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Disposition kinetics of moxifloxacin in calves following a single intravenous bolus dose

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Abstract
The objective of this study was to determine the pharmacokinetics of moxifloxacin following single intravenous (IV) administration in five healthy female Sahiwal calves. Moxifloxacin was administered intravenously (5 mg.kg^{-1} bodyweight) and blood samples were collected prior to drug administration and up to 48 hr after injection. Plasma concentrations of moxifloxacin were examined by microbiological assay method. The disposition of plasma moxifloxacin is characterized by two compartment open model. The pharmacokinetic parameters obtained after IV administration (mean ± *SE*) were $t_{½\alpha}$ 0.12 ± 0.00 h, $t_{½\beta}$ 8.16 ± 0.16 h, AUC 46.65 ± 1.70 µg.ml^{-1}.h, AUMC 531.69 ± 16.72 µg.ml^{-1}.h^2, MRT 11.41 ± 0.20 h, Vd_{area} 1.27 ± 0.06 L.kg^{-1}, and Cl_B 0.10 ± 0.00 L.kg^{-1}.h^{-1}. A dosage regimen of 5 mg.kg^{-1} bodyweight at 24 h interval following IV injection of moxifloxacin would maintain the plasma levels required to be effective against the bacterial pathogens with MIC values ≤ 0.25 µg.ml^{-1}. The suggested dosage regimen of moxifloxacin has to be validated in the disease models before recommending for clinical use in calves.

Keywords: Intravenous, microbiological assay, moxifloxacin, pharmacokinetics, sahiwal calves

Introduction
Moxifloxacin is a fourth generation fluoroquinolone with a methoxy group in the C-8 position and C-7 side chain. Moxifloxacin has *in vitro* activity similar to that of older fluoroquinolones against Gram-negative bacteria, but shows improved activity against Gram-positive cocci, aerobic, anaerobic intracellular bacteria, as well as atypical organisms, such as Mycoplasma and Chlamydia, compared with older fluoroquinolones. As a member of the fluoroquinolone group, moxifloxacin acts on bacterial DNA topoisomerases II and IV [1, 6, 8, 12].
Moxifloxacin was discovered in 1999 by addition of an azabicyclo-substitution at C-7, which is associated with activity against a broad spectrum of pathogens, encompassing Gram-negative and Gram-positive bacteria [4].
Pharmacokinetics of moxifloxacin following intravenous (IV) administration have been reported in buffalo calves, goats, lactating goats, sheep, lactating ewes, camels and muscovy ducks [1, 5, 6, 8, 9, 10, 11, 12]. However, there is no published report on the disposition kinetics of moxifloxacin following IV administration in female Sahiwal calves. Keeping the above facts in view and considering the common route of drug administration in field conditions, this study was conducted to investigate the disposition kinetics of moxifloxacin following single intravenous administration.

Materials and Methods
For the present study, five apparently healthy female Sahiwal calves (A to E) aging 4-6 months and weighing between 40-60 kg were taken from Livestock Research Station, Kodamdesar, RAJUVAS, Bikaner. Animals were kept and maintained in the respective farm in standard management conditions and were protected against endoparasites and ectoparasites. The animals had free access to roughage and water and were given standard ration. The experimental protocol and use of animals for conducting the present study had approval of Animal Ethics committee (IAEC).
Moxifloxacin hydrochloride (inj. Mofoi™ 10 per cent w/v; Bovian Health care Pvt. Ltd., Secunderabad, Telangana, India) was administered as single intravenously on jugular vein in calves at the dose rate of 5 mg.kg^{-1} body weight. Blood samples (4-6 ml) were collected in test tubes containing EDTA as anticoagulant, immediately before administration of moxifloxacin (0 h) and at 0.04, 0.08, 0.17, 0.25, 0.5, 0.75, 1.0, 1.5, 2, 4, 6, 8, 10, 12, 24, 36 and 48 h after administration of the drug. Blood samples at 0.04, 0.08 and 0.17 h were drawn from the jugular vein other than that was used to administer the drug. Blood samples were centrifuged

at 3000 rpm for 15 min to separate the plasma. The plasma samples were stored at −20°C until assayed.

Concentration of moxifloxacin in plasma samples were determined by microbiological assay method using MTCC equivalent *Escherichia coli* MTCC 443 [2].

The plasma moxifloxacin concentration time profile of each animal following intravenous administration were used to determine the pharmacokinetic variables describing the absorption, distribution and elimination characteristics of moxifloxacin in calves. To determine the different disposition kinetic variables, plasma drug concentration–time data were analysed by employing the compartmental pharmacokinetic models [3, 7].

Results and Discussion

Following intravenous administration of moxifloxacin at the dose rate of 5 mg.kg^{-1} body weight in calves, the plasma concentration of moxifloxacin was observed 11.70 ± 0.21 at 0.04 h and it was found higher than reported in buffalo calves 9.63 ± 0.21 µg.ml^{-1} [12].

Evaluation of the plasma moxifloxacin concentration time data after intravenous administration and its semi-logarithmic plot (Fig.1) revealed that the data could be best fitted to a two compartment open model.

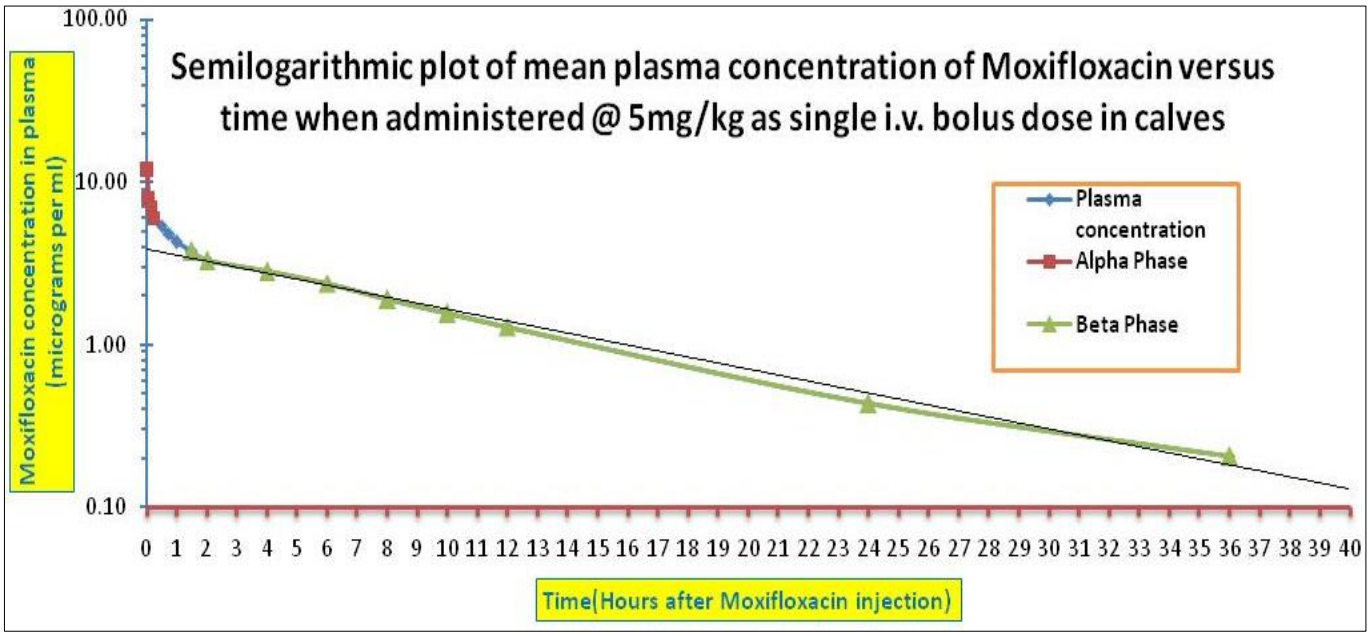

Fig 1: Semilogarithmic plot of mean plasma concentration of moxifloxacin versus time

Pharmacokinetics of moxifloxacin has been described by two compartment open model in buffalo calves, lactating goats, lactating ewes and sheep while by three compartment open model in camel [1, 5, 6, 8, 12].

The mean (±*SE*) pharmacokinetic parameters are presented in Table 1.

Table 1: Pharmacokinetic determinants of moxifloxacin in calves following a single intravenous dose of 5 mg.kg^{-1} body weight employing compartmental analysis.

Parameter	Unit	Animal Number					Mean ± S.E.
		A	B	C	D	E	
A	µg.ml^{-1}	8.3004	8.6579	8.0159	8.5136	6.3116	7.95 ± 0.42
α	h^{-1}	5.6751	5.0754	6.0398	5.5360	4.6408	5.39 ± 0.24
$t_{½\alpha}$	h	0.1221	0.1365	0.1147	0.1252	0.1493	0.12 ± 0.00
B	µg.ml^{-1}	4.0054	3.1648	4.1020	3.6341	4.3276	3.84 ± 0.20
β	h^{-1}	0.0891	0.0804	0.0838	0.0829	0.0887	0.08 ± 0.00
$t_{½\beta}$	h	7.7778	8.6194	8.2697	8.3595	7.8129	8.16 ± 0.16
CP^0	µg.ml^{-1}	12.3058	11.8227	12.1179	12.1477	10.6392	11.80 ± 0.30
AUC	µg.ml^{-1}.h	46.4166	41.0691	50.2771	45.3750	50.1492	46.65 ± 1.70
AUMC	µg.ml^{-1}.h^2	504.7918	489.9280	584.3472	529.0734	550.3401	531.69 ±16.72
MRT	h	10.8752	11.9294	11.6225	11.6600	10.9741	11.41 ± 0.20
K_{el}	h^{-1}	0.2651	0.2879	0.2410	0.2737	0.2122	0.25 ± 0.01
K_{12}	h^{-1}	3.5919	3.4504	3.7826	3.6682	2.5770	3.41 ± 0.21
K_{21}	h^{-1}	1.9073	1.4175	2.1000	1.6770	1.9403	1.80 ± 0.11
K_{12}/K_{21}	Ratio	1.8832	2.4341	1.8012	2.1873	1.3281	1.92 ± 0.18
V_c	L.kg^{-1}	0.4063	0.4229	0.4126	0.4027	0.4700	0.42 ± 0.01
Vd_{area}	L.kg^{-1}	1.2090	1.5143	1.1867	1.3292	1.1240	1.27 ± 0.06
Vd_B	L.kg^{-1}	1.2483	1.5799	1.2189	1.3759	1.1554	1.31 ± 0.07
Vd_{ss}	L.kg^{-1}	1.1715	1.4523	1.1558	1.2832	1.0942	1.23 ± 0.06
Cl_B	L.kg^{-1}.h^{-1}	0.1078	0.1218	0.0994	0.1102	0.0997	0.10 ± 0.00
f_C	Ratio	0.3361	0.2793	0.3477	0.3029	0.4180	0.33 ± 0.02
T/P	Ratio	1.9753	2.5804	1.8760	2.3014	1.3923	2.02 ± 0.20

The distribution half-life ($t_{1/2\alpha}$) was found to be 0.12 ± 0.00 h after intravenous administration. Comparable value of $t_{1/2\alpha}$ (0.10 ± 0.00 h) has been reported in buffalo calves [12]. Longer $t_{1/2\alpha}$ values of moxifloxacin have been observed in goats, lactating ewes, camels and muscovy ducks with corresponding values of 0.74 ± 0.04 h, 0.22 ± 0.02 h, 0.25 ± 0.03 h and 0.22 ± 0.10 h, respectively [1, 8, 9, 11].

The elimination half-life ($t_{1/2\beta}$) of moxifloxacin in calves was found to be 8.16 ± 0.16 h. However, shorter $t_{1/2\beta}$ values of moxifloxacin have been observed in buffalo calves, goats, lactating ewes, camel and muscovy ducks with corresponding values of 2.69 ± 0.14 h, 4.12 ± 0.30 h, 1.77 ± 0.23 h, 1.87 ± 0.16 h, and 2.49 ± 0.26 h, respectively [1, 8, 9, 11, 12].

The average value of AUC after intravenous administration of moxifloxacin in calves was 46.65 ± 1.70 $\mu g.ml^{-1}.h$ which is higher than reported in lactating goats, lactating ewes, sheep and muscovy ducks with the corresponding values of 11.71 ± 0.67 $\mu g.ml^{-1}.h$, 14.74 ± 2.16 $\mu g.ml^{-1}.h$, 11.25 ± 0.18 $\mu g.ml^{-1}.h$ and 16.74 ± 2.16 $\mu g.ml^{-1}.h$, respectively [6, 8, 9, 10]. The value of area under moment curve (AUMC) after intravenous administration of moxifloxacin in calves was found to be 531.69 ± 16.72 $\mu g.ml^{-1}.h^2$. Lower AUMC values have been reported in lactating goats, goats, lactating ewes, sheep and camel with corresponding values of 21.19 ± 1.93 $\mu g.ml^{-1}.h^2$, 24.92 ± 2.13 $\mu g.ml^{-1}.h^2$, 33.39 ± 4.36 $\mu g.ml^{-1}.h^2$, 31.68 ± 1.55 $\mu g.ml^{-1}.h^2$ and 79.04 ± 39.15 $\mu g.ml^{-1}.h^2$, respectively [1, 6, 8, 10, 11].

The MRT calculated following single dose intravenous administration of moxifloxacin was 11.41 ± 0.20 h. The lower values of MRT 1.81 ± 0.15 h in lactating goats, 7.02 ± 0.48 h in goats, 2.36 ± 0.25 h in lactating ewes, 5.87 ± 0.32 h in sheep, 5.77 ± 1.83 h in camels and 3.45 ± 0.52 h in muscovy ducks were reported [1, 6, 8, 9, 11, 13].

The Vd_{area} in calves was found to be 1.27 ± 0.06 $L.kg^{-1}$ which is comparable with the values of Vd_{area} of 1.43 ± 0.08 $L.kg^{-1}$ reported in buffalo calves and 1.44 ± 0.30 $L.kg^{-1}$ in lactating goats [6, 12]. However, higher values of Vd_{area} 3.49 ± 0.32 $L.kg^{-1}$ in goats and 2.51 ± 0.17 $L.kg^{-1}$ in sheep have been reported [10, 11].

After intravenous administration of moxifloxacin in calves, the total body clearance Cl_B was calculated to be 0.10 ± 0.00 $L.kg^{-1}.h^{-1}$. Higher clearance of the drug have been reported in buffalo calves 0.37 ± 0.01 $L.kg^{-1}.h^{-1}$, lactating goats 0.43 ± 0.02 $L.kg^{-1}.h^{-1}$, goats 0.59 ± 0.03 $L.kg^{-1}.h^{-1}$, lactating ewes 0.34 ± 0.04 $L.kg^{-1}.h^{-1}$, sheep 0.60 ± 0.02 $L.kg^{-1}.h^{-1}$, camels 0.34 ± 0.02 $L.kg^{-1}.h^{-1}$ and muscovy ducks 0.32 ± 0.11 $L.kg^{-1}.h^{-1}$ [1, 6 , 8, 9, 11, 12, 13].

Conclusion

The present study was planned to conduct disposition kinetics of moxifloxacin in calves following a single intravenous administration at the dose rate of 5 $mg.kg^{-1}$ body weight. After intravenous administration of moxifloxacin, the drug could be detected in plasma (11.70 ± 0.21 $\mu g.ml^{-1}$) with in 0.04 h and rapidly declined to 6.02 ± 0.11 $\mu g.ml^{-1}$ at 0.25 h. The plasma levels above the minimum inhibitory concentration (MIC) level of ≥ 0.25 $\mu g.ml^{-1}$ were maintained up to 24 h following intravenous administration of moxifloxacin. So, as per general recommendation that AUC/MIC and C_{max}/MIC should be >125 and >10, respectively to ensure an optimal bactericidal effect, a twenty four hour dosing interval at the dose of 5 $mg.kg^{-1}$ by intravenous in calves is suggested.

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