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# Influence of ofloxacin on the disposition kinetics of meloxicam following single intravenous administration in goats

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**ABSTRACT**

The objective of the present study was to investigate the effect of ofloxacin (10 mg/kg) on the pharmacokinetics of meloxicam (0.5 mg/kg) in goats, when administered concurrently by intravenous route. Meloxicam concentration in plasma was measured using HPLC assay. The pharmacokinetics of meloxicam were best described by the two-compartment open model. Following concurrent administration of meloxicam and ofloxacin, the mean plasma level of meloxicam was only found to be significantly higher ($P<0.05$) at 15 min compared to its alone administration. Statistical analysis of data revealed that there were no statistically significant differences in PK parameters between the two treatments, except $K_{21}$. Therefore, the results of the present study suggest that concurrent administration of ofloxacin and meloxicam in goats does not require any adjustment in dosage regimens. Based on PK determinants, meloxicam may be administered by i.v. route at 0.86 and 0.65 mg/kg, as loading and maintenance doses respectively, and is to be repeated at 8 h intervals.

**Key words:** meloxicam, ofloxacin, HPLC, pharmacokinetic, interaction, goats

## Introduction

Meloxicam is known to preferentially inhibit cyclo-oxygenase-2 and is not only effective in the treatment of inflammatory conditions, but also does not adversely affect platelet aggregation or renal prostaglandin biosynthesis (VANE and BOTTING, 1995; ALENCAR et al., 2002). The pharmacokinetics of meloxicam have been investigated in rabbits (TURNER et al., 2006), cats (LEHR et al., 2009), dogs (BUSCH et al., 1998; MONTOYA et al., 2004), sheep and goats (SHUKLA et al., 2007), piglets (FOSSE et al., 2008), horses

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(LEES et al., 1991; TOUTAIN et al., 2004), chickens and four other species of birds (BAERT and DE BACKER, 2003), calves (MOSHER et al., 2012) and vultures (NAIDOO et al., 2008). Good absorption, longer elimination half-life and optimum bioavailability attributes make it an ideal and suitable NSAID for use in animals (BUSCH et al., 1998).

NSAIDs and antibacterials, including fluoroquinolones, are often used concomitantly in clinical practice. Fluoroquinolones have been reported to interact with NSAIDs at the pharmacokinetic and pharmacodynamic level (LANGTRY and LAMB, 1998). On concurrent administration, gatifloxacin has been reported to alter the pharmacokinetics of meloxicam in buffalo calves (DUMKA et al., 2007). The elimination half-life of meloxicam was found to be significantly reduced in the presence of enrofloxacin, as compared to meloxicam alone (TOPPO et al., 2011). Similarly, VERMA et al. (2007) reported that meloxicam prolonged the retention time of enrofloxacin and ciprofloxacin in goats. However, AHMED et al. (2005) did not observe any significant alteration in the pharmacokinetic profile of enrofloxacin in calves in the presence of diclofenac sodium.

Although the PK profile of meloxicam alone (SHUKLA et al., 2007) or ofloxacin alone (BARUAH et al., 2004) have been reported in goats, no studies have been undertaken on the pharmacokinetic interaction between these two drugs when administered concomitantly. Therefore, the present study was undertaken to determine the influence of ofloxacin on the disposition kinetics of meloxicam following their concurrent intravenous administration in goats.

## Materials and methods

*Experimental animals.* Ten healthy female Barberi goats, aged between 1.2 and 2.0 years and weighing 18 to 22 kg, were procured from the livestock farm of the University. The animals were examined for apparent clinical signs of illness prior to starting the study and they were maintained under standard management conditions and provided concentrate feed, green fodder and straw. The animals had free access to drinking water. All the animals were dewormed using a single oral dose of fenbendazole at 5 mg/kg prior to the start of the experiment. A minimum washout period of 21 days was allowed between different treatments (ofloxacin and meloxicam). The experimental protocol was approved by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) on the recommendation of the Institutional Animal Ethics Committee (IAEC).

*Drugs and chemicals.* For preparation of the standard curve, meloxicam was purchased from Sigma-Aldrich. Injectable oflaxacin (Olone®- DS; Rodec Pharmaceuticals Pvt. Ltd., New Delhi) and meloxicam (Melonex®; Intas Pharmaceutical Ltd., Ahmedabad) were purchased from the local market. HPLC grade water was prepared in the laboratory using Millipore water purification assembly (Milli-Q®) and all the chemicals and solvents used were of HPLC grade.

*Experimental design.* Ten healthy female goats were divided into two groups, I and II of five animals each, which were used separately for PK studies on meloxicam and ofloxacin alone, respectively. Thereafter, three animals from each group were randomly selected for interaction studies between meloxicam and ofloxacin, therefore, the only meloxicam group consisted of five goats while the interaction group consisted of six animals.

*Dosing and sampling.* Meloxicam was injected into five goats in Group I by intravenous (IV) route at the dose rate of 0.5 mg/kg body weight. In the other group of six animals, meloxicam (0.5 mg/kg) and ofloxacin (10 mg/kg) were concurrently administered through opposite jugular veins. Blood samples for estimation of meloxicam from each goat were collected from the contralateral jugular vein into heparinized tubes before drug administration (0 hour) and at 2.5, 5, 10, 15, 30, 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36 and 48 hours post-drug administration. Blood samples were centrifuged at 3000 rpm for 20 min to separate plasma. Plasma samples were stored in storage vials at -20 °C until assayed.

*Extraction of meloxicam from plasma.* Meloxicam was extracted from plasma samples employing the slightly modified extraction method for enrofloxacin (NIELSEN and GYRD-HANSEN, 1997). For deproteinization, 0.5 mL HPLC grade acetonitrile was added into a 0.5 mL plasma sample. The mixture was vortexed and centrifuged at 9000 rpm for 10 min. The supernatant (0.5 mL) was collected in a microcentrifuge tube and 0.5 mL of HPLC grade water was added. This mixture was filtered through a 0.22 µm Millipore cellulose acetate membrane filter and an aliquot of 20 µL of the sample was injected into the HPLC system for assay of meloxicam.

*Assay method.* HPLC system (Waters, USA), having a photodiode array detector with Empower software and C18 reverse phase column (particle size 5 µm; 4.6 x 250 mm, Waters Spherosorb®), was used for assay of meloxicam in blood, employing the modified HPLC method of DASANDI et al. (2002).

The mobile phase was prepared using 60% buffer and 40% acetonitrile. The buffer used consisted of 170 mM sodium acetate trihydrate in water and 0.12% v/v triethylamine, and its pH was adjusted to 3.3 using acetic acid. The detection wavelength was set at 355 nm. 20 µL samples were injected at a mobile phase flow rate of 1.20 mL/min and at an ambient temperature of 25.0 ± 0.5 °C. Retention time of meloxicam was 4.6 ± 0.1 min. A stock solution (100 µg/mL) of meloxicam was prepared in HPLC water.

Working plasma standards were prepared from the stock solution of meloxicam in pooled plasma from untreated goats. The method was found to be consistent and reproducible, and the standard curve was linear in the concentration range of 0.1 to 6.40 µg/mL, and the correlation coefficient (R^2) was 0.999. The intra-day and inter-day coefficients of variation were less than 10 per cent. Mean recovery was more than 90 per

cent. Goat blank plasma produced no endogenous interferences in meloxicam retention time.

*Pharmacokinetics and statistical analysis of data*. The plasma meloxicam concentration time profile of each animal following intravascular administration were used to determine the pharmacokinetic variables, employing a non-linear iterative curve fitting the computer program PHARMKIT (version 2.10, Johnson and Woolard, 1988), and other parameters were determined using the equations described by BAGGOT (1977) and GIBALDI and PERRIER (1982). All the data were expressed as mean ± SE, except $t_{½\alpha}$ and $t_{½\beta}$ which were expressed as harmonic mean values. The data generated was subjected to statistical analysis employing the Student′s *t*-test (SNEDECOR and COCHRAN, 1967).

The dosage regimen of meloxicam was computed using the equations suggested by BAGGOT (1977).

**Results**

Following single intravenous injection (0.5 mg/kg), the mean plasma level of meloxicam was found to be 2.99 ± 0.13 µg/mL at 2.5 min, which rapidly decreased to 1.85 ± 0.11 µg/mL at 15 min, and thereafter gradually to 0.22 ± 0.03 µg/mL at 12 h as summarized in Table 1 and shown in Fig. 1.

Evaluation of the observed plasma levels of meloxicam versus time data indicated that the data could be best fitted to a two-compartment open model and adequately described by the biexponential equation:

$$CP = Ae^{-\alpha t} + Be^{-\beta t}$$

where Cp is the plasma concentration of meloxicam at time t, A and B are the zero time plasma drug concentration intercepts of the biphasic disposition curves, and α and β are the first order rate constants of distribution and elimination phases, respectively and "e" is the base of natural logarithm. The detailed pharmacokinetic parameters obtained by compartmental analysis are presented in Table 2.

The mean values of distribution half-life ($t_{½\alpha}$) and elimination half-life ($t_{½\beta}$) of meloxicam in goats were found to be 5.77 min and 234.85 min, respectively. The average values for the area under plasma drug concentration time curve (AUC), the area under the first moment curve (AUMC), apparent volume of distribution ($Vd_{(area)}$) and total body clearance ($Cl_B$) were 601.72 ± 42.77 µg.min/mL, 205095.9 ± 22941.00 µg.min$^2$ /mL, 0.28 ± 0.02 L/kg and 0.00085 ± 0.01 L/min/kg, respectively. The value of $K_{21}$ was 0.061 ± 0.01 min$^{-1}$ while the ratio of drug concentration between tissue and central compartment (T/P) was 0.88 ± 0.16, and the overall mean residence time (MRT) was 336.31 ± 14.61 min.

Table 1. Comparative plasma meloxicam concentrations (mean ± SE) following single intravenous administration of meloxicam (0.5 mg/kg) alone and concurrent administration of meloxicam (0.5 mg/kg) and ofloxacin (10 mg/kg) in goats

| Time (Min) | Mean plasma concentrations (µg/mL) | |
|---|---|---|
| | Meloxicam (n = 5) | Ofloxacin + Meloxicam (n = 6) |
| 2.5 | 2.99 ± 0.13 | 3.35 ± 0.12 |
| 5 | 2.50 ± 0.18 | 2.93 ± 0.12 |
| 10 | 2.20 ± 0.13 | 2.45 ± 0.09 |
| 15 | 1.85 ± 0.11 | 2.20 ± 0.08* |
| 30 | 1.71 ± 0.11 | 1.80 ± 0.08 |
| 45 | 1.59 ± 0.10 | 1.64 ± 0.09 |
| 60 | 1.45 ± 0.07 | 1.47 ± 0.07 |
| 90 | 1.22 ± 0.06 | 1.30 ± 0.08 |
| 120 | 1.08 ± 0.08 | 1.15 ± 0.05 |
| 180 | 0.97 ± 0.04 | 0.84 ± 0.07 |
| 240 | 0.80 ± 0.05 | 0.68 ± 0.08 |
| 360 | 0.58 ± 0.04 | 0.47 ± 0.05 |
| 480 | 0.39 ± 0.07 | 0.34 ± 0.04 |
| 720 | 0.22 ± 0.03 | 0.20 ± 0.02 |

*P <0.05

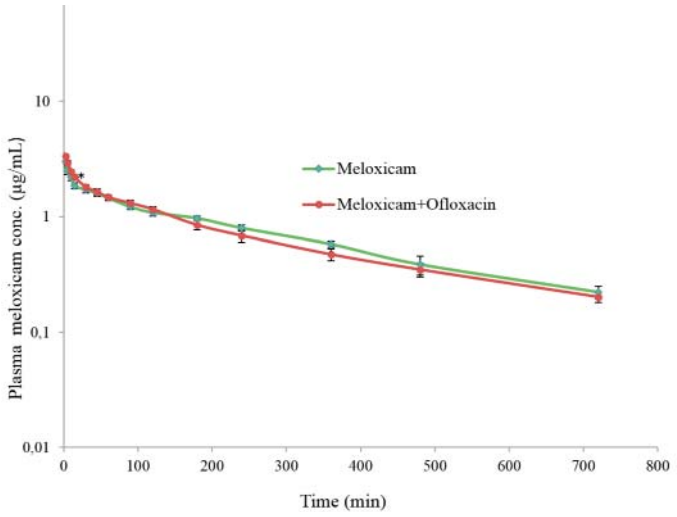


Fig. 1. Semilogarithmic plot of comparative meloxicam levels following a single intravenous administration of meloxicam (0.5 mg/kg) alone and concurrent administration of meloxicam (0.5 mg/kg) and ofloxacin (10 mg/kg) in goats. Data presented are mean ± SE of 5-6 animals. *P<0.05.

Table 2. Comparative pharmacokinetic parameters of meloxicam (mean ± SE) following single intravenous administration of meloxicam alone and concurrent administration of meloxicam and ofloxacin in goats

| Parameters (Units) | Meloxicam (n = 5) | Ofloxacin + Meloxicam (n = 6) |
|---|---|---|
| A (µg/mL) | 1.65 ± 0.19 | 1.92 ± 0.12 |
| B (µg/mL) | 1.70 ± 0.08 | 1.77 ± 0.07 |
| α ($min^{-1}$) | 0.11 ± 0.01 | 0.09 ± 0.00 |
| β ($min^{-1}$) | 0.003 ± 0.00 | 0.003 ± 0.00 |
| $t_{½α}$ (min) | 5.77# | 7.40# |
| $t_{½β}$ (min) | 234.85# | 213.75# |
| AUC (µg.min/mL) | 601.72 ± 42.77 | 568.47 ± 35.11 |
| AUMC (µg.$min^2$ /mL) | 205095.90 ± 22941.00 | 179848.2 ± 18436.40 |
| MRT (min) | 336.31 ± 14.61 | 312.20 ± 16.49 |
| $Vd_{area}$( L/kg) | 0.28 ± 0.02 | 0.27 ± 0.01 |
| Vdss (L/kg) | 0.28 ± 0.01 | 0.27 ± 0.01 |
| $Cl_B$ (L/min/kg) | 0.00085 ± 0.01 | 0.0009 ± 0.00005 |
| $K_{el}$ ($min^{-1}$) | 0.0056 ± 0.00 | 0.0066 ± 0.00 |
| $K_{12}$ ($min^{-1}$) | 0.05 ± 0.01 | 0.04 ± 0.00 |
| $K_{21}$ ($min^{-1}$) | 0.06 ± 0.01 | 0.04 ± 0.00* |
| $K_{12}/K_{21}$ (ratio) | 0.88 ± 0.11 | 0.93 ± 0.06 |
| Vc (L/kg) | 0.15 ± 0.01 | 0.14 ± 0.005 |
| Vp (L/kg) | 0.13 ± 0.01 | 0.13 ± 0.008 |
| T/P (ratio) | 0.88 ± 0.16 | 0.98 ± 0.03 |
| $f_c$ (ratio) | 0.54 ± 0.04 | 0.50 ± 0.00 |

#Harmonic mean values ; *P <0.05; A - zero time intercept of the distribution phase; B - zero time intercept of the elimination phase; $t_{½α}$ - distribution half-life; $t_{½β}$ - elimination half-life; α - distribution rate constant; β - elimination rate constant; AUC - total area under the plasma drug concentration time curve; AUMC - total area under the first moment of plasma drug concentration time curve; $K_{el}$ - the elimination rate constant of the drug from central compartment; $K_{21}$ - the rate constant of transfer of drug from tissues to the central compartment; $K_{12}$ - the rate constant of transfer of drug from the central to tissue compartment; $f_c$ - fraction of drug present in the central compartment; $Vd_{area}$ - the volume of distribution of drug based on area; Vc - the volume of distribution of drug in central compartment; Vp - the volume of distribution of drug in peripheral compartment; $Vd_{ss}$ - the volume of distribution of drug at steady state; $Cl_B$ - the total body clearance of drug; T/P - ratio of the drug concentration between peripheral and the central compartment; MRT - mean residence time.

Following concurrent administration of meloxicam and ofloxacin by intravenous route, mean plasma concentration of meloxicam was found to be 3.35 ± 0.12 µg/mL at 2.5 min, which rapidly declined to 1.80 ± 0.08 µg/mL at 30 min and thereafter slowly to 0.20 ± 0.02 µg/mL at 12 h of drug administration.

In interaction group (ofloxacin + meloxicam), the mean values of $t_{½\alpha}$ and $t_{½\beta}$ were found to be 7.40 min and 213.75 min, respectively and values of AUC, AUMC, $Vd_{(area)}$ and $Cl_B$ were 568.47 ± 35.11 µg.min/mL, 179848.2 ± 18436.40 µg.min$^2$/mL, 0.27 ± 0.01 L/kg and 0.0009 ± 0.00005 L/min/kg, respectively. The ratio of drug concentration between tissue and central compartment (T/P) was 0.98 ± 0.03 and the overall mean residence time (MRT) was found to be 312.2 ± 16.49 min.

**Discussion**

Evaluation of the semilogarithmic plot of plasma meloxicam concentration-time data following its administration alone or concurrent administration with ofloxacin indicated the two-compartment pharmacokinetic behaviour of meloxicam in goats, as has been reported in horses (LEES et al., 1991), chickens (BAERT and DE BACKER, 2003) and sheep (SHUKLA et al., 2007).

Following intravenous administration of meloxicam in goats, higher values of the distribution rate constant (0.11 min$^{-1}$) and the corresponding short distribution half-life of 5.77 min indicated the rapid distribution of meloxicam in goats. However, a many times higher distribution half-life value of the test drug has been reported in sheep (0.41 ± 0.20 h; SHUKLA et al., 2007) and horses (0.40 ± 0.2 h: LEES et al., 1991).

The elimination half-life of meloxicam in the present study in goats was found to be 234.85 min, however, SHUKLA et al. (2007) observed a comparatively higher (6.73 h) value in goats. Compared to the elimination half-life values observed in goats in the present study or those reported by SHUKLA et al. (2007), longer elimination half-life values of 8.54 h, 24.0 h and 10.85 h have been reported in horses, dogs and sheep after intravenous administration at 0.6 mg/kg, 0.2 mg/kg, 0.5 mg/kg, respectively (TOUTAIN et al., 2004; BUSCH et al., 1998; SHUKLA et al., 2007). However, comparatively shorter elimination half-lives have been documented in chickens (3.2 h; BAERT and DE BACKER, 2003) and pigs (2.7 h; FOSSE et al., 2008).These observations evidently reveal marked species dependent differences in the disposition kinetic behaviour of meloxicam. Goats have greater drug metabolizing enzyme activities in the liver and other organs, and eliminate antipyrine, sulphadimidine and isometamidium at a significantly faster rate than sheep (ELSHEIKH et al., 1988, 1991a, 1991b, 1997; WESONGAH et al., 2004), therefore, the short elimination half-life of meloxicam in goats compared to sheep, horse and dogs is expected.

In the present study, the AUC value of meloxicam in goats was 601.72 µg/mL. min, but higher AUC values have been documented in sheep (31.88 µg/mL.h; SHUKLA et al., 2007) and horses (18.8 µg /mL.h; SINCLAIR et al., 2006).

The mean value of the apparent volume of distribution ($Vd_{area}$) of meloxicam in goats in the present study was calculated to be 0.28 L/Kg, which was almost comparable to that of 0.27 L/kg in horses (SINCLAIR et al., 2006) 0.25 L/kg in sheep (SHUKLA et al., 2007) but

higher than that reported in pigs (0.19 L/kg: FOSSE et al., 2008). The $Vd_{area}$ value obtained in the present study and reported in other species indicates that the drug is not freely distributed to different body tissues and fluids, which may be due to the relatively high ionization state of meloxicam at physiological pH and/or its high plasma protein binding, as reported in other species (SCHMID et al., 1995; BUSCH et al., 1998).

The mean residence time provides a useful estimate of the persistence time of a drug in the body. In the present study, the MRT value of meloxicam in goats was 336.31 min but comparatively lower values of MRT have been reported in mice (3.02 h) and chickens (4.41 h) by BUSCH et al. (1998) and BAERT and DE BACKER (2003), respectively, contrary to the higher values in sheep (15.13 h) and dogs (34.8 h) by SHUKLA et al. (2007) and BUSCH et al. (1998), respectively.

The total body clearance of meloxicam in goats in the present study was 0.00085 L/min/kg and this value was almost three times higher than in sheep ( 0.016 L/h/kg; SHUKLA et al., 2007) and conspicuously higher than in horse (0.034 L/h/kg; SINCLAIR et al., 2006) and dogs (0.01 L/h/kg; BUSCH et al., 1998) but almost comparable to that of 0.06 L/h/kg in pigs (FOSSE et al., 2008).

Mean meloxicam plasma levels, following concurrent IV administration of meloxicam (0.5 mg/kg) and ofloxacin (10 mg/kg), were higher compared to the meloxicam alone group at 2.5 min to 45 min However, it was only statistically significant at 15 min, and thereafter the plasma levels either did not differ or were slightly lower in the meloxicam+ofloxacin concurrent group. Statistical analysis of the pharmacokinetic data from the meloxicam alone and the meloxicam+ofloxacin concurrent groups revealed that none of the pharmacokinetic determinants differed significantly from each other, except $K_{21}$ which was significantly lower in the latter group. These observations therefore suggest that there is no significant interaction between meloxicam and ofloxacin, except a slight possibility of a reduced rate of transfer of the drug from the peripheral compartment to the central compartment. Therefore, the PK interaction between the two drugs did not seem to be clinically important and does not require readjustment in dosage regimens.

In human whole blood, meloxicam has been found to inhibit 50% COX-1 activity ($IC_{50}$) at 1.15 µg/mL while COX-2 activity at 0.088 µg/mL (PAIRET et al., 1998). Therefore, meloxicam is considered to be a selective COX-2 inhibitor. The effective plasma concentration of meloxicam has been reported to be 0.73 µg/mL in horses (TOUTAIN et al., 2004). Based on the in vitro $EC_{50}$ value of 0.088 µg/mL (reported in human whole blood) and the observed mean plasma concentrations of meloxicam in goats above for up to 12 h (0.22 µg/mL), it may be inferred that a 0.5 mg/kg dosage level of meloxicam is sufficient for a satisfactory therapeutic effect in goats. However, taking into considerations the effective plasma concentration of meloxicam reported in horses (0.73 µg/mL) and the PK determinants in goats in the present study, the loading and maintenance doses of

meloxicam were found to be 0.86 and 0.65 mg/kg, respectively and should be repeated at 8 h intervals. Pharmacokinetic interaction between ofloxacin and meloxicam in goats is not substantive and does not warrant any adjustment of dosage regimen as a result of its concurrent use with ofloxacin.

## References

AHMED, F. A., P. MOHAN, C. C. BARUA, D. J. DUTTA (2005): Effect of intramuscular diclofenac sodium on pharmacokinetics of intravenous enrofloxacin in calves. Indian J. Pharmacol. 37, 189-190.

ALENCAR, M. M. A., M. T. PINTO, D. M. OLIVEIRA, A W. de. P. PESSOA, I. A. CANDIDO, C. G. VIRGINIO, H. de S. M. COELHO, M. F. G. ROCHA (2002): Margin of safety of meloxicam in dogs: deleterious effects on blood cells and gastrointestinal tract. Ciencia Rural. 33, 525-532.

BAERT, K., P. DE BACKER (2003): Comparative pharmacokinetics of three non-steroidal anti-inflammatory drugs in five bird species. Comp. Biochem. Physiol. Part C. 134, 25-33.

BAGGOT, J. D. (1977): Principles of drug disposition in domestic animals: The Basis of Veterinary Clinical Pharmacology. W.B. Saunders, Co., Philadelphia, USA.

BARUAH, H., D. C. ROY, R. K. ROY, H. N. KHONIKOR (2004): Pharmacokinetics, tissue residue and plasma protein binding of ofloxacin in goats. J. Vet. Sci. 5, 97-101.

BUSCH, U., J. SCHMID, G. HEINZEL, H. SCHMAUS, J. BAIERL, C. HUBER, W. ROTH (1998): Pharmacokinetics of meloxicam in animals and the relevance to humans. Drug Metab. Dispos. 26, 576-584.

DASANDI, B., SHIVPRAKASH, H. SAROJ, K. M. BHAT (2002): LC determination and pharmacokinetics of meloxicam. J. Pharm. Biomed. Anal. 28, 999-1004.

DUMKA, V. K., H. S. SANDHU, N. RAJPUT (2007): Effect of gatifloxacine on the pharmacokinetics of meloxicam in buffalo calves. Indian J. Anim. Sci. 77, 1270-1272.

ELSHEIKH, H. A, B. H. ALI, A. M. HOMEIDA, T. HASSAN, H. J. HAPKE (1991a): Pharmacokinetics of antipyrine and sulphadimidine (sulfamethazine) in camels, sheep and goats. J. Vet. Pharmacol. Ther. 14, 269-275.

ELSHEIKH, H. A., B. H. ALI, A. M. HOMEIDA, H. J. HAPKE (1991b): Activities of glutathione-S-transferase and ethoxycoumarin-O-deethylase in tissues of camels, sheep, goats and rats. Comp. Biochem. Physiol. C. 98, 293-297.

ELSHEIKH, H. A., B. H. ALI, A. M. HOMEIDA, T. HASSAN, H. J. HAPKE (1988): The activities of aminopyrine N-demethylase, aniline 4-hydroxylase and UDP-glucuronyltransferase in tissues of camels, desert sheep and Nubian goats. Gen. Pharmacol. 19, 713-717.

ELSHEIKH, H. A., I. A. OSMAN, B. H. ALI (1997): Comparative pharmacokinetics of ampicillin trihydrate, gentamicin sulphate and oxytetracycline hydrochloride in Nubian goats and desert sheep. J. Vet. Pharmacol. Ther. 20, 262-266.

FOSSE, T. K., H. A. HAGA, V. HORRMAZABAL, G. HAUGEJORDEN, T.E. HORSBERG , B. RANHEIM (2008): Pharmacokinetics and pharmacodynamics of meloxicam in piglets. J. Vet. Parmacol. Ther. 31, 246-252.

GIBALDI, M., D. PERRIER (1982): Pharmacokinetics. Marcel-Dekker. Inc., New York, 1982.

LANGTRY, H. D., H. M. LAMB (1998): Levofloxacin: its use in infections of the respiratory tract, skin, soft tissues and urinary tract. Drugs. 56, 487-515.

LEES, P., A. D. SEDGWICK, A. J. HIGGINS, K. E. PUGH, U. BUSCH (1991): Pharmacodynamics and pharmacokinetics of meloxicam in the horse. Br. Vet. J. 147, 97-108.

LEHR, T., R. NARBE, O. JONS, C. KLOFT, A. STAAB (2009): Population pharmacokinetic modelling and simulation of single and multiple dose administration of meloxicam in cats. J. Vet. Parmacol. Ther. 33, 277-286.

MONTOYA, L., L. AMBROS, V. KREIL, R. BONAFINE, G. ALBARELLOS, R. HALLU, A. SORACI (2004): A pharmacokinetic comparison of meloxicam and ketoprofen following oral administration to healthy dogs. Vet. Res. Commun. 28, 415-428.

MOSHER, R. A., J. F. COETZEE, C. A. CULL, R. GEHRING, B. KUKANICH (2012): Pharmacokinetics of oral meloxicam in ruminant and pre-ruminant calves. J. Vet. Pharmacol. Ther. 35, 373-381.

NAIDOO, V., K. WOLTER, A. D. CROMARTY, P. BARTELS, L. BEKKER, L. MCGAWL, M. A. TAGGART, R. CUTHBERT, G. E. SWAN (2008): The pharmacokinetics of meloxicam in vultures. J. Vet. Parmacol. Ther. 31, 128-134.

NIELSEN, P., N. GIRD-HANSEN (1997): Bioavailability of enrofloxacin after oral administration to fed and fasted pigs. Pharmacol. Toxicol. 80, 246-250.

PAIRET, M., J. VAN RYN, H. SCHIEROK A. MAUZA, G. TRUMMLITZ, G. ENGELHARDT (1998): Differential inhibition of cyclooxygenase-1 and 2 by meloxicam and its 4′- isomer. Inflamm. Res. 47, 270-276.

SCHMID, J., U. BUSCH, G. HEINZEL, G. BOZLER, S. KASCHKE, M. KUMMER (1995): Meloxicam pharmacokinetics and metabolic pattern after intravenous infusion and oral administration to healthy subjects. Drug. Metab. Dispos. 23, 1206-1213.

SHUKLA, M., G. SINGH, B. G. SINDHURA, A. G. TELANG, G. S. RAO, J. K. MALIK (2007): Comparative plasma pharmacokinetics of meloxicam in sheep and goats following intravenous administration. Comp. Biochem. Physiol. C. 145, 528-532.

SINCLAIR, M. D., K. L. MEALEY, N. S. MATTHEWS, K. E. PECK, T. S. TYLOR, B. S. BENNE (2006): Comparative pharmacokinetics of meloxicam in clinically normal horses and donkeys. Am. J. Vet. Res. 67, 1082-1085.

SNEDECOR, G. W., W. G. COCHRAN (1967): Statistical Methods: Oxford and IBH Publishing Co., New Delhi, pp 593.

TOPPO, R., B. K. ROY, A. K. MISHRA (2011): Effects of concurrent administration of meloxicam on pharmacokinetic parameters of enrofloxacin in turkeys. J. Bioanal. Biomed. 3, 108-112.

TOUTAIN, P. L., N. REYMOND, V. LAROUTE, P. GARCIA, M.A. POPOT, Y. BONNAIRE, A. HIRSCH, R. NARBE (2004): Pharmacokinetics of meloxicam in plasma and urine of horses. Am. J. Vet. Res. 65, 1542-1547.

TURNER, P. V., H. C. CHEN, W. M. TAYLOR (2006): Pharmacokinetics of meloxicam in rabbits after single and repeat oral dosing. Comp. Med. 56, 63-67.

VANE, J. R., R. N. BOTTING (1995): New insight into the mode of action of anti-inflammatory drugs. Inflamm. Res. 44, 1-10.

VERMA, R., G. K. CHOUDHARY, R. SAJAN (2007): Pharmacokinetics of enrofloxacin and ciprofloxacin as a metabolite and its interaction with meloxcam in jamunapari goats. J. Vet. Pharm. Toxicol. 6, 11-14.

WESONGAH, J. O., T. W. JONES, J. K. KIBUGU, G. A. MURILLA (2004): A comparative study of the pharmacokinetics of isometamidium chloride in sheep and goats. Small. Rumin. Res. 53, 9-14.

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**SAŽETAK**

Istražen je učinak ofloksacina (10 mg/kg) na farmakokinetiku meloksikama (0,5 mg/kg) u koza pod uvjetima istodobne intravenske primjene. Koncentracija meloksikama u plazmi utvrđena je visokotlačnom tekućinskom kromatografijom. Kao najbolji model za opis njegove farmakokinetike korišten je otvoreni model s dvama odjeljcima. Istodobnom primjenom meloksikama i ofloksacina, srednja razina meloksikama u plazmi bila je statistički značajno viša ($P<0,05$) samo 15 minuta u usporedbi s primjenom samog meloksikama. Statistička analiza podataka pokazala je da između dva načina primjene ne postoje značajne razlike farmakokinetičkih pokazatelja, osim za $K_{21}$. Rezultati istraživanja pokazuju da kod koza doziranje ofloksacina i meloksikama prilikom njihove istovremene primjene ne treba mijenjati. Na temelju farmakokinetičkih pokazatelja, meloksikam se može primijeniti intravenski u početnoj dozi od 0,86 mg/kg, te u dozi za održavanje od 0,65 mg/kg, uz ponavljanje u vremenskim razmacima od 8 sati.

**Ključne riječi:** meloksikam, ofloksacin, visokotlačna kromatografija, farmakokinetika, koze