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Preeti Bisht
Veterinary officer, Uttarakhand Government, Uttarakhand, India

AH Ahmad
Professor (Dept. of Pharmacology and Toxicology) College of Veterinary and Animal Sciences, G.B.P.U.A &T. Pantnagar, Uttarakhand, India

Alok Mishra
Assistant Professor, RGSC, IAS, BHU, Barkachha, Mirzapur, Uttar Pradesh, India

Manu Jaiswal
Assistant Professor, RGSC, IAS, BHU, Barkachha, Mirzapur, Uttar Pradesh, India

Narendra Kumar
Assistant Professor, RGSC, IAS, BHU, Barkachha, Mirzapur, Uttar Pradesh, India

Correspondence
Alok Mishra
Assistant Professor, RGSC, IAS, BHU, Barkachha, Mirzapur, Uttar Pradesh, India

Pharmacokinetic study of Meloxicam in poultry following multiple doses by intramuscular administration

Preeti Bisht, AH Ahmad, Alok Mishra, Manu Jaiswal and Narendra Kumar

Abstract
The present study was undertaken to investigate the pharmacokinetics and tissue residue study of meloxicam at a dose rate of 0.5 mg/kg body weight in poultry (n=8) following multiple (5) doses intramuscular administration. The concentration of meloxicam in plasma and tissue of these animals were analysed by High-performance liquid chromatography (HPLC) with Ultra Violet (UV) detector. Following multiple doses i.m. administration volume of distribution, clearance, area under curve (AUC) and elimination half-life were estimated after first dose was 194.38 $ml.kg^{-1}$, 57.19 $ml.h^{-1}.kg^{-1}$, 8.91 $h.\mu g.ml^{-1}$ and 2.42h, respectively and 189.32 $ml.kg^{-1}$, 67.56 $ml.h^{-1}.kg^{-1}$, 8.32 $h.\mu g.ml^{-1}$ and 2.18h after the last dose. Residue of meloxicam was not found in kidney, liver and muscle up to 48 hour post administration of meloxicam.

Keywords: poultry, meloxicam, HPLC, pharmacokinetics and tissue residue

Introduction
Meloxicam is new non steroidal anti-inflammatory drug (NSAID) with preferential COX-2 inhibitory activity and possesses zwitter-ionic property with pk_a values of 1.09 and 4.18 and is practically insoluble under acidic conditions. The pharmacokinetic behavior of meloxicam has been investigated in rats (Busch *et al*., 1998) [3], cats (Lehr *et al*., 2009) [7], dogs (Busch *et al*., 998 [3]; Montoya *et al*., 2004) [9], sheep and goats (Shukla *et al*., 2007) [12], piglets (Fosse *et al*., 2008) [4], horses (Lees *et al*., 1991 [6]; Toutain *et al*., 2004) [13], chickens (Baert and De Backer, 2003) [1], ostriches (Baert *et al*., 2002) [2] and vultures (Naidoo *et al*., 2008) [10]. Favourable kinetic properties of meloxicam like good absorption, longer elimination half-life and optimum bioavailability make it an ideal and suitable NSAID for use in animals (Busch *et al*., 1998) [3]. In view of the marked species variation in the kinetic data of drugs, the present study was undertaken to determine the pharmacokinetics and tissue residue study of meloxicam in poultry following multiple (5) doses i.m. administration.

Material and Methods
The pharmacokinetic and tissue residue study of meloxicam was conducted in eight poultry birds with an average weight of 1.0± 0.5kg. Melonex (Meloxicam 0.5% w/v, M/s Intas Pharm. Ltd., Ahmadabad) was injected as multiple doses (one dose at an interval of 24hrs for 5 days) at a dose rate of 0.5mg/kg body weight intramuscular (i.m.) in poultry birds. The blood samples on 2nd, 3rd and 4th days of drug administration were collected by left and right brachial veins or from jugular vein immediately prior to drug administration and at 15 and 30 minute post administration. On 1st and 5th day of drug administration, blood samples were collected at 0, 2.5, 5, 15, 30 minute and 1, 2, 4, 8, 12 and 24 hour after drug administration. Plasma was separated and stored at -30^{0}C till analysis. The plasma proteins were removed via acetonitrile precipitation; equal amount of plasma and acetonitrile were added and vigorously shaken. The precipitated proteins were removed via centrifugation at 9000 rpm for 10 min. Subsequently, 20 μl of the supernatant were injected into the column. All samples were analyzed within one week. The solvents used during the chromatographic analysis of the drug were HPLC grade.
For tissue residue study four birds were sacrificed at 24 and 48h after the last dose (5th dose). Blood samples were collected immediately prior to sacrifice. A postmortem examination was performed and samples of liver, kidney and muscle were collected, frozen and stored at -40°C until analyzed. Drug extraction of meloxicam from tissues was carried out by the method as described by Gracia–Ovando *et al*. (1997) [5]. 04gm of thawed tissue with double amount of

acetonitrile homogenized, triturated and was subjected to sonicated at 10 amplitude microns for 30secs, with a pause of 5 seconds total 15 cycles) by using ultrasonic tissue disintegration and centrifuged at 9000 rpm for 15min and supernatant dried at 60^0C. Clean up process was carried out using solid- phase extraction C_{18} cartridges. The dried eluate was reconstituted in 2ml of acetonitrile and loaded onto the conditioned C_{18} cartridges (conditioning was done first with water and then by acetonitrile) and allowed to pass through vacuum (20 mmHg). The cartridges were washed with 2 ml of acetonitrile. The eluate which was obtained after loading of cartridges was filtered through 0.22 µm filter paper. 20 µl of the sample thus obtained was injected into HPLC system for analysis. An isocratic mobile phase used for plasma and tissue samples estimation which was consisted of (50%) buffer and (50%) acetonitrile. The buffer was consisting of 170 mmol of sodium acetate trihydrate in water and pH was adjusted to 3.3 using acetic acid with a flow rate of 1.0 ml.min^{-1} to be detected at UV wavelength of 355 nm. The standards for meloxicam were made by dissolving 5 mg of pure meloxicam (Sigma Aldrich Ltd.) in water. Further dilutions were made from this stock solution in water in the concentrations of 10.0, 5.0, 2.5, 1, 0.5, 0.25, 0.1, 0.05 and 0.025µg.ml^{-1}. The calibration curves of plasma were prepared with different concentrations between 0.025 and 10 μg.ml^{-1} using blank poultry plasma. Limit of quantification (LOQ) of meloxicam in plasma was 0.025µg.ml^{-1} and limit of detection (LOD) after first and last dose were 0.17 and 0.20 µg.ml^{-1}. Pharmacokinetic analysis of plasma and tissue meloxicam concentration versus time data was conducted by using WinNonLin Professional version 5.3 software package (Pharsight Corporation, Mountain View, California).

Result and Discussion

A one compartment model with first order rate of absorption adequately described plasma concentration-time profile of meloxicam in poultry following multiple (5) dose (0.5mg/kg) i.m. administration. In multiple dose therapy, the ultimate purpose is to achieve a steady drug effect or response with minimum side effects. The basic mathematical relationships applicable to single dose administration kinetics is also valid for multiple dose kinetics.

In the present study, the peak plasma concentration after first (2.49 µg.ml^{-1}) and last (2.54 µg.ml^{-1}) dose were almost similar to peak concentration observed after single (2.47µg.mL^{-1}) dose administration and were observed after 30 mins post-drug administration. The elimination rate constant (K_{10}) after first and last dose were 0.30h^{-1} and 0.37h^{-1} with an elimination half-life (K_{10}_HL) of 2.42h and 2.18h, respectively, which is lower as compared to that of 9 h in sheep. But much higher elimination half life value of 37.88 h and 23.41h has been reported in buffalo calves (Mody and Patel, 2007)[8] and dogs respectively.

The volume of distribution (V_D) was estimated to be 194.38 ml.kg^{-1} and 189.32 ml.kg^{-1} after first and last dose of administration of meloxicam, respectively which is lower than reported in buffalo calves 260 ml.kg^{-1} (Mody and Patel, 2007). The clearance (CL) of meloxicam was 57.19 ml.h^{-1}.kg^{-1} after first dose and 67.56 ml.h^{-1}.kg^{-1} after the last dose which is higher as compared to 20 ml.h^{-1}.kg^{-1} and lesser than 80 ml.h^{-1}.kg^{-1}, reported in sheep and buffalo calves (Mody and Patel, 2007)[8], respectively. This low volume of distribution of the drug indicates its high plasma protein binding and less distribution to different body tissues and high clearance indicates that birds have an advanced ability to clear drug from the circulation compared to other species these may be the reasons that no drug residue was found in liver, kidney and muscles. The mean area under curve (AUC) after first and last dose were 8.91and 8.32h.µg. ml^{-1}, respectively was lower than that reported in sheep (26.67 hr.µg.ml^{-1}) and buffalo calves (105 hr.µg.ml^{-1}; Mody and Patel, 2007) [8]. The values of Cmax and Tmax were 2.34µg.ml^{-1} and 0.39h after first dose and 2.25µg.ml^{-1} and 0.48h after the last dose of administration of meloxicam.

No residual concentration of meloxicam was found in liver, kidney and muscles. If successive dose is administered every half -life, this should maintain a desired steady state commencing with the first dose. This is acceptable dosage regimen for drugs whose half- lives are intermediate (4-12 h) and therapeutic index is high so that 3-4 doses can be administered daily. Repeated or multiple administration may often lead to drug accumulation in the body (Shargel and Andrew, 1992) [11]. Accumulation is generally noticed following administration of a new dose while the drug is still in the body. When a gap of 4-5 half lives exist between two doses in multiple administration therapy, over 98% of the previous dose is eliminated, before a new dose is administered and accumulation is avoided. However such approach is not desirable as it results in longer periods of ineffective concentrations. The plasma concentration time curve for meloxicam following multiple (5) dose i.m. administration in poultry is depicted in Fig.1. Pharmacokinetic values describing the disposition kinetics of meloxicam following multiple (5) dose (0.5mg.kg^{-1}) i.m. administration in poultry are presented in Table1. Residual concentration of meloxicam was depicted in Table 2.

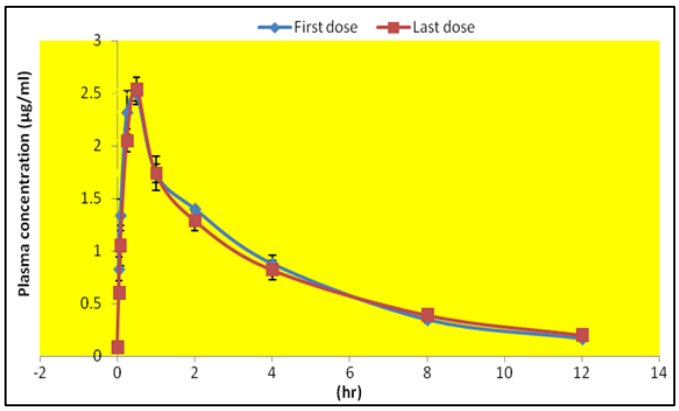

Fig 1: Plasma concentration (µg.ml^{-1}) of meloxicam (Mean±S.E.) after first and last dose following multiple (5) dose (0.5mg/kg) intramuscular administration in poultry (n=8)

Table 1: Pharmacokinetic parameters of meloxicam in plasma following multiple (5) dose (0.5 mg/kg) intramuscular administration in poultry (n=8)

Pharmacokinetic parameters	Units	Mean± S.E.	
		First dose	Last dose
V_D	ml.kg^{-1}	194.38± 10.72	189.32±9.78
K_{01}	h^{-1}	9.61±0.89	7.22±1.29
K_{10}	h^{-1}	0.30±0.03	0.37±0.07
AUC	h.µg.ml^{-1}	8.91±0.44	8.32±0.94
K_{01}_ HL	h	0.07±0.01	0.11±0.01
K_{10}_ HL	h	2.42±0.22	2.18±0.28
CL_F	ml.h^{-1}.kg^{-1}	57.19±3.22	67.56±9.71
T_{max}	h	0.39±0.03	0.48±0.05
C_{max}	µg.ml^{-1}	2.34±0.14	2.25±0.08

K_{10}_*HL*: elimination half life (for i.m.); K_{01}_ *HL*: absorption half life; V_D: volume of distribution where the absorption of drug is not known; *CL_F*: total body clearance where the absorption of drug is not known***;*** *AUC*: area under the curve from zero to infinity by the trapezoidal integral; *MRT*: mean residence time; *C* max: maximum plasma concentration; *T* max: time to peak concentration; K_{10}: rate constant for elimination of drug; $K_{01:}$ first order absorption rate constant;

Table 2: Residual concentration ($\mu g.g^{-1}$) of meloxicam in various tissues after 24 and 48h following multiple (5) dose (0.5 $mg.kg^{-1}$) intramuscular administration in poultry (n=4)

Tissue	Mean ±S.E	
	24h	48h
Liver	N.D.	N.D.
Kidney	N.D.	N.D.
Muscles	N.D.	N.D.

N.D. - Not detectable

Conclusion

The present investigation conclude that multiple doses of meloxicam by intramuscular administration, volume of distribution, clearance, area under curve (AUC) and elimination half-life were estimated after first dose was 194.38 $ml.kg^{-1}$, 57.19 $ml.h^{-1}.kg^{-1}$, 8.91 $h.\mu g.ml^{-1}$ and 2.42h, respectively and 189.32 $ml.kg^{-1}$, 67.56 $ml.h^{-1}.kg^{-1}$, 8.32 $h.\mu g.ml^{-1}$ and 2.18h after the last dose. Residue of meloxicam was not found in kidney, liver and muscle up to 48 hour post administration of meloxicam.

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