Comparison of efficacy and safety of paste formulations of firocoxib and phenylbutazone in horses with naturally occurring osteoarthritis

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Objective—To compare efficacy and safety of paste formulations of firocoxib and phenylbutazone in horses with naturally occurring osteoarthritis.

Design—Randomized controlled clinical trial.

Animals—253 client-owned horses with naturally occurring osteoarthritis.

Procedures—Horses were treated with firocoxib (0.1 mg/kg [0.045 mg/lb], PO, q 24 h) or phenylbutazone (4.4 mg/kg [2 mg/lb], PO, q 24 h) for 14 days. Physical examinations and lameness evaluations were performed prior to treatment and after 7 and 14 days. Clinical improvement was defined as a reduction of at least 3 points in scores for pain during manipulation or palpation, joint swelling, joint circumference, and range of motion.

Results—Proportion of horses clinically improved on day 14 for the firocoxib group (104/123 [84.6%]) was not significantly different from the proportion for the phenylbutazone group (103/119 [86.6%]). Proportion of horses that were improved on day 14 was significantly greater for horses treated with firocoxib than for horses treated with phenylbutazone with regard to score for pain on manipulation or palpation (P = 0.028), joint circumference score (P = 0.026), and range of motion score (P = 0.012), but not for overall lameness score or joint swelling score. No direct treatment-related adverse effects were detected during the study.

Conclusions and Clinical Relevance—Results suggested that overall clinical efficacy of a paste formulation of firocoxib in horses with naturally occurring osteoarthritis was comparable to efficacy of a paste formulation of phenylbutazone. (J Am Vet Med Assoc 2008;232:91–97)

Nonsteroidal anti-inflammatory drugs are commonly used in veterinary medicine for their anti-inflammatory, analgesic, and antipyretic effects. The biological actions of NSAIDs are a result of their ability to interfere with prostaglandin production through inhibition of COX. It is believed that their primary effects are attributable to inhibition of the inducible isoform, COX-2, and that their typical adverse effects, such as gastrointestinal tract ulceration, are largely attributable to inhibition of the constitutive isoform, COX-1.

For more than 30 years, phenylbutazone has been the most commonly administered NSAID in horses.

**Abbreviations**

<table>
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<tr>
<th>NSAID</th>
<th>COX</th>
<th>Nonsteroidal anti-inflammatory drug</th>
<th>Cyclooxygenase</th>
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<tr>
<td>Firocoxib</td>
<td>2</td>
<td>COX-2 inhibitor</td>
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<td>Phenylbutazone</td>
<td>1 and 2</td>
<td>Nonselective COX inhibitor</td>
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Although phenylbutazone is the current standard for treatment of osteoarthritis, it is documented that it has a limited safety margin, likely because phenylbutazone inhibits both COX-1 and COX-2 when administered at therapeutic dosages in horses. A relatively new class of NSAIDs known as coxibs that selectively inhibit COX-2 rather than COX-1 has...
been developed over the past 10 years, and several coxibs have recently become available for use in animals. Indications for the use of coxibs are similar to reported indications for the use of other NSAIDs, with the most common reason for their use being the control of pain and inflammation associated with osteoarthritis or surgery.6,7 Although several studies8–10 have reported the use of coxibs in dogs, few have investigated their use and efficacy in horses. In 1 study11 that has been published, treatment of horses with flunixin meglumine, a nonselective COX inhibitor, prior to colic surgery may have impeded recovery of ischemic jejenum and increased intestinal wall permeability, whereas treatment with deracoxib, which has been determined to selectively inhibit COX-2 in dogs, may have had less impact on recovery. Although deracoxib has not been proven to selectively inhibit COX-2 in horses, results of this study suggest that the use of coxibs in horses with colic warrants further investigation. To our knowledge, no studies evaluating the use of coxibs for the control of pain and inflammation in horses with osteoarthritis have been published to date.

Firocoxib, a member of the coxib class of NSAIDs, has been determined to selectively inhibit COX-2 activity, with concentrations of firocoxib required to inhibit 50% of COX-1 activity being 384, 58, and 643 times, respectively, the concentrations required to inhibit 50% of COX-2 activity in dogs,12 cats,13 and horses.14 Firocoxib has been determined to be efficacious when administered prophylactically or therapeutically to dogs with experimentally induced synovitis12 and when administered therapeutically to dogs with naturally occurring osteoarthritis.15,16 Firocoxib is the first highly selective COX-2 inhibitor developed specifically for use in horses, and preclinical studies4 in horses have revealed that firocoxib is effective at attenuating lameness. A commercial formulation of firocoxib has recently been approved in the United States for the treatment of horses with pain and inflammation associated with osteoarthritis.17 However, the efficacy of firocoxib in relation to standard treatment with phenylbutazone is not known. The purpose of the study reported here, therefore, was to compare efficacy and safety of paste formulations of firocoxib and phenylbutazone in horses with naturally occurring osteoarthritis.

Materials and Methods

Subjects—The study was designed as a multicenter, randomized, controlled field trial. Nine study locations in the United States and Canada were included in the study. Horses enrolled in the study consisted of client-owned horses examined because of osteoarthritis that had a lameness score of at least 3 on a scale from 0 to 5 (American Association of Equine Practitioners lameness scoring criteria were used) or a lameness score of 2 and a score of at least 2, on a scale from 0 to 3, for signs of pain during manipulation or palpation of the affected joint, range of motion, or severity of joint swelling. Only those horses with chronic lameness (ie, >4 weeks’ duration) were used to ensure consistency of the gait anomaly and that the lameness was attributable to osteoarthritis. In all horses, evidence of osteoarthritis was confirmed by means of radiography within 28 days prior to enrollment in the study. Horses with distal sesamoid (navicular) bone degeneration were enrolled in the study provided there was clear evidence of bony changes (eg, cystic [lollipop] lesions, synovial invagination of the distal border, flexor cortex erosions, loss of corticomedullary demarcation, and other radiographic lesions consistent with navicular syndrome18) because clinical signs of navicular syndrome are frequently similar to clinical signs of osteoarthritis. Horses were eligible for enrollment regardless of whether a forelimb or hind limb was involved. For horses in which >1 limb was involved, the most severely affected limb at the time of the initial examination was used for all assessments performed throughout the study.

Horses that had been treated within the previous 7 days with NSAIDs, glycosaminoglycans, or other antiarthritic agents, including horses that had received any alternative treatments during this period such as homeopathic remedies, acupuncture, and extracorporeal shockwave therapy, and horses that had received corticosteroids orally, systemically, or by intra-articular injection within the previous 30 days were excluded from the study.

Management of horses during the study was unchanged from management prior to enrollment. Horses were housed in their typical environments throughout the study, except that in some instances, horses were transported to a study location and briefly housed there to facilitate assessments. All horses were fed and watered according to customary practice. Study subjects were handled in compliance with the guidelines of the Merck Institutional Animal Care and Use Committee, all applicable local regulations, and requirements of any local animal care and use committee. All owners signed an informed consent form prior to inclusion of their horses in the study.

Study design—For each study location, replicates of 2 horses were formed on the basis of order of enrollment following allocation to forelimb lameness and hind limb lameness groups. Within each replicate, one horse was randomly assigned to a firocoxib treatment group and the other horse was assigned to a phenylbutazone treatment group.

Horses in the firocoxib group were treated with a paste formulation of firocoxib19 (0.82% wt/wt) administered at a dosage of 0.1 mg/kg (0.045 mg/lb), PO, every 24 hours. Horses in the phenylbutazone group were treated with a paste formulation of phenylbutazone20 at the recommended label dosage of 1 g/500 lb (approx 4.4 mg/kg [2 mg/lb]), PO, every 24 hours. Dosages were calculated on the basis of body weight at the time of study enrollment. Treatments were generally administered by the owners. Syrings containing the firocoxib formulation included body weight marks at 250-lb increments and notches at approximately 50-lb increments. Syrings containing the phenylbutazone formulation had markings at 1-g increments.

All horses were treated for 12 to 16 days. Medications were packaged in plain syringes, which were individually coded and distributed to the owners by a technician who was not otherwise involved in the study. Thus, even though syringes for the 2 medications differed slightly in appearance, owners would not
have been expected to know that there were differences between syringes and, thus, did not know whether they were administering firocoxib or phenylbutazone, although they were informed that syringes contained an NSAID. In addition, investigators involved in assessing the effects of treatment were blinded to treatment group of the horses. Each horse was reexamined by the same investigator throughout the study.

For all horses, a complete physical examination, including a lameness evaluation, was performed prior to enrollment in the study (day –4), the day treatment was initiated (day 1), between 4 and 10 days after initiation of treatment (day 7), and between 11 and 17 days after the initiation of treatment (day 14). Physical examination included measurement of respiration rate, heart rate, rectal temperature, and body weight (days –4 and 1 only) and evaluation for any adverse effects. The lameness evaluation included evaluation of the overall degree of lameness, severity of signs of pain during manipulation or palpation of the affected joint, severity of joint swelling, measurement of joint circumference (if applicable), and evaluation of range of motion of the affected joint. Blood samples were collected at each examination time and submitted for hematologic and serum biochemical testing. On days 7 and 14, owners were asked to subjectively score the overall degree of improvement as 0 (horse was worse, compared with initial condition), 1 (horse was unchanged, compared with initial condition), or 2 (horse was improved, compared with initial condition). Owners were asked to maintain a daily diary throughout the study and to record any adverse changes in health, any medications given during the study, and observations related to dosing of the horse. At the end of the study, owners were asked to evaluate acceptability and convenience of administration of the medication.

During the lameness examination, overall degree of lameness was scored as 0 (no lameness), 1 (lameness difficult to observe and not consistently apparent regardless of circumstance, such as when carrying a weight or circling or when walking on an incline or hard surface), 2 (lameness difficult to observe at a trot or when trotting in a straight line, but consistently apparent under certain circumstances, such as when carrying a weight or circling or when walking on an incline or hard surface), 3 (lameness consistently observable at a trot under all circumstances), 4 (lameness obvious with marked nodding, hitching, or shortening of the stride), or 5 (minimal weight bearing while in motion or at rest or inability to move). Severity of signs of pain during manipulation or palpation of the affected joint was scored as 0 (no response to firm pressure), 1 (signs of mild pain such as muscle tremors or slight avoidance movement in response to digital palpation or compression), 2 (signs of moderate pain such as definite limb withdrawal in response to digital palpation or compression), or 3 (signs of severe pain such as marked withdrawal from attempted digital palpation or compression). Severity of joint swelling was scored as 0 (no swelling or not applicable), 1 (mild swelling characterized by fibrosis or mild, but palpable, fluid distention), 2 (moderate swelling characterized by obvious, palpable, fluctuant fluid distention), or 3 (severe swelling characterized by pronounced, palpable, firm fluid distention). When possible, maximum circumferences of the affected and contralateral joints were measured with a measuring tape, and joint circumference was scored as 0 (circumference of affected joint ≤ 3% greater than circumference of contralateral joint), 1 (circumference of affected joint > 3% but ≤ 10% greater than circumference of contralateral joint), 2 (circumference of affected joint > 10% but ≤ 20% greater than circumference of contralateral joint), or 3 (circumference of affected joint > 20% greater than circumference of contralateral joint). Horses in which circumference of the affected joint could not be measured (eg, distal interphalangeal joint) and horses with navicular syndrome were assigned a missing score and were not included in analyses of joint circumference. Range of motion was scored as 0 (expected), 1 (< 25% reduction in range, compared with expected range), 2 (25% to 50% reduction in range, compared with expected range), or 3 (> 50% reduction in range, compared with expected range).

**Statistical analysis**—The primary efficacy variable was clinical improvement at the end of the treatment period (day 14), although data for clinical improvement midway through the treatment period (day 7) were also evaluated. Horses were considered to have been clinically improved if overall lameness score was decreased by at least 1 point or if the combined reduction in scores for pain during manipulation or palpation, joint swelling, joint circumference, and range of motion was at least 3 points. Horses with navicular syndrome and horses with other conditions not amenable to ancillary scoring were considered to have been clinically improved only if overall lameness score was decreased by at least 1 point. None of the horses were removed from the study. Therefore, all horses were included in analyses of clinical improvement. For horses with missing values, the last observed value was carried forward. Proportions of horses clinically improved were compared between the treatment (firocoxib) and control (phenylbutazone) groups by means of the normal approximation to the binomial. Because the comparison of proportions of horses that were clinically improved represented a noninferiority comparison, the 1-sided lower 95% confidence interval for the difference in percentage improvement between the 2 treatment groups was calculated and evaluated against the margin of –13%.

Secondary efficacy variables that were analyzed included overall lameness score; scores for pain on manipulation or palpation, joint swelling, joint circumference, and range of motion; and owner-reported score for degree of improvement. For each of these variables, horses were considered improved if score was decreased by at least 1 point, and proportions of horses improved were compared between the treatment and control groups as described for overall clinical improvement. In addition, the Cochran-Mantel-Haenszel row mean scores test was performed on the change from baseline score for each variable. The change from baseline score during each evaluation was calculated as the pretreatment score minus the score assigned during that evaluation.

Overall incidences of reported adverse effects (ie, health and behavioral problems) were calculated for
Results

A total of 253 client-owned horses (5 sexually intact males, 97 sexually intact females, 150 castrated males, and 1 spayed female) of various breeds were enrolled in the study. Horses ranged from 2 to 37 years old; approximate weight ranged from 270 to 745 kg (595 to 1,638 lb).

There were 127 horses treated with firocoxib and 126 horses treated with phenylbutazone. No horses were removed from the study. However, efficacy data were not available or were excluded for 4 horses treated with firocoxib and 7 horses treated with phenylbutazone because of protocol violations or for other reasons (eg, intra-articular injections given within too short an interval prior to enrollment, concurrent treatment with a nutraceutical, improper dosing, or unrelated injury during the study).

For each anatomic area, the proportion of horses in the firocoxib group in which that area was involved was numerically similar to the proportion of horses in the phenylbutazone group in which that area was involved (Figure 1).

The proportion of horses classified as clinically improved at the end of the treatment period (day 14) for horses in the firocoxib group (104/123 [84.6%]) was not significantly different from the proportion for horses in the phenylbutazone group (103/119 [86.6%]). Similarly, proportions of horses classified as clinically improved on day 7 were not significantly different between groups (101/123 [82.1%] and 103/119 [86.3%] for horses in the firocoxib and phenylbutazone groups, respectively).

Proportion of horses that were improved on day 14 was significantly greater for horses treated with firocoxib than for horses treated with phenylbutazone with regard to score for pain on manipulation or palpation ($P = 0.028$), joint circumference score ($P = 0.026$), and range of motion score ($P = 0.012$), but not for overall lameness score or joint swelling score (Figure 2).

On day 14, the change from baseline score was significantly higher for horses treated with firocoxib than for horses treated with phenylbutazone with respect to scores for pain on manipulation ($P = 0.024$), joint circumference ($P = 0.047$), and range of motion ($P = 0.016$; Figure 3).

When owners were asked to subjectively score the overall degree of improvement, owners of 87 of the 123 (70.7%) horses treated with firocoxib and 80 of the 119 (67.2%) horses treated with phenylbutazone reported that their horses were improved on day 7, compared with baseline, and owners of 91 of the 123 (74.0%) horses treated with firocoxib and 86 of the 119 (72.3%) horses treated with phenylbutazone reported that their horses were improved on day 14, compared with baseline. These proportions were not significantly different between groups.

Adverse effects (ie, health and behavioral abnormalities) were reported for 3 of the 123 (2.4%) horses treated with firocoxib and 4 of the 119 (3.4%) horses treated with phenylbutazone. After assessment by the investigators for potential associations between these reported abnormalities and NSAID treatment, it was concluded that no direct treatment-related adverse effects were detected during the study.

Figure 1—Anatomic regions involved in 253 client-owned horses enrolled in a randomized controlled clinical trial of the efficacy and safety of paste formulations of firocoxib and phenylbutazone in horses with naturally occurring osteoarthritis.

Figure 2—Percentages of horses improved on day 14 with respect to secondary efficacy variables in a randomized controlled trial of efficacy and safety of paste formulations of firocoxib and phenylbutazone in horses with naturally occurring osteoarthritis.
For all hematologic and serum biochemical variables, mean values were within reference limits. Significant changes from baseline values were found on day 7 or 14 for 1 or both groups with respect to WBC count, basophil count, basophil fraction, neutrophil count, neutrophil fraction, albumin-globulin ratio, calcium concentration, total globulin concentration, total protein concentration, and SUN concentration. Although individual horses had isolated values outside reference limits, none of these values were considered clinically important.

Least-squares mean changes from baseline to day 7 values or from baseline to day 14 values were significantly different between groups with regard to calcium, creatinine, total globulin, total protein, and SUN concentrations. With the exception of total globulin concentration, mean values were within reference limits, with isolated animals having values outside the reference range. Differences were small, and none of these changes were considered clinically important. For horses treated with firocoxib, mean value for total globulin concentration was slightly outside the reference range prior to treatment and on days 7 and 14.

Owners of 124 of the 127 (97.6%) horses treated with firocoxib and 120 of the 126 (95.2%) horses treated with phenylbutazone reported that the paste formulation was accepted by their horses. Owners of 121 of the 127 (95.3%) horses treated with firocoxib and 124 of the 126 (98.4%) horses treated with phenylbutazone reported that the paste formulation was convenient to administer.

Discussion

Results of the present study suggested that overall clinical efficacy of firocoxib in horses with naturally occurring osteoarthritis was comparable to the efficacy of phenylbutazone. Although proportions of horses that were clinically improved were comparable between groups, a significantly greater proportion of horses treated with firocoxib had improvement in regard to some of the individual secondary efficacy variables, including signs of pain on manipulation, joint circumference, and range of motion. Thus, our findings indicate that firocoxib was efficacious in controlling pain and improving function in horses with chronic osteoarthritis.

The fact that the prevalence of clinical improvement was not significantly different between groups in the present study can largely be attributed to the fact that lameness score was the main criterion for identifying clinical improvement and that the change in lameness score was comparable between groups. Although lameness score is believed to represent severity of pain associated with osteoarthritis and is often used to evaluate the response to treatment, lameness can be a result of various factors, such as permanent changes in conformation or in joint mobility, that are unrelated to pain but have an effect on gait. Chronic osteoarthritis has also been described as causing variable lameness when > 1 limb is affected, as was the case for many horses in the present study. Because the experimental protocol required investigators to evaluate the same limb on all visits, it was possible that the limb with the worst score prior to treatment may no longer have been the limb with the worst score at the end of the study, and this may have affected our results. Furthermore, severity of pain and lameness in horses with osteoarthritis are associated with various factors such as level of activity, ambient temperature, and weight gain. Although attempts were made to control for such covariates in this study by maintaining horses under their customary management conditions, the possibility that other factors had an effect on lameness scores at various evaluation times cannot be completely ruled out. Finally, it is important to mention that clinical improvement
was based on a change in lameness score of at least 1 point, compared with baseline score, or a total change of at least 3 points, compared with baseline scores, for secondary efficacy variables. In contrast, secondary efficacy variables were analyzed to take into account the overall change from baseline score, indicating that scores for pain on manipulation or palpation improved in a higher proportion of horses treated with firocoxib but also improved to a greater degree.

Given that the ratio for concentrations of firocoxib required to inhibit 50% of COX-1 activity versus 50% of COX-2 activity in horses is 643:1, it can be assumed that at a given therapeutic concentration, firocoxib inhibits COX-2 in a far greater degree than it inhibits COX-1 and that, accordingly, its clinical efficacy can primarily be related to COX-2 inhibition. Results of the present study, therefore, support the premise that COX-2 is the primary COX isoform responsible for pain and inflammation in horses with chronic osteoarthritis as has been reported in other species, firocoxib may control pain and inflammation locally, via inhibition of inflammatory prostaglandins, as well as centrally, in that COX-2 has been determined to be involved in modulating pain responses in the CNS. In animals and humans, CNS COX-2 activity and prostaglandin concentration are increased by peripheral inflammation. Because many coxibs have been determined to penetrate the blood-CSF barrier in animals and humans, they may provide analgesia centrally. Furthermore, peripheral and central sensitization and neuronal plasticity are important phenomena in the pathogenesis of pain and in the transition from acute to chronic pain. Thus, firocoxib’s role in the control of chronic pain associated with central sensitization in horses with osteoarthritis warrants investigation.

Although horses with osteoarthritis involving various joints and horses with navicular syndrome were included in the present study, the distribution of anatomic areas involved was similar for the 2 groups, allowing results to be compared between groups. In addition, horses enrolled in the study were required to have chronic osteoarthritis, as determined on the basis of duration and severity of clinical signs, and most horses had radiographic evidence of bony changes, confirming the chronic nature of the condition. Nonetheless, 204 of the 242 (84.3%) horses were classified as clinically improved after only 7 days of treatment, indicating that firocoxib and phenylbutazone both had rapid onsets of action. Whereas studies involving acute, experimentally induced pain and inflammation in horses, dogs, and cats have determined firocoxib to be efficacious, further clinical studies involving animals with acute conditions and animals with chronic conditions that have a sudden worsening of signs would be of interest because other coxibs have been determined to be indicated in these situations owing to their rapid onset of action.

The issue of safety is often an important factor when selecting an NSAID for long-term use. In the present study, firocoxib was well tolerated for the 14-day study period. In addition, despite numerous reports of a low therapeutic index for phenylbutazone in horses, there were few adverse effects reported in the present study, and there was no significant difference in the rate of adverse effects between groups. This finding may largely be attributable to the fact that both drugs were administered at the recommended dosage for a relatively short time in horses with no history of or risk factors for gastrointestinal tract or renal toxicosis. It has been documented that phenylbutazone can cause severe ulceration of the glandular gastric mucosa following administration at high dosages for as short as a few days and that even coxibs can cause gastrointestinal tract toxicosis in humans and dogs when administered at higher-than-approved dosages or in close temporal association with other NSAIDs. It has also been determined in several species that COX-2 expression plays a role in healing of gastrointestinal tract ulcers. Consequently, NSAIDs should not be used or should be used only with caution in horses known to have gastrointestinal tract ulcers.

Both COX-1 and COX-2 appear to be expressed constitutively in the kidneys, and it is now believed that although prostaglandins do not play a major role in homeostasis of the kidneys in healthy individuals, they are critical in individuals with renal disease and volume depletion. There was no evidence of renal toxicosis among horses treated with either drug in the present study, and none of the hematologic or serum biochemical changes were considered to be of clinical importance.

In a toxicity study in horses, firocoxib was not associated with gastrointestinal tract ulceration when administered at recommended dosages, and increases in prevalences of reversible oral mucosal lesions and classic NSAID-associated nephropathy were detected only when dosages 3 to 5 times the recommended dosage were administered for 30 to 92 days. Thus, firocoxib appears to be a safe alternative to the long-term use of phenylbutazone in horses.

Palatability for the patient and acceptability by the owner are important factors related to compliance and continuation of long-term treatment in veterinary patients. The paste formulation of firocoxib used in the present study was found to be of equivalent acceptability and ease of administration as the commercially available paste formulation of phenylbutazone.

References
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