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Pharmacokinetic evaluation of cefquinome in febrile goats following intravenous administration

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ABSTRACT

Pharmacokinetics of cefquinome was studied in febrile female goats following its intravenous (IV) administration at the dose rate of 2 mg/kg body weight. The fever was induced by administration of *Escherichia coli* lipopolysaccharide (lμg/kg body weight). Cefquinome concentration in plasma of goats was estimated using HPLC. The drug was detected upto 24 h in febrile goats. The disposition kinetics of the drug was described by two-compartment open model. PK-PD indices; AUC_{24h}/MIC, C_{max}/MIC, T>MIC were calculated by integrating *in-vivo* PK data with earlier generated MIC data against *Pasteurella* (*P.*) *multocida*. A favourable PK and PK-PD indices suggested that the dose of 2 mg/kg/24 h of cefquinome would be effective clinically to treat goats affected with *P. multocida* infections.

Keywords: Cefquinome, *E. coli* LPS, Fever, Goats, Intravenous, Pharmacokinetics, PK-PD

Cefquinome, an aminothiazolyl fourth generation cephalosporin has been developed exclusively for veterinary use to treat infections caused by gram positive and gram negative bacteria. The chemical modifications of the basic cephalosporin structure provide a zwitter-ionic property to cefquinome that facilitates rapid penetration across biological membranes including porins of the bacterial cell wall, enhances bioavailability and spectrum of antibacterial activity compared to the second and third generation cephalosporins (Guerin-Faublee *et al.* 2003, Thomas *et al.* 2006, Shantier 2018). As a result of molecular structure, cefquinome is stable against chromosomally and plasmid-encoded β-lactamases that are produced by a majority of clinically important bacteria (Shantier 2018).

Appropriate dosing of the antimicrobial agent is determined by considering the pharmacokinetic (PK)–pharmacodynamics (PD) relationships of the antimicrobial agent. In general, these studies are conducted in healthy animals and dosing determined from these trials is frequently extrapolated for use in sick animals. However, pathophysiological changes in sick animals can affect PK-PD properties of drugs and extrapolation of dosing in sick animals compared to healthy animals may become inadequate because of alterations in physiological parameters due to disease. Suboptimal concentrations of antimicrobials are clinically relevant as they lead to reduced antimicrobial activity and hence, compromise clinical efficacy and trigger the development of drug resistance (Lees *et al*. 2006, Ambrose *et al*. 2007, Mouton *et al*. 2011).

The veterinarians are facing the challenge of managing infectious disease outbreaks in goats due to increasing trend of goat population and production in India and other countries including China and United States. Respiratory tract infections associated with *Pasteurella* (*P.*) *multocida* are one of the leading causes of mortality and morbidity in sheep and goats ((Momin*et al*. 2011, Sirous *et al*. 2011, Salaheddin and Hanan 2012). Use of antimicrobials is the only effective alternative to treat sick animals affected with Pasteurellosis. Several publications have reported emerging resistance of various antibiotics against *P. multocida* from different parts of the world (Jamali 2014, Sarangi *et al*. 2015, Pipoz *et al*. 2016). To combat threat of resistance emergence, there is urgent need to develop optimal dosing regimen of antimicrobial to guarantee successful clinical outcome and minimizing the risk of selection and amplification of resistant mutants. Therefore, it is important to establish PK data of antimicrobial agents in healthy and febrile animals. The study was carried out to extend our previous findings of cefquinome PK in healthy goats to febrile goats to generate comparative PK data for optimization of dosing regimen of cefquinome in diseased goats.

MATERIAL AND METHODS

Animals: The study was performed on four adult female

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goats (20±4 kg) of approximately 2–3 years of age, purchased from the local farmer. The goats were acclimatized for 2 weeks in the department animal shed prior to the commencement of experiment. During this period, all animals were dewormed and subjected to regular clinical examination. The animals were maintained on green pasture and concentrate mixture. Goats were healthy and didn't receive any antimicrobial treatment during a month prior to the study. Water was provided *ad lib*. The study protocol followed the institutional ethical guidelines on the proper care and use of experimental animals.

Induction of fever: Four female goats were administered with lipopolysaccharide (LPS) derived from *Escherichia coli* (*E. coli*) 0127:B8 (Sigma-Aldrich, USA) intravenously (IV) at the dose rate of 1 µg/kg body weight to induce fever. The dose of LPS used for induction of fever was on the basis of a pilot study (data not shown) using three doses (0.5, 1, 2 µg/kg) of LPS. Once fever was induced, cefquinome sulfate powder with solvent for injection (Intas Pharmaceuticals Ltd, Ahmedabad, India) was administered IV into the right jugular vein at a dose of 2 mg/kg. Blood samples (~ 9–10 mL/each sample) were collected from the left jugular vein by venipuncture in heparinized sterile test tubes at time points: 0, 1, 2.5, 5, 10, 20, 30, 60 min and 2, 4, 6, 8, 12 and 24 h after drug administration. Blood samples were immediately transferred on ice for no longer than 2 h prior to centrifugation for 10 min at 1,500 g. Plasma was separated and stored at –20°C in Eppendorf tubes till further analysis.

Determination of cefquinome concentration: Plasma concentrations of cefquinome were determined using high performance liquid chromatography (HPLC) with UV/VIS detector (Perkin Elmer 200 series) following the method of Uney *et al.* (2011), details have been described in our companion paper (Sagar *et al*. 2015). The HPLC system (Perkin Elmer) consists of a single pump (mode series 200) and auto-sampler injector with 200 µl loop, dual wavelength UV detector (model 200 series) and Total Chrome software® for analysis. A reverse phase C_{18} column (Merck® Particle size 5 µ, and 4.6×150 mm, Waters USA) was used as a stationary phase. The binary-gradient mobile phase consisted of water containing 0.1% TFA (mobile phase A): acetonitrile (mobile phase B): (Merck, Germany) in the ratio (80:20, v/v). The detection of cefquinome was performed by UV detection at the wavelength of 268 nm. The retention time of cefquinome was about 6.1 min with a total run time of 15 min. The plasma from control goats was spiked with concentration range of 0.02–40 µg/ml of cefquinome for preparation of calibration curve. The standard curve of cefquinome was linear in the range of 0.04–40 µg/ml with regression coefficient (r^2) of 0.999. The limit of quantitation (LOQ) for the method was found to be 0.04 µg/ml for cefquinome in goat plasma. The limit of detection (LOD) was 0.02 µg/ml with 92.8% recovery of cefquinome. The coefficients of variation for repeatability and reproducibility of cefquinome were 2.75% and 4.15%, respectively. The accuracy and coefficient of variation for precision of cefquinome were 96.4% and 3.97%, respectively.

Pharmacokinetic analysis: The plasma concentration versus time data for each goat following IV administration of cefquinome was subjected to PK analysis using Win-Nonlin Software (Phoenix® Win-Nonlin® 7.0, Certara, Inc. Princeton, NJ, USA) based on least square non-linear regression method. The mean PK parameters were obtained by averaging the parameters calculated for drug disposition in each goat. The PK parameters, viz. elimination rate constant and half-life (β and $t_{½}β$), area under the plasma concentration-time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$), volume of distribution (Vd_{ss}), total body clearance which is the sum of all clearance processes in the body (Cl_B) were calculated using compartment modelling. The best fitting model was chosen using Minimum Akaike Information Criterion Estimates. Data of cefquinome plasma levels vs. time was subject to non-compartment analysis using the statistical moment approach (Gibaldi and Perrier 1982). The AUC and area under the first moment curve (AUMC) were determined by linear trapezoidal method. The mean residence time (MRT) was calculated from AUMC/AUC.

Statistical analysis: The PK data are presented as arithmetic mean±SD, except for $t_{½}β$ where harmonic mean was used as a measure of accuracy (Lam *et al*. 1985). The SD for means is provided to give an indication of the variation in the data. Plasma concentrations versus time data of cefquinome following IV administrations in febrile goats were collected in a spread sheet (Microsoft Excel® 2016, Microsoft Corporation) for subsequent calculations. Differences between two means based on individual observations were evaluated using ANOVA with the assumption that data were not normally distributed. The statistical significance was assayed at 5% ($P<0.05$) levels. All calculations were done using SPSS® 16.0 (IBM) software package.

RESULTS AND DISCUSSION

Pharmacokinetic studies of cefquinome have been conducted in healthy animals of various species including cattle (Ehinger *et al.* 2006, Shan *et al*. 2014), buffaloes (Dinakaran *et al*. 2013), camel (Al-Taher 2010), goat (Dumka *et al*. 2013, Sagar *et al*. 2015), pig (Li *et al*. 2008), Sheep (Tohamy*et al*. 2011, Uney *et al*. 2011), horse (Allan and Thomas 2003) and rabbits (Shalaby *et al*. 2014). However, there is no information on PK-PD of cefquinome in diseased animals; therefore, we attempted to establish PK of cefquinome in febrile goats and applied PK-PD principles for optimization of dosage regimen. In all goats, the LPS dose (1 µg/kg) was precise enough to produce fever in quantifiable degrees which was reversible and gave minimum discomfort to goats. The LPS had been used previously to induce fever in buffalo calves and pigs (Dardi *et al*. 2005, Balaje *et al*. 2013).

The pyrexia (~1.5–2°C) in goats was maintained up to 12 h and body temperature returned to normal at 24 h after

Table 1. Plasma concentrations (µg/ml) of cefquinome following its single IV administration at the dose rate of 2 mg/kg in febrile goats

Time (h)	Goat 1	Goat 2	Goat 3	Goat 4	Mean	SD
0.017	9.140	9.070	9.030	9.030	9.067	0.051
0.042	8.800	8.620	8.830	8.830	8.770	0.100
0.083	8.010	8.210	8.120	8.120	8.115	0.082
0.167	7.530	7.890	7.701	7.710	7.707	0.147
0.333	7.360	7.421	7.011	7.010	7.201	0.221
0.500	5.630	6.040	5.720	5.721	5.777	0.180
1.000	4.700	4.640	4.410	4.410	4.540	0.152
2.000	3.530	3.620	3.541	3.539	3.557	0.042
4.000	3.310	3.238	3.310	3.311	3.293	0.035
6.000	2.022	2.290	2.631	2.330	2.318	0.249
8.000	1.800	1.748	1.750	1.752	1.763	0.025
12.00	0.918	0.920	0.882	0.884	0.901	0.021
24.00	0.415	0.365	0.378	0.402	0.390	0.022

LPS administration. There was no rise in temperature in control animals at any time point. All the goats were alert and normal at 24 h after LPS administration. No animal showed any adverse reaction following IV administration of cefquinome @ 2 mg/kg body weight. Table 1 shows the mean plasma concentrations of cefquinome at various time intervals following its single IV administration. The PK parameters which describe the distribution and elimination of cefquinome following a single IV administration in goats have been presented in Table 2. Semi-logarithmic plot of mean plasma concentrations of cefquinome versus time has been shown in Fig. 1. At 1 min, average plasma concentration±SD of cefquinome was 9.067±0.052 µg/mL, after that a gradual decrease in drug concentrations resulted into a level of 0.387±0.022 µg/mL at 24 h following cefquinome administration. Data showed a biphasic curve and it gave fitting to two compartmental modelwith a first order kinetics in all animals (Fig. 1). Pharmacokinetic parameters of cefquinome indicated rapid distribution of drug in the central compartment and moderately rapid into peripheral/tissue compartment. The drug was eliminated with mean $t_{½}\beta$ of 6.139 h with elimination rate constant (β) of 0.113/h. The mean total body clearance (Cl_B) was 0.047 L/kg/h and Vd_{ss} of cefquinome was 0.395 L/kg. The PK data of cefquinome obtained by compartmental modelling were consistent with the PK parameters calculated with non-compartment method (Data not shown). The mean $AUC_{0-\infty}$ and $AUMC_{0-\infty}$ were 42.48 µg/ml×h& 357.3 µg/ml×h^2, respectively. Mean residence time from time 0 extrapolated to infinity ($MRT_{0-\infty}$) was 8.408 h in febrile goats.

The cefquinome PK-PD indices, AUC_{24h}/MIC, C_{max}/MIC, T>MIC were calculated by integrating *in vivo* PK data with earlier generated MIC data against *P. multocida* from Schwarz *et al*. (2004) and Thomas *et al*. (2006) (Table 3). PK-PD data showed that cefquinome concentration in febrile goats were $T>MIC_{90}$ (0.030–0.125 µg/ml) of *P. multocida* for 24 h following IV administration. However, $T>MIC_{90}$ for cefquinome was 18 h against staphylococci isolated from equines suffering from respiratory infections.

Mean plasma concentrations of cefquinome in febrile goats were slightly greater in febrile animals at all time-

Table 2. Pharmacokinetics parameters of cefquinome in febrile goats following single IV administration at the dose rate of 2 mg/kg body weight

Parameter	Unit	Goat 1	Goat 2	Goat 3	Goat 4	Mean	SD
A	µg/mL	4.701	4.549	4.596	4.715	4.640	0.080
B	µg/mL	4.444	4.568	4.643	4.503	4.539	0.085
α	h^{-1}	1.983	1.775	2.288	2.166	2.053	0.224
β	h^{-1}	0.111	0.115	0.113	0.112	0.113	0.002
$t_{1/2}\alpha$	h	0.349	0.390	0.303	0.319	0.341	0.038
$t_{1/2}\beta$	h	6.220	6.014	6.118	6.204	6.139	0.094
K_{10}	h^{-1}	0.216	0.216	0.215	0.216	0.216	0.001
K_{12}	h^{-1}	0.857	0.727	0.981	0.945	0.877	0.112
K_{21}	h^{-1}	1.021	0.947	1.206	1.115	1.072	0.112
$t_{1/2}K_{10}$	h	3.202	3.208	3.225	3.194	3.207	0.013
$AUC_{0-\infty}$	h.µg/ml	42.254	42.203	42.990	42.492	42.485	0.359
*$AUMC_{0-\infty}$	h^2.µg/ml	359.100	345.400	362.600	361.800	357.200	8.052
*$MRT_{0-\infty}$	h	8.498	8.183	8.434	8.516	8.408	0.154
CL	mL/h/kg	47.330	47.380	46.520	47.060	47.070	0.396
CL_d	mL/h/kg	187.400	159.600	212.300	205.100	191.100	23.470
V_1	mL/kg	218.700	219.300	216.500	217.000	217.900	1.372
V_2	mL/kg	183.580	168.500	175.940	183.910	178.000	7.316
V_{ss}	mL/kg	402.300	387.800	392.400	400.900	395.800	6.892

A, intercept of the distribution phase; B, intercept of the elimination phase; α, distribution rate constant; β, elimination rate constant; $t_{1/2}\alpha$, distribution phase half-life; $t_{1/2}\beta$, elimination phase half-life; CL, total body clearance; CL_d, distribution clearance; $AUC_{0-\infty}$, area under the plasma concentration-time curve extrapolated to infinity; K_{10}, elimination rate constant from central compartment; K_{12}, rate of transfer of drug from central to peripheral compartment; K_{21}, rate of transfer of drug from peripheral to central compartment; V_1, volume of central compartment; V_2, volume of peripheral compartment; V_{ss}, volume of distribution at steady state. *Values obtained using non-compartment model; *AUMC, area under first moment curve; *MRT, mean residence time.

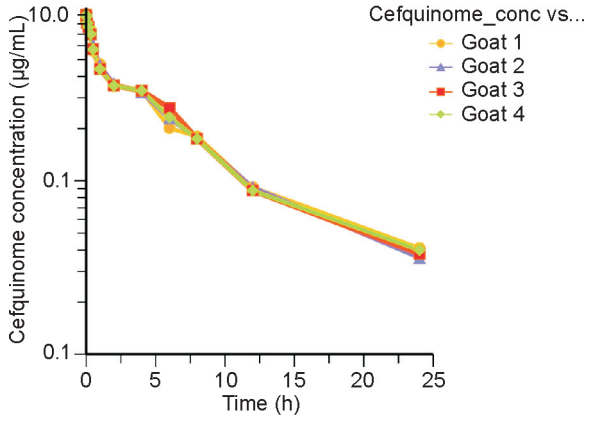

Fig. 1. Cefquinome concentrations in plasma of individual goats (n=4) following IV administration of cefquinome plotted on semi-log scale.

Table 3. Integration of PK-PD data obtained following cefquinome administration at the dosage of 2 mg/kg IV in febrile goats (n=4)

MIC/ MIC_{90}	AUC_{24h}	C_{max}	AUC_{24h}/ MIC	C_{max}/ MIC	T >MIC (h)
0.030[a]	42.48	9.07	1416	302	24
0.06[b]	42.48	9.07	708	151	24
*0.125[c]	42.48	9.07	340	73	24
**0.50[d]	42.48	9.07	85	18	12

*MIC_{90}=0.125 µgD mL of *Pasteurella multocida*; **MIC_{90}=0.50 µgD mL of Staphylococci; C_{max}/MIC, ratio of peak concentration at first time point (1 min) to *in vitro* MIC; $AUC_{24\ h}$/MIC, ratio of *in vivo* AUC for 24 h to *in vitro* MIC; T >MIC, time taken from observed data for which mean cefquinome concentration exceeds MIC. [ab]MIC used from Schwarz *et al.* 2004; [cd]MIC used from Thomas *et al.* (2006).

points but statistically significant (P<0.05) differences were obtained at 8 h, 12 h and 24 h after IV administration of cefquinome compared to the values obtained in healthy goats. The plasma concentrations (0.36–0.41 µg/ml) in febrile goats at 24 h were ~ two folds higher than concentration (0.20 µg/ml) of healthy goats (Sagar *et al.* 2015). In febrile goats, increased influx of drug due to endothelial damage that promotes diffusion of drug across capillary walls might have resulted into elevated plasma drug concentrations (Washburn *et al.* 2005). The lower serum concentrations in febrile buffalo calves than healthy calves have been reported for enrofloxacin after LPS administration (Balaje *et al.* 2013). Elimination half-life (6.139 h) of cefquinome was two folds longer than buffalo calves, yellow cattle (2.40–3.91 h) (Tohamy *et al.* 2011, Dinakaran *et al.* 2013, Shan *et al.* 2014) but difference was > 6 times compared to value reported for sheep (0.78 h) (Uney *et al.* 2011). This indicates that interspecies difference in PK of cefquinome exists within ruminant species. The elimination half-life (6.13 h) obtained in the present study was approximately similar to the values (5.76–6.21 h) reported previously for healthy goats following IV

Table 4. Comparative PK variables (mean±SD) of cefquinome after single IV administration of cefquinome (2 mg/kg body weight) in healthy (n=4) and febrile goats (n=4) using two-compartment modelling

Parameter	Unit	Febrile	*Healthy
α	h^{-1}	2.053±0.224	1.190±0.080
β	h^{-1}	0.113±0.002	0.110±0.008
$t_{1/2}\alpha$	h	0.341±038	0.591±0.040
$t_{1/2}\beta$	h	6.139±0.094	6.210±0.510
$AUC_{0-\infty}$	h.µg/mL	42.48±0.359	43.57±1.31
$AUMC_{0-\infty}$	h^2.µg/mL	357.2±8.052	307.5±5.83
$MRT_{0-\infty}$	h	8.408±0.154	7.06±0.19
Vd_{ss}	L/kg	0.396±0.068	0.325±0.010
CL	mL/h/kg	47.07±0.396	40.00±0.100

*Data for healthy goats has been used from Sagar *et al.* 2015; **Values of PK variables for cefquinome in febrile goats were significantly (P<0.05) different than corresponding values in healthy goats.

administration (Table 4, Dumka *et al.* 2013, Sagar *et al.* 2015). A greater $t_{½}K_{10}$ = 7.96 h in febrile buffalo calves compared to healthy calves (5.21 h) had been determined for enrofloxacin (Balaje *et al.* 2013). In febrile goats, total systemic clearance (0.047 L/kg/h) of the drug from the body was not significantly different (P>0.05) than the healthy goats (0.040 L/kg/h) (Table 4, Sagar *et al.* 2015). A significantly higher clearance of cefquinome was observed in treated calves compared to untreated buffalo calves (Dinakaran and Dumka 2015). The mean volume of distribution (Vd_{ss}=0.395 L/kg) in febrile goats was in accordance to the value of 0.320 L/kg reported in previous study conducted in healthy goats (Sagar *et al.* 2015). Limited distribution of cefquinome following IV administration had been obtained in other ruminant species including buffalo, cattle, sheep (Uney *et al.* 2011, Dinakaran *et al.* 2013, Shan *et al.* 2014, Dinakaran and Dumka 2015). Cefquinome is hydrophilic in nature and its pKa is 2.51–2.91. Limited ability of cefquinome to cross lipophilic membranes can be the reason for restricted distribution of the drug to tissues and extravascular fluids.

Application of PK-PD concepts for optimization of dosage regimens of antimicrobials can minimize the risk of emerging problem of bacterial resistance in human and veterinary medicine (Lees *et al.* 2006, Levison and Levison 2009). Cefquinome is classified as an antimicrobial producing time-dependent antibacterial activity against *P. multocida* (Thomas *et al.* 2006, Shan *et al.* 2014). Therefore, cefquinome may be most effective for time when serum concentrations are maintained above the MIC of the target pathogen, therefore, T>MIC has been considered as an important predictor of efficacy for cefquinome (Lees *et al.* 2006, Roberts *et al.* 2007). The T>MIC =>50% of dosage interval has been proposed as a minimum requirement to achieve clinical success, however, T>MIC =100% has been correlated with better therapeutic efficacy of cephalosporins (Roberts *et al.* 2007). In human studies, AUC_{24h}/MIC and T > MIC were PK-PD indices that accurately predicted the

clinical outcome of patients treated with ceftazidime or cefepime for treatment of serious infections (Levison and Levison 2009, Roberts *et al*. 2007). In agreement to these studies, Sidhu and co-workers suggested the use of AUC_{24h}/MIC and T>MIC as predictors of therapeutic outcome of ceftiofur against *P. multocida* in goats (Sidhu *et al*. 2018). Using MIC_{90}=0.125 µg/mL for *P. multocida* determined previously for clinical isolates (Thomas *et al*. 2006), T>MIC (24 h) was 100% for a 24 h dosage interval and AUC_{24h}/MIC (340 h) exceeded the predictive effective values (Table 3). This suggests that cefquinome at the dose rate of 2 mg/kg at the dosage interval of 24 h can be used successfully in febrile goats to treat respiratory infections associated with *P. Multocida* or other pathogens having MIC≤0.125 µg/mL. Similar dosage regimen of 2 mg/kg/24 h against susceptible bacteria of MIC (range 0.035–0.39 µg/mL) had been calculated for cefquinome used IV in healthy goats (Sagar *et al*. 2015). However, 2 mg/kg/24 h dose of cefquinome is not adequate to treat *Staphyloccoci* or other pathogens with MIC_{90}=0.50 µg/mL because both indices; AUC_{24h}/MIC (85) and T>MIC (12 h) fell short of predictive required values (Thomas *et al*. 2006). The findings should be used carefully for further clinical testing because MIC_{90} values of *P. Multocida* and *Staphyloccoci* used for determination of dosage regimen had been obtained from bovine/equine isolates. For future studies, it would be our preference to determine MIC_{90} values of cefquinome against *P. multocida* strains and other pathogens of caprine origin.

From the study, it can be concluded that the PK of cefquinome following IV administration was not much different in febrile goats as compared to healthy goats. The PK of cefquinome was characterized by moderate elimination half-life and slow and limited distribution to the tissues. A favourable PK and PK-PD indices suggested that the dose of 2 mg/kg/24 h of cefquinome would be effective clinically to treat goats affected with *P. multocida* or other infections caused by sensitive bacteria. The study indicated that the dose of 2 mg/kg/24 h will not only assure therapeutic success against *P. multocida* infections but will minimize the risk of resistance emergence for cefquinome in goats.

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