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ORIGINAL ARTICLE

Pharmacokinetics of meloxicam following intravenous administration at different doses in sheep

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Abstract

The aim of this study is to determine the pharmacokinetic change after intravenous administration of meloxicam at doses of 0.5, 1 and 2 mg/kg to sheep. The study was carried out on six Akkaraman sheep. Meloxicam was administered intravenously to each sheep at 0.5, 1, and 2 mg/kg doses in a longitudinal pharmacokinetic design with a 15-day washout period. Plasma concentrations of meloxicam were determined using the high performance liquid chromatography-ultraviolet, and pharmacokinetic parameters were evaluated by non-compartmental analysis. Meloxicam was detected up to 48 h in the 0.5 mg/kg dose and up to 96 h in the 1 and 2 mg/kg doses. As the dose increased from 0.5 to 2 mg/kg, terminal elimination half-life, and dose normalized area under the concentration versus time curve increased and total clearance decreased. Compared to the 1 mg/kg dose, it was determined that V_{dss} decreased and $C_{0.083h}$ increased in the 2 mg/kg dose. Meloxicam provided the therapeutic concentration of >0.39 μg/mL reported in other species for 12, 48 and 96 h at 0.5, 1 and 2 mg/kg doses, respectively. These results show that meloxicam exhibits non-linear pharmacokinetics and will achieve unpredictable plasma concentrations when administered IV for a rapid effect at dose of ≥1 mg/kg in sheep.

KEYWORDS
increasing dose, meloxicam, pharmacokinetics, sheep

1 | INTRODUCTION

NSAIDs are widely used in farm animals such as sheep due to their analgesic, antipyretic and anti-inflammatory effects (Corum et al., 2018). Meloxicam is an oxicam-class NSAID with analgesic, antipyretic, and anti-inflammatory properties (Turk et al., 2021). The pharmacological effect of meloxicam is attributed to its ability to suppress the activity of the cyclooxygenase (COX) enzyme and, therefore, reduce the production of prostaglandins (Gates et al., 2005). Meloxicam has low adverse effects on the gastrointestinal tract in general due to its inhibitory effects on the COX-2 enzyme (Woodland et al., 2019). Meloxicam is used in animals painful and inflammatory conditions such as acute mastitis, acute respiratory tract infection, septicemia, diarrhea, osteoarthritis, soft tissue and orthopedic surgery (CVMP, 2006). In Canada, Australia and New Zealand, meloxicam is approved for intravenous, intramuscular and subcutaneous use at a dose of 1 mg/kg for the treatment of pain and inflammation in sheep and lambs 14-days of age or older (Anonymous, 2023).

In previous studies, meloxicam has been used in sheep at a dose range of 0.5 and 2 mg/kg (Shukla et al., 2007; Stock et al., 2013; Woodland et al., 2019). When the efficacy of different doses of

meloxicam (0.5, 1, 1.5, and 2 mg/kg) was compared in the turpentine-induced lameness model in sheep, it was reported that there was no efficacy difference between 1 mg/kg dose and 1.5–2 mg/kg doses (Colditz et al., 2019; Woodland et al., 2019). The increase in the doses of drugs for which metabolic degradation is important in elimination, such as meloxicam (CVMP, 2006), causes unpredictable changes in their pharmacokinetics, as there will be saturation in the enzymes responsible for metabolism. Significant changes in plasma concentration of meloxicam were determined after subcutaneous administration at doses of 1 and 2 mg/kg to sheep (Woodland et al., 2019). Intravenous (IV) administration is one of the most preferred routes of administration of meloxicam and is preferred for rapid onset of action in acute infections (CVMP, 2006). In addition, IV administration is the ideal route to determine pharmacokinetic parameters such as total body clearance (Cl_T), and volume of distribution at steady state (V_{dss}) without the effect of bioavailability. In this study, we hypothesized that meloxicam at increasing doses may exhibit dose-dependent pharmacokinetics with saturation of plasma protein binding and elimination pathways. To our knowledge, there is no study comparing the pharmacokinetic changes after IV administration of different doses of meloxicam to sheep. The aim of this study was to determine the pharmacokinetic changes after IV administration of meloxicam to sheep at doses of 0.5, 1 and 2 mg/kg.

2 | MATERIALS AND METHODS

2.1 | Chemicals

Meloxicam analytical standard (>98%) was obtained from Sigma–Aldrich. Methanol and acetonitrile were used in analytical purity grade (VWR International). Potassium dihydrogen phosphate and orthophosphoric acid were supplied from Merck. Parenteral formulation of meloxicam (Metacam, 20 mg/mL, Injection Solution, Boehringer Ingelheim) was used for drug administration to sheep.

2.2 | Animals

All study procedures were approved (2020/05/20) by the Local Ethics Committee of the Animal Experiments of Sivas Cumhuriyet University (Sivas, Turkiye). The experimental procedure was carried out in a local farm (Sivas/Turkiye). The study was carried out on six female Akkaraman sheep (1.7 ± 0.3 years and 43 ± 6.52 kg of body weight), which were determined to be healthy by clinical examination, serum biochemistry panel, and complete blood count. They had not received any other medications for at least 2 months prior to the start of this study. All sheep were housed in a separate compartment (40 m^2), and were moved into this compartment 1 week before the study to acclimate. They were fed with drug-free concentrate feed twice a day and had ad-libitum access to Alfalfa hay and water.

2.3 | Experimental design

The investigation was conducted in three periods using a longitudinal pharmacokinetic design, with a 15-day washout period between administrations. The animals were administered meloxicam by IV route (left jugular vein) at doses of 0.5, 1, and 2 mg/kg. The sheep were administered meloxicam at a dose of 0.5 mg/kg in the first period, 1 mg/kg in the second period, and 2 mg/kg in the third period of the study with a 15-day washout period. By the end of the study, each sheep had received three doses of meloxicam. Blood samples (2 mL) were collected from the right jugular vein into heparin tubes at 0 (pre-treatment), 0.08, 0.17, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, and 96 h post-dosing. Blood samples were collected from the right jugular vein via a catheter in the first 12 h and by venipuncture at other sampling times. The blood samples were centrifuged (4000 *g* for 10 min), and the plasma was harvested and stored at −80°C until assay.

2.4 | Analytical procedure

The plasma concentrations of meloxicam were assayed by high performance liquid chromatography (HPLC) with ultraviolet detection (UV) using a previous published method (Corum et al., 2022; Coskun, Corum, Durna Corum, & Uney, 2023). A total of 400 μL of methanol (0.1% formic acid) was added to 200 μL of plasma samples. They were mixed for 40 s in the vortex, and the mixture was centrifuged at 12,000 *g* for 12 min. The supernatant was transferred to autosampler vials, and 20 μL was injected into an inertsil column (ODS-3, 4.6 × 250 mm; 5 μm; GL Sciences), which was maintained at 40°C. The mobile phase consisted of 40% acetonitrile and 60% potassium dihydrogen phosphate (pH:2.5) at a flow rate of 1.2 mL/min. The concentration of meloxicam was determined using an HPLC system (Shimadzu) comprised of a degasser (DGU-20A), column oven (CTO-10A), auto-sampler (SIL 20A), pump (LC-20AT controlled by the CBM-20A), and UV–VIS detector (SPD-20A) with absorbance set at 355 nm.

The chromatographic method was validated according to EMA (2011) guidelines. The stock solution for meloxicam was prepared with NaOH (0.05 M) to obtain a concentration of 500 μg/mL. Working standard solutions were prepared using the appropriate dilutions (0.04, 0.1, 0.2, 0.4, 1, 2, 4, 10, 20, and 40 μg/mL) of the stock solution with purified water. The selectivity of method was evaluated by extracting blank plasma samples from six individual animals for interference from plasma. Calibration standards (0.04, 0.1, 0.2, 0.4, 1, 2, 4, 10, 20, and 40 μg/mL) and quality control samples were prepared by adding working standard solutions of meloxicam into blank sheep plasma. Meloxicam calibration curve was linear ($R^2 > 0.9989$) over the range of 0.04–40 μg/mL. The quality control samples (0.1, 1, and 10 μg/mL) were analyzed in five replicates within 5 days to assess recovery, precision, and accuracy. The recovery of meloxicam was ≥90%. The lower limit of quantification was 0.04 μg/mL for meloxicam in sheep plasma with the bias of ±15%

and the coefficient of variation <20%. The intra-day and inter-day coefficients of variation were ≤6.8% and ≤7.4%, respectively. The intra-day and inter-day bias were ±7.8% and ±8.8%, respectively.

2.5 | Pharmacokinetic analysis

Plasma concentrations of meloxicam from each sheep were analyzed by non-compartmental analysis using WinNonlin 6.1.0.173 software program (Pharsight Corporation, Scientific Consulting Inc.). Following meloxicam administration, the elimination rate constant (λ_z), terminal elimination half-life ($t_{1/2\lambda z}$), area under the concentration versus time curve (AUC), AUC extrapolated from t_{last} to ∞ in % of the total AUC (AUC_{extrap} %), mean residence time (MRT), Cl_T, and V_{dss} were determined. The peak plasma concentration ($C_{0.083h}$) was directly obtained from first sampling (0.083 h) data of concentration–time curves. The λ_z was estimated by linear regression analysis of the terminal slope of the plasma concentration versus time curve using >3 data points. The body extraction ratio (E_{body}) for meloxicam was calculated using CL_T/Q_C, and Q_C (mL/kg/min) was the cardiac output calculated according to the allometric equation with 180 × body weight (in kg)$^{-0.19}$ (Toutain & Bousquet-Mélou, 2004a).

2.6 | Statistical analysis

Plasma concentrations of meloxicam are presented as mean ± SD. All pharmacokinetic parameters were presented as geometric mean (min–max) except for $C_{0.083h}$, which is displayed as mean ± SD. The AUC and $C_{0.083h}$ were normalized to the 0.5 mg/kg dose of meloxicam prior to statistical analysis. The normality of the homogeneity of variance and the data distribution were assessed with Levene's test and Shapiro–Wilk test, respectively. The pharmacokinetic parameters were analyzed using one-way analysis of variance and post hoc Tukey tests (SPSS 22.0, IBM Corp). $p < .05$ was considered to be statistically significant.

3 | RESULTS

The semi-logarithmic plasma concentration–time curves and pharmacokinetic parameters of meloxicam following IV administrations at a dose of 0.5, 1 and 2 mg/kg to sheep are presented in Figure 1 and Table 1, respectively. Meloxicam was detected up to 48 h in the 0.5 mg/kg dose and up to 96 h in the 1 and 2 mg/kg doses. After IV administration at doses of 0.5, 1, and 2 mg/kg, the $C_{0.083h}$ values of meloxicam were 4.17 ± 0.61, 9.25 ± 0.67, and 23.95 ± 2.32 μg/mL, respectively. Then, after administration of 0.5, 1, and 2 mg/kg, the plasma concentration of meloxicam dropped to 0.07 ± 0.02, 0.12 ± 0.03, and 0.65 ± 0.10 μg/mL at the last sampling time. Following IV administration at dose of 0.5 mg/kg, $t_{1/2\lambda z}$, $AUC_{0\text{-last}}$ Cl_T and V_{dss} were 10.33 h, 25.58 h*μg/mL, 18.76 mL/h/kg and 247.10 mL/kg, respectively. While $t_{1/2\lambda z}$, MRT, and dose-normalized AUC increased with the increasing dose, Cl_T decreased. The V_{dss} and $C_{0.083h}$ were significantly different at the 1 mg/kg dose than at the 2 mg/kg dose. E_{body} values of meloxicam in the 0.5, 1 and 2 mg/kg doses were 0.15 (0.11–0.20), 0.09 (0.07–0.11) and 0.05 (0.03–0.07), respectively. The linear relationship between $AUC_{0-\infty}$ and dose was 0.9347 (Figure 2). The percentage AUC extrapolated values for all age groups were less than 20%.

4 | DISCUSSION

In our study, the $t_{1/2\lambda z}$, Cl_T and V_{dss} of meloxicam after IV administration at 0.5 mg/kg dose were 10.33 h, 18.76 mL/h/kg and 247.10 mL/kg, respectively. These data showed that meloxicam was eliminated slowly and had a low volume of distribution, similar to those previously reported in lambs and sheep ($t_{1/2\lambda z}$, 10.85–14 h; Cl_T, 10.20–16.00 mL/h/kg; V_d, 180–320 mL/kg, Coskun, Corum, Durna Corum, Cetin, et al., 2023; Shukla et al., 2007; Stock et al., 2013). The low V_d of meloxicam may be due to its high plasma protein binding, and ionization at physiological pH. V_{darea} and V_{dss} are the volume in pseudo-equilibrium conditions and steady-state, respectively (Toutain &

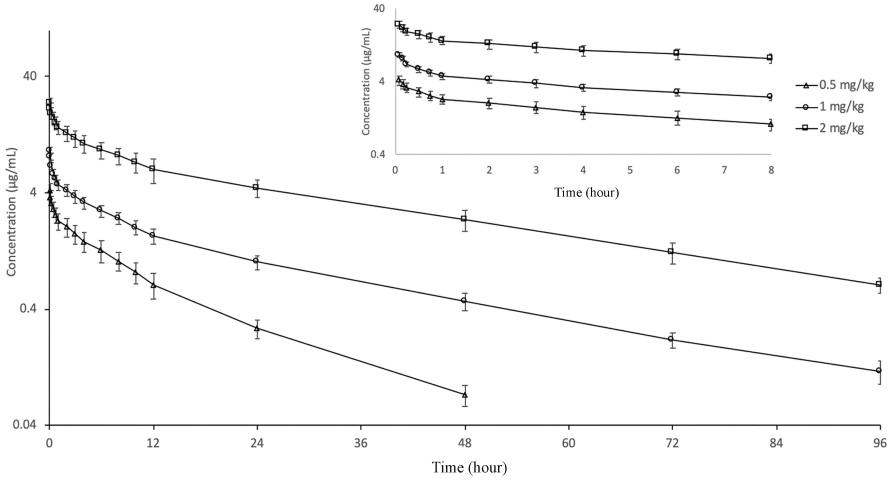

FIGURE 1 Semi-logarithmic plasma concentration–time curves following intravenous administration of meloxicam at 0.5, 1, and 2 mg/kg doses in sheep (mean ± SD, $n = 6$).

TABLE 1 Pharmacokinetic parameters following intravenous administration of meloxicam at 0.5, 1, and 2 mg/kg doses in sheep ($n = 6$).

Parameters	0.5 mg/kg	1 mg/kg	2 mg/kg
λ_z (1/h)	0.07 (0.06–0.07)[a]	0.04 (0.03–0.04)[b]	0.03 (0.03–0.03)[b]
$t_{1/2\lambda z}$ (h)	10.33 (9.63–11.17)[c]	19.75 (18.61–20.70)[b]	24.74 (21.49–26.17)[a]
$AUC_{0\text{-last}}$ (h*µg/mL)	25.58 (18.92–31.79)[c]	81.84 (67.28–97.25)[b]	324.56 (254.98–403.72)[a]
$AUC_{0\text{-}\infty}$ (h*µg/mL)	26.66 (19.62–33.07)[c]	85.16 (69.91–101.51)[b]	347.78 (274.82–433.21)[a]
AUC_{extrap} (%)	4.01 (3.43–5.16)	3.82 (2.57–4.57)	6.59 (4.59–7.37)
$MRT_{0\text{-}\infty}$ (h)	13.17 (12.37–13.94)[c]	26.08 (24.34–27.20)[b]	33.46 (28.88–35.56)[a]
Cl_T (mL/h/kg)	18.76 (15.12–25.49)[a]	11.74 (9.85–14.30)[b]	5.75 (4.62–7.28)[c]
V_{dss} (mL/kg)	247.10 (198.53–322.87)[ab]	306.24 (267.96–368.10)[a]	192.39 (152.88–244.39)[b]
V_{darea} (mL/kg)	279.44 (219.04–375.00)[ab]	334.54 (294.19–397.17)[a]	205.28 (164.13–274.75)[b]
$C_{0.083h}$ (µg/mL)	4.17 ± 0.61[b]	9.25 ± 0.67[b]	23.95 ± 2.32[a]
E_{body}	0.15 (0.11–0.20)	0.09 (0.07–0.11)	0.05 (0.03–0.07)

Note: Data were presented as the geometric mean (min-max), except for $C_{0.083h}$, which is displayed as mean ± SD.

Abbreviations: λ_z, elimination rate constant; $t_{1/2\lambda z}$, elimination half-life; AUC, area under the plasma concentration–time curve; AUC_{extrap} %, area under the plasma concentration–time curve extrapolated from t_{last} to ∞ in % of the total AUC; MRT, mean residence time; Cl_T, total body clearance; V_{dss}, volume of distribution at steady state; V_{darea}, apparent volume of distribution; $C_{0.083h}$, plasma concentration at time 0.083 h; E_{body}, body extraction ratio.

[abc]Varied characters in the same row are statistically significantly different ($p < .05$).

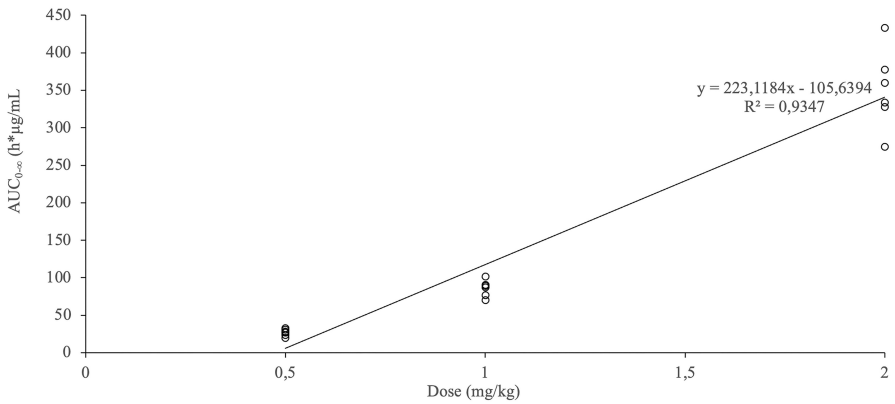

FIGURE 2 Linear regression relationship between the area under the curve from time zero to infinity ($AUC_{0\text{-}\infty}$) and meloxicam dose.

Bousquet-Mélou, 2004b). In this study, V_{darea} and V_{dss} were 247.10 and 279.44 mL/h/kg, respectively. Similar values in V_{darea} and V_{dss} exhibited that the minimal amount of meloxicam was eliminated during the distribution phase.

The plasma concentration-time profiles of meloxicam showed no parallel at the three dose levels. The $AUC_{0\text{-}\infty}$ after doses of 0.5, 1, and 2 mg/kg were 26.66, 85.16, and 347.78 h*µg/mL, respectively. There is a disproportionate increase in $AUC_{0\text{-}\infty}$ with increasing doses of meloxicam in sheep. $AUC_{0\text{-}\infty}$ can be calculated by dividing the dose by the Cl_T. In this study, Cl_T and $t_{1/2\lambda z}$ of meloxicam decreased from 18.76 to 5.75 mL/h/kg and prolonged from 10.33 to 24.74 h, respectively, with increasing dose. The disproportionate increase in $AUC_{0\text{-}\infty}$ of meloxicam seems to be related to the decrease in Cl_T with increasing dose. The typical feature of nonlinear elimination kinetics is the dose-dependence of Cl_T and $t_{1/2\lambda z}$ (Ludden, 1991). In this study, the dose-dependent decrease of Cl_T and prolongation of $t_{1/2\lambda z}$ demonstrate the nonlinear pharmacokinetics of meloxicam. However, meloxicam has been showed linear kinetics when administered extravascularly to sheep (1–2 mg/kg, intramuscular and subcutaneous, Woodland et al., 2019), mice (10–20 mg/kg, subcutaneous, Kim et al., 2023), rabbit (0.3–1.5 mg/kg, oral, Turner et al., 2006), cows (1–30 mg/kg, oral, Fritz et al., 2023; Shock et al., 2019), zebra finces (1–2 mg/kg, intramuscular, Miller et al., 2019) and humans (5–30 mg, intramuscular, Narjes et al., 1996) at different doses.

Following IV administration, the nonlinearity of drug can be related to nonlinear distribution and nonlinear elimination (Ludden, 1991). Differences in plasma concentrations may impact the binding ratio of drugs to plasma proteins. It was reported that no correlation was determined between meloxicam concentration (0.5, 2 and 6 µg/mL for koalas, and 0.5 and 5 µg/mL for guinea pigs) and plasma protein binding ratio in studies performed in koalas and guinea pigs (Kimble et al., 2013; Moeremans et al., 2019). However, for meloxicam highly bound (>96%) to plasma proteins (CVMP, 2006; Kimble et al., 2013; Tekeli et al., 2020), in this study, much high concentrations (9.25–23.95 µg/mL) of meloxicam following IV rapid bolus administration for 1 and 2 mg/kg doses in sheep may result in saturation of plasma proteins.

After IV administration at doses of 0.5, 1, and 2 mg/kg, the $C_{0.083h}$ values of meloxicam were 4.17 ± 0.61, 9.25 ± 0.67, and

23.95 ± 2.32 μg/mL, respectively. There is a linear increase in $C_{0.083h}$ up to 1 mg/kg dose, but not for 2 mg/kg dose. $C_{0.083h}$ can be calculated by dividing the dose by the V_{darea}. According to this equation, V_{darea} should be independent of dose for linear relationship. Therefore, meloxicam can exhibit linearity in V_{darea} up to of 1 mg/kg dose, but the saturation of tissue distribution at 2 mg/kg dose.

Nonlinear elimination may be related to capacity-limited metabolism (Ludden, 1991). Meloxicam is extensively metabolized by phase I reactions (primarily by CYP2C9 enzymes and, to a lesser extent, CYP3A4 enzymes) in cattle, mini pigs, rat and mice, and less than 10% is excreted unchanged in the urine (Corum et al., 2022; CVMP, 2006). This indicates that metabolic degradation is important in the elimination of meloxicam. After IV administration of meloxicam at doses of 0.5, 1, and 2 mg/kg, E_{body} values were 0.15, 0.09, and 0.05, respectively. E_{body} was reported as 0.05 for low, 0.15 for medium, and 0.35 for high (Toutain & Bousquet-Mélou, 2004a). Therefore, the E_{body} of meloxicam was low at high dose and medium at other doses. When the dose groups were compared, it was determined that the Cl_T of meloxicam decreased with increasing dose. Therefore, it can be concluded that the nonlinearity of meloxicam is due to saturation in the elimination process. However, further studies are needed to reveal the mechanisms in the elimination process.

The therapeutic concentration range needed for meloxicam to provide analgesic and anti-inflammatory effects in sheep is unknown. The suggested effective plasma concentrations for anti-inflammatory effect in horses and dogs are 0.13–0.2 μg/mL (Toutain & Cester, 2004), and 0.21–0.39 μg/mL (Jeunesse et al., 2011), respectively. If these values are considered effective plasma concentrations for sheep, the plasma concentrations were >0.39 μg/mL at 12 h for 0.5 mg/kg, 48 h for 1 mg/kg, and 96 h for 2 mg/kg. In experimental studies in sheep, it has been reported that the efficacy is similar between 1, 1.5 and 2 mg/kg doses of meloxicam, and therefore, 1 mg/kg dose can be used (Colditz et al., 2011, 2019; Woodland et al., 2019). However, when the pharmacokinetic data obtained in our study are examined, a longer duration of meloxicam in the body at a dose of 2 mg/kg may provide a long-lasting effect. There was no adverse effect after a single dose of 2 mg/kg meloxicam to sheep (Woodland et al., 2019; Yipel & Gungor, 2021).

The limitation of this study are the lack of determination of plasma protein binding ratio, metabolism, and therapeutic efficacy of meloxicam. Plasma concentrations of NSAIDs do not reflect their therapeutic efficacy, as they tend to accumulate in the area of inflammation due to their acidic structure and high ratio plasma protein binding (Cetin et al., 2022). Therefore, there is a need for studies that reveal the pharmacokinetic/pharmacodynamic relationship of meloxicam in the area of inflammation. The 99.9% of drugs are eliminated from the body in 10 times the $t_{1/2\lambda z}$ (Riviere, 2009). Accordingly, complete elimination of meloxicam from the body of sheep takes 4.3 days for 0.5 mg/kg, 8.2 days for 1 mg/kg, and 10.3 days for 2 mg/kg. This should be taken into account when adjusting the dose interval in multiple-dose administrations and determining the withdrawal period of drug before slaughter.

In conclusion, non-parallel plasma concentration-time profile, disproportionate increase in AUC, prolonged $t_{1/2\lambda z}$ and decreased Cl_T with increasing dose suggested nonlinearity in the distribution and elimination of meloxicam in sheep. This demonstrates that meloxicam in sheep will achieve unpredictable plasma concentrations when administered IV for a rapid effect at doses of ≥1 mg/kg. Meloxicam provided the therapeutic concentration of >0.39 μg/mL reported for anti-inflammatory effect in other species for 12 h at 0.5 mg/kg, for 48 at 1 mg/kg h, and for 96 h at 2 mg/kg. Although nonlinearity is an undesirable drug property, the nonlinearity that occurs at therapeutic levels of meloxicam can provide prolonged action or wide dose intervals following a IV administration at dose of ≥1 mg/kg in sheep. However, such use requires determination of the safety of meloxicam for wide therapeutic concentrations in sheep.

AUTHOR CONTRIBUTION

All authors have read and approved the final manuscript. OC, HG, DDC and KU contributed to conception, experimental design, and analysis, drafted the manuscript, critically revised the manuscript, provided final approval, and agreed to be accountable for all aspects of work ensuring integrity and accuracy. DC, ASK, GY, and AC contributed to experimental design and provided final approval.

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None.

CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The experiment was approved (2020/05/20) by the Local Ethics Committee of the Animal Experiments of Sivas Cumhuriyet University (Sivas, Turkiye) and carried out in accordance with the European Directive (2010/63/EU).

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