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RESEARCH ARTICLE

Pharmacokinetics of Meloxicam Following Repeated Intravenous Administrations in Sheep

Orhan ÇORUM[1*], Duygu DURNA ÇORUM[1], Kamil ÜNEY[2], Ayşe ER[2], Muammer ELMAS[2]

[1]Hatay Mustafa Kemal University, Faculty of Veterinary Medicine, Department of Pharmacology and Toxicology, Hatay, Türkiye
[2]Selçuk University, Faculty of Veterinary Medicine, Department of Pharmacology and Toxicology, Konya, Türkiye

ABSTRACT

The purpose of this study was to investigate the pharmacokinetics of meloxicam following repeated intravenous injection in sheep. Five male merino sheep were used in the study. Meloxicam was administered intravenously to sheep at 0.5 mg/kg once daily for 5 days. Meloxicam analysis from plasma samples was performed by high-pressure liquid chromatography. Non-compartmental analysis was used to establish the pharmacokinetic parameters. Following the first dose of meloxicam, the values for the plasma concentration at the first sampling time ($C_{0.08}$), area under the plasma concentration-time (AUC_{0-24}), elimination half-life ($t_{1/2\lambda z}$), total body clearance (Cl_T), and volume of distribution at steady state (V_{dss}), were 2.53 µg/mL, 12.30 hour*µg/mL, 8.97 hour, 0.03 L/hour/kg, and 0.40 L/kg, respectively. Compared to the first dose, AUC_{0-24} and $C_{0.08}$ increased, Cl_T and V_{dss} decreased after the last dose administration. Following the first and final administration, the $t_{1/2\lambda z}$ values were similar. The accumulation levels of R_1 and R_2 were 2.48 and 2.81, respectively. In conclusion, repeated administration of meloxicam in sheep caused pharmacokinetic changes and accumulation. Therefore, the safety and therapeutic effect of meloxicam after repeated administration in sheep should be established.

Keywords: Intravenous, Meloxicam, Pharmacokinetics, Repeated dose, Sheep

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Koyunlarda Meloksikamın Tekrarlanan İntravenöz Uygulamasını Takiben Farmakokinetiği

ÖZ

Bu çalışmanın amacı, koyunlarda meloksikamın tekrarlanan intravenöz enjeksiyonunu takiben farmakokinetiğini belirlemektir. Araştırma 5 baş Merinos ırkı erkek koyun üzerinde gerçekleştirildi. Meloksikam koyunlara günde bir defa 5 gün boyunca 0.5 mg/kg dozunda intravenöz olarak uygulandı. Plazma örneklerinden meloksikam analizi yüksek basınçlı sıvı kromatografisi ile gerçekleştirildi. Farmakokinetik parametreleri kompartmansız analiz ile belirlendi. Meloksikamın ilk dozundan sonra ilk örnekleme zamanındaki plazma konsantrasyonu ($C_{0.08}$), plazma konsantrasyon-zaman eğrisi altında kalan alan (AUC_{0-24}), eliminasyon yarı ömrü ($t_{1/2\lambda z}$), toplam vücut klirensi (Cl_T) ve kararlı durum dağılım hacmi (V_{dss}) değerleri, sırasıyla 2.53 µg/mL, 12.30 saat*µg/mL, 8.97 saat, 0.03 L/saat/kg ve 0.40 L/kg olarak bulundu. İlk doza göre, son doz uygulamasından sonra AUC_{0-24} ve $C_{0.08}$ artarken, Cl_T ve V_{dss} azaldı. İlk ve son uygulamayı takiben $t_{1/2\lambda z}$ değerleri benzerdi. R_1 ve R_2 birikim seviyeleri sırasıyla 2.48 ve 2.81 idi. Sonuç olarak, koyunlarda meloksikamın tekrarlanan uygulanması farmakokinetik değişikliklere ve birikime neden oldu. Bu nedenle, koyunlarda tekrarlanan uygulamadan sonra meloksikamın güvenliği ve terapötik etkisi belirlenmelidir.

Anahtar kelimeler: Damar içi, Farmakokinetik, Koyun, Meloksikam, Tekrarlanan doz

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ORCID ID; *OÇ: 0000-0003-3168-2510, DDÇ: 0000-0003-1567-991X, KÜ: 0000-0002-8674-4873, AE: 0000-0002-6900-0055, ME: 0000-0001-9059-7151*
*Corresponding author e-mail: orhancorum46@hotmail.com

INTRODUCTION

Sheep are a significant livestock species extensively cultivated for their products, including meat, milk, and wool (Li et al. 2021). In recent years, sheep meat output has risen to 9.78 million tons, constituting 2.93% of total red meat production (Cordeiro et al. 2022). Sheep are susceptible to several disorders characterized by pain and inflammation, including lameness, castration, musculoskeletal pain, foot rot, mastitis, pneumonia, and enteritis, throughout their lives (Corum et al. 2018). Therefore, analgesic drugs are commonly used in sheep.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are extensively utilized in animals due to their anti-inflammatory, analgesic, and antipyretic properties. They show their effects by inhibiting the cyclooxygenase (COX) enzymes responsible for prostaglandin synthesis (Gates et al. 2005). The COX enzyme is present in two forms: COX-1 (constitutive) and COX-2 (inducible). NSAIDs that are more efficient against COX-2 enzymes cause less gastrointestinal adverse effects. Meloxicam is in the oxicam class and is one of the most commonly used NSAIDs in animals (Tekeli et al. 2020). Meloxicam has low gastrointestinal adverse effects since it inhibits the COX-2 enzyme (Woodland et al. 2019). Meloxicam is approved for parenteral use in mammals for musculoskeletal disorders, movement disorders, mastitis, septicemia, enteritis, and acute respiratory tract infections (CVMP 2006). It is also used in cases of pain and inflammation in fish, birds and reptiles (Corum et al. 2022a; Coskun et al. 2023a; Sladky 2003). Although meloxicam is not approved for use in sheep in our country, it is approved in some countries (Sim 2016).

The pharmacokinetics of meloxicam has been established in sheep. This research examined the impact of administration route (Woodland et al. 2019), dosage (Gungor et al. 2024), and age (Coskun et al. 2023b) on the single-dose pharmacokinetics of meloxicam. It is recommended to use a single dose of meloxicam in sheep (Sim 2016). However, it has been stated that it can be used repeatedly depending on the severity of pain and inflammation (Anonymous 2024). Drug repeated administration may change pharmacokinetics, hence affecting therapeutic effects as well as side effects (Corum et al. 2022b). Therefore, it is very important to conduct pharmacokinetic studies after repeated administration. Although the pharmacokinetics of meloxicam following repeated oral administration in sheep have been demonstrated (Depenbrock et al. 2021), no information has been found regarding repeated intravenous administration. Because meloxicam has a long half-life (10-24 hours, Coskun et al. 2023b; Gungor et al. 2024) in sheep, it was hypothesized that repeated intravenous administration might alter its pharmacokinetics. This study aims to determine the pharmacokinetics of meloxicam after repeated (once a day for 5 days) intravenous administration of 0.5 mg/kg to sheep.

MATERIALS and METHODS

Animals

The research was conducted on five male Merino sheep (10-12 months old, 55±5 kg weight). The study comprised sheep that were verified to be healthy by anamnesis and clinical assessment. The sheep were transferred to different pens a week before the research and remained there throughout. Both ear tags and numbered collars were used to number the sheep. The sheep were given hay and water continuously, and commercial feed was also given morning and evening, by their age and weight. The Selçuk University Veterinary Faculty Ethics Committee approved the experimental investigation on sheep.

Experimental Design

For drug administration to sheep, their body weights were weighed. The right and left jugular veins were used for drug administration and blood collection, respectively. Meloxicam (Maxicam x 4, Injection Solution, Sanovel, Türkiye) was administered intravenously to sheep at a dose of 0.5 mg/kg once daily for 5 days. Blood samples were taken at 0, 0.08, 0.17, 0.25, 0.33, 0.42, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 hours on the first (1) and last (5) day. Blood samples were taken at 0.08, 1, 8, and 24 hours on other days. Blood samples were collected using a catheter for the first 12 hours of the first and last days and the venipuncture method for the rest of the time and placed in tubes containing heparin. Plasma samples were obtained by centrifuging blood samples at 4000 g for 10 minutes and thereafter kept at -80 °C until the analysis of meloxicam.

HPLC Analysis

Meloxicam concentrations were analyzed by high-performance liquid chromatography (HPLC)-UV employing a previously established methodology (Tekeli et al. 2020). Following the addition of 0.4 mL of methanol (containing 0.1% formic acid) to 0.2 mL of plasma, vortexing was conducted for 45 seconds, followed by centrifugation for 12 minutes at 12,000 g. 0.2 mL of supernatant was transferred to autosampler vials, and 20 µL was injected onto an Inertsil ODS-3 column maintained at 40 °C. Meloxicam was detected with a UV-VIS detector (SPD-20A) adjusted to 355 nm.

Meloxicam was dissolved in NaOH (0.05 M) to achieve a concentration of 0.5 mg/mL. This stock solution was used to prepare working standards of 0.04–10 µg/mL in water. Calibration standards (0.04–10 µg/mL) were prepared in drug-free sheep plasma using working standards. The calibration curves,

spanning from 0.04 to 10 μg/mL, exhibited linearity with a correlation value of 0.9992. Three concentrations (0.1, 1, and 10 μg/mL) were analyzed 5 times daily for 5 days to determine recovery, intra-day and inter-day precision and accuracy. The limit of detection, limit of quantification, and mean recovery values of meloxicam were 0.02 μg/mL, 0.04 μg/mL, and >93%, respectively. The coefficient of variation and bias values were <6 and ±5.2%, respectively.

Pharmacokinetic Calculation

Plasma concentration time curves were plotted for each sheep. The appropriate pharmacokinetic model was determined via visual examination of individual concentration–time curves and the use of Akaike's Information Criterion. The pharmacokinetic parameters were evaluated by non-compartmental analysis using WinNonlin software. The accumulation ratios (R) of meloxicam in plasma were calculated using the formula previously reported (Colburn 1983; Corum et al. 2019).

Statistical Analysis

The pharmacokinetic data were presented as the geometric mean (minimum-maximum). Levene's test analyzed the homogeneity of variance, whereas the Shapiro-Wilk test tested the normality of data distribution. The paired t-test (SPSS 22.0) was employed to analyze statistical differences between the data from the first and last day. A p-value of less than 0.05 was deemed statistically significant.

RESULTS

The plasma concentrations are presented in Figure 1. The plasma concentrations at the first (0.08 hour) and last (24 hour) sampling times of the first and last days were 2.53 and 5.07 μg/mL, and 0.17 and 0.49 μg/mL, respectively.

The pharmacokinetic parameters are presented in Table 1. Following the first dose of meloxicam, the values for the area under the plasma concentration-time (AUC_{0-24}), elimination half-life ($t_{1/2\lambda z}$), total body clearance (Cl_T), and volume of distribution at steady state (V_{dss}) were 12.30 hour*μg/mL, 8.97 hour, 0.03 L/hour/kg, and 0.40 L/kg, respectively. As compared to the first dose, the last dose resulted in an increase in AUC_{0-24} values and a decrease in Cl_T and V_{dss} values. The $t_{1/2\lambda z}$ was similar in the first and last doses. The drug accumulation level on day 5 following intravenous administration of repeated doses was 2.48 for R_1 and 2.81 for R_2.

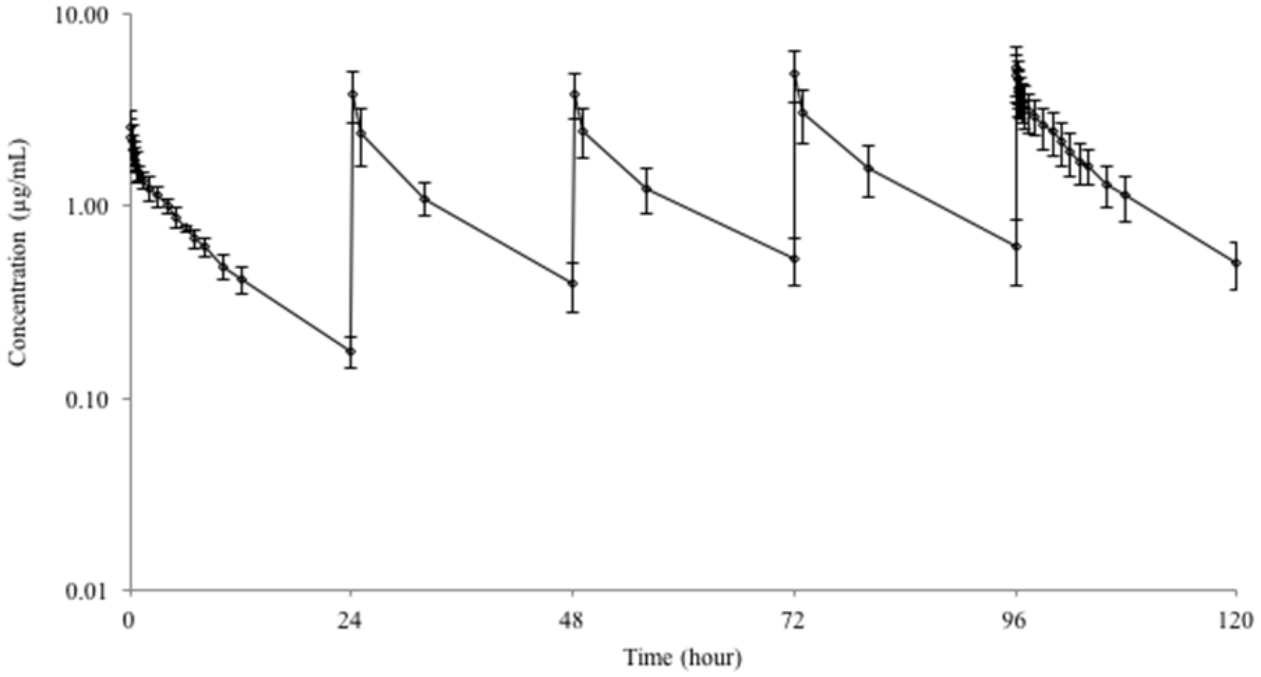

Figure 1: Semi-logarithmic plasma concentration–time curves of meloxicam in plasma after repeated intravenous administrations at the dose of 0.5 mg/kg every 24 hour for 5 days in sheep (mean ± SD, n = 5).

Table 1. Pharmacokinetic parameters for meloxicam in plasma after repeated intravenous administrations at the dose of 0.5 mg/kg every 24 hour for 5 days in sheep (n = 5).

Parameters	First (1) day	Last (5) day
$t_{1/2\lambda z}$ (hour)	8.97 (8.28-10.32)	9.83 (7.91-12.02)
AUC_{0-24} (hour*µg/mL)	12.30 (10.21-13.47)	30.54 (19.53-39.20)*
$AUC_{0-\infty}$ (hour*µg/mL)	14.58 (11.79-16.02)	37.69 (24.00-46.74)*
MRT_{0-24} (hour)	7.28 (6.98-7.72)	7.66 (7.16-8.14)
Cl_T (L/hour/kg)	0.03 (0.03-0.04)	0.01 (0.01-0.02)*
V_{dss} (L/kg)	0.40 (0.37-0.46)	0.18 (0.13-0.27)*
$C_{0.08}$ (µg/mL)	2.53 (2.03-3.35)	5.07 (3.05-6.95)*
R_1	-	2.48 (1.91-2.92)
R_2	-	2.81 (2.40-3.51)

Note: Data were presented as geometric mean (min-max).
*; Value is significantly different from the first day ($p<0.05$).
$t_{1/2\lambda z}$, elimination half-life; AUC, area under the plasma concentration–time curve; MRT, mean residence time; Cl_T, total body clearance; V_{dss}, volume of distribution at steady state; $C_{0.08,}$ plasma concentration at first sampling time, R_1, $AUC_{(0-24)5day}/AUC_{(0-24)1day}$; R_2, $C_{(min)5day}/C_{(min)1day}$. $C_{(min)}$: concentration at 24 hours on the first (1) and last (5) day.

DISCUSSION

The pharmacokinetic changes of meloxicam following repeated oral administration of 1 mg/kg for 10 days were previously demonstrated in sheep (Depenbrock et al. 2021). In this study, the pharmacokinetics of meloxicam after repeated intravenous administration of 0.5 mg/kg to sheep were demonstrated for the first time. Meloxicam dosing on a repeated basis resulted in considerable alterations in pharmacokinetic parameters.

Meloxicam at 0.5 mg/kg dosages was administered intravenously to sheep repeatedly (every 24 hours for 5 days) with no local or systemic adverse pharmacological effects identified. It has been reported that meloxicam is well tolerated in sheep at doses of 0.5–2 mg/kg parenterally or orally (Woodland et al. 2019; Stock et al. 2013). The best route to determine Cl_T and V_d is by intravenous administration, as they have no effect on bioavailability. Therefore, intravenous administration was preferred in this study.

The V_{dss} of meloxicam in sheep after the first and last doses were 0.40 and 0.18 L/kg, respectively. The V_{dss} decreased in the last dose compared to the first dose. Meloxicam is generally low in volume of distribution due to its high (>96%) binding to plasma proteins and its ionization at blood pH (CVMP 2006; Corum et al. 2022a; Gungor et al. 2024). Plasma protein binding is inversely proportional to volume of distribution (Sakai 2009). Since meloxicam is highly bound to plasma proteins, we reasoned that after repeated administration, the binding would reach saturation and the amount of free drug would increase, thus increasing V_{dss}. However, it was unexpected that the V_{dss} decreased. The formula V_d = dose/concentration is used to compute V_d. The last dose concentration of meloxicam is approximately 2 times the first dose concentration. The decrease in V_{dss} after repeated application is probably due to this situation.

The Cl_T of meloxicam in sheep after the first and last doses was 0.03 and 0.01 L/hour/kg, respectively. The Cl_T decreased in the last dose compared to the first dose. Meloxicam undergoes significant metabolism via phase I reactions, predominantly by CYP2C9 enzymes and, to a lesser degree, CYP3A4 enzymes, in animals, with fewer than 10% excreted unaltered in the urine. Meloxicam and its metabolites are excreted in urine and bile (CVMP 2006; Adawaren et al. 2019). The small amount excreted unchanged indicates that metabolic degradation plays an important role in the removal of meloxicam. The decrease in CL of meloxicam with repeated doses may be due to saturation of metabolism. The $t_{1/2\lambda z}$ after the first and last doses was similar. The $t_{1/2\lambda z}$ is a hybrid parameter that is directly proportional to V_d and inversely proportional to Cl_T (Turk et al. 2021). The fact that $t_{1/2\lambda z}$ did not change in this study may be due to the decrease in both V_d and Cl_T values.

Following five days of intravenous meloxicam treatment to sheep at a dosage of 0.5 mg/kg, the accumulation ratios for R_1 and R_2 were 2.48 and 2.81, respectively. The accumulation ratios of medicines are categorized as mild ($1.2 \leq R < 2$), moderate ($2 \leq R < 5$), and high ($R \geq 5$) (Li et al. 2013). The data indicate that intravenous injection of meloxicam every 24 hours for 5 days results in moderate accumulation in the body. However, repeated oral administration to horses and rabbits did not cause accumulation (Toutain et al. 2004; Carpenter et al. 2009). The increase in the accumulation ratio of the drug may also cause toxic effects. Therefore, after repeated administration of meloxicam in sheep, the dosing interval should be extended and adverse effects should be observed.

The therapeutic concentration necessary for meloxicam to provide analgesic and anti-inflammatory actions in sheep remains unidentified. However, effective concentrations for lameness in arthritis in horses and acute paw edema in dogs were reported as 0.13-0.20 µg/mL and 0.21-0.39 µg/mL, respectively (Jeunesse et al. 2011; Toutain and Cester 2004). When these values are considered in sheep, meloxicam maintained an efficacious concentration for 12 hours following the first dose and for 24 hours following the last dose. Nevertheless, it has been reported that NSAIDs accumulate at a higher concentration in the inflammatory site than in plasma due to their strong binding to plasma proteins (Lindemann et al. 2016). Therefore, it is important to evaluate their effectiveness in the inflammatory area, as plasma levels will not reflect their effectiveness.

CONCLUSION

The repeated treatment of meloxicam in sheep reduced excretion and extended retention time. Intravenous treatment of meloxicam to sheep at a dosage of 0.5 mg/kg over 5 days resulted in moderate accumulation. Therefore, the safety and therapeutic effect of meloxicam after repeated administration in sheep should be established.

Conflict of interest: The authors declare that there are no real, potential or perceived conflicts of interest for this manuscript.

Ethical approval: The research was discussed by Selçuk University Experimental Animals Local Ethics Committee on 26.03.2015 and session numbered 2015/03 and ethics committee permission was obtained with decision numbered 2015/30.

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