Use of force plate analysis to compare the analgesic effects of intravenous administration of phenylbutazone and flunixin meglumine in horses with navicular syndrome

Ronald S. Erkert, DVM; Charles G. MacAllister, DVM; Mark E. Payton, PhD; Cyril R. Clarke, BVSc, PhD

Objective—To use force plate analysis to evaluate the analgesic efficacies of flunixin meglumine and phenylbutazone administered IV at typical clinical doses in horses with navicular syndrome.

Animals—12 horses with navicular syndrome that were otherwise clinically normal.

Procedure—Horses received flunixin (1.1 mg/kg), phenylbutazone (4.4 mg/kg), or physiologic saline (0.9% NaCl; 1 mL/45 kg) solution administered IV once daily for 4 days with a 14-day washout period between treatments (3 treatments/horse). Before beginning treatment (baseline) and 6, 12, 24, and 30 hours after the fourth dose of each treatment, horses were evaluated by use of the American Association of Equine Practitioners lameness scoring system (half scores permitted) and peak vertical force of the forelimbs was measured via a force plate.

Results—At 6, 12, and 24 hours after the fourth treatment, subjective lameness evaluations and force plate data indicated significant improvement in lameness from baseline values in horses treated with flunixin or phenylbutazone, compared with control horses; at those time points, the assessed variables in flunixin- or phenylbutazone-treated horses were not significantly different.

Conclusions and Clinical Relevance—In horses with navicular syndrome treated once daily for 4 days, typical clinical doses of flunixin and phenylbutazone resulted in similar significant improvement in lameness at 6, 12, and 24 hours after the final dose, compared with findings in horses treated with saline solution. The effect of flunixin or phenylbutazone was maintained for at least 24 hours. Flunixin meglumine and phenylbutazone appear to have similar analgesic effects in horses with navicular syndrome. (*Am J Vet Res* 2005;66:284–288)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly administered compounds for the treatment of musculoskeletal pain in horses.[1] In adult horses, the most frequently used analgesic agents are phenylbutazone and flunixin meglumine,[2,3] which are commonly used for the treatment of pain and inflammation. Anecdotally, some NSAIDs, such as phenylbutazone, are believed to provide better analgesia for musculoskeletal pain than other types of pain in horses, whereas other NSAIDs appear to provide better relief from visceral pain.[4,5] Although flunixin meglumine is considered the NSAID of choice for treatment of colic pain in horses,[6] phenylbutazone is most commonly used for the treatment of lameness.[5,7]

Analgesia induced by NSAIDs is primarily dependent on inhibition of the **cyclooxygenase (COX)** enzyme system.[2,8] Two COX isoforms of primary importance have been identified. The constitutive COX-1 isoform is present in most tissues. The inducible COX-2 isoform is upregulated in monocytes, fibroblasts, synoviocytes, and chondrocytes in response to inflammatory stimuli. However, pain is not caused directly by prostaglandins or leukotrienes. These products induce hyperalgesia by lowering the nociceptor threshold level and allowing a pain response to typically nonpainful stimuli.[9] Inhibition of COX by NSAIDs results in decreased prostaglandin production, thereby inhibiting alterations of the nociceptor threshold.

In horses, pharmacokinetic-pharmacodynamic modeling[10] predicts a maximal effect for typical clinical doses of 4.4 mg of phenylbutazone/kg and 1.1 mg of flunixin meglumine/kg. The model predicts a dose-dependent duration of effect of approximately 16 hours for both drugs at those doses in horses. This maximal effect is supported by force plate data obtained in a study[11] to investigate the potential dose-related analgesic effect of phenylbutazone administered IV at low (4.4 mg/kg) and high (8.8 mg/kg) doses every 24 hours for 4 days to chronically lame horses; there was no significant difference in improvement of lameness between the 2 drug dosages. However, there continued to be a significant improvement of lameness at 24 hours after both the final high- and low-dose treatment with phenylbutazone. This may indicate an accumulation of drug in the inflamed tissues similar to that detected in inflammatory exudate.[8,12]

Navicular syndrome is one of the most common causes of forelimb lameness in horses.[13–16] The lameness is usually progressive, chronic, and bilateral; it may be characterized by asymmetrical alternating forelimb lameness, hoof abnormalities, and radiographic evidence of changes in the navicular bone and surrounding soft tissue.[15] The exact etiology of the syndrome is

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From the Departments of Veterinary Clinical Sciences, (Erkert, MacAllister) and Physiological Sciences (Clarke), College of Veterinary Medicine, and the Department of Statistics (Payton), College of Arts and Sciences, Oklahoma State University, Stillwater, OK 74078.
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Address correspondence to Dr. Erkert.

unclear, but it is believed to be either vascular or biomechanical in origin (or, more likely, a combination of factors). The navicular bone undergoes remodeling changes and increased vascularization with a combination of active arterial hyperemia and passive venous congestion.[15,17] Congestion causes increased bone marrow pressure and results in pain.[18,19] Signs of pain in horses also appear to originate from the supporting ligaments and deep digital flexor tendon.[15,20]

Force plates allow the quantification of ground reaction force measurements.[21–27] They can be used to collect quantitative data in sound and lame horses, whereas subjective lameness evaluation can provide only qualitative data and is affected by the skill of the evaluator.[28] Because velocity has a significant effect on stance time and ground reaction force, there is a need to use a narrow velocity range in force plate analyses.[21,23] Measurements of ground reaction force, especially **peak vertical force (PVF)**, are inversely correlated to the degree of lameness when all forces are normalized with respect to weight.[24,25]

The purpose of the study reported here was to use force plate analysis to evaluate the analgesic efficacies of flunixin meglumine and phenylbutazone administered at typical clinical doses in horses with navicular syndrome. The typical clinical dosages for phenylbutazone (4.4 mg/kg, IV, q 24 h) and flunixin meglumine (1.1 mg/kg, IV, q 24 h) were selected on the basis of pharmacokinetic-pharmacodynamic predictions[10] of equivalent durations of action (approx 16 hours). The primary endpoints of this study were a subjective lameness evaluation and measurement of **mean peak vertical force (mPVF)** before starting treatment (baseline) and 6, 12, 24, and 30 hours after the fourth treatment with each drug.

Materials and Methods

Animals—Twenty adult mixed-breed horses (mean ± SD age, 11.9 ± 5.7 years; weight, 583 ± 22 kg) were selected for possible inclusion in this study. All horses had chronic forelimb lameness of at least 4 months' duration. Selection criteria included forelimb lameness detected during a subjective lameness evaluation, pain response to hoof testers applied over the caudal third of the hoof, improvement of lameness after administration of palmar digital nerve blocks, and radiographic evidence of degenerative changes in the navicular bone of at least 1 foot. Individual number tags on halters were used to identify horses. The animals were owned by the Oklahoma State University College of Veterinary Medicine and housed on pasture at the Equine Research Park. The horses were fed a diet of Bermuda grass hay (free choice) and had free access to water and mineral salt blocks. The horses were acclimated to their environment for a minimum of 14 days; they were dewormed with ivermectin prior to starting the study, but no other drugs were administered during the acclimatization period. During this period and at least 7 days before force plate analysis, all horses had their hooves trimmed and balanced. Horses were observed daily throughout the study to monitor health. The Oklahoma State University Institutional Animal Care and Use Committee approved the study protocol.

Inclusion criteria—Horses were evaluated by use of the force plate at least 7 days prior to the start of treatments. At each force plate evaluation, a physical assessment was performed including measurement of body weight, rectal temperature, heart rate, and respiratory rate. Subjective lameness evaluations were performed by 1 investigator (CGM), and a lameness score was assigned on the basis of the **American Association of Equine Practitioners (AAEP)** 5-point lameness grading scale.[29] Half scores were used as determined by the investigator. Horses were ranked by the SD value of their mPVF measurement, and the 12 horses with the lowest SD values were selected for inclusion in the study. The remaining horses were maintained with the study herd as alternates if needed.

Force plate data acquisition before treatment—To confirm chronic and stable lameness, prior to the first treatment period each horse was evaluated twice by use of the force plate, once during the interval of days –10 to –7 and again on days –2 or –1 (with at least 7 days between evaluations). If a horse had > 10% difference in mPVF values in either forelimb between the 2 force plate evaluations, it was eliminated from the study and replaced by the next lowest ranked horse among those not included at the initial selection. Once the final selection was made, no additional horses were entered into the study. Data obtained on days –2 or –1 were used for baseline PVF data for the first treatment period. For subsequent treatment periods, baseline PVF data were obtained 1 to 2 days before starting treatment.

Study design—A crossover study with repeated measures in which each horse underwent all 3 treatments was used. Twelve horses were randomly assigned to 1 of 3 treatment groups; treatments included phenylbutazone,[a] flunixin meglumine,[b] and saline (0.9% NaCl) solution[c] administered IV every 24 hours for 4 days at dosages of 4.4 mg/kg, 1.1 mg/kg, and 1 mL/45 kg, respectively. Subsequent treatments were assigned by use of a 3 × 3-Latin square with 4 horses/replicate. Beginning at 6 AM with 20 minutes between processing of horses, treatments were administered via jugular venipuncture by an investigator (RSE) on each study day. The first day of treatment was designated day 0. There was a minimum 14-day washout period between trials. Force plate evaluations after treatment were performed at 6, 12, 24, and 30 hours after administration of the final dose on day 3 of each treatment period.

Force plate data acquisition—Each individual force plate session consisted of 6 valid trials in which a handler led the horse at a trot across a centrally positioned floor-mounted force plate.[d] Trials were considered valid if the hoof of the horse's forelimbs struck squarely on the force plate, the horse had a constant gait as it moved across the force plate, and the velocity of the horse moving across the force plate was 2.50 to 2.90 m/s. Trials were rejected if the timer failed to trigger, hoof strikes were partial or questionable, hoof strikes were abnormal because of changes in gait, or velocities were outside the established range. For each trial, an observer confirmed proper gait and acceptable hoof strikes. During each trial, the horse's forward velocity was measured by use of a millisecond timer and 2 photoelectric switches[e] placed 3 m apart. Valid strikes were analyzed by use of specialized computer software.[f] For each valid trial, force plate data were collected for each forelimb and normalized with respect to the horse's body weight. All valid trials were recorded and stored for later evaluation. The study was masked such that the investigator (CGM) who conducted all subjective lameness evaluations was not aware of the treatment each horse had received.

Data analyses—The primary endpoints were the subjective lameness scores and the mPVF values at baseline and 6, 12, 24, and 30 hours after the last treatment. The means of the mPVF of all horses were determined with respect to treatment and time. For the subjective lameness score data analy-

sis, the mean post-treatment scores were expressed as ratios of the baseline. The percentage increases in mPVF from baseline were calculated for the force plate data. All data were analyzed by use of statistics software.[g] Effects of treatments were analyzed via ANOVA techniques with repeated measures by use of an autoregressive covariance structure.[h] Time by treatment interaction was investigated. Simple effects of treatment with given times and time with given treatment interactions were assessed prior to conducting post hoc multiple comparisons.[i] Multiple comparisons for time were performed when appropriate. Effects were considered significant at values of $P < 0.05$.

Results

Twenty horses were identified that conformed to the selection criteria. Of these, 3 horses were removed from the study for reluctance to jog (n =1), concurrent hind limb lameness (1), and fractious behavior (1). Seventeen horses were ranked on the basis of the SD value of their mPVF measurements, and 12 horses with the lowest SD values were selected for inclusion in the study. The remaining 5 horses were maintained with the study herd as alternates. On comparison of data obtained during the first and second pretreatment force plate evaluations, 2 horses had > 10% difference in mPVF and were replaced by alternate horses that did not have > 10% variation in mPVF values. The remaining 3 alternate horses that were not used were removed from further consideration. The 12 horses selected for inclusion remained healthy throughout the study period with no changes in heart rate, respiration rate, or rectal temperature noted during the treatment periods.

Subjective lameness evaluation—For each treatment group, the subjective lameness evaluation (expressed as a fraction of baseline [time-0 data]) was calculated for each time point (**Figure 1**). At 6, 12, and 24 hours after drug administration, horses treated with either flunixin meglumine or phenylbutazone had significant observable improvement in lameness, compared with the control horses treated with saline solution. At these times, there were no significant differences in observable improvement in lameness between horses treated with flunixin meglumine or phenylbutazone. At 30 hours after drug administration, horses treated with flunixin meglumine or phenylbutazone had somewhat greater observable improvement in lameness than did control horses, but there was no significant difference in observable improvement in lameness among the treatment groups.

Force plate analysis—The percentage increase of mPVF from baseline values for each treatment group at each time point was calculated (**Figure 2**). Regardless of treatment, horses had an increase in mPVF at all time points after treatment. At 6, 12, and 24 hours after the final treatment, the improvements in mPVF for the flunixin meglumine- and phenylbutazone-treated horses were significantly greater than that detected in the control horses treated with saline solution. This indicated the analgesic efficacy of flunixin meglumine and phenylbutazone, which was expected of these drugs. However, at all time points assessed, there was no significant difference in the increase in mPVF between the flunixin meglumine- and phenylbutazone-treated horses, indicating similar efficacy of these drugs in providing analgesia for navicular pain. At 6 and 12 hours after drug administration, mPVF values in the flunixin meglumine-treated horses were slightly higher than those of the phenylbutazone-treated horses; however, this difference was not significant and was not maintained at 24 or 30 hours after drug administration. At 30 hours after treatment, there was no significant difference in mPVF values among the 3 treatment groups, although mPVFs in the flunixin meglumine- and phenylbutazone-treated horses were greater than the mPVF of the control horses.

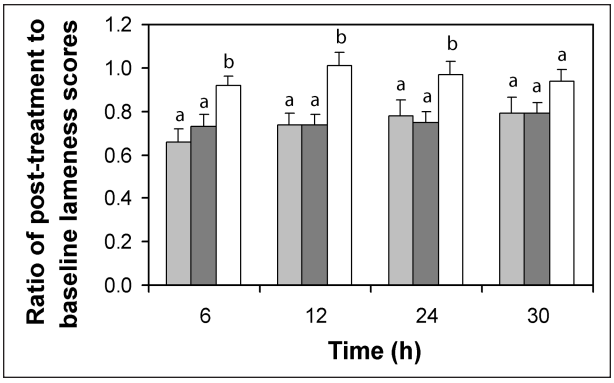

Figure 1—Ratio of mean post-treatment to baseline (0 hours) subjective lameness evaluation scores* in 12 horses with navicular syndrome at 6, 12, 24, and 30 hours after the final dose of flunixin meglumine (light gray bars), phenylbutazone (dark gray bars), or saline (0.9% NaCl) solution (white bars) administered IV every 24 hours for 4 days at dosages of 1.1 mg/kg, 4.4 mg/kg, and 1 mL/45 kg, respectively, in a crossover study. *Assigned on the basis of the American Association of Equine Practitioners 5-point lameness grading scale[29]; half-point scores were permitted. [a,b]At a given time period, mean values with the same letter are not significantly ($\alpha = 0.05$) different as determined by use of a least significant difference procedure.

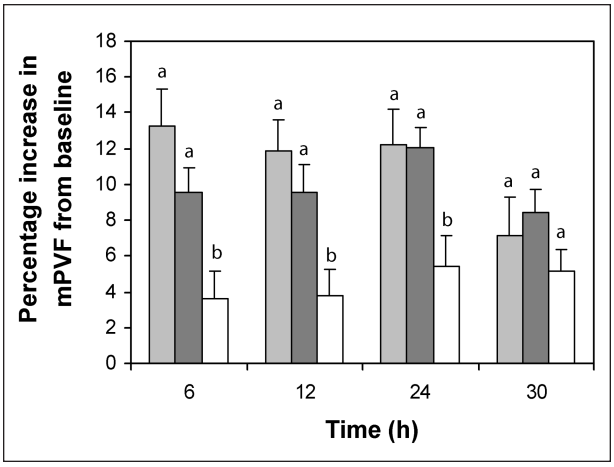

Figure 2—Mean percentage increase in mean peak vertical force (mPVF) from baseline values (0 hours) in 12 horses with navicular syndrome at 6, 12, 24, and 30 hours after the final dose of flunixin meglumine (light gray bars), phenylbutazone (dark gray bars), or saline solution (white bars) administered IV every 24 hours for 4 days at dosages of 1.1 mg/kg, 4.4 mg/kg, and 1 mL/45 kg, respectively, in a crossover study. [a,b]At a given time period, mean values with the same letter are not significantly ($\alpha = 0.05$) different as determined by use of a least significant difference procedure.

Discussion

The results of both subjective and objective evaluations performed in the present study indicated that

flunixin meglumine and phenylbutazone have similar analgesic effects in horses with chronic navicular syndrome. This finding contradicts anecdotal assumptions regarding preferential analgesic activities of phenylbutazone and flunixin meglumine in the treatment of musculoskeletal and visceral pain, respectively. Our data also indicate that the analgesic effects of both drugs are maintained for at least 24 hours after 4 once daily IV administrations at typical clinical doses.

Traditionally, subjective lameness evaluation has been used to determine the clinical effects of analgesic agents. However, that evaluation is dependent on the experience of the evaluator.[28] The AAEP has provided a standardized 5-point lameness scale,[29] but even this is subject to the clinician's opinion. Also, although a horse may have clinical improvement after administration of an analgesic drug, it may still be assigned the same lameness score during a post-treatment subjective lameness evaluation as it was during a pretreatment evaluation. For this reason, half scores were allowed in the present study to more accurately characterize the lameness of each horse. Under the conditions imposed in our study, subjective lameness data provided by an experienced clinician, who was allowed to assign scores by use of half points, mirrored the force plate data. But despite attempts to standardize the scoring system, subjective lameness data remains dependent on investigator experience and opinion.

Force plates are useful for kinematic and locomotor studies.[21–27,30] The PVF is a useful measurement for quantitative and objective determination of the force with which an animal strikes the ground with any given limb. A clinically sound horse should strike the force plate with its forelimbs at a force that measures 104% (range, 95% to 116%) of its body weight while trotting with a velocity of 2.5 to 2.9 m/s.[30] This force decreases proportionally and is distributed to the other limbs with experimentally induced lameness.[24,25,31] Therefore, the mPVF value can be used in studies in which lameness is used as an endpoint as it was in the study of this report. In a recent study,[30] 24 horses with chronic navicular syndrome were evaluated via determination of PVF during a 3-week period; the mPVF value of the group did not change from day to day or week to week. This appears to indicate that navicular syndrome is a stable lameness that is useful for pharmacodynamic studies. The force plate data obtained in our study indicated that the mPVF value increased significantly from baseline values in horses after the administration of flunixin meglumine or phenylbutazone, unlike the value in the control horses treated with saline solution. This suggests that these drugs have a similar analgesic effect with similar durations of effect, given the conditions of this study.

Phenylbutazone, a pyrazalone derivative, undergoes hepatic metabolism forming 2 primary metabolites, oxyphenbutazone and γ-hydroxyphenylbutazone. Oxyphenbutazone is a pharmacologically active metabolite, although it is not as potent as the parent drug. In horses, the half-life of phenylbutazone is biexponential and dose dependent with a mean elimination half-life of 5.5 hours after IV administration of 4.4 mg/kg.[32] The drug has a high degree of protein binding and fairly good tissue penetration. Following distribution of phenylbutazone, the kidneys contain the highest concentration; liver, lungs, and heart have moderate concentrations; and muscles and tendons have the lowest concentrations.[32] Approximately 40% of administered phenylbutazone and its metabolites is excreted via the kidneys; the route of elimination of the remaining 60% of the drug is unknown but may involve biliary excretion.[32] Flunixin meglumine, a carboxylic acid salt, is lipid-soluble with rapid distribution into highly perfused tissues. As with phenylbutazone, flunixin meglumine has a high degree of protein binding. The half-life of flunixin meglumine has been determined to be approximately 1.5 hours.[33] Approximately 75% of flunixin meglumine is excreted unchanged via the kidneys 24 hours after IV administration of 1.1 mg/kg but can be detected in urine for 5 to 6 days after a single dose. Both phenylbutazone and flunixin meglumine induce analgesia via inhibition of the COX enzyme system; the drugs inhibit the conversion of arachidonic acid into prostaglandin H_2, the precursor of thromboxane and protective prostanoids such as prostaglandin E_2 and prostacyclin.[2,8] Some NSAIDs, such as aspirin, irreversibly bind to binding sites on the COX enzyme, whereas other NSAIDs may be displaced.[2]

Pharmacokinetic-pharmacodynamic modeling[10] predicted that maximal effects of phenylbutazone and flunixin meglumine would be obtained at doses of 2.0 and 1.0 mg/kg, respectively. Although there were no increases in maximal effect at higher doses, based on this model, dose-dependent increases in durations of effect were observed. Duration of effect was predicted to be approximately 16 hours for phenylbutazone at a dose of 4 mg/kg, IV and for flunixin meglumine at a dose of 1 mg/kg, IV. Force plate data[11] obtained in horses with navicular syndrome after administration of phenylbutazone at 4.4 or 8.8 mg/kg, IV, every 24 hours for 4 days indicated a maximal effect at both doses (with no significant difference in improvement of lameness between doses) at 6, 12, and 24 hours following the last treatment. Those data also indicated a significant analgesic effect for a period of at least 24 hours, suggesting duration of effect longer than that predicted by use of the pharmacokinetic-pharmacodynamic model. Under the conditions of the study reported here, there was also a significant improvement in lameness at 24 hours after the last treatment of phenylbutazone or flunixin meglumine, which was much greater than the duration of effect predicted via pharmacokinetic-pharmacodynamic modeling. This may indicate an accumulation of these drugs in inflamed tissues similar to that detected in inflammatory exudate[8,12,34,35] or irreversible enzyme binding, as has been suggested.[34]

The clinical dosages used in our study provided administered molalities of 1.43×10^{-5} and 3.71×10^{-6} molals for phenylbutazone and flunixin meglumine, respectively, which yielded a phenylbutazone-to-flunixin meglumine molal ratio of 3.85. Considering that the analgesic effects at these dosages were similar, flunixin meglumine had greater potency than phenylbutazone, as previously described.[2] From the pharmacokinetic-pharmacodynamic model, a maximal effect is obtained at a dose of 2 mg of phenylbutazone/kg and

1 mg of flunixin meglumine/kg, which yields a phenylbutazone-to-flunixin meglumine ratio of 1.9; however, this dose of phenylbutazone is predicted to have a shorter duration of effect than that of flunixin. Also, by use of the pharmacokinetic-pharmacodynamic model, it was predicted that there should be an absence of effect for phenylbutazone and flunixin meglumine at doses of 1 and 0.5 mg/kg, respectively. However, minimum threshold doses for therapeutic analgesia have not been established for either drug.

The results of the study reported here indicated that both flunixin meglumine and phenylbutazone have notable analgesic effects, compared with the effects achieved via administration of saline solution. However, contrary to anecdotal assumptions, there was no significant difference in the mPVF values between the flunixin meglumine- and the phenylbutazone-treated horses after once-daily dosing with those drugs for 4 days. Both drug dosages resulted in similar analgesic effects for horses with navicular syndrome, a musculoskeletal disease. Our data also confirmed that force plate analysis is useful for obtaining accurate quantitative endpoint data for pharmacodynamic evaluations of analgesic drugs in horses.

a. Equi-Phar (20% phenylbutazone solution), Phoenix Scientific, St Joseph, Mo.
b. Banamine, Schering-Plough, Union, NJ.
c. 0.9% sodium chloride injection, Abbott Laboratories, North Chicago, Ill.
d. Piezoelectric Biomechanics force plate system (type 9287920311), Kistler, Amherst, NY.
e. Infrared photoelectric sensor (model No. 49-551A), Radioshack, Fort Worth, Tex.
f. Bioware, version 3.22 (type 2812A1-3), Kistler, Amherst, NY.
g. PC SAS, version 8.2, SAS Institute, Cary, NC.
h. PROC MIXED in PC SAS, version 8.2, SAS Institute, Cary, NC.
i. SLICE option in an LSMEANS statement.

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