

Pharmacokinetics of meloxicam in plasma and urine of horses

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Objective—To determine pharmacokinetic parameters for meloxicam, a nonsteroidal anti-inflammatory drug, in horses.

Animals—8 healthy horses.

Procedure—In the first phase of the study, horses were administered meloxicam once in accordance with a 2 X 2 crossover design (IV or PO drug administration; horses fed or not fed). The second phase used a multiple-dose regimen (daily oral administration of meloxicam for 14 days), with meloxicam administered at the recommended dosage (0.6 mg/kg). Plasma and urine concentrations of meloxicam were measured by use of validated methods with a limit of quantification of 10 ng/mL for plasma and 20 ng/mL for urine.

Results—Plasma clearance was low (mean \pm SD; 34 ± 0.5 mL/kg/h), steady-state volume of distribution was limited (0.12 ± 0.018 L/kg), and terminal half-life was 8.54 ± 3.02 hours. After oral administration, bioavailability was nearly total regardless of feeding status ($98 \pm 12\%$ in fed horses and $85 \pm 19\%$ in nonfed horses). During once-daily administration for 14 days, we did not detect drug accumulation in the plasma. Meloxicam was eliminated via the urine with a urine-to-plasma concentration that ranged from 13 to 18. Concentrations were detected for a relatively short period (3 days) after administration of the final daily dose.

Conclusions and Clinical Relevance—Results of this study support once-daily administration of meloxicam regardless of the feeding status of a horse and suggest a period of at least 3 days before urine concentrations of meloxicam reach concentrations that could be used in drug control programs. (*Am J Vet Res* 2004;65:1542–1547)

Meloxicam is a **nonsteroidal anti-inflammatory drug (NSAID)** intended to be administered IV or PO to horses for the treatment of inflammatory conditions, particularly orthopedic disorders. By use of dose-titration and **pharmacokinetic-pharmacodynamic (PK-PD)** approaches in another study¹ conducted by our laboratory group, a dosage of 0.6 mg/kg was pro-

posed. In that study, only the IV route was tested. Thus, the question of a dosing regimen of meloxicam for the oral route, which is a more convenient means of administration for prolonged treatments, was in order. One of the main advantages of the PK-PD approach is that it is not necessary to conduct new dose-titration or PK-PD experiments for investigating the dosing regimen for a new route of administration. Indeed, in the PK-PD approach, the **median effective concentration (EC₅₀)**, which is the plasma concentration of a drug at half of the maximum effect, is computed as the measurement of drug potency. In contrast to the **median effective dose (ED₅₀)**, which is the dose of a drug at half of the maximum effect, EC₅₀ can be considered as a genuine drug pharmacodynamic parameter.² In other words, for a given endpoint, a single EC₅₀ value exists that is not influenced by pharmacokinetic parameters, route of administration, or formulation. Thus, the PK-PD approach precludes the need for multiple experiments to determine dosing regimens and document a new route of administration or a new formulation. Therefore, only a single new pharmacokinetic study is sufficient to investigate the possible influence of **bioavailability (F)** on drug effects.

For several NSAIDs in horses, F (rate and extent) after oral administration is influenced to a large degree by the feeding status of an animal. Administration of a drug after food has been withheld for a few hours leads to rapid absorption, whereas drug administration during or after a meal may result in sustained and erratic absorption.³ Because efficacy of meloxicam is related to the achieved plasma concentration, the first objective of the study reported here was to determine F of meloxicam in horses for the oral route of administration and qualify the influence of feeding conditions (fed vs not fed) on the rate and extent of meloxicam absorption.

Similar to other NSAIDs, meloxicam is considered a prohibited substance by racing authorities, and horses will be subjected to testing for meloxicam as part of illicit drug control programs. Practical consequences dictate that practitioners need to recommend a withdrawal period between administration of the last dose and the day of racing. Such a withdrawal period depends on many factors, including unknown information such as performance of the analytic technique used by the drug control agency. This precludes that drug companies formally propose a withdrawal time for competition horses, which is in contrast to the situation for withdrawal periods to prevent violative drug residues in edible tissues of food-producing animals. However, a general PK-PD approach has been proposed⁴ for evaluating plasma and urine concentrations of drugs that can be used to assist racing authorities

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when selecting an appropriate range of performance for their analytic techniques. The objective of the study reported here was to determine urine and plasma concentrations of meloxicam and information about the elimination of meloxicam in the urine of horses during once-daily oral administration for a period of 14 days.

Materials and Methods

Animals—Pharmacokinetic investigations were conducted in 8 riding horses (4 geldings and 4 females) that each weighed 350 to 606 kg. The horses were in good health but not in training. During the acclimatization period (2 weeks), the horses were observed to ensure that they were in good general health and blood samples were collected for use in clinical biochemical and hematologic tests. All the investigated variables were within the respective reference ranges. The horses were dewormed by administration of ivermectin^a 1 month before the beginning of the study. The horses were routinely vaccinated (\geq 1 month before the beginning of the study) and did not receive any other drug during the 6 months preceding the study. Horses were housed separately in box stalls bedded with flax^b during the first phase of the study and with wheat straw during the second phase of the study.

Unless otherwise stated, the horses were fed a diet of hay and concentrate.^c Food was provided twice daily at 10 AM and 7 PM. Each feeding consisted of approximately 0.5 kg of concentrate/100 kg and approximately 1 kg of hay. Tap water was provided ad libitum. Animal care and conduct of the study was performed in agreement with the principles of Good Laboratory Practice of the Organization for Economic Co-operation and Development.

Experimental design—The study was conducted in 2 phases. During phase 1, a classical 2 \times 2 crossover design was performed to measure F of meloxicam in nonfed horses. The horses were randomly assigned to 2 groups (each group consisted of 2 geldings and 2 females). Food was withheld overnight, and the following morning, a single dose of meloxicam (0.6 mg/kg) was administered by the IV or oral route. After a washout period of 7 days, the experimental groups were crossed (ie, the group of horses that initially received meloxicam by the oral route now received it via the IV route and vice versa).

After a washout period of 6 weeks, phase 2 was conducted. Eight horses were used, but because of illness unrelated to the study, 2 horses used in the first phase were replaced by 2 other horses. During phase 2, horses received multiple doses of meloxicam (once-daily administration for 14 consecutive days) in accordance with the intended therapeutic use. During phase 2, horses had unlimited access to straw bedding during the night and the morning meal was provided immediately after meloxicam administration.

Drug administration—For IV administration, meloxicam^d was administered at a rate of 0.6 mg/kg via a catheter inserted into the right jugular vein. For oral administration, a suspension of meloxicam^e was mixed with approximately 200 g of moist wheat bran and given at the rate of 0.6 mg/kg. During phase 1, the single dose of meloxicam was administered approximately 13 hours after the preceding evening meal, which was 2 hours before the regularly scheduled morning meal. For phase 2, meloxicam was administered each day immediately before the regularly scheduled morning meal.

Sample collection—Blood samples (5 or 10 mL) were collected by direct venipuncture of the left jugular vein by use of a 5-mL syringe.^f Blood was transferred from the syringe into 5-mL lithium-heparinized tubes.^g The tubes

were stored on ice until centrifuged (1,400 \times g for 10 minutes at 10° to 12°C); all samples were centrifuged within 1 hour after collection. Plasma was then harvested and stored at -20°C until assayed to determine meloxicam concentration.

Blood samples were collected immediately before (time 0) and 1, 2, 4, 8, 15, and 30 minutes and 1, 2, 4, 8, 12, 24, and 36 hours after IV administration of meloxicam. Blood samples were collected immediately before (time 0) and 5, 10, 15, and 30 minutes and 1, 2, 4, 8, 12, 24, and 36 hours after oral administration during phase 1. For phase 2, blood samples were collected before (time 0) and 5, 10, 15, and 30 minutes and 1, 2, 4, 8, 12, and 24 hours after the first daily administration; samples were also collected immediately before and 5, 10, 15, and 30 minutes and 1, 2, 4, 8, 12, 24, and 36 hours after the last daily administration. In addition, single isolated samples were collected during phase 2 immediately before oral administration of meloxicam on days 4, 6, 8, 10, and 12 (day 0 was the first day of meloxicam administration).

Urine samples were collected during phase 2. Naturally voided urine samples were collected from the geldings into plastic bags by use of a urine collection apparatus put in place immediately after the first daily drug administration. The exact time of urination was recorded. For urine collection from mares, a urinary catheter^h was inserted into the bladder. Urine was obtained for control conditions (ie, before administration of the first dose of meloxicam), during treatment (ie, approx 8 hours after the first administration and again after the 7th, 11th, and 14th administration), and after treatment (days 1, 2, 3, 7, 11, 14, and 18 after the last oral administration). Urine samples (approx 50 mL) were stored at -20°C until analyzed.

Sample analysis—Plasma samples were analyzed by use of a validated high-performance liquid chromatography (HPLC) procedure that was conducted by use of UV detection. Briefly, an internal standard (piroxicam) and meloxicam were extracted from plasma by solid-phase extraction. The HPLC apparatus consisted of a pump system equipped with an automatic injector and ultraviolet detector (360 nm). Separation was achieved by use of a reverse-phase columnⁱ and a guard column.^j The mobile phase consisted of a mixture (40:60) of acetic acid: 1% methanol at a flow rate of 0.4 mL/min. For these conditions, meloxicam and piroxicam were eluted at a retention time of 7.6 and 5.2 minutes, respectively.

Results for the method are linear over the calibration range of 10 to 1,250 ng/mL, as determined by use of a weighted linear regression model. Within-day and day-to-day precision were < 9%. Accuracy ranged from 96% to 99%. Interference of endogenous compounds was verified on blank plasma from untreated horses, which provided the specificity of the method. Meloxicam was stable in equine plasma after 3 freeze-thaw cycles. Validated limit of quantification (LOQ) was 10 ng/mL.

A sensitive HPLC-electrospray ionization (ESI)-mass spectrometry-(MS)-MS assay method was developed for analysis of meloxicam in equine urine. The internal standard was meloxicam D₃ that was synthesized in our laboratory. Meloxicam and meloxicam D₃ were extracted from urine by solid-phase extraction on an encapped cartridge.^k Urine (5 mL) was hydrolyzed by use of sodium hydroxide (100 μ L). After 30 minutes, pH was adjusted to 5.9 and the samples were centrifuged. After centrifugation, solid-phase extraction was performed. The cartridge was conditioned with methanol (2 mL) and water (2 mL). A sample was loaded on the cartridge, the cartridge was rinsed with water (3 mL) followed by hexane (3 mL), and it was allowed to dry. Samples were eluted by use of chloroform (3 mL). After evaporation, the residue was dissolved in 500 μ L of a solution

(50:50) of methanol:water and subjected to HPLC-ESI-MS-MS analysis. The HPLC apparatus consisted of a pump system^l equipped with an automatic injector^m connected to an ion-trap mass spectrometer instrument.ⁿ Separation was achieved by use of a reverse-phase column.^o The mobile phase consisted of a gradient of methanol in water with 0.25% acetic acid; flow rate was 0.8 mL/min. For these conditions, meloxicam and meloxicam D₃ were eluted at a retention time of 12 and 13 minutes, respectively. The atmospheric pressure ionization source operated in the ESI-negative mode. Capillary temperature was maintained at 200°C, and voltage of 4.5 kV was applied. Ions at m/z 350 and 353 were selected for meloxicam and meloxicam D₃, respectively. The following settings were selected for the 2 compounds: isolation width, 1.7 μm; activation amplitude, 22%; activation q/z, 0.45; activation time, 30 milliseconds; and mass range, 200 to 360 atomic units of mass.

Results for the method are linear over the calibration range of 20 to 300 ng/mL, as determined by use of a weighted linear regression model. Within-day and day-to-day precision were < 11%. Accuracy ranged from 96% to 101%. Lack of interference by endogenous compounds was verified on blanks consisting of urine of untreated horses, thus proving specificity of the method. Validated LOQ of the assay was 20 ng/mL.

Pharmacokinetic analysis—Pharmacokinetic analysis was performed by use of commercially available software.^p Data were subjected to noncompartmental and compartmental analysis. A noncompartmental analysis was performed for the single IV administration of meloxicam, single oral administration of meloxicam, and the first and last oral administrations of the multiple oral regimen of meloxicam.

For IV administration, plasma clearance, mean residence time (MRT_{IV}), area under the plasma concentration versus time curve (AUC_{IV}), and steady-state volume of distribution were calculated for each horse by use of the linear trapezoidal rule with extrapolation to infinity in accordance with a classical equation.⁵

For the single oral administrations (nonfed conditions), MRT (ie, MRT_{oral}) and AUC (ie, AUC_{oral}) were obtained for each horse by use of a linear trapezoidal rule with extrapolation to infinity. Peak of drug concentration in plasma (C_{max}) and time of C_{max} (T_{max}) were obtained directly from the raw data.

The F was obtained by use of the following equation:

$$F = (AUC_{\text{oral}}/AUC_{\text{IV}}) \times (\text{Dose}_{\text{IV}}/\text{Dose}_{\text{oral}}) \times 100$$

where Dose_{IV} and Dose_{oral} are the actual doses administered IV and orally, respectively.

Mean absorption time (MAT) was obtained by use of the following equation:

$$\text{MAT} = \text{MRT}_{\text{oral}} - \text{MRT}_{\text{IV}}$$

For the first oral administration in fed horses (phase 2), the AUC for 0 to 24 hours (ie, AUC_{0 to 24}) was calculated by use of the linear trapezoidal rule but without extrapolation to infinity. The AUC_{0 to 24} corresponding to the last oral administration during phase 2 was calculated by use of the linear trapezoidal rule without extrapolation to infinity. Then, the accumulation of meloxicam after multiple dose administration was assessed by use of the following ratio:

$$\text{Last dose:first dose} = (AUC_{0 \text{ to } 24} \text{ for last dose}/AUC_{0 \text{ to } 24} \text{ for first dose}) \times (\text{first dose/last dose})$$

where first dose and last dose are the actual first and last doses of meloxicam administered during the multiple oral administration.

Compartmental analysis was performed for the single IV administration (nonfed horses) and the multiple oral administration (once-daily administration for 14 days) for use in calculating the compartmental overall F for the 14 administrations. For the single IV administration, data were fitted to 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; Y₁, Y₂, and Y₃ are preexponential coefficients; and λ₁, λ₂, and λ₃ are exponents of the first, second, and third phases of decay of the plasma concentrations, respectively. Values for AUC_{oral} and AUC_{IV} were obtained by integration of this triexponential equation.

Terminal half-life was calculated as 0.693/λ₃, with λ₃ defined as the exponent of the third phase of decay of the plasma concentrations.

For multiple oral administration (phase 2) and accounting for actual administered doses, data corresponded to an open bicompartamental model with an absorption phase. Data were fitted to the following triexponential equation:

$$Y(t) = ((Y_1 + Y_2) \times e^{-[K_a \times (t - \text{lag})]}) + (Y_1 \times e^{-\lambda_1 \times (t - \text{lag})}) + (Y_2 \times e^{-\lambda_2 \times (t - \text{lag})})$$

where K_a is a rate constant for the absorption phase; λ₁ and λ₂ are the slopes of the distribution and elimination phases, respectively; and lag is the time delay attributable to absorption. Values for AUC_{oral} and AUC_{IV} were calculated by integration of this triexponential equation and adjusted to the scaling dose. The scaling dose was set at the dose used for IV administration.

Overall F for the 14-day treatment was calculated as follows:

$$F = (AUC_{\text{oral}}/AUC_{\text{IV}}) \times 100$$

where AUC_{oral} and AUC_{IV} were obtained by integration of the fitted equation.

Statistical analysis—Descriptive values were reported as mean ± SD. Statistical analysis was performed by use of a computer program.^q For comparisons of F, MRT, MAT, C_{max}, and T_{max}, an ANOVA was performed by use of an additive model. Pairwise mean comparisons were performed by use of the Bonferroni test. Values of P < 0.05 were considered significant.

Results

Semilogarithmic graphs were generated of plasma concentrations of meloxicam versus time after a single IV administration and a single oral administration in nonfed conditions (Figure 1). Dosage for IV administration ranged from 0.59 to 0.61 mg/kg (mean, 0.60 ± 0.076 mg/kg). Plasma clearance was low (range, 24 to 41 mL/kg/h; mean ± SD, 34 ± 5.7 mL/kg/h). Steady-state volume of distribution was limited (range, 0.10 to 0.16 L/kg; mean, 0.12 ± 0.018 L/kg). The MRT_{IV} ranged from 2.78 to 4.76 hours (mean, 3.60 ± 0.63 hours), and terminal half-life ranged from 5.15 to 14.48 hours (mean, 8.54 ± 3.02 hours).

After the single oral administration in nonfed horses, F ranged from 63.4% to 126.7% (mean, 85.3 ± 19.4%), MRT_{oral} ranged from 4.96 to 10.20 hours (mean, 7.22 ± 1.69 hours), and MAT ranged from 2.07 to 6.32 hours (mean, 3.62 ± 1.39 hours). The C_{max} (range, 1.48 to 3.46 μg/mL; mean, 2.58 ± 0.58 μg/mL) was detected 1.0 to 4.0 (mean, 1.5 ± 1.07) hours after meloxicam administration.

Semilogarithmic graphs were generated of observed and fitted meloxicam concentrations versus time for the multiple oral administration of meloxicam (Figure 2). Visual inspection of these graphs revealed that trough concentrations measured immediately before meloxicam administration on days 4, 8, 10, and 12 were extremely similar, which indicated steady-state conditions. This was confirmed by the accumulation ratio of meloxicam during the 14 days of meloxicam administration (range, 0.95 to 1.25; mean, 1.08 ± 0.11).

The F calculated for the first oral administration in fed horses during phase 2 (range, 84.0% to 117.1%; mean, $95.9 \pm 13.2\%$) was determined for only 6 of the 8 horses (ie, those used in phase 1 and 2) and was not significantly different from the F in the 8 nonfed horses ($85.3 \pm 19.4\%$) or the overall F (the same 6 fed horses) calculated during the 14 days of meloxicam administration (range, 85.2% to 114.5%; mean, $97.6 \pm 12.5\%$). The MRT after the first oral dose in the 8 fed horses during phase 2 (range, 7.72 to 12.66 hours; mean, 9.30 ± 1.59 hours) was significantly higher than the MRT obtained in nonfed horses during phase 1 (mean, 7.22 ± 1.69 hours). The MAT after the first dose for 6 of the 8 fed horses during phase 2 (range, 4.30 to 8.78 hours; mean, 5.71 ± 1.82 hours) was significantly higher than the MAT obtained in nonfed horses during phase 1 (mean, 3.62 ± 1.39 hours). The C_{max} after administration of the first dose to the 8 fed horses during phase 2 ranged from 1.01 to 3.00 $\mu\text{g/mL}$ (mean, $1.73 \pm 0.61 \mu\text{g/mL}$). The T_{max} for phase 2 (range, 1.0 to 4.0 hours; mean, 3.4 ± 1.19 hours) was significantly higher than that in nonfed horses (mean, 1.5 ± 1.07 hours).

In plasma samples obtained from the 8 fed horses during phase 2, the half-life of λ_1 (ie, slope of the distribution phase) ranged from 1.05 to 2.48 hours (mean, 1.64 ± 0.50 hours), half-life of λ_2 (slope of the elimination phase) ranged from 5.26 to 11.36 hours (mean, 7.76 ± 1.99 hours), and half-life of K_a (rate constant for the absorption phase) ranged from 0.54 to 1.80 hours (mean, 1.14 ± 0.40 hours). The value for t_{lag} during phase 2 ranged from 0.07 to 0.21 hours (mean, 0.14 ± 0.038 hours).

Semilogarithmic graphs were generated of the urinary concentration of meloxicam versus time (Figure 3). Visual inspection of these graphs revealed that during administration, urine concentrations of meloxicam were rather constant. Eight hours after the first administration, mean meloxicam concentration

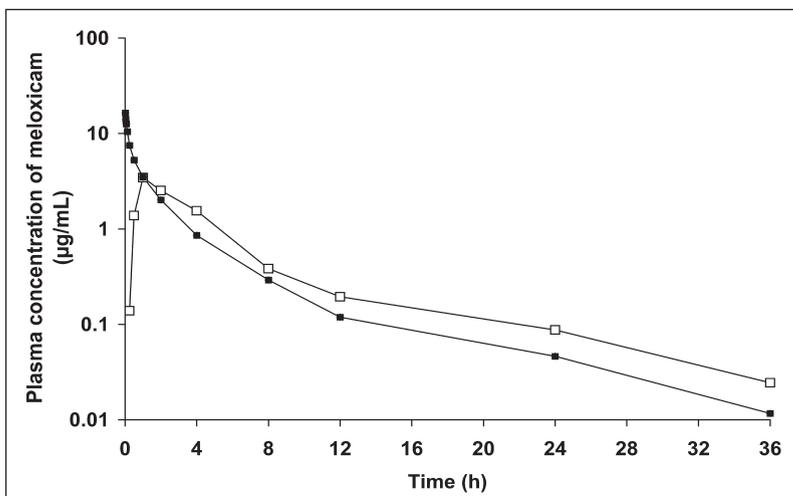


Figure 1—Semilogarithmic graph of observed plasma concentrations of meloxicam in a representative horse after oral (white squares) and IV (black squares) administration of a single dose of meloxicam (0.6 mg/kg). Food was withheld from the horse prior to administration of meloxicam. Time 0 represents the time of meloxicam administration.

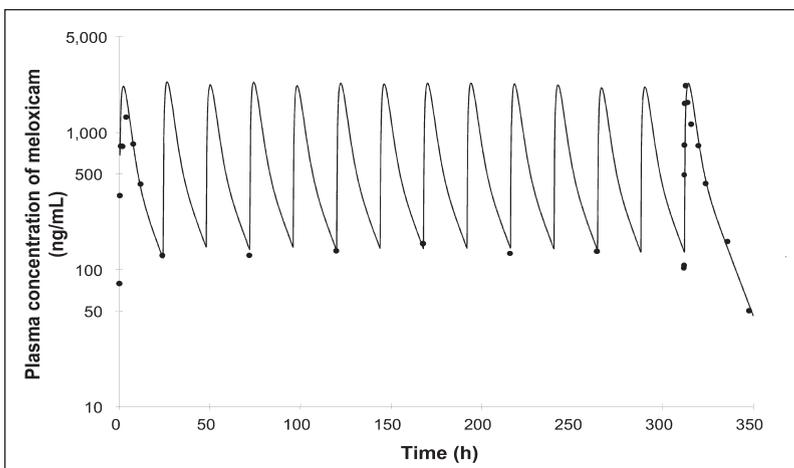


Figure 2—Semilogarithmic graph of observed (black circles) and predicted (line) plasma concentrations of meloxicam in a representative horse after once-daily oral administration of multiple doses of meloxicam (0.6 mg/kg, PO, q 24 h for 14 days). Data were fitted to a triexponential equation corresponding to a bicompartmental model with a phase of absorption. Time 0 represents the time of administration for the first daily dose of meloxicam.

was $1,981 \pm 890 \text{ ng/mL}$. Trough concentration in urine was between $1,376 \pm 560 \text{ ng/mL}$ and $1,922 \pm 1,358 \text{ ng/mL}$. Urinary concentrations of meloxicam 24 and 48 hours after the last meloxicam administration were $860 \pm 607 \text{ ng/mL}$ and $44 \pm 25 \text{ ng/mL}$, respectively. Urine samples obtained > 48 hours after the last oral administration contained meloxicam concentrations that were less than the LOQ of the analytic technique (ie, < 20 ng/mL).

The urine-to-plasma concentration ratio was calculated for each horse during steady-state conditions (ie, by use of data for urine samples collected 6, 10, and 13 days after initial meloxicam administration). The corresponding fitted plasma concentrations were calculated by solving the equation to fit plasma concentrations. Overall urine-to-plasma concentration ratio for each horse ranged from 13 to 18.

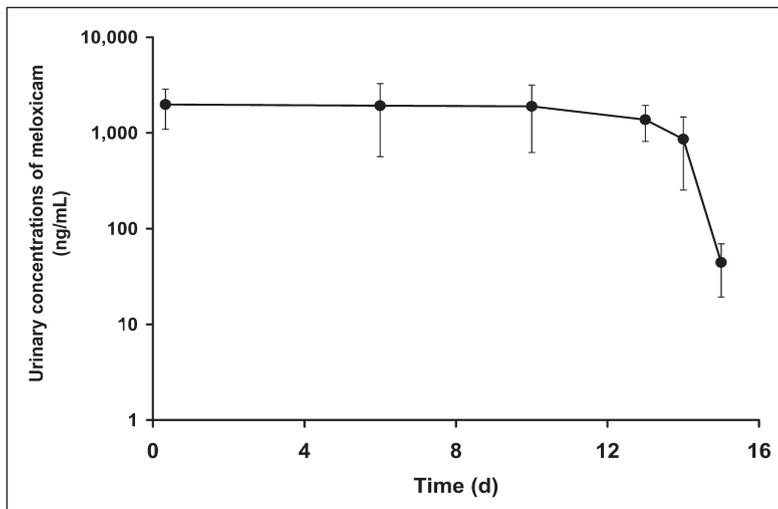


Figure 3—Semilogarithmic graph of mean \pm SD urinary concentrations of meloxicam in 8 horses after once-daily oral administration of multiple doses of meloxicam (0.6 mg/kg, PO, q 24 h for 14 days).

Discussion

Plasma clearance obtained in the study reported here was rather low (34 mL/kg/h) and similar to that reported⁶ in ponies (42 mL/kg/h) but lower than that obtained in horses (81 mL/kg/h) in another study¹ conducted by our laboratory group. The origin of these differences (eg, horses or analytic techniques) remains unclear; however, influence of Freund's adjuvant and the associated inflammation in that other study¹ cannot be ruled out because Freund's adjuvant can influence drug disposition in rats.^{7,8}

Plasma clearance is the parameter that allows computation of a dose when the target (effective) plasma concentration is known. In another study¹ conducted by our laboratory group, we reported an EC_{50} for lame horses of approximately 0.2 μ g/mL. Considering the plasma clearance obtained in the study reported here and the F (which was nearly total) for the oral route of administration, it can be calculated that the daily ED_{50} (ie, daily clearance \times target concentration) is approximately 0.16 mg/kg, which indicates that the recommended dosage (0.6 mg/kg) is much greater than the ED_{50} .

It is interesting that the plasma clearance of meloxicam is 3 to 5 times higher in horses⁹ than it is in humans and that the doses that are efficacious in humans (7.5 to 15 mg in toto) are one fifth to one half the dose in horses. Similarly, plasma clearance in dogs (10 mL/kg/h)¹⁰ is about one third that in horses, and the recommended dose of 0.2 mg/kg (loading dose) in dogs is also one third that in horses.

Terminal half-life in the study reported here (8.54 hours) was greater than the value we determined in another study¹ conducted by our laboratory group and suggests that the difference between the 2 studies may be of analytic origin (ie, the LOQ of the study reported here allowed us to monitor the decrease of plasma concentrations for a longer time and then to estimate more accurately the true terminal phase). A terminal half-life of 8 hours is sufficient to justify a once-daily dosing regimen for an NSAID and yet avoid

any accumulation as proved by the accumulation index ratio that we calculated, which was close to 1. This indicates that meloxicam plasma patterns should be almost identical after each administration, precluding the need for any loading dose. The steady-state volume of distribution was limited (0.12 L/kg), probably as a result of extensive protein binding (98.4% to 98.6%).^{5,r}

Feeding conditions of horses can influence the plasma concentration patterns of several NSAIDs.^{3,11} Therefore, the influence of the feeding conditions on meloxicam disposition was investigated by use of 2 feeding regimens (fed and nonfed). The study reported here documented that the F for the oral route of administration was high for both regimens ($85 \pm 19\%$ for nonfed horses and $96 \pm 13\%$ for fed horses) and not significantly different.

This also indicates lack of a major hepatic first-pass effect. In contrast, MRT , MAT , and T_{max} were significantly greater and C_{max} was significantly less in fed than in nonfed horses. This suggests that the physiologic status of the gastrointestinal tract (ie, containing food) substantially slows the rate of meloxicam absorption after oral administration, whereas the absolute F of meloxicam remains unchanged.

The rate of meloxicam absorption was evaluated by use of the MAT and can be considered relatively rapid (3.62 hours in nonfed horses and 5.71 hours in fed horses), which suggests that absorption is mainly in the proximal part of the digestive tract (ie, duodenum). In contrast, for some NSAIDs that bind to cellulose, absorption is delayed for several hours and likely is in the distal segment of the digestive tract.³

Meloxicam is intended for repeated administrations. The study reported here documented that with respect to F , there was no significant difference between the first and last oral administrations and that the data fit a bicompartmental model well, which is consistent with the hypothesis that meloxicam disposition (absorption, distribution, and elimination) is independent of time and dose. In addition, the accumulation ratio was low (1.08 ± 0.111), which suggests that the steady-state concentration was achieved immediately.

After the first meloxicam administration, urinary concentrations of meloxicam remained fairly constant, confirming that there is no accumulation of meloxicam after multiple doses. It then decreased to less than the LOQ within 3 days after the final dose.

Urinary concentrations of meloxicam will be monitored during drug control programs, and the study reported here offers the opportunity to compute the order of magnitude of the urinary concentration that should be used to ensure lack of effect as determined by use of a general procedure proposed elsewhere.⁴ The overall effective plasma concentration was estimated as 0.73 μ g/mL (ie, recommended dose divided by daily clearance). The plasma concentration below which there is no relevant effect is obtained by dividing the effective plasma concentration by a safety (uncertain-

ty) factor of 500, which yields a plasma concentration of approximately 1.5 ng/mL.

Computation of a urinary concentration below which there is no relevant effect requires knowledge of the plasma-to-urine ratio. In the study reported here that was conducted in steady-state conditions, such a ratio was easy to determine because trough concentrations of meloxicam remained fairly constant during the multiple dosing regimen. Considering the urine-to-plasma concentration ratio was approximately 13 to 18, the urinary concentration below which there is no relevant effect would be approximately 19 to 27 ng/mL. Assuming such a value is adopted by racing authorities, a minimal withdrawal time of 3 days should be adequate because, for our experimental conditions, the urinary concentration of meloxicam was less than the LOQ (20 ng/mL) within 3 days after the last administration of meloxicam.

The study reported here provides evidence that a once-daily dose at a rate of 0.6 mg of meloxicam/kg is appropriate for use in horses when the oral route of administration is selected. We documented that the feeding regimen influences the rate of absorption of orally administered meloxicam but not the extent of F , which is almost complete and appears to be independent of feeding status. Regarding multiple oral administrations of meloxicam at the recommended dosage, the disposition of meloxicam can be considered linear (time and dose) and there is no drug accumulation. This study provides useful information that can help racing authorities determine the performance of their analytic techniques and practitioners determine an appropriate withdrawal time.

Because of a nearly total systemic availability after administration by the oral route, the same dosage can be given IV and orally. In addition, we documented that meloxicam can have several desirable pharmacokinetic properties in horses, including F that is apparently not influenced by the feeding status, total F that limits the possible inter-horse variability observed with NSAIDs that have a low and erratic F , appropriate terminal half-life for a once-daily dosing regimen, lack of drug accumulation, and relatively rapid disappearance from urine after the final dose of multiple meloxicam administrations, which is an advantage with respect to drug control programs.

^aEqvalan paste, Merial SAS, Lyon, France.

^bFlax bedding, Linabox, Corosville, France.

^cLegend, Ralston Purina, Duquesne, France.

^dMetacam 2%, Boehringer Ingelheim Vetmedica GmbH, Ingelheim, Germany.

^eMetacam oral suspension (15 mg/mL), Boehringer Ingelheim Vetmedica GmbH, Ingelheim, Germany.

^fBD Discardet II, Becton-Dickinson, Frago, Spain.

^gTK 75 PP heparine-Li, Subra, Toulouse, France.

^hLevin tube, LI25 2IFR, Vygon, Ecouen, France.

ⁱProntosil C₁₈, 3 μ m, 125 \times 3.0 mm, ICS, Toulouse, France.

^jProntosil C₁₈, 10 \times 30 mm, ICS, Toulouse, France.

^kC18 encapped cartridge, 500 mg, 3 mL, Varian, les Ulis, France.

^lP4000, Thermofinnigan, les Ulis, France.

^mAS 3000, Thermofinnigan, les Ulis, France.

ⁿThermoquest, Thermofinnigan, les Ulis, France.

^oNucleosil C18 AB column, 5 μ m, 250 \times 4.6 mm, Macherey-Nagel, Hoerd, France.

^pWinNonlin, version 3, Pharsight Corp, Mountain View, Calif.

^qSYSTAT, version 8.0, SPSS Inc, Chicago, Ill.

^rBoehringer data files, Boehringer Ingelheim Vetmedica GmbH, Ingelheim, Germany.

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