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Pharmacokinetics of cefquinome in Marathwadi buffalo calves

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Abstract
Experiment was performed on six healthy Marathwadi buffalo calves of either sex to study the different pharmacokinetic parameters after single intramuscular administration @ 2 mg/kg body weight by microbiological assay technique. Absorption half-life, distribution half-life, elimination half-life, volume of distribution, total body clearance, AUC, AUMC, MRT and bioavailability values found were 0.24 ± 0.02 h, 0.30 ± 0.03 h, 2.54 ± 0.12 h, 1.85 ± 0.17L/kg ($Vd_{(B)}$) and 1.95 ± 0.19 L/kg (Vd_{ss}), 0.52 ± 0.04 L/kg.h^{-1}, 3.99 ±0.35 µg/ml.hr, 14.93 ±1.48 µg/ml.hr^2, 3.75± 0.18 h and 165.38% respectively. It may be concluded that the elimination half-life of cefquinome was 2.54 h in buffalo calves indicating the repeating of doses at 12 to 15 h intervals in buffalo calves. The loading dose would be double than the maintenance dose of cefquinome after intramuscular administration.

Keywords: Pharmacokinetics, cefquinome, buffalo calves, intramuscular, microbiological assay technique

Introduction
In veterinary medicine, the cephalosporin cefquinome is approved and used for several animal species in many countries worldwide (Aarestrup and Skov, 2010) [1]. In comparison with the so called third generation cephalosporin's, it shows a higher degree of activity against gram negative bacteria (Suhren and Knappstein, 2003) [17]. Fourth generation show marked resistance to β-lactamases and increased outer membrane permeability, when compared with third generation cephalosporin's (Hancock and Bellido, 1992). 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; Murphy *et al.*, 1994; Shpigel *et al.*, 1997) [11, 13, 15]. Cefquinome has been shown to have good activity against respiratory tract infections, diarrheoa and mastitis in cattle and buffalo (Kikuchi *et al.*, 1995; Wilson *et al.*, 1996; Barkema *et al.*, 1998) [3, 9, 19]. 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 buffalo calves 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.

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 buffalo calves comprising six animals was administered with cefquinome @ 2mg/kg bwt by intramuscular 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 Osmanabadi goat.

Intramuscular (IM) injection of the drug was given to the left side of neck using 20G x 25mm sterile needle. The site of prick for blood collection was washed, shaved and cleaned with alcohol. After intramuscular 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 intramuscular administration was at 0, 15, 30 min and 1, 1.5, 2, 4, 6, 8, 10, 12 and 24 hr. 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) [5, 6].

The different pharmacokinetics parameters like 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 (Baggot, 1977; Gibaldi and Perrier, 1982; Riviere *et al*., 2011) [2, 8, 14].

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) [16]

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Results and Discussion

The various pharmacokinetic parameters estimated were depicted in table 1.

Absorption half-life, 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 mean residence time in buffalo calves were found to be 0.24 ± 0.02 h, 0.30 ± 0.03 h, 2.54 ± 0.12 h, 1.85 ± 0.17L/kg ($Vd_{(B)}$) and 1.95 ± 0.19 L/kg (Vd_{ss}), 0.52 ± 0.04 L/kg.h^{-1}, 3.99 ± 0.35 µg/ml.hr, 14.93 ± 1.48 µg/ml.hr^2, 3.75± 0.18 h, respectively after intramuscular administration of single dose of cefquinome.

Errecalde *et al.* (2002) [7] 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.

The total body clearance of 1.20 L/hr/kg in buffalo calves after intramuscular administration of cefquinome @ 2 mg/kg bwt reported by Errecalde *et al.* (2002) [7]. Which was higher as compared to that observed in the present study in buffalo calves, which might be due to species variation? Tohamy *et al.* (2006) [18] 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 was towards higher side as compared to the range of half-life reported in the present study.

Limbert *et al.* (1991) [11] reported volume of distribution as 0.23 L/kg in calves these values are at lower side as compared with the values of buffalo calves in the present study.

Yang *et al.* (2009) [20] studied pharmacokinetics of cefquinome (2mg/kg) in pig and observed AUC as 4.12 mcg/L/hr after IM administration. Which was in partial agreement with the present study. At the same dose and routes of administration Li *et al.* (2008) [10] in piglets observed AUC as 7.58 ± 1.59 (mcg/ml). hr after intramuscular administration of single dose of cefquinome (@2mg/kg bwt). 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) [7] 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 present study.

The bioavailability (F) recorded in the present study was 100% in buffalo calves after single intramuscular administration of cefquinome intramuscularly. Maha (2005) [12] reported the bioavailability in broiler chickens as 103.17% after administration of cefquinome @ 1mg/kg bwt. At the same dose, Yang *et al.* (2009) [20] reported it as 102.37% in pigs. The values of bioavailability reported by Maha, 2005 [12] and Yang *et al.* were slightly higher 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 1: Pharmacokinetic parameters in marathwadi buffalo calves (@ 2mg/kg bwt) after intramuscular administration of cefquinome

Parameters	Units	Goats	
		Mean	± S.E.
A	µg/ml	8.82	1.17
B	µg/ml	1.13	0.11
A’	µg/ml	0.24	0.03
$t_{½\beta}$	hr	2.54	0.12
$t_{½\alpha}$	hr	0.30	0.03
$t_{½ka}$	hr	0.24	0.02
B Bβ	hr^{-1}	0.28	0.01
A	hr^{-1}	2.41	0.25
Ka	hr^{-1}	2.91	0.18
AUC	µg/ml.hr	3.99	0.35
AUMC	µg/ml.hr^2	14.93	1.48
MRT	hr	3.75	0.18
K_{21}	hr^{-1}	0.52	0.03
K_{12}	hr^{-1}	0.87	0.12
K_{el}	hr^{-1}	1.31	0.16
C_{max}	µg/ml	2.25	0.10
T_{max}	hr	0.74	0.01
Vd_B	L/kg	1.85	0.17
Vd_{ss}	L/kg	1.95	0.19
Cl_B	L/kg.hr	0.52	0.04
Fc		0.23	0.03
T/P		3.81	0.64
Td	hr	13.16	
F	%	165.38	
$C_{p\ (min)}{}^{\alpha}$		0.00654	
LD	mg/kg	3.9379	
MD	mg/kg	1.99	

It was concluded that the elimination half-life of cefquinome was 2.54 h in buffalo calves indicating the repeating of doses at 12 to 15 h intervals in buffalo calves. The bioavailability of cefquinome in buffalo calves was found to be 165.38%. 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.

References

1. Aarestrup FM, Skov RL. Evaluation of ceftiofur and cefquinome for phenotypic detection of methicillin resistance in *Staphylococcus aureus* using disk diffusion testing and MIC-determinations. Veterinary Microbiology 2010;140:176-179.
2. Baggot JD. Principle of drug disposition in domestic animals. In "The basis of Veterinary Clinical Pharmacology" ed. 1st W. B. Saunders Co. Philadelphia 1977, 238.
3. Barkema HM, Schukken YH, Lam TGM, Beiboer ML, Wilmine H *et al*. Incidence of clinical mastitis in dairy herds grouped in three categories by bulk milk somatic cell counts. Journal of Dairy Science 1988;81:411-419.
4. Bennet JV, Brodie JL, Benner EJ, Kirby MM. Simplified accurate method for antibiotic assay in clinical specimen. Applied Microbiology 1966;14:170-177.
5. Black WD, Holt JD, Gentry RD. Pharmacokinetic study of neomycin in calves following intravenous and intramuscular administration. Canadian Journal of Comparative Medicine 1983;47:433-435.
6. Burrows GE, Barto PB, Martin BM. Comparative pharmacokinetics of gentamicin, neomycin and oxytetracycline in newborn calves. Journal of Veterinary Pharmacology and Therapeutics 1987;10:54-63.
7. Errecalde CA, Guillermo FP, Pulles Ignacio, Luders CF, Ovando H G. Farmacocinetica de cefquinome en terneros por aplicacion intramuscular. Rev Col Cience Pec 2002;15(3): 281-285.
8. Gibaldi M, Perrier D. Pharmacokinetics. 2nd Edn. Marcel Dedder, New York 1982, 494. https://doi.org/10.1002/bdd.2510040213.
9. Kikuchi N, Kagota C, Nomura T, Hiramune T, Takahashi T, Yanagawa R. Plasmid profiles of *Klebsiella pneumoniae* isolated from bovine mastitis. Veterinary Microbiology 1995;47:9-15.
10. Li XB, Wu WX, Su D, Wang ZJ, Jiang HY, Shen JZ. Pharmacokinetics and bioavailability of cefquinome in healthy piglets. Journal of Veterinary Pharmacology & Therapeutics 2008;31:523-527.
11. Limbert M, Dieter I, Norbert K, Astrid M, Karl S, Gerhard S *et al*. Antibacterial activities *in vitro* and *in vivo* and pharmacokinetics of cefquinome (HR 111V), a new broad-spectrum cephalosporin. Antimicrobiological Agents Chemotherapy 1991;35(1):14-19.
12. Maha ZG. Pharmacokinetics of cefquinome and tissue concentration in broilers. Bulletin of Faculty of Pharmacy, Cairo University 2005;43(2):201-207.
13. Murphy SP, Erwin ME, Jones RN. Cefquinome (HR 111V) *In vitro* evaluation of a broad-spectrum cephalosporin indicated for infections in animals. Diagnostic Microbiology & Infectious Diseases 1994;20:49-55.
14. Riviere JE, Papich MG, Richard AH. Veterinary Pharmacology and Therapeutics. 9th Edition. Wiley Blackwell, United states 2011, 1552.
15. Shpigel NY, Levin D, Winkler M, Saran A, Ziv G, Bottner A. Efficacy of cefquinome for treatment of cows with mastitis experimentally induced using *Escherichia coli*. Journal of Dairy Science 1997;80:318-323.
16. Snecdecor GW, Cochran WG. Statistical methods. Oxford and IBH Publication Co., Calcutta 1994, 534.
17. Suhren G, Knappstein K. Detection of cefquinome in milk by liquid chromatography and screening methods. Analytica Chimica Acta 2003, 363-372.
18. Tohamy MA, Smail MI, EI-Gendy AM. Comparative pharmacokinetics of cefquinome in ruminants. Egyptian Journal of Social Pharmacology and Experimental Therapeutics 2006;4:12-18.
19. Wilson DJ, Gonzalez RN, Das HH. Bovine mastitis pathogens in New York and Pennsylvania: Prevalence and effects of somatic cell count and milk production. Journal of Dairy Research 1996;80:2592-2598.
20. Yang Dawei, Chen Zhang, Liu Ding, Huan Zhong, Shen Xiang Guang, Xu Susi *et al*. Pharmacokinetics and bioavailability of cefquinome in pigs. Chinese Journal of Veterinary Science 2009;29(9):1182-1185.