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Pharmacokinetics of cefquinome and cefquinome concentration in various biological fluids in Marathwadi buffaloes

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Abstract
Experiment was performed on six healthy Marathwadi buffaloes to study the different pharmacokinetic parameters and cefquinome concentration in various biological fluids after single intramuscular @ 1 mg/kg body weight by microbiological assay technique. The peak serum concentration, absorption half-life, distribution half life, elimination half life, volume of distribution, total body clearance, AUC, AUMC, MRT and bioavailability values of cefquinome after intramuscular administration found were 25.67 ± 4.65 mcg/ml**,** 0.21 ± 0.02h, 0.39 ± 0.05 h, 2.30 ± 0.12 h, 0.13 ± 0.02 L/kg ($Vd_{(B)}$) and 0.14±0.02 L/kg (Vd_{ss}), 0.04 ± 0.00 L/kg.h^{-1},27.24±3.67µg/ml.hr, 92.43 ± 13.30µg /ml.hr^2, 3.40± 0.19 h and 177.22%, respectively. The cefquinome concentration in saliva, nasal secretion, urine and milk was recorded as 0.29 ± 0.01, 0.33 ± 0.01, 2.60 ± 0.35 and 0.258 ± 0.01 mcg/ml respectively at twelve hours, however at the same time cefquinome concentration in serum could not be detected. It may be concluded that Cefquinome persists for 10 hours in buffaloes with the peak concentrations 0.76 hours after IM administration**.** The elimination half life of cefquinome was 2.3 h in adult buffaloes indicating the repeating of doses at 12 to 15 h intervals in buffaloes. The loading dose would be double than the maintenance dose of cefquinome after intramuscular administration.

Keywords: Pharmacokinetics, cefquinome, buffaloes, intramuscular, biological fluids, microbiological assay technique

1. Introduction
In veterinary medicine, the cephalosporin cefquinome is approved and used for several animal species in many countries worldwide [1]. In comparison with the so called third generation cephalosporin's, it shows a higher degree of activity against gram negative bacteria [18]. Fourth generation show marked resistance to β-lactamases and increased outer membrane permeability, when compared with third generation cephalosporin's [10]. In addition, it has a broad spectrum and is susceptible to clinically important bacteria such as *Streptococcus* spp., *Staphylococcus* spp., *Pseudomonas* spp., *Moraxella* spp., *Haemophilus* spp., *Corynebacteriae*, *Enterococci*, *Escherichia coli* and gram positive anaerobes tested *in vitro* (Limbert *et al.*, 1991) [12] (Murphy *et al.*, 1994) [14] (Shpigel *et al.*, 1997) [16]. Cefquinome has been shown to have good activity against respiratory tract infections, diarrheoa and mastitis in cattle and buffalo [11, 20, 3]. Moreover, it is highly stable to β-lactamases produced by most of the pathogenic bacteria. It is approved for the treatment of respiratory tract diseases and mastitis for livestock on worldwide.
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 buffaloes was observed. Thus many data is required to be produce in different species of animals by using different routes of administration for its use in veterinary practice on large scale.

2. Materials and Methods
For this study, Six Marathwadi buffaloes of age 6-7 years weighing between 400 to 450 Kg 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.

Cefquinome was diluted with sterile distilled water and was administered to buffaloes by intramuscular route @ 1 mg/kg bwt.

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.

The site of prick for blood collection was washed, shaved and cleaned with alcohol. After intramuscular administration of the drug, blood samples (4ml each) of Marathwadi lactating buffaloes were collected from external jugular vein using disposable needles in clot activator tubes (M/s Ambica Diagnostics, Parbhani) at different time intervals. The schedule of blood collection for pharmacokinetic studies after intramuscular administration was 0, 15, 30 min and 1, 1.5, 2, 4, 6, 8, 10, 12 and 24 hr of cefquinome administration. Serum obtained in clot activator tubes was collected in sterilized plastic vials (M/s Hi Media, Mumbai) and stored in refrigerator until assayed.

The serum levels of cefquinome were estimated by microbiological assay technique using large glass plate [4, 5, 6].

Various body fluids such as nasal secretion, saliva and urine samples were collected from Marathwadi lactating buffaloes after intramuscular administration at 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 hrs. Whereas milk samples were collected at hourly interval up to 4 h and after 4 hour samples were collected at an interval of two hours up to 12 hrs. The body fluids were collected in sterilized plastic vials (M/s HiMedia, Mumbai) and stored in the refrigerator until assayed.

The different pharmacokinetics parameters like peak serum concentration, distribution rate constant, elimination rate constant, absorption half life, 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 etc. were calculated as described by [2, 9, 15].

Various pharmacokinetic parameters data were analyzed by randomized block design and the significance was tested at 5% and 1% levels as per [17].

3. Results and Discussion

The cefquinome concentration in different biological fluids and various pharmacokinetic parameters estimated were depicted in table 1 and 2, respectively.

Table 1: Cefquinome concentration in various biological fluids after intramuscular administration (@ 1mg/kg bwt) in Marathwadi lactating buffaloes**.**

Time (hrs)	Concentration in mcg/ml				
	Serum	Saliva	Nasal secretion	Urine	Milk
	Mean ± SE	Mean ± SE	Mean ± SE	Mean ± SE	Mean ± SE
0	-	-	-	-	-
0.25	8.53±1.19	ND	ND	ND	ND
0.50	16.75±2.09	ND	ND	ND	ND
0.75	25.67±4.65	ND	ND	ND	ND
1	21.43±5.70 ^{b}	4.66±0.32 ^{c}	7.63±0.68 ^{c}	66.33±1.59 ^{a}	0.344±0.04 ^{c}
1.5	11.37±2.08	--	--	--	--
2	6.62±1.31 ^{b}	3.58±0.21 ^{b}	4.12±0.42 ^{bc}	20.62±1.79 ^{a}	0.307±0.01 ^{d}
3	--	2.95±0.15 ^{b}	1.98±0.27 ^{b}	37.75±3.95 ^{a}	0.305±0.01 ^{b}
4	2.50±0.36 ^{b}	2.48±0.12 ^{b}	1.30±0.12 ^{b}	34.58±3.03 ^{a}	0.294±0.02 ^{b}
5	--	1.88±0.07 ^{b}	0.70±0.13 ^{b}	32.75±3.20 ^{a}	-
6	1.07±0.09 ^{b}	1.31±0.06 ^{b}	0.67±0.03 ^{b}	16.75±2.12 ^{a}	0.286±0.02 ^{b}
7	--	0.81±0.04 ^{b}	0.60±0.03 ^{b}	22.96±3.52 ^{a}	-
8	0.46±0.04 ^{b}	0.52±0.02 ^{b}	0.55±0.02 ^{b}	39.92±4.90 ^{a}	0.283±0.01 ^{b}
9	-	0.44±0.01 ^{b}	0.48±0.02 ^{b}	30.83±3.15 ^{a}	-
10	0.21±0.01 ^{b}	0.39±0.01 ^{b}	0.41±0.02 ^{b}	12.40±1.67 ^{a}	0.263±0.02 ^{b}
11	--	0.33±0.01 ^{b}	0.36±0.01 ^{b}	7.10±0.79 ^{a}	-
12	ND	0.29±0.01 ^{b}	0.33±0.01 ^{b}	2.60±0.35 ^{a}	0.258±0.01 ^{b}

ND = Not detected.

The values bearing common superscript do not differ significantly.

The cefquinome concentration in saliva, nasal secretion, urine and milk was established as 4.66 ± 0.32, 7.63 ± 0.68, 66.33 ± 1.59 and 0.344 ± 0.04 mcg/ml respectively at one hour after its intramuscular administration in lactating buffaloes. The corresponding cefquinome concentration in serum at 1 hour was 21.43 ± 5.70 mcg/ml. The cefquinome concentrations in saliva and nasal secretions were three to four folds lower whereas cefquinome concentrations in urine was three fold higher as compared to its corresponding serum cefquinome concentrations. At the same time cefquinome concentrations in milk was found to be lowest amongst other biological fluids selected for the study. The cefquinome concentration in saliva, nasal secretion, urine and milk was recorded as 0.29 ± 0.01, 0.33 ± 0.01, 2.60 ± 0.35 and 0.258 ± 0.01 mcg/ml respectively at twelve hours, however at the same time cefquinome concentration in serum could not be detected.

After intramuscular administration of cefquinome, concentrations in saliva and nasal secretions were increased eight hours onwards which might be due to release of cefquinome from the corresponding tissues in the secretions and therefore the corresponding serum levels were observed comparatively less.

The cefquinome concentrations in urine were not decreased consistently and were observed as ups and downs during the twelve hour period. This is attributed towards that the urine is formed continuously and stored in the bladder and thus the concentrations were found those were actually cumulative concentration for the one hour. Secondly, cefquinome concentrations in urine were much higher to that of the corresponding serum levels attributing that urinary route is the

major route of drug excretion.

The peak serum concentration, absorption half-life, distribution half life, elimination half life, volume of distribution, total body clearance, AUC, AUMC, MRT and bioavailability values of cefquinome after intramuscular administration found were 25.67 ± 4.65 mcg/ml**,** 0.21 ± 0.02h**,** 0.39 ± 0.05 h, 2.30 ± 0.12 h, 0.13 ± 0.02 L/kg ($Vd_{(B)}$) and 0.14±0.02 L/kg (Vd_{ss}), 0.04 ± 0.00 L/kg.h^{-1},27.24±3.67µg/ml.hr, 92.43 ± 13.30µg /ml.hr^2, 3.40± 0.19 h and 177.22%, respectively.

[8] reported the absorption half-life and distribution half life of cefquinome in calves as 0.57 ± 0.06 h and 0.59 ± 0.12 h; respectively these values are higher than the values obtained in the present study in buffaloes. The difference was might be due to age difference.

The total body clearance of 1.20 L/hr/kg in buffalo calves after intramuscular administration of cefquinome @ 2 mg/kg bwt was reported by (Errecalde *et al.*, 2002) [8]. This was higher as compared to that observed in the present study in buffaloes, which might be due to age variation. (Tohamy *et al*., 2006) [19] administered the long acting cefquinome formulation in different species of animals and they observed the elimination half-lives as 13.46 h in cattle calves and 12.86h in buffalo calves. The average elimination half-life reported in the present study was towards lower side as compared to the range of half-life noted by(Tohamy *et al*., 2006) [19].

(Limbert *et al*., 1991) [12] reported volume of distribution as 0.23 L/kg in calves these values are at higher side as compared with the values of buffaloes in the present study.

The area under plasma concentration time curve (AUC) is an important parameter used to calculate clearance, volume of distribution and bioavailability of drugs in pharmacokinetic studies. (Champawat *et al*., 2018) [7] recorded low value than the value of AUC found in present study and recorded average value of area under the curve (AUC) after intramuscular administration of cefquinome in goats was 14.44 ± 0.82 µg ml-1 h. (Yang *et al*., 2009) [21] studied pharmacokinetics of cefquinome (2mg/kg) in pig and observed AUC as 4.12 mcg/L/hr after IM administration. This was also lower than the value calculated in present study in buffaloes. It might be due to species variation or variation in method used for study of cefquinome concentration in blood and method may be one of the factors for difference in values**.** (Errecalde *et al.*, 2002) [8] reported MRT as 1.64 ±0.23 h in calf after administration of cefquinome (IM) at the dose rate of 1 mg/kg bwt which was lower than the value reported in buffaloes in present study at the same dose rate.

The bioavailability (F) recorded in the present study was 177.22% in buffaloes after single intramuscular administration of cefquinome. (Maha, 2005) [13] reported the bioavailability in broiler chickens as 103.17% after administration of cefquinome @ 1mg/kg bwt. At the same dose, (Yang *et al*., 2009) [21] reported it as 102.37% in pigs. The values of bioavailability reported by (Maha, 2005) [13] and (Yang *et al*., 2009) [21] were lower than the value reported 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.

Table 2: Pharmacokinetic parameters in Marathwadi buffaloes (@ 1mg/kg bwt) after intramuscular administration of cefquinome**.**

Parameters	Units	Marathwadi buffaloes	
		Mean	± S. E.
A	µg/ml	135.83	61.25
B	µg/ml	8.52	1.22
A’	µg/ml	1.86	0.57
$t_{½\beta}$	hr	2.30	0.12
$t_{½\alpha}$	hr	0.39	0.05
$t_{½ka}$	hr	0.21	0.02
B Bβ	hr^{-1}	0.31	0.02
A	hr^{-1}	1.92	0.25
Ka	hr^{-1}	3.42	0.24
AUC	µg/ml.hr	27.24	3.67
AUMC	µg/ml.hr^2	92.43	13.30
MRT	hr	3.40	0.19
K_{21}	hr^{-1}	0.44	0.03
K_{12}	hr^{-1}	0.41	0.06
K_{el}	hr^{-1}	1.38	0.23
C_{max}	µg/ml	0.03	0.01
T_{max}	hr	0.76	0.04
Vd_B	L/kg	0.13	0.02
Vd_{ss}	L/kg	0.14	0.02
Cl_B	L/kg.hr	0.04	0.00
Fc	-	0.26	0.05
T/P	-	3.62	0.82
Td	hr	9.82	
F	%	177.22	
$C_{p(min)}{}^{\alpha}$	-	0.0462	
LD	mg/kg	1.9849	
MD	mg/kg	0.999	

4. Conclusion

It was concluded that the elimination half life of cefquinome was 2.3 h in buffaloes indicating the repeating of doses at 12 to 15 h intervals in buffalo calves. The bioavailability of cefquinome in buffaloes was found to be 177.22%. Further it is concluded that the loading dose would be double than the maintenance dose of cefquinome after intramuscular 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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