepted by the University of Missouri Animal Care and Use Committee. Informed consent for use of privately owned horses was obtained before entry in the study.

Objective evaluation of lameness—During a period of 3 days, all horses were trained to trot on a tread-

mill.^c During this period, the optimal speed for each horse was determined. Optimal speed was selected when a horse maintained position on the treadmill without coaxing by a handler who held a lead shank attached to the horse's halter.

Objective lameness evaluations were performed by use of computer-assisted kinematic analysis in accordance with described techniques and lameness detection algorithms.^{3,4} Briefly, reflective spheres were affixed to the poll of the head, dorsum of the pelvis, and lateral surfaces of the hoof walls of the right forelimb and hind limb of each horse. The 3-dimensional movements of the markers were tracked with 5 visible red light-detecting cameras at 120 frames/s while the horses were trotting on the treadmill at the selected optimal speed (± 0.1 m/s) for each horse. Data collection began 1 minute after optimal speed was achieved. Movement was tracked for 3 separate trials (30 s/trial). Between successive trials, horses continued to trot on the treadmill at the same speed. Approximately 30 seconds elapsed between successive trials. This amount of data collection resulted in tracking of 90 to 120 complete strides/evaluation (30 to 40 strides/trial).

From the 3-dimensional data collected, vertical head, pelvis, and right hoof displacement were extracted for each 30-second trial. Vertical head and pelvis displacement were then adjusted for random movement by subtracting a moving-window average (size of window was equal in duration to 2 complete strides). Next, the adjusted vertical head and pelvis displacement signals were converted into a frequency domain by use of another moving-window, curve-fitting technique. Forelimb lameness was quantified by calculating the temporal asymmetry of adjusted vertical head movement between the left and right halves of the forelimb stride. Hind limb lameness was quantified by calculating the temporal asymmetry of adjusted vertical pelvic movement between the left and right halves of the hind limb stride. Temporal asymmetry was expressed as a ratio of the root mean square of the amplitude of the first harmonic (ie, A1) to the second harmonic (ie, A2) of the adjusted vertical displacement signal. The first harmonic is the periodic component of the adjusted vertical displacement signal at the frequency of stride rate. The second harmonic is the periodic component of the adjusted vertical displacement signal at a frequency of twice the stride rate (because the head moves up and down twice in 1 complete stride). Raw vertical displacements of the right hooves were used to distinguish the right and left stance phase and swing phase of the stride. Side of lameness was determined for each stride by calculating the sign (positive or negative) of the difference in adjusted vertical head or pelvic height between right and left forelimb or hind limb stance phases. By use of this technique, a switching of the side of lameness could still be evaluated as a worsening in lameness.

Study design—In a crossover study, objective lameness evaluations were performed on each horse before and after treatment with 2 NSAID regimens. Each horse served as its own control animal. One treatment was phenylbutazone administered at approximately 2.2 mg/kg, PO, q 12 h for 5 days. The other treatment was concurrent administration of phenylbutazone (approx

2.2 mg/kg, PO, q 12 h for 5 days) and flunixin meglumine (1.1 mg/kg, IV, q 12 h for 5 days). Order of the 2 treatment regimens was randomly assigned, and horses were allowed a washout period of at least 14 days between successive treatment regimens.

Phenylbutazone was administered orally as a paste formulation by dissolving 1-g tablets in a small amount of corn syrup. Phenylbutazone was administered at 8 AM and 8 PM. Each dose was calculated and rounded up to the nearest quarter of a tablet. No attempt was made to withhold feed or wash out the mouths of the horses before each treatment. All horses were fed a ration of grass hay and complete pelleted feed^d at approximately the same time twice daily (8 AM and 4 PM). Horses were fed immediately after the morning dose of medication and approximately 4 hours before the evening dose of medication.

Flunixin meglumine was administered IV within a few minutes after oral administration of phenylbutazone. Flunixin meglumine was administered via jugular venipuncture by an experienced equine veterinarian or, in a few cases, via an indwelling catheter inserted in a jugular vein. During the 5 days of treatment, horses were confined to their stalls and hand walked at least once a day for 20 minutes.

Objective lameness evaluations were performed at 4 time points for each horse. Evaluation 1 was performed before the first dose of the first treatment regimen. Evaluation 2 was performed 12 (\pm 1) hours after the last dose of the first treatment regimen. Evaluation 3 was performed before the first dose of the second treatment regimen. Evaluation 4 was performed 12 (\pm 1) hours after the last dose of the second treatment regimen. Objective evaluations of lameness were conducted without knowledge of the current treatment status.

Plasma samples for determination of phenylbutazone and flunixin meglumine concentrations were obtained from each horse 12 hours after administration of the last dose of each treatment regimen, immediately before the posttreatment objective lameness evaluation. Plasma samples were analyzed by use of high-performance liquid chromatography with UV detection (sensitivity, 0.01 μ g/mL).^e Plasma samples were not tested for phenylbutazone metabolites. As part of another study, samples were obtained from 3 horses for use in

measurement of plasma total protein concentrations, and gastroscopic examinations were conducted in those 3 horses after food was withheld for 24 hours at the end of each treatment regimen.

Data analysis—Temporal asymmetry of the adjusted vertical movement (ie, A1/A2) of the head and pelvis was recorded as the measure of lameness severity. Normality of A1/A2 values for each evaluation time point was evaluated with a Shapiro-Wilk test.^f Differences among evaluation time points were evaluated by use of a nonparametric, repeated-measures ANOVA (Friedman test).^g Significance was set at values of $\alpha = 0.05$.

Results

One horse with forelimb lameness died during the study. The horse died acutely during the washout period between the first and second treatments. Necropsy diagnosis for this horse was acute necrotizing colitis, with lesions most severe in the right dorsal colon. Retrospectively, it was determined that the horse had just completed the combination phenylbutazone–flunixin meglumine treatment. Data collected from this horse were not used in subsequent analyses.

Twenty-eight horses (20 geldings and 8 mares) completed both treatment regimens. There was no significant ($P = 0.611$) difference in lameness severity between initial evaluations before either treatment; therefore, results for these trials were combined and the mean A1/A2 values computed and used as the control (ie, before-treatment) values.

When evaluating all 28 horses, there was significant clinical improvement after administration of the combination of phenylbutazone and flunixin meglumine, but lameness was not alleviated significantly after oral administration of phenylbutazone alone (Table 1). As a group, horses with forelimb lameness ($n = 20$) did not have significant clinical improvement with either treatment regimen. Five horses with forelimb lameness actually had an increase in lameness after both NSAID treatment regimens. Three of these 5 horses had osteoarthritis in the carpal joint, 1 had osteoarthritis in the metacarpophalangeal joint, and 1 had osteoarthritis in the proximal interphalangeal joint. All 4 horses with navicular disease had clinical improvement after at least

Table 1—Mean \pm SD severity of lameness (A1/A2 value) in horses 12 hours after administration of the last dose of a treatment regimen that consisted of phenylbutazone alone (2.2 mg/kg, PO, q 12 h for 5 days) or concurrent administration of phenylbutazone (2.2 mg/kg, PO, q 12 h for 5 days) and flunixin meglumine (1.1 mg/kg, IV, q 12 h for 5 days).

| Group | Before treatment | Phenylbutazone alone | Phenylbutazone and flunixin meglumine |
|--|------------------|----------------------|---------------------------------------|
| All horses ($n = 28$) | 0.87 \pm 0.43 | 0.70 \pm 0.28 | 0.65 \pm 0.37* |
| Horses with clinical improvement ($n = 23$) | 0.91 \pm 0.46 | 0.67 \pm 0.26† | 0.59 \pm 0.32* |
| Horses with forelimb lameness ($n = 20$) | 0.85 \pm 0.40 | 0.72 \pm 0.27 | 0.70 \pm 0.34 |
| With clinical improvement ($n = 15$) | 0.91 \pm 0.43 | 0.68 \pm 0.20 | 0.63 \pm 0.26† |
| Without clinical improvement ($n = 5$) | 0.67 \pm 0.20 | 0.84 \pm 0.28 | 0.94 \pm 0.43 |
| Horses with navicular disease ($n = 4$) | 0.75 \pm 0.13 | 0.61 \pm 0.24† | 0.67 \pm 0.21† |
| Horses with hindlimb lameness ($n = 8$) | 0.91 \pm 0.53 | 0.63 \pm 0.37† | 0.53 \pm 0.42* |
| With distal tarsal joint arthritis ($n = 6$) | 0.71 \pm 0.45 | 0.56 \pm 0.37† | 0.50 \pm 0.45† |

Numbers in parentheses indicate the number of horses.
*Within a row, value is significantly ($P < 0.05$) less than the value before treatment and the value for phenylbutazone alone. †Within a row, value is significantly ($P < 0.05$) less than the value before treatment.

one of the NSAID treatment regimens. Three of the 4 improved more after oral administration of phenylbutazone alone. Only 1 horse with navicular disease (after administration of the combination of phenylbutazone and flunixin meglumine) switched over such that the lameness was predominant in the contralateral forelimb (data not shown).

All 8 horses with hind limb lameness had clinical improvement after both treatment regimens. Horses with hind limb lameness had more improvement after treatment with the combination of phenylbutazone and flunixin meglumine than after administration of phenylbutazone alone. All horses with arthritis in the distal tarsal joint had improvement after both treatment regimens. Five of 6 horses with arthritis in the distal tarsal joint had more improvement after the combination phenylbutazone–flunixin meglumine treatment regimen. No horses with arthritis of the distal tarsal joint switched over such that the lameness was predominant in the contralateral hind limb (data not shown).

Twenty-seven of 28 horses had detectable plasma NSAID concentrations 12 hours after the last treatment. One horse did not have detectable concentrations of flunixin meglumine after administration of the combination treatment. The plasma sample was lost for 1 horse after oral administration of phenylbutazone alone. Plasma concentrations of phenylbutazone and flunixin meglumine were highly variable, ranging from 0.28 to 8.58 $\mu\text{g/mL}$ (mean, 3.67 $\mu\text{g/mL}$) and 0.04 to 0.58 $\mu\text{g/mL}$ (mean, 0.22 $\mu\text{g/mL}$), respectively. For phenylbutazone administered alone, mean \pm SD plasma concentration of phenylbutazone was $3.60 \pm 1.68 \mu\text{g/mL}$ (range, 0.86 to 7.64 $\mu\text{g/mL}$). For the combination regimen, mean plasma concentration of phenylbutazone was $3.73 \pm 2.24 \mu\text{g/mL}$ (range, 0.28 to 8.58 $\mu\text{g/mL}$) and mean plasma concentration of flunixin meglumine was $0.22 \pm 0.13 \mu\text{g/mL}$ (range, < 0.01 to 0.58 $\mu\text{g/mL}$).

Discussion

Stacking of NSAIDs by oral administration of phenylbutazone and concurrent IV administration of flunixin meglumine for 5 days resulted in better clinical improvement of the lameness condition 12 hours after the last dose, compared with results for administration of phenylbutazone alone. After horses that did not improve with either NSAID treatment regimen (ie, NSAID nonresponsive lameness) were excluded, both treatment regimens significantly alleviated lameness 12 hours after administration of the last dose. On the basis of other kinematic studies^{4,5} of induced lameness conducted by our laboratory group in which the same measure of lameness was used, approximate thresholds of A1/A2 values were established for horses with forelimb (A1/A2 threshold, 0.50) and hind limb (A1/A2 threshold, 0.17) lameness. In the study reported here, mean A1/A2 values after either treatment regimen for both forelimb and hind limb lameness were above these thresholds. Therefore, neither treatment regimen was successful at completely masking lameness.

An alternate method of testing the effectiveness of an NSAID and its dosage is to measure specific inflammatory mediators in plasma or tissue. Phenylbutazone and flunixin meglumine, as well as most NSAIDs, are

nonselective inhibitors of the cyclooxygenase enzyme system that lead to decreased synthesis of mediators of inflammation, principally prostaglandins and thromboxanes.⁶ In another study,⁷ IV administration of a single dose of flunixin meglumine (1.1 mg/kg) to horses caused a significant decrease in serum TBXB2 concentrations at 6, 8, and 12 hours after administration, compared with the decrease after a single IV administration of phenylbutazone (2.2 mg/kg). Phenylbutazone administered alone caused a significant decrease in serum TBXB2 concentrations for only 8 hours, and flunixin meglumine administered alone caused a decrease for 12 hours, but a combination treatment (2.2 mg of phenylbutazone/kg and 1.1 mg of flunixin meglumine/kg) caused a significant decrease in serum TBXB2 concentrations for up to 24 hours. The magnitude of the decrease in serum TBXB2 concentrations after the combination treatment was not significantly greater than the magnitude for administration of flunixin meglumine alone, but both the combination treatment and administration of flunixin meglumine alone decreased serum TBXB2 concentrations more than did administration of phenylbutazone alone. Those results support the hypothesis that concurrent administration of phenylbutazone and flunixin meglumine, as was used in the study reported here, does not result in additive effects (ie, increase in maximum result) but does prolong the duration of action.

The plasma elimination half-life for phenylbutazone and flunixin meglumine is 3 to 10 hours⁸ and 1.6 hours,⁹ respectively, but their durations of action are much longer. A single dose of phenylbutazone (4.4 mg/kg, IV) reduces eicosanoid concentrations in equine inflammatory exudate for 24 hours,¹⁰ and 1 dose of flunixin meglumine (1.1 mg/kg, IV) inhibits prostaglandin production in equine inflammatory exudate for the same duration.¹¹ Concentrations of NSAIDs in inflammatory exudate begin to exceed plasma concentrations within 12 hours for phenylbutazone and 6 hours for flunixin meglumine.^{12,13} A search of the literature did not reveal the same information for a single dose of phenylbutazone (2.2 mg/kg, IV). There is some evidence that NSAIDs do not accumulate in normal tissue,¹² but the increased protein content (NSAIDs are highly protein-bound substances) and hyperemia associated with inflammatory tissue and exudate may result in NSAID accumulation in areas of inflammation.^{13,14}

The ultimate test of any pharmaceutical, including NSAIDs, should be performed in clinical situations, ideally with an unbiased objective indicator of effectiveness. A few studies have determined the effectiveness of phenylbutazone and flunixin meglumine in various dosage regimens for decreasing clinical signs associated with pain or lameness. Horses administered phenylbutazone (2.2 mg/kg, IV, q 12 h for 5 doses) after arthroscopic surgery had a decrease in a subjectively graded pain index, but biochemical variables associated with pain (plasma catecholamine, β -endorphin, and cortisol concentrations) were unchanged.¹⁵ In a study¹⁶ on experimentally induced arthritis in the carpal joint, stride length was a good indicator of improvement in horses with lameness after a single-dose IV administration of phenylbutazone or flunixin meglumine. In that study,

pharmacokinetic modeling predicted the maximum effect for phenylbutazone at 2 mg/kg and for flunixin meglumine at 1 mg/kg, with durations of action of 8 and 16 hours, respectively. Increasing the phenylbutazone dosage to 4 and 8.8 mg/kg increased the duration of action to approximately 14 and 24 hours, respectively, whereas increasing the flunixin meglumine dosage to 2 mg/kg increased the duration of action to 24 hours. In a study¹⁷ in which investigators used horses with navicular disease, once-daily IV administration of phenylbutazone at 4.4 mg/kg or flunixin meglumine at 1.1 mg/kg for 4 days increased vertical ground reaction forces in the forelimbs (ie, improvement in lameness condition) equally and significantly for 24 hours after administration of the last dose. In another study¹⁸ in which the same lameness model and method of lameness quantification was used, phenylbutazone administration at 8.8 mg/kg, q 24 h for 4 days increased vertical ground reaction forces in the forelimbs and decreased clinical lameness scores for 24 hours after administration of the last dose, whereas administration at 4.4 mg/kg increased vertical ground reaction forces in the forelimbs for 24 hours but caused a decrease in clinical lameness scores for only 12 hours. In the study reported here, we used an equivalent daily dose of phenylbutazone (4.4 mg/kg) and twice the daily dose of flunixin meglumine (2.2 mg/kg) as were used in the aforementioned study, but we split it into 2 doses that were administered 12 hours apart. Despite its longer half-life, compared with the half-life for flunixin meglumine, phenylbutazone may lose its effectiveness more rapidly than flunixin meglumine does at this dose. The increased effectiveness of stacking of NSAIDs to alleviate lameness may not have been evident had we instead chosen a once-daily administration protocol or daily dosage of 1.1 mg/kg for flunixin meglumine.

In the study reported here, the variation in lameness reduction after NSAID administration was large, but the horses had a wide array of lameness conditions (various joints and anatomic structures of the forelimbs and hind limbs) with a substantial range of lameness severity. A more homogeneous sample, which could have been achieved by selecting only horses with specific lameness conditions or by limiting selection to horses with a single grade of lameness, may have decreased variation. Despite the heterogeneous sample population, we were still able to detect a difference in response between treatment regimens. Therefore, the inferences of this study may be more applicable to horses with lameness in general than for a more restricted lameness population (eg, only horses with navicular disease or arthritis of the distal tarsal joint).

Another source of variation in response in our study could have been the differences in gastrointestinal absorption after oral administration of phenylbutazone. Although the biological availability of phenylbutazone after oral administration exceeds 70%,¹⁹ not withholding hay before administration can significantly delay peak plasma concentrations by up to 18 hours.⁹ Not withholding hay before oral administration of phenylbutazone can also result in double peaks in plasma concentrations (the first peak within a few hours after administration and a second peak > 8 hours af-

ter administration²⁰). Feed-deprived horses have more rapid and less variable gastrointestinal absorption.¹³ In the study reported here, horses were fed pellets and hay in the morning at the same time or slightly after administration of medication and in the afternoon approximately 4 hours before the second daily dose of medication. A delay in absorption of phenylbutazone could have contributed to a less-than-maximum effect for the lameness evaluation conducted 12 hours after the last dose. We selected oral administration of phenylbutazone and did not withhold feed from horses before administering medication because this is the typical procedure in on-farm settings. Also, all lameness evaluations were performed 12 hours after the evening medication for horses that had received medication 4 hours after feeding. With this protocol, we achieved means and ranges of plasma concentrations of phenylbutazone (3.6 µg/mL [range, 1.7 to 7.6 µg/mL] for oral administration of phenylbutazone alone and 3.7 µg/mL [range, 0.28 to 8.58 µg/mL] for the combination phenylbutazone and flunixin meglumine treatment) that are similar to the mean and range measured 12 hours after a single IV administration of 4.4 mg/kg to 5 horses and to the estimated plasma concentration for half maximum effect of 3.6 µg/mL.^{13,16} In addition, assuming biological availability of 70% and a high estimate of clearance for phenylbutazone (991 mL/kg/24 h), the expected effective plasma concentration of phenylbutazone is 3.1 µg/kg,²¹ which is similar to our mean plasma concentrations. We measured phenylbutazone and flunixin meglumine concentrations to determine whether the dosing regimen would result in plasma concentrations similar to those expected after administration of NSAIDs in accordance with the USEF guidelines. We achieved expected effective plasma concentrations; however, because we only measured NSAID concentrations at 1 time point, we did not determine whether oral administration of phenylbutazone and the schedule for administration resulted in delayed or reduced absorption of phenylbutazone.

Not all of the horses in the study had improvement in the lameness condition after administration of NSAIDs. Five horses had an increase in lameness after both NSAID treatment regimens. This increase in lameness may have been caused by the initial exercise required for acquiring baseline data. Also, before entering the study, many of these horses were athletes that had been retired to pasture. The periods of inactivity before the study and during the washout period between treatments may have generally lessened the severity of clinical signs only to have them progressively worsen once they were accepted into the study and treadmill exercise was initiated. A better experimental model, although more expensive in that it would require an additional washout period between treatments, would have been to randomize the order of 4 treatments (before treatment [control period], after phenylbutazone only, after flunixin meglumine only, and after the combination of phenylbutazone and flunixin meglumine). Use of a control group without any NSAID treatment would have required additional horses, but this experimental model would have accounted for any worsening of lameness attributable to treadmill exercise. Most of the horses in the study were retired racehorses with

substantial lameness problems. Repeatedly exercising them on a treadmill without NSAID treatment was not considered appropriate by the authors, nor was it allowed by the caretakers of the horses.

It is interesting that 3 of 5 horses with osteoarthritis of the carpal joints, but only 1 of 7 horses with osteoarthritis of the metacarpophalangeal joint, had an increase in lameness after both NSAID treatment regimens. All 12 horses with navicular disease or with lameness of the distal tarsal or stifle joints had improvement after at least one of the NSAID treatment regimens. Osteoarthritis of the carpal joint may not be as responsive to NSAIDs as other conditions that cause lameness in horses; however, the small number of affected horses in the study reported here did not allow a full testing of this suspicion. Despite including the data from the 5 horses with osteoarthritis of the carpal joint, we were still able to detect significant differences between treatment regimens. Excluding data from these 5 horses before further analysis clarified but did not change the substance of their interpretation.

Our method of objective lameness evaluation was based on detecting and quantifying the asymmetry of vertical head and pelvic movement (A1/A2 values). This method can reliably detect onset of mild to moderate forelimb and hind limb lameness and can be used to quantify changes in severity.^{3,4} The mean A1/A2 value before treatment for the 15 horses with forelimb lameness that had clinical improvement after NSAID treatment was 0.91. After oral administration of phenylbutazone alone, the mean A1/A2 value was 0.68, a 25% decrease in lameness severity, compared with the value before treatment. After administration of the combination treatment regimen, the mean A1/A2 value was 0.62, an insignificant decrease in lameness severity, compared with the value for treatment with phenylbutazone alone. However, for horses with hind limb lameness, the mean A1/A2 value after oral administration of phenylbutazone was 0.63, a 31% improvement in lameness severity, compared with the value (0.91) before treatment. After treatment with the combination regimen, the A1/A2 value was 0.53, a 42% improvement in lameness severity, compared with the value before treatment, and a 16% improvement, compared with the value for phenylbutazone alone.

These differences between no treatment and NSAID treatment (for both forelimb and hind limb lameness) and between oral administration of phenylbutazone alone and the combination of phenylbutazone and flunixin meglumine (for hind limb lameness only) may be clinically important. In other studies,^{17,18} clinically important results have been detected with changes in other objective measures of lameness severity of < 15%. However, whether this difference in movement asymmetry between the combination of NSAIDs and oral administration of phenylbutazone alone can be recognized in a competitive event, such that a horse treated with a combination of NSAIDs would receive an advantage, cannot be determined from the results of the study reported here.

It should be pointed out that the method of objective lameness evaluation was based on measuring symmetry. It is theoretically possible for a horse with bi-

lateral lameness to have equivalent pain in both limbs. If this were true for most strides, then this technique of lameness analysis could potentially indicate that a lame horse was sound or that an increase in lameness in 1 or both limbs (resulting in them becoming more similar in severity) would simulate a decrease in lameness. However, in the study reported here, symmetry was calculated on a stride-by-stride basis, and all of the horses with lameness conditions that are commonly bilateral (4 with navicular disease and 6 with arthritis of the distal tarsal joint) favored 1 limb over the contralateral limb. This asymmetry switched sides in only 1 horse with navicular disease after administration of the combination treatment regimen.

The maximum permitted plasma concentrations of phenylbutazone and flunixin meglumine set by the USEF for sanctioned events and competitions are 15 and 1 µg/mL, respectively.¹ For competitors to remain under these limits, the USEF advises that when phenylbutazone is administered orally, it should be administered at no more than 2.2 mg/kg twice daily for no more than 5 consecutive days. When flunixin meglumine is administered, the USEF advises treatment with 1.1 mg/kg every 24 hours for no more than 5 continuous days. For both drugs, the USEF advises administration of the last dose no sooner than 12 hours before competition. Our dosage of phenylbutazone was equivalent to the maximum advised by the USEF. Our dosage of flunixin meglumine, which was administered twice daily, was twice that advised by the USEF. However, the plasma half-life of flunixin meglumine, when administered IV, is extremely short (< 2 hours),⁹ and the systemic clearance is extremely rapid (1.5 mL/min/kg).⁶ By contrast, phenylbutazone, when administered orally, has a more variable but longer half-life (3 to 10 hours)⁸ and a slower systemic clearance (approx 0.3 mL/min/kg).¹² Despite the twice-daily dosing regimen for flunixin meglumine, the resulting plasma concentrations (mean, 0.22 µg/mL; < 0.01 to 0.58 µg/mL) in the study reported here were far below the threshold allowed by the USEF (≤ 1.0 µg/mL). We administered flunixin meglumine at 1.1 mg/kg every 12 hours on the basis of pharmacokinetic measures and because that dosage is commonly used when NSAIDs are stacked in an attempt to alleviate lameness in horses.

Another issue that was not addressed in the study but that is nevertheless important is the potential adverse effects on the gastrointestinal tract and renal system from dual administration or high-dose NSAID use. Flunixin meglumine has a wider safety margin than does phenylbutazone.²² Intravenous administration of flunixin meglumine to horses at 5.4 mg/kg every 24 hours for 5 days does not induce changes in blood or urine variables.²³ Foals treated with flunixin meglumine (2.2 mg/kg, IV) once daily for 5 days did not have blood and serum abnormalities or gross or histologic abnormalities of the gastrointestinal tract.²⁴ By contrast, phenylbutazone administered orally at 4.4 mg/kg every 12 hours for 4 days, followed by administration at 2.2 mg/kg every 12 hours for 4 days, and then followed by administration at 2.2 mg/kg once daily for 7 days results in significant decreases in serum total protein and albumin concentrations.²⁵ In the study reported here,

1 horse died suddenly after receiving the combined NSAID treatment. Necropsy diagnosis was acute, necrotizing colitis, which was consistent with toxic effects of NSAIDs. In addition, mean serum protein concentrations were significantly lower and gastroscopic grades of mucosal ulcers significantly higher after combined NSAID treatment than before treatment or after oral administration of phenylbutazone alone.²⁶ Considering that the phenylbutazone and flunixin meglumine dosages were lower than those that reportedly cause toxic effects, it is likely that it was the combination of NSAIDs, as well as the total increase in concentration irrespective of type, that was responsible for these abnormalities.

For the conditions of the study reported here, stacking of NSAIDs by concurrent administration of multiple doses of a combination of NSAIDs was more successful in some horses at improving the lameness condition than after oral administration of phenylbutazone alone. However, concurrent administration of phenylbutazone and flunixin meglumine at the dosages used will probably not completely alleviate or mask a major lameness to the point that an affected horse would appear to be sound.

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