Comparative Medicine
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Vol 56, No 1
February 2006
Pages 63-67

Clinical Investigations

Pharmacokinetics of Meloxicam in Rabbits After Single and Repeat Oral Dosing

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We evaluated the pharmacokinetic profile of meloxicam (0.3 and 1.5 mg/kg) given as single and repeated (once daily for 5 d) oral doses to female rabbits (n = 5/group) to define the optimal dose and dosing interval for clinical use. Clinical signs, body weight, and serum chemistry parameters (sodium, potassium, chloride, total protein, urea, creatinine, glucose, alkaline phosphatase, gamma glutamyl transferase, and alanine aminotransferase) were evaluated before and 5 d after dosing to monitor safety at the 2 dose levels in both studies. Plasma samples were collected serially, and concentrations were determined by high performance liquid chromatography. After single oral dosing at 0.3 or 1.5 mg/kg, maximal plasma concentrations of meloxicam were achieved at 6 to 8 h and were 0.14 and 0.3 μg/ml, respectively. Plasma drug levels decreased rapidly to near-undetectable levels by 24 h. There was moderate interindividual variability in plasma meloxicam concentrations with less than proportional increases in peak plasma concentration and area under the concentration curve values at the higher dose after the single and repeat dosing. The elimination half-life was approximately 8 h at both dose levels, suggesting that metabolism was not saturated. Oral clearance of meloxicam is high in rabbits, indicating rapid metabolism and elimination. There was no accumulation of meloxicam when given at 0.3 or 1.5 mg/kg for 5 d, and meloxicam was rapidly eliminated after discontinuation of dosing. Rabbits may require a dose exceeding 0.3 mg/kg given once daily to achieve optimal plasma levels of meloxicam over a 24-h interval.

Abbreviations: AUC, area under the plasma concentration–time curve; IC_{50}, drug concentration that inhibits 50% of enzyme activity

Pain management in companion and laboratory animals is an important welfare issue for veterinarians, investigators, and pet owners alike. To minimize pain and distress in animals, veterinarians need to know when pain will occur, how long it will last, and how it will respond to therapy. Furthermore, veterinarians need to be able to weigh the advantages and disadvantages of pain management therapies and how best to apply them clinically.

Some small mammal species, such as rabbits, show limited signs of pain and distress, even in familiar environments, and this trait can present a prominent hurdle to veterinarians seeking to refine the animals' care. Rabbits frequently present for a number of potentially painful conditions or procedures, for example, ovariohysterectomy, castration, foreign body removal, trauma, long bone fractures, soft tissue injuries, and dental abscesses and fistulas. They may not receive adequate analgesia because of difficulty in evaluating whether they are experiencing pain. Rabbits in an unfamiliar environment or experiencing stress from transportation are often immobile. Similarly, rabbits experiencing discomfort and pain are immobile, and it is difficult for the practitioner to differentiate between these conditions. Clinical evaluation of an animal in a painful state may result in shock and sudden death. The problem of adequate pain management in rabbits is exacerbated by a lack of specific pharmacologic data for various analgesic agents. Frequently, use of such agents is estimated and off-label.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used routinely in companion animals to provide analgesia. NSAIDs may be combined with opioids pre- and postoperatively to provide synergistically increased analgesic potency.[2] Side effects of NSAIDs include gastrointestinal toxicity, bleeding, and renal and hepatic failure. Most of these side effects are dose-dependent (both absolute dose and dosing interval), emphasizing the importance of knowing the pharmacokinetic parameters of these compounds prior to routine use.[9,10,20]

Meloxicam is a novel cyclooxygenase-2 (COX-2) selective NSAID that has been used extensively as an analgesic agent in humans and, more recently, in some companion animals. Unlike many other NSAIDs, meloxicam has high oral bioavailability and has a long half-life, making it an attractive analgesic for use in veterinary practice. In all species studied, meloxicam undergoes extensive hepatic metabolism into 4 inactive metabolites that are excreted in both urine and feces.[19] Compared with traditional NSAIDs, the pharmacokinetics of meloxicam vary markedly among species studied to date. For example, when meloxicam is given at similar doses to mice and minipigs, there is an 18-fold increase in half-life and a 3-fold decrease in clearance in minipigs compared with mice, whereas there is a 3-fold increase in half-life and a 14-fold decrease in clearance in dogs compared with values in mice.[3] In rats, although experimental anti-inflammatory activity has been demonstrated at oral doses as low as 0.2 mg/kg, in clinical practice, doses less than 1 to 2 mg/kg do not appear to notably attenuate pain after surgery.[3,6,7,13,16] An accurate grasp of

Received: 28 July 2005. Revision requested: 14 Nov 2005. Accepted: 15 Nov 2005.
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species-specific pharmacokinetics and toxicity is essential, because in rats, repeated administration of meloxicam at ≥2.4 mg/kg daily led to gastric ulcers.[6,13,25] Meloxicam pharmacokinetics in rabbits have not been investigated, and this information is clearly essential for optimizing the dose in this species while minimizing the potential for adverse effects.

In this investigation, we evaluated the pharmacokinetic profiles of 2 dose levels of meloxicam given as single and repeated doses to define the pharmacokinetics and optimal dosing interval for clinical use in rabbits. In addition, clinical chemistry parameters were evaluated, to monitor clinical safety at the 2 dose levels after single and repeat dosing.

Materials and Methods

Animals. The study population comprised ten 3-month-old (approximately 3 kg), female New Zealand White rabbits (*Oryctolagus cuniculi*; Charles River Canada, St. Constant, Quebec, Canada) group-housed in floor pens on kiln-dried, autoclaved pine shavings (Pestell Shavings, Guelph, Ontario, CA), on a 12:12-h light:dark cycle at constant temperature (20 ± 4 °C) and relative humidity (30% to 70%). Rabbits were fed twice daily (Teklad Global High Fiber Rabbit Diet, Harlan Teklad, Madison, WI) and provided with timothy hay and fresh water ad libitum. Feeding occurred after dosing. Vendor surveillance reports indicated that animals were from colonies negative for *Encephalitozoon cuniculi*, cilia-associated respiratory bacillus, *Clostridium piliforme*, reovirus, rotavirus, *Pasteurella multocida*, *Salmonella* spp, *Bordatella bronchiseptica*, *Pseudomonas aeruginosa*, *Clostridium perfringens*, and hepatic and intestinal coccidiosis. Animals were acclimated for 7 d and habituated to handling prior to study initiation. The facilities and procedures involving animals were and are in compliance with the Animals for Research Act of Ontario and the *Guidelines of the Canadian Council on Animal Care*.[4] The University of Guelph Animal Care and Use Committee approved the study protocol.

Experimental design. Animals were randomized into initial treatment groups. Animals receiving the low dose of meloxicam in the single-dose study (rabbits 1 to 5) received the high dose in the repeat-dose study, whereas rabbits 6 to 10 received the high dose of meloxicam in the single-dose study and the low dose in the repeat-dose study. For the single-dose study, meloxicam suspension (1.5 mg/ml; Metacam, Boehringer-Ingelheim, Burlington, Ontario, Canada) was administered orally to 5 rabbits/group at either 0.3 mg/kg or 1.5 mg/kg. The oral route of administration was chosen as it is well tolerated by rabbits and is the intended route of delivery clinically. The low dose of 0.3 mg/kg was selected based on empirical, positive impressions of clinical efficacy in rabbits.[21] The high dose was selected on the basis of clinical efficacy studies in rats.[12] Adverse effects were not expected because rabbit reproductive toxicology studies indicated no clinical toxicity after a single dose of meloxicam of ≤20 mg/kg.[13] For both studies, animals were dosed at 08:00. After local anesthesia of ears with a topical lidocaine–prilocaine cream (EMLA, AstraZeneca, Wayne, PA), samples (1 ml) of citrated blood were collected at 0, 0.5, 1, 2, 4, 6, 8, 24, 48, 72, and 96 h after dosage and immediately placed on ice prior to separation of plasma. Plasma samples were stored at –70 °C until analysis of meloxicam concentration. A 14-day washout period occurred between the single- and repeat-dose studies.

For the repeat-dose study, meloxicam was administered orally to rabbits (n = 5/group) at 0.3 or 1.5 mg/kg daily for 5 d. Blood samples were collected at 0, 4, 24, 28, 48, 96, 100, 120, and 144 h after dosage. Samples were separated and stored as described earlier.

Animals were evaluated clinically throughout the course of the study, and body weights were collected weekly. Clinical chemistries (sodium, potassium, chloride, total protein, urea, creatinine, glucose, alkaline phosphatase, gamma glutamyl transferase, and alanine aminotransferase) were conducted on blood samples of all rabbits by using an automatic analyzer (Hitachi 911, Roche Diagnostics, Laval, Quebec, Canada) prior to study to establish baseline serum biochemistry parameters and at 5 d at dosing in each of the single- and repeat-dose studies.

Plasma meloxicam levels. Meloxicam plasma concentrations were determined by high-performance liquid chromatography (HPLC) with UV detection by using the method of Baert and de Backer.[1] Briefly, samples were prepared by combining 0.5 ml plasma, 50 µl internal standard (piroxicam; 10 µg/ml in methanol; Sigma Chemicals, St. Louis, MO), 150 µl 1 M HCl, and 5 ml diethyl ether. After centrifugation, the organic layer was removed and evaporated under nitrogen at 40 °C. The residue was resuspended in 200 µl mobile phase, and 50 µl was injected. Chromatographic assays were conducted by the Toxicology Laboratory (Laboratory Services Division, University of Guelph, Guelph, Ontario, Canada) with a Shimadzu HPLC system (Mandel Scientific, Mississauga, Ontario, Canada) with SCL-10A controller, SIL-10A autoinjector, LC-10AD pump, and SPD-10AV UV detector set at 355 µM and Shimadzu EZChrom Chromatography Data System, version 4.3 (Shimadzu Scientific Instruments, 1998). A reversed phase column (length, 125 mm; inner diameter, 3 mm; 5 µm Nucleosil 100-C18, Macherey–Nagel, distributed by Fisher Scientific, Guelph, Ontario, Canada) attached to a guard column (length, 4 mm; inner diameter, 2 mm; Octadecyl C18 ODS, Phenomenex, Torrance, CA) was used. The mobile phase consisted of 65% water–acetic acid (99:1, v/v) and 35% acetonitrile. An isocratic elution was used at a flow rate of 0.7 ml/min. HPLC methods were validated prior to assay, and calibration curves were prepared by spiking blank rabbit plasma with known concentrations of meloxicam (Sigma Chemicals, St. Louis, MO) and internal standard (piroxicam). The limit of detection were determined as 3 times the signal noise at the time of elution (0.01 µg/ml), and the limit of quantification was calculated as twice the limit of detection (0.02 µg/ml).

Data analyses. The maximal plasma concentration and time to maximal plasma concentration were determined by direct observation of data. Pharmacokinetic parameters (elimination constant; elimination half-life; apparent volume of distribution; area under the plasma concentration–time curve, AUC; and apparent oral clearance) were determined using noncompartmental analyses. The elimination constant was calculated by logarithmic linear regression of the plasma concentration–time curve. The elimination half-life was calculated as 0.693 divided by the elimination constant. The AUC to the final measurable sample was determined using the trapezoidal rule[8] and extrapolated to infinity with the final plasma concentration being divided by the elimination constant, calculated from the apparently linear portion of the log plasma concentration–time curve. The extrapolated area was <5% of the total. Apparent oral clearance was calculated by dividing the dose by AUC, and apparent volume of distribution was calculated by dividing the dose by the product of the elimination constant and AUC.

Results

There were no significant clinical findings or alterations in weekly body weights in rabbits after dosing at 0.3 or 1.5 mg/kg

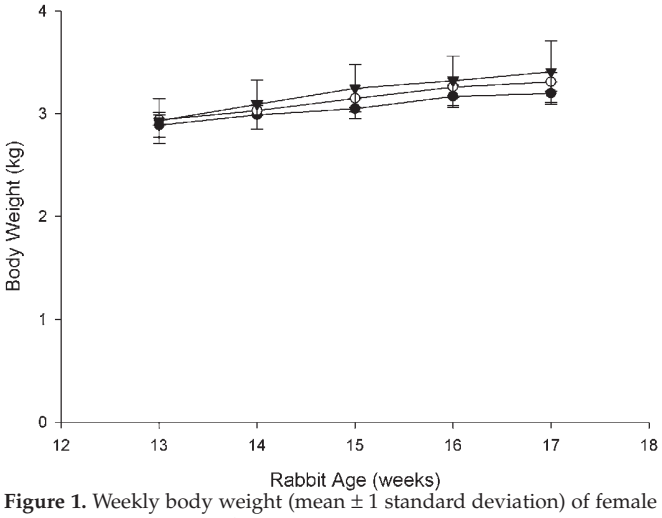

Figure 1. Weekly body weight (mean ± 1 standard deviation) of female rabbits over the course of the study. ▩, rabbits 1 to 5; ▨, rabbits 6 to 10; ▧, vendor-supplied growth data for female New Zealand White rabbits.

in both the single- and repeat-dose studies (Figure 1). Animals continued to gain weight as expected during the course of both studies. There were no biologically significant changes in clinical chemistry parameters from prestudy values for animals in either dose group after single or repeated dosage (Table 1).

After single oral dosing at 0.3 or 1.5 mg/kg, maximum plasma concentrations of meloxicam were achieved at 6 to 8 h (Figure 2). Peak plasma concentration and AUC values obtained for the high-dose group increased less than proportionally, calculated as just over twice that obtained for the group dosed at 0.3 mg/kg (Table 2). Plasma drug levels decreased rapidly to near-undetectable levels by 24 h, and concentrations (mean ± standard error) were 0.025 ± 0.06 µg/ml and 0.069 ± 0.021 µg/ml for animals in the low- and high-dose groups, respectively. There was moderate interindividual variability in plasma meloxicam concentrations, particularly at the higher dose level during both the single- and repeat-dose phases of the study. Both apparent oral clearance and volume of distribution increased by approximately 2.8 times, between groups dosed singly at 0.3 or 1.5 mg/kg. The elimination half-life was approximately 8 h at both dose levels, suggesting that metabolism was not saturated at the higher dose.

Results of the repeat-dose studies indicated that there was no accumulation of meloxicam when given at 0.3 or 1.5 mg/kg for 5 d and that meloxicam is rapidly eliminated after discontinuation of dosing (Figure 3). Plasma drug levels at 4 h postdosage on days 1, 2, and 4 were similar throughout the course of the repeat-dose study at both 0.3 and 1.5 mg/kg and similar to those obtained during the single-dose study.

Discussion

The results of this study demonstrate that rabbits may be treated safely for ≤5 consecutive days with 0.3 or 1.5 mg/kg meloxicam orally. The moderate interindividual variation noted in the plasma concentrations of meloxicam in this study may be reflective of absorption, metabolic, and elimination differences between individuals. Similar within-breed, -strain, and -species variation has been noted for rats, Beagle dogs, minipigs, and baboons, with coefficients of variation for mean plasma concentrations ranging from 12% to 50%.[3]

The peak plasma concentration values of meloxicam determined in this study for single and repeated doses were lower than those obtained using similar doses in other species, for example, 0.464 µg/ml in Beagle dogs after a single oral dose of 0.2 mg/kg and 1.48 µg/ml in male rats receiving 0.3 mg/kg orally for 11 d.[3] The relatively low peak plasma concentration and AUC values obtained for both doses in the current study and the less-than-proportional increases in peak plasma concentration and AUC between the low and high doses are more likely reflective of incomplete absorption rather than metabolic saturation, particularly as the elimination half-life was constant between the 2 doses. Oral bioavailability of meloxicam is reported to be high (≥86%) for most species, but the oral absorption of NSAIDs and other drugs can be altered by fed and fasted states.[18,22] The rabbits in our study were not fed pellets prior to dosing, but animals had ad libitum access to timothy hay. Horses given meloxicam in the fed and fasted state showed little alteration in total bioavailability, but mean peak plasma concentrations were reduced approximately 50% and average time to peak plasma concentrations increased 126% in fed animals, compared with nonfed animals given the same dose of meloxicam.[22] These findings indicate that food and roughage may substantially slow absorption of orally administered meloxicam and may contribute to interindividual variability in pharmacokinetics.

Although not evaluated in this study, marked gender-specific differences in plasma levels of meloxicam have been noted in rats and dogs, with higher and lower plasma drug levels measured, respectively, in females compared to males. In rats, this difference is attributable to reduced levels of cytochrome P450 2C11 in females, important for biotransformation of meloxicam in this species.[3] Male rabbits have been reported to exhibit non-

Table 1. Serum chemistry parameters (mean ± 1 standard deviation) after single and repeat oral treatment of female rabbits with meloxicam

	Treatment and animal numbers						
	Pretest		After single-dose study		After repeat-dose study		Reference
Parameter	nos. 1–5	nos. 6–10	nos. 1–5	nos. 6–10	nos. 1–5	nos. 6–10	range
Na^+ (mM)	144 ± 2	147 ± 2	143 ± 1	143 ± 1	143 ± 1	144 ± 0.9	130–155
K^+ (mM)	4.1 ± 0.5	4.2 ± 0.4	3.9 ± 0.3	4.4 ± 0.2	4.2 ± 0.2	4.4 ± 0.3	3.6–6.9
Cl^- (mM)	111 ± 1	112 ± 0.5	108 ± 3	111 ± 0.1	109 ± 0.2	112 ± 0.9	92–120
Total protein (g/l)	53 ± 2	55 ± 2	51 ± 1	50 ± 3	50 ± 1	52 ± 0.7	48–79
Urea (mM)	4.9 ± 0.7	4.6 ± 0.5	5.7 ± 0.7	6 ± 2	6 ± 0.4	5.5 ± 0.9	3.2–11.1
Creatinine (uM)	77 ± 6	68 ± 2	88 ± 14	81 ± 11	108 ± 9	102 ± 11	44–221
Glucose (mM)	7.5 ± 0.4	7.5 ± 0.3	6.9 ± 0.6	6.9 ± 0.1	6.8 ± 0.2	6.8 ± 0.2	4.1–8.6
Alkaline phosphatase (U/l)	104 ± 18	88 ± 37	158 ± 26	115 ± 13	119 ± 18	110 ± 31	12–216
Gamma glutamyl transferase (U/l)	5.4 ± 2.1	5 ± 2	6.5 ± 1.3	6 ± 0.1	6.2 ± 1.3	7 ± 1.6	0–14
Alanine aminotransferase (U/l)	49 ± 10	41 ± 8	32 ± 8	29 ± 1	32 ± 10	29 ± 3	25–80

In the single-dose study, rabbits 1 to 5 received 0.3 mg/kg meloxicam and rabbits 6 to 10 received 1.5 mg/kg meloxicam. In the repeat-dose study, rabbits 1 to 5 received 1.5 mg/kg meloxicam daily for 5 d and rabbits 6 to 10 received 0.3 mg/kg meloxicam daily for 5 d. For both studies, blood was collected for serum chemistry evaluation 5 d after the last dose of meloxicam.

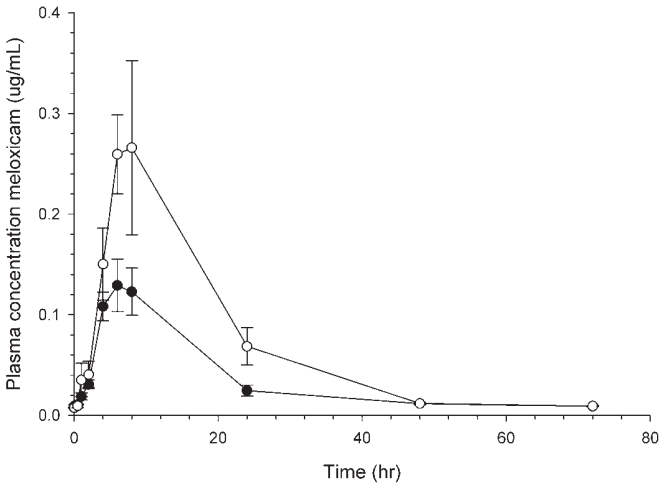

Figure 2. Meloxicam concentrations (mean ± standard error) in plasma of female rabbits after single oral administration of 0.3 (⊠) or 1.5 (⊠) mg/kg (n = 5/group).

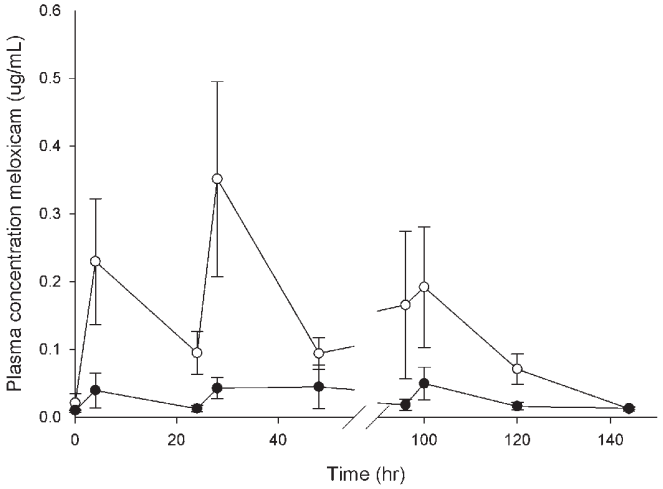

Figure 3. Meloxicam concentrations (mean ± standard error) in plasma of female rabbits after daily oral administration of 0.3 (⊠) or 1.5 (⊠) mg/kg for 5 d (n = 5/group).

Table 2. Pharmacokinetic parameters (mean ± standard error) after oral administration of 0.3 or 1.5 mg/kg meloxicam to female rabbits (n = 5/group)

Parameter	Units	Dose (mg/kg) 0.3	1.5
Peak plasma concentration	µg/ml	0.14 ± 0.02	0.30 ± 0.09
Time to peak plasma concentration	h	6.4 ± 0.8	6.8 ± 0.5
Area under the concentration–time curve	mg·h/l	2.57 ± 0.21	5.20 ± 1.29
Elimination half-life	h	8.16 ± 2.19	8.39 ± 1.17
Apparent volume of distribution	l/kg	1.46 ± 0.48	4.14 ± 1.03
Apparent oral clearance	l/h·kg	0.12 ± 0.01	0.33 ± 0.06

metabolic increases in clearance for some compounds attributable to increased in renal elimination compared to females.[5] It is not known whether metabolism or elimination of meloxicam would vary significantly between male and female rabbits or between different species of rabbits. In our study, apparent oral clearance and volume of distribution values are expressed relative to bioavailability, because intravenous data on meloxicam in rabbits were not obtained. The small volume of distribution suggests that meloxicam distributes primarily in the extracellular space. This distribution is expected from the high degree of plasma protein binding reported in other species and the relatively high ionization state of the compound at physiologic pH.[3,18]

Meloxicam undergoes extensive metabolism through cytochrome P450 2C11 and elimination of the nonbiologically active major metabolites occurs largely through the kidney.[19] The rate of meloxicam elimination was similar for both the low- and high-dose groups, as demonstrated by their similar terminal half-lives. A terminal half-life of 8 h is sufficient to justify once-daily dosing interval of meloxicam in rabbits while avoiding drug accumulation.

Oral clearance of meloxicam in female rabbits after oral dosing at 0.3 mg/kg is 10 times higher than in dogs treated orally or intravenously at the recommended canine dose of 0.2 mg/kg (0.01 l/h/kg) and is similar to that obtained in male mice treated intravenously with 10 mg/kg meloxicam (0.155 l/h/kg;[3,14]). The increases in apparent oral clearance and volume of distribution between our high- and low-dose groups are attributed to incomplete absorption rather than alterations in metabolism or elimination. Oral clearance might increase when there is significant enterohepatic recirculation of a drug, but this increase typically would accompany concomitant decrease in elimination half-life, a change not noted in the current rabbit study. Similar interindividual variations in clearance (13% to 30%) and volume of distribution (6% to 47%) have been noted in other species treated with meloxicam, including horses, dogs, rats, minipigs, and humans.[3,22,23]

To determine the recommended dose for treatment of rabbits, further studies are required to examine the effective plasma concentration. The results of the current study have determined that the mean maximal plasma concentration after a dose of 0.3 mg/kg meloxicam in rabbits is 0.14 µg/ml (Table 2), and the mean plasma concentration at 24 h is 0.025 µg/ml. Horses also are thought to have a high clearance rate for meloxicam and in them, the effective plasma concentration of meloxicam is estimated to be 0.73 µg/ml, while the minimum relevant plasma concentration is estimated to be 0.001 µg/ml.[22] The rabbit plasma concentrations determined after oral dosage of 0.3 mg/kg seem to fall in this range. Comparison with in vitro findings of cyclooxygenase inhibitory activity also is instructive for approximating efficacious blood drug levels, although one must be cautious of making direct evaluations between in vitro and in vivo findings. In general, inhibition of COX-2 activity is desired for anti-inflammatory response, whereas COX-1 activity is linked to physiologic functions.[11] Prolonged and marked inhibition of COX-1 activity is associated with adverse gastrointestinal and renal effects. In an in vitro assay using human whole blood, the concentration of meloxicam inhibiting 50% of COX-1 activity (IC_{50}) was 1.15 µg/ml, whereas the IC_{50} for COX-2 was 0.088 µg/ml.[15] These data contrast with assays in lipopolysaccharide-unstimulated and -stimulated canine DH82 monocyte–macrophage cell lines, in which the IC_{50} for COX-1 was 23.69 µg/ml and that for COX-2 was 1.93 µg/ml.[12] Clearly, if rabbit tissues behave as do human erythrocytes, COX-2 IC_{50} concentrations would be reached at peak plasma concentration after dosing at 0.3 mg/kg, although the COX-2 IC_{50} would not be reached at 24 h. However, if rabbit tissues are more similar to canine cell lines, COX-2 IC_{50} concentrations would not be reached at all using a dose of 0.3 mg/kg. These studies emphasize the difficulty comparing data between species, as there is obviously wide species-specific variation in meloxicam COX-2 inhibitory efficacy.

A recent study examining the effect of meloxicam on the mini-

mum alveolar concentration of isoflurane in rabbits demonstrated that doses of either 0.3 or 1.5 mg/kg both induced similar reductions in isoflurane requirements in the presence of butorphanol.[24] Extrapolating from these data and in vitro COX-2 inhibition studies with meloxicam, these findings suggest that a dose of 0.3 mg/kg may be clinically efficacious in rabbits; however, beneficial COX-2 inhibiting effects may not persist for 24 h. For any species, the optimal dose should be selected based on information regarding pharmacokinetics, efficacy, and safety. Because meloxicam is COX-2-selective, it is considered a relatively safe NSAID, in terms of potential for induction of adverse gastrointestinal side effects. In rats, the dose of meloxicam required to inhibit carageenan-induced paw swelling in 50% of animals was found to be 0.12 mg/kg, whereas the dose producing gastrointestinal ulceration in 50% of rats was 2.4 mg/kg, giving a therapeutic index of 20.[3] This finding compares favorably with therapeutic indices determined for piroxicam and indomethacin in rats of 1.4 and 3.5, respectively.[3] Although meloxicam appeared clinically safe in rabbits at both 0.3 and 1.5 mg/kg, further studies are required to determine the optimal therapeutic dose. The lowest efficacious dose should be selected to minimize risks of adverse effects.

In conclusion, our findings suggest that rabbits metabolize meloxicam much faster than do dogs, humans, and rats, although absorption may be less complete. Similar to these species, rabbits show significant interindividual variability in absorption and clearance of oral meloxicam. A dose exceeding 0.3 mg/kg given once daily may be required to achieve optimal analgesic effects over a 24-h interval. Rabbits may be treated safely for at least 5 d continuously with oral meloxicam at either 0.3 or 1.5 mg/kg, without accumulation of drug.

Acknowledgments

This project was jointly funded by the Ontario Veterinary College Pet Trust Fund and Boeringher–Ingelheim Canada. We thank Amanda Healy for technical assistance. Healy was supported by an Ontario Veterinary College Summer Student Scholarship.

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