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ORIGINAL RESEARCH

Pharmacokinetic studies of meloxicam after its intravenous administration in local goat (*Capra hircus*) of Assam

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Abstract

Aim: The aim of the present study was to determine the meloxicam concentrations in the plasma of goats at different time intervals after its administration by IV route and data were used to determine the different pharmacokinetic parameters and the bioavailability of meloxicam in goats.

Materials and Methods: The present study was conducted on 12 to 18 months old, five adult male local goats (*Capra hircus*) of Assam, with body weight ranging between 10 to 18 kg. All goats were clinically sound and healthy and reared at Goat Research station, Burnihat, Assam. A single dose of meloxicam was administered intravenously into the jugular vein of goats at the rate of 1 mg/kg body weight. Blood samples were analyzed with the help of high performance liquid chromatography (HPLC) system.

Results:After single intravenous administration of meloxicam at the dose rate of 1mg/kg, the mean peak plasma level of the drug was 6.538±0.1189 µg/ml at 2 min. The mean elimination half life ($t_{1/2\beta}$) and mean distribution half life ($t_{1/2\alpha}$) were 484.5±85.1202 min and 28.68±1.4206 min respectively. The mean values of *AUC and AUMC were* 2635.272±94.2389 µg.min/ml and 1620332±92456.46 µg.min^2/ml respectively. The mean values of volume of distribution (Vd) and mean residence time (MRT) were 0.276±0.0103 L/kg and 612.948±14.5771 min respectively.

Conclusion: After calculating various pharmacokinetic determinants, dosage regimens were computed for meloxicam in goats, based on minimum effective therapeutic plasma concentration of 0.7 µg/ml.To maintain the minimum effective concentration of 0.7 µg/ml in plasma for 25 hours following iv administration of meloxicam,an initial loading dose of 1.1 mg/kg body weight followed by a maintenance dose of 1mg/kg body weight/day is recommended.

Keywords: goat, meloxicam, pharmacokinetic parameters

Introduction

Meloxicam (MEL) (4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide) is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class belonging to the group of enolic acids, having a molecular formula $C_{14}H_1N_3O_4S_2$, molecular weight 351.4, melting point 254ºd, used widely in both human and veterinary medicine [1]. The importance of NSAIDS especially meloxicam has been proved beyond any doubt. Meloxicam is a novel NSAID that has effectively replaced the old pain killers particularly diclofenac sodium which has high toxicity [1]. Besides this meloxicam has high anti-inflammatory efficacy with low ulcerogenic potency and shows less gastric irritation and local tissue irritation in comparison to other NSAIDS. It is a broad spectrum drugs that covers a number of diseases especially canine osteoarthritis [2,3]. Hence its indiscriminate use should be avoided and appropriate rational therapy should be followed according to proper dose schedule. This has made the detailed pharmacokinetic study of the drug compulsory.

Meloxicam is used in cattle for the treatment of acute respiratory infection in combination with appropriate antibiotic, diarrhea with oral rehydration, acute mastitis along with antibiotic therapy. In swine, meloxicam is used in non-infectious locomotor disorders to reduce lameness and inflammation and for adjunctive therapy in septicemia and toxemia (mastitis-metritis-agalactia syndrome) with appropriate antibiotic therapy. In horses, it is indicated for the reduction of inflammation and pain associated with chronic musculoskeletal disorders. The intended indications for goats are adjunctive therapy of acute mastitis and acute respiratory infection with appropriate antibiotic therapy.

Meloxicam has been shown to have a high anti-arthritic activity, anti-inflammatory activity and at the same time it causes less gastric and local tissue irritation as compared to NSAIDs available prior to its develop-ment [4,5]. It was used in the management of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis by relieving pain and reducing swelling and inflammation [6], with higher therapeutic index than that of other NSAIDS,including piroxicam,diclofenac and indomethacin.

Meloxicam selectively inhibits cyclooxygenase-2 leading to inhibition of prostaglandin synthesis, which is induced by inflammatory stimuli in pathophysio-

logical conditions rather than cyclooxy-genase-1 which is responsible for physiological processes [5,7]. It has also potential analgesic and antipyretic activities [8].In contrast with other NSAIDs, it has neither acute nor chronic gastrointestinal toxicity but has high intrinsic activity [5]. Integrating PK and PD data can also provide a basis for selecting clinically relevant dosing schedules of meloxicam for subsequent evaluation in disease models and clinical trials. Pharmacokinetic parameters serve as a useful tool to a clinician in framing the dose/dosage or drug formulation, dosing frequency or dosing interval [9].

Till now, the pharmacokinetic behavior of meloxicam has been studied extensively in cattle [10,11] sheep and goat [12] dogs, mini-pig, baboons, mice [13] rabbit [14] vulture [15] human beings [1] horses [16] camels [17] piglets [18] green iguanas [19] cats [20] llamas [21,22] goat kids [23] and dogs [24]. There is lot of interspecies variation in the pharmacokinetic profile of meloxicam and hence its disposition kinetics in one species cannot be extrapolated for use in other species. Goat is an important meat animal and is reared extensively in the state of Assam as well as all other Indian states. Despite the tremendous therapeutic potential of meloxicam in small ruminants, not much information is available on the pharmacokinetics of meloxicam in sheep and goat.

Hence, the present study of determination of pharmacokinetics of meloxicam in local goat of Assam was undertaken with the following objectives:

a) Determination of plasma level of meloxicam following i.v administration in local goat of Assam.
b) Determining the kinetic profile of meloxicam following i.v administration in local goat of Assam.
c) Determining the dose and dosage frequency of meloxicam for local goat of Assam.

Materials and Methods

Experimental animals: The present study was conducted on 12 to 18 months old, five adult male local goats (*Capra hircus*) of Assam, with body weight ranging between 10 to 18 kg. All goats were clinically sound and healthy and reared at Goat Research station, Burnihat, Assam.

Ethical approval: All the ethical principles were followed during the course of research and the experiments were carried out in accordance with the guidelines laid down by the International Animal Ethics Committee (IAEC) and in accordance with the local laws and regulations. The animals were housed in animal shed with wooden floor and were provided with concentrate, green fodder and dry grass. Water was provided *ad libtum*. Deworming was done 15 days prior to the start of the experiment with the help of albendazole given @ 1ml/kg.The average temperature of the environment in and around the goat research station was around 30ºc during the course of experiment.

Instruments required: High performance liquid chromatography (HPLC) system. Waters HPLC system consisting of a Degasser, two pumps A and B (Waters 515 HPLC pump), an injecter, C-18 symmetry column (particle size 5 µm;4.6mm ×250mm), Waters 2487 dual λ absorbance detector and a screen was used. (Waters Breeze Software, Ireland),Centrifuge machine (Labnet), Two micro pipettes 100 µl (fixed) and 2-20 µl (adjustable),Vortex mixer cum shaker, BD Vacutainer (sodium Heparin [NH] 68 USP units plus blood collection tubes,5ml),Tarsons 1.5 ml micro-centrifuge tubes,0.22 µm nylon filter, Test tubes, Flasks, measuring cylinders, spirit, cotton, scissors, syringes (2 ml and 5 ml).

Drugs and chemicals used: Pure standard Meloxicam compound (Intas Pharma, Ahmedabad, India), Melonex (Meloxicam oral suspension BP vet,1.5mg/ml, Intas Pharma., Ahmedabad, India), Melonex (IV solution, 5mg/ml, Intas Pharma., Ahmedabad, India), HPLC grade Acetonitrile. (EMERCK), HPLC grade Water. (EMERCK).

Estimation of meloxicam: Each animal was weighed on a balance to evaluate the dose .A single dose of meloxicam was administered intravenously into the jugular vein of goats at the rate of 1 mg/kg body weight. Blood samples (3-4 ml) were collected by jugular vein puncture with the help of a 5ml syringe, into vacutainer heparinised tubes from each animal prior and after both drug administration. The time of blood collection after IV administration was 2,5, 10, 15,30,45,60,120,240,360,480,720,1440 and 2880 min respectively. The plasma was extracted after centrifugation of blood samples at 3500 rpm for 10 min at room temperature. Extracted plasma was stored in 1.5ml capped micro-centrifuge tubes in a refrigerator at -5ºc, until analysed. Analysis of the samples were carried out within 3-4 days of collection of plasma.

For the quantitative estimation of meloxicam in the plasma samples of goat, HPLC method by Baert and De Backer [25] was followed with slight modification. Plasma analysis was performed on a High Performance Liquid Chromatography (HPLC). The mobile phase used for the HPLC system consisted of a mixture of 65% water : acetic acid (99:1, v/v) and 35 % acetonitrile with a flow rate of 0.8 ml/min. Detection of meloxicam was done at 355 nm wavelength with a column oven temperature 35 ºc.The retention time of meloxicam was about 6.65 min.

Chemical analysis of meloxicam: The previously collected plasma samples were used for meloxicam estimation. 0.5 ml of Acetonitrile was added to 0.5 ml of plasma samples in the ratio of 1:1.This was mixed thoroughly with the help of a Vortex Mixer for 1-2 min and then centrifuged for 15 min at 6000 rpm. The clear supernatant so obtained was transferred to a clean tube. Again 0.5 ml of the supernatant was added to 0.5 ml of HPLC Grade water and mixed well. Then the aliquot was filtered through 0.22 µm nylon filter paper. Finally 20 µl of the aliquot was injected into HPLC system for the analysis.

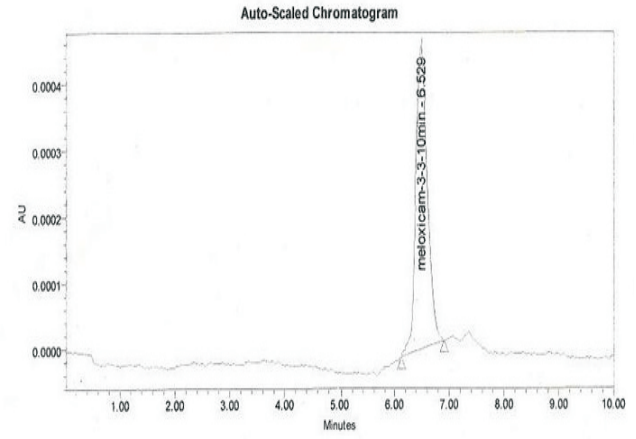

Figure-1. Plasma concentration of Meloxicam in HPLC data system after IV administration

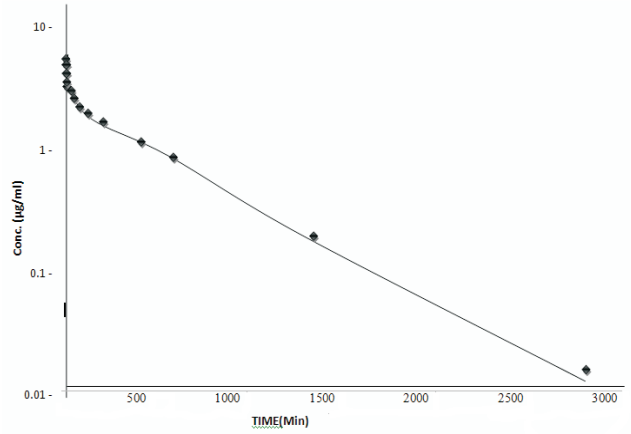

Figure-2. Mean plasma values of Meloxicam in goat after iv administration at the dose of 1mg/kg.

Table-1. Plasma concentrations (µg/ml) of Meloxicam in goats after intravenous administration at the dose rate of 1 mg/kg body weight.*(n=5)

Time (minutes)	Animals*					Mean ± SE
	1	2	3	4	5	
2	6.24	6.70	6.35	6.90	6.50	6.538±0.1189
5	5.40	5.94	5.52	6.12	5.64	5.724±0.1336
10	5.11	5.46	5.15	5.60	5.29	5.322±0.0927
15	4.80	5.12	4.82	5.33	5.09	5.032±0.0996
30	4.44	4.72	4.55	4.84	4.62	4.634±0.0688
45	4.10	4.32	4.16	4.42	4.22	4.244±0.0571
60	3.74	4.08	3.82	4.16	4.02	3.964±0.0793
120	2.36	2.46	2.29	2.49	2.38	2.396±0.0358
360	1.82	2.02	1.88	2.00	1.96	1.936±0.0376
480	1.52	1.62	1.56	1.66	1.74	1.62±0.0384
720	1.01	1.41	1.01	1.10	1.22	1.15±0.0755
1440	0.44	0.48	0.36	0.54	0.62	0.488±0.0441
2880	0.03	0.04	0.02	0.04	0.01	0.028±0.0058

Preparation of standard curve: Blank plasma collected before the injection of the drug into the goats was spiked with the standard of meloxicam at a concentration of 0.5,1.0,1.75,2.5,5.0,7.5,10.0,15.0 and 20.0 µg/ml of plasma. These plasma standards were prepared and extracted as described above for the experimental samples. Meloxicam was quantified from its respective peak area and the concentrations in the plasma samples were determined by means of calibration curves. Figure-1 shows the representative sample analysis of goat plasma for meloxicam concentration in the HPLC system after its intravenous administration.

Pharmacokinetic analysis of data: Pharmacokinetic parameters were determined for each animal individually from log plasma drug concentration versus time profile by "two compartment open model" as described by Gibaldi [26]. For each parameter the mean and its SE were obtained from the parameters estimates of five animals. Statistical analysis was done following standard statistical method [27].

Results

A number of such studies every year are being conducted in almost all the domestic animals both in India and abroad. However, very little information is available on the pharmacokinetics of meloxicam in goats. In the present study, from the observed meloxicam concen-trations in plasma at different time intervals, various pharmacokinetic parameters have been determined. The plasma levels of meloxicam following single intravenous administration at the dose rate of 1 mg/kg at different time intervals in goats have been presented in Table -1.

After intravenous administration of meloxicam at the dose rate of 1mg/kg in goats, pharmacokinetic behavior of meloxicam was best fitted to the two compartmental open model and followed the first order rate kinetics. NSAIDS have been reported to follow a two compartmental open model [13].

The decline of plasma concentration of meloxicam with respect to time in goats after its intravenous administration is shown in Fig-2.

The mean peak plasma level of meloxicam was 6.538±0.1189 µg/ml at 2 min, which declined rapidly to 3.964±0.0793 µg/ml at 60 min of time, thereafter the decline was steady and the lowest concentration of about 0.028±0.0058 µg/ml was observed at 2880 min. With the help of plasma drug concentrations the different pharmacokinetic parameters of Meloxicam were calculated in goat and shown in the Table -2.

The value of mean elimination half life ($t_{1/2\beta}$) was 484.5±85.1202 min. The value of mean distribution half life ($t_{1/2\alpha}$) was 28.68±1.420683 min. The mean values of AUC and AUMC were 2635.272±94.23893 µg.min/ml and 1620332±92456.46 µg.min^2/ml respec-

Table-2. Pharmacokinetics of Meloxicam after single intravenous administration at the dose rate of 1 mg/kg body weight in goat.

Parameters & Unit	Animals*					Mean ± SE
	1	2	3	4	5	
A µg/ml	3.44	3.59	3.26	3.55	4.10	3.588±0.1401
B µg/ml	2.39	2.72	2.35	2.92	2.64	2.604±0.1060
A min^{-1}	0.023	0.024	0.026	0.021	0.028	0.0244±0.0012
$t_{1/2\alpha}$ min	30.13	28.87	26.65	33.00	24.75	28.68±1.4206
B min^{-1}	0.002	0.001	0.002	0.001	0.002	0.0016±0.0002
$t_{1/2\beta}$ min	346.5	693	345	693	345	484.5±85.1202
Vd Lit/kg	0.29	0.27	0.30	0.28	0.24	0.276±0.0102
AUC µg.min/ml	2455.56	2802.23	2362.32	2745.48	2810.77	2635.272±94.2389
AUMC µg.min^2/ml	1484448.6	1764421.8	1321634.2	1752832.61	1778322.36	1620332±92456.46
MRT min	604.52	629.64	559.46	638.44	632.68	612.948±14.5771
Clb L/min.kg	0.0004	0.00035	0.00042	0.00036	0.00035	0.000376±0.00001
Kel min^{-1}	0.0023	0.0022	0.0023	0.0023	0.0023	0.00228±0.00002
K_{21} min^{-1}	0.0106	0.0109	0.0119	0.010	0.0122	0.01112±0.000409
K_{12} min^{-1}	0.0121	0.0119	0.0138	0.0097	0.0155	0.0126±0.000975

tively. The mean values of volume of distribution (Vd) and mean residence time (MRT) were 0.276±0.0102 L/kg and 612.948±14.5771 min respectively. The minimum effective therapeutic concentration or minimum effective plasma concentration of meloxicam is about 0.7 µg/ml. This amount was detectable up to 1400 min following single intravenous administration.

Discussion

The present study, the plasma level of meloxicam was 6.538±0.1189 µg/ml at 2 min, which declined rapidly to 3.964±0.0793 µg/ml at 60 min of time, thereafter the decline was steady and the lowest concentration of 0.028±0.0058 µg/ml was observed at about 2880 min. Similar patterns of plasma levels were also observed in other animals [12]. The value of distribution half life ($t_{1/2\alpha}$) was 28.68±1.4206 min. Similar values of distribution half life for meloxicam have been observed in horses (24 min) and sheep (26 min) respectively [12,16].The value of short half life indicates that the drug is distributed quite rapidly in goats.

The value of mean elimination half life ($t_{1/2\beta}$) was 484.5±85.1202 min which was lesser than in sheep (660 min) [12] and horses (550 min) [16].Shorter values of $t_{1/2\beta}$ have been observed in chickens (200 min) and turkeys (60 min) [25].The comparatively smaller value of $t_{1/2\beta}$ observed in the present study in goats implies that the drug is eliminated at faster rate as compared to sheep and horses.This is supported by the fact that goats possess higher drug metabolizing activities in liver and other organs and have been shown to eliminate sulphadimidine, antipyrine, ampicillin and isometamidium at a significantly faster rate than sheep [28].

The area under curve is an important pharmacokinetic determinant. It forms the basis for the calculation of other pharmacokinetic parameters such as MRT, Vd, F etc. The value of AUC obtained in the present study of meloxicam was 2635.272±94.2389 µg.min/ml. This is lower than that of cattle (4940.4 µg.min/ml) [10,11]. This implies that the drug is eliminated at a faster rate from the body of goats in comparison to cattle.

MRT is the average or mean time required for a drug molecule to travel or traverse throughout the body and thus reflects the time associated with absorption, distribution, metabolism and elimination. This is very useful in calculating the dosing interval of a drug in a particular species. MRT obtained in the present study was 612.948±14.5771 min which is lower than that of sheep (920 min) [12] and cattle (1700 min) [10,11]. This again reflects that the drug is eliminated at a faster rate in goats than in sheep and cattle which is very consistent with other observations of the study.The value of volume of distribution (Vd) in the present study was observed 0.276±0.156 L/kg which was more than cattle (0.171 L/kg) [10,11].This indicates that the meloxicam is well distributed in goats than in cattle when given intravenously.

Conclusion

Results obtained in goat revealed that the data followed the first order rate kinetics like many other NSAIDS and that it could be best fitted to a two compartmental open model. The minimum effective therapeutic concentration or minimum effective plasma concentration of meloxicam is about 0.7 µg/ml. This amount was detectable upto 1440 min following single intravenous administration of the drug. Hence iv dose should be reduced to avoid the drug accumulation. After calculating various pharmacokinetic determinants, dosage regimens were computed for meloxicam in goats,based on minimum effective therapeutic plasma concentration of 0.7 µg/ml.To maintain this minimum effective concentration of 0.7 µg/ml in plasma for 25 hours following iv administration of meloxicam,an initial loading dose of 1.1mg/kg body weight followed by a maintenance dose of 1mg/kg body weight/day is recommended. The drug was distributed in the body very quickly with a mean distribution half life ($t_{1/2\alpha}$) of 28.68±1.4206 min. The mean value of volume of distribution (Vd) after iv administration was 0.276±0.0103 L/kg. This again indicates that the distribution of meloxicam was faster and better after IV administration The drug was eliminated from the body somewhat quickly with a

mean elimination half life ($t_{1/2\beta}$) of 484.5±85.1202 min. But the overall elimination rate of Meloxicam in goats is faster than sheep and cattle. The mean values of AUC and AUMC were 2635.272±94.2389 µg. min/ ml and 1620332±92456.46 µg.min^2/ml respectively. Mean residence time (MRT) is 612.948±14.5771 min and is less than half after IV administration than after oral administration.

Authors' contribution

ARW, RKR and DCR implemented the study design. ARW, AA recorded and analysed the data. ARW, RKR and DCR drafted and revised the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interest.

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