Comparative pharmacokinetics of meloxicam in clinically normal horses and donkeys

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Objective—To determine the disposition of a bolus of meloxicam (administered IV) in horses and donkeys (Equus asinus) and compare the relative pharmacokinetic variables between the species.

Animals—5 clinically normal horses and 5 clinically normal donkeys.

Procedures—Blood samples were collected before and after IV administration of a bolus of meloxicam (0.6 mg/kg). Serum meloxicam concentrations were determined in triplicate via high-performance liquid chromatography. The serum concentration-time curve for each horse and donkey was analyzed separately to estimate standard noncompartmental pharmacokinetic variables.

Results—In horses and donkeys, mean ± SD area under the curve was 18.8 ± 7.31 µg·h/mL and 4.6 ± 2.55 µg·h/mL, respectively; mean residence time (MRT) was 9.6 ± 9.24 hours and 0.6 ± 0.36 hours, respectively. Total body clearance (CLt) was 34.7 ± 9.21 mL/kg/h in horses and 187.9 ± 147.26 mL/kg/h in donkeys. Volume of distribution at steady state (Vdss) was 270 ± 160.5 mL/kg in horses and 93.2 ± 33.74 mL/kg in donkeys. All values, except Vdss, were significantly different between donkeys and horses.

Conclusions and Clinical Relevance—The small Vdss of meloxicam in horses and donkeys (attributed to high protein binding) was similar to values determined for other nonsteroidal anti-inflammatory drugs. Compared with other species, horses had a much shorter MRT and greater CLt for meloxicam, indicating a rapid elimination of the drug from plasma; the even shorter MRT and greater CLt of meloxicam in donkeys, compared with horses, may make the use of the drug in this species impractical. (Am J Vet Res 2006;67:1082–1085)

Nonsteroidal anti-inflammatory drugs are used for their anti-inflammatory, analgesic, antipyretic, antithrombotic, and antiendotoxic properties. There are differences in the efficacy of NSAIDs among individual animals and among species. These differences may be caused by variability in pharmacokinetics, half-life, plasma protein concentrations, and circadian rhythms; drug interactions; and renal or hepatic disease. Because of the large differences among the published pharmacokinetic values of meloxicam in animals, it is clear that there are marked species differences. This species individuality of meloxicam distribution is similar to the distributions of other NSAIDs and heightens the importance of pharmacokinetic modeling in each species prior to clinical use of a drug.

Meloxicam is an enolic acid NSAID of the oxicam group and is approved for use in dogs in Europe, Canada, and the United States. In small animals, meloxicam is used for the treatment of musculoskeletal injuries, osteoarthritis, and perioperative pain. In horses, NSAIDs are used primarily to treat musculoskeletal injury and minimize abdominal pain; however, they are also commonly given perioperatively for analgesia. To date, the NSAIDs that are most commonly used in equids are phenylbutazone and flunixin meglumine, which have been used in horses since the 1930s and 1970s, respectively. The extent and duration of the use of these 2 drugs in horses are presently reflected in numerous scientific, pharmacokinetic, and comparative pain articles.

It is now well known that there are 2 COX isoforms, COX-1 and COX-2, and that the extent of NSAID-associated inhibition of COX-1 and COX-2 activities differs depending on the drug administered. Most NSAIDs inhibit COX-1 and COX-2 to various degrees; however, the newer drugs including meloxicam are more selective for the COX-2 isoenzyme. Because of the greater COX-2 selectivity of meloxicam and other new-generation NSAIDs, these drugs may be associated with a decreased occurrence of adverse effects such as inhibition of platelet function, development of gastrointestinal tract ulcers, and impairment of renal function. Despite the potential advantages of meloxicam administration in equids, understanding of the pharmacokinetics of meloxicam is limited in healthy adult horses and, to our knowledge, nonexistent in donkeys (Equus asinus). The pharmacokinetics of several drugs have been shown to differ between horses and donkeys, but we are not aware of any

ABBREVIATIONS

NSAID Nonsteroidal anti-inflammatory drug
COX Cyclooxygenase
Vdss Volume of distribution at steady state
CLt Total body clearance
AUC Area under the serum versus time curve
MRT Mean residence time
AUMC Area under the first moment curve
published information regarding the comparative disposition of meloxicam in horses and donkeys. Therefore, the purpose of the study reported here was to determine the disposition of meloxicam (administered IV) in horses and donkeys and compare the relative pharmacokinetic variables between the species.

**Materials and Methods**

**Animals**—Five clinically normal horses (3 mares, 1 stallion, and 1 gelding) and 5 clinically normal standard donkeys (3 geldings and 2 females) were used in the study. The age of the horses ranged from 2 to 12 years (mean age, 5 years), and their weight ranged from 333 to 458 kg (mean weight, 406 kg). The age of the donkeys ranged from 12 to 15 years (mean age, 13 years), and their weight ranged from 236 to 351 kg (mean weight, 282 kg). The horses and donkeys were judged to be clinically normal on the basis of results of a physical examination, CBC, and serum biochemical analyses. Animals were acclimatized to their surroundings and allowed free access to water and hay, except during the first hour of blood collection. The study was conducted in accordance with the state guidelines of animal care, and the protocol was approved by the institutional laboratory animal use and care committee.

**Experimental design and sample collection**—In each horse and donkey, 1 jugular vein was catheterized with an indwelling catheter that was secured in place. Meloxicam (0.6 mg/kg, IV) was administered as a bolus injection into the catheterized jugular vein of each animal over a period of approximately 1 minute. The catheters were used to collect blood samples and were flushed adequately with saline (0.9% NaCl) solution containing heparin before and after sample collections. For all animals, blood samples were collected at time zero (before) and at 5, 10, 15, 20, 30, and 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 28, 32, 36, and 48 hours after the administration of meloxicam.

**Sample analysis**—Sera were obtained from the blood samples and were stored at −20°C until time of analysis. Determinations of serum meloxicam concentrations were randomized and performed in triplicate via high-performance liquid chromatography (similar to the method of Peck et al). In summary, meloxicam was extracted into 2 mL of acetonitrile from 1 mL of serum containing 200 mg of NaCl and internal standard (piroxicam, 6.1 µg/mL). The limit of quantification of meloxicam was 0.1 µg/mL at 352 nm. The limit of quantification was determined by spiking serum samples at various concentrations (0.08, 0.1, and 0.12 µg/mL) with resulting values having no greater than 20% variance from the spiked value against the calibration curve. Piroxicam and meloxicam were resolved (3.7 and 7.8 minutes, respectively) on a C18 column with a flow rate of 0.2 mL/min of acetonitrile with 0.19N phosphoric acid (58:42 solution). The injection volume was 15 µL. The standard curve was plotted for donkeys and horses versus time profiles for the first 12 hours after injection (Figure 1).

**Pharmacokinetic analysis**—Serum meloxicam concentration versus time data for each animal were analyzed by use of a computer software program to estimate variables through standard noncompartmental analysis. Pharmacokinetic data, including VDss, CLT, AUC, and MRT, were calculated for horses and donkeys by use of statistical moment theory. The equations used were as follows:

- **VDss** = Dose × AUMC/AUC²
- **CLT** = Dose/AUC
- **MRT** = AUMC/AUC

**Statistical analysis**—The Mann-Whitney U text was used to compare the pharmacokinetic values of AUC, VDss, CLT, and MRT between horses and donkeys. A value of P < 0.05 was considered significant.

**Results**

Mean ± SD serum concentration of meloxicam versus time profiles for the first 12 hours after injection was plotted for donkeys and horses (Figure 1). Pharmacokinetic variables of meloxicam after IV administration (dose, 0.6 mg/kg) were determined for each horse and donkey (Table 1). Compared with pharmacokinetic data of meloxicam in other species (pigs, humans, dogs, and cows), the horses of our study had a much shorter MRT (mean, 9.6 ± 9.24 hours; median, 4 hours) and greater CLT (mean, 34.7 ± 9.21 mL/kg/h; median, 38 mL/kg/h). In the donkeys, the MRT (mean, 0.6 ± 0.35 hours; median, 2.3 hours) of meloxicam was significantly shorter and CLT (mean, 187.9 ± 147.26 mL/kg/h; median, 128 mL/kg/h) was significantly greater than the values in the horses. The AUC in horses (mean, 18.8 ± 7.31 µg/mL/h; median,
16 µg/mL/h) was significantly larger than the value in donkeys (mean, 4.5 ± 2.5 µg/mL/h; median, 4.7 µg/mL/h). The VDSS of meloxicam in horses (mean, 270 ± 160.5 mL/kg; median, 185 mL/kg) was greater than the value in donkeys (mean, 93.2 ± 33.7 mL/kg; median, 88 mL/kg), but these values were not significantly different (P = 0.06). None of the animals had noticeable adverse reactions after receiving meloxicam.

**Discussion**

Results of our study complement and extend the results of an earlier study of meloxicam in ponies. The pharmacokinetic disposition of meloxicam in horses was similar to findings in New Forest ponies despite the use of different pharmacokinetic software models in our analysis.4 Our investigation has also provided new data regarding the pharmacokinetics of meloxicam in donkeys and has highlighted the differences in meloxicam disposition between horses and donkeys.

The dose of meloxicam (0.6 mg/kg, IV) was chosen on the basis of an existing report for horses and limited clinical drug usage. In a study by Lees et al,4 a dose of 0.6 mg of meloxicam/kg (administered IV) was chosen because earlier preliminary work had revealed short half-lives for meloxicam in horses of 1.9 and 2.1 hours for doses of 0.2 and 0.5 mg/kg, IV, respectively (1 animal/dose group). In addition, by use of a carageenan-sponge model of acute inflammation, that study revealed anti-inflammatory effects of meloxicam at a dose of 0.6 mg/kg. Therefore, we selected a dose of 0.6 mg of meloxicam/kg for administration IV to both the horses and donkeys to achieve plasma concentrations of meloxicam that were likely to have an effect against inflammation. The anti-inflammatory or analgesic effects of the plasma drug concentrations achieved at this dose were not assessed in our study, and scientific information is not currently available to quantify the minimum effective concentration for meloxicam in either species.

In the present study, the MRT of meloxicam in horses was 9.6 ± 9.24 hours and CLT was 34.7 ± 9.21 mL/kg/h. Mean residence time is a noncompartmental variable that is based on statistical moment theory and is analogous to a half-life calculation in compartmental analysis.13 In dogs, humans, and rats given clinical doses of meloxicam, MRT was 34.8, 18.2, and 18 hours and CLT was 10, 10, and 15 mL/kg/h, respectively.14 Because the clearance of meloxicam in horses in the present study was at least twice as rapid as values reported for those other species, horses may require more frequent administrations of the drug than the once-daily dose currently recommended for dogs. However, flunixin meglumine has an even faster elimination from the plasma in horses with a reported MRT of 110 ± 24.1 min and CLT of 1.1 ± 2 mL/kg/min at the standard dose of 1.1 mg/kg.11 Hence, the faster plasma elimination of meloxicam in horses may not preclude the use of this drug in equine practice. This is supported by the fact that acidic NSAIDs, including phenylbutazone, flunixin meglumine, and meloxicam, have rapid plasma clearance but relatively slow clearance from inflammatory exudates, and, therefore, may still be clinically effective as anti-inflammatory agents.13-17

Compared with values determined in the horses of the present study and those reported for dogs, humans, and rats, MRT (0.6 ± 0.35 h) was shorter and CLT (187.9 ± 147.26 mL/kg/h) was greater in donkeys. This suggests that meloxicam use in this species might be impractical because plasma clearance is so rapid; however, clinical trials would be necessary to evaluate effectiveness. Our results indicated that the pharmacokinetic variables of meloxicam in donkeys differed significantly from those in horses. The shorter MRT and faster plasma clearance of meloxicam in donkeys, compared with horses, are similar to findings of other comparative studies with flunixin meglumine (55 ± 7.2 min and 1.8 ± 0.5 mL/kg/min, respectively, in donkeys vs 110 ± 24.1 min and 1.1 ± 0.2 mL/kg/min, respectively, in horses)15 and phenylbutazone (1.77 ± 0.73 hours and 170 ± 54.4 mL/kg/h, respectively, in donkeys vs 3.61 ± 0.16 hours and 29 ± 4.6 mL/kg/h, respectively, in horses).16 Although it is expected that the renal clearance of meloxicam is faster in donkeys than in horses, only CLT was measured, not urine clearance; therefore, direct conclusions cannot be made.

The VDSS of NSAIDs is consistently small in most species and is attributed to the relatively high protein-binding characteristics of these drugs, which limit their ability to reach extravascular compartments. However, protein binding was not directly measured in our study. Despite other pharmacokinetic value differences, the VDSS of meloxicam in horses (270 ± 160.5 mL/kg) of the present study was similar to that reported for flunixin meglumine (117 ± 16.4 mL/kg)15 and phenylbutazone (174 ± 12.4 mL/kg).16 In donkeys, the VDSS for meloxicam was smaller (93.2 ± 33.74 mL/kg) than the value in horses, which suggests that even more protein binding may be occurring in donkeys or that there is a relatively smaller extracellular fluid compartment in this species.14

In the present study, there was variation in pharmacokinetic values among individual animals. The values for 1 horse and 1 donkey contributed greatly to the variability in the data. In this horse, AUC was 31.8 µg/mL/h, MRT was 25.1 hours, CLT was 18.9 mL/kg/h, and VDSS was 474.1 mL/kg; in the donkey, AUC was 1.4 µg/mL/h, MRT was 0.3 hours, CLT was 441.2 mL/kg/h, and VDSS was 123.3 mL/kg. The horse was a 6-year-old Quarter Horse mare (weight, 416 kg), and the donkey was a 12-year-old standard donkey (weight, 246 kg). Both animals were healthy and were not receiving any concurrent medication. The dose of meloxicam administered and calculations were accurate for these 2 animals. There were no physical or clinicopathologic abnormalities to suggest liver or kidney disease and no plasma protein concentration abnormalities; all blood samples were collected at the same time of day to rule out circadian rhythm differences among horses and donkeys. The horse was difficult to catch for the 10- and 24-hour blood sample collections, and consequently, these samples were obtained approximately 20 to 30 minutes later than scheduled. However, these sampling time difficulties cannot be expected to account for the variability in the data.

The authors recognize that additional numbers of horses and donkeys might have strengthened the phar-
The pharmacokinetic data by minimizing the effects of individual variation in the data, as reflected by the large SD values. Unfortunately, assessment of additional animals was not possible at the time of our study. Hence, we have reported the findings from all animals and have elected to highlight the individual pharmacokinetic variation of 2 of these animals. Fairly large individual pharmacokinetic variability has been reported for NSAIDs and other drugs.\[^{3,4}\]

The horse and donkey that appeared to be outliers with regard to the pharmacokinetic data were neither particularly old nor particularly young. The most important factors contributing to differences in drug distribution in pediatric animals, compared with older animals, are the differences in body fluid compartments and protein binding of drugs. In older animals, the major concerns are altered drug disposition and response to drugs.\[^{3,4}\] Although there appeared to be a slight difference in age between the horses (range, 2 to 12 years; mean age, 3 years) and donkeys (range, 12 to 15 years; mean age, 13 years) used in the present study, neither group consisted of truly pediatric or geriatric animals. It is difficult to speculate what effect this overall age range had on the pharmacokinetic data differences, but it may account for some of the individual variation identified within species.

Nonsteroidal anti-inflammatory drugs have an important role in the adjunctive treatment of many different inflammatory diseases as well as painful conditions. With our recent understanding of the importance of pain management and multi-modal analgesic techniques, NSAIDs are also commonly used perioperatively as analgesic agents in horses and other species. With the potential advantages of meloxicam as a newer-generation NSAID, compared with the older-class NSAIDs such as flunixin meglumine and phenylbutazone, it would be ideal to perform trials to assess the analgesic benefits of meloxicam in clinical case management in these species. Although the findings of the present study provide pharmacokinetic data for meloxicam in horses and donkeys, further studies are required to explore the pharmacodynamics of this drug in healthy horses or donkeys or those with signs of pain that are or are not undergoing surgery. In addition, evaluation of the efficacy of meloxicam in the treatment of different types of pain (eg, visceral, musculoskeletal, or surgically induced pain) is required to assess the benefits of this drug, compared with other NSAIDs that are commonly used in these species.

a. Angiocatheter-14 ga, Becton Dickinson Infusion Therapy Systems Inc, Sandy, Utah.
b. Metacam 0.5% injection, Boehringer Ingelheim Ltd, Burlington, Ontario, Canada.
c. HP 1090 series II diode array, Agilent Technologies, Palo Alto, Calif.
d. Luna Rp C18(2), 250 × 2.00 mm, Phenomenex, Torrance, Calif.
e. Meloxicam, Sigma-Aldrich, St Louis, Mo.
f. PKAnalyst, MicroMeth, Salt Lake City, Utah.

References