

Original Research Article

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Disposition Kinetics of Cefquinome in Calves after a Single Intramuscular Bolus Dose

Hemvati, Pratishtha Sharma* and Ashok Gaur

Department of Veterinary Pharmacology and Toxicology, College of Veterinary and Animal Science, Rajasthan University of Veterinary and Animal Sciences (RAJUVAS), Bikaner-334001, Rajasthan, India

*Corresponding author

ABSTRACT

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Cefquinome is fourth generation cephalosporin developed exclusively for veterinary use. The present research was aimed to investigate the disposition kinetic profile of cefquinome at the dose level of 2 mg.kg⁻¹ body weight following single intramuscular administration. Cefquinome concentrations in plasma were determined by microbiological assay technique using *Kocuria rhizophila* MTCC 1541 as the test organism. The plasma concentration-time profile following intramuscular administration was best described by one-compartment open model. The peak plasma concentration (C_{max}) of 5.79 ± 0.35 µg.ml⁻¹ was achieved at 1.10 ± 0.17 h (t_{max}). The absorption half-life (t_{1/2ka}), elimination half-life (t_{1/2p}), area under plasma drug concentration-time curve (AUC) and apparent volume of distribution (Vd_{area}) of cefquinome were 0.25 ± 0.04 h, 1.68 ± 0.16 h, 16.02 ± 1.11 µg.ml⁻¹.h and 0.30 ± 0.03 L.kg⁻¹, respectively. Cefquinome @ 2 mg.kg⁻¹ at 12 hour dosing interval is sufficient to maintain desired therapeutic level in calves considering MIC ≤ 0.25 µg.ml⁻¹.

Introduction

Cefquinome is a potent and efficacious fourth generation aminothiazolyl cephalosporin with broad spectrum of activity against Gram-positive and Gram-negative bacteria, developed exclusively for veterinary use including food animals (Murphy *et al.*, 1994). It has certain advantages over the earlier cephalosporins which include extended spectrum activity, penetration ability into the periplasmic space of Gram negative bacteria, enhanced binding with penicillin-binding

proteins and improved bioavailability. It has time-dependent bactericidal effect, as shown by β-lactam antibiotics, and is stable against chromosomal as well as plasmid-encoded β-lactamases that are produced by a majority of clinically important bacteria (Limbert *et al.*, 1991; Bryskier, 1997; Thomas *et al.*, 2006).

The chemical modifications in the basic cephalosporin structure made cefquinome a zwitterion, the property that facilitates rapid penetration across the biological membranes, including the porins of the bacterial cell wall,

improving bioavailability and the enhancing spectrum of antimicrobial activity, in comparison with second and third generation cephalosporins (Sader and Jones, 1993; Shpigel *et al.*, 1997; Guerin-Faubleee *et al.*, 2003; Thomas *et al.*, 2006). The principal chemical difference between cefquinome and third generation cephalosporins (e.g. cefotaxime or ceftriaxone) is the introduction of a quarternary ammonium side chain attached at C-3 of the beta-lactam nucleus (Bryskier, 1997).

Cefquinome is time-dependent bactericidal agent and its pharmacokinetic behavior is dose-independent (Limbert *et al.*, 1991; Yuan *et al.*, 2011). It shows rapid and complete absorption following intramuscular administration, widely distributed throughout body tissues and fluids including bronchial mucosal tissues, peritoneal fluid, biliary fluid and milk (Ehinger *et al.*, 2006; Uney *et al.*, 2011). Cefquinome has excellent penetration in udder with experimentally-induced mastitis in cows with *Escherichia coli* (Shpigel *et al.*, 1997). Cefquinome is excreted mainly by kidneys within 24 h of administration, 60 and 80% of the administered dose was recovered in the urine of mice and dogs, respectively (Limbert *et al.*, 1991).

Pharmacokinetic studies of cefquinome have been conducted in other species but there is paucity of pharmacokinetic data in calves, so the present study was undertaken to generate disposition kinetic parameters of cefquinome after intramuscular administration in calves and to determine the appropriate dosage regimen in calves.

Materials and Methods

Drug

Cefquinome 2.5% ready-to-use suspension for intramuscular injection of a multinational

commercial brand was purchased from local market. It gives 25 mg cefquinome per ml.

Animals

Five clinically healthy male calves of 4-6 months age and weighing 40-60 kg were used. Animals were kept under good hygienic condition and maintained on green fodder, concentrated mixture and water was provided *ad libitum*. None of the animals were been treated with antimicrobials for one month prior to the trial. The study was approved by the Institutional Ethics committee of Rajasthan University of Veterinary and Animal Sciences, Bikaner.

Experimental design

Each animal was given a single intramuscular bolus dose of 2 mg.kg⁻¹ body weight on the lateral aspect of neck. Blood samples were collected in EDTA containing test tubes from jugular vein at 0, 0.08, 0.17, 0.33, 0.5, 0.75, 1.0, 1.5, 2, 4, 6, 8, 10, 12 and 24 h after administration of the drug. Blood samples were centrifuged at 3000 rpm for 15 min to separate the plasma. Plasma samples were stored at -20°C until analysis.

Drug assay

Cefquinome concentrations in plasma samples were determined by microbiological assay method described by Arret *et al.*, (1971) using *Kocuria rhizophila* MTCC 1541 as test organism which is equivalent of *Micrococcus luteus* ATCC 9341 (El-Badawy *et al.*, 2015). Six wells were made at equal distance in standard petri-dishes containing 25 ml of seeded agar. The wells were filled with 100 µl of either the test samples or cefquinome standard concentrations. The plates were incubated at 37°C for 24 h. The inhibition zone diameters were measured and the cefquinome concentrations in the test samples

were extrapolated from the standard curve. The lowest detection limit of the cefquinome assay was 0.1 µg/ml. Standard curve were prepared using antibacterial-free pooled plasma collected from the animals prior to the experiment. Cefquinome standard solutions of concentrations of 0.098, 0.195, 0.391, 0.78, 1.56, 3.125, 6.25, 12.5 and 25 µg.ml⁻¹ were prepared. Semi-logarithmic plots of the zone of inhibitions versus standard cefquinome concentrations were linear with typical correlation coefficient of 0.990.

Pharmacokinetic analysis

Based on the apparent visual curve fitting of semi-logarithmic plots of plasma cefquinome concentrations versus time data of individual animals following administration by intramuscular route, pharmacokinetic determinants were determined. Plasma cefquinome levels-time data after attainment of peak levels were best fitted to a one compartment open model using the mono exponential equation:

$$C_p = B e^{-\beta t} - A' e^{-K_a t}$$

Where C_p is the plasma concentration at time 't'; K_a , and β are absorption, and elimination rate constants; A' and B are the zero time intercepts of absorption and elimination phases, respectively; and "e" is base of the natural logarithm.

The rate constants, so derived, were used to calculate the respective half life values. Other pharmacokinetic parameters were computed according to the standard formulae (Baggot, 2001; Gibaldi and Perrier, 2007). Values of all the pharmacokinetic parameters have been expressed as the mean \pm SE.

Results and Discussion

Plasma cefquinome concentration versus time data is plotted on a semi logarithmic graph

shown in Figure 1. Following intramuscular administration of cefquinome, the drug concentration of 0.95 ± 0.18 µg.ml⁻¹ was observed with in 2.5 min which gradually increased and reached at peak plasma concentration (C_{max}) of 5.37 ± 0.40 µg.ml⁻¹ at 1 h (t_{max}). After reaching to maximal, plasma levels declined gradually to 0.28 ± 0.03 µg.ml⁻¹ at 8 h. cefquinome concentrations around the MIC value of 0.25 µg.ml⁻¹ were observed up to 8 h only.

The plasma concentration versus time profile following single intramuscular dose of cefquinome was best described by a mono - compartment open model which is similar to that described in goats (Champawat *et al.*, 2018), camel (Al-Taher, 2010) and dog (Zhou *et al.*, 2015). However, a two-compartment open model was described in sheep (Tohamy, 2011), piglets (Li *et al.*, 2008) and ducks (Yuan *et al.*, 2011).

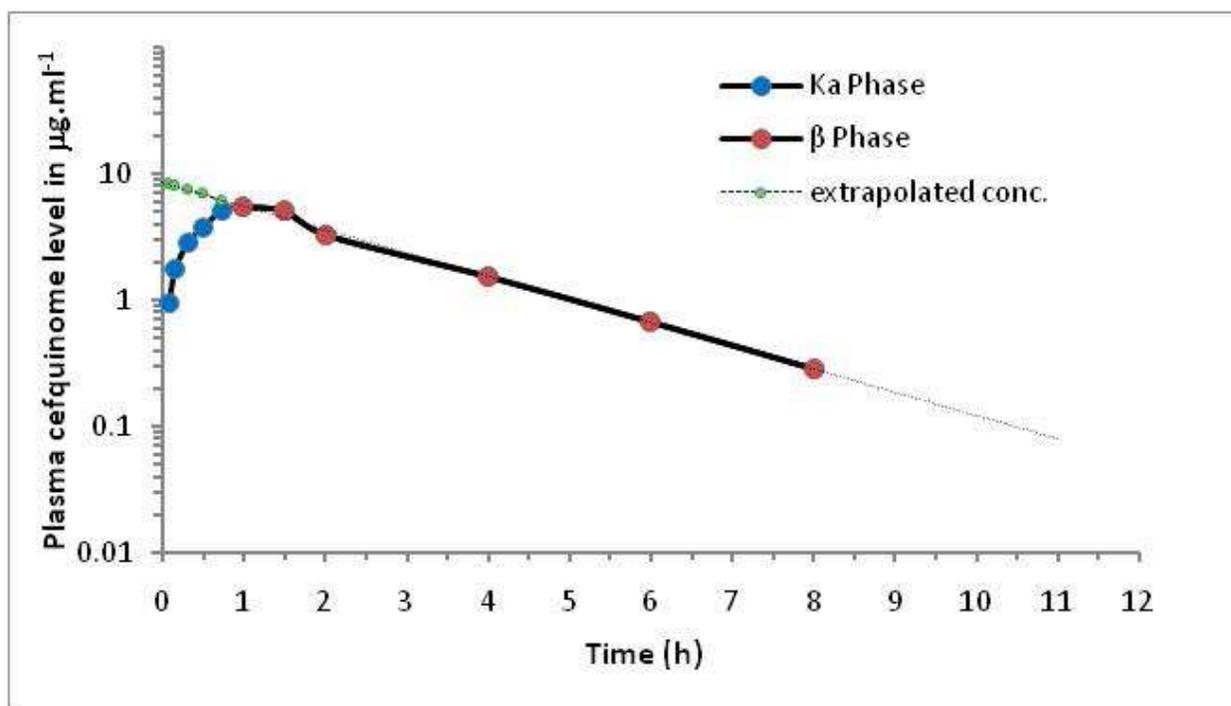
Different disposition kinetic parameters have been summarized in Table 1. Following IM administration, absorption of cefquinome was apparently very fast as revealed by initial plasma drug concentrations with in 2.5 min of drug administration (Figure 1) and also the respective absorption half life ($t_{1/2K_a}$) values of 0.25 ± 0.04 h and the t_{max} value of 1.10 ± 0.17 (Table 1). Comparable value of $t_{1/2K_a}$ have been reported in goats (0.29 ± 0.04 h) (Champawat *et al.*, 2018) and rabbit (0.28 ± 0.02 h) (Shalaby *et al.*, 2014). However, higher $t_{1/2K_a}$ values of cefquinome have been observed in sheep (Rana *et al.*, 2015) and camel (Al-Taher, 2010) with corresponding values of 0.61 ± 0.10 h and 4.35 ± 0.27 h, respectively. Lower $t_{1/2K_a}$ value of 0.14 ± 0.05 h was reported in beagle dogs (Zhou *et al.*, 2015).

Elimination half-life ($t_{1/2\beta}$) of cefquinome in calves in the present study was found to be 1.68 ± 0.16 h following IM administration. It is comparable to $t_{1/2\beta}$ in ducks (1.79 ± 0.13 h) (Yuan *et al.*, 2011).

Table.1 Pharmacokinetic determinants of cefquinome in calves following a single intramuscular bolus dose at the rate of 2 mg.kg⁻¹ body weight

Parameter	Unit	Mean ± S.E.
A'	µg.ml ⁻¹	10.43 ± 1.35
Ka	h ⁻¹	2.97 ± 0.41
t _{½ka}	h	0.25 ± 0.04
B	µg.ml ⁻¹	8.46 ± 1.03
β	h ⁻¹	0.42 ± 0.03
t _{½β}	h	1.68 ± 0.16
C _{max(obs)}	µg.ml ⁻¹	5.79 ± 0.35
t _{max(obs)}	h	1.10 ± 0.17
AUC	µg.ml ⁻¹ .h	16.02 ± 1.11
AUMC	µg.ml ⁻¹ .h ²	46.26 ± 4.88
MRT	h	2.88 ± 0.23
Vd _{area}	L. kg ⁻¹	0.30 ± 0.03
Cl	ml. kg ⁻¹ .h ⁻¹	122.35 ± 7.10

Fig.1 Semi logarithmic plot of mean (n=5) plasma concentration versus time curve of cefquinome given intramuscularly in calves at the dose of 2 mg.kg⁻¹ body weight. Data presented are mean ± SE of five animals



Higher $t_{1/2\beta}$ values have been reported in buffalo calves (3.73 ± 0.10 h) (Venkatachalam *et al.*, 2018), sheep (12.29 ± 2.62 h) (Rana *et al.*, 2015), piglet (4.36 ± 2.35 h) (Li *et al.*, 2008) and camel (10.24 ± 0.8 h) (Al-Taher, 2010). Lower value of $t_{1/2\beta}$ (1.48 ± 0.04 h) has been reported in goats (Champawat *et al.*, 2018).

The AUC values of cefquinome in calves after IM administration were calculated to be $16.02 \pm 1.11 \mu\text{g}\cdot\text{ml}^{-1}\cdot\text{h}$. Almost similar values of AUC of cefquinome have been reported in sheep (Rana *et al.*, 2015), goats (Champawat *et al.*, 2018) and camel (Al-Taher, 2010) but higher values of AUC were reported in chickens (El- Sayed *et al.*, 2015) and rabbits (Shalaby *et al.*, 2014). Lower value of AUC was reported in Beagle dogs (Zhou *et al.*, 2015).

In conclusion, cefquinome is a beta-lactam antimicrobial and acts as a time-dependent bactericidal drug (Thomas *et al.*, 2006), the most appropriate PK/PD parameter to describe drug efficacy is the time during which the drug's concentration exceeds the MIC ($T > \text{MIC}$) (McKellar *et al.*, 2004; Zonca *et al.*, 2011). It is generally recommended that $T > \text{MIC}$ should be at least 50% of the dosage interval to ensure an optimal bactericidal effect (Winther *et al.*, 2011). In the present study, the plasma levels above the minimum inhibitory concentration (MIC) level of $\geq 0.25 \mu\text{g}\cdot\text{ml}^{-1}$ were maintained up to 8 h following intramuscular administration of cefquinome. Cefquinome, therefore, at the dose rate of $2 \text{ mg}\cdot\text{kg}^{-1}$ body weight intramuscularly and at twelve hour dosing interval is recommended to ensure an optimal bactericidal effect in calves.

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