Available online at www.ijpcr.com
International Journal of Pharmaceutical and Clinical Research 2012; 4(3), 24-30

ISSN 0975 1556

Research Article

Pharmacokinetic and Dosage Regimen of Gatifloxacin in Crossbred Cow Calves After Single Intravenous Administration

[1]Sunil Kumar Shakya, *[2]Nitesh Kumar

[1]Madhya Pradesh Pashu Chikitsa Vigyan Vishwavidyalaya, Jabalpur-482001, M.P., India
[2]Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science & Animal Husbandry, Mhow-453446

ABSTRACT

Pharmacokinetics of gatifloxacin (Gatiquin® - Cipla Ltd. Ahmedabad., India) in six cross bred cow calves following intravenous (IV) administration (4 mg/kg body weight). Estimation of gatifloxacin in plasma samples was analyzed by microbiological assay technique by using E. coli as test organism. Kinetic parameters of gatifloxacin were calculated by using two-compartment open model. Therapeutic concentration of gatifloxacin (0.2 µg/ml) was maintained up to 16 h and the drug was detectable up to 24 h. Distribution half life ($t_{1/2}$ α), elimination half life ($t_{1/2}$ β), mean residential time (MRT), Volume of distribution during area under curve (Vd_{area}) and total body clearance (Cl_B) of 0.125 ± 0.01 h, 13.17 ± 0.16 h, 18.54 ± 0.26 h, 1.81 ± 0.02 L/kg and 0.076 ± 0.01 L/kg/h, respectively were obtained for gatifloxacin. For maintaining therapeutic concentration of 0.2 µg/mL, a loading dose (D*) of around 0.8 mg/kg and maintenance dose (D_0) of 0.4 mg/kg may be used at the dosage interval (τ) of 16 h for treating systemic infections.

Key word: Pharmacokinetic, Gatifloxacin, Dosage regimen and Crossbred cow calves.

INTRODUCTION

Fluoroquinolones are the most potent group of antimicrobials being used in the field of medical and veterinary practices, for treating infections caused by both gram positive and gram-negative micro-organisms [1] and also inhibit certain intracellular micro-organisms [2]. The fluoroquinolones are a class of compounds that comprise a large and expanding group of synthetic antimicrobial agents. Structurally, all fluoroquinolones contain a fluorine molecule at the 6-position of the basic quinolone nucleus. Despite the basic similarity in the core structure of these molecules, their physicochemical properties, pharmacokinetic characteristics and microbial activities can vary markedly across compounds [3]. Gatifloxacin, a recently introduced fluoroquinolones, possesses good activity against a wide range of gram-positive and gram-negative pathogens, atypical organisms and some anaerobes [4]. It is commonly indicated for the treatment of acute bacterial sinusitis, chronic bronchitis, pneumonia, urinary tract infections, acute pyelonephritis and gonorrhoea [5]. Fluoroquinolone resistance relates directly to human and veterinary usage and emerging bacterial resistance poses the single greatest threat to the future survival of fluoroquinolone drugs as an antibiotic class [6]. Pharmacokinetic studies of gatifloxacin in healthy cross bred cow calves was carried out to obtain the detailed pharmacokinetic data and so as to derive appropriate dosage regimen of gatifloxacin to treat various systemic infections.

MATERIALS AND METHODS

Experimental animals and drug administration: Six healthy male calves of cross bred cow, ranging between 1-1.5 years of age and 60-140 kg body weight were used for the study. The animals were maintained on seasonal green fodder, wheat straw and water *ad libitum.* The average day temperature in the shed was about 25^0C during the experimental period. The experimental protocol followed the ethical guidelines on the proper care and use of animals. Gatiquin (0.5% gatifloxacin) - Cipla Ltd. Ahmedabad., India was administered intravenous at the dose rate of 4 $mg.kg^{-1}$ body weight into the jugular vein.

Collection of samples: Blood samples (2 mL approx) were withdrawn from the jugular vein into heparinized glass centrifuge tubes before and at 0.042, 0.083, 0.167, 0.25, 0.333, 0.50, 0.75, 1, 2, 4, 6, 8, 12, 16 and 24 h after administration of the drug. Plasma was separated by centrifugation at 2000 g for 10 min at room temperature and kept at - 20 ^{0}C until analysis, which was usually done on the next day after collection.

Estimation of drug: The concentration of gatifloxacin in plasma was determined by microbiological assay technique [7] using *E.coli* (ATCC 25922) as the test organism. This method estimated the level of drug and its active metabolites with antibacterial activity. The assay could detect a minimum of 0.1 $µg.mL^{-1}$ of gatifloxacin. For each sample, 9 replicates were analyzed and compared with the zone of inhibition of the reference solution of gatifloxacin (0.2 $µg.mL^{-1}$) the level of gatifloxacin in the samples was calculated as $µg.mL^{-1}$ of plasma.

Author for correspondence: E-mail – niteshprof@gmail.com

Table 1: Plasma concentrations (μg/ml) of gatifloxacin after single dose intravenous administration (4 mg/kg) in crossbred cow calves

Time (h)	Plasma concentration (μg/ml)						
	Crossbred cow calves number						Mean ± S.E
	C1	C2	C3	C4	C5	C6	
0.042	4.55	4.76	4.66	4.69	4.60	4.62	4.64 ± 0.03
0.083	4.35	4.41	4.38	4.40	4.38	4.39	4.38 ± 0.01
0.167	3.83	3.96	3.90	3.91	3.86	3.88	3.89 ± 0.02
0.25	3.62	3.72	3.68	3.70	3.64	3.66	3.67 ± 0.02
0.333	3.51	3.60	3.55	3.58	3.54	3.54	3.55 ± 0.01
0.50	2.75	2.81	2.78	2.79	2.76	2.78	2.78 ± 0.01
0.75	2.09	2.15	2.10	2.12	2.11	2.14	2.12 ± 0.01
1	2.00	2.02	2.01	2.00	2.05	2.03	2.02 ± 0.01
2	1.86	1.96	1.90	1.98	1.88	1.91	1.91 ± 0.02
4	1.76	1.85	1.78	1.80	1.78	1.81	1.80 ± 0.01
6	1.48	1.53	1.5	1.52	1.50	1.52	1.51 ± 0.01
8	1.36	1.45	1.41	1.42	1.38	1.40	1.40 ± 0.01
12	1.21	1.22	1.21	1.23	1.22	1.20	1.21 ± 0.004
16	1.01	1.00	0.92	0.95	1.02	1.01	1.00 ± 0.01
24	0.06	0.58	0.59	0.57	0.55	0.56	0.57 ± 0.01

Pharmacokinetic variables and dosage regimen: The plasma concentration-time profile of gatifloxacin after intravenous administration in each animal was used to establish various pharmacokinetic determinants and mean kinetic variables were obtained by averaging the variables calculated for individual animals. The log plasma drug concentrations *versus* time profile showed a biphasic curve and thus, followed a two-compartment open model as described [8]. Various kinetic parameters were obtained by least square regression method. Appropriate loading (D*) and maintenance (D_0) dose for maintaining minimum therapeutic concentration (C_p^{∞} min = MIC) of 0.2, 0.3 and 0.4 μg/mL at desired dosage interval (γ) of 8, 12 and 16 h were also derived [9] as per the following equation:

$$D^* = C_p^{\infty}(\min) \cdot Vd_{area} \cdot (e^{\beta.\gamma})$$

$$D_0 = C_p^{\infty}(\min) \cdot Vd_{area} \cdot (e^{\beta.\gamma} - 1)$$

RESULTS AND DISCUSSION

Plasma levels: The plasma levels of gatifloxacin at different time intervals following its single Intravenous injection at the dose rate of 4 $mg.kg^{-1}$ body weight in crossbred cow calves are presented in Table 1. Following intravenous administration of gatifloxacin, the mean peak plasma drug concentration of 4.64 ± 0.03 μg/mL was observed at 0.042 h, which rapidly declined to 1.91 ± 0.02 μg/mL at 2 h. Thereafter, the drug concentration in plasma diminished gradually and was detectable up to 24 h. The mean drug concentration of 0.57 ± 0.01 μg/mL in plasma was detected at 24 h. The drug was not detected in plasma samples collected 30 h post intravenous administration of gatifloxacin in crossbred cow calves.

The plasma concentration of gatifloxacin at various time intervals following intravenous administration (4 mg. kg^{-1}) after 0.042 h, the peak plasma level (4.64 ± 0.03 μg/mL) was approximately 23 fold higher than minimum therapeutic level of gatifloxacin (0.2 $\mu g.mL^{-1}$). Drug was detected above the minimum therapeutic plasma concentration up to 24 h of administration. In contrast to present study, at 1 min of IV injection of gatifloxacin (4 mg/kg), the peak plasma level (12.5 ± 0.74 μg/mL) was approximately 60 fold higher than minimum therapeutic level of gatifloxacin (0.2 $\mu g.mL^{-1}$) which rapidly declined to 3.25 ± 0.1 $\mu g.ml^{-1}$ at 30 min and the drug was detected above the minimum therapeutic plasma concentration up to 12 h of administration in buffalo calves [10]. The higher mean peak plasma drug level (11.3 ± 0.37 μg/mL) at 1 minute of intravenous injection of levofloxacin (4 mg/kg) concurrently with subcutaneous injection of meloxicam (0.5 mg/kg) in cross-bred calves [11].

Pharmacokinetic parameter: In present study the plasma drug concentrations, measured at various time intervals following intravenous administration of gatifloxacin in crossbred cow calves were employed for the calculation of various pharmacokinetic parameters like distribution half-life, elimination half-life, apparent volume of distribution, volume of distribution at steady state, total body clearance and mean residence time of the drug. Table 2 shows the pharmacokinetic parameters that describe the distribution and elimination pattern of gatifloxacin in crossbred cow calves. Following intravenous administration of the drug in healthy crossbred cow calves, the distribution rate constant (α) varied from 4.66 to 7.00 h^{-1} with a mean of 5.67 ± 0.32h^{-1}. The distribution half-life ($t_{1/2\alpha}$) ranged between 0.099 to 0.15 h with a mean of 0.125 ± 0.01h. The mean values of apparent volume of distribution (Vd_{area}) and volume of distribution at steady-state (Vd_{ss}) were calculated to be 1.81 ± 0.02 and 1.70 ± 0.07 L/kg, respectively. The range of elimination rate constant (β) was 0.050 to 0.54 h^{-1} with a mean of 0.053 ± 0.01 h^{-1}. The elimination half-life ($t_{1/2\beta}$) ranged from 13.88 to 12.83 h with a mean of 13.17 ± 0.16 h. The elimination rate of the drug from the central compartment (K_{el}) was calculated to be 0.166 ± 0.01 h^{-1}.

Table 2: Pharmacokinetic parameters of gatifloxacin after single dose intravenous administration (4 mg/kg) in healthy crossbred cow calves

Kinetic parameters	Buffalo Calves Number Unit	C1	C2	C3	C4	C5	C6	Mean ± S.E
A	μg/mL	4.16	5.02	4.98	6.35	4.89	4.61	5.00 ± 0.30
B	μg/mL	2.09	2.20	2.14	2.19	2.17	2.18	2.16 ± 0.02
C_P^o	μg/mL	6.25	7.22	7.12	8.54	7.06	6.79	7.16 ± 0.31
α	h^{-1}	4.66	5.98	5.33	7.00	5.68	5.35	5.67 ± 0.32
$t_{1/2\,\alpha}$	H	0.15	0.12	0.13	0.099	0.12	0.13	0.125 ± 0.01
β	h^{-1}	0.05	0.053	0.052	0.45	0.053	0.054	0.053 ± 0.01
$t_{1/2\,\beta}$	H	13.88	13.07	13.33	12.83	13.07	12.83	13.17± 0.16
AUC	μg.h/mL	42.69	42.48	42.14	41.47	41.81	41.99	42.10 ± 0.18
AUMC	$\mu g.h^2/mL$	836.18	784.81	793.85	750.1	772.39	746.74	780.68 ± 13.45
MRT	H	19.60	18.47	18.84	18.09	18.47	17.78	18.54 ± 0.26
K_{12}	h^{-1}	2.46	3.78	3.57	5.03	3.78	3.52	3.69 ± 0.33
K_{21}	h^{-1}	2.14	1.77	1.64	1.84	1.87	1.71	1.81 ± 0.07
Kel	h^{-1}	0.11	0.17	0.169	0.21	0.17	0.17	0.166 ± 0.01
Fc		0.46	0.31	0.31	0.26	0.31	0.32	0.33 ± 0.03
T ≈P		1.18	2.203	2.25	2.82	2.19	2.12	2.13 ± 0.22
Vd_{area}	L/kg	1.87	1.78	1.88	1.79	1.81	1.76	1.81 ± 0.02
Vdss	L/kg	1.38	1.74	1.78	1.75	1.78	1.80	1.70 ± 0.07
Cl_B	L/h/kg	0.09	0.094	0.04	0.10	0.034	0.095	0.076 ± 0.01
AUC/MIC		213.45	212.42	210.7	207.4	209.05	209.95	210.49 ± 0.91

A = zero time intercept for distribution phase; B = zero time intercept for elimination phase; C_p^0 *(μg/mL) = theoretical zero time concentration (A+B);* α *= distribution rate constant;* $t_{1/2}\ \alpha$ *= distribution half life;* β *= elimination rate constant;* $t_{1/2}\ \beta$ *= elimination half life; AUC = total area under plasma drug concentration curve; AUMC = area under first moment curve; MRT = mean residence time;* K_{12} *= rate constant of drug transfer from central compartment to peripheral compartment;* K_{21} *= rate constant of drug transfer from peripheral to central compartment; Kel = rate constant of drug elimination from central compartment; Fc = fraction of drug available for elimination from central compartment;* $T \approx P$ *= approximate tissue to plasma concentration ratio;* Vd_{area} *= apparent volume of distribution;* Vd_{SS} *= volume distribution at steady state;* Cl_B *= total body clearance*

The mean value of total body clearance (Cl_B) of the drug was 0.076 ± 0.01 L/h/kg with mean residence time (MRT) of 18.54 ± 0.26 h. The average values for area under plasma drug concentration-time curve ($AUC_{0-\infty}$) and area under first moment curve (AUMC) were 42.10 ± 0.18 μg.h/mL and 780.68 ± 13.45 $\mu g.h^2/mL$, respectively.

The high values of distribution rate constant (α) 5.67 ± 0.32 h^{-1} and low values of elimination rate constant (β) 0.053 ± 0.006 h^{-1} observed in the present study following intravenous administration (4 mg/kg) of gatifloxacin in crossbred cow calves indicated that the drug is rapidly distributed in the body and then relatively slowly eliminated from the body of crossbred cow calves. Similarly the higher values of distribution rate constant (6.07 ± 0.74 h^{-1}) and elimination rate constant (0.09 ± 0.008 h^{-1}) were observed following intravenous administration of gatifloxacin in buffalo calves [10] and almost similar elimination rate constant (β) values of 0.059 ± 0.005 h^{-1} in goats [12]. The distribution half-life ($t_{1/2\alpha}$) of the drug was calculated to be (0.125 ± 0.007 and 0.17 ± 0.055 h) in present study is higher than value of $t_{1/2\alpha}$ (0.11 ± 0.01 h) reported in crossbred calves [10] and lower than values of $t_{1/2\alpha}$ of levofloxacin was reported in sheep 0.25 ± 0.01h [13], in goats 0.31 ± 0.11 h [12], in camels 0.26 ± 0.21 h [14], stallions 0.21 ± 0.13 h [15] and in cats 0.26 ± 0.18 h [16], respectively.

The elimination half-life ($t_{1/2\beta}$) of gatifloxacin following intravenous administration of gatifloxacin in crossbred cow calves was calculated to be (13.17 ± 0.161 h) while, lower value of elimination half-life ($t_{1/2\beta}$) 7.45 ± 0.55 h

Table 3: Dosage regimens of gatifloxacin after single dose intravenous administration (4 mg/kg) in healthy crossbred cow calves

C_P^{∞} min (µg/mL)	τ (h)	Dose (mg/kg)	Buffalo Calves Number C1	C2	C3	C4	C5	C6	Mean ± SE
		D*	0.56	0.54	0.56	0.55	0.55	0.54	0.55± 0.0036
	8	D_0	0.18	0.19	0.19	0.19	0.19	0.19	0.19± 0.0017
		D*	0.68	0.67	0.70	0.68	0.68	0.67	0.68± 0.0045
0.2	12	D_0	0.31	0.31	0.32	0.33	0.32	0.32	0.32± 0.0031
		D*	0.83	0.83	0.84	0.85	0.82	0.83	0.83± 0.0042
	16	D_0	0.46	0.47	0.49	0.25	0.48	0.48	0.44± 0.038
		D*	0.84	0.84	0.85	0.83	0.83	0.81	0.83± 0.0052
	8	D_0	0.28	0.28	0.29	0.29	0.69	0.28	0.35± 0.07
		D*	1.02	1.01	1.05	1.03	1.02	1.01	1.02± 0.0061
0.3	12	D_0	0.46	0.47	0.49	0.49	0.48	0.48	0.48± 0.0043
		D*	1.25	1.24	1.29	1.27	1.27	1.25	1.26± 0.0075
	16	D_0	0.69	0.71	0.73	0.73	0.72	0.72	0.72± 0.0061
		D*	1.12	1.09	1.14	1.10	1.11	1.08	1.11± 0.0088
	8	D_0	0.37	0.38	0.39	0.39	0.38	0.38	0.38± 0.0031
		D*	1.37	1.34	1.40	1.37	1.37	1.34	1.36± 0.0092
0.4	12	D_0	0.62	0.63	0.65	0.65	0.64	0.64	0.64± 0.0048
		D*	1.67	1.66	1.73	1.70	1.69	1.67	1.69± 0.011
	16	D_0	0.92	0.95	0.98	0.50	0.97	0.97	0.88± 0.076

*D** = *Priming or Load dose*
D_0 = *Maintenance dose*
τ = *Dosage interval*
C_P^{∞} *min* = *Minimum therapeutic concentration in plasma*

has also been reported in buffalo calves [10, 17]. While in case of levofloxacin very lower value (1.61 ± 0.07 h) has also been reported in cow calves [18] and lower values of $t_{1/2\beta}$ reported in goats (2.95 ± 0.27 h) [12], camels (2.92 ± 0.61 h) [14], stallions (2.58 ± 0.51 h) [15], sheep (2.38 ± 0.22 h) [13], goats (4.04 ± 0.24 h) [19] and cats (9.31 ± 1.63 h) [16] for levofloxacin.

The K_{12} /K_{21} ratio of gatifloxacin following intravenous administration of gatifloxacin in crossbred cow calves was (2.04) which indicate a faster drug transportation rate from the central to the peripheral compartment than redistribution from the peripheral to the central compartment. To know the extent of penetration of drug in body tissue, the knowledge of apparent volume of distribution is necessary. The mean apparent volume of distribution (Vd_{area}) and volume of distribution at steady state (Vd_{ss}) calculated following intravenous administration of gatifloxacin at dose rate of 4 mg/kg body weight in crossbred cow calves were (1.81 ± 0.021 L/kg) and (1.70 ± 0.07 L/kg), respectively. The higher Vd_{area} of gatifloxacin found in buffalo calves is 3.20 ± 0.08 L/kg [10]. The more or less similar values of Vd_{area} of levofloxacin were observed in sheep (1.95 ± 0.16) [13], goats (1.89 ± 0.18 L/kg) [19] and cats (1.57 ± 0.51 L/kg) [16], respectively. However, lower apparent volume of distribution of levofloxacin was reported in goats (0.70 ± 0.07 L/kg) [20] and in cow calves (0.74 ± 0.03 L/kg) [18]. In buffalo calves, the (Vd_{ss}) of gatifloxacin (2.82 ± 0.086 L/kg) was reported [10].

One of the most fundamental parameters 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 physiologically meaningful pharmacokinetic parameters like bioavailability, volume of distribution and clearance. The area under the curve following intravenous administration of gatifloxacin was calculated to be 42.10 ± 0.18 µg.h/ml in the present study however, lower observed value of AUC for gatifloxacin in buffalo calves was reported 12.96 ± 0.65 $\mu g.ml^{-1}.h$ [10] and 12.0 ± 0.68 $\mu g.ml^{-1}.h$ [17], respectively.

The total body clearance is an important pharmacokinetic parameter that gives sum of clearances by eliminating organ. The extent of renal elimination varies across the fluoroquinolone. Gatifloxacin is eliminated primarily by the kidney, with the renal clearance exceeding creatinine clearance. The total body clearance of gatifloxacin following intravenous administration of gatifloxacin in crossbred cow calves was calculated to be 0.143 ± 0.003 L/h/kg in the present study, which is lower to the clearance of the drug 0.301± 34.4 L/h/kg [10] and 0.337 ±19.9 $L. kg^{-1}. h^{-1}$ [17] in buffalo calves. However, more or less similar clearance of the levofloxacin has been reported in goats (0.18 ± 0.04 L/h/kg) [12], camels (0.28 ± 0.03 L/h/kg) [14], stallions (0.21 ± 0.18 L/h/kg) [15] and cats (0.14 ± 0.04 L/h/kg) [16], respectively.

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 MRT calculated following intravenous administration of gatifloxacin in crossbred cow calves was 13.72 ± 0.38 h which is higher to the value of MRT (9.03 ± 0.43 h) of the drug reported in buffalo calves [10]. In case of

Table 4 depicts efficacy predictors (C_p^o/MIC and AUC/MIC) estimated for gatifloxacin in crossbred cow calves using different MIC values.

	MIC 0.2 (µg/mL)	MIC 0.3 (µg/mL)	MIC 0.4 (µg/mL)
C_p^o/MIC	35.8	23.87	17.9
AUC/MIC	210.5	140.33	105.25

For calculations the applied values were: C_p^o = 7.16 µg/mL, AUC = 42.10 µg / mL.h in crossbred cow calves

levofloxacin, lower value of MRT (2.13 ± 0.09 h) was reported in cow calves [18].

Dosage regimens: The dosage regimens required to maintain the different levels of therapeutic concentration (C_p^0 min = 0.2, 0.3, and 0.4 µg/mL) in plasma for intravenous route in crossbred cow calves at different dosage intervals (τ) of 8, 12 and 16 h are presented in Table 3.

Following intravenous administration, for maintaining C_p^0 min of 0.2 µg/mL, the loading doses (D*s) were calculated to be 0.55 ± 0.004, 0.68 ± 0.004 and 0.83 ± 0.0042 mg/kg while maintenance doses (D_0s) were calculated to be 0.19 ± 0.002, 0.32 ± 0.003 and 0.44 ± 0.038 mg/kg at the dosage intervals (τ) of 8, 12 and 16 h, respectively. The D*s were calculated to be 0.83 ± 0.005, 1.02 ± 0.006 and 1.26 ± 0.008 mg/kg while D_0s were found to be 0.35 ± 0.07, 0.48 ± 0.004 and 0.72 ± 0.006 mg/kg at τ of 8, 12 and 16 h respectively, for maintaining C_p^0 min of 0.3 µg/mL. Likewise, to maintain C_p^o min of 0.4 µg/mL, the D*s were calculated to be 1.11 ± 0.01, 1.36 ± 0.009 and 1.69 ± 0.01 mg/kg while D_0s were found to be 0.38 ± 0.003, 0.64 ± 0.005 and 0.88 ± 0.076 mg/kg at τ of 8, 12 and 16 h, respectively.

Thus, the loading and maintenance dosage of gatifloxacin to maintain an MIC of 0.4 µg.mL^{-1} to be repeated at an interval of 16 hrs in crossbred cow calves would be 1.69± 0.011 mg.kg^{-1} and 0.88 ± 0.076 mg.kg^{-1}, respectively. The major objective of the present study was to calculate and modify the dosage regimen of gatifloxacin. However, under field conditions, gatifloxacin is recommended at the dose rate of 1.7 mg.kg^{-1} followed by 0.9 mg.kg^{-1} to be repeated at 16 hrs intervals to treat severe systemic infections. Similarly, a dose rate of 2.5 mg.kg^{-1} of enrofloxacin to be repeated at 8 hrs intervals has recommended in buffalo calves [21]. The calculated dosage for pefloxacin and ciprofloxacin have recommended at the dose rates 7 mg.kg^{-1}and 6 mg.kg^{-1} b. wt., respectively and repeated at 6 h interval in buffalo calves [22]. A very high loading and maintenance dosage of gatifloxacin (3.74 mg.kg^{-1} and 3.10 mg.kg^{-1}) to maintain an MIC of 0.2 µg.mL^{-1} to be repeated at an interval of 18 h in buffalo calves have reported [10]. The variation among species, breed, sex, age and different methods for estimation of drugs may contribute to the wide discrepancies in kinetic parameters as suggested by various workers [23].

Efficacy predictors: The individual pharmacokinetic/pharmacodynamic (PK/PD) ratios for the assumed MIC_{90} values for gatifloxacin are summarized in Table 4. The threshold AUC/MIC_{90} for a successful clinical/microbiological outcome of >100–125 was achieved at MIC_{90} of 0.3 µg/mL and optimal C_p^o/MIC (>10) was attained at MIC_{90} of 0.4 µg/mL in crossbred cow calves. The highest gatifloxacin MIC_{90} of bacteria that fulfills the minimum AUC/MIC ratio (>100-125) for the present dosage regimen is 0.3 µg/mL. To achieve the optimal C_p^o/MIC (>10), the present dosing regimen would allow an MIC_{90} of 0.4 µg/mL for Gram-negative and Gram-positive pathogens.

There is general consensus that the clinical and microbiological outcomes of fluoroquinolone treatment are favourable and selection of a mutant subpopulation is preventable if an AUC/MIC ≥ 100–125 and a C_{max}/MIC of 10 are achieved in Gram-negative infections[24,25]. For Gram-positive pathogens, the minimum required C_{max}/MIC is also 10, while the optimum AUC/MIC target values are still a topic of debate[24]. An AUC/MIC of 30–50 is claimed to be optimal in numerous studies performed mainly in *in-vitro* or animal models [26]. Other studies conducted on different patient populations suggested a minimum AUC/MIC of 87-125 to achieve a favourable outcome and to avoid development of resistance regardless of whether the organism is Gram-positive or Gram-negative[25].

Considering the AUC/MIC_{90} and C_p^o/MIC_{90} ratios obtained in the present study, it can be stated that gatifloxacin administered intravenously in the dosing schedule applied is efficacious against bacteria with MIC_{90} values under 0.4 µg/mL in crossbred cow calves. The high value of AUC/MIC_{90} (210.5) and C_p^o/MIC_{90} (35.8) obtained in the present study, provides support for excellent clinical and bacteriological efficacy of gatifloxacin in crossbred cow calves. In agreement with the present results, a C_{max}/MIC ratio of more than 10 has been reported following subcutaneous administration of both danofloxacin and enrofloxacin in calves [27]. The AUC/MIC ratio was higher in present study than the values of 76.6 reported for levofloxacin administered intramuscularly in calves [28] and for other fluoroquinolones, 40.7 for marbofloxacin in cows [29]. However, it is necessary to note that the numerical values of AUC/MIC_{90} and C_{max}/MIC_{90} used as a surrogate marker to predict optimal dosage, have been generated in experimental infections in laboratory animals or in human clinical trials [30].

CONCLUSION

In conclusion, the fact that general adverse reactions were not observed in any crossbred cow calves and favourable pharmacokinetic properties of gatifloxacin, such as long half-life and high mean residence time with wide penetration into different body fluids and tissues from blood, were found. Based on the calculated AUC/MIC_{90} and C_p^o/MIC_{90}, a dosage of 0.8 mg/kg could be effective in crossbred cow calves to maintain the $MIC_{90} \geq 0.2$ µg/mL following intravenous route.

ACKNOWLEDGEMENTS

The authors express their sincere gratitude to The Dean, College of Veteinary Science and Animal Husbandry, Mhow, Madhya Pradesh, India for his constant encouragement and help rendered during the present investigation.

REFERENCES

1. Sanders CC. Ciprofloxacin, in vitro activity, mechanism of action and resisteance. Rev Infect Dis 1988; 10**:** 516-527.
2. Leysen DC, Haemers A, Pattyan SR. Mycobacteria and the new quinolones. Antmicrob Agent Chemother1989; 33: 1-5.
3. Martinez M, McDermott P, Walker R. Pharmacology of the fluoroquinolones: a perspective for the use in domestic animals. Vet J 2006; 172(1): 10-28.
4. Perry CM, Ormrod D, Hurst M, Onrust SV. Gatifloxacin: a review of its use in the management of bacterial infection. Drug 2002; 62(1): 169-207.
5. Daniel AH. New drugs of 2000. J Am Pharm Assoc 2001; 41: 229-272.
6. Brakken JS. The fluoroquinolones: now long will their utility last? Scand J Infected Dis 2004; 36: 85-92.
7. Arret B, Johnson DP, Krishbaum A. Outline of details for microbiological assay of antibiotics: Second revision. J Pharm Sci 1971; 60: 1689-94.
8. Notari RE. Biopharmaceutics and clinical pharmacokinetics. Edn 3, Marcel Dekkar Inc., New York, 1980.
9. Baggot JD. Principles of drug distribution in domestic animals. The Basis of Veterinary Clinical Pharmacology. Edn 1, WB Saunders Company, Philadelphia, London, Toranto, 1977.
10. Raipuria M, Dumka VK, Sandhu HS. Plasma concentration, pharmacokinetic and urinary excretion of gatifloxacin after single IV injection in buffalo calves. Vet Res commun 2007; 31(8): 1013-1320.
11. Dumka VK, Singh H, Srivastava AK. Disposition kinetics and urinary excretion of levofloxacin on concomitant administration with meloxicam in cross-bred calves. Envirol Toxicol Pharmacol 2008; 26: 56–60.
12. Goudah A, Abo-El-Sooud K. Pharmacokinetics, urinary excretion and milk penetration of levofloxacin in lactating goats. J Vet Pharmacol Therap 2009; 32(1): 101-104.
13. Patel UP. Pharmacokinetics of levofloxacin following intravenous and subcutaneous administration in healthy, febrile and ketoprofen treated sheep. Compendium of 9th annual conference of ISVPT and National symposium on "Xenobiotic Residues and Food safety" and "Pharmacogenomics and Toxicogenomics: New Horizons in Veterinary Pharmacology and Toxicology" AAU, Anand Gujarat, India, 2009.
14. Goudah A. Pharmacokinetics of levofloxacin in male camels (*Camelus dromedarius*). J Vet Pharmacol Therap 2009; 2(3): 296-299.
15. Goudah A, Abo-El-Sooud K, Shim JH, Shin HC, Abd-El-Aty AM. Characterization of the pharmacokinetic disposition of levofloxacin in stallions after intravenous and intramuscular administration. J Vet Pharmacol Therap 2008; 31(5): 399-405.
16. Albarellos GA, Ambros LA, Landoni MF. Pharmacokinetics of levofloxacin after single intravenous and repeat oral administration to cats. J Vet Pharmacol Therap 2005; 28: 363–369.
17. Dumka VK, Sandhu HS, Rajput N. Plasma levels, pharmacokinetics and dosage regimen of intravenously administered gatifloxacin in buffalo calves (*Bubalus bubalis)* on coadministration with meloxicam. Braz J Vet Res Anim Sci 2010; 47(6): 461-467.
18. Dumka VK, Srivastava AK. Disposition kinetics, urinary excretion and dosage regimen of levofloxacin formulation following single intravenous administration in crossbred calves. Vet Res Commun 2007; 31: 873–879.
19. Ram M, Prasad R, Singh V, Roy BK. Comparative pharmacokinetics of levofloxacin after single intravenous administration in healthy and mastitic goats. Abstract in VIII Annual conference of Indian society of Veterinary Pharmacology and Toxicology and National symposium on "Medicinal plants and wildlife, Mathura, India, 2008, 146.
20. Mishra VK, Roy BK, Singh JK. Verma DK. Pharmacokinetics of levofloxacin after oral administration in healthy and febrile goats. Compendium of 5th Annual Conference of ISVPT, Chennai, India, 2005, 42.
21. Amorena M, Olivia G, Luna RD, Cresceuzo G, Ciaramella P, Vincentiis L D **et al**. Pharmacokinetics of enrofloxacin (Bytril) in the blood of buffaloes. Atti della-Sociela-Italiana-di-Buyiatria 1992; 24: 605-613.
22. Saini SPS, Srivastava AK. The disposition kinetics, urinary excretion and dosage regimen of ciprofloxacin in buffalo calves (*Bubalus bubalis*). Vet Res Commun 2001; 25: 641-649.
23. Jayachandran C, Singh MK, Banerjee NC. Pharmacokinetics and distribution of ampicillin in plasma, milk amd uterine fluid of female buffaloes. Vet Res Commun 1990; 14: 47-51.
24. Kiem S, Schentag JJ. Relationship of minimal inhibitory concentration and bactericidal activity to

efficacy of antibiotics for treatment of ventilator-associated pneumonia. Sem Resp Crit Care M 2006; 27: 51 – 67.
25. Forrest A, Nix DE, Ballow CH, Goss TF, Birmingham MC, Schentag JJ. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother 1993; 37: 1073 - 1081.
26. Lister PD. Impact of AUC/MIC ratios on the pharmacodynamics of the des-F (6) quinolone garenoxacin (BMS-284756) is similar to other fluoroquinolones. J Antimicrob Chemother 2003; 51: 199 – 202.
27. TerHune TN, Skogerboe TL, Shostorm VK, Weigel DJ. Comparison of pharmacokinetics of danofloxacin and enrofloxacin in calves challenged with *Mannheimia haemolytica*. American J Vet Res 2005; 66: 342 - 349.
28. Dumka VK, Srivastava AK. Pharmacokinetics, urinary excretion and dosage regimen of levofloxacin following a single intramuscular administration in cross bred calves. J Vet Sci 2006; 7: 333 - 337.
29. Schneider M, Valle M, Woehrle F, Boisrame B. Pharmacokinetics of marbofloxacin in lactating cows after repeated intramuscular administrations and pharmacodynamics against mastitis isolated strains. J Dairy Sci 2004; 87: 202 - 211.
30. Touitan PL, Lees P. Integration and modelling of pharmacokinetic and pharmacodynamic data to optimize dosage regimens in veterinary medicine. J Vet Pharmacol Ther 2004; 27: 467 – 477.