

Pharmacokinetics of Meloxicam in Healthy Dogs

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ABSTRACT

Meloxicam has been reported as an alternate of diclofenac sodium which was banned for veterinary use during 2005-06, due to its relay toxicity associated with the catastrophic decline in vulture populations in Indian subcontinent. It is a preferential cyclooxygenase-2 (COX-2) inhibitor with higher therapeutic index as compared to diclofenac, indomethacin and piroxicam. The pharmacokinetics (PK) of a non-steroidal anti-inflammatory drug meloxicam was studied in dogs. Eight dogs used in the experiment were administered @ 0.2 mg/kg body weight as an intravenous (IV) bolus of meloxicam through cephalic vein. Blood samples (3-5 ml) were drawn pre 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 University of Veterinary and Animal Sciences and Lahore College for Women University, Lahore Pakistan. The plasma concentration versus time profile was prepared. 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 26.97 ± 0.256 $\mu\text{g}\cdot\text{h}/\text{ml}$, 0.22 ± 0.002 L/Kg, $23.39 \pm 0.4\text{h}$, $33.69 \pm 0.56\text{h}$ and 0.01 ± 0.003 L/h/Kg, respectively. These parameters of meloxicam in dogs were comparable to the reported values in dogs but different when compared with PK values in many other species like sheep, goats, horses, chicken, rabbits and rats. The pharmacokinetic parameters were put in different PK-equations for calculations of dose. We recommend a single IV dose of 0.2mg /Kg body weight of meloxicam in dogs.

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed and 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 (Huskisson *et al.*, 1996). It has been established scientifically that relay toxicity of diclofenac sodium was responsible for dramatic fall in vulture population within Indian subcontinent. This freely available NSAID was extensively used in veterinary practice as an analgesic and anti-inflammatory agent (Prakash *et al.*, 2003; Green *et al.*, 2004). However, Diclofenac sodium was banned for veterinary use in Pakistan, India and Nepal during 2005-06.

Another NSAID, meloxicam has been reported as a safe substitute of diclofenac sodium (Swan *et al.*, 2006). Meloxicam is chemically designated as 4-hydroxy-2-methyl-N-(5-methyl-2-thiazalyl)-2H-1,2-benzothiazine-3-

carboxamide-1,1-dioxide (BNF, 2003) and belongs to oxicam class of NSAIDs. It has the molecular weight of 351.4 dalton and its formula is shown in Fig. 1.

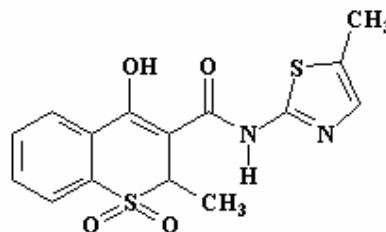


Fig. 1: Chemical formula for Meloxicam ($\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_4\text{S}_2$).

It preferentially inhibits cyclooxygenase-2 which is responsible for pathophysiological conditions rather than cyclooxygenase-1 responsible for physiological processes (Churchill *et al.*, 1996). 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%; Davies and Skjodt, 1999). The therapeutic index of meloxicam is higher when compared with other NSAIDs like piroxicam, diclofenac and indomethacin. Meloxicam undergoes fast elimination, leading to a shorter $t_{1/2}$ in comparison with piroxicam and tenoxicam. It has no capability for nephrotoxicity (Woolf and Radulovic, 1989; Schmid *et al.*, 1995; Schoenfeld, 1999.).

Meloxicam has been reported as an effective drug in acute synovitis and lameness improvements in dog (Cross *et al.*, 1997). The clinical trial had indicated that meloxicam was effective and safe analgesic in dogs (Mathews *et al.*, 2001). Moreover, preoperative single IV-dose of meloxicam-butorphanol was equivalent to or slightly better than the administration of 2 perioperative doses of butorphanol for the control of postoperative signs of pain in dogs (Budberg *et al.*, 2002).

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 dogs under local conditions of Pakistan and to make some recommendation regarding its dose in dogs.

MATERIALS AND METHODS

Experimental animals

Eight healthy and clinically normal adult dogs with average weight of 20 Kg were used in the study. All the dogs were tagged and acclimatized to the experimental environment at the animal sheds of Department of Pharmacology and Toxicology, University of Veterinary and Animal Sciences, 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 reagent grade were used in this experiment.

Design, drug treatment, sampling and analysis

Experimental dogs were administered an intravenous bolus of meloxicam 0.2 mg/kg body weight, via cephalic vein. Blood samples (3-5 ml) were collected from all the eight dogs 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 (Mahmood and Ashraf, 2008). 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 $8000 \times g$ 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 0.5 ml/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 dogs 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 ($\mu\text{g/ml}$) versus time profile of meloxicam in dogs was prepared.

Pharmacokinetics

The computer software APO was used for calculation of pharmacokinetic parameters. The following equations were used for different calculations:

$$\begin{aligned} \text{Cl} &= \text{Dose}/\text{AUC}; \\ \text{AUMC} &= \text{MRT} \times \text{AUC}; \\ \text{Dose} &= \frac{\text{VD}_{\text{ss}} \times \text{AUC}^2}{\text{AUMC}} \end{aligned}$$

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

Statistical analysis

The software SPSS 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

Plasma concentrations ($\mu\text{g/ml}$) of meloxicam were determined at various time intervals after intravenous administration at dose of 0.2 mg/Kg body weight in dog. The results are given in Table 1. The graphical representation of plasma concentrations ($\mu\text{g/ml}$) of meloxicam in dogs versus time is given in Fig. 2. The pharmacokinetics of meloxicam in dogs was best fitted to a two compartment model. The PK profile is given in Table 2.

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 $26.97 \pm 0.256 \mu\text{g.h/ml}$, $0.22 \pm 0.002 \text{ L/Kg}$, $23.39 \pm 0.4\text{h}$, $33.69 \pm 0.56\text{h}$ and $0.01 \pm 0.003 \text{ L/h/Kg}$, respectively.

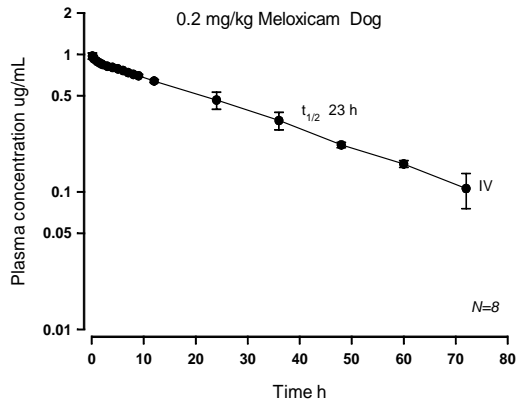


Fig. 2: Mean plasma concentration-time curves of meloxicam in dogs after intravenous administration at dose of 0.2 mg/kg body weight (n=8).

DISCUSSION

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 (Lees *et al.*, 1991; Rani *et al.*, 2004; Toutain *et al.*, 2004).

The dose of meloxicam as 0.2 mg/Kg, IV was selected for investigation of characterization of the

pharmacokinetic parameters of meloxicam in dogs as per recommendation of manufacturing company (Boehringer Ingelheim Vetmedica GmbH, Germany) selling meloxicam suspension for dogs in UK and USA. As per information provided to USA Government by the manufacturing company Boehringer (US Patent 6,184,2200), the terminal elimination half life after a single dose of 0.2 mg/Kg was estimated to be approximately 24 hrs (+/-30%) regardless of route of administration.

The Mean (\pm SEM) pharmacokinetic parameters of meloxicam determined in healthy dogs were, AUC ($26.97 \pm 0.256 \mu\text{g.h/ml}$), Cl ($0.0067 \pm 0.003 \text{ L/h/Kg}$), V_{DSS} ($0.22 \pm 0.002 \text{ L/Kg}$), $t_{1/2}$ $23.395 \pm 0.402\text{h}$ and MRT ($33.693 \pm 0.41\text{h}$). These values were comparable to the reported pharmacokinetic parameters of meloxicam in dog. The reported values were, AUC $21.5 \mu\text{g.h/ml}$, Cl 0.010 L/h/Kg , V_{DSS} 0.24 L/Kg , $t_{1/2}$ 24h , and MRT 34.8h (Busch *et al.*, 1998).

However, PK-values for meloxicam in dogs were different when compared with PK values in many other species. The mean (\pm SEM) values of AUC, Cl, V_{DSS} , $t_{1/2}$, and MRT reported for goats were $19.23 \pm 2.23 \mu\text{ml}$, $0.03 \pm 0.01 \text{ L/h/Kg}$, $0.25 \pm 0.01 \text{ L/Kg}$, $6.73 \pm 0.58 \text{ h}$ and $9.37 \pm 0.83 \text{ h}$ and for sheep were $31.88 \pm 2.97 \mu\text{g h/ml}$, $0.016 \pm 0.002 \text{ L/h/Kg}$, $0.24 \pm 0.02 \text{ L/Kg}$, $10.85 \pm 1.21\text{h}$ and $15.13 \pm 1.67\text{h}$ (Shukla *et al.*, 2007).

The half lives of meloxicam reported for sheeps and goats were 10.85 ± 1.21 and $6.73 \pm 0.58\text{h}$, respectively. Relatively shorter elimination half-lives for meloxicam have been reported in ducks (0.72h), turkeys (0.99h) and ostriches (0.5h) by Baert and Backer (2003), whereas $t_{1/2}$ of 2.7h reported in piglets (Fosse *et al.*, 2008). The $t_{1/2}$ reported in horses was $8.54 \pm 3.02\text{h}$ (Toutain *et al.*, 2004). However, meloxicam has longer half lives in albino rat (49.9h), and human 15 to 20h (Davies and Skjodt, 1999). Vultures eliminate meloxicam extremely rapidly with a $t_{1/2}$ of 1h (Naidoo *et al.*, 2008).

Table 1: The plasma concentration ($\mu\text{g/ml}$) versus time profiles of meloxicam in dogs after intravenous administration at dose of 0.2 mg/Kg body weight (n=8)

Time (hours)	Range ($\mu\text{g/ml}$)	Mean ($\mu\text{g/ml}$)	SEM	SD	CV (%)	Median
0.12	0.93-1.05	0.974	0.018	0.05	5.13	0.95
0.25	0.929-1.00	0.954	0.011	0.0312	3.27	0.94
0.5	0.881-0.939	0.923	0.007	0.018	1.95	0.929
1	0.855-0.912	0.893	0.004	0.012	1.34	0.893
1.5	0.839-0.898	0.868	0.008	0.023	2.65	0.858
2	0.814-0.884	0.848	0.01	0.029	3.42	0.838
3	0.79-0.869	0.82	0.011	0.03	10.71	0.823
4	0.77-0.842	0.804	0.009	0.027	3.36	0.8
5	0.764-0.816	0.787	0.007	0.02	2.54	0.785
6	0.743-0.791	0.764	0.007	0.019	2.49	0.759
7	0.71-0.767	0.738	0.007	0.02	2.71	0.738
8	0.69-0.743	0.716	0.007	0.019	2.65	0.715
9	0.68-0.721	0.7	0.006	0.016	2.29	0.692
12	0.627-0.684	0.641	0.006	0.017	2.65	0.64
24	0.437-0.63	0.466	0.023	0.066	14.16	0.443
36	0.301-0.443	0.331	0.017	0.048	14.50	0.312
48	0.207-0.24	0.22	0.004	0.01	4.55	0.22
60	0.14-0.165	0.16	0.003	0.009	5.63	0.16
72	0.097-0.12	0.106	0.018	0.0305	141.20	0.11
84-96	0	0	0	0	0	0

Table 2: Pharmacokinetic parameters of meloxicam in dogs following intravenous administration of meloxicam @ 0.2 mg/Kg body weight (n=8)

Pharmacokinetic Parameters	Range	Mean	SEM	St. Dev	CV (%)	Median
AUC ($\mu\text{g}\cdot\text{h}/\text{ml}$)	25.28-27.57	26.97	0.256	0.724	2.68	27.09
Clearance ($\text{l}/\text{hr}/\text{kg}$)	0.006495-0.0069	0.01	0.003	0.001	10.00	0.010
VDss (l/kg)	0.2123-0.2268	0.22	0.002	0.006	2.73	0.224
$t_{1/2}$ Half Life (hr)	21.99-24	23.39	0.402	1.136	4.856	23.99
MRT (hr)	31.72-35.29	33.69	0.563	1.593	4.73	34.50

The higher value of MRT and smaller value of clearance indicated that meloxicam was eliminated at a slow rate in dogs. The smaller values of Vdss observed for meloxicam is typical of the class NSAIDs. It may be due to high protein binding. However, protein binding was not measured in the present study.

In conclusion, results of the present study indicate that variations exist in pharmacokinetics behaviour of meloxicam in dogs when compared with other species. Keeping in view different pharmacokinetic parameters, single IV-dose of 0.2 mg/Kg is recommended for use in dog.

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