

Pharmacokinetics of Ecofriendly Meloxicam in Healthy Goats

Khawaja Tahir. Mahmood¹ Muhammad. Ashraf² Fatima Amin³, Ikram. Ul .Haq⁴
and Mansoor Ud Din Ahmad⁵

DTL, Health Department, Punjab, Lahore¹ Department of Pharmacology & Toxicology, UVAS; Lahore²,
Department of Pharmacy, LCWU, Lahore³ Akhter Saeed College of Pharmaceutical Sciences, Baheria Town, Lahore⁴
Department of Epidemiology and Public Health, UVAS, Lahore⁵

Abstract:

Diclofenac Sodium, a Non-steroidal anti-inflammatory drug (NSAID) was banned for veterinary use in Pakistan, India and Nepal in 2005-06 due to its relay toxicity associated with catastrophic decline in the populations of vulture in South Asia. The main aim of the present research was to study pharmacokinetics of meloxicam in goats under local conditions. Meloxicam is another NSAID, reported as a safe alternate to diclofenac. It is a preferential cyclooxygenase-2 (COX-2) inhibitor with higher therapeutic index as compared to diclofenac, indomethacin and piroxicam. Eight healthy goats investigated, were administered meloxicam 0.6 mg.kg⁻¹b.wt, as intravenous bolus, into the jugular vein. Blood samples(5mL) were collected before medication and then up to 96 hours post medication. Plasma concentrations of meloxicam were measured in triplicate by HPLC method developed and validated at laboratories of UVAS and Lahore College for Women University, Lahore Pakistan. The plasma concentration versus time profile was prepared. Mean(± SEM) values of pharmacokinetic parameters viz area under curve(AUC); steady state volume of distribution(V_{DSS}), half-life(t_{1/2}); mean residence time(MRT) and clearance(CI) were 22.81±1.25 µg.h/mL, 0.266±0.007 L/kg, 7.34±0.31 h, 7.34±0.46 h and 0.026±0.002 L/h/kg respectively. These values were comparable to value reported for goats. However, these pharmacokinetic parameters were significantly different when compared with other species including livestock. The pharmacokinetic parameters were put in different equations for calculations of dose. In conclusion interspecies variations exist in pharmacokinetics of meloxicam. Furthermore, a single IV injection of meloxicam @ dose of 0.6 mg.kg⁻¹b.wt may safely be used therapeutically in goats.

Keywords: NSAIDs; diclofenac toxicity; meloxicam; HPLC, pharmacokinetics goats.

Introduction:

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed and highly utilized drugs. These drugs are commonly used in humans, as well as in animals, to reduce pain, fever and inflammation for the treatment of different clinical conditions such as rheumatic disorders and mastitis etc. [1,2,3,4]. The vultures are of great significance for maintaining balance of ecosystem in South Asia including Pakistan and India. It had been established scientifically that relay toxicity of a non-steroidal anti-inflammatory drug diclofenac sodium was responsible for catastrophic / dramatic fall in Asian vulture population within Indian subcontinent [5,6,7,8] Diclofenac sodium was banned for veterinary use in Pakistan, India and Nepal during 2005-06.

Meloxicam which is another NSAID, has been reported as a safe substitute of diclofenac sodium. This drug was directly

administered to Gyps vulture in captivity at a dose starting from 0.5 mg /kg vulture body weight to the highest dose of 2 mg /kg. The likely maximum level of exposure [MLE] of meloxicam to wild vultures was calculated as 1.83 mg /kg vulture body weight. All meloxicam treated birds survived at all doses and none suffered any obvious clinical adverse effects, [9] It has been reported that meloxicam was eliminated from vulture at very fast rate indicating that there was no possibility of accumulation of this drug, [10] Thus, one NSAIDs diclofenac was responsible for eco damage whereas another NSAID meloxicam was adjudged as ecofriendly substitute of toxic diclofenac. Meloxicam is chemically designated as 4-hydroxy-2-methyl- N -[5-methyl-2-thiazalyl)-2 H -1,2-benzothiazine-3-carboxamide-1,1-dioxide [11] and belongs to oxycam class of NSAIDs. It has the molecular weight of 351.4 Dalton and its formula is shown in fig 1.

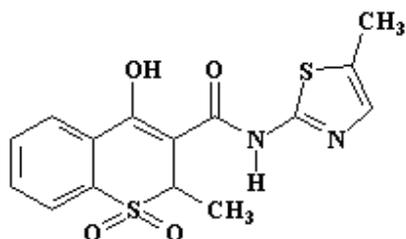


Figure 1: Chemical formula for Meloxicam
[C₁₄H₁₃N₃O₄S₂]

It preferentially inhibits cyclooxygenase-2 which is responsible for pathophysiological conditions rather than cyclooxygenase-1 responsible for physiological processes [12] It has a half-life of 20-24 hours in human and once-daily administration is considered appropriate. It is strongly bound to plasma proteins [99.5%) [13] The therapeutic index of meloxicam is higher when compared with other NSAIDs like piroxicam, diclofenac and indomethacin. [14] Meloxicam undergoes fast elimination, leading to a shorter $t_{1/2}$ in comparison with piroxicam and tenoxicam. It has no capability for nephrotoxicity [15,16, 17]

The study of pharmacokinetics is of great significance for evaluating therapeutic use of the drug in any species. The basic aim of the present study was to determine pharmacokinetics of meloxicam in goats under local conditions of Pakistan, to explore interspecies variation and to make some recommendations regarding its dose in goats.

Materials and Methods:

Experimental animals:

Eight healthy and clinically normal adult goats with average weight of 35kg were used in the study. All the goats were tagged and acclimatized to the experimental environment at the animal sheds of Department of Pharmacology and Toxicology, UVAS, Lahore, Pakistan. Standard food was provided with water supply *ad libitum*. Health status of these

experimental animals was regularly monitored throughout the experiment.

Experimental chemicals and drugs:

The standard of meloxicam (Sigma); HPLC grade water, phosphoric acid and acetonitrile (E. Merck Germany); injections of meloxicam manufactured by INTAS Pharmaceutical Limited Ahmadabad, India and chemicals of analytical grade were used in this experiment.

Design, drug treatment, sampling and analysis

Experimental goats were administered an intravenous bolus of meloxicam 0.6 mg/kg body weight, via jugular vein. Blood samples (5 mL) were collected from all the eight goats in heparinized vacutainer test tubes before medication and then 0.12, 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 7.0, 8.0, 9.0, 12.0, 18.0, 24.0, 36.0, 48.0, 60.0, 72.0 and 96.0 hours post medication. The saline (0.9% NaCl) solution was used to wash IV cannula pre and post sampling. Plasma was separated from blood samples by centrifugation at 3000 rpm for 10 minutes and stored at -20°C till analyzed.

HPLC analysis

Meloxicam in plasma was measured in triplicate by a simple, specific, precise and accurate, HPLC method developed and validated previously, [18] In brief, HPLC grade acetonitrile (1 mL) was added to 1mL plasma for extraction of meloxicam. The mixture was subjected to high speed vortex mixing at 1500 rpm for 3 minutes, followed by ultra-centrifugation at 8000 x g for 15 minutes. The clear supernatant (1 mL) was mixed well with 1 mL of HPLC grade water and filtered through 0.22 μm filter. Ten micro liters [μl] of the aliquot were injected into HPLC system for the analysis through an injector valve with a 10 μl sample loop. The mobile phase comprising of phosphate buffer and acetonitrile (38:62, v/v) was pumped into Water 1525 Binary HPLC Pump 1525 at the rate 0.5mL/minute.

Separation was achieved by using a reversed phase C18 column (Phenomenex, particle size 5 μm ; 4.6 mm \times 150 mm) at retention time of 7.4 minutes. Oven temperature was set at 25°C. The meloxicam was detected at 352 by using a Water 2487 dual absorbance detectors. Meloxicam (Sigma) was used as external standard.

The distinct peak observed in chromatograms of meloxicam extracted from plasma of goats was similar to the peak in chromatogram of external standard at retention time of 7.4 minutes. Similarity between peaks indicated specificity. The recovery of meloxicam from the plasma spiked with the drug >92% had indicated accuracy. The value 1.8% CV (RSD) had indicated precision of the method. The intraday and interday assays had shown that method was reproducible within acceptable variation of < 2% and < 3%, respectively. Five reading were taken. The limit of detection (LOD) and limit of quantification were 0.06 and 6 (μg) respectively. The plasma concentration ($\mu\text{g}/\text{mL}$) versus time profile of meloxicam in goats was prepared.

Pharmacokinetics

The computer software Software APO PC-Program, MWPHARM Version. 3.02, a MEDIWARE product, Holland. was used for calculation of pharmacokinetic parameters. This software calculates parameters for compartmental and non compartmental models.

The following equations were used for different calculations:

$$Cl = \text{Dose}/\text{AUC};$$

$$\text{AUMC} = \text{MRT} \times \text{AUC};$$

$$\text{Dose} = \frac{\text{VD}_{\text{SS}} \times \text{AUC}^2}{\text{AUMC}}$$

Where, AUC = Area under the curve, CL = Clearance, MRT = Mean residence time and AUMC = Area under the first moment curve.

Statistical analysis

The software SPSS (Statistical Package for the Social Sciences) 13.0 was used for statistical analysis. The values in the raw data were expressed as range, mean, SEM (standard error of means); median and standard deviation.

Results and Discussion:

Plasma concentrations ($\mu\text{g}/\text{mL}$) of meloxicam were determined at various time intervals after intravenous administration at dose of 0.6 mg/kg body weight in goats. The results are given in Table 1. The graphical representation of plasma concentrations ($\mu\text{g}/\text{mL}$) of meloxicam in goats versus time is given in Figure.2. The pharmacokinetics of meloxicam in goats was best fitted to a two compartment model. The PK profile is given in Table.2

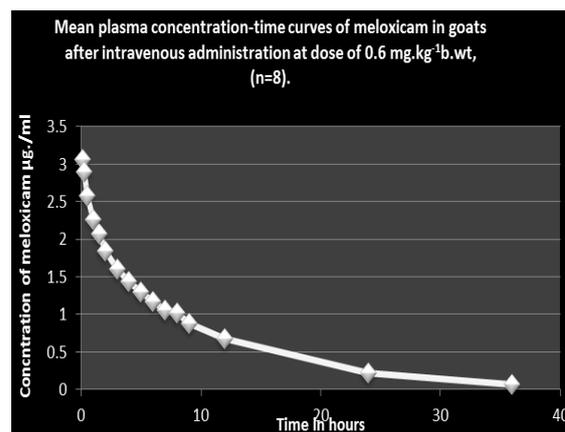


Figure 2: Mean plasma concentration-time curves of meloxicam in goats after intravenous administration at dose of 0.6 mg.kg⁻¹B.WT, (N=8).

The results had indicated that PK-values determined in present study were comparable to the reported pharmacokinetic parameters of meloxicam in goats. These pharmacokinetic parameters were different when compared with other species human, horses, donkeys, sheep's, piglets, ducks, vultures and turkeys. 0.6 mg dose of meloxicam in goats was calculated by use of Pk. equations given above.

Table 1: The plasma concentration ($\mu\text{g/mL}$) versus time profiles of meloxicam in goats following intravenous administration at dose of $0.6 \text{ mg.kg}^{-1}\text{b.wt}$, (n=8).

Time(hrs)	Range [$\mu\text{g/mL}$]	Mean \pm SEM [$\mu\text{g/ml}$]	CV%
0.12	2.972-3.109	3.06 \pm 0.015	1.37
0.25	2.888-2.912	2.894 \pm 0.004	0.38
0.5	2.271-2.717	2.575 \pm 0.046	5.09
1	2.137-2.459	2.261 \pm 0.046	5.75
1.5	1.885-2.600	2.069 \pm 0.087	11.89
2	1.710-2.109	1.841 \pm 0.062	9.51
3	1.466-1.887	1.605 \pm 0.064	11.34
4	1.300-1.707	1.435 \pm 0.063	12.33
5	1.167-1.552	1.298 \pm 0.060	13.02
6	1.050-1.410	1.177 \pm 0.057	13.76
7	0.894-1.284	1.058 \pm 0.058	15.50
8	0.807-1.555	1.014 \pm 0.092	25.64
9	0.770-1.063	0.875 \pm 0.054	17.37
12	0.507-0.867	0.675 \pm 0.048	20.15
24	0.170-0.345	0.219 \pm 0.025	31.51
36	0.050-0.141	0.071 \pm 0.012	47.89

Table 2: Pharmacokinetic parameters of meloxicam in goats following intravenous administration of meloxicam at a dose of $0.6 \text{ mg.kg}^{-1}\text{b.wt}$, (n=8).

PK_Parameter	Units	Range	Mean \pm SEM
AUC	$\mu\text{g.h/mL}$	21.95-26.82	23.15 \pm 1.139
AUC Polyexponential	$\mu\text{g.h/mL}$	22.39-27.02	22.39 \pm 1.198
AUC trapezoidal	$\mu\text{g.h/mL}$	20.210-27.420	22.81 \pm 1.247
AUMC	$\mu\text{g.h}^2/\text{mL}$	219.5-252.6	204.65 \pm 10.90
Cl	L/hr/kg	0.0208-0.0296	0.026 \pm 0.002
Vd _[area]	L/kg	0.1785-0.1882	0.1880 \pm 0.005
VD _{SS (Steady State)}	L/kg	0.2342-0.2781	0.265 \pm 0.007
Vdcp	L/kg	0.2648-0.2898	0.2768 \pm 0.003
Half life phase 1 t _{1/2} (α)	h	0.6417-.0.6587	0.6487 \pm 0.008
Half life phase 2 t _{1/2} (β)	h	6.824-9.310	7.341 \pm 0.312
K ₁₀ (Elimination rate Constant)	L/h	0.1367-0.1418	0.1379 \pm 0.003
K ₁₂	L/h	0.2887-0.3109	0.2987 \pm 0.003
K ₂₁	L/h	0.7255-0.7834	0.7255 \pm 0.004
MRT	h	7.811-9.415	8.84 \pm 0.86

CP= Central compartment ,K₁₀ =Rate constant of elimination from central - compartment , K₁₂=Rate constant of transfer between central compartment and tissue compartment and K₂₁=Rate constant of transfer between tissue compartment and central compartment

The biological processes of absorption, distribution, metabolism and excretion (ADME) of drugs affects the level of drug and its movements towards site of action. Thus, ADME greatly influences pharmacological action of drugs. Genetics and environmental factors affecting ADME are responsible for inter-individual, inter-ethnic and inter-species variations to clinical response during any drug therapy. Previous studies have indicated inter species and interethnic variations in clinical response to meloxicam [19,20,21] The pharmacokinetics of meloxicam under local conditions of Pakistan has never been reported in goats.

The IV dose 0.6 mg/kg, of meloxicam had produced anti-inflammatory effects in carrageenan-sponge model of acute inflammation in horses. [19] So, this 0.6 mg/kg dose of meloxicam/kg for IV administration was chosen for the goats, to achieve plasma concentrations of meloxicam that were likely to have an effect against inflammation.

The present study indicated that mean [\pm SEM) values of pharmacokinetic parameters viz area under curve (AUC); steady state volume of distribution (V_{Dss}), half-life ($t_{1/2}$); mean residence time (MRT) and clearance (Cl) were 22.81 ± 1.25 $\mu\text{g}\cdot\text{h}/\text{mL}$, 0.266 ± 0.007 L/kg, 7.34 ± 0.31 h, 10.41 ± 0.46 h and 0.026 ± 0.002 L/h/kg respectively. These values were comparable to the reported pharmacokinetic parameters of meloxicam in goats. The mean \pm SE values of AUC, Cl, V_{Dss} , $t_{1/2}$, MRT reported for goats were 19.23 ± 2.23 $\mu\text{g}/\text{mL}$, 0.03 ± 0.01 l/h/kg, $0.25 \pm 0.011/\text{kg}$, 6.73 ± 0.58 h and 9.37 ± 0.83 h. The PK-values reported for sheep were 31.88 ± 2.97 μg h/mL, 0.016 ± 0.002 l/h/kg, 0.24 ± 0.02 l/kg 10.85 ± 1.21 h and 15.13 ± 1.67 h [22]

These reported values indicated that meloxicam was eliminated at a faster rate in goats compared to sheep. The smaller value of AUC of meloxicam observed in goats as

compared to reported value for sheep also indicates that clearance of the drug was faster in goat as compared to sheep. This may be explained by referring to metabolic pattern of meloxicam which is eliminated mostly as metabolites formed as a result of biotransformation. The higher drug metabolizing enzyme activities in the liver and other organs of goat have been linked with fast elimination of antipyrine, ampicillin [23], sulphadimidine [24] and isometamidium [25] Interspecies variation was demonstrated and clearly visible in the level and activity of many biotransformation enzymes among farm animal species [26] However, PK-values for meloxicam observed in goats were different when compared with PK values in many other species. Relatively shorter elimination half-lives for meloxicam have been reported in ducks (0.72 h); turkeys (0.99 h) and ostriches (0.5 h) [27] whereas $t_{1/2}$ of 2.7 h reported in piglets [28] Vultures eliminate meloxicam extremely rapidly with a $t_{1/2}$ of 1 h [10] The $t_{1/2}$, reported in horses was 8.54 ± 3.02 h [21] However, meloxicam has longer half lives in albino rat (49.9 h); and human 15 to 20 h [13] The different mean \pm SE elimination half-lives of 23.51 ± 0.746 , 15.431 ± 0.628 h and 8.174 ± 0.602 h for meloxicam have been reported in healthy dogs, healthy lactating buffalo and healthy horse. [29,30, 31]

The pharmacokinetic parameters determined in goat in the present research work were put in the above Pk. equations. A single IV-dose of 0.6 mg / Kg is recommended for use in goats.

In conclusion, results of the present study indicate that variations exist in pharmacokinetics behaviour of meloxicam in goats when compared with other species even closely related livestock species. Thus, pharmacokinetics of meloxicam could not be extrapolated from one species to another.

We need to carry out research in target species under local conditions.

The livestock sector is fully aware that better high quality yields of meat, milk and other dairy product depend on better health of animals. The infections, inflammations and pain may adversely affect livestock sector. So, we need to carry out trials for assessment of minimum effective plasma concentration of meloxicam for management of different pains emerging from clinical conditions such as musculoskeletal disorders and mastitis. The interaction with antibiotics must be studied as NSAIDs are usually co administered as an adjunct to anti-microbial therapy in veterinary practice.

The Government of Pakistan should encourage national industry for development of cost effective bioequivalent generics of meloxicam in order to ensure free availability of meloxicam at low price which will encourage end user to switch on to ecofriendly meloxicam and also help in eliminate diclofenac sodium from veterinary practice.

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