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Pharmacokinetics of Cefquinome on Single Intravenous Administration in Marathwadi Buffalo Calves by Microbiological Assay Technique

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ABSTRACT

Experiment was performed on six healthy Marathwadi buffalo calves of either sex of age above 6 months and weighing between 80 to 120 kg to study the different pharmacokinetic parameters after single intravenous administration @ 2 mg/kg body weight by microbiological assay technique. After intravenous administration of the drug, blood samples (4 ml each) of buffalo calves were collected from external jugular vein using disposable needles in clot activator tubes at different time intervals. The schedule of blood collection for pharmacokinetic studies after intravenous administration was at 0, 5, 10, 15, 30 min and 1, 2, 4, 6, 8, 10, 12 and 24 hrs. The serum levels of cefquinome were estimated by microbiological assay technique using large glass plate. Different Pharmacokinetic parameters were calculated as described by different scientists. The peak serum concentration, elimination half life, volume of distribution, total body clearance, absorption half life and area under curve values found were 1.74 ± 0.151 mcg/ml at 2.5 min of sampling time, 1.97±0.14 h, 3.97 ± 0.83 L/kg ($Vd_{(B)}$) and 2.86 ± 0.34L/kg (Vd_{ss}), 1.11 ± 0.13 $L/kg.h^{-1}$, 0.10 ± 0.02 h, and 1.93 ± 0.23 µg/ml/hr respectively. The bioavailability of cefquinome in buffalo calves was found to be 100 %. It may be concluded that the elimination half life of cefquinome was 2.54 h in Marathwadi buffalo calves indicating the repeating of doses at 12 to 15 h intervals in Marathwadi buffalo calves and the loading dose would be double than the maintenance dose of cefquinome after intravenous administration.

HIGHLIGHTS

- Pharmacokinetics of Cefquinome on Single Intravenous in buffalo calves.
- The elimination half life of cefquinome was 2.54 h.
- Loading dose would be double than the maintenance dose of cefquinome after intravenous administration.

Keywords: Pharmacokinetics, cefquinome, buffalo calves, intravenous, microbiological assay

Cephalosporins are antibacterial agents that are active against many strains of Gram-positive and Gram-negative bacterial species. The key features of 4th generation cephalosporins include their wide range of spectrum, having resistance against degradation by β-lactamase enzymes and improved pharmacokinetic properties (Champawat *et al.,* 2018). It is effective against the treatment of calf septicemia, foot rot in cattle, acute mastitis and pulmonary infections (Venkatachalam *et al*., 2018).

The pharmacokinetics of cefquinome is studied in different animals such as camel, sheep, piglets, chicken, mice, dogs, pigs and calves. However, these studies are conducted in different parts of the world and there are no data available from India. Further no data on pharmacokinetic study in buffalo calves was observed. Thus many data is required

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to be produce in different species of animals by using different routes of administration for its use in veterinary practice on large scale.

MATERIALS AND METHODS

For this study, six Marathwadi buffalo calves of either sex were selected. All the animals were kept under observation for a period of two weeks prior to the experiment. During the entire period of experimentation, the animals were provided ad-libitum dry as well as green fodder, concentrates and clean drinking water.

Group of Marathwadi buffalo calves comprising six animals was administered with cefquinome @ 2 mg/kg b. wt. by intravenous route. In the present study microbiological assay was performed for estimation of serum cefquinome concentrations. For this assay, *Escherichia coli* (MTCC 739) were procured from Microbial Type Culture Collection (MTCC), Chandigarh, UT. Cefquinome was diluted with sterile distilled water and administered @ 2 mg/kg body weight in Marathwadi buffalo calves. Intravenous (IV) injection of the drug was given in the left jugular vein using 20G × 25 mm sterile needle.

The site of prick for blood collection was washed, shaved and cleaned with alcohol. After intravenous administration of the drug, blood samples (4 ml each) of Marathwadi buffalo calves were collected from external jugular vein using disposable needles in clot activator tubes at different time intervals. The schedule of blood collection for pharmacokinetic studies after intravenous administration was at 0, 5, 10, 15, 30 min and 1, 2, 4, 6, 8, 10, 12 and 24 hrs. Serum obtained in clot activator tubes was collected in sterilized plastic vials and stored in refrigerator until assayed.

The serum levels of cefquinome were estimated by microbiological assay technique using large glass plate (Bennett *et al*., 1966; Black *et al*., 1983; Burrows *et al*., 1987).

The different pharmacokinetics parameters like distribution rate constant, elimination rate constant, distribution half-life, elimination half-life, volume of distribution, body clearance of drug, bioavailability, area under curve, mean residence time, Zero time plasma drug concentration, AUMC, drug concentration between tissue and plasma. Peak plasma drug concentration, time of peak plasma drug concentration, loading dose, Maintenance dose, duration of pharmacological effect and the minimum steady-state plasma level etc. were calculated as described by {Baggot (1977); Gibaldi and Perrier (1982); Riviere *et al*. (2011)}.

Various pharmacokinetic parameters data were analyzed by randomized block design and the significance was tested at 5% and 1% levels as per (Snedecor and Cochran, 1994).

RESULTS AND DISCUSSION

Table 1: Pharmacokinetic parameters in Marathwadi buffalo calves (@ 2 mg/kg b.wt. after intravenous administration of cefquinome

Parameters	Unit	buffalo calves	
		Mean	±S.E.
$t_{½\alpha}$	hr	0.10	0.02
$t_{½\beta}$	hr	2.03	0.12
A	hr^{-1}	7.56	1.07
B	hr^{-1}	0.35	0.02
A	µg/ml	1.48	0.13
B	µg/ml	0.62	0.14
C_p^{α}	µg/ml	2.11	0.22
AUC	µg/ml.hr	1.93	0.23
$AUMC$	$\mu g/ml.hr^2$	4.87	0.47
K_{el}	hr^{-1}	1.12	0.08
K_{21}	hr^{-1}	2.51	0.51
K_{12}	hr^{-1}	4.28	0.72
MRT	Hr	2.56	0.13
V_c	L/kg	0.99	0.09
Vd_{area}	L/kg	3.33	0.52
Vd_B	L/kg	3.97	0.83
Vd_{ss}	L/kg	2.86	0.34
Cl_B	L/kg.hr	1.11	0.13
Fc		0.32	0.04
T/P		2.31	0.38
Td	hr	16.83	
$C_{p(min)}^{\alpha}$		0.501	
LD	mg/kg	3.67	
MD	mg/kg	1.998	

The various pharmacokinetic parameters estimated were depicted in table 1. Zero hour plasma concentrations

of cefquinome after its intravenous administration in Marathwadi buffalo calves (C_p^o) was 2.11±0.22 µg/ml.

In the present study, the peak serum concentration, distribution half-life ($t_{1/2(\alpha)}$), elimination half-life ($t_{½(\beta)}$), volume of distribution $Vd_{(B)}$ and (Vd_{ss}), total body clearance, AUC, AUMC and MRT values of cefquinome for Marathwadi buffalo calves were 1.74 ± 0.151 mcg/ml at 2.5 min of sampling time, 0.10 ± 0.02 h, 1.97±0.14 h, 3.97 ± 0.83 L/kg ($Vd_{(B)}$) and 2.86 ± 0.34L/kg (Vd_{ss}), 1.11 ± 0.13 L/kg.h^{-1}, 1.93 ± 0.23 µg/ml/hr, 4.87± 0.47 µg/ml.hr^2 and 2.56 ± 0.13 h respectively after intravenous administration of cefquinome.

The distribution half-life ($t_{1/2(\alpha)}$) in sheep was recorded as 0.06 ± 0.04 h by IV route by (Uney *et al*., 2011) by administrating the cefquinome @ 2mg/kg. The distribution half –life reported by (Uney *et al*., 2011) was lower than the values found in present study.

Limbert *et al*. (1991) has reported the elimination half-life of 1.33 ± 0.41h in calves after intravenous administration of cefquinome @ 10 mg/kg body weight. The half-lives values of cefquinome in buffalo calves obtained in the present study are corresponding to this study. (Tohamy *et al*., 2006) administered the long acting cefquinome formulation in different species of animals and they observed the elimination half-life as 12.86 h in buffalo calves. The elimination half life found in present study was more than the elimination half life reported by (Limbert *et al*., 1991) and less than values reported by (Tohamy *et al*., 2006). This difference was might be due to different body size of animals under study, which is related to metabolism rate.

Volume of distribution (*V*d) is a theoretical concept that connects the administered dose with the actual initial concentration present in the circulation. Volume of distribution values in buffalo calves indicated extensive distribution of cefquinome in different body compartments. This explains the shorter persistence of drug in plasma of Marathwadi buffalo calves. (Uney *et al*., 2011) studied pharmacokinetics of cefquinome (@ 2mg/kg bwt IV) in sheep and observed Vd_{ss} as 0.36 ± 0.06 L/kg, which is less as compared to Marathwadi buffalo calves in the present study. This difference was might be due to species difference under experiment.

Clearance of drug occurs by the perfusion of blood to the organs of extraction. Clearance of drug is a fraction of apparent volume of distribution from which drug is removed per unit time. Total body clearance reported by (Uney *et al*., 2011) was 0.34 ± 0.03 L/hr/kg in sheep after cefquinome (@ 2 mg/kg bwt, IV) and (Errecalde *et al.*, 2002) reported this as 1.20 L/hr/kg in calves receiving cefquinome at the rate of 1mg/kg by IM route, which is higher as compared to that observed in the present study (1.11 ± 0.13 L/kg.h^{-1}) in Marathwadi buffalo calves, which might be due to species variation and changes in protein binding of the drug.

Dinkaran *et al*. (2013) reported the AUC and AUMC values as 32.9± 0.56 and 140 ± 3.96 mcg.hr/ml respectively in buffalo calves after intravenous administration of cefquinome @ 2 mg/Kg body weight. (Uney *et al*., 2011) studied pharmacokinetics of cefquinome (@ 2mg/kg bwt) in sheep and observed the AUC as 5.83 ± 0.45 mcg.hr/ml after IV and 5.19 ± 0.25 mcg.hr/ml after IM administration. These AUC and AUMC values are higher than the AUC values of Marathwadi buffalo calves obtained in the present study. It might be due to species variation and variation in method used for study of cefquinome concentration in blood and method may be one of the factors for difference in values.

Dinkaran *et al*. (2013) reported the MRT value as 4.24±0.09 h in buffalo calves after intravenous administration of cefquinome. (Tohamy, 2011) reported MRT as 7.27 ± 0.44, 4.75 ± 0.47 and 5.13 ± 0.37 h in one months, six months and one year old sheep respectively after administration of cefquinome (10 mg/kg bwt, IM). The MRT value found in present study was lower than the MRT values reported by (Dinkaran *et al*., 2013; Tohamy, 2011). This indicated the variation in MRT values due to the age difference of the animals.

The values of elimination rate constant, first order rate constant of cefquinome transfer from peripheral to central (blood) compartment and first order rate constant of cefquinome transfer from central (blood) to peripheral (tissue) compartment found were 1.12 ±0.08, 2.86±0.34 and 4.28±0.72 hr^{-1}.

The apparent volume of central compartment (V_c) recorded in the present study was 0.99±0.09 L/Kg. (Yang *et al.*, 2009) reported apparent volume of distribution as 0.20 L/kg in pigs after administration of cefquinome @ 1mg/kg bwt. At the same dose in chickens, (Maha, 2005) recorded it as 0.04 L/kg. The values recorded by (Yang

et al., 2009; Maha, 2005) were lower than the value of apparent volume of distribution reported in the present study. This difference might be due to the age, sex and species variation.

In this study the loading dose and maintenance dose of cefquinome found was 3.67 and 1.998 mg/kg body weight respectively.

The bioavailability (F) recorded in the present study was 100 % in Marathwadi buffalo calves after single administration of cefquinome intravenously.

At the dose rate of 2 mg/kg bwt, cefquinome bioavailability was recorded as 95.13 ± 9.93% in piglets (Li *et al*., 2008) and 95.23 ± 9.84% in rabbits (Hwang *et al.,* 2011) Which was lower than the bioavailability value noted in Marathwadi buffalo calves in present study. This difference in bioavailability was might be due to difference in absorption, food effect, drug metabolism/ biotransformation, energy dependent efflux transporters, physico-chemical factors and first pass metabolism.

CONCLUSION

From the results it may be concluded that the elimination half life of cefquinome was 2.54 h in Marathwadi buffalo calves indicating the repeating of doses at 12 to 15 h intervals in Marathwadi buffalo calves. The bioavailability of cefquinome in Marathwadi buffalo calves was found to be 100 %. Further it is concluded that the loading dose would be double than the maintenance dose of cefquinome after intravenous administration and the microbiological assay technique was found to be suitable for the estimation of serum cefquinome concentration in the laboratories where the LC/MS facilities are not available.

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