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Pharmacokinetic study of single dose intramuscular administration of meloxicam in Barbari goats

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Abstract
Pharmacokinetic studies of meloxicam, was conducted in six healthy goats after intramuscular administration @ 0.50mg/kg b.w. The study was performed by cross-over design. Blood samples were collected from jugular vein at predetermined time intervals after drug administration. Plasma concentrations of meloxicam were measured by high performance liquid chromatography. Various pharmacokinetic parameters were calculated using non-compartmental model. The drug showed absorption half life ($t_{1/2ka}$) of 0.33±0.03h and elimination half life ($t_{1/2\beta}$) of 7.34±0.24h. Large volume of distribution (Vd_{area}) of 370.71±12.18ml.kg^{-1} in goats indicated high distribution of drug into various body fluids and tissues. The average values for area under plasma drug concentration-time curve ($AUC_{(0-\infty)}$) and area under first moment curve (AUMC) was 14.29±0.23µg.ml^{-1}.h and 154.52±4.73µg.ml^{-1}.h^2, with mean residence time (MRT) of 10.82±0.30h respectively.

Keywords: meloxicam, pharmacokinetic, intravenous, goats

1. Introduction
Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective for managing acute and chronic orthopedic pain as well as post-surgical pain [1, 2, 3, 5, 6, 7]. A variety of non-steroidal drugs have been administered to farm animal, including, paracetamol, meloxicam and phenylbutazone etc. Meloxicam, a new anti-inflammatory drug is a member of the oxicam family of NSAIDs [11]. Meloxicam has high anti-inflammatory efficacy with low ulcerogenic potency and shows less gastric irritation and local tissue irritation in comparison to other NSAID. Meloxicam is used in animals for the treatment of acute respiratory infection in combination with appropriate antibiotic, in cases of infection associated with pain, fever or anti-inflammatory conditions and in acute mastitis [12]. The main advantage of meloxicam over other NSAIDs is that it has greater inhibitory action against the inducible COX–2 isoform, which is responsible for the inflammatory response. Meloxicam is used in dogs, cats, pigs, goat, horse and cattle etc to treat inflammation and for management of postoperative pain. The present study was conducted to determine the pharmacokinetics and dosing regimen of this drug after its intramuscular administration in Barbari goats.

2. Materials and Methods
The injectable meloxicam (Melonex) was obtained from Intas Pharmaceuticals, Ahmedabad, Gujrat (India). External standards of meloxicam were obtained from Sigma-Aldrich, St. Louis, USA. Other essential chemicals like acetonitrile, and water procured form M/s Merck Specialties Private limited, Mumbai. The present study was conducted on 1-2 years old, six clinically healthy Barbari goats of livestock farm, Amanala, NDVSU, Jabalpur. The average weight of goats were 22-25 kg. All the goats were ear tagged with identification number and kept under observation for two weeks prior to commencement of experiment. Animal were housed in hygienic conditions and provided balance ration with *ad-lib* water. All necessary management procedures were adopted to keep the animals free from undue stress and CPCSEA guidelines were followed for care and management of animals. The study was approved by Institutional Animal Ethics Committee of College of Veterinary Science and Animal Husbandry, Jabalpur, Madhya Pradesh, India.

a) Experimental design and samples Collection
A single dose of meloxicam was administered intramuscularly into the jugular vein of goats at the dose rate of 0.5mg/kg body weight. Blood samples (1.5ml) were collected from jugular vein in vacutainer tubes containing K_3EDTA at 0 minutes (before drug administration),

0.017, 0.033, 0.083, 0.125, 0.167, 0.25, 0.5, 0.75, 1.5, 2, 4, 6, 8, 10, 12, 18, 24, 30 and 36 hours after administration of drug following aseptic precaution. Blood samples were centrifuged at 5000 RPM for 10 minutes at 4ºC, and obtained plasma samples were stored at -20ºC until analyzed by UHPLC within 24 to 36hours of collection.

b) UHPLC assay procedure

Plasma concentration of meloxicam were measured by Ultra High Performance Liquid Chromatography System (Shimadzu Corporation, Japan) equipped with binary gradient solvent delivery pump (SIL-30AC) and Photo diode array Detector (SPD-M20A) using C_{18} reverse phase column (Supelco Discovery Column 25cm x 4.6mm, particle size 5µ). For meloxicam estimation water and acetonitrile were used as mobile phase. Water with acetic acid (99:1, v/v) mixture and acetonitrile were used in the ratio of 50:50. Mobile phases were filtered by 0.22 µ nylon syringe filter before use. Flow rate for the mobile phase was 1 $ml.min^{-1}$. The temperature of column oven was 40ºC. The injection volume of the sample was 10µl. The effluent was monitored at 364nm wavelength.

c) Sample preparation for meloxicam

In the collected plasma sample, protein was precipitated using equal quantity of acetonitrile, this mixture was then vortexed for 1 minute and centrifuged at 5ºC for 10 minutes at 4000 rotations per minutes using refrigerated centrifuge. Supernatant was taken out of centrifuge tube and filtered through 0.22µ nylon syringe filter. This filtrate is kept in screw tight 2 ml auto-sampler glass vial, which latter kept in HPLC auto-sampler at designated place.

d) Preparation of standard concentration in plasma for enrofloxacin

Meloxicam was quantified by calibration curve drawn between the plasma having the spiked and known concentration of meloxicam and obtain peak area. The assay was sensitive and reproducible and linearity was observed from 50 to 0.050 $\mu g.ml^{-1}$ with coefficient of correlation (R^2) was 0.99.

3. Results and Discussion

In the present study, concentrations of meloxicam in plasma at various time intervals following its single intramuscular injection at the dose rate of 0.5$mg.kg^{-1}$ body weight have been shown in Table 1 and figure 1. The highest plasma concentration of meloxicam (1.28±0.02$\mu g.ml^{-1}$) was obtained at 1.0h. This concentration declined rapidly to 0.62±0.02$\mu g.ml^{-1}$ at 8h and after that meloxicam gradually disappeared from plasma and a concentration of 0.19±0.01$\mu g.ml^{-1}$ was detected at 24h. The peak plasma level was approximately 1.83 fold higher than minimum therapeutic level of meloxicam (0.7$\mu g.ml^{-1}$) and the drug was detected above effective level for 6h. In agreement to the present research work, a concentration of 0.88±0.03$\mu g.ml^{-1}$ in plasma was achieved at 0.5 hour and 1.08±0.06$\mu g.ml^{-1}$ after 1h of intramuscular administration of meloxicam at the dose rate of 0.5$mg.kg^{-1}$ b.w. in goats. The value of absorption half-life ($t_{1/2ka}$) of meloxicam was 0.33±0.03h after intramuscular administration at dose rate of 0.5$mg.kg^{-1}$.

Table 1: Plasma concentration of meloxicam (0.5$mg.kg^{-1}$) following single intramuscular administration in Barbari goats

Time (h)	Mean ±S.E.($\mu g.ml^{-1}$)	Time (h)	Mean ±S.E. ($\mu g.ml^{-1}$)
0.017	0.08±0.01	2	1.11±0.03
0.033	0.10±0.01	4	0.96±0.03
0.083	0.12±0.01	6	0.92±0.03
0.125	0.31±0.02	8	0.62±0.02
0.167	0.48±0.05	10	0.57±0.02
0.25	0.67±0.04	12	0.31±0.03
0.5	0.88±0.03	24	0.19±0.01
0.75	1.03±0.04	30	0.08±0.01
1	1.28±0.02	36	0.04±0.01
1.5	1.26±0.02	48	ND

In the present study, the value of volume of distribution (Vd_{area}) was 370.71±12.18$ml.kg^{-1}$ in goats indicated high distribution of drug into various body fluids and tissues. Shukla *et al*. (2007) [8] and Yadav *et al*. (2014) [13] observed the volume of distribution in goat on single intravenous administration respectively as 0.26±0.01 $L.kg^{-1}$ and 0.28±0.02 $L.kg^{-1}$ [8, 13]. Wani, *et al*. (2013) reported the value of Vd_{area} as 0.267±0.0102 $L.kg^{-1}$ for goat after single intravenous (1$mg.kg^{-1}$ b. w.) administration of meloxicam [12]. The mean value of volume of distribution at steady state (Vd_{ss}) observed in the present study was 379.14±12.53$ml.kg^{-1}$, which is comparable to the value observed by Singh *et al*. (2008) as 0.38±0.01$L.kg^{-1}$ [10]. On administration of drug by intravenous route the Vd_{ss} was 0.25±0.01$L.kg^{-1}$, 0.265±0.007$L.kg^{-1}$ and 0.28±0.1$L.kg^{-1}$ were reported respectively by Shukla, *et. al*., (2007), Mahmood *et al*. (2011) and Yadav *et al*. (2014) [4, 8, 13]. Following intramuscular administrations of meloxicam in present study, the values of AUC was 14.29±0.23$\mu g.ml^{-1}$.h in goats, which is consistent to the observation by Singh (2005) as 16.42±1.46$\mu g.ml^{-1}$.h in goats. Moreover, slightly higher AUC was observed for intravenous administration of meloxicam in goats as 19.23±2.23$\mu g.ml^{-1}$.h by Shukla *et al*. (2007) [8] where as Mahmood *et al*. (2011) reported still higher AUC (23.15±1.139 $\mu g.ml^{-1}$. h) for goats [4].

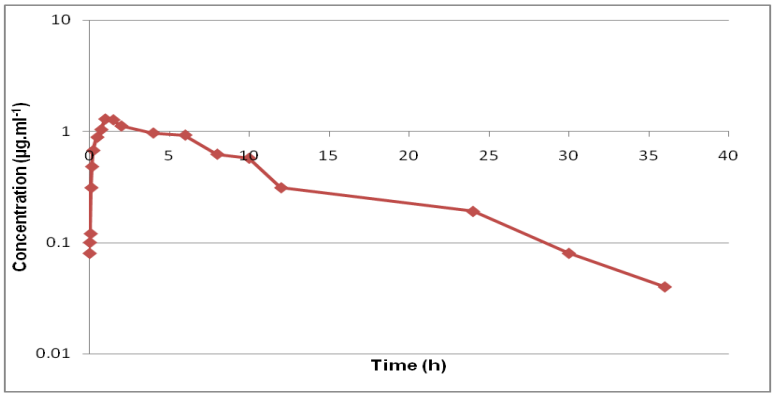

Fig 1: Semi logarithmic plot of plasma concentration of meloxicam by intramuscular route at different time interval in Barbari goats

The elimination half-life of meloxicam in goat in the present study was 7.34±0.24h. which is in agreement to the observations of Singh (2005) as7.72±0.49h in goats at the intramuscular at the dose rate of 0.5mg.kg^{-1} [9]. Shukla *et al*. (2007) [8] and Yadav *et al*. (2014) [13] observed the value of $t_{1/2\beta}$ as 6.73±0.58h and 3.91h respectively, for meloxicam on intravenous administration at the dose rate of 0.5mg.kg^{-1} body weight in goat [8, 13]. Total body clearance (Cl_B) of meloxicam, which represents the sum of metabolic and excretory processes was 35.04±0.57ml.kg^{-1}.h^{-1} in barbari goats. Similar value of Cl_B (0.03±0.01L.kg^{-1}.h^{-1}) in goat was reported by Singh (2005) [9]. As reported by other workers the value of total body clearance 0.03±0.01L.h^{-1}.kg^{-1}, 0.026±0.002L.h^{-1}.kg^{-1} and 0.00085±0.01L.min^{-1}.kg^{-1} by Shukla *et al*. (2007) [8], Mahmood *et al*. (2011) and Yadav *et al*. (2014) [13] respectively for intravenous administration of meloxicam in goats [4, 8, 13]. The MRT calculated following single dose intramuscular administration of meloxicam sodium was 10.82±0.30h in barbari goats. Singh (2005) observed the value of MRT for meloxicam was 11.78±0.74h which is in agreement of our findings (Table 2). However, lower values of MRT as 9.37±0.83h and 8.84±0.86h was reported respectively by Shukla *et al*. (2007) [8] and Mahmood *et al*. (2011) on intravenous administration of meloxicam [4, 8]. Likewise Yadav *et al*. (2014) [13] reported MRT for meloxicam as 336.31±14.61minutes on intravenous administration of meloxicam in goats.

Table 2: Pharmacokinetic parameters of meloxicam (0.5mg.kg^{-1}) following single intramuscular administration in barbari goats

Kinetic parameters	Unit	Mean ± S.E.
A	µg.ml^{-1}	1.57±0.23
B	µg.ml^{-1}	1.39±0.04
Ka	h^{-1}	0.96±0.07
β	h^{-1}	0.04±0.001
$t_{1/2ka}$	H	0.33±0.03
$t_{1/2\beta}$	H	7.34±0.24
$AUC_{(0-\infty)}$	µg.ml^{-1}.h	14.29±0.23
AUMC	µg.ml^{-1}.h^2	154.52±4.73
Vd_{area}	ml.kg^{-1}	370.71±12.18
Vd_{ss}	ml.kg^{-1}	379.14±12.53
Cl_B	ml.kg^{-1}.h^{-1}	35.04±0.57
MRT	H	10.82±0.30

Cp^0= Theoretical concentration of drug in plasma at zero time A = zero-time intercept of distribution phase; B = zero-time intercept of elimination phase; α = distribution constant; β = elimination constant; $t_{1/2\alpha}$ = half-life of distribution phase; $t_{1/2\beta}$ = half-life of elimination phase; AUC = area under the concentration-time curve; AUMC= area under the movement curve; K_{12} = rate constant from central to peripheral compartment; K_{21} = rate constant from peripheral to central compartment; Kel: elimination from central compartment; Vd_{area} = volume of drug distribution; Vd_{ss}=Volume of distribution in steady state; Cl_B = total body clearance of the drug; MRT = mean residence time.

4. Conclusion

The present study is concluded that meloxicam is an effective nonsteroidal anti-inflammatory drug for routine anti-inflammatory purposes by intramuscular route. Kinetic parameters of meloxicam showed the appropriate concentration in the body, for long time effectiveness for therapeutic doses. Thus it can be used as analgesic and anti-inflammatory drug in goats.

5. Acknowledgement

We declare that we have no conflicts of interest.

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