Clinical Application of Firocoxib Canine Chews in Equine Practice

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ABSTRACT

The purpose of this study was to compare the bioavailability of equine firocoxib to canine chews in horses as well as evaluate therapeutic levels with clinical response. Horses (n=8) received a single loading dose of firocoxib (0.3 mg/kg) as an oral paste, chew, or intravenously in a randomized triple cross over study. Firocoxib was quantitated by high performance liquid chromatography (25-2,500 ng/ml). Data was subjected to non-compartmental analysis. An in vitro analysis was performed to determine appropriate handling of firocoxib during collection and storage. Samples from client horses (n=44) treated with firocoxib chews were evaluated for drug levels and clinical response. This study failed to find statistically significant differences in Cmax and absolute oral bioavailability at a power of greater than or equal to 90%. Firocoxib should be transported and stored in glass vials. Clinical patients appear to respond favorably to treatment with chews without adverse effects.

INTRODUCTION

Firocoxib is a member of the coxib class of NSAIDs. Firocoxib, described as COX-2 selective, has recently been approved for use in both horses as a paste and for dogs as a chew by the United States Department of Agriculture and European Union.[1] However, the preparations differ, with the paste (56.8 mg of firocoxib/tube, able to be

administered in 11.4 mg increments (250 lb doses) and chew as a tablet (57 to 227 mg tablets that can be scored in half). Firocoxib made its debut in veterinary medicine in dogs, demonstrating efficacy for treatment of experimental induced synovitis and naturally occurring osteoarthritis.[2,3]

According to the Policy of Extra-Label Drug Use, which describes the criteria for extra-label drug use in food animals, the substitution of the canine chew for the equine paste is illegal in the United States[1,4] However, substitution of the chew for paste is none-the-less becoming increasingly popular in equine practice. Despite improved safety, the therapeutic index of COX-2 selective drugs remains sufficiently narrow, suggesting use should be based on disposition studies in the target species. The purpose of this study was three-fold:

1. To determine, in horses, the disposition of firocoxib when administered at the recommended (labeled) loading dose (0.3 mg/kg) in equine formulations, either as the intravenous solution or as the oral paste, and with the canine chew tablets;
2. We sought to compare the absolute bioavailability of the two oral products;
3. Collect clinical samples from equine patients who were being treated with the canine chew and compare response of therapy to firocoxib plasma levels.

Initially, the authors anticipated the firocoxib product prepared as a chewable tablet might not be a readily absorbed in horses, and thus hypothesized that the chews would be 30% less bioavailable compared to the paste at an equivalent dose.

MATERIALS AND METHODSs

Eight healthy, adult horses (7 geldings, 1 mare) were studied using a randomized, triple cross-over design. The sample size (8 horses) was based on the number necessary to demonstrate a 50% difference in Cmax based on a reported variability of 31% around the mean. Animals included both client owned animals and horses from the equine teaching herd. All procedures were approved for use by the Institutional Animal Care and Use Committee, which included approval of a client-informed consent form which was signed by participating clients.

Horses were randomly assigned to one of three initial treatment groups, with each group receiving (0.3 mg/kg oral [PO] and 0.2 mg/kg intravenous (IV)) firocoxib (Equioxx;equine IV or paste formulations), Merial, Duluth, GA):

- Group 1 - a single intravenous dose
- Group 2 – single dose of oral paste
- Group 3 – single dose of chewable tablets

The chewable tablets (Previcox,canine formulation, Merial, Duluth, GA) were offered by hand (n=6) or, if the horse was reluctant to eat the tablets, were administered by syringe application after mixing the tablets with 30 ml water (n=2).

Prior to drug administration (day 0), 20 mL of blood was withdrawn from the jugular vein for a complete blood count and serum chemistry profile to ensure the animal had no underlying systemic disease. A 14 gauge 13.75 cm intravenous catheter (Abbocath, Hospira, Lake Forest, IL, USA) was then placed in the jugular vein using sterile technique. Once the catheter was placed, the horse received its pre-assigned treatment and blood samples (10 mLs) were collected through the indwelling catheter. If the horse assigned to the intravenous treatment group, the loading dose of the intravenous solution was administered through a percutaneous injection into the opposite external jugular vein from where the catheter was placed. After each sample collection, the catheter was flushed thoroughly with heparinized saline.

Samples were collected at 30 minutes, 1, 2, 4, 8, 16, 24, 48, 72, and 96 hours after dosing. Blood was placed in heparinized glass collection tubes (BD Vacutainer, Sodium Heparin, BD, Franklin Lakes, NJ, USA). After the 24-hour sample time point, the indwelling catheter was removed and the remaining samples were collected through a 20 gauge needle and 12 mL syringe from

alternate right or left jugular veins. Blood samples were separated into their components (packed red blood cells and plasma) by centrifugation, and plasma was stored frozen at -80 degrees Fahrenheit in glass vials (e. Borosilicate Glass Disposable Culture Tube, VWR®, Radnor, PA, USA) until analyzed. Following a washout period (approximately 5 drug half-lives), animals were crossed over to their next study group and the process repeated until each animal had received all three treatments. After the last sample was collected for the last study in each horse, a complete blood cell count and serum chemistry profile was repeated.

In addition to pre- and post-complete blood cell count and serum biochemistry monitoring, a physical examination was performed twice daily during the study period. Horses were also observed for evidence of NSAID toxicity, including, abdominal discomfort, weight loss, fever, or diarrhea. Any horses that elicited any of the above clinical signs would result in the immediate discontinuation of the study for that horse, confirmed diagnosis of gastric ulceration or NSAID toxicity, and initiation of necessary treatment.

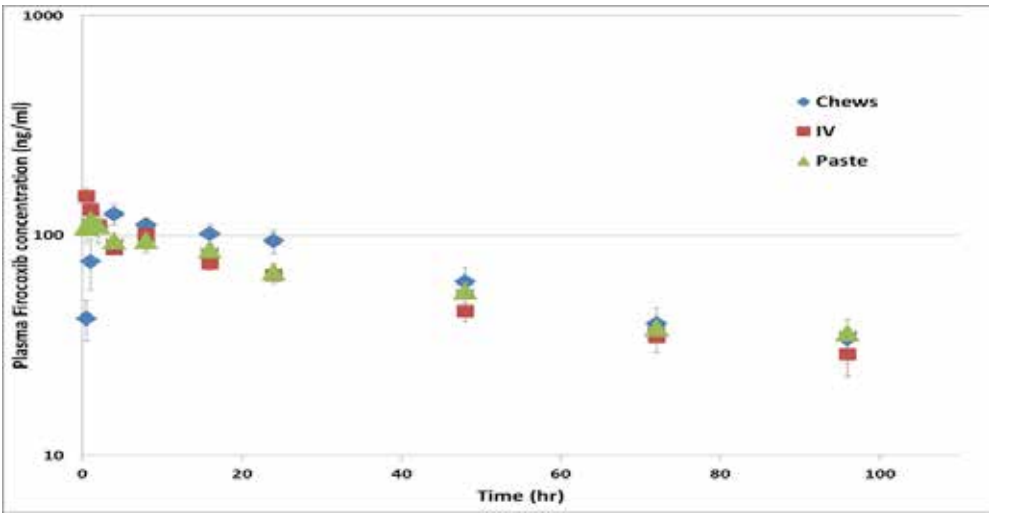
Horse plasma was analyzed for firocoxib concentrations by high pressure liquid chromatography (HPLC) with ultraviolet (UV) detection. The HPLC system consisted of a Waters 2695 separation module and a 2489 UV-Visible detector (Waters Oasis® HLB, Waters Corporation™, Milford, MA, USA). Separation was achieved with a Sunfire C18, 5 µm, 150 x 4.6 mm column (Waters Oasis® HLB, Waters Corporation™, Milford, MA, USA) maintained at 40 °C.[1,5] The mobile phase consisted of 45:55:0.025 acetonitrile/water/trifluoroacetic acid (VWR®, Radnor, PA, USA) with the flow rate set to 1 mL/min.[1,5,6] The standard curve was generated ranging from 25 to 2,500 ng/mL by fortifying equine plasma with known amounts of firocoxib (Toronto Research Chemicals Inc. (TRC), Toronto, Ontario, Canada) reference standard and accepted if the coefficient of determination (r2) was at least 0.999 and the predicted concentrations were within 10% of the actual concentrations.

Firocoxib was extracted from horse plasma with solid phase extraction (SPE) cartridges (3 mL, 60 mg) (Waters Oasis® HLB, Waters Corporation™, Milford, MA, USA). Briefly, previously frozen plasma samples were thawed and vortexed. The SPE cartridges were conditioned with 2 mL acetonitrile and then 2 mL water. Aqueous plasma samples (1 mL of plasma plus 2.0 mL water) were loaded and allowed to elute by gravity. The cartridges were rinsed with 2.0 mL of 5% acetonitrile in water (gravity elution) and a vacuum of ~10 in of Hg was used to remove the residual solvent. Firocoxib was eluted with 2.0 mL acetonitrile which was then evaporated to dryness under a stream of nitrogen during 25 min at 40°C. The residue was reconstituted with 250 µL of 40 % acetonitrile/water, with vortex/mixing for 20 sec and then the solution was centrifuged at 1900 x g.[1,5] The injection volume was 100 µL. The retention time for firocoxib was 8.6 min and UV absorbance was monitored at 290 nm.[1,5,6]

Unknown concentrations of firocoxib in each sample were determined by comparing the signal to a calibration curve. The standard curve was generated by fortifying equine plasma with known amounts of firocoxib that ranged from 25-2,500 ng/mL.6 A calibration curve was accepted if the coefficient of determination (r2) was at least 0.999 and the predicted concentrations were within 10% of the actual concentrations. The linear correlation coefficient for firocoxib was 0.9999. The lower limit of detection was 10 ng/mL and the lower and upper limits of quantification (LOQ) for firocoxib were 25 ng/mL and 2,500 ng/mL respectively. The relative measurement of uncertainty (RSD %) for firocoxib 25, 100, 1,000, 2,500 and 5,000 ng/mL were 9.1%, 4.9%, 2.1%, 1.1% and 1.1% respectively. Intra and inter assay variability was less than 10% for all controls.

In order to determine appropriate handling, processing and storing of the

Figure 1. *Mean plasma firocoxib concentration by formulation. Mean + SE plasma Firocoxib versus time concentration in 8 apparently healthy horses when administered at 0.3 mg/kg as three different preparations: Red = IV Equioxx®, Green = Equioxx® paste, Blue = Previcox®*



firocoxib, a bench top in vitro analysis was performed to determine whether or not firocoxib was capable of binding to plastic tubes (especially important for sample collection and storage). To do this, whole blood (6 mL) was collected from a horse and transferred into a heparin glass containers (BD Vacutainer, Sodium Heparin, BD, Franklin Lakes, NJ, USA). Plasma was separated by centrifugation at 1,900 g (3,000 rpm) for 30 min at room temperature, and then transferred to either a glass or plastic disposable culture tubes and spiked with firocoxib standard at 50, 1,000 and 10,000 ng/mL to test the binding of the drug to the storage vial. Plasma samples were allowed to sit 60 hours inside of refrigerator (4 °C) and then tested under the same sample preparation procedure and HPLC chromatographic conditions previously described. From this analysis, the area under the curve (AUC) from time 0 (time of firocoxib injection into plasma) to 60 hours (time of completion of in vitro study) of firocoxib was determined for both glass and plastic tubes.

In the second phase of this study, plasma samples were collected from private practice veterinarians who were currently prescribing firocoxib as the canine preparation. Samples were admitted into the study as long as the horse had been on a maintenance dose of firocoxib (0.1 mg/kg once daily by mouth) for a period of 3 to 5 days, and were not concurrently on any other medications at the time of the sample collection. Along with the sample for submission, veterinarians were asked to record the horse's age, breed, collection time, time of last dose, reason for treatment, and perceived response. Whole blood samples (10 mls) were collected from the external jugular vein at either a peak (2 hours post dose) or trough (prior to the next dose). Once returning to the clinic, the whole blood was separated into its components and the plasma achieved was frozen for transport to the Auburn University Clinical Pharmacology laboratory for the samples to be evaluated with HPLC as described above. A total of 42 samples were evaluated from the submitting practices. Combining the therapeutic levels achieved from these samples with the veterinarians submitting information (indicating reason for treatment, clinical response, or adverse events), authors were able to quantify firocoxib levels plasma levels and compare them to therapeutic

Table 1. *Mean pharmacokinetic parameters for firocoxib when administered as either canine chews or equine paste in apparently healthy horses (n=8). Significant differences could not be detected for any parameters between paste and chews. C0 = maximum plasma drug concentration after IV administration; Cmax =maximum plasma drug concentration; AUC = area under the curve; t1/2 = elimination half life; CL = clearance; MRT = mean resonance time, MAT = mean absorption time; F = bioavailability, Relative F (paste vs. chews)*

Parameter	Route	Mean	SE	Lower CI	Upper CI
AUC (ng/ml/ hr)	IV	8028	3856	4172	11884
	Chew	8686	2498	6187	11184
	Paste	8898	2254	6645	11152
C_0 (ng/ml)	IV	268	58	210	326
C_{max} (ng/ml)	Chew	135	17	117	152
	Paste	143	21	122	165
t1/2 (hours)	IV	61	42	19	102
	Chew	49	11	38	59
	Paste	58	19	40	77
MRT	IV	87	56	31	143
	Chew	70	12	58	83
	Paste	85	26	59	111
MAT	Chew	13	13	-11	37
	Paste	24	14	-2	50
Tmax (hours)	Chew	4	1	-2	10
	Paste	2	1	-4	8
CL (hours)	IV	47	6	40	53
F	Chews	91%	27%	64%	118%
	Paste	90%	24%	66%	114%
Relative F		108%	35%	73%	143%

response.

STATISTACAL ANALYSIS

Plasma firocoxib concentration versus time data (both in vitro and in vivo) samples were subjected to non-compartmental analysis (Phoenix Winnonlin,® Pharsight,® Sunnyvale, CA, USA) using the log-linear trapezoidal method. Parameters of interest included AUC (ng*hr/ml), Cmax (oral, mcg/ml) at time (Tmax;h); t1/2 (h); mean residence time (MRT; h), mean absorption time (MAT [h] where MAT = MRT_{oral} – MRT_{IV}), and absolute (AUC_{oral}/AUC_{IV}) and relative ($AUC_{oral\ paste}$/$AUC_{oral\ chews}$) bioavailability. For in vitro samples, only AUC were determined. Descriptive statistics (mean + standard error of the mean and 95th upper and lower confidence intervals) were generated for each parameter. Parameters were compared between oral paste and chew using Proc GLM (SAS/IML 9.1, User's Guide: statistics, Cary, NC) using Tukey's test for multiple comparison for repeated measures. A one way ANOVA was used to compare differences in the firocoxib plasma levels between sample collection groups.

Table 2. *Percent difference between firocoxib concentration after being stored in either a glass or plastic tubes for 60 hours.*

	Glass Tubes	Plastic Tubes	AUC (ng/ml/hr) (Difference)	
Firocoxib Concentration ng/mL	**AUC**	**AUC**	**Glass vs. Plastic**	**Percent Difference**
50	21151	16654	-4497	21.26%
1000	515677	303324	-212353	41.18%
10000	5218493	2585592	-2632901	50.45%

Significance was considered at $P<0.05$.

RESULTS

During the time course of the pharmacokinetic study, no animals appeared to experience any adverse events. Further, physical examinations and clinical laboratory blood work did not statistically differ and were within clinical reference ranges.

Pharmacokinetic parameters for each preparation are listed in (Table 1, Fig 1). Relevant parameters with corresponding standard errors were: C0 (ng/ml): 268 ± 58; Cmax (ng/ml): 143 ± 21 (paste); 135 ± 17 (chew); t1/2 (hr): 58 ± 19 (paste), 49 ± 11 (chew); 61 ± 42 (IV); AUC (ng/ml/hr): 8898 ± 2254 (paste); 8686 ± 2498 (chew); 8028 ± 3856 (IV). The absolute bioavailability (F) of firocoxib was 90% ± 24% (paste) vs 91% ± 27% (chew). Relative bioavailability for paste vs. chews was 108% ± 35%, indicating unity of absorption between the two products. This study failed to find statistically significant differences in Cmax and absolute oral bioavailability at a power of greater than or equal to 90%.

For the in vitro study, the AUC in plastic tubes was less than the AUC in glass tubes. The percent difference for firocoxib AUC for 50, 1,000, and 10,000 ng/mL were 21.26%, 41.18%, and 50.45% respectively (Table 2). From this methodology, we were able to determine the necessity that the samples be collected and stored within glass tubes.

A total of 42 samples were evaluated from submitting private practices. Of the samples being submitted, all samples were evaluated from patients receiving the canine formulation of firocoxib. Of the submitting horses, ages ranged from 5-26 years of age (mean = 14. 2 years, +/- 5.5 years). Breeds represented in the sample pool included:

- Domestic warm blood (n= 19)
- Thoroughbred (n= 12)
- Quarter Horse (n= 4)
- Irish Sport Horse (n= 2)
- Standard Bred (n=1)
- Irish Draft (n=1)
- Arabian (n=1)
- Morgan (n=1) andWelsh cross (n=1)
- Quarter Horse/Thoroughbred (n=1)
- Thoroughbred/Warm Blood (n=1).

Sample collection times were broken down into three different groups: peak (0-2 hours post- dose administration) n=7, mid dosing period (3-21 hours) n=28, and trough concentration (22-26 hours) n = 9.

Firocoxib concentrations for the peak dosing group were 65.16 ± 32.35 ng/ml; mid dosing 80.26 ± 54.65, and 60.38 ± 27.39 ng/ml. A statistical difference of firocoxib drug concentrations between the treatment groups could not be detected. The reason for treatment were broken down into soft tissue (n=12), musculoskeletal (n=15), and generalized lameness (n=17). A favorable response to treatment was recorded in (n=35) and unknown in (n= 9).

DISCUSSION

Although this study may have established equivalent bioavailability between the two products, this study is not intended to sup-

port such extra label drug use. Indeed, other considerations should be taken when using canine chews in horses. Accordingly, the veterinarian prescribing or administering canine chews to horses in lieu of an equine formulation is placing him or herself in a position to be held both criminally and civilly liable for such use. Although this study may have established bioequivalence when an equal mg/kg dose is administered, the canine preparation may not allow for the same level of dosing accuracy that the equine paste presents. Thus, for a small horse (miniature, foal, pony), an accurate dose can be metered out from the paste tube, but the smallest tablet size of the canine chew is 57 mg. The tablets are only half scored, and the risk of unequal distribution of drug within a tablet may prevent an equivalent dose from being administered should a fraction of a tablet be administered. Thus, extra precaution is recommended when smaller horses are being dosed.

The heme containing COX enzyme plays an important role in the production of prostaglandins and thromboxane molecules that are responsible for the maintenance of normal physiology of multiple organ systems, including inflammation, hemostasis, joint heath, renal function, and the gastrointestinal system. As such, nonselective inhibition of the COX isoenzymes results in a narrow therapeutic window for these traditional drugs. Not surprisingly, their use is associated with serious adverse events, including gastrointestinal ulceration (both gastric and right dorsal colitis), renal and hepatic toxicity (dogs), and prolonged bleeding times.[1,3,5]

Although long-term use of firocoxib in horses at the recommended dose has not yet been effectively assessed, the Adverse Event Reporting site at the Food and Drug Administration's Center for Veterinary Medicine indicates that oral ulcerations is the 3rd most common adverse event thus far reported.[11] However, animal safety studies performed in horses during the equine formulations approval process demonstrated that a 3- to 5-fold dose increase was associated with ulceration of the oral gingiva and stomach, pathology associated with the kidneys (tubulointerstitial nephropathy and papillary necrosis), and elevations in liver enzymes.

The chemical structure of firocoxib (a weak acid) facilitates efficient absorption from the gastrointestinal tract at the level of the stomach. In the horse, firocoxib administered as the paste has an absolute bioavailability of 79%, due to low first pass metabolism (via dealkylation and glucuronidation).[12] In contrast, bioavailability of the drug in the dog based on the package insert is cited at 38%.[13] It is not clear if the differences between bioavailability between the species are due to the active ingredient's activity in the different gastrointestinal systems or differences in the preparation itself (ie, chew tablet versus paste).

Once in circulation, firocoxib is highly protein bound (98%) to albumin. Despite this high protein binding in horses, the unbound drug is characterized by a large volume of distribution, which contributes to a long t1/2 (30 to 40 hours) in horses.[12] The half-life in horses is 3 to -10x longer than the t1/2 reported for other non-selective NSAIDs currently used to control pain in horses (eg, phenylbutazone, flunixin meglumine, naproxen).[1,14]

In contrast to horses, the elimination half-life of firocoxib in dogs is only 8 hours. The longer half- life in horses impacts therapeutic use of firocoxib in several ways. First, it allows once a day dosing in horses, facilitating owner compliance, as well as providing longer pain relief. Second, the longer half-live firocoxib results in a 50-fold oral dose differential between the two species: horses are dosed at 0.1 mg/kg/day compared to 5 mg/kg/day in dogs.

It is this 50-fold difference in dose that has led equine practitioners to administer the canine preparation rather than the approved horse product to equine patients. Despite the size difference, the canine preparation is cheaper (approximately 50% more expensive) when dosed in horses.

Third, the longer t1/2 in horses also results in different times to steady-state between the species. In dogs, firocoxib does not reach a true steady-state when using the labeled dosing interval. However, in horses, with a 40-hour half-life, drug concentrations in horses will minimally fluctuate during a 24-hour dosing interval. Further, because little drug is eliminated during each interval, drug will accumulate with each subsequent dose until steady-state is reached. Thus, the full effect of the drug in horses will not be realized until 3 to 5 drug half-lives – or approximately 5 to 7 days – have lapsed once a dosing regimen is implemented. This delay to steady-state necessitates a loading dose (0.3 mg/kg) in horses if a rapid onset in effect is desired. By administering an initial loading dose, the patient reaches therapeutic drug levels after the first dose and a clinical response is appreciated within the first 24 hours of treatment.

The Federation Equestre Internationale (FEI) has listed firocoxib as a controlled medication for equine competitors. Firocoxib is commonly administered prior to sanctioned athletic competitions and as such, studies at that loading dose are prudent. Among the more important reasons to study firocoxib after IV administration of a loading dose is the United States Equestrian Federation has established that maximum permitted plasma concentration of firocoxib be less than 0.240 µg/ml at competition time.[15] Compared to this standard, when firocoxib is administered at the manufacturer's recommended loading dose, drug levels were below the standard of limitations 30 minutes to an hour after IV administration. After an oral loading dose, neither preparation (paste or chew) achieved levels higher than USEF standards at any time point after the administration of medication.

In horses, NSAIDs are generally well absorbed from the gastrointestinal tract through oral dosing. However, we were concerned that firocoxib would be less bioavailable when administered as the chew compared to the paste for two reasons.

First, in herbivores, and specifically horses, oral medication may bind to hay or other ingesta, thus affecting oral absorption and the ability of the drug to reach effective levels.

Second, studies have demonstrated variable oral absorption of NSAIDs in horses, depending on the formulation used. For example, after administration of ketoprofen in an oil-based formulation, bioavailability in horses was <5%. When the formulation was changed to a gelatin capsule, bioavailability increased to 50%.[16] A major difference between the paste and the chew are the inactive ingredients; these could negatively impact oral absorption thus increasing potential for therapeutic failure, or increased absorption, which would increase potential for an adverse event.

This study confirmed that despite the different formulations available for firocoxib, once administered at the same mg/kg dose, they are similarly bioavailable, and based on the clinical samples collected, are capable of controlling both soft tissue and orthopedic pain.

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DISCLOSURE OF STATEMENT

Authors do not have any conflicts of interest.

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