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Effect of Meloxicam on Pharmacokinetics of Long Acting Moxifloxacin in Goats

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A B S T R A C T

Present study was conducted for pharmacokinetic interaction of long acting moxofloxacin (LA moxifloxacin) with meloxicam at the dose rate of 7.5 mg.kg^{-1} and 0.5 mg.kg^{-1} respectively following intramuscular (IM) administration. Peak plasma concentrations of drug were estimated by using HPLC florescence detector. The values of different pharmacokinetic parameter of long acting moxifloxacin along with *viz.,* β and t1/2β were found to be 0.058 ± 0.004 h^{-1} and 12.297 ± 0.843 h. respectively. The mean value of Cmax was 1.56 μg.ml^{-1} and Tmax was 1.5 h. The average value for AUC and AUMC was 18.53 ± 0.754 μg.h.ml^{-1} and 251.183 ± 20.501 μg.h^2.ml^{-1}. The value of mean residence time (MRT) was 13.467 ± 0.726 h. The mean values of $V_{d(area)}$ and $V_{d(ss)}$ were 7.249 ± 0.645 and L.kg^{-1}, respectively. The mean value for total body clearance (Cl$_B$) was 0. 408 ± 0.01 L.h^{-1}.kg^{-1}. Present investigation revealed that meloxicam interacts with Long Acting moxifloxacin.

Introduction

Meloxicam, is most commonly used non steroidal anti inflammatory drug (NSAIDS) in veterinary practices. It is an enolic acid class non steroidal anti inflammatory drug preferentially inhibits inducible Cyclooxygenase-2(Cox-2) over Cox- 1and have anti inflammatory, analgesic and antipyretics activities (Euller-Ziegler and Velicitat, 2001). Moxifloxacin is a new 8-methoxy quinolone, chemotherapeutic agent with broad spectrum of antibacterial activities against Gram-positive and Gram-negative bacteria, anaerobes and typical organism such as *Mycoplasma* and *Chlamydia* Spp (Sullivan

et al., 1999 and Noel *et al.,* 2005). It has the highest potency against *Staphylococcus aureus*, *Staphylococcus epidermidis* and also possess large volume distribution, low plasma protein binding and relatively low MICs against susceptible target microorganisms. Moxifloxacin is highly effective against *Mycobacterium leprae*, used for treatment of leprosy, it significantly kill microorganism upto 81% to 91% (Pardillo *et al*., 2008). The drug thus seems to be extremely useful in a variety of infections including those of urinary tract, respiratory tract, soft tissues, bones and joints. The combined use of

antibiotics and NSAIDS is very common in Veterinary Practices (Deleforge *et al.*, 1994). Concurrent use of Meloxicam alters the pharmcokinetics of certain drugs, like furosemide and levofloxacin (Muller *et al.,* 1997; Dumka *et al.,* 2008).

Pharmacokinetics of Moxifloxacin as well as Meloxicam investigated alone in different species but the effect of Meloxicam on Pharmacokinetics of LA Moxifloxacin has not been investigated in goats. Hence the objective of present investigation was to determine pharmacokinetic interaction of LA moxifloxacin along with meloxicam.

Materials and Methods

Experimental animals

Six healthy male Mehsana goats of body weight between 25 – 35 kg of 2-3 year of age were dewormed and acclimatized for 30 days in experimental animal shed before starting the experiment. They were maintained on concentrate, adequate green and dry fodder and *ad libitum* fresh water.

The experimental protocol was approved by Institutional Animal Ethical Committee and all the measures for welfare of experiment animals were taken as per committee for purpose of control and supervision on experiment on animal guideline.

Drugs and chemicals

Long acting Moxifloxacin (10% moxifloxacin in solution with L-arginine, N-butyl alcohol and benzyl alcohol) injectable solution and moxifloxacin base powder were obtained from INTAS Animal health, Gujrat India water, acetonitrile and tetrabutyl ammonium hydrogen sulfate of HPLC grade were procured from S.D Fine Chem. Ltd Mumbai.

Experimental design

Six goats were administered long acting moxifloxacin at the dose rate of 7.5 mg kg^{-1} b.wt through intramuscular (i.m) in gluteal muscles. For pharmacokinetics study blood samples (approx 5 ml) were collected from each goat in heparin containing test tube with the help of an intravenous catheter (Venflon) fix into Jugular Vein at zero time before drug administration and at different time interval like 0.083 (5 min), 0.166 (10 min), 0.5, 1, 2, 4, 8, 12, 24, 36, 48, 60, 72 and up to 96 h Post administration of drug. Plasma was separated after centrifugation of blood samples at 1660 revolutions per minute (rpm) for 10 minutes. The plasma samples were transferred to cryo-vials and stored at $-$ 4°C until assayed. After two weeks of wash out period interaction study was performed in same animals for this long acting moxifloxacin were given dose @ 7.5 mg.kg^{-1} b.wt. and meloxicam dose @ 0.5 mg.kg $^{-1}$ body weight concomitantly at different body sites. Collection of blood samples at different time interval and preparation of plasma were as same as per kinetics study.

HPLC analysis

Plasma concentrations of long acting moxifloxacin was assay by High Performance Liquid Chromatography (Agilent-1100) system was equipped with a model LC-9A (gradient solvent delivery Pump), a model RF-551 fluorescence detector as per method described by Fernandez-Varon *et.al.* 2006. Chromatographic separation was performed by using C_{18} column (Supelcosil; 250 x 4.6 mm, 5μ) at room temperature. Effluent was monitored at excitation wavelength at 296 nm and emission wavelength of 504 nm. Mobile phase was prepared by mixing buffer and acetonitrile in the ratio of 4:1 [80:20]. Plasma samples were extracted by adding 1000 μl plasma and 1000-

µl acetonitrile for precipitation of protein after shaking with vortex shaker for 10 sec. followed by centrifugation at 1660 rpm for 10 min. Supernatants fluid were diluted four-fold with 4000 µl of 0.067 M disodium hydrogen phosphate buffer (pH 7.5) and transferred to HPLC sample vials for estimation.

Pharmacokinetic parameters

The various pharmacokinetic parameters depicted in table 1 were calculated by software PK solution (version 2.0). Summit research service USA. This programme uses non compartmental model of Pharmacokinetic analysis of long acting moxifloxacin. Interaction of Pharmacokinetic parameters were statistically analyzed using students t-test as per method described by Snedecor and Cochran 1967

Results and Discussion

The initial plasma concentration of LA moxifloxacin was 0.237 ± 0.015 µg.ml^{-1} and 0.446 ± 0.043 µg.ml^{-1} were found at 0.083 h when LA moxifloxacin given alone and along with meloxicam respectively. The mean peak plasma concentration of LA moxifloxacin was 1.8 ± 0.077 µg.ml^{-1} achieved at 4 h when LA moxifloxacin given alone but when given along with meloxicam mean peak serum concentration of LA moxifloxacin was 1.57 ± 0.061 µg.ml^{-1} achieved at 2 h. The lowest plasma drug concentration 0.010 ± 0.002 µg.ml^{-1} and 0.0086 ± 0.003µg.ml^{-1} detectable up to 96 h and 72 h when LA moxifloxacin given alone and along with meloxicam respectively Mean plasma drug concentration versus time profile depicted in figure 1.
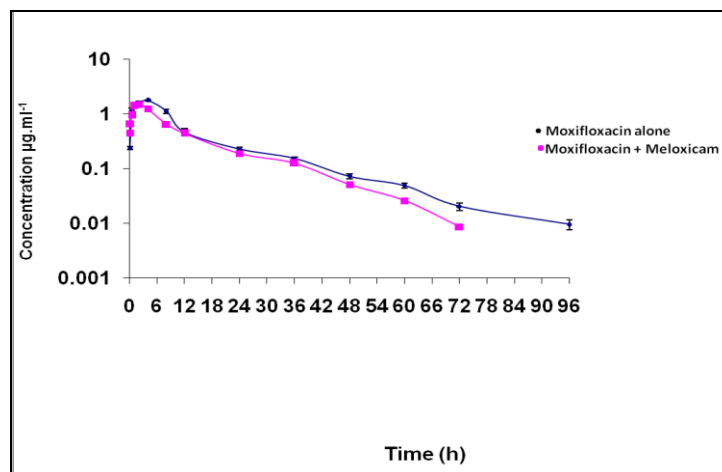
Table.1 Kinetic parameters of Long Acting moxifloxacin after single IM administration (7.5 mg.kg^{-1} b. wt.) alone and along with meloxicam (0.5mg/kg) in male Mehsana goats

Pharmacokinetic parameters	Unit	Values of Pharmacokinetic parameters	
		LA moxifloxacin alone	**LA moxifloxacin +Meloxicam**
β	h^{-1}	0.047 ± 0.002	0.058 ± 0.004
$t_{1/2\beta}$	h	15.194 ± 0.687	$12.297 \pm 0.843^{*}$
C max	µg.ml^{-1}	1.800 ± 0.077	$1.567 \pm 0.061^{*}$
Tmax	h	3.667 ± 0.333	$1.500 \pm 0.224^{*}$
AUC	µg. h ml^{-1}	24.117 ± 1.155	$18.533 \pm 0.754^{*}$
AUMC	µg.h^{2}.ml^{-1}	380.40 ± 4.96	$251.183 \pm 5.501^{*}$
MRT	h	15.617 ± 0.523	$13.467 \pm 0.726^{*}$
$V_{d(area)}$	L.kg^{-1}	6.829 ± 0.455	7.249 ± 0.645
$V_{d (ss)}$	L.kg^{-1}	5.06 ± 0.289	5.66 ± 0.19
Cl_B	L.h^{-1}.kg^{-1}	0.307 ± 0.015	$0.408 \pm 0.017^{*}$
F	%	107.97 ± 9.5	$84.271 \pm 3.97^{*}$

* $p<0.05$

Elimination rate constant (β), Elimination half life ($t_{1/2\beta}$), Maximum concentration (Cmax), Time at maximum concentration (Tmax), Area under the curve (AUC), area under the first moment of curve (AUMC), Maximum resident time (MRT), Apparent volume of distribution V d(area), Volume of distribution at steady state ($V_{d (ss)}$), Total body clearance ClB, bioavailability (F),

Fig.1 Comparative semilogrithmic plot of LA moxifloxacin following single dose IM administration (7.5 mg.kg^{-1} b.wt.) alone and in combination with meloxicam (NSAIDs) administered   (0.5 mg.kg^{-1} b.wt.) intramuscularly, in male Mehsana goats

The detailed Pharmacokinetics parameters of long acting moxifloxacin when given alone and concomitant with meloxiacm tabulated in table 1.

In the present study, the mean peak plasma level of LA moxifloxacin level (C_{max}) in goats was observed as 1.57 µg.ml^{-1} at 1.50 h (T_{max}) after its single IM administration (7.5 mg.kg^{-1} b.wt) with concomitant administration of meloxicam (NSAIDs) 0.5 mg.kg^{-1} intramuscularly. However this observed concentration is approximately equal or slightly lower than the LA moxifloxacin concentration observed when it was administered alone supported with Patel S.D.et al.2011. Drug was detected in plasma at the level of 0.009 ± 0.003 µg.ml^{-1} for up to 72 h post administration. Goudah (2008) have reported higher peak plasma levels of 2.21 ± 0.27 µg.ml^{-1} at 1.45 ± 0.02 h in lactating ewes after single IM administrations (5 mg.kg^{-1} b.wt.). Similar findings of peak plasma level of 2.16 ± 0.13 µg.ml^{-1} found at almost in same duration (1.04 ± 0.14 h) in healthy male camels was reported following single IM administration 5 mg.kg^{-1} b.wt. of moxifloxacin (Abd El-Aty *et al*., 2007).

In this study, therapeutically effective concentration and C_{max} attained within 5 min. and 2 h post administration of LA moxifloxacin. LA moxifloxacin retained above the MIC_{90} level (0.03-0.12 µg.ml^{-1}) from 5min. to 60 h. This may be due to LA formulation of moxifloxacin, which cover most pathogens (Fernandez-Varon *et al*., 2005). the value of elimination rate constant as 0.058 ± 0.004 h^{-1} was found following single dose IM administrations of LA moxifloxacin (7.5 mg.kg^{-1} b.wt.) with concomitant administration of meloxicam (NSAIDs) (0.5 mg kg^{-1} b.wt.) IM in goats, the observed value is equal to elimination rate constant when LA moxifloxacin administered alone. Goudah (2008), have reported high value of moxifloxacin elimination rate constants (β= 0.26 ± 0.13 h^{-1}) in lactating ewes with same dose. Similar value of elimination rate constant has been reported by Abd El-Aty *et al.,* (2007) in camels. Value of β as 0.34 h^{-1} has also been reported for moxifloxacin in rabbits (Fernandez-Varon *et al.,* 2006). The $t_{1/2\beta}$ was found to be 12.297 ± 0.843 h were approx equal or slightly lower to alone.

The present study reveals and concluded favorable pharmacokinetic variability of LA moxifloxacin show along with meloxicam, hence it can be concluded that meloxicam interacted with certain pharmacokinetic parameters of long acting moxifloxacin and it may be uses for treatment of infection caused by various organism in goats.

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