Efficacy of Firocoxib in Preventing Urate-Induced Synovitis, Pain, and Inflammation in Dogs*

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CLINICAL RELEVANCE

This positive-control study evaluated the efficacy of firocoxib versus carprofen, deracoxib, and meloxicam for the prevention of pain and inflammation in a urate crystal synovitis model of lameness. Lameness scoring and force plate gait analysis were used to assess efficacy. The resulting lameness scores and force plate ground reaction forces after urate crystal injection were not significantly different among the groups. Relative to each group's baseline (nonlame) score, only the firocoxib group was not significantly lame, based on lameness score, at the model's peak effect.

INTRODUCTION

NSAIDs are the most commonly used analgesics for treating osteoarthritis (OA) in humans and animals.[1,2] Veterinary NSAID use has blossomed over the past decade with the introduction of products featuring improved safety profiles compared with aspirin, the primary NSAID used in dogs before the mid-1990s. Gastrointestinal side effects often limited the duration of aspirin treatment, frustrating those treating osteoarthritic dogs. Research to improve NSAID safety and efficacy has been fervent and often focused on investigating cyclooxygenase (COX) activity of NSAIDs with therapeutic potential.

COX-1 is the isoform thought to be responsible for basal physiologic prostaglandin functions, whereas COX-2 is thought to be responsible for inflammatory prostaglandin.[3] This concept may be overly simplistic, but it has resulted in an intense search for agents that suppress COX-2 while sparing COX-1. As new products became available, studies were conducted to compare NSAIDs and their ability to inhibit COX in vitro. This ability is frequently expressed as the concentration ratio (COX-1: COX-2) that results in the inhibition of 50% or 80% of COX activity (IC_{50} and IC_{80}, respectively).[4–7] These studies provided much-needed information regarding techniques for preliminary evaluation of new NSAIDs, but the results should not be overinterpreted, especially when extrapolating to clinical situations. Differences in COX-1–sparing ratios in vitro do not necessarily correlate with differences in

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TABLE 1. Treatment Dosage

Group	*Product*	*Label Dosage (mg/kg/day)*	*Study Dosage Range[a] (mg/kg/day)*
1	Firocoxib	5	5.30–8.66
2	Carprofen	4.4	4.43–5.00
3	Deracoxib	1–2	1.17–1.91
4	Meloxicam	0.2	0.20

[a]Dosages were based on body weight and rounded to the nearest half-tablet increment to ensure that at least the labeled dosage was achieved for carprofen, deracoxib, and firocoxib. For meloxicam, the liquid suspension was dosed to the exact body weight.

prostaglandin production in vivo,[8] but the inability of nonselective NSAIDs to spare COX-1 has been shown to be a major factor contributing to adverse effects associated with their use.[9] Obviously, the decisive NSAID selection points, as with any drug, are safety and efficacy in the patient.

Firocoxib is a highly selective inhibitor of COX-2 developed specifically for veterinary use. Its efficacy and safety were demonstrated in support of its approved indication for control of pain and inflammation associated with OA in dogs (NADA 141-230). A preclinical study found that firocoxib has 380-fold selectivity for COX-2 over COX-1 (more precisely, the IC_{50} ratio of COX-1:COX-2 was calculated as 384) and, with the use of the urate crystal (UC) model of lameness, demonstrated that firocoxib provided greater efficacy than carprofen whether given as a preventive or as a treatment for induced lameness.[10]

Practitioners can choose from many NSAIDs in several classes to provide safe and effective control of the pain associated with OA.[1] This study evaluated the relative efficacy of a new veterinary NSAID, firocoxib (Previcox, Merial [ML-1,785,713]). Of the drugs compared in this study, firocoxib and deracoxib (Deramaxx, Novartis) belong to the coxib class of nonnarcotic NSAIDs, carprofen (Rimadyl, Pfizer Animal Health) belongs to the propionic acid class, and meloxicam (Metacam, Boehringer Ingelheim Vetmedica) belongs to the oxicam class. These drugs are indicated for either the relief or control of pain and inflammation associated with OA in dogs. The NSAIDs selected for comparison with firocoxib were chosen because they have achieved high levels of acceptance by the veterinary profession.

This study evaluated the efficacy of these NSAIDs to prevent lameness associated with a UC lameness model. This method of acute synovitis induction in dogs and humans was first documented in 1962.[11] In that study, the authors injected themselves with 20 mg of UC in the knee and followed the progression of inflammation and pain. The injection of UCs elicits an intense inflammatory response, which includes neutrophil migration and release of such inflammatory mediators as prostaglandins, leukotrienes, and others. The model has been refined over the years and has been widely used to assess NSAID efficacy.[10–18] Although the inflammatory response is an acute process, many components are similar to those that occur in chronic conditions. In dogs, lameness is evident within 2 hours after UC injection, reaches a peak at approximately 4 hours, and then gradu-

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ally resolves spontaneously. Most dogs return to full weight-bearing capacity by 24 to 36 hours after the injection. The intense yet temporary nature of the inflammatory insult caused by intraarticular UC injection makes it a suitable model to evaluate NSAID efficacy.

The objective of this study was to compare the efficacy of four widely used NSAIDs (carprofen, deracoxib, firocoxib, and meloxicam) in the UC lameness model. Comparing the firocoxib group with three NSAID positive-control groups provided a humane method of evaluating firocoxib efficacy without the need for an untreated negative-control group.

TABLE 2. Treatment Schedule[a]

	Period 1 (Day 0)	*Period 2 (Day 7)*	*Period 3 (Day 14)*	*Period 4 (Day 21)*
Sequence 1	1L	2R	3L	4R
Sequence 2	2L	3R	4L	1R
Sequence 3	3L	4R	1L	2R
Sequence 4	4L	1R	2L	3R

[a]Dogs were assigned to replicates based on body weight and randomly assigned to sequences within replicates.
1–4 = treatment group; L = left stifle; R = right stifle.

MATERIALS AND METHODS

Study Animals and Treatment Allocation

Eight healthy mixed-breed dogs (four males and four females), approximately 70 months of age and weighing 15 to 28 kg, were used in this positive-control, blinded, four-period crossover study using a randomized block design based on pretreatment body weights. All animals were managed similarly, with due regard for their well-being, and were handled in compliance with Merial Institutional Animal Care and Use Committee approvals. Carprofen, deracoxib, firocoxib, and meloxicam were administered orally at the approved label dosages for control of pain and inflammation associated with OA (Table 1).[19–22] The dosage of products available as a tablet formulation (i.e., carprofen, deracoxib, and firocoxib) was rounded to the nearest half-tablet increment that provided at least the labeled dosage. For deracoxib, the dosage for OA differs from that for acute surgical pain; the OA dose was used because the other drugs were administered based on their OA dosages and the UC synovitis lameness model is representative of the more intense end of the pain and inflammatory spectrum possible with OA.

For allocation, the four heaviest dogs were assigned to replicate 1 and the remaining four dogs were assigned to replicate 2. Within each replicate, each dog was randomly allocated to one of four treatment sequences. By the end of the study, each treatment had been assessed in each of the eight dogs. The UC injections were alternated between left and right stifles for each treatment period. Treatment periods were separated by a 7-day washout period. The details of the treatment schedule are outlined in Table 2.

Lameness Model and Assessment

The induced lameness model based on intraarticular injection of monosodium UC has been described elsewhere.[10,17,18] Briefly, the UC suspension was prepared fresh for each dog by adding 1.5 ml of 0.9% NaCl to 28.5 mg of monosodium UC (Sigma Chemical) and sonicating for 20 minutes. Dogs were anesthetized with propofol intravenously before intraarticular injection of UC. The skin over the stifle joint was clipped and prepared for an aseptic procedure. A 20-gauge, 1.5-inch needle was inserted into the joint. Once synovial fluid was evident, 1 ml of suspension containing 19 mg

TABLE 3. Procedure Schedule

Procedure	*Time*	*Day*
Baseline lameness score	Within 24 hr before UC injection	–1, 6, 13, 20
Baseline force plate gait analysis	Within 24 hr before UC injection	–1, 6, 13, 20
Body weight determined	Within 24 hr before UC injection	–1, 6, 13, 20
NSAID treatment administered	Hr 0	1, 7, 14, 21
UC injection to induce synovitis	Hr 10	1, 7, 14, 21
4-hour post-UC lameness score	Hr 14	1, 7, 14, 21
4-hour post-UC force plate gait analysis	Hr 14	1, 7, 14, 21
8-hour post-UC lameness score	Hr 18	1, 7, 14, 21
8-hour post-UC force plate gait analysis	Hr 18	1, 7, 14, 21

UC = urate crystal.

of monosodium UC was injected into the joint. The stifle was then extended and flexed several times to distribute the UC suspension.

Baseline lameness score and force plate gait analysis of ground reaction force (GRF) were performed the day before treatment within 24 hours of lameness induction. NSAID treatment was given at hour 0, the start of each treatment period. Lameness was induced by UC injection of the stifle 10 hours after NSAID administration to assess treatment efficacy during the middle to end of the dosing period. Lameness was scored as follows:

0 = No lameness

1 = Mild lameness, including toe touch to floor (i.e., weight bearing) on all of the strides

2 = Moderate lameness, including toe touch to floor on all of the strides

3 = Severe lameness, including toe touch to floor on 50% or more of the strides

4 = Non–weight-bearing lameness, including toe touch to floor on less than 50% of the strides

Lameness score and force plate gait analysis of GRF were performed at hours 14 and 18 (4 and 8 hours after UC injection, respectively). Following the hour 18 assessment, rescue medication was allowed for any dog that the investigator judged to need it. The schedule of these procedures is detailed in Table 3.

Force plate gait analysis of GRF was performed using a floor-mounted system to determine the peak vertical force (PVF) and vertical impulse (VI). The equipment (Model OR6-7-1000 Biomechanics Force Platform, Advanced Mechanical Technology, Watertown, MA) and methodology were similar to those used in other studies analyzing GRF to evaluate and quantify the degree of lameness.[17,23,24] The target or goal was to make at least six valid observations for the affected rear leg at each time point for every dog. Dogs were trotted at a targeted velocity range of 1.5 to 3.0 m/sec and an acceleration of 0 ± 1.0 m/sec^2. If the dog had non–weight-bearing lameness, force plate gait analysis was not performed and a value of 0.0 was recorded. The primary endpoint of the force plate gait analysis was determination of the weight-bearing PVF of the affected limb,

TABLE 4. Individual Mean Velocities During Force Plate Gait Analysis

	Velocity (m/sec)				*Mean Velocity (m/sec) across*		
Dog ID	*Period 1*	*Period 2*	*Period 3*	*Period 4*	***Periods***	***Range***	Δ
72823	1.96	2.09	2.02	2.03	2.03	1.9–2.10	0.13
72824	2.29	2.18	2.42	2.35	2.31	2.18–2.35	0.17
72883	2.46	2.20	2.27	2.14	2.27	2.14–2.46	0.32
72901	2.13	2.07	1.97	1.89	2.02	1.89–2.13	0.24
72905	2.32	2.03	2.16	1.92	2.11	1.92–2.32	0.40
72924	2.29	2.23	2.17	2.17	2.22	2.17–2.29	0.12
72998	2.12	2.21	2.13	2.06	2.13	2.06–2.21	0.15
446A	1.91	2.09	1.92	1.97	1.97	1.91–2.09	0.18

which was measured in Newtons/kg body weight (N/kg) and expressed as a percentage of the baseline PVF. A secondary endpoint was determination of VI, which was measured in Newton-seconds/kg body weight (N-sec/kg).

All personnel making efficacy observations were blinded to treatment. The person administering the treatments was not blinded but did not participate in making any efficacy observations.

Statistical Analysis

A separate analysis was performed at each time point (baseline, hour 14, and hour 18) using analysis of variance for a crossover design on a model including treatment, sequence, period, and carryover effects as fixed effects and replicate and the interaction of replicate and treatment as random effects. Preliminary statistical analyses revealed there was no carryover effect for any variables in the lameness scores or the force plate gait analysis. As such, a reduced statistical model including treatment, sequence, and period as fixed effects and replicate and the interaction of replicate and treatment as random effects was used. Differences among the treatments were tested comparing firocoxib with each of the other three treatments. Each treatment baseline PVF value was also compared with the same treatment's 4-hour post-UC injection value and expressed as a percentage of baseline. Each comparison was tested at a two-sided significance level of $P < .05$.

RESULTS

Baseline lameness score was 0 for each group and time period. Baseline force plate gait analysis values for each dog and leg were not significantly different, with an average decrease in PVF of 2.2% from the first to second injection in the same leg. Although a relatively broad range of velocities was permitted to accommodate the individual dogs, the overall mean velocity was 2.13 m/sec and the mean difference in velocities for a given dog across the four periods was 0.21 m/sec (range: 0.12–0.40 m/sec; Table 4). The mean acceleration was 0.025 m/sec^2 (SD: 0.48 m/sec^2; Table 5).

Fourteen hours after NSAID treatment, during the peak of the UC-induced lameness effect (4 hours postinjection), there was a significant difference between the lameness score

TABLE 5. Mean (±SD) Acceleration Values (m/sec) by Study Period

Period 1	*Period 2*	*Period 3*	*Period 4*
0.090 ± 0.540	–0.005 ± 0.456	–0.004 ± 0.508	0.020 ± 0.424

TABLE 6. Lameness Score Results—Treatment vs. Baseline

	Hour 14 (4 hr after UC injection)	
Treatment	*Least Squares Mean*	P *Value*[a]
Firocoxib	0.75	.086
Carprofen	2.00	.007
Deracoxib	2.00	.007
Meloxicam	1.63	.012

[a] *P* values are the contrast between the treatment group and baseline.

reported for each of the carprofen, deracoxib, and meloxicam groups relative to that treatment group's baseline (nonlame) score, but the difference in the lameness scores between the firocoxib-treated group and its baseline was not significant (Table 6).

Although numeric values indicated less lameness and more weight-bearing capacity in the firocoxib-treated group, there were no significant differences among the treatment groups for either lameness score or force plate gait analysis based on a mixed model analysis of variance for a four-period crossover design. Regarding lameness score of the firocoxib group versus the comparative NSAIDs, at hour 14 the firocoxib group had the lowest lameness score, 0.75, compared with a range of 1.63 to 2.0 for the meloxicam, deracoxib, and carprofen groups (P = .057 to .125; Figure 1). This trend was maintained at hour 18, with the firocoxib group lameness score of 0.25 compared with a range of 0.75 to 1.25 for the other groups (P = .181 to .450).

Regarding force plate gait analysis of GRF and the resultant percentage of baseline PVF values, the firocoxib group had the highest numeric scores (most weight-bearing capacity) for least squares mean. The percentage of baseline PVF in the firocoxib group was 84.5 at hour 14 compared with a range of 53.2 to 63.2 for the other groups (P = .078 to .170, Figure 2). Similarly, at hour 18 the percentage of baseline PVF in the firocoxib group was 94.5 compared with a range of 75.6 to 87.2 for the other groups (P = .179 to .536).

Regarding force plate gait analysis of GRF and the resultant percentage of baseline VI values, at hour 14 the firocoxib group value was 76.1 compared with a range of 48.7 to 59.0 for the other groups (P = .094 to .228). Similarly, at hour 18 the firocoxib group percentage of baseline VI was 89.3 compared with a range of 77.9 to 87.4 for the other groups (P = .421 to .887).

DISCUSSION

To understand how well the NSAIDs provided relief throughout the day, the lameness challenge was initiated 10 hours after a single dose of NSAID was administered and effects were assessed at 14 and 18 hours after treatment. Considering the rigorous challenge provided by the UC lameness model (intraarticular injection of 19 mg of UC), all of the NSAIDs provided a positive benefit compared with historical untreated control dogs.[10,13,17]

In an effort to evaluate firocoxib using the most humane methods possible, there was no negative-control group, a situation considered and evaluated here in depth as a potential study deficiency. In lieu of a control group, one can look to other studies to see what has typi-

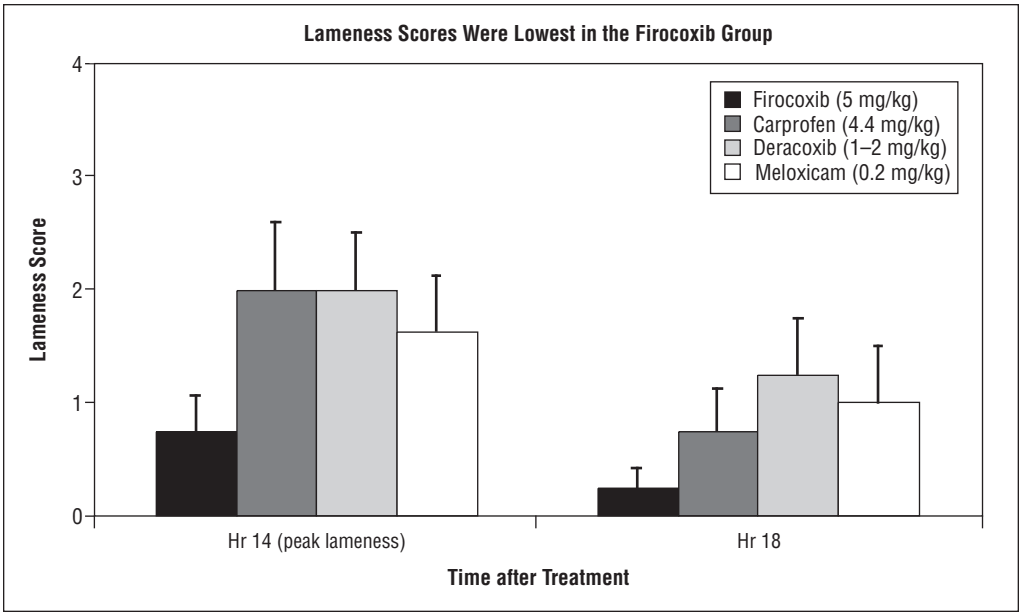

Figure 1. *Lameness score results (mean ± SEM; range: 0 [normal] to 4 [non–weight-bearing lameness]). Comparison between firocoxib and comparative NSAIDs had* P *values of .057 (carprofen and deracoxib) to .125 (meloxicam) at hour 14 and .181 (deracoxib) to .450 (carprofen) at hour 18.*

cally been reported when lameness is induced by UC injection in dogs. The same lameness model, using 19 mg of sodium urate, was used in a ketoprofen dose study in which the placebo control group had percentage of baseline PVF scores of 19.0 and 44.4 at 2 and 6 hours after lameness induction, respectively.[13] The percentage of baseline PVF scores in the placebo control group in another study using the same model but 17 mg of sodium urate was 0.0 at both 4 and 8 hours after UC injection, and the duration of the lameness effect lasted as long as 72 hours rather than the more typical 24 hours.[17] In another NSAID efficacy study, the percentage of baseline PVF scores for the placebo control group was 0.0 at 4 hours after injection of 15 mg of sodium urate, 10.3 at 6 hours, and 27.2 at 8 hours.[15]

Using even lower doses of UC has been associated with less-consistent results because of the weak challenge of control subjects and subsequent insufficient differentiation between control and treatment. An estimate of the percentage of baseline PVF scores in a study using 10 mg of UC demonstrated the effect of a weak challenge.[16] Values taken from a chart of PVF as a percentage of body weight and recalculated as percentage of baseline PVF reveal that the placebo group had a value of approximately 56% of baseline PVF at 2 hours after UC injection; the figure climbed to about 71% at 4 hours and about 81% at 8 hours. In controlled studies with limited sample size, it is difficult to demonstrate a meaningful effect when the PVF in the untreated control group after lameness induction is close to the baseline PVF and that of treatment groups at the time points evaluated.

The 19-mg dose of UC provides a rigorous lameness challenge model that is sufficient to

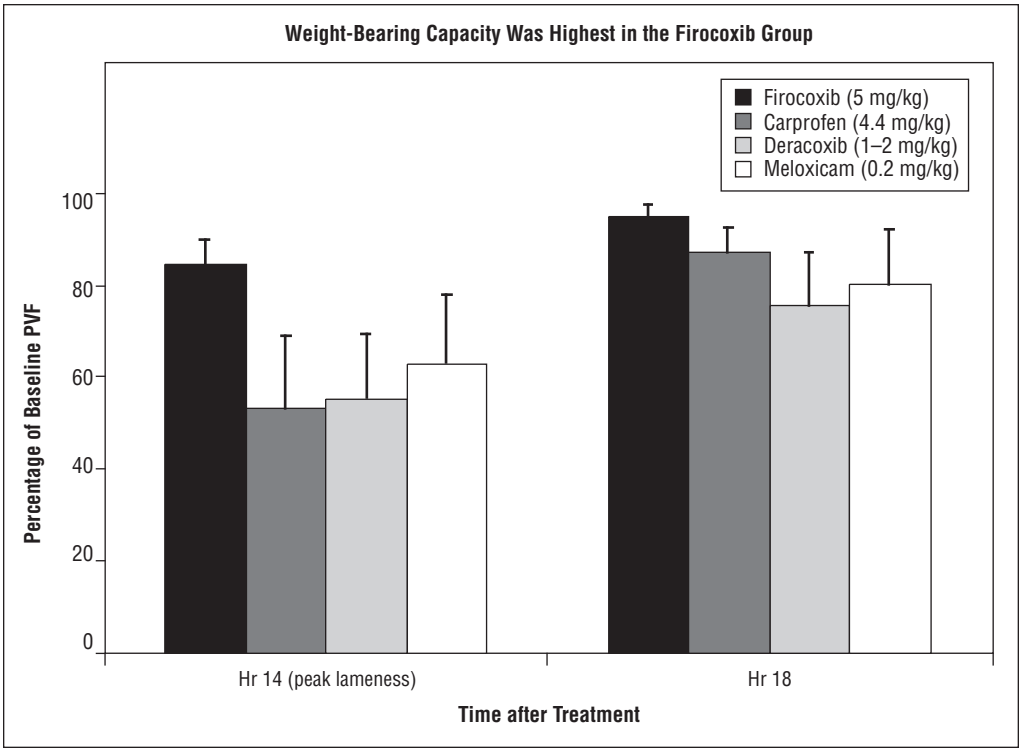

Figure 2. *Percentage of baseline peak vertical force (PVF) (mean ± SEM). Comparisons between firocoxib and comparative NSAIDs had* P *values of .078 (carprofen) to .170 (meloxicam) at hour 14 and .179 (deracoxib) to .536 (carprofen) at hour 18.*

demonstrate therapeutic effect. This was illustrated during preclinical and dose titration prophylactic efficacy studies with firocoxib that included vehicle control groups. The resultant scores for percentage of baseline PVF in the untreated control group was 0.0 at 4 hours after UC injection and ranged from 0 to 6.9 at 8 hours.[10,25] In contrast, values in the firocoxib group receiving the therapeutic dose of 5 mg/kg was greater than 70% of baseline PVF at both time points. Evaluation of negative-control groups in these studies provided ample evidence of the reproducible nature of the challenge caused by the reversible UC lameness model using 19 mg of UC for intraarticular injection and alleviated the need for a negative-control group in the current study.

As previously mentioned, although all the NSAIDs tested in the current study appeared to provide benefit against this lameness challenge, only the firocoxib group had no significant difference between the lameness scores at baseline (nonlame) and at hour 14 (4 hours after UC injection). Similarly, in multicenter, double-blind, randomized clinical field studies in dogs with OA, firocoxib demonstrated greater levels of improvement in lameness compared with etodolac and carprofen when the NSAIDs were administered for 30 days.[26,27] These results suggest that it is possible to observe differences in the efficacy response with different NSAIDs and that the UC lameness model is a predictor of such difference.

CONCLUSION

These data demonstrate that the ability of firocoxib to prevent pain in a UC lameness model compares favorably with that of carprofen, deracoxib, and meloxicam. Although there was no significant difference in efficacy among groups, only the firocoxib group had no significant difference between lameness score at the peak of the lameness effect and the group's baseline (nonlame) lameness score.

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