DOI: 10.2478/fv-2025-0038

FOLIA VETERINARIA, 69, 4: 73—78, 2025

ORIGINAL ARTICLE

COMPARATIVE PHARMACOKINETICS OF INTRAVENOUS AND INTRAMUSCULAR MELOXICAM IN AWASSI SHEEP: IMPLICATIONS FOR EXTENDED THERAPEUTIC EFFICACY

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Citation: Abdelqader, N. M., Mohammed, A. T., Albadrany, Y. M. A., 2025: Comparative pharmacokinetics of intravenous and intramuscular meloxicam in Awassi sheep: Implications for extended therapeutic efficacy. Folia Veterinaria, 69, 4, 73–78.

Received: July 30, 2025

Accepted: October 11, 2025

Published: December 15, 2025

Ethical considerations: When reporting experiments on animals Observation of the ARRIVE guidelines 2.0: Updated guidelines for reporting animal research, published on July 14, 2020 (DOI: 10.1371/journal.pbio.3000410), is applied. The authors ensure that all procedures were performed in compliance with the guidelines for animal care of their institutions or with national/international guidelines.

ABSTRACT

Meloxicam, a COX-2 preferential NSAID, is broadly used in veterinary medicine for analgesic and anti-inflammatory activity, but pharmacokinetic data in sheep remain restricted. This study compared plasma pharmacokinetic profiles of meloxicam administered intravenously (IV) and intramuscularly (IM) in Awassi sheep. A two-phase crossover design study with a 12-day washout was conducted in five healthy male Awassi sheep (26–34 kg). Meloxicam (0.5 mg/kg) was administered by IV or IM. Blood samples were collected at determined intervals (IV: 0.083–24 h; IM: 0.5–24 h). Plasma concentrations were quantified via spectrophotometry, and Pharmacokinetic (PK) parameters resulted from non-compartmental analysis. IV administration showed rapid distribution (C_{max}: 7.17 ± 0.17 µg/mL at 0.083 h) and prolonged $t_{1/2\beta}$ (13.02 h). IM administration showed delayed absorption (T_{max}: 4 h; C_{max}: 7.08 ±0.04 µg/mL) and comparable $t_{1/2\beta}$ (14.77 h). Both routes maintained plasma concentrations >1 µg/mL for >24 h. Key parameters include volume of distribution (V_d) (IV: 0.094 L/kg; IM: 0.078 L/kg), clearance (Cl) (IV: 0.0050 L/h/kg; IM: 0.0036 L/h/kg), and area under the plasma concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$) (IV: 98.95 µg×h/mL; IM: 135.36 µg×h/mL). Meloxicam revealed satisfactory PK properties with sustained therapeutic concentrations beyond 24 hours, supporting once-daily dosing for long-term pain management in sheep.

Key words: Awassi sheep; intramuscular; intravenous; meloxicam; pharmacokinetics

INTRODUCTION

Meloxicam, a selective cyclooxygenase-2 (COX) inhibitor, is extensively utilized in veterinary medicine for its anti-inflammatory and analgesic effects [1]. While its pharmacodynamics have been well-documented in humans [2], horses [3], calves [4], and cattle [5], data in sheep, particularly for intramuscular administration, remain sparse. In ruminants, meloxicam is employed to manage pain associated with surgical procedures, mastitis, and dystocia [6]. However, interspecies variability in drug metabolism, driven by differences in cytochrome p450 enzyme activity and protein binding, necessitates species-specific PK evaluation [7].

Existing studies in sheep report an elimination half-life ($t_{1/2\beta}$) of 10.85−14 hours flowing IV dosing [8, 9], but IM data are limited to a single study using a higher dose (1 mg/kg) [10]. This study addresses this gap by comparing IV and IM PK profiles of meloxicam (0.5mg/kg) in Awassi sheep, a breed prevalent in Middle Eastern livestock system. The findings aim to optimize dosing regimens and inform clinical use in ovine medicine.

MATERIALS AND METHODS

Animals & study design

Five healthy male Awassi sheep (11–12 months; 26–34 kg) were acclimatized in individual pens with *ad libitum* water and forage. A randomized crossover design with a 12-day washout period was employed. Sheep received meloxicam (0.5 mg/kg; Ashish Life Science, India) via IV (jugular vein) or IM routes. Blood samples were collected into EDTA tubes at specified intervals (IV: 0.083, 0.5, 1, 2, 4, 8, 16, 24 h; IM: 0.5, 1, 2, 4, 8, 16, and 24 h). Plasma was separated by centrifugation (1500 ×g, 10 min) and stored at −18°C.

Preparation of the standard solution

A standard solution of meloxicam (0.5 mg/mL) was prepared using 50% methanol, and secondary standard dilutions were prepared using methanol at concentrations of 0.5, 1, 1.75, 2.5, 5, 7.5, and 10 µg/mL.

Meloxicam quantification in the plasma protocol

The quantification of meloxicam in plasma was performed using a validated UV-visible spectrophotometric method, with sample extraction steps adapted from the HPLC protocol of Bae et al. (2007) [2]. Briefly , 500 microliter aliquots of plasma or calibration standards were transferred to glass test tubes and acidified with 100 microliter of 5 M hydrochloric acid (HCl), followed by brief homogenization by vortex mixing. Liquid-liquid extraction was initiated by adding 6mL of diethyl ether, after which samples were agitated for 30 minutes to ensure phase equilibration. Post- extraction, samples were vortexed briefly and centrifuged at 2500 rpm for 10 minutes to separate phases. The organic layer (diethyl ether) was quantitatively transferred to a fresh tube and evaporated to dryness under a controlled nitrogen stream. The residue was reconstituted in 1mL of methanol, and meloxicam concentration was determined spectrophotometrically by measuring absorbance at 355 nm using UV-vis spectrophotometer. A calibration curve (0.5–10 µg/mL; R^2 = 0.9325) was constructed from reference standards to calculate plasma concentrations of meloxicam by linear regression. This modified method was validated for linearity, precision, and reproducibility within the therapeutic concentration range relevant to sheep pharmacokinetic analysis.

Meloxicam quantification in sheep plasma analysis

The quantification of meloxicam concentrations in ovine plasma was achieved via a validated spectrophotometric method, with absorbance measured at 355 nm. A standard calibration curve was created through simple linear regression analysis (R^2 = 0.9325), resulting from laboratory-prepared reference dilutions of known meloxicam concentrations. The regression equation is expressed as y = 239.63x + −236.36, where y represents the absorbance value, x denotes the analyte concentration (µg/mL), m (slope) is 239.63, and b (y-intercept) is –236.36. Unknown plasma concentrations were calculated by readjusting the regression equation to x = (y + 236.36)/239.63, ensuring traceable calibration of experimental samples. Data processing and regression analysis were conducted using Microsoft Excel 2013, with methodological details demonstrated in Figure 1. This approach obeys to robust analytical principles for pharmacokinetic studies, leveraging linear regression's predictive accuracy within the validated dynamic range.

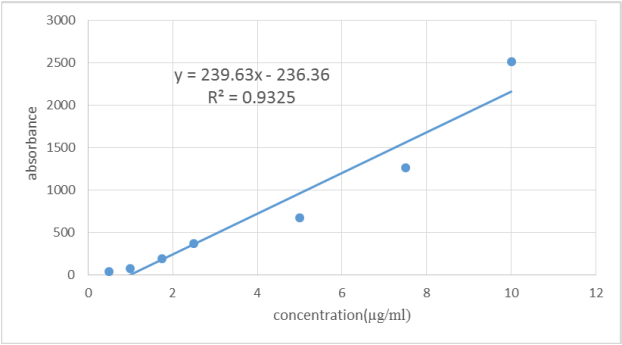

Fig. 1. Standard meloxicam calibration curve (0.5–10 µg/mL; R^2=0.932)

Pharmacokinetics of meloxicam in sheep

The objective of this study was to determine the pharmacokinetic profile of meloxicam following single-dose intravenous (IV) and intramuscular (IM) administration in sheep at a dosage of 0.5 mg/kg. Plasma concentrations of meloxicam were quantified through spectrophotometric analysis at determined time intervals. Pharmacokinetic parameters were derived via non-compartmental pharmacokinetic analysis using the pharmacokinetic modeling software PK Solver [11]. Key parameters measured included elimination half-life ($t_{1/2\beta}$), elimination rate constant (kel), volume of distribution (Vd), total systemic clearance (Cl), mean residence time (MRT), time to maximum concentration (T_{max}), peak plasma concentration (C_{max}), and the area under the plasma concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$). These parameters were evaluated to describe the drug's absorption, distribution, and elimination kinetics through both administration routes, verifying a comprehensive understanding of its *in vivo* behavior in the ovine model.

RESULTS

Plasma concentrations and pharmacokinetic parameters following intravenous administration

Meloxicam (0.5 mg/kg) was administered intravenously (IV) to sheep; plasma concentrations peaked at 7.17 ± 0.17 µg/mL within 0.083 hours (5 minutes) and declined progressively over 24 hours (Table 1). Pharmacokinetic analysis showed an elimination half-life ($t_{1/2\beta}$) of 13.02 hours, a volume of distribution (Vd) of 0.094 L/kg, and a total clearance (Cl) of 0.0050 L/h/kg. The area under the plasma concentration-time curve ($AUC_{0-\infty}$) was 98.952 µg×h/mL, and the mean residence time (MRT) was 18.27 hours (Table 2).

Table 1. Plasma concentrations of meloxicam after intravenous administration (0.5 mg/kg) in sheep

Time (h)	Concentration µg/mL
0.083	7.17±0.17
0.5	6.50±0.10
1	5.66±0.11
2	5.00±0.04
4	4.20±0.06
8	3.30±0.08
16	2.06±0.05
24	1.46±0.03

Table 2. Pharmacokinetic parameters of meloxicam after intravenous administration (0.5 mg/kg) in sheep

parameters	values	units
$t_{1/2\beta}$	13.02	h
T_{max}	0.08	h
C_{max}	7.17	µg
K_{el}	0.053	h^{-1}
MRT	18.27	h
V_d	0.094	L/kg
Cl	0.0050	L/h/kg
$AUC_{0-\infty}$	98.952	µg× h/mL

$t_{1/2\beta}$ = Terminal Elimination Half-Life, T_{max} = Time to Maximum Plasma Concentration, C_{max} = Maximum Plasma Concentration, K_{el} = Terminal Phase Elimination Rate Constant, MRT = Mean Residence Time, V_d = Volume of Distribution, Cl = Clearance, $AUC_{0-\infty}$ = Area Under the Curve from time 0 to infinity.

Plasma concentrations and pharmacokinetic parameters following intramuscular administration

Intramuscular (IM) administration of meloxicam (0.5 mg/kg) resulted in a delayed T_{max} of 4 hours, with a C_{max} of 7.08 ± 0.04 µg/mL (Table 3). The elimination half-life ($t_{1/2\beta}$) was prolonged to 14.77 hours, with an $AUC_{0-\infty}$ of 135.362 µg×h/mL. The volume of distribution (Vd) and total clearance (Cl) were 0.078 L/kg and 0.0036 L/h/kg, respectively, while the MRT extended to 20.21 hours (Table 4).

Table 3. Plasma concentrations of meloxicam after intramuscular administration (0.5 mg/kg) in sheep

Time (h)	Concentration µg/mL
0.5	5.98±0.17
1	6.31±0.13
2	6.67± 0.07
4	7.08±0.04
8	4.13±0.16
16	2.78±0.06
24	1.95±0.06

Table 4. Pharmacokinetic parameters of meloxicam after intramuscular administration (0.5 mg/kg) in sheep

parameters	values	units
$t_{1/2\beta}$	14.77	h
T_{max}	4	h
C_{max}	7.08	µg
K_{el}	0.046	h^{-1}
MRT	20.21	h
V_d	0.078	L/kg
Cl	0.0036	L/h/kg
$AUC_{0-\infty}$	135.362	µg× h/mL

$t_{1/2\beta}$ = Terminal Elimination Half-Life, T_{max} = Time to Maximum Plasma Concentration, C_{max} = Maximum Plasma Concentration, K_{el} = Terminal Phase Elimination Rate Constant, MRT = Mean Residence Time, V_d = Volume of Distribution, Cl = Clearance, $AUC_{0-\infty}$ = Area Under the Curve from time 0 to infinity.

Comparative pharmacokinetic profile

The $AUC_{0-\infty}$ and MRT were notably higher following IM administration compared to IV (135.362 vs. 98.952 µg×h/mL and 20.21 vs. 18.27 h, respectively). Both routes sustained plasma concentrations above the therapeutic threshold (1 µg/mL) for over 24 hours, with IM administration exhibiting a delayed absorption phase but comparable bioavailability (Figure 2).

DISCUSSION

The study employed a randomized two-phase crossover design with a 12-day washout period, verifying elimination of residual drug between IV and IM administration. This approach reduces inter-individual variability through using the same animals for both routes. However, the small sample size (n = 5) raises questions about statistical power and generalizability. While common in veterinary studies including large animals, bigger cohort would support conclusions. The use of Awassi sheep, a breed predominant in arid regions, additions ecological relevance but highlights the need for breed-specific pharmacokinetic (PK) data due to potential genetic and metabolic differences.

The present study explores the pharmacokinetic characteristics of meloxicam in Awassi sheep after intravenous (IV) and intramuscular (IM) administration at doses of 0.5 mg/kg. Both routes showed a sustained plasma concentrations above the therapeutic threshold (≥1 µg/mL) [12] for over 24 hours, highlighting the drug's prolonged therapeutic efficacy in this species. Remarkably, the elimination half-life ($t_{1/2\beta}$) of meloxicam in sheep (13.02 h IV; 14.77 h IM) in consist with prior reports in ruminants but diverges from values detected in humans [2], horses [3], and avian species [13], conforming interspecies variability in drug metabolism.

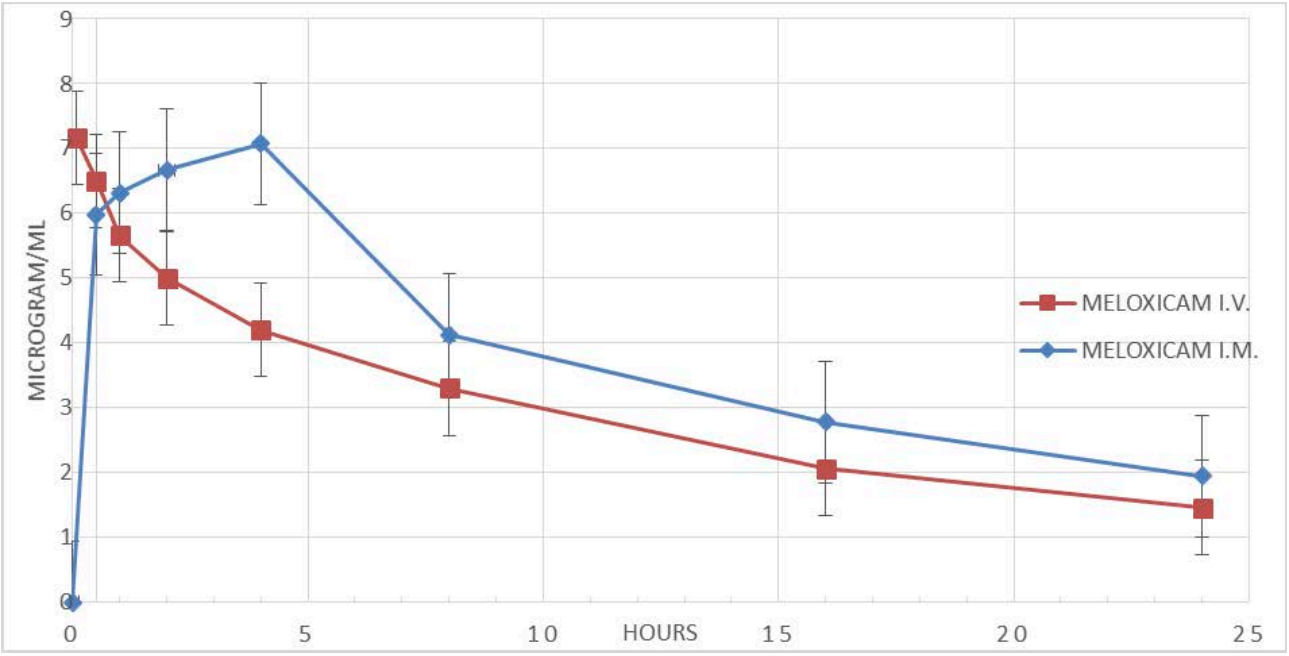

Fig. 2. Plasma concentration-time profile following IV and IM administration (Mean ± SE)

The prolonged $t_{1/2\beta}$ and mean residence time (MRT) observed in this study recommend meloxicam's potential for once-daily dosing in sheep, a critical advantage in clinical settings demanding prolonged analgesia. The significantly higher $AUC_{0-\infty}$ following IM administration for IV (135.362 vs. 98.952 µg×h/mL) indicates near-complete bioavailability by this route, consistent with efficient systemic absorption from the muscle compartment. However, the delayed T_{max} (4 h IM vs. 0.08 h IV) reflects slower absorption kinetics inherent to IM delivery, possibly influenced by formulation characteristics such as solvent composition or drug solubility.

Comparative analysis with present literature reveals notable inter-study variability in ovine pharmacokinetic parameters. For example, the IV $t_{1/2\beta}$ (13.02 h) aligns closely with values reported by Stock et al. (14 h) in Dorset cross sheep [9] but differs from Shukla et al.'s results (10.85 h) in crossbred females [8]. Such differences may arise from breed-specific dissimilarities in metabolic enzyme activity, principally cytochrome P450 isoforms responsible for meloxicam's hepatic metabolism. Similarly, the IM C_{max} (7.08 µg/mL) and $t_{1/2\beta}$ (14.77 h) in this study contrast with Woodland et al.'s data (9.77 µg/mL; 12.63 h) at a higher dose (1 mg/kg) [10], further highlighting the influence of genetic and methodological factors on pharmacokinetic outcomes.

The sustained therapeutic plasma levels (>1 µg/mL) observed beyond 24 hours post-administration confirm meloxicam's efficacy in managing chronic inflammatory conditions in sheep, such as mastitis or post-surgical pain. This prolonged activity, coupled with its satisfactory safety profile in ruminants, positions meloxicam as a valuable NSAID in veterinary practice. However, the lower volume of distribution (Vd) and clearance (Cl) following IM administration propose potential tissue-binding differences between routes, warranting further investigation into tissue-specific pharmacokinetics.

Therapeutic outcomes

•Sustained Therapeutic Levels: Both routes sustained plasma concentrations >1 µg/mL for >24 hours, supporting once-daily dosing in clinical settings. This is critical for managing chronic conditions (e.g., post-surgical pain, mastitis) in sheep.

•Practical Advantages of IM Route: The delayed T_{max} and prolonged $t_{1/2\beta}$ make IM administration ideal for field use, avoiding the need for IV catheterization.

Limitations of the study

•Small Sample Size: Limits statistical robustness and generalizability.

•Single-Dose Design: Precludes assessment of drug accumulation, safety with repeated dosing, or dose-response relationships.

•Lack of Clinical Endpoints: PK parameters alone do not approve therapeutic efficacy. Future studies should correlate plasma levels with pain relief or anti-inflammatory outcomes.

•Bioavailability Paradox: The higher AUC for IM despite identical dosing requires clarification, potentially through mass spectrometry validation or urinary excretion studies.

CONCLUSION

In conclusion, this study provides robust pharmacokinetic evidence supporting the clinical use of meloxicam in sheep, with both IV and IM routes offering sustained therapeutic coverage. The delayed absorption kinetics of IM administration and breed-related variability in drug metabolism underscore the need for tailored dosing regimens. Future research should explore the impact of formulation additives and genetic factors on meloxicam's disposition to optimize therapeutic outcomes in diverse ovine populations. This work underscores the necessity of species- and breed-specific PK studies to optimize veterinary drug regimens and improve animal welfare.

Data Availability Statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Statement

The study protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the College of Veterinary Medicine, University of Mosul, approval number (9/13/1526).

Conflict of Interest

No conflict of interest.

Funding

This study was financially supported by the authors.

Authors' Contributions

Yasser M. Albadrany: Conceptualization, Methodology, Writing and editing.

Nagham M. Abdelqader & Ahmed T. Mohammed: Sampling and methodology, Data collection, Data analysis.

Generative AI Statement

The authors declare that no generative AI was used in the creation of this manuscript.

Acknowledgements

We would like to express our heartfelt gratitude to the College of Veterinary Medicine at the University of Mosul for their support in completing this research, which is part of the first and second authors' bachelor's thesis.

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