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RESEARCH ARTICLE
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Pharmacokinetic parameters of meloxicam after its oral administration in goat

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Abstract

Aim: The objective of the present study was to find out the levels of analgesic drug meloxicam in the blood plasma of young goats. The drug was given to them through oral route. Data was used to elucidate the Pharmacokinetic determinants of the drug which were employed to arrive at the dose schedule and frequency of the drug in goats.

Materials and Methods: Elaborate pharmacokinetic research of the drug meloxicam was done on 18 to 24 months old, five adult male local goats (*Capra hircus*) of Assam weighing 20 to 25 kg.The drug was given orally at the dose rate of 0.35 mg/kg at the Goat Rearing farm, Guwahati, Assam. Analysis of blood was done by high performance liquid chromatography (HPLC) system.

Results: The mean values of area under curve (AUC) and mean area under curve (AUMC) were 3137.488 ± 125.3749 µg.min/ml and 4650460 ± 380892.4744 µg.min^2/ml respectively .The mean peak plasma level of meloxicam was 1.972 ± 0.0477 µg/ml at 600 min. The mean values of elimination half life ($t_{1/2\beta}$) and absorption half life ($t_{1/2Ka}$) were 693±0.00 min and 170.6 ± 17.0076 min respectively. The mean values of volume of distribution (Vd) and mean residence time (MRT) were 0.114 ± 0.0156 L/kg and 1472.264 ± 63.336 min respectively. The mean value of T_{max} was found to be 497 ± 19.8040 min. Following single oral administration the minimum effective therapeutic concentration or minimum effective plasma concentration of meloxicam was detectable up to 1200 min. The bioavailibity (F) of the drug was 80.5 ± 10.0150%.

Conclusion: These pharmacokinetic determinants were used to determine the frequency and dose schedule of meloxicam in goats. The minimum effective concentration of the drug is 0.7 µg/ml in plasma. To maintain this, an initial loading dose of 0.5 mg/kg body weight should be followed by a maintenance dose of 0.4 mg/kg body weight/10 hour.

Keywords: half-life, male Assam goat, meloxicam, oral administration.

Introduction

Meloxicam is a potent anti-inflammatory agent, being a relatively selective Cox-2 inhibitor [1], in comparison to older non-steroidal anti inflammatory drugs (NSAIDs) which none selectively also inhibit Cox-1 isoenzyme, leading to serious gastrointestinal and renal side effects. Meloxicam is 12 times more selective in inhibiting Cox-2 activity than Cox-1 activity [2, 3]. The higher selectivity results in low ulcerogenic potential and less gastrointestinal irritation as compared to other NSAIDs [4,5]. This less toxicity of the drug makes it a broad spectrum drug covering a varying number of diseases. In conjunction with a suitable antibiotic, it is used as a drug of choice in many diseases [4,5]. Meloxicam prevents ongoing occurrence of inflammation by inhibiting prostaglandin production, that sensitize the afferent nociceptors at peripheral sites of inflammation [6,7].

In man it is used for treating non descriptive pyrexia, painful conditions due to acute and chronic inflammation, muscular pain, joint pain, rheumatic pain, neuralgia, soft tissue injuries and immobility associated with lameness, arthritis and myositis [1,4, 5]. In veterinary practice Meloxicam was introduced for management of canine osteoarthritis and since then it is being used for the management of pain and inflammation, arising from both acute and chronic conditions [3,7,8]. In cattle it is used to treat pain, mastitis, pneumonia and other inflammatory conditions [9,10]. Indications for meloxicam use in farm animals include respiratory infections and acute mastitis [11]. It is being increasingly used in manage-ment of musculoskeletal disorders for reduction in pain and inflammation [12].

Pharmacokinetic profile of meloxicam has been elucidated in human beings [1,4], cattle [10,11], sheep and goat [13,14], rabbit [15], vulture [16], horses [17], camels [18], piglets [19], green iguanas [20], cats [21], llamas [22] and many other species of animals.. But data of one species cannot be extrapolated and used in other species due to high interspecies variation in the metabolism of meloxicam. Interspecies variation along with local and regional factors further compound the problem. Goat is called as poor man's cow owing to its utility and popularity among the farmers of India. Also

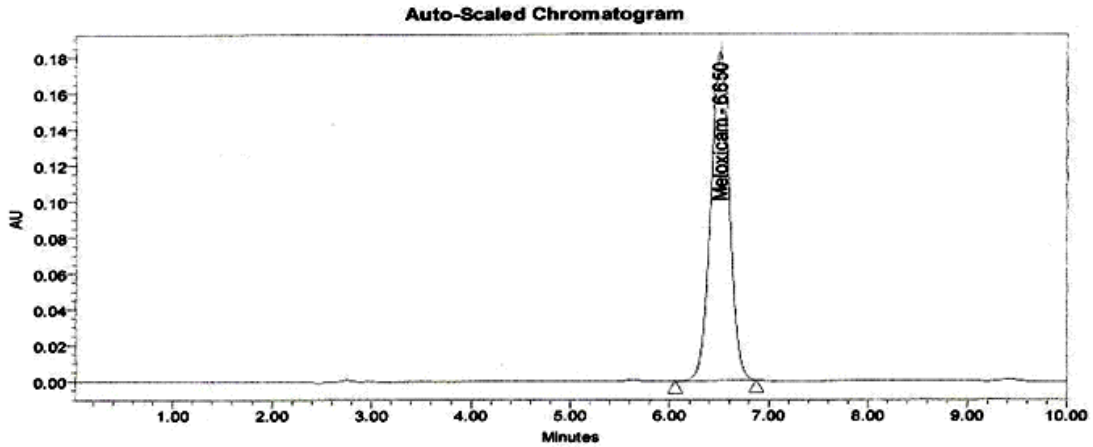

Figure-1. Plasma concentration of Meloxicam in HPLC data system after oral administration

much information is not available on the pharmacokinetic profile of this drug in small ruminants. Hence the present study was conducted to determine the complete pharmacokinetics, dosing schedule and dosing frequency of this drug after its oral administration in the domestic goat of Assam.

Materials and Methods

Experimental animals: Experimental animals were 20 to 24 months old, five male goats (*Capra hircus*) of Assam, with body weight ranging between 20 to 25 kg. Clinically all the animals were sound and healthy and were raised at Goat rearing farm, Guwahati, Assam.

Ethical approval: Adherence to all the concerned ethical principles as enumerated by the International Animal Ethics Committee, was observed strictly throughout the course of this study. Animals were handled gently and carefully. Deworming was done one month before the start of experimentation with the help of fenbendazole which was given at the rate 1ml/kg body weight.

Instruments used: High performance liquid chromatography (HPLC) system. Waters HPLC system consisting of a Degasser, two pumps A and B (Waters 515 HPLC pump), an injector, C-18 symmetry column (particle size 5 µm; 4.6 mm x 250 mm), Waters 2487 dual λ absorbance detector and a screen was used. (Waters Breeze Software, Ireland). Centrifuge machine (Labnet). Two micropipettes 100 µl (fixed) and 2-20 µl (adjustable).Vortex mixer cum shaker. BD Vacuntainer (sodium Heparin [NH] 68 USP units plus blood collection tubes, 5ml).Tarpons 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 (Meloxicam oral suspension BP vet, 1.5 mg/ml, Meloxicam i.v solution 5 mg/ml). HPLC grade Acetonitrile and HPLC grade water.

Estimation of meloxicam: A single dose of meloxicam was administered orally into the animals at the rate of 0.35 mg/kg as per their body weights. Blood samples (5 ml) were collected from jugular vein with the help of a 5ml syringe from all the goats, into vacuntainer heparinized tubes before and after the drug administration. Blood was collected at 30, 45, 60, 120, 180, 240, 360, 480, 540, 600, 720, 840, 1440 and 2880 minutes respectively. Blood samples were centrifuged at 3600 rpm for 12 minutes and the plasma thus extracted was stored in 1.5ml capped micro-centrifuge tubes in a refrigerator at -5ºC till further processing which was done within 5 days of plasma collection. The drug was quantitatively estimated from the plasma of animals by advanced Baert and De Backers HPLC method [23]. Mobile phase used for chromatography was a mixture of 65% water: acetic acid (99:1, v/v) and 35 % acetonitrile with a flow rate of 0.8 ml/min. Drug detection was done at 355 nm wavelength. Column temperature of the oven was 35 ºc and drugs retention time was 6.65 min.

Chemical assay of meloxicam: The above collected plasma was used for the analysis of the drug. 0.5 ml of plasma was mixed with 0.5 ml of acetonitrile. Vortex Mixer was used to mix the two and the mixture was then centrifuged for 20 minutes at 6200 rpm. Clear supernatant was collected and 0.5 ml of HPLC grade water was added to it. The aliquot thus obtained was filtered through 0.22 µm nylon filter paper. 20 µl of this filtrate was introduced into HPLC system.

Preparation of standard curve: Drug free plasma was spiked with the standard 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 and then plasma standards were prepared. Quantification of drug was done from its respective peak area and calibration curves were employed to determine the concentration of drug in plasma samples. Determination of meloxicam concentration in a representative sample of goat is depicted in Figure-1.

Pharmacokinetic analysis of data: Log of plasma drug concentration versus time profile was employed to arrive at pharmacological determinants of every animal by Gibaldis "two compartment open model" [24]. Mean and SE for each determinant was obtained from the whole data. Standard statistical method was employed for statistical interpretation [25].

Table-1. Plasma concentrations (µg/ml) of meloxicam in goat after oral administration at the dose rate of 0.35mg/kg body weight.

Time(minutes)	Animals (n=5)					Mean ± SE
	1	2	3	4	5	
30	0.40	0.33	0.46	0.51	0.49	0.438±0.0327
45	0.48	0.41	0.53	0.62	0.58	0.524±0.0369
60	0.66	0.59	0.61	0.69	0.66	0.642±0.0215
120	0.70	0.69	0.67	0.71	0.70	0.691±0.0212
180	0.98	0.93	0.89	0.96	0.94	0.94±0.0151
240	1.40	1.21	1.28	1.38	1.42	1.338±0.0401
360	1.68	1.45	1.52	1.64	1.71	1.6±0.0494
480	1.94	1.88	1.87	1.72	2.18	1.918±0.0748
540	1.99	2.01	1.94	1.79	2.02	1.95±0.0423
600	2.10	2.04	1.99	1.84	1.89	1.972±0.0476
720	1.60	1.72	1.78	1.58	1.64	1.664±0.0376
840	1.28	1.24	1.36	1.30	1.39	1.314±0.0271
1440	0.70	0.69	0.67	0.74	0.72	0.684±0.0354
2880	0.34	0.31	0.38	0.24	0.40	0.3314±0.0271

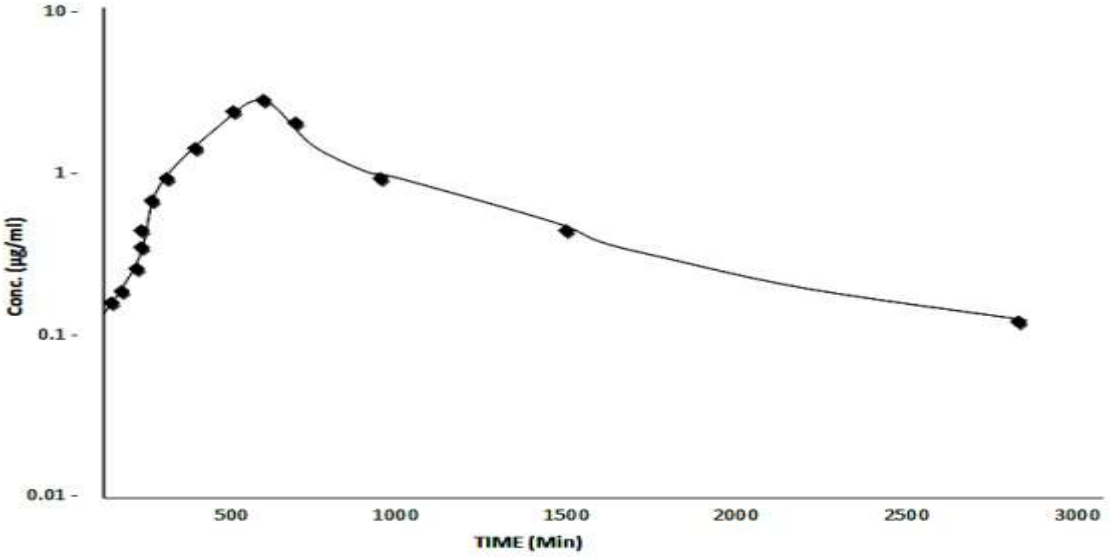

Figure-2. Mean plasma values of Meloxicam in goat after oral administration at the dose rate of 0.35 mg/kg.

Table-2. Pharmacokinetics of Meloxicam after single oral administration at the dose rate of 0.35 mg/kg in goat. (n=5)

Time(minutes)	Units	Animals (n=5)					Mean ± SE
		1	2	3	4	5	
A	µg/ml	3.93	2.80	2.60	2.77	2.77	2.974±0.2415
B	µg/ml	4.04	2.88	2.74	2.8	2.77	3.046±0.2495
Ka	min-^{1}	0.003	0.004	0.004	0.005	0.005	0.0042±0.0003
t1/2Ka	min	231	173	173	138	138	170.6±17.0076
β	min-^{1}	0.001	0.001	0.001	0.001	0.001	0.001±0.00
t1/2β	min	693	693	693	693	693	693±0.00
Vd	Lit/kg	0.09	0.12	0.12	0.12	0.12	0.114±0.156
F	%	61.5	109	70	100	62	80.5±10.0149
AUC	µg.min/ml	3019.55	3075.34	3342.8	2768.41	3481.34	3137.488±125
AUMC	µg.min2/ml	4167907	4478290	5373214	3588243	5644645	4650460±380892
Cmax	µg/ml	1.70	1.50	1.55	1.60	1.69	1.608±0.0389
Tmax	min	522	528	528	426	481	497±19.8041
MRT	min	1380.30	1456.19	1607.30	1296.13	1621.4	1472.264±63.3305
Clb	L/min/kg	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001±0.00
Kel	min-^{1}	0.0026	0.0018	0.0015	0.002	0.0015	0.00188±0.0002
K21	min-^{1}	0.002	0.0025	0.0025	0.003	0.003	0.0026±0.00018
K12	min-^{1}	0.0006	0.0007	0.001	0.001	0.0015	0.00096±0.00015

Results

Amount of the drug present in the plasma samples of the goats at different time periods was used to elucidate different pharmacokinetic determinants. Magnitude of drug at varying times in the plasma of goats after its single oral administration has been presented in Table-1.

Mean peak plasma level of drug was 1.972± 0.047 µg/ml at 600 min, which decreased quickly to 1.314± 0.0271 µg/ml at 840 min of time. From this time onwards the decrease is uniform and the smallest concentration of about 0.3314±0.0271µg/ml was detected at 2880

min. This decrease of drug with respect time in goat plasma has been depicted in Figure-2.

This quantification of meloxicam in plasma samples of goat was used to arrive at different pharmacokinetic determinants which have been presented in Table-2.

The value of elimination half-life ($t_{1/2\beta}$) was 693 ± 0.00 min. The value of mean absorption half life ($t_{1/2Ka}$) was 170.6 ± 17.0076 min. The mean values of T_{max} and bioavailibity (F) were found to be 497 ± 19.8041 min and 80.5 ± 10.01498 % respectively. 0.7 µg/ml of plasma is the minimum effective therapeutic concentration of drug and it was present up to 1200 min after a single oral administration. The mean values of AUC and AUMC were 3137.488±125.3749 µg/min/ml and 4650460 ± 380892.4744 µg.min^2/ml respectively. Mean value of volume of distribution (Vd) was 0.114 ± 0.156 L/kg. Mean residence time (MRT) of the drug was found to be 1472.264 ± 63.3305 min.

Discussion

In the present study, meloxicam was administered orally at a dose rate of 0.35 mg/kg of body weight in goats. Similar dose rate in the range of 0.2 to 0.6 mg/kg of body weight were used in horses [17], rabbits [15] and Vultures [16]. The mean peak plasma level of meloxicam was 1.972 ± 0.0476 at 600 min, which declined rapidly to 1.314 ± 0.0271 µg/ml at 840 min of time, thereafter the decline was steady and the lowest concentration of 0.334 ± 0.0282 µg/ml was observed at 2880 min.

The time to achieve maximum plasma concentration (T_{max}) was found to be 497 ± 19.8040 min which was less than that observed in calves [9,10] but was more than dogs (450 min) [26,27] and rabbits (360 min) [15]. This implies that the peak drug concentration is achieved rapidly in the plasma of goats in comparison to cattle.

The value of bioavailibity (F) was found to be 80.5 ± 10.0150 % in the present study. This is less than that found in cattle (100%) and horses (98 %) [10,17]. This low bioavailability of meloxicam in goats indicates that the drug is available less adequately to systemic circulation after its oral administration. This may be due to ion trapping effect as the drug is acidic in nature or due to its quicker biotransformation [13]. The value of mean absorption half life ($t_{1/2Ka}$) was found to be 170.6 ± 17.0076 min indicating good absorption rate of the drug after oral administration.

The value of mean elimination half-life ($t_{1/2\beta}$) was 693 ± 0.00 min which was less than in cattle (1600 min) [10,11] but comparable to that of horses (510 min) [16] and rabbits (480 min) [15]. This reflects an overall enhanced persistence of meloxicam in the plasma of goats and points to the fact that meloxicam is excreted quickly in goats in comparison to other species [28]. This is in accordance to the finding that hepatic tissue of goats possesses higher concentration of drug degrading enzymes than sheep [29] and cattle [10].

The mean residence time (MRT) observed in the present study was 1472.264 ± 63.3305 min which is significantly lower than in cattle (2700 min) [9,10], again indicating that the drug is excreted quickly in goats than in cattle. This is supported by the fact that meloxicam has a bit more tissue binding in cattle than in goat [4]. The values of AUC and AUMC obtained after oral administration of 0.35 mg/kg body weight were 3137.488 ± 125.3749 µg/min/ml and 4650460 ± 380892.4744 µg/min^2/ml respectively. The mean value of volume of distribution (Vd) was 0.114 ± 0.156 L/kg which is less than cattle (0.242 L/kg) [10]. This indicates that the meloxicam is well distributed in cattle than in goats when given orally.

Conclusion

As per the interpretation of results, data follows a first order rate kinetics fitting into a two compartmental open model as do many other NSAIDS. When given orally the bioavailability of the drug was better because of its better dissolution and absorption. Effective concentration of the drug was present upto 20 hours in the blood plasma. Following oral administration of meloxicam, an initial loading dose of 0.5 mg/kg body weight succeeded by a maintenance dose of 0.4 mg/kg body weight/10 hours is advised to maintain its effective concentration. The elimination of the drug was slow and the mean value of volume of distribution (Vd) was lesser after oral administration which indicates that the overall absorption and distribution of the drug after oral administration was very slow when compared to intravenous route of administration. Mean residence time is more than double after oral administration than after IV administration

Authors' contributions

Implementation of study design, experimentation and data recording was done by ARW and RKR. SUN, OSS, SAB and NAK carried out analysis. ARW drafted and revised the manuscript. All the authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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