Pharmacokinetics of Intravenous and Oral Meloxicam in Ruminant Calves*

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CLINICAL RELEVANCE

The purpose of this study was to investigate the pharmacokinetics and oral bioavailability of meloxicam in ruminant calves. Six Holstein calves (145 to 170 kg) received meloxicam at 0.5 mg/kg IV or 1 mg/kg PO in a randomized crossover design with a 10-day washout period. Plasma samples collected up to 96 hours after administration were analyzed by liquid chromatography/mass spectrometry followed by noncompartmental pharmacokinetic analysis. A mean peak plasma concentration of 3.10 µg/ml (range, 2.64 to 3.79 µg/ml) was recorded at 11.64 hours (range, 10 to 12 hours) with a half-life of 27.54 hours (range, 19.97 to 43.29 hours) after oral meloxicam administration. The bioavailability of oral meloxicam corrected for dose was 1.00 (range, 0.64 to 1.66). These findings indicate that oral meloxicam administration might be an effective and convenient means of providing long-lasting analgesia to ruminant calves.

INTRODUCTION

Castration of male calves intended for beef production, one of the most common livestock management practices performed in the United States, amounts to approximately 15 million procedures per year.[1] The public's perception of the pain associated with routine livestock management procedures such as castration and de-

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horning is increasingly negative.[2] Several organizations, including the National Cattlemen's Beef Association[3] and the American Veterinary Medical Association,[4] have stated that pain and distress resulting from castration should be minimized. Studies have demonstrated that NSAID administration before dehorning and castration mitigates plasma cortisol response.[5–8] However, currently there are no analgesic drugs specifically approved for the alleviation of pain in livestock in the United States.[4]

Meloxicam, an NSAID of the oxicam class, is approved in the European Union for adjunctive therapy of acute respiratory disease, diarrhea, and acute mastitis when administered at 0.5 mg/kg IV or SC.[9] Heinrich et al[7] demonstrated that calves receiving meloxicam (0.5 mg/kg IM) combined with a cornual nerve block before cautery dehorning had a reduced serum cortisol response for a longer period compared with calves receiving only local anesthesia. Furthermore, calves receiving meloxicam had lower heart rates and respiratory rates than placebo-treated control calves during the 24 hours after dehorning. Stewart et al[8] found that meloxicam administered at 0.5 mg/kg IV combined with a cornual nerve block mitigated the onset of pain responses, as measured by heart rate variability and eye temperature, compared with administration of a nerve block alone. These reports indicate that meloxicam administration at 0.5 mg/kg IV or IM before dehorning apparently is effective in alleviating pain and distress.

The pharmacokinetics of meloxicam administered PO or IV to calves has not been reported in the published literature. If oral meloxicam administration resulted in plasma concentrations comparable to those of parenteral administration, veterinarians would have a practical and cost-effective way to reduce the pain and distress associated with dehorning and castration. The objective of the study reported here was to evaluate the pharmacokinetics of IV and PO meloxicam in ruminant calves.

MATERIALS AND METHODS

This study was approved by the Institutional Animal Care and Use Committee at Kansas State University (protocol #2649).

Animals and Housing

Six male Holstein calves approximately 3 months of age were obtained from a commercial dairy in southwest Kansas. Mean (±SD) weights at first and second treatment administrations were 159.1 ± 5.26 kg and 172.3 ± 9.63 kg, respectively. Weights for dose calculation were determined by weighing the calves 24 hours before treatment administration.

Study animals were acclimated in group housing comprising six calves/pen for approximately 3 weeks before study commencement. Housing consisted of an outdoor concrete pad (9.75 × 18.29 m) with a partial roof on straw bedding. Cattle were fed a typical receiving diet composed of cracked corn, oats, soybean meal, molasses, and a protein–vitamin–mineral supplement at 8 kg/head/day throughout the experiment. Prairie hay and water were offered ad libitum. Feed was not withheld before study commencement.

Calves receiving meloxicam had lower heart rates and respiratory rates than placebo-treated control calves during the 24 hours after dehorning.

Experimental Design

A crossover study design was used, with calves randomly assigned to one of two dosing regimens. The observed washout period between treatment administrations was 10 days.

Approximately 12 hours before each phase of the study began, the calves were restrained for IV catheter placement. After restraint, the area over the jugular vein was clipped and disinfected with 70% isopropyl alcohol and povidone–iodine scrub swabs. The catheter site was infiltrated with 2% lidocaine injection (Hospira; 1 ml SC) before placement of a 14-gauge, 130-mm extended-use catheter (Milacath, MILA International, Florence, KY), which was sutured to the skin with #3 nylon suture. Calves assigned to the IV meloxicam regimen were fitted with two catheters, one designated for drug administration and the other for blood sample collection. Catheter patency was maintained with a heparin–saline flush containing 3 USP units of heparin sodium/1 ml saline (Heparin Sodium Injection, Baxter Healthcare).

Each calf was subjected to one of the following two treatments in each treatment period (*n* = 3 calves/treatment/period).

- IV injection of 0.5 mg/kg of meloxicam (Metacam 5 mg/ml Solution for Injection [NADA 141-219]; Boehringer Ingelheim Vetmedica; lot #118ZN15) administered as a bolus in the jugular vein with a designated catheter. The catheter was flushed with 5 ml of heparin–saline and removed immediately after administration.
- Oral meloxicam administered at 1 mg/kg (meloxicam, 15-mg tablets [NDC 60505-2554-1]; Apotex Corporation, Weston, FL; lot #JD9485). Tablets were dissolved in 50 ml of water within 5 minutes of administration by stomach tube. The stomach tube was flushed with 1 L of water before removal.

The IV dose was rounded to the nearest 0.5 ml and administered with a 20-ml syringe. The oral dose was rounded to the nearest whole tablet.

Calves were manually restrained with a rope halter for blood collection. In the calves receiving IV meloxicam, approximately 10 ml of blood was collected at 0, 3, 6, 10, 20, and 40 minutes and 1, 3, 6, 12, 24, 36, and 48 hours after dosing. In the calves receiving oral meloxicam, blood samples were collected at 0, 15, and 30 minutes and 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, and 48 hours after administration. Based on the results of the first phase, an additional sample was collected from calves (*n* = 3/treatment) at 72 and 96 hours after administration in the second treatment period of the study. Blood was drawn into a collection syringe and immediately transferred to lithium–heparin Vacutainer tubes (BD Diagnostics). Samples were stored on ice. Within 30 minutes of collection, the samples were centrifuged for 10 minutes at 1,500 ×*g*. Plasma was then pipetted to cryovials and frozen at –70˚C until analysis.

Plasma Drug Analysis

Plasma concentrations of meloxicam (mass:charge ratio [*m/z*] 352.09→114.90) were determined with high-pressure liquid chromatography (Shimadzu Prominence, Shimadzu Scientific Instruments, Columbia, MD) and mass spectrometry (API 2000, Applied Biosystems, Foster City, CA). Plasma samples or standards (100 µl) were added to 100 µl of internal standard (piroxicam 0.5 µg/ml in methanol, *m/z* 332.12→95.10) and 300 µl of methanol with 0.1% formic acid to precipitate the proteins. The samples were vortexed for 5 seconds and centrifuged for 10 minutes at 10,000 ×*g*. The supernatant, 200 µl, was transferred to an injection vial with the injection volume set to 10 µl. The mobile phase consisted of A: acetonitrile and B: 0.1% formic acid at a flow rate

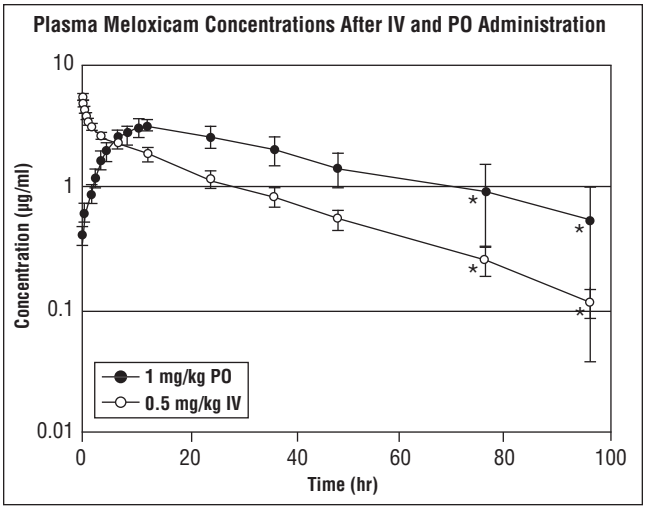

Figure 1. *Mean (±SD) plasma meloxicam concentrations following a single administration at 0.5 mg/kg IV or 1 mg/kg PO. * = 3/6 calves.*

of 0.4 ml/min. The mobile phase consisted of 85% B from 0 to 0.5 minutes with a linear gradient to 50% B at 2.5 minutes, which was maintained until 3 minutes, followed by a linear gradient to 85% B at 4 minutes, with a total run time of 5 minutes. Separation was achieved with a C8 column (Supelco Discovery C8, 50 mm × 2.1 mm × 5 µm; Sigma-Aldrich, St. Louis, MO) maintained at 40˚C. The standard curve was linear from 0.01 to 10 µg/ml and was accepted if the correlation coefficient exceeded 0.99 and predicted values were within 15% of the actual values. The accuracy of the assay was 103% ± 7% of the actual value, and the coefficient of variation was 7%, determined on replicates of 5 each at 0.025, 0.5, and 5 µg/ml.

Pharmacokinetic Analysis

Pharmacokinetic analyses were performed with computer software (WinNonlin 5.2, Pharsight Corporation, Mountain View, CA). The variables calculated included the area under the curve from time 0 to infinity (AUC_{INF}) using the linear trapezoidal rule, area under the first moment curve from time 0 to infinity ($AUMC_{INF}$), plasma clearance (Cl), plasma clearance per fraction of the dose absorbed (Cl/F), apparent volume of distribution at steady state (Vss), apparent volume of distribution of the area (Vz), apparent volume of distribution of the area per fraction of the dose absorbed (Vz/F), first-order rate constant (λ_z), terminal half-life ($T_{½}\ \lambda_z$), and mean residence time extrapolated to infinity (MRT). The maximum serum concentration (C_{max}) and time to maximum serum concentration (T_{max}) were determined directly from the data. The concentration at time 0 (C0) was calculated by log-linear regression using the first two time points after IV administration. The mean absorption time (MAT) was calculated by subtracting the intravenous from the oral MRT. The fraction of the dose absorbed (F [i.e., bioavailability]) for oral meloxicam was determined by dividing the AUC_{INF} per dose after oral administration by the AUC_{INF} per dose after IV administration.

RESULTS

No adverse effects were noted after IV or oral meloxicam administration. The mean time-concentration profile for meloxicam in calves after IV administration of 0.5 mg/kg is presented in Figure 1. The calculated noncompartmental pharmacokinetic parameters for each animal are summarized in Table 1. After IV administration, meloxicam demonstrated a relatively small mean Vss of 0.171 L/kg (range, 0.15 to 0.19 L/kg) and a slow Cl from the central compartment of 0.1 ml/min/kg (range, 0.08 to 0.12 ml/kg/min). This resulted in a relatively long mean plasma $T_{½}\ \lambda_z$ of 20.35 hours (range, 17.84 to 22.76 hours).

The calculated noncompartmental pharmacokinetic parameters for meloxicam following oral administration at 1 mg/kg are presented in Table 2. Based on these data, a mean peak plasma meloxicam concentration of 3.10 µg/ml (range, 2.64 to 3.79 µg/ml) was recorded at approximately 12 hours (range, 10 to 12 hours) after oral administration. The AUC following oral administration was similar to that of IV administration, with a calculated bioavailability of 1.00 (range, 0.64 to 1.66). One calf (#16) eliminated meloxicam more slowly than the other calves in the study after oral administration, which resulted in a higher AUC and therefore an inflated oral bioavailability estimate. The reason for this outlier is not known.

DISCUSSION

The purpose of this study was to investigate the pharmacokinetics and oral bioavailability of meloxicam in ruminant calves. The study's results indicate that a mean C_{max} of 3.10 µg/ml occurred approximately 12 hours after oral meloxicam administration. The combination of a small volume of distribution and slow clearance resulted in a mean $T_{½}$ λ_z of 27.54 hours. Oral meloxicam demonstrated excellent bioavailability when corrected for dose. These findings suggest that oral administration of meloxicam might be an effective and convenient means of providing long-lasting analgesia to ruminant calves once efficacy has been demonstrated.

To better characterize the elimination profile of oral and IV meloxicam in cattle, the sampling times were increased in the second period to include 72 and 96 hours after administration. The large extrapolation of the AUC in the first period (range, 15% to 20% after IV dosing and 33% to 39% after oral dosing) could decrease the

TABLE 1. Meloxicam Pharmacokinetic Parameters Following a Single Administration at 0.5 mg/kg IV

	Calf No.						*Geometric*			
Parameter	*16*	*18*	*23*	*31*	*40*	*44*	***Mean***	***Min***	***Median***	***Max***
$AUC_{EXTRAPOLATED}$ (%)	17.07	4.90	3.79	15.26	20.06	3.63	8.40	3.63	10.08	20.06
AUC_{INF} (hr*µg/ml)	89.19	100.62	83.70	72.19	79.43	72.35	82.34	72.19	81.57	100.62
$AUMC_{INF}$ (hr*hr*µg/ml)	2,400.61	3,177.29	2,472.52	1,779.60	2,351.43	1,982.72	2,321.34	1,779.60	2,376.02	3,177.29
C0 (µg/ml)	6.56	6.36	6.66	5.48	5.08	5.62	5.93	5.08	5.99	6.66
Cl (ml/min/kg)	0.09	0.08	0.10	0.12	0.10	0.12	0.10	0.08	0.10	0.12
$T_{½}$ λ_z (hr)	19.16	22.76	21.53	17.84	21.08	20.10	20.35	17.84	20.59	22.76
λ_z (1/hr)	0.036	0.031	0.032	0.039	0.033	0.035	0.034	0.031	0.034	0.039
MRT (hr)	26.92	31.58	29.54	24.65	29.60	27.40	28.19	24.65	28.47	31.58
Vss (L/kg)	0.151	0.157	0.177	0.171	0.186	0.189	0.171	0.151	0.174	0.189
Vz (L/kg)	0.155	0.163	0.186	0.178	0.192	0.200	0.178	0.155	0.182	0.200

$AUC_{EXTRAPOLATED}$ = extrapolated area under the curve; AUC_{INF} = area under the curve from time 0 to infinity; $AUMC_{INF}$ = area under the first moment curve from time 0 to infinity; C0 = concentration at time 0; Cl = plasma clearance; max = maximum; min = minimum; MRT = mean residence time extrapolated to infinity; $T_{½}$ λ_z = terminal half-life; λ_z = first-order rate constant; Vss = apparent volume of distribution at steady state; Vz = apparent volume of distribution of the area.

TABLE 2. Meloxicam Pharmacokinetic Parameters Following a Single Administration at 1 mg/kg PO

	Calf No.						*Geometric*			
Parameter	*16*	*18*	*23*	*31*	*40*	*44*	***Mean***	***Min***	***Median***	***Max***
$AUC_{EXTRAPOLATED}$ (%)	23.01	30.01	39.43	4.14	5.85	33.02	16.71	4.14	26.51	39.43
AUC_{INF} (hr*µg/ml)	295.80	129.03	153.46	140.60	153.18	156.84	164.46	129.03	153.32	295.80
$AUMC_{INF}$ (hr*hr*µg/ml)	19,736.82	5,205.64	8,017.42	4,730.72	6,087.68	6,837.34	7,384.86	4,730.72	6,462.51	19,736.82
Cl/F (ml/min/kg)	0.06	0.13	0.11	0.12	0.11	0.11	0.10	0.06	0.11	0.13
C_{max} (µg/ml)	3.79	2.93	2.64	3.33	2.83	3.19	3.10	2.64	3.06	3.79
$T_{½} \lambda_z$ (hr)	43.29	24.85	34.10	19.97	21.41	27.83	27.54	19.97	26.34	43.29
λ_z (1/hr)	0.016	0.028	0.020	0.035	0.032	0.025	0.025	0.016	0.026	0.035
MRT (hr)	66.72	40.35	52.24	33.65	39.74	43.59	44.90	33.65	41.97	66.72
T_{max} (hr)	10.00	12.00	12.00	12.00	12.00	12.00	11.64	10.00	12.00	12.00
Vz/F (L/kg)	0.211	0.278	0.321	0.205	0.202	0.256	0.242	0.202	0.234	0.321
MAT (hr)	39.81	8.77	22.70	8.99	10.14	16.19	15.07	8.77	13.17	39.81
F	1.66	0.64	0.92	0.97	0.96	1.08	1.00	0.64	0.97	1.66

$AUC_{EXTRAPOLATED}$ = extrapolated area under the curve; AUC_{INF} = area under the curve from time 0 to infinity; $AUMC_{INF}$ = area under the first moment curve from time 0 to infinity; Cl/F = plasma clearance per fraction of the dose absorbed; C_{max} = maximum serum concentration; F = fraction of the dose absorbed; MAT = mean absorption time; max = maximum; min = minimum; MRT = mean residence time extrapolated to infinity; $T_{½} \lambda_z$ = terminal half-life; λ_z = first-order rate constant; T_{max} = time to maximum serum concentration; Vz/F = apparent volume of distribution of the area per fraction of the dose absorbed.

robustness of the pharmacokinetic model. A potential problem with large extrapolations of the AUC is that the true terminal phase of the plasma profile may be missed, decreasing the robustness of the pharmacokinetic parameters. The plasma profile was similar in both periods for both routes of administration, suggesting the true terminal phase was identified in both periods. Therefore, despite the large extrapolated AUC in the first period, the estimated pharmacokinetic parameters appear accurate.

There currently are no analgesic drugs specifically approved in the United States for alleviating pain in livestock.[4] The FDA Center for Veterinary Medicine guidance for the development of effectiveness data for NSAIDs indicates that validated methods of pain assessment must be used for a drug to be indicated for pain relief in the target species.[10] This requirement explains the lack of analgesic drugs approved in the United States for pain relief in livestock, because there currently are no validated methods of pain assessment in food-producing animals. The unavailability of approved analgesic drugs is a substantial obstacle to providing pain relief to food animals in the United States.[4]

In the United States, meloxicam administered to cattle by any route constitutes extra-label drug use (ELDU). Under the Animal Medicinal Drug Use Clarification Act (AMDUCA), ELDU is permitted for relief of suffering in cattle only if

specific conditions are met: (1) ELDU is permitted only by or under the supervision of a veterinarian; (2) it is allowed only for FDA-approved animal and human drugs; (3) it is permitted only when the health of the animal is threatened and not for production purposes; (4) ELDU in feed is prohibited; and (5) it is not permitted if it results in a violative food residue.[11] Therefore, the use of oral meloxicam to alleviate suffering associated with dehorning and castration in calves in the United States would be required by law to comply with these regulations.

The unavailability of approved analgesic drugs is a substantial obstacle to providing pain relief to food animals in the United States.

Currently, the only NSAID approved for use in cattle in the United States is flunixin meglumine.[12] The plasma elimination half-life of flunixin is reported to be 3 to 8 hours; therefore, this agent requires once-daily administration.[13] Although NSAIDs are recognized as having analgesic properties, flunixin is indicated only for controlling fever associated with respiratory disease or mastitis or fever and inflammation associated with endotoxemia, not for pain control.[14] Studies demonstrating the analgesic effects of flunixin at the approved dosage of 2.2 mg/kg are deficient in the published literature. Use of flunixin meglumine is further complicated by the requirement for IV administration,[14] which is more stressful on the animal and involves more skill and training on the part of the operator. Several reports have suggested that IM administration of flunixin also may result in significant myonecrosis and tissue residues.[12] In the absence of data demonstrating that flunixin reduces signs of pain and distress associated with dehorning and castration in calves, it could be argued that use of meloxicam for this purpose is justified under AMDUCA.[11]

Meloxicam (20 mg/ml) is approved for use in cattle in several European countries, with a 15-day meat withdrawal time and a 5-day milk withholding time after administration of 0.5 mg/kg IV or SC.[12] An oral meloxicam suspension (1.5 mg/ml) and injectable formulation (5 mg/ml) are approved in the United States for controlling pain and inflammation associated with osteoarthritis in dogs. Furthermore, an injectable formulation (5 mg/ml) is approved for controlling postoperative pain and inflammation in cats.[12] Several generic tablet formulations containing meloxicam (7.5 and 15 mg) were approved recently for relieving signs and symptoms of osteoarthritis in humans. The cost of administering IV meloxicam to calves in the present study was approximately $58.00/100 kg; the cost of administering oral meloxicam was $0.30/100 kg.

The goal of providing pain control in the immediate perioperative period is to decrease central sensitization (wind-up) and the ensuing hypersensitivity to pain.[15,16] Surgery-induced central sensitization has two phases: an immediate incisional phase and a prolonged inflammatory phase due to tissue damage.[15] Because inflammatory injury plays the dominant role, the antinociceptive effects of the perioperative analgesic drugs ideally should extend into the postoperative period. The pharmacokinetic profile of meloxicam described in this report suggests that oral preemptive analgesia should be administered 12 hours before surgery so that surgery coincides with peak plasma drug concentrations. Furthermore, oral meloxicam may

provide effective analgesic concentrations for several days after surgery, based on the calculated mean plasma half-life of approximately 28 hours. Given that the plasma half-life of meloxicam is longer than the half-lives previously reported for ketoprofen (0.42 hours),[17] salicylate (0.5 hours),[6] and flunixin (4 to 8 hours),[13] this suggests that meloxicam may provide extended duration of activity compared with other NSAIDs currently available in the United States.

CONCLUSION

To our knowledge, this is the first published report describing the pharmacokinetics of meloxicam in calves following oral and IV administration. These pharmacokinetic findings support previous clinical reports suggesting prolonged analgesic effects of meloxicam in calves following IM and IV administration. These results suggest that oral meloxicam administration may offer a long-acting, safe, and practical alternative to injectable preemptive analgesia. Further assessment of oral meloxicam in established pain models is required to formulate science-based analgesic recommendations to enhance animal well-being after dehorning and castration.

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