Disposition kinetics of long acting moxifloxacin following intravenous administration in Sheep

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Abstract

Aim: The objective of the present study was to study the disposition kinetics and dosage regimens of long acting moxifloxacin following intravenous administration at the dose rate of 7.5 mg/kg^{-1} b. wt. in six male sheep and to calculate dosage regimens of the same in sheep.

Materials and Methods: The study was conducted using six healthy male sheep. Long acting Moxifloxacin solution (10 % moxifloxacin in solution with L- arginine, N-butyl alcohol and benzyl alcohol) was injected in jugular vein and periodical blood samples were collected from contra-lateral jugular vein in test tubes containing 30-50 IU heparin (anticoagulant) at 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. Drug concentration in plasma was determined using High Performance Liquid Chromatography (HPLC) with Fluorescence Detector. The blood concentrations versus time data were analyzed using software.

Results: After single dose intravenous administration of long acting moxifloxacin the plasma concentration of 0.016 ± 0.001 µg/ml^{-1} was maintained for up to 72 h. Distribution half-life ($t_{1/2}$) and elimination half-life ($t_{1/2}$) were 1.637 ± 0.053 h, and 12.130 ± 0.202 h, following IV administration. The mean values of apparent volume of distribution $V_{d(area)}$ 5.436 ± 0.135 L/kg^{-1} as well as mean residence time 10.02 ± 4.787 minute were detected with IV administration.

Conclusion: The long acting Moxifloxacin @ the dose 7.5 mg/kg IV maintains the effective therapeutic concentration in the plasma of sheep for up to 72 hours. The long acting Moxifloxacin at this dose rate can be used to treat sensitive bacteria causing infectious diseases in sheep.

Key words: Disposition kinetics, Intravenous, Long acting Moxifloxacin, Sheep.

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Introduction

Moxifloxacin is a new 8-methoxy-quinolone with a broad spectrum of antibacterial activity against Gram-positive and Gram-negative bacteria, anaerobes and atypical organisms such as *Mycoplasma* and *Chlamydia* spp. Fluroquinolones are considered to have a concentration dependent effect, although a time dependent bactericidal effect against some Gram positive bacteria has also been described [1,2]. The MIC of moxifloxacin for *Mycobacterium ulcerans* ranged from 0.015-0.5 µg/ml^{-1} [3], for *S. aureus* from 0.03-0.12 µg/ml^{-1} [4]. It has the highest potency in its class against *Staphylococcus aureus* and *Staphylococcus epidermidis* [5]. Outstanding pharmacokinetics properties of Moxifloxacin includes large volume of distribution, low plasma protein binding and relatively low MICs against susceptible target microorganisms [1,6]. Pharmacokinetics studies of moxifloxacin would be of great use as it provides a basis for the determination of satisfactory dosage regimen in sheep under our tropical climate. These have been studied exclusively by in various animals species like lactating goats [7], lactating ewes [8], camel [9], rabbits [4], Mice [10] and Horse [11]. As the effectiveness of an antibacterial agent depends on its efficacy, safety and pharmacokinetic disposition in the target animal, the aim of the present study was to investigate the plasma pharmacokinetics of long acting moxifloxacin in sheep after single intravenous (IV) administration.

Materials and Methods

Experimental animals: Six healthy adult male sheep weighing 38-45 kg were used in present study. Sheep

were housed at the livestock research station, Sardarkrushinagar Dantiwada Agricultural University, Sardarkrushinagar. The sheep were housed in well ventilated appropriately spaced animal shed and fed with good quality fodder and concentration. Animal had free access to clean and potable water during course of experiment. All animals were accelerated far period of 15 days and observed clinically daily to confirm any illness or disease. Animals were not treated earlier by any drugs. The experimental protocol was approved by Institutional Animal Ethics Committee and all the measures for welfare of experiment animal were taken as per Committee for Purpose of Control and Supervision on Experiment on Animal guide line.

Drug 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, Gujarat, India. Water, acetonitrile and tetrabutyl ammonium hydrogen sulfate of HPLC grade were procured from S. D. Fine Chem. Ltd, Mumbai. 0.067M disodium hydrogen phosphate and hydrochloric acid of analytical grade were purchased from S. D. Fine Chem. Ltd, Mumbai.

Experimental design and drug administration: Six sheep were administered long acting moxifloxacin at dose rate of 7.5 $mg.kg^{-1}$ through intravenous route via jugular vein. Blood samples (approximately 5 ml) were collected from each treated sheep in heparin containing test tubes with the help of an intravenous catheter (Venflon) fixed into jugular vein at 0 time (before drug administration) and at 0.08 (5 min), 0.25 (15 min), 0.5 (30 min), 1, 2, 4, 8, 12, 24, 36, 48, 60, 72 and 96 h after drug administration. 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 (3 ml capacity) and stored at - $4^{o}C$ until assayed for long acting moxifloxacin concentration using HPLC assay.

Moxifloxacin HPLC assay: Plasma concentrations of moxifloxacin were measured using a modified HPLC method previously reported by Siefert et al. (1999a). The HPLC (AGILENT-1100) system was equipped with a modal LC-9A (gradient solvent delivery pump), a modal RF-551 Fluorescence Detector, a modal SIL-6B automatic sampler and column heater (CTO-6A). Plasma samples were extracted in aliquots by adding 200 µl of plasma to 200 µl of acetonitrile. Plasma proteins were precipitated by shaking in an ultrasonic bath followed by centrifugation for 10 min at 1660 rpm speed. Supernatant was diluted four-fold with 0.067M disodium hydrogen phosphate buffer with pH 7.5 and transferred to HPLC auto sampler vials.

The HPLC separation was performed using a reserve phase C_{18} (Supelco, 5 µ, 4.6 × 150 mm) with an injection volume of 50 µL. The mobile phase consisted of acetonitrile (20%) and tetrabutyl ammonium hydrogen sulphate solution 10g/L (80%). Mobile phase was filtered by 0.22 µm filter and degassed by sonicator and then pumped into column at a flow rate of 1.00 $ml.min^{-1}$ at ambient temperature. The fluorescence detection was performed at excitation wavelength of 296 nm excitation and an emissions wavelength of 504 nm.

Pharmacokinetic analysis: Various pharmacokinetic parameters like absorption, distribution, elimination half-life, apparent volume of distribution and total body clearance were calculated by PK Solutions Version 2.0 computer software, Summit research services, USA. This program uses non-compartmental model of pharmacokinetic analysis of long acting moxifloxacin.

Results

The mean recovery of long acting Moxifloxacin from plasma was 85.14 % at 25 ng/ml. The sensitivity of long acting Moxifloxacin assay was 25 $\mu g/ml^{-1}$. The assay was sensitive, reproducible and linearity was observed from 0.025 to 20 $\mu g/ml^{-1}$. The mean correlation coefficient (r^2) of long acting Moxifloxacin was 0.99997. The lower limit of quantitation (LLOQ) was 25 $\mu g.ml^{-1}$.

The mean (± SE) plasma concentrations of long acting moxifloxacin following single dose intravenous administration are tabulated in Table-1 and the associated the mean plasma, concentrations versus time profile plotted logarithmically are illustrated in Figure-1. The initial plasma drug concentration was 7.212 ± 0.107 $\mu g/ml^{-1}$ achieved at 0.083 h (5 min). The lowest detectable plasma long acting moxifloxacin level as 0.016 ± 0.001 μ/ml^{-1} was found at 72 h. The therapeutically effective concentrations maintained from 0.083 to 72 h. The minimum inhibitory contraction of moxifloxacin is 0.1 – 0.5 $\mu g/ml^{-1}$[12].

The detailed Pharmacokinetic parameters of long acting moxifloxacin calculated for sheep were presented in the table 2. The mean extrapolated zero time concentration of the drug in plasma during distribution (A), elimination(B) phase and theoretical zero time concentration (Cp_o^{-} = A+ B) were noted to be 4.648 ± 0.091, 0.773 ± 0.026 and 5.400 ± 0.090 $\mu g/ml^{1}$,

Table-1. Plasma concentrations of long acting moxi-floxacin after single dose intravenous administration (7.5 mg.kg^{-1} body weight) in male Sheep (n=6).

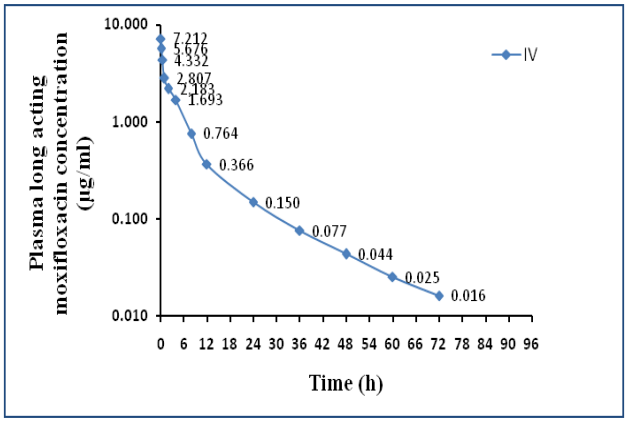
Time after drug administration (h)	Mean ± S.E. (µg/ml^{-1})
0.083	7.212 ± 0.107
0.166	5.676 ± 0.046
0.5	4.332 ± 0.185
1	2.807 ± 0.120
2	2.183 ± 0.057
4	1.693 ± 0.064
8	0.764 ± 0.019
12	0.366 ± 0.015
24	0.150 ± 0.0009
36	0.077 ± 0.001
48	0.044 ± 0.001
60	0.025 ± 0.0006
72	0.016 ± 0.001
96	ND

Table-2. Pharmacokinetic parameters of long acting moxi-floxacin following single dose (7.5 mg.kg^{-1}) IV in sheep (n=6).

Pharmacokinetic Variables	Units	Mean ± S. E. IV
CpO	µg.ml^{-1}	5.400 ± 0.090
A	µg.ml^{-1}	4.648 ± 0.091
B	µg.ml^{-1}	0.773±0.026
K(a)	h^{-1}	0.425 ± 0.012
ß	h^{-1}	0.057 ± 0.009
$t_{½\ alpha}$ / $t_{½\ K(a)}$	H	1.637 ± 0.053
$t_{½\ ß}$	H	12.13 ± 0.202
AUC	µg.h.ml^{-1}	24.18 ± 0.365
AUMC	µg.h^2.ml^{-1}	242.0 ± 3.364
Vd (area)	L.kg^{-1}	5.436 ± 0.135
V d (ss)	L.kg^{-1}	3.112 ± 0.091
$Cl_{(B)}$	L.h^{-1}.kg^{-1}	0.308 ± 0.005
MRT	h	10.02 ± 4.787
K12	h^{-1}	0.150 ± 0.008
K21	h^{-1}	0.110 ± 0.003
K_{12}/K_{21}	h^{-1}	1.374 ± 0.059

A and B, extrapolated zero time plasma drug concentration intercepts of absorption and elimination phases, respectively; Ka, distribution rate constant; $t_{1/2}$, distribution half life; β, elimination rate constant; $t_{½\ ß}$ elimination half life; AUC, total area under plasma concentration – time curve; AUMC, area under the first moment of plasma concentration time curve; MRT, mean resident time; K_{12}, rate constant of a drug from central to peripheral compartment; K_{21}, rate constant of drug from peripheral to central compartment; $Cl_{(B)}$, total body clearance of drug; $Vd_{(area)}$, volume of distribution; $Vd_{(ss)}$, volume of distribution of drug at steady-state

Figure-1. Plasma concentrations of long acting moxifloxacin following single dose IV administration at the dose rate of (7.5 mg/kg^{-1} of b. wt.) in sheep.



respectively. The distribution half life, elimination half life, apparent volume of distribution of drug at steady-state, area under curve and total body clearance were 1.637 ± 0.053 h. 12.130 ± 0.202 h, 3.112±0.091 L.kg^{-1}, 24.18±0.365 µg.h.ml^{-1} and 0.057±0.0009 h^{-1}, respectively. Rate constant for transfer of long acting moxifloxacin from central to the tissue compartment (K_{12}), tissue to the central compartment (K_{21}) and elimination rate constant from central compartment (Kel) were 0.150, 0.110 and 0.221 h^{-1}, respectively. The ratio of K_{12} / K_{21} was 1.374.

Discussion

Plasma levels and pharmacokinetics of moxifloxacin following single intravenous administration have been studied exclusively by scientists in various animals like lactating goats [7], lactating ewes [8], camel [9], rabbits [4], Mice [10] and Horse [11].

The elimination half-life 12.13±0.202 h determined in present study is longer than the reported in calves 3.29 h [13], 3.908 ± 0.258 h in sheep [14], 4.121 ± 0.302 h in goats [15], and 4.329 ± 0.024 h in buffalo calves [16]. Comparatively very lower value of $t_{1/2\beta}$ as

1.94 ± 0.41, 1.77 ± 0.23, 1.87 ± 0.16 and 1.84 ± 0.12 h have been reported in goats [7], sheep [8], camel [9] and rabbits [4], respectively following IV administrations of moxifloxacin.

The $Vd_{(ss)}$ is the constant that expresses the amount of the drug in the body at steady state as a proportion of the corresponding Css (the expected plasma concentration at steady-state). The $Vd_{(ss)}$ for moxifloxacin was 3.112 ± 0.091 $L.kg^{-1}$. This shows that in ewes there is a relatively quick and wide distribution of moxifloxacin after IV administration. Similarly high values of Vd(ss) 5.0, 0.26 and 1.25 $L.kg^{-1}$ respectively were reported in goats [15], buffalo calves [16] and in sheep [14] for conventional moxifloxacin. but higher than those reported by Fernandez-Varon *et al.,* [4] in rabbits, Fernandez-Varon *et al.,* [7] in lactating goats and Carceles *et al.,* [17] in rabbits, 1.95 0.79 and 2.08 L/kg, respectively. The good tissue diffusion may be related to low molecular weight of the drug's affinity for lipid-bearing tissues. Species differences are relatively common and are frequently related to inter-species variation, assay method used, the amount of time between blood samplings, health status and age.

Clearance of long acting moxifloxacin was observed to be is 0.308 ± 0.005 $L.h^{-1}.kg^{-1}$. Similar to values was found as 0.34 ± 0.04 and 0.34 ± 0.02 $L.h^{-1}.kg^{-1}$ were reported for moxifloxacin study in lactating ewes [8] and camels [9], respectively.

One of the most fundamental parameter of pharmacokinetic is area under plasma concentration time curve (AUC), which is proportionate to the systemic exposure to a drug. By itself, the AUC has little relevance. However, the AUC can be used in calculation of several more clinically significant pharmacokinetic parameters like bioavailability, volume of distribution and clearance. In the present study mean value of AUC was 24.18 $\mu g.h.ml^{-1}$ after intravenous administration of long acting moxifloxacin (7.5 $mg.kg^{-1}$ b.wt.). However lower values of AUC have been reported by Fernandez-Varon *et al.* [7] in lactating goats, Goudah *et al.* [8] in lactating ewes and [9] in male camels as 11.71 ± 0.67, 14.74 ± 2.16 and 14.72 ± 0.69 $\mu g.h.ml^{-1}$ respectively following 5 $mg.kg^{-1}$ b.wt intravenous administration of moxifloxacin. Results of Fernandez-Varon *et al.* [4] for pharmacokinetic study of moxifloxacin in rabbits have shown similar findings of low values of AUC as 6.28 ± 0.13 $\mu g.h.ml^{-1}$. The difference in AUC values indicates species variation and may be due to different of formulation.

Conclusion

The outstanding pharmacokinetic characteristics observed in this study and extremely low MIC values of long acting moxifloxacin against common animal pathogens make long acting moxifloxacin suitable for its use in sheep. The long acting moxifloxacin has potential future in treatment of infectious diseases of sheep. The long acting moxifloxacin at the dose rate of 7.5 mg/kg after single intravenous injection in sheep maintains the effective therapeutic concentration for up to 36 hours and does not need repeated administration daily. This would be very economical and convenient for clinicians in treating infection diseases caused by moxifloxacin sensitive bacteria in sheep.

Author's contribution

All authors contributed equally. All authors read and approved the final manuscript.

Competing interest

Authors declare that they have no competing interest.

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