Pharmacokinetics of firocoxib after administration of multiple consecutive daily doses to horses

Laura T. Letendre, PhD; Ronald K. Tessman, DVM, PhD; Scott R. McClure, DVM, PhD; Valerie J. Kvaternick, MS; James B. Fischer, PhD; Peter D. Hanson, DVM, PhD

Objective—To determine pharmacokinetic parameters and variables, firocoxib concentrations in urine and plasma, urine-to-plasma ratios, and the urine depletion profile of firocoxib and to evaluate whether the pharmacokinetic behavior of firocoxib was governed by linear processes after multiple doses of firocoxib were administered IV and orally.

Animals—6 healthy female horses (5 Paint horses and 1 Quarter Horse) in experiment 1 and 12 healthy male and female horses in experiment 2.

Procedures—in experiment 1, 6 horses were orally administered firocoxib paste once daily for 12 consecutive days, and plasma and urine samples were obtained and analyzed. In a second experiment, 12 horses received IV injections of firocoxib solution once daily for 9 consecutive days, and plasma was obtained and analyzed.

Results—Mean ± SD clearance and steady-state volume of distribution of firocoxib were 40.5 ± 14.7 mL/h/kg and 2.3 ± 0.7 L/kg, respectively. Mean half-life was 44.2 ± 21.6 hours and 36.5 ± 9.5 hours for IV and oral administration, respectively. The urine concentration–time curve decreased in parallel with the plasma concentration–versus-time curve. Renal clearance (0.26 ± 0.09 mL/kg/h) was low, compared with total body clearance, which indicated that the main route of elimination was hepatic clearance.

Conclusions and Clinical Relevance—The pharmacokinetics of firocoxib during prolonged use were determined. Use of plasma or urine to ascertain drug concentrations in horses is scientifically valid because the plasma-to-urine ratio was consistent over time and among horses. (Am J Vet Res 2008;69:1399–1405)

Firocoxib, 3-(cyclopropylmethoxy)-4-(4-(methylsulfonyl)phenyl)-5,5-dimethylfuranone, is a coxib-class NSAID approved for use in horses to control pain and inflammation associated with osteoarthritis. In general, NSAIDs are indiscriminate inhibitors of COX, an enzyme involved in the synthesis of prostaglandins that has at least 2 major isoforms, COX-1 and COX-2. In contrast, coxib-class drugs selectively inhibit the COX-2 isozyme. Inhibition of the COX-2 isozyme prevents the production of prostaglandins that function primarily as inflammatory mediators; this inhibition leads to the therapeutic effects of NSAIDs. However, inhibition of COX-1 may lead to undesirable effects, such as gastric irritation and blood thinning, because COX-1 is involved in processes designed to protect gastric and renal function (such as mucosal blood flow) and it aids in hemostasis. Development of the new coxib-class NSAIDs began in the 1990s after the discovery of a mitogen-inducible form of COX (also known as prostaglandin G/H synthase). Two groups of researchers each discovered that this second COX gene, on the basis of its pattern of regulation and expression, appeared to be the sole isozyme that produced prostaglandins responsible for potentiating inflammatory processes. The recognition that inhibition of COX-2 may be sufficient to achieve the anti-inflammatory benefits of NSAIDs and that the adverse effects commonly associated with NSAIDs were attributable, at least in part, to the indiscriminate inhibition of COX-1 resulted in the development of new drugs that would selectively inhibit COX-2. This class of drugs (ie, coxibs), which includes firocoxib, has now evolved to second-generation drugs that are highly selective for COX-2, thus sparing COX-1 at therapeutic concentrations and po-

Received September 11, 2007.
Accepted March 5, 2008.
From Merial Ltd, 3239 Satellite Blvd, Duluth, GA 30096 (Letendre, Tessman, Kvaternick, Fischer, Hanson); and the Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Iowa State University, Ames, IA 50011 (McClure).
The authors thank Dr. Marlene Drag, Dr. Diane Larsen, Dr. Bruce Kunkle, Thomas Malinski, and Jill Wortmann for assistance.
Address correspondence to Dr. Letendre.
temporarily reducing the incidence of adverse effects associated with COX-1 inhibition, such as gastrointestinal irritation. 

This hypothesis was supported by studies involving laboratory animals with experimentally induced disease and by human clinical trials in which the gastrointestinal toxicity of coxibs and traditional NSAIDs were compared. It has also been suggested that inhibition of both COX-1 and COX-2, and not inhibition of COX-1 alone, is required to cause gastric irritation and damage. It is inferred from the outcomes of these studies that there will be substantially fewer clinically important gastrointestinal events in horses.

On the other hand, when there are preexisting conditions (such as ulcers), the use of COX-2-selective inhibitors may not be as advantageous. Studies have indicated a protective or housekeeping function of COX-2 with regard to the healing process of ulcers. Suppression of this constitutive COX-2 expression by selective inhibitors may delay gastric healing via reductions in gastric blood flow and suppression of the mucosal production of prostaglandin E
.

Additionally, constitutive expression of COX-2 has also been identified in a variety of noninflammatory tissues, such as the kidneys and bones. A third COX isozyme (ie, COX-3), which is derived from the COX-1 gene and found mainly in the cerebral cortex, is also inhibited by some NSAIDs and may represent another mode of action, although COX activity of this isozyme is evident only after N-linked glycosylation.

The metabolism and pharmacokinetics of firocoxib after administration of a single dose to horses have been reported. Similar to most NSAIDs, firocoxib is rapidly and nearly completely absorbed after oral administration in horses. Total body clearance in horses is relatively low and similar in magnitude to that for other NSAIDs, such as meloxicam, flunixin meglumine, phenylbutazone, and tolfenamic acid.

The main elimination pathway is hepatic via dealkylation and glucuronidation of firocoxib; hydroxylation is a minor metabolic pathway. Both the parent drug and metabolites have been detected in the urine. Firocoxib is widely distributed in tissues, partially as a result of its physicochemical properties, such as high lipophilicity and low ionizability at physiologic pH. The volume of distribution is much higher than that for many NSAIDs, which results in a mean ± SD of 33.8 ± 11.2 hours after IV administration that is longer than the value determined for other NSAIDs. Protein binding is generally high for NSAIDs, and > 97% of firocoxib is bound to plasma proteins at concentrations up to 1.0 mg/mL. Dose proportionality of pharmacokinetic variables was established over the range of 0.5 to 2 times the recommended dosage of 0.1 mg/kg. Because of the high potency and long half-life, once-daily administration is sufficient for prolonged treatment of animals with chronic pain and inflammation. Single-dose pharmacokinetic parameters and variables have been determined.

Associations that govern equine performance and racing events have differing rules regarding the use of NSAIDs preceding competition. Humane consideration of athletic horses requires medical treatment for injury or illness on the basis that persistent untreated pain can lead to hormonal, nervous, and psychologic abnormalities in animals. To allow for treatment of horses prior to racing or performance events, withdrawal periods or allowable drug concentrations for each regulated drug may be set by the various associations, although in some equine sports (such as endurance racing), no detectable concentrations of a drug are allowed. As part of this drug-monitoring process, analytic methods must be available to determine drug concentrations in plasma and urine. Because analytic methods are often highly sensitive, physiologically relevant concentrations of NSAIDs must be determined to set threshold drug concentrations in plasma and urine that are to be used for drug monitoring, instead of relying on the detection limits of the analytic methods. Because urine may be easier to obtain than plasma, it is important to determine the relationship between drug concentrations in urine and plasma after a single dose and at a steady state. One of the objectives of the study reported here was to gain an understanding of the pharmacokinetics after administration of multiple doses of firocoxib in horses by expressing plasma and urine concentrations of firocoxib. We also wanted to determine whether plasma concentrations after administration of multiple doses could be predicted from single-dose pharmacokinetic parameters and whether the pharmacokinetic behavior was governed via first-order processes at a steady state.

**Materials and Methods**

**Animals**—Eighteen horses were used in 2 experiments. For experiment 1, 6 nonpregnant female horses (5 Paint horses and 1 Quarter Horse) between 2 and 4 years of age and weighing between 445 and 505 kg were used. Each horse was housed separately in a stall in an environmentally controlled building. Horses were fed oats and alfalfa hay twice daily, and tap water was available ad libitum. For experiment 2, 12 healthy male and female horses (predominantly Quarter Horse breed) > 2 years old and weighing between 373 and 447 kg were used. These horses were housed on pasture, except they were housed separately in pens for treatments and blood collections. Horses were fed commercial feed and grass hay twice daily, and tap water was available ad libitum.

All horses were acclimated to their surroundings for at least 7 days prior to initiation of the experiments. No concurrent medications were administered during the course of the study. Horses were cared for in compliance with procedures approved by the Merial Institutional Animal Care and Use Committee and were observed at least once daily to monitor for health problems.

**Study design**—The study consisted of 2 experiments. The first experiment involved oral administration of firocoxib. Each of the 6 horses was orally administered firocoxib (0.1 mg/kg) as a 0.82% (wt/wt) paste once daily for 12 consecutive days. First day of firocoxib administration was designated as day 0. Firocoxib was administered before the morning feeding. Forage and oats were withheld until after paste administration to ensure no complications because of
feed boluses remaining in a horse’s mouth. No further restrictions on feeding were applied before or after administration. Blood samples (approx 10 mL) were collected from a jugular vein of each horse into heparinized tubes. On days 0 and 11, blood samples were collected before and 0.25, 1, 2, 4, 6, 12, and 24 hours after the firocoxib treatment. Blood samples were also collected on days 1 through 10 before each daily treatment. Samples were collected immediately before firocoxib treatment on days 7, 8, and 11 to confirm that steady state was achieved. Blood samples were also collected at approximately 32, 48, 72, and 96 hours after administration of the final dose. Plasma was separated from blood samples and stored frozen at approximately –80°C until analysis.

Urine samples were collected via a urinary catheter inserted aseptically into the bladder and connected to a urine collection bag. The catheter and urine collection bag were maintained throughout the collection period. This allowed for accurate determination of urine volumes while avoiding the necessity for multiple catheterization procedures. Urine samples were collected from each horse before treatment on day 0, for an interval of approximately 2 hours immediately before treatment on days 1, 7, 8, and 11; and over the collection intervals of 1 to 3, 3 to 5, 5 to 7, 11 to 13, 23 to 25, 31 to 33, 47 to 49, 71 to 73, and 93 to 97 hours after the final administration. Plasma samples were obtained at approximately the midpoint of the urine collection intervals. Each urine sample was mixed thoroughly to ensure homogeneity and stored frozen at approximately –80°C until analysis.

For experiment 2, each of the 12 horses received IV administration of firocoxib (0.2 mg/kg) as a 2% (wt/vol) solution. Firocoxib was administered immediately before the morning feeding, and there were no restrictions on feeding prior to or after treatment. Treatments were administered once daily in a jugular vein on days 0 to 8. Blood samples (approx 10 mL) were collected into heparinized tubes from the contralateral jugular vein on days 0, 1, 6, 7, and 8 at approximately 5 and 30 minutes and 1, 2, 4, 6, 8, and 24 hours after treatment and on days 2 through 5 at approximately 24 hours after treatment. Blood samples were also collected at approximately 36, 48, and 120 hours after the final treatment. Plasma was separated from blood samples and stored frozen at approximately –80°C until analysis.

Analytic procedures—Plasma samples obtained from the horses after IV administration were analyzed by use of a validated method30 that involved solid-phase extraction, liquid chromatography, and UV detection, whereas urine and plasma samples obtained from the horses after oral administration were analyzed by use of a liquid chromatography–mass spectrometry–mass spectrometry method.30 At least 2 standard calibration curves ranging from 1 to 3,000 ng/mL (plasma) or 5 to 3,000 ng/mL (urine) for firocoxib extracted in an identical manner to the procedures used for the samples were included with each analytic set. A minimum of 6 quality-control samples at 3 concentrations and 2 control samples of plasma (or urine) were also analyzed with each set. Firocoxib peak areas from the fortified matrix standards were used to generate a 1/x weighted regression for calculating the quality-control and unknown concentrations of firocoxib in plasma or urine samples.

Pharmacokinetic analysis—Results from single-dose experiments were used for comparison and prediction of multiple-dose concentrations and are described elsewhere.21 Pharmacokinetic parameters for the multiple-dose experiments were calculated with commercial software by use of a noncompartmental model–independent method. The Cmax, time to Cmax, and Cmin for each dosing interval were obtained directly from the plasma concentration data. The value for λz was estimated via linear regression of the logarithmic plasma concentration–versus-time curve. The plasma τ1/2 was calculated by (ln 2)/λz. The notation AUC(n, τ) indicated that the AUC was calculated over the nth dosing interval from time 0 (ie, time of administration of the nth dose) to the time τ after dose n (τ = 24 hours). The AUCs were calculated by use of the linear-logarithmic trapezoidal method. Mean concentration at steady state after oral administration of multiple doses was calculated by use of (AUC[n, τ])/τ, where n equals 12 corresponds to the last dose. The theoretic accumulation index based on linear pharmacokinetics was calculated by use of the equation (1 – exp[–λz • τ])/τ, where exp is the exponential function, and the value for λz was obtained from a single-dose study. For oral administration of multiple doses, the experimental accumulation index was determined by use of the equation (AUC[12, τ])/AUCC[1, τ], where 12 and 1 corresponded to the last dose and first dose, respectively. In the experience of one of the investigators (VJK), the plasma concentration–time curves were highly variable during the absorption phase for the first 4 hours after oral administration of a single dose of firocoxib. The shape of the plasma concentration–time curves also varied greatly among animals. For these reasons, use of a compartmental model that would adequately fit the profile of all of the horses while making assumptions about absorption kinetics was not practical. Therefore, a nonparametric superposition of plasma concentrations after oral administration of a single dose was chosen to predict the plasma concentrations after oral administration of multiple doses. A superposition for the plasma concentration–time curve of each animal in the single-dose study21 was performed, and the predicted multiple-dose curves were then averaged. For each horse, the predicted curve was calculated by use of the following equation:

\[ Y(t) = \sum_{j=1}^{12} (D_j/D) \times Y(t - [j \times t]) \text{ for } j = 1 \text{ to } 12 \]

where t is the time since the first dose, Dj is dose j, D is the first dose, t is time, τ is 24 hours, and Y(t – [j • τ]) = 0 for t ≤ τ.

To simulate the data after IV administration of multiple doses, an equation was obtained from fitting the plasma concentrations after a single dose administered IV by use of an open 3-compartment model with bolus IV input. The 3-compartment model was defined by use of the following triexponential equation:

\[ Y(t) = (Y_1 \times e^{-\lambda_1 t}) + (Y_2 \times e^{-\lambda_2 t}) + (Y_3 \times e^{-\lambda_3 t}) \]
where $Y(t)$ is the predicted concentration at time $t$; $Y_0$, $Y_1$, and $Y_2$ are preexponential coefficients; and $\lambda_1$, $\lambda_2$, and $\lambda_3$ are the first, second, and third phases of the decay of plasma concentrations, respectively. The equation was used to simulate the plasma concentration-versus-time curve after 9 consecutive daily doses (0.2 mg/kg, IV) of firocoxib to horses.

The amount of firocoxib in each urine sample was determined by multiplying the measured concentration by the total volume collected. Excretion rate was the amount of firocoxib in each urine sample divided by the collection interval (approx 2 hours). Renal clearance was then determined for each steady-state urine sample by dividing the excretion rate by the plasma concentration determined at the midpoint of the collection interval. Renal clearance was standardized on the basis of the body weight of the horse and averaged over each time point for that horse.

### Statistical analysis

Arithmetic means and SDs were determined. Data were analyzed for a normal distribution, and a paired Student $t$ test was then performed with commercial statistical software to compare trough plasma concentrations at steady state. Mean and SD of the $t_{max}$ in plasma, Cmax, time to Cmax, Cmin, mean concentration at steady state, AUC($n$, $\tau$) for the first dose and at steady state, experimental accumulation index, renal and total clearance, volume of distribution, urine-to-plasma ratio, and half-life in urine were determined.

### Results

**Animals**—All horses appeared to be healthy during the course of the study, and no treatment-related health problems were evident. There were no circumstances that adversely affected the quality or integrity of the data.

**Oral administration**—Limit of detection of the analytic method was 1 ng/mL in equine urine and 0.25 ng/mL in equine plasma. The LOQ of the analytic method was 5 ng/mL in equine urine and 1 ng/mL in equine plasma. Plasma quality-control samples at concentrations of 3, 250, and 2,500 ng/mL were included with each set; mean accuracy was between 91% and 103% (6 replicates), and coefficients of variation were $\leq 9.5\%$. Concentrations in all plasma samples were higher than the LOQ at all sampling times and ranged from 2.8 to 217 ng/mL. Mean accuracy for urine quality-control samples was between 90% and 102% (4 replicates), and coefficients of variation were $\leq 11\%$. Concentrations in urine samples were higher than the LOQ for all samples (range, 6 to 67 ng/mL), except for a single sample collected at 96 hours after administration of the final dose. The $R^2$ of each standard curve was $>0.99$, and the accuracy of each standard was between 83% and 115%.

### IV administration

The limit of detection and LOQ of the analytic method were 10 ng/mL and 25 ng/mL, respectively. Concentrations in plasma samples ranged from 41 to 677 ng/mL, except for a few samples that had concentrations less than the LOQ of the analytic method. Several quality-control samples (concentrations of 50 or 100 ng/mL) were included with each set. Accuracy of plasma quality-control samples ranged between 85% and 110%, and coefficients of variation were $<10\%$. The $R^2$ of each standard curve was $>0.99$.

### Pharmacokinetics

The plasma pharmacokinetic parameters from the multiple-dose experiments conducted here and single-dose experiments reported elsewhere were summarized (Table 1). A semilogarithmic plot was generated of the mean plasma concentration-versus-time and urine concentration-versus-time curves after oral administration of 12 consecutive daily doses (Figure 1). Steady state was achieved by the seventh daily dose, as predicted for consecutive daily oral administration of a drug with a mean SD single-dose plasma $t_{max}$ of 29.0 $\pm$ 7.5 hours. Plasma trough concentrations did not differ significantly ($P > 0.05$) in samples

---

**Table 1**—Mean $\pm$ SD values for pharmacokinetic parameters for a single dose of firocoxib administered to horses in another study, multiple doses of firocoxib (0.2 mg/kg) administered IV daily to 12 horses for 9 consecutive days in the study reported here, and multiple doses of firocoxib (0.1 mg/kg) administered orally daily to 6 horses for 12 consecutive days in the study reported here.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Single dose*</th>
<th>Multiple dose IV</th>
<th>Multiple dose orally</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IV Oral</td>
<td>After first dose</td>
<td>After last dose</td>
</tr>
<tr>
<td>$t_{max}$ (h)</td>
<td>33.8 $\pm$ 11.2</td>
<td>29.6 $\pm$ 7.5</td>
<td>ND 44.2 $\pm$ 21.6</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>229 $\pm$ 65</td>
<td>3.90 $\pm$ 4.40</td>
<td>NA 523 $\pm$ 126</td>
</tr>
<tr>
<td>Cmin (ng/mL)</td>
<td>75.0 $\pm$ 33.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>$C_{max}$ (ng/mL)</td>
<td>55.4 $\pm$ 9.3</td>
<td>181.0 $\pm$ 74.0</td>
<td>NA 229 $\pm$ 73</td>
</tr>
<tr>
<td>AUC(n, $\tau$) (ng.h/mL)</td>
<td>1.22 $\pm$ 0.26</td>
<td>0.96 $\pm$ 0.26</td>
<td>2.00 $\pm$ 0.30</td>
</tr>
<tr>
<td>Accumulation index</td>
<td>NA</td>
<td>2.8 $\pm$ 1.11</td>
<td>NA 0.63 $\pm$ 0.17</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>79 $\pm$ 31</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Clearance($t_{max}$) (mL/h/kg)</td>
<td>367 $\pm$ 13.3</td>
<td>—</td>
<td>40.5 $\pm$ 14.7</td>
</tr>
<tr>
<td>$V_d$ (L/kg)</td>
<td>1.7 $\pm$ 0.4</td>
<td>—</td>
<td>2.3 $\pm$ 0.7</td>
</tr>
</tbody>
</table>

*Values determined in another study; $^2$ except for $V_d$ and $C_{max}$, which were calculated from unpublished experiments performed at Merial Ltd by TLT. $^3$ Mean $\pm$ SD expected accumulation index (assuming linear kinetics) is 2.7 $\pm$ 0.6.

$\tau$ = Time to $C_{max}$. $C_{max}$ = Initial concentration extrapolated back to time 0 for a dose administered IV. $C_{max}$ = Mean plasma concentration over the dosing interval at steady state. AUC(n, $\tau$) = The AUC calculated by use of the linear-logarithmic trapezoidal method calculated over the nth dosing interval from time 0 (i.e., time of administration of the nth dose) to the time $\tau$ after dose $n$ ($\tau$ = 24 hours) the AUC at steady state after administration on day 0 ($n$ = 1) or day 11 ($n$ = 12). Accumulation index was determined at steady state by use of the equation [AUC(12, τ)/AUC(1, τ)], where 12 and 1 corresponded to the last dose and first dose, respectively. Clearance($t_{max}$) = Total body clearance estimated at steady state. $V_d$ = Volume of distribution at steady state. NA = Not applicable. ND = Not determined. — = Not reported.
obtained immediately before dosing on days 7, 8, and 11 of the experiment, which confirmed that a steady state had been reached by day 7. Mean plasma Cmin at steady state was 104 ± 33 ng/mL.

Mean ± SD plasma Cmax was 45.0 ± 11.3 ng/mL, which was reached 7.80 ± 4.80 hours after the first oral administration. Absorption was slow after the first orally administered dose (Cmax of 173 ± 44 ng/mL was reached 0.79 ± 0.70 hours after administration), compared with absorption after the last dose. Mean plasma t½, after the final dose was 36.5 ± 9.5 hours.

Mean ± SD plasma AUC values for the first (AUC(1, t)) and last (AUC(12, t)) oral dosing interval were 0.83 ± 0.17 (h·µg)/mL and 3.12 ± 0.86 (h·µg)/mL, respectively, which led to a mean accumulation index of 3.8 ± 0.7. This ratio was slightly higher than the ratio of 2.70 ± 0.60 predicted by use of the plasma t½ for single-dose oral administration.21 Mean plasma concentration of firocoxib at steady state was 130 ± 36 ng/mL. A simulated plasma concentration-versus-time curve for oral administration of multiple doses was generated by use of data from the nonparametric superposition of the single-dose oral administration data reported elsewhere21 (Figure 2). There was good agreement between simulated and actual steady-state concentrations, which indicated linear pharmacokinetic behavior.

The firocoxib concentration in urine samples decreased in parallel to the firocoxib concentrations in the plasma samples. Maximum concentrations in urine were detected during the first 1 to 3 hours after the final dose. Concentrations in urine then decreased exponentially and in parallel to concentrations in plasma, with a mean ± SD t½ of 35.3 ± 7.8 hours after the final dose. The concentration of firocoxib in urine was less than that in plasma, and the ratio of the concentration in urine to the concentration in plasma was approximately 0.35 at all time points. Mean renal clearance was 0.26 ± 0.09 mL/kg/h.

Plasma pharmacokinetic parameters were also determined for horses receiving 9 consecutive doses of a firocoxib solution IV. Mean ± SD AUC(1, t) was 2.0 ± 0.3 (h·µg)/mL, and mean AUC(9, t) was 5.5 ± 1.7 (h·µg)/mL. This led to an accumulation index of 2.8 ± 1.1, which was comparable to the predicted accumulation index of 2.70 ± 0.60. The mean AUC(9, t) was also comparable to the AUC(0 to infinity) after a single dose was administered IV (2.98 ± 0.80 [h·µg]/mL for a dose of 0.1 mg/kg),21 which indicated that clearance was not changed after multiple doses. Mean concentration at steady state was 228 ± 72 ng/mL, and mean plasma t½ after the final dose was 32.0 ± 14.1 hours. Steady-state clearance (40.5 ± 14.7 mL/h/kg) and volume of distribution (2.3 ± 0.7 L/kg) were comparable to those calculated after administration of a single dose.

Curves generated after IV administration of a single dose in another study21 were plotted, and the parameters calculated were used to simulate the plasma
Accumulation of a drug in plasma after multiple doses depends on both the half-life and the dosing interval. When the pharmacokinetic behavior of the drug is linear after multiple doses and the half-life is known, plasma concentrations at any time during the dosing regimen as well as the accumulation can be predicted accurately. The accumulation index relates the amount of drug in the plasma at any time after steady state is reached to the corresponding values after a single dose. Mean ± SD expected accumulation index of firocoxib in plasma for this dosing regimen was 2.7 ± 0.6, and the observed accumulation index after oral administration was 3.8 ± 0.7. The accumulation index was higher than expected, but it was not because of nonlinearity of the processes governing the clearance mechanisms or distribution behavior of firocoxib, as indicated by the good agreement of the theoretic and experimental accumulation ratios after IV administration and the good correlation between the experimental and simulated plasma concentration–time curves after IV administration of multiple doses (Figure 3). The higher-than-expected accumulation ratio was more likely attributable to a difference in the extent or rate of absorption between the first and last dose (the predicted curve was increased by 1 SD to account for the increased accumulation ratio). The time to Cmax was 7.80 ± 4.80 hours after the first dose, but it was 0.79 ± 0.70 hours after the last dose. The more rapid or more complete absorption resulted in a greater amount of drug absorbed during the last 24-hour period than after the first dose and a higher accumulation ratio than predicted on the basis of the t1/2. The reason for the increased rate or extent of absorption of the last dose was not determined in the study reported here. One possibility is a difference in the feeding time relative to administration of the paste. Differences in mean absorption time with changes in feeding conditions for horses have been reported for NSAIDs and are attributed to a delay in absorption because of binding of the drug to cellulose in the feed. Food was not withheld from horses in the study to more accurately replicate actual use of firocoxib in field conditions. The extent of absorption could also have been influenced by a saturation of first-pass metabolism. Despite the differences in absorption during the first and last period, the plasma t1/2 after discontinuation of daily dosing was comparable to that after IV administration of a single dose and therefore was not influenced by continued absorption.

Concentration-versus-time curve after daily administration of multiple doses (Figure 3). There was good agreement between simulated and experimental data after both IV and oral administration.

**Discussion**

Although plasma concentrations may not be representative of tissue concentrations for all drugs, a correlation between the 2 compartments is believed to exist for NSAIDs. On the basis of in vitro experiments, the concentration of firocoxib that inhibits 50% of COX-2 activity (determined in equine whole blood incubated with lipopolysaccharide to induce COX-2) is approximately 30 ng/mL with a corresponding concentration of firocoxib that inhibits 80% of COX-2 activity of 67 ng/mL. Plasma concentrations were < 30 ng/mL by 96 hours after the final dose of firocoxib administered orally during a steady state. Plasma concentrations exceeded 67 ng/mL at steady state and decreased to less than that concentration by 72 hours after the final dose of firocoxib administered orally during a steady state.

Concentrations of firocoxib in plasma and urine samples obtained from horses are predictable after single-dose or multiple-dose administration. Use of plasma or urine to ascertain drug concentrations in horses is scientifically valid and robust because the plasma-to-urine ratio is stable over time and among animals. The pharmacokinetic behavior of firocoxib was linear after multiple doses administered IV and orally.

---

**References**


7. Kujuba DA, Fletcher BS, Varnum BC, et al. T150, a phorbol ester tumor promoter-inducible mRNA from Swiss 3T3 cells, encodes a novel prostaglandin synthase/cyclooxygenase homo-

8. Stichtenoth DO, Fredich JC. The second generation of COX-


11. Forsyth SF, Guilford WG, Lawoko CRO. Endoscopic evalu-


