# PHARMACOKINETICS OF MOXIFLOXACIN AFTER SINGLE INTRAVENOUS ADMINISTRATION IN COW CALVES

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### ABSTRACT

Moxifloxacin is a novel fourth generation fluoroquinolone that has been extensively used for the treatment of bacterial infections in human beings and now increasing demands and use in veterinary medicine due to broad-spectrum activity. The present study was conducted to observe the pharmacokinetics of moxifloxacin after single intravenous administration in cow calves to decide the therapeutic window. Blood samples were collected at different pre-determined time intervals and plasma from these blood samples were separated. The concentrations of moxifloxacin in these plasma samples were estimated by microbiological assay technique. Following single intravenous administration of moxifloxacin in healthy cow calves, the drug was rapidly absorbed from i.v. injection site. The peak plasma level  $(4.01 \pm 0.10 \ \mu g.ml^{-1})$  was attained at 45 min and the drug was detected in plasma upto 12 h. The absorption half-life  $(t_{1/2ka})$ , AUC<sub>0---</sub>, Vd<sub>area</sub>,  $t_{1/2\beta}$  and Cl<sub>B</sub> were  $0.470 \pm 0.017$  h,  $11.27 \pm 0.200 \ \mu g.ml^{-1}$ , h,  $1.53 \pm 0.021$  L.kg<sup>-1</sup>,  $2.38 \pm 0.025$  h and  $0.444 \pm 0.008$  L.kg<sup>-1</sup>.h<sup>-1</sup>, respectively. The values of elimination half-life and AUC<sub>0---</sub> were significantly lower and the values of volume of distribution, total body clearance and mean residence time were significantly higher after i.v. administration of moxifloxacin in healthy cow calves. The systemic bioavailability of moxifloxacin after i.v. injection was  $88.14 \pm 2.72$  per cent. The most suitable dosage regimen of moxifloxacin calculated on the basis of pharmacokinetic data was 7.82 followed by  $7.06 \ mg.kg^{-1}$  b.wt. to be repeated at 8 h interval. The favourable pharmacokinetic behaviour viz. high values of volume of distribution, half-life, MRT and systemic bioavailability indicates that moxifloxacin at the dose of 5 mg.kg<sup>-1</sup> b.wt. can be administered by i.v. route in cow calves.

Moxifloxacin is a novel fourth generation fluoroquinolone that has been extensively used for the treatment of bacterial infections in human beings and now in increasing demands and use in veterinary medicine. This drug kills bacteria by inhibiting DNA synthesis. It has a broad spectrum of antibacterial activity against grampositive, gram-negative, anaerobic bacteria and atypical organisms such as Mycoplasma and Chlamydia spp. It also had good to moderate activity against Bacillus spp., Corynebacterium spp., Enterococcus faecalis and methicillin-resistant Staphylococci. It has significant activity against some non-fermentative gram-negative bacilli including Acinetobacter spp., Flavobacterium spp., Pseudomonas spp. and Stenotrophomonas maltophilia (Rolston et al., 2003). Moxifloxacin is useful for the treatment of respiratory tract infections, intra-abdominal infections, endocarditis, meningitis, cellulitis, anthrax and tuberculosis (Ball, 2000; Blondeau and Hansen, 2001 and Goudah and Hasabelnaby, 2010). In the present study, we have taken account to explore pharmacokinetics of moxifloxacin in cow calves following single intravenous administration to decide therapeutic window.

## MATERIALS AND METHODS

The study was conducted in the Department of Veterinary Pharmacology and Toxicology, College of

Veterinary Science and Animal Husbandry Mhow, Nanaji Deshmukh Veterinary Science University, Jabalpur (M.P.). The experiments were conducted in the 5 healthy male cow calves (Gir breed, aged 6 month to 1 year) at an interval of 20 days between two sets of experiments. Before repeating the drug in the same animals, the blood samples were collected to ensure that there were no traces of drug. The experimental schedule is shown in the Table 1.

**Collection, processing and storage of samples:** Ethical permission to conduct experiment was approved by university ethical committee (order no. 432/2013/vety/ mhow). All the experimental animals were kept in the department animal shed ensuring an ideal condition with *ad lib* water and food as per standard requirement of ration. Health status was checked to ensure normal physiology of the animals with a 3 days period of accommodation. Weight of each animal was recorded before administration of moxifloxacin. After administration of the drug, blood samples (5 ml) were collected from contralateral jugular

## Table 1

Experimental schedule to study the pharmacokinetics of moxifloxacin following single intravenous administration in healthy cow calves

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Animal No.	Drug	Dose	Route	Study conducted
$\frac{\text{Cow calves:}}{\text{C}_1\text{-}\text{C}_5}$	Moxifl- oxacin	5 mg.kg <sup>-1</sup>	iv	Plasma levels, Pharmacokinetics and Dosage regimen

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vein with the help of i.v catheter (Kethin,  $20 \times 0.9 \times 25$  mm) into heparinized test tubes at different time intervals *viz.*, before (0 min.) and at 1, 2.5, 5, 7.5, 10, 15, 30, 45 min and 1,1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 h after administration of the moxifloxacin in cow calves. Plasma from the samples was separated by centrifugation at 3000 rpm for 15 min and stored at -20 °C untill analysis, which was usually done on the next day after collection of samples. The extracted plasma from each sample was suitably diluted with distilled water before final estimation of moxifloxacin.

# Estimation of concentration of moxifloxacinin plasma samples

Assay procedure: "Punch Bioassay Technique", which was the modified method of Standard Cylinder Plate Bioassay Technique (Arret *et al.*, 1971), was used to estimate the concentration of moxifloxacin in plasma. In this technique, only a seed layer with bacterial suspension (*E. coli*, MTCC 739) is poured on assay plates and the wells were prepared on assay plates after punching the media (Antibiotic no-1 and 11), instead of putting the steel cylinders. The following are the details of estimation of moxifloxacin by Punch Bioassay Technique:

**Preparation of standard curve of moxifloxacin:** Standard curve of moxifloxacin in distilled water was prepared by adding different known concentrations of drug, viz., 0.0625, 0.125, 0.25, 0.50, 1 and  $2\mu$ g.ml<sup>-1</sup>. These standard samples were processed for drug analysis as follows:

- 1. Assay plates were prepared after pouring seed layer (25 ml) and six wells (100 ml capacity) were punched by punching machine.
- 2. The punched wells on the assay plates were filled with different known concentrations of moxifloxacin. Three plates were used for each concentration.
- 3. These assay plates were incubated at 32 °C for a period of 6 hours.
- 4. At the end of incubation period, the diameters of zone of inhibition for standard drug concentrations were recorded.
- 5. The values of diameters of zone of inhibition were corrected for each concentration. The standard curve of moxifloxacin is presented in Fig. 1.

**Estimation of moxifloxacin in plasma:** The stored samples were thawed at room temperature and then they were diluted with distilled water so that the zone of inhibition of sample came near to that of reference concentration of moxifloxacin. All the samples were processed in a similar



Fig. 1. Standard curve of moxifloxacin in distilled water, Each point represents mean of standard drug

way as mentioned for preparation of standard curve. Three alternate wells of assay plate were filled with reference concentration of drug i.e.  $0.50 \ \mu g.ml^{-1}$  for moxifloxacin and the remaining three wells were filled with diluted sample. At the end of incubation, the zones of inhibition of reference concentrations as well as samples were measured. The values of replicates of each sample were corrected with zone of standard concentrations and the concentration of moxifloxacin was calculated as  $\mu g.ml^{-1}$  of plasma (Table 2).

**Pharmacokinetic analysis:** The various pharmacokinetic parameters were calculated from plasma moxifloxacin concentration - time profile after its single dose (5 mg.kg<sup>-1</sup> b.wt.) intravenous administration in cow calves by software "PK Solution" (version 2.0). "PK Solutions 2.0" relies on the use of non-compartmental method of analysis for the estimation of pharmacokinetic parameters.

**Statistical analysis:** The statistical analysis was done by ttest for pharmacokinetic study and least square difference test for safety profile study by using SPSS software.

# **RESULTS AND DISCUSSION**

The low value of distribution half-life of moxifloxacin  $(0.160 \pm 0.005 \text{ h})$  indicated the rapid distribution of drug from central to peripheral compartment in healthy cow calves (Table 3). The value of  $t_{1/2\alpha}$  obtained in the present study was close to the value of 0.10 h in buffalo calves (Pathania and Sharma, 2010), and 0.12 h in rabbits (Fernandez-varon et al., 2005). However, the present result is in contrast to the comparatively high value of  $t_{1/2\alpha}$ , 0.25 h in camel (Abd El-Aty et al., 2007), 0.26 h in chickens (Goudah, 2009), 0.36 h in goats (Fernandezvaron et al., 2006), 3.91 h in sheep (Modi et al., 2012b) and 3.55 h in sheep (Sadariya et al., 2014). The volume of distribution (Vd) refers to fluid volume that would be required to contain all the drug in the body at the same concentration as in the blood or plasma (Benet et al., 1996). In the present study, the value of  $Vd_{area}$  (1.35±0.028)

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Time after moxifloxacin						
administration (ii)		Mean ± SE				
	1	2	3	4	5	
0.017	11.10	11.30	12.30	11.80	11.70	$11.60 \pm 0.21$
0.042	8.40	8.83	9.50	9.20	9.10	$9.01 \pm 0.19$
0.083	8.00	8.45	8.65	8.60	8.50	$8.44 \pm 0.12$
0.125	7.00	7.50	7.70	7.60	7.45	$7.45\pm0.12$
0.167	5.70	6.00	6.30	6.20	6.10	$6.06 \pm 0.10$
0.25	4.10	4.35	5.00	4.78	4.55	$4.56 \pm 0.16$
0.50	3.30	3.48	3.70	3.67	3.50	$3.53\pm0.07$
0.75	2.90	3.02	3.06	3.04	3.03	$3.01\pm0.03$
1	2.40	2.50	2.68	2.53	2.51	$2.52\pm0.05$
1.5	1.98	2.02	2.15	2.10	2.10	$2.07\pm0.03$
2	1.76	1.84	2.00	1.88	1.85	$1.87 \pm 0.04$
3	1.44	1.62	1.74	1.71	1.70	$1.64 \pm 0.05$
4	1.18	1.17	1.27	1.23	1.18	$1.20 \pm 0.02$
6	0.44	0.45	0.56	0.50	0.47	$0.48\pm0.02$
8	0.33	0.34	0.39	0.37	0.35	$0.36 \pm 0.01$
10	0.20	0.21	0.23	0.22	0.21	$0.21\pm0.005$
12	0.12	0.12	0.13	0.13	0.12	$0.12 \pm 0.005$
16	BDL	BDL	BDL	BDL	BDL	BDL
24	BDL	BDL	BDL	BDL	BDL	BDL

 Table 2

 Plasma levels of moxifloxacin in healthy cow calves following a single intravenous administration of 5 mg.kg<sup>-1</sup> body weight

**BDL-Below Detection Limit** 

Table 3

Parameter	Unit		Mean ± SE				
		1	2	3	4	5	
A	mg.ml <sup>-1</sup>	6.14	6.52	7.62	7.08	6.81	$6.83 \pm 0.251$
a	$h^{-1}$	4.07	4.13	4.93	4.31	4.39	$4.37 \!\pm\! 0.153$
t <sub>½α</sub>	h	0.170	0.168	0.141	0.161	0.158	$0.160 \pm 0.005$
K <sub>12</sub>	$h^{-1}$	2.08	2.12	2.69	2.27	2.28	$2.29 \pm 0.108$
K <sub>21</sub>	$h^{-1}$	1.54	1.56	1.74	1.56	1.63	$1.61 \pm 0.036$
$K_{12}/K_{21}$	ratio	1.35	1.36	1.55	1.45	1.40	$1.42 \!\pm\! 0.037$
AUC <sub>0-∞</sub>	g.ml <sup>-1</sup> .h	12.5	13.1	14.2	13.7	13.3	$13.36 \pm 0.286$
AUMC	$mg.ml^{-1}.h^2$	36.4	37.8	42.1	40.2	38.6	$39.02 \pm 0.985$
Vd <sub>area</sub>	L.kg <sup>-1</sup>	1.45	1.37	1.28	1.33	1.34	$1.35 \!\pm\! 0.028$
$Vd_{ss}$	L.kg <sup>-1</sup>	1.17	1.11	1.04	1.07	1.08	$1.09 \pm 0.022$
$f_c$	Ratio	0.378	0.377	0.354	0.363	0.370	$0.368 \pm 0.005$
T/P	Ratio	1.65	1.65	1.82	1.75	1.70	$1.71 \pm 0.032$
AUC/MIC	Ratio	25	26.2	28.4	27.4	26.6	$26.72 \!\pm\! 0.571$

L.kg<sup>-1</sup>) in cow calves indicated good distribution of drug into various body fluids and tissues (Table 3). In agreement to the present finding, similar value of Vd<sub>area</sub> has been reported in buffalo calves (1.43 L.kg<sup>-1</sup>) after single i.v. administration of moxifloxacin (Pathania and Sharma, 2010). However, the present result is in contrast to the high value of Vd<sub>area</sub>, 2.12 L.kg<sup>-1</sup> in rabbits (Fernandez-varon *et* 

*al.*, 2005), 2.51 L.kg<sup>-1</sup> in sheep (Modi *et al.*, 2012b), 3.49 L.kg<sup>-1</sup> in goat (Patel *et al.*, 2011), 4.88 L.kg<sup>-1</sup> in sheep (Sadariya *et al.*, 2014) and 5.44 L.kg<sup>-1</sup> in sheep (Modi *et al.*, 2012a).

The volume of distribution at steady state  $(Vd_{ss})$  is the constant that expresses the amount of the drug in the body at steady state. Moxifloxacin exhibited a relatively

 Table 4

 Elimination kinetics of moxifloxacin in healthy cow calves following single intravenous administration.

Parameter	Unit		Animal number					
		1	2	3	4	5		
C <sup>o</sup>	mg.ml <sup>-1</sup>	9.20	9.75	11.13	10.41	10.13	$10.12 \pm 0.323$	
В	mg.ml <sup>-1</sup>	3.06	3.23	3.51	3.33	3.32	$3.29 \!\pm\! 0.072$	
b	$\mathbf{h}^{-1}$	0.276	0.279	0.276	0.274	0.280	$0.277 \!\pm\! 0.001$	
$t_{\nu_{2\beta}}$	h	2.51	2.49	2.52	2.53	2.47	$2.50 \pm 0.011$	
K <sub>el</sub>	$\mathbf{h}^{-1}$	0.730	0.741	0.780	0.755	0.756	$0.752 \pm 0.008$	
t <sub>1/2Kel</sub>	h	0.949	0.935	0.888	0.918	0.917	$0.921 \pm 0.010$	
Cl <sub>B</sub>	$L.kg^{-1}.h^{-1}$	0.401	0.383	0.351	0.365	0.375	$0.375 \pm 0.008$	
V <sub>c</sub>	$L.kg^{-1}$	0.543	0.513	0.449	0.480	0.493	$0.496 \!\pm\! 0.016$	
MRT	h	2.9	2.9	3.0	2.9	2.9	$2.92\pm0.02$	

#### Table 5

Intravenous priming (D) and maintenance (D/) doses of moxifloxacin in healthy cow calves at various dosage intervals for microorganisms of different susceptibility

Microorganisms susceptibility (MIC) <sup>a</sup>	Dosage regimen of moxifloxacin (mg.kg <sup>-1</sup> )						
	Dose	Dosage interval (h)					
		6	8	10	12		
0.0625	D	0.45	0.78	1.35	2.35		
	D/	0.36	0.69	1.26	2.27		
0.125	D	0.89	1.55	2.70	4.70		
	D/	0.72	1.38	2.53	4.53		
0.25	D	1.79	3.11	5.41	9.40		
	D/	1.45	2.77	5.06	9.06		
0.50	D	3.57	6.21	10.81	18.81		
	D/	2.89	5.53	10.13	18.13		
1.0	D	7.14	12.42	21.62	37.62		
	D/	5.78	11.07	20.26	36.26		
2.0	D	14.27	24.84	43.23	75.24		
	$\mathbf{D}/$	11.56	22.13	40.52	72.53		

<sup>a</sup> Values given are expressed as  $\mu$ g.ml<sup>-1</sup>

high Vd<sub>ss</sub> as 1.09±0.022 L.kg<sup>-1</sup> in cow calves which shows that there is a relatively quick and wide distribution of moxifloxacin after intravenous administration. This value is consistent with that reported by Goudah and Hasabelnaby (2010) in ducks (1.02 L.kg<sup>-1</sup>), Goudah (2009) in chickens (1.04 L.kg<sup>-1</sup>) and Modi *et al.* (2012b) in sheep (1.25 L.kg<sup>-1</sup>). This estimated value of Vd<sub>ss</sub> in the present study was higher than that recorded in lactating goats (0.79L.kg<sup>-1</sup>) by Fernandez-varon *et al.* (2006) but lower than that reported in buffalo calves (1.58L.kg<sup>-1</sup>) by Pathania and Sharma (2010), in camel (1.78 L.kg<sup>-1</sup>) by Abd El-Aty *et al.* (2007), in sheep (3.49 L.kg<sup>-1</sup>) by Sadariya *et al.* (2014), in goat (5.00 L.kg<sup>-1</sup>) by Patel *et al.* (2011) and in rabbits (1.95 L.kg<sup>-1</sup>) by Fernandez-varon *et al.* (2005). The volume of distribution at steady state Vd<sub>ss</sub> suggested a wide penetration through biological membrane and good tissue distribution. Further, the T/P ratio of  $1.71 \pm 0.032$  observed in the present study, reflected high concentration of moxifloxacin in body fluids and tissues as compared to that in plasma of cow calves (Table 3).

One of the most fundamental parameters of pharmacokinetics is area under plasma concentration-time curve (AUC), which is proportionate to the systemic exposure to a drug. In the present study, mean value of AUC was  $13.36 \pm 0.286 \,\mu\text{g.ml}^{-1}$ .h after intravenous administration of moxifloxacin (Table 3). In accordance to the present findings, almost similar value of AUC following single i.v. injection has been reported for moxifloxacin as  $12.9 \,\mu\text{g.ml}^{-1}$ .h

in buffalo calves (Pathania and Sharma, 2010), 11.25  $\mu$ g.ml<sup>-1</sup>.h in sheep (Modi *et al.*, 2012b), 14.72  $\mu$ g.ml<sup>-1</sup>.h in camel (Abd El-Aty *et al.*, 2007) and 14.74  $\mu$ g.ml<sup>-1</sup>.h in ewes (Goudah, 2008). In contrast to present findings, low value of AUC was reported for moxifloxacin in rabbits (6.28  $\mu$ g.ml<sup>-1</sup>.h) by Fernandez-varon *et al.* (2005), sheep (8.38  $\mu$ g.ml<sup>-1</sup>.h) by Sadariya *et al.* (2014) and goats (8.65  $\mu$ g.ml<sup>-1</sup>.h) by Patel *et al.* (2011). However, higher values of AUC (24.18  $\mu$ g.ml<sup>-1</sup>.h) has been reported in sheep (Modi *et al.*, 2012a). The difference in the values of AUC may be due to species variation and difference in formulation.

Half-life provides a good indicator of time required to reach steady state after a dosage regimen has been initiated. The elimination half-life of moxifloxacin in cow calves in the present study was to  $2.50 \pm 0.011$  h (Table 4). In accordance to the present findings, almost similar values of t<sub>1/28</sub>, 2.69 h in buffalo calves (Pathania and Sharma, 2010), 2.49 h in ducks (Goudah and Hasabelnaby, 2010), 2.27 h in chickens (Goudah, 2009), 2.15 h in rabbits (Carceles et al., 2006) were observed after single i.v. administration of moxifloxacin. In contrast, moxifloxacin was rapidly eliminated in rabbits, camels and goats. The value of  $t_{1/2\beta}$  has been reported as 1.84 h in rabbits (Fernandez-varon et al., 2005), 1.87 h in camels (Abd El-Aty et al., 2007) and 1.94 h in goats (Fernandez-varon et al., 2006). However, the value of elimination half-life of moxifloxacin in cow calves in present study is shorter than the value reported as 3.91 h in sheep (Modi et al., 2012b), 4.12 h in goats (Patel et al., 2011), 5.70 h in sheep (Sadariya et al., 2014) and 12.13 h in sheep (Modi et al., 2012a). The elimination rate constant of moxifloxacin from central compartment (K<sub>el</sub>) was  $0.752 \pm 0.008$  h<sup>-1</sup> in the present study (Table 4). However, comparatively lower value of  $K_{a1}$  0.39 h<sup>-1</sup> in ewes (Goudah, 2008), 0.37 h<sup>-1</sup> in camel (Abd El-Aty et al., 2007), 0.32 h<sup>-1</sup> in chickens (Goudah, 2009) and 0.28 h<sup>-1</sup> in ducks (Goudah and Hasabelnaby, 2010) was observed.

Total body clearance  $(Cl_B)$  is an important pharmacokinetic parameter that represents the sum of metabolic and excretory processes. Fluoroquinolones are eliminated primarily by the kidney, with the renal clearance exceeding creatinine clearance by 60% (Martinez *et al.*, 2006), suggesting the involvement of both glomerular filteration and tubular secretion (Okazaki *et al.*, 1991). The total body clearance of moxifloxacin in healthy cow calves following single intravenous dose was  $0.375 \pm 0.008 \text{ L.kg}^{-1}.\text{h}^{-1}$  (Table 4), which was comparable to the values reported by Pathania and Sharma (2010) in buffalo calves ( $0.371 \text{ L.kg}^{-1}.\text{h}^{-1}$ ), Goudah (2009) in chickes ( $0.36 \text{ L.kg}^{-1}.\text{h}^{-1}$ ), Goudah, (2008) in ewes ( $0.34 \text{ L.kg}^{-1}.\text{h}^{-1}$ ), Abd El-Aty *et al.* (2007) in camels ( $0.34 \text{ L.kg}^{-1}.\text{h}^{-1}$ ), Goudah and Hasabelnaby (2010) in ducks ( $0.32 \text{ L.kg}^{-1}.\text{h}^{-1}$ ), Modi *et al.* (2012a) in sheep ( $0.308 \text{ L.kg}^{-1}.\text{h}^{-1}$ ) and Fernandez-varon *et al.* (2006) in goats ( $0.43 \text{ L.kg}^{-1}.\text{h}^{-1}$ ) but lower than the values reported by Patel *et al.* (2011) in goats ( $0.59 \text{ L.kg}^{-1}.\text{h}^{-1}$ ), Sadariya *et al.* (2014) in sheep ( $0.60 \text{ L.kg}^{-1}.\text{h}^{-1}$ ) and Fernandez-varon *et al.* (2006) in rabbits ( $0.78 \text{ L.kg}^{-1}.\text{h}^{-1}$ ) and Fernandez-varon *et al.* (2005) in rabbits ( $0.80 \text{ L.kg}^{-1}.\text{h}^{-1}$ )

The time required for an intact drug molecule to transit through body is termed as mean residence time (MRT). Thus MRT becomes an excellent parameter to describe the length of drug persistence in the body, as much as half-life used in the pharmacokinetic models. The value of MRT of moxifloxacin in cow calves  $(2.92 \pm 0.02 \text{ h})$ (Table 4) was almost similar to the value reported as 2.81 h in sheep (Modi et al., 2012a), 2.61 h in rabbits (Carceles et al., 2006), 2.44 h in rabbits (Fernandez-varon et al., 2005), 2.36 h in ewes (Goudah, 2008) but longer than the MRT value of 1.81 h reported in goats (Fernandez-varon et al., 2006). The higher value of MRT for moxifloxacin have been observed as 3.45 h in ducks (Goudah and Hasabelnaby, 2010), 5.77 h in camel (Abd El-Aty et al., 2007), 5.87 h in sheep (Sadariya et al., 2014) and 7.02 h in goats (Patel et al., 2011). Lower value of MRT in the present study indicates that moxifloxacin remains for quite shorter span of time in the body of cow calves due to comparatively faster elimination of the drug.

# CONCLUSION

Moxifloxacin shows favourable pharmacokinetic behaviour viz. high values of volume of distribution, T/P ratio, elimination half-life and MRT following intravenous administration at the dose of 5 mg.kg<sup>-1</sup> b.wt. The systemic bioavailability of moxifloxacin following intravenous administration was high which suggests that moxifloxacin could be administered by i.v. route in cow calves. The priming and maintenance doses of moxifloxacin to be administered by i.v. routes to maintain the MIC of 0.50  $\mu$ g.ml<sup>-1</sup> in cow calves would be 6.21 mg.kg<sup>-1</sup> b.wt. followed by 5.53 mg.kg<sup>-1</sup> b.wt. at 8 h interval (Table 5). Further other routes of administration in cow calves and other species of animals are needed to check the therapeutic efficacy of moxifloxacin.

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