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PHARMACOKINETICS OF CEFQUINOME FOLLOWING INTRAVENOUS AND INTRAMUSCULAR INJECTION IN CAMELS

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ABSTRACT

The pharmacokinetics of cefquinome was determined in camels following single intravenous and intramuscular injection at a dose of 1 mg/kg into 5 healthy she-camels. A crossover study was carried out in 2 periods separated by 30 days clearance period. Cefquinome concentrations in plasma were determined by LC-MS/MS assay. Cefquinome concentration *vs* time data after IV and IM was best fitted to a two-compartment open model. Cefquinome mean values of area under concentration–time curve (AUC) were 15.37 ± 1.06 and 12.85 ± 2.15 µg/ml/h after IV and IM injection, respectively. Distribution and elimination half-lives were 0.14 ± 0.04 h and 3.15 ± 0.22 h after IV dose and 1.42 ± 0.11 h and 6.68 ± 0.87 h after IM administration. The value of total body clearance (Cl_{tot}) was 0.07 ± 0.001 L/kg/h and volume of distribution at steady state (V_{ss}) was 0.27 ± 0.02 L/kg. In conclusion, cefquinome persisted in plasma for 12 hours at concentration that exceeds the MIC for many microorganisms such as *Streptococcus* spp., *Staphylococci*, *Klebsiella* spp., *Pasteurella* spp., *Salmonella* spp. and enteric and systemic *Escherichia coli*. Therefore, it is suggested using cefquinome twice daily intravenously or intramuscularly at a dose of 1mg/kg in camels.

Key words: Camels, cefquinome, LC-MS/MS assay, pharmacokinetics

Cefquinome is an injectable aminothiazolyl cephalosporin derivative. In veterinary medicine, cefquinome is approved and used for several animal species in many countries worldwide (Aarestrup and Skov, 2010).

The pharmacokinetics of cefquinome has been studied in various animal species including, sheep (Uney *et al,* 2011), goats (Dumka *et al,* 2013), buffalo calves (Dinakaran *et al,* 2013), cattle (Shan *et al,* 2014; Ahmad *et al,* 2015), piglets (Li *et al,* 2008), horses (Winther *et al,* 2011), dogs (Zhou *et al,* 2015), boars (Liu *et al,* 2012), ducks (Yuan *et al,* 2011) and chickens (Xie *et al,* 2013). Camels have peculiar physiological and biochemical features, which may be revealed in their response to xenobiotics and in the disposition of drugs given to them (Kadir *et al,* 1997 and Oukessou *et al,* 1999). Camels have comparatively low glomerular filtration rate and renal plasma flow (Etzion and Yagil, 1986). The pharmacokinetics of cefquinome in camels following IM injection was studied. Data concerning the pharmacokinetic profile of cefquinome after IV injection and bioavailability after IM injection in camels are lacking. The aim of this study was to investigate pharmacokinetic profile of cefquinome in healthy camels following single IV and IM administration and to recommend a rational dosage schedule for potential use of cefquinome in camel diseases caused by susceptible microorganisms.

Materials and Methods

Drugs

Cefquinome sulfate analytical standard was obtained from Intervet International (Mechelen, Belgium). Cefquinome (Cobactan® IV 4.5%) was procured from Intervet International Company, Netherlands for present study.

Animals

The present experiment was accomplished at the Centre for the Studies and Development of Camels in Matrouh Governorate (Animal Production Research Institute), Egypt. The study was conducted on 5 she-camels with 440-570 kg body wt. Animals were kept under the best hygiene condition, fed on green fodder, concentrated mixture, hay and water was provided *ad-libitum*. None of the animals

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were treated with chemical agents for one month before the trial. Apparently healthy animals were clinically inspected and blood and faecal samples were examined to assure that animals are free from blood and intestinal parasites. The she-camels were injected into the left jugular vein with cefquinome 1 mg/kg. b.wt. The animals were then marked and blood samples (10 ml) were collected before and at 5, 15 and 30 min, 1, 2, 3, 4, 6, 8, 12 and 24 h after cefquinome injection from the right jugular vein. The samples were drawn into heparinised tubes and the plasma was separated immediately by centrifugation at 3000 rpm for 20 min and stored at -20°C until analysis. Animals were then left for 30 days after the intravenous injection to ensure complete elimination of cefquinome from their bodies. Then, each she-camel was injected intramuscularly into the deep gluteal muscle of the hindquarter with cefquinome in the same dose. Blood samples were withdrawn after intravenous injection and plasma was collected for determination of cefquinome concentration.

Analysis of cefquinome

Preparation of standard solution

Stock standard solutions of cefquinome were prepared at concentrations of approximately 1000 µg /ml in MeOH, divided into small portions and stored in amber glass vials at −20°C. Working solutions for plasma (0.005, 0.01, 0.05, 0.1, 0.5,1, 2, 5, 10 µg/ml) were obtained by further diluting the stock solution with MeOH. Standard curve in plasma solution was drawn by plotting the peak area against the corresponding concentration of cefquinome. All chemicals utilised in this study were of analytical grade or HPLC grade quality.

LC/MS analysis:

LC/MS/MS 4000 QTRAP (Applied Bioscience): Advanced Linear ion trap liquid chromatography was utilised for quantitative analysis of cefquinome. The mass conditions were adopted according to Shi-juan *et al* (2012). The extraction procedure was carried out according to the method described by Li *et al* (2014). The European Commission guidelines and criteria were utilised to assess the method validation. Selectivity was determined from retention time, ion ratios and identification points (IP) for cefquinome (EC, 2006).

Pharmacokinetic analysis

The pharmacokinetic parameters were calculated by PK Solver: An add-in program for Microsoft Excel, version 2 (Zhang *et al,* 2010). The mean pharmacokinetic variables were obtained by averaging the variables calculated for drug disposition after IV or IM administration to each camel. The proper pharmacokinetic model was determined by visual examination of individual concentration–time curves and by application of Akaike's Information Criterion (AIC).

Statistical Analysis

Differences between means of data obtained from intravenous and intramuscular routes were tested for significance by the Student 't' test using SPSS 14.

Results and Discussion

No clinical signs of adverse effects or intolerance were observed to cefquinome after IV injection in camels. The used analytical method proved linear and reproducible for the detection of cefquinome in plasma samples at concentration ranged from 0.005 to 10 µg/ml. The limit of detection (LOD) and the limit of quantification (LOQ) of the assay were 0.001 and 0.005 µg/ml, for plasma the recovery of cefquinome in plasma was 91.16 ± 0.036%. The intraday and the interday variation coefficients were less than 10 and 15% in all cases, respectively.

Following a single intravenous or intramuscular injection of cefquinome in camels, the drug plasma concentration *vs* time followed the 1st order 2 compartments open model (Fig 1). Cefquinome was detected in plasma after 24 h of IV and IM administration at a concentration of 0.023 ± 0.003 and 0.017 ± 0.002 µg/ml, respectively (Fig 1 and 2). The pharmacokinetic parameters of cefquinome following IV and IM injection are recorded in table 1. Cefquinome after an intravenous dose revealed a rapid distribution half-life ($t_{½\alpha}$) of 0.14 ± 0.04 h). The apparent volume of distribution at steady state (V_{ss}) was 0.27 ± 0.02 l/kg. The half-life ($t_{½\beta}$) of elimination was 3.15 ± 0.22 h. Cefquinome was cleared by all clearance processes in the body at a rate of 0.07 ± 0.001 l/kg/h. The mean residence time (MRT) was 4.21 ± 0.29 h.

Following a single IM injection, cefquinome achieved maximum serum concentration (C_{max}) of 3.2 ± 0.39 µg/ml after a maximum time (T_{max}) of 0.82 ± 0.06 h. The absorption half-life ($t_{½ab}$) was 0.26 ± 0.03. The elimination half-life $t_{½\beta}$ was 6.68 ± 0.87 hours. The mean systemic bioavailability of cefquinome following a single IM injection was 85.52 ± 11% (Table 1).

In Comparison of pharmacokinetics parameters of cefquinome following a single intravenous and intramuscular injection, the results revealed that A, α, B, β, k_{10}, k_{12}, k_{21} were significantly lower after intramuscular than those after intravenous administration of the same dose. On the other hand, the $t_{1/2\alpha}$, $t_{1/2\beta}$ and MRT were significantly longer although, the AUC was lower after intramuscular injection.

Cefquinome plasma concentration following a single intravenous (IV) injection in healthy camels indicated that the disposition of cefquinome obeyed the 1st order 2 compartments open model, as the decline in the drug concentrations is curvilinear on the semilogarithmic scale. In this study, the difference between the distribution rate constant (α, 5.28 ± 1.59 h^{-1}) and the slow post-distribution rate constant (β, 0.22 ± 0.02 h^{-1}) is vast. This indicates the existence of a two-compartment model (Jambhekar and Breen, 2009) and reflecting a very short distribution half-life in comparison to the long elimination half-life, the fact that was obvious in the present study. The obtained result was consistent with those reported for cefquinome in sheep (Uney *et al,* 2011), goats (Dumka *et al,* 2013), buffalo calves (Dinakaran *et al,* 2013), cattle (Shan *et al,* 2014; Ahmad *et al,* 2015), piglets (Li *et al,* 2008), horses (Winther *et al,* 2011), dogs (Zhou *et al,* 2015), boars (Liu *et al,* 2012), chickens (Xie *et al,* 2013) and ducks (Yuan *et al,* 2011). Plasma cefquinome concentration decreased gradually until reaching to 0.02 ± 0.003 µg/ml 24 hours post intravenous injection.

In this study, the 1st-order elimination rate constant of cefquinome from the central compartment (K_{10}) following a single IV injection (0.59 ± 0.05 h^{-1}) indicates the faster elimination rate. This observation is about similar to that reported after IV administration of cefquinome in buffalo calves (Dinakaran *et al,* 2013) and in cattle (Shan *et al,* 2014). However, higher values were previously recorded for cefquinome in goats (Dumka *et al,* 2013) and in porcine (Zhang *et al,* 2014) but lower values were registered in horse (Winther *et al,* 2011) and cattle (Ahmad *et al,* 2015).

Cefquinome was transferred from the central to the peripheral compartment at higher rate (K_{12} = 2.96 ± 1.09 h^{-1}) than its passage from the peripheral to the central compartment (K_{21} = 1.95 ± 0.47 h^{-1}). This pattern coincided with that reported for cefquinome in cattle (Shan *et al,* 2014). The value of K_{12} was about like to that reported for cefquinome in the porcine (Zhang *et al,* 2014). The value of K_{21} of cefquinome in camel was higher than the value in goat (Dumka *et al,* 2013), in horse (Winther *et al,* 2011), in cattle (Ahmad *et al,* 2015) but it was lower than the value in porcine (Zhang *et al,* 2014).

The elimination rate constant [β] of cefquinome following a single IV injection was 0.22 ± 0.02 h^{-1}. This

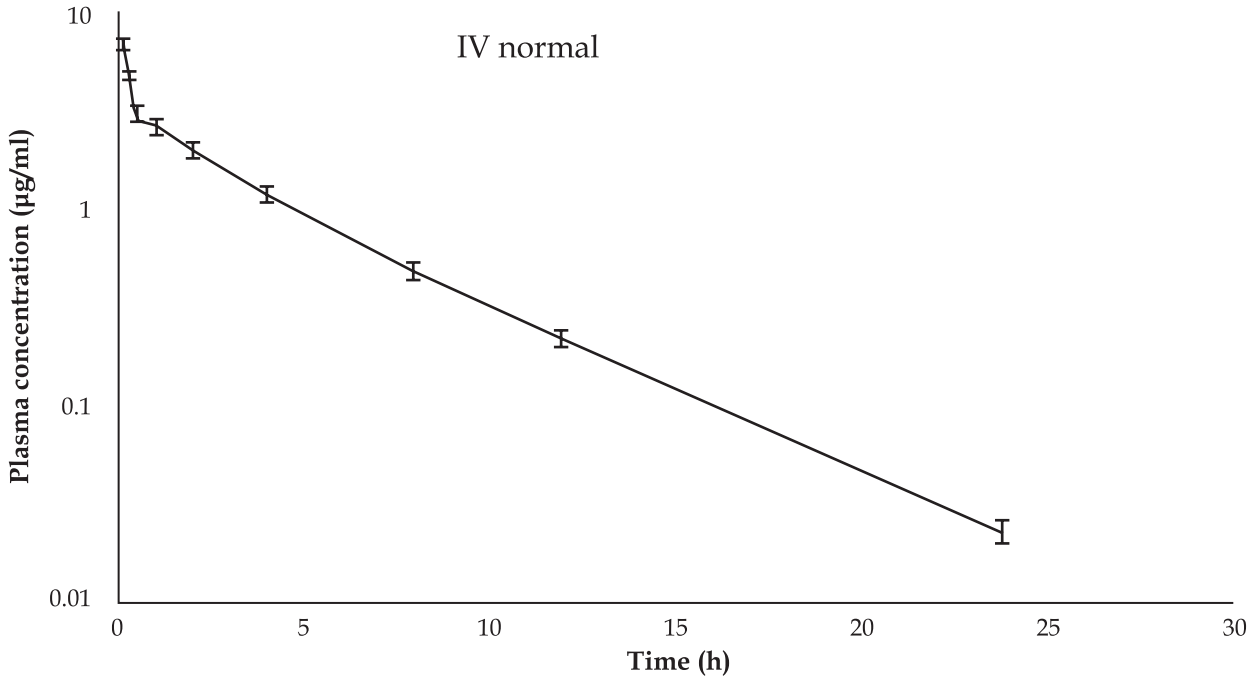

Fig 1. Semilogarithmic graph depicting the time course of cefquinome in plasma of camels (n=5) following a single intravenous injection of 1 mg/kg b.wt.

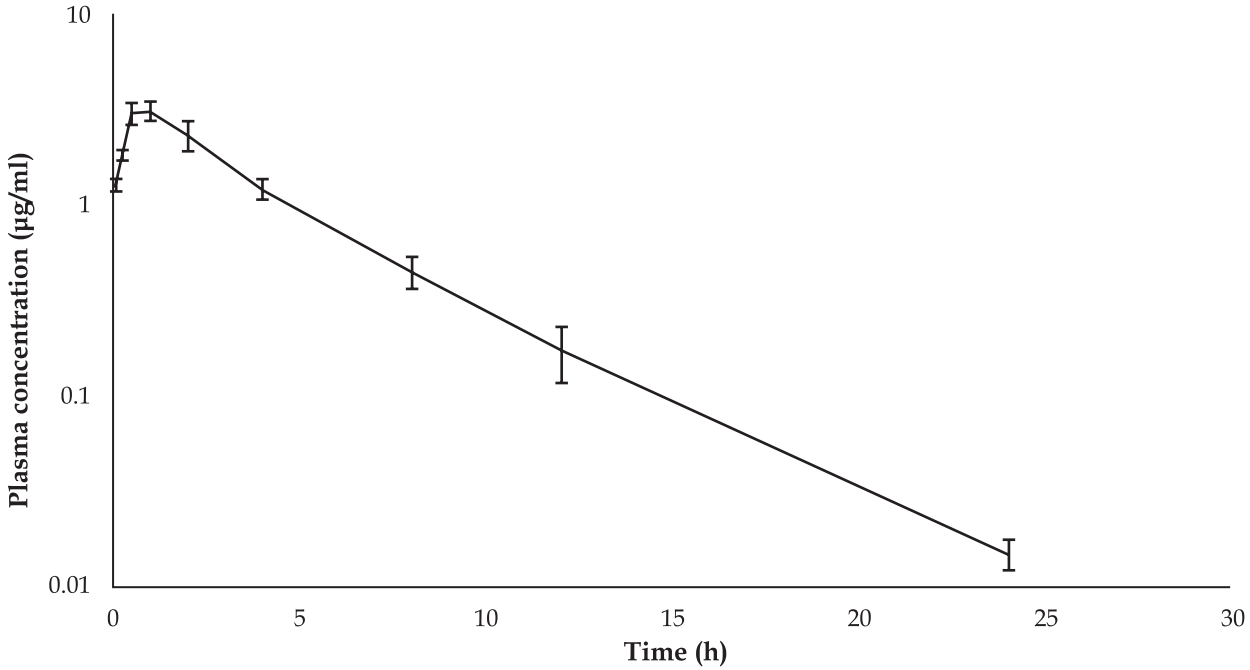

Fig 2. Semilogarithmic graph depicting the time course of cefquinome in plasma of camels (n=5) following a single intramuscular injection of 1 mg/kg b.wt.

is nearly similar to that reported in the horse (Winther *et al,* 2011). However, the obtained value was shorter than that recorded in other species such as dogs (Zhou *et al,* 2015) and piglets (Li *et al,* 2008). The elimination half-life ($t_{½\beta}$; 3.15 ± 0.22 h) of cefquinome following a single IV injection was nearly similar to that reported in the horse (Winther *et al,* 2011) and buffalo calves (Dinakaran *et al,* 2013). On the contrary, this obtained value was longer than that recorded in cattle (Ahmad *et al,* 2015), dog (Zhou *et al,* 2015) and piglet (Li *et al,* 2008; Zhang *et al,* 2014) but it was shorter than that reported in goat (5.76 ± 0.19 h) (Dumka *et al,* 2013).

The value of AUC obtained in the present study was 15.44 ± 1.07 µg/ml.h. This value is consistent with the values reported in the horse following IV administration of similar dosage rate (Winther *et al,* 2011) and nearly similar to that reported in crossbred wild boars (13.85 ± 2.57 µg/ml.h) following IV administration of cefquinome at double doses (Liu *et al,* 2012). Although it is much lower than that reported in goats (33.83 ± 2.53 µg/ml.h) (Dumka *et al,* 2013) and buffalo calves (32.9 ± 0.56 µg/ml.h) (Dinakaran *et al,* 2013) following IV of double the dose. On the contrary, this obtained value was higher than that reported in other species such as sheep (5.83 ± 0.45 µg/ml.h)(Uney *et al,* 2011), piglets (8.07 ± 1.91 µg/ml.h) (Li *et al,* 2008) following IV administration of 2 mg/kg b.wt. It appears that species of the animal rather than dose is the more important factor for these discrepancies.

The rate of total body clearance of cefquinome (CL_{tot}; 0.07 L/kg/h) was similar to that reported in buffalo calves (0.06 L/kg/h) (Dinakaran *et al,* 2013) after IV administration of 2 mg/kg. On the contrary, the reported value, was lower than that reported after IV administration of cefquinome in the horse (0.12 ± 0.02 L/kg/h) (Winther *et al,* 2011) and cattle (CL 0.12 ± 0.00 L/kg/h) (Ahmad *et al,* 2015) and (0.11 ± 0.02 L/kg/h) (Shan *et al,* 2014) after IV administration of cefquinome at a similar dosage rate. The slower clearance rate (CL_{tot}) of cefquinome in camel in comparison to other species could be related to the comparatively low glomerular filtration rate and renal plasma flow in camels (Etzion and Yagil, 1986) and to their specific physiological and biochemical features, which may be reflected to their response to xenobiotics and in the disposition of drugs given to them (Kadir *et al,* 1997; Oukessou *et al,* 1999). Dissimilarities in the kinetic parameters of drugs are relatively common and might be attributed to assay methods used, age, animal species, breed, health status of the animal and formulation of the used drug (El-Sayed *et al,* 1989).

In the present study, cefquinome was rapidly absorbed from the site of injection after a single IM administration with a short absorption half-life ($t_{½ab}$; 0.26 ± 0.03 hours). This value was about like

Table 1. Pharmacokinetic parameters of cefquinome following a single IV and IM injection of 1 mg/kg b.wt. in camels (mean ± SD, n=5).

Parameters	Unit	Intravenous	Intramuscular
B.wt	Kg	519.4 ± 46.57	519.4 ± 46.57
A	µg/ml	6.02 ± 1.02	4.98 ± 0.77***
α	h^{-1}	5.28 ± 1.59	0.49 ± 0.04***
B	µg/ml	3.15 ± 0.33	0.57 ± 0.24***
β	h^{-1}	0.22 ± 0.02	0.11 ± 0.01***
k_a	h^{-1}	-	2.7 ± 0.35
k_{10}	h^{-1}	0.59 ± 0.05	0.35 ± 0.01***
k_{12}	h^{-1}	2.96 ± 1.09	0.1 ± 0.02***
k_{21}	h^{-1}	1.95 ± 0.47	0.15 ± 0.03***
$t_{1/2\alpha}$	h	0.14 ± 0.04	1.42 ± 0.11***
$t_{1/2\beta}$	h	3.15 ± 0.22	6.68 ± 0.87***
$t_{1/2ab}$	h	-	0.26 ± 0.03
C^0	µg/ml	9.18 ± 1.26	-
T_{max}	h	-	0.82 ± 0.06
C_{max}	µg/ml	-	3.2 ± 0.39
V	L/kg	0.11 ± 0.01	-
V/F	L/kg	-	0.22 ± 0.05
Cl_{tot}	L/kg/h	0.07 ± .001	-
V_2	L/kg	0.16 ± 0.02	-
V_2/F	L/kg	-	0.15 ± 0.02
CL_2	L/kg/h	0.32 ± 0.07	-
CL/F	L/kg/h	-	0.08 ± 0.02
CL_2/F	L/kg/h	-	0.02 ± 0.001
AUC_{0-24}	µg/ml.h	15.37 ± 1.06	12.85 ± 2.15*
$AUC_{0-\infty}$	µg/ml.h	15.44 ± 1.07	13.25 ± 2.23
AUMC	$\mu g/ml.h^2$	65.06 ± 7.04	68.64 ± 14.58
MRT	h	4.21 ± 0.29	5.14 ± 0.27***
V_{ss}	L/kg	0.27 ± 0.02	-
F	(%)	-	85.52 ± 11.0

C^0 plasma concentration, α and β, distribution and elimination rate constants; k_{10}, k_{12}, k_{21} and k_a; the first-order rate constants, $t_{1/2\alpha}$, $t_{1/2\beta}$ and $T_{1/2ab}$ distribution, elimination and absorption half-life, V and V_2 apparent volume of central and peripheral compartment, Cl_{tot} and CL_2; total body and intercompartmental clearances; T_{max}, the time point of maximum plasma concentration C_{max}, AUC_{0-24} and $AUC_{0-\infty}$, area under plasma drug concentration vs time curve to 24h and to infinity, AUMC, area under the first moment curve; MRT, mean residence time; V_{ss}, volume of distribution at steady state; F%, Bioavailability, V/F, volume of central compartment corrected for bioavailability; CL/F, body clearance corrected for bioavailability; V_2/F, volume of peripheral compartment corrected for bioavailability; CL_2/F, intercompartmental clearance corrected for bioavailability.

to that reported for cefquinome in cattle (0.29 ± 0.07 h) (Shan *et al,* 2014), sheep (0.31 ± 0.05 h) (Uney *et al,* 2011), goats (0.64 ± 0.23 h) (Dumka *et al,* 2013) and piglets (0.41 ± 0.36 h) (Li *et al,* 2008), although higher value was reported previously in camel (4.35 ± 27 h) (Al-Taher, 2010) who used the microbiological assay method for estimation of cefquinome concentration. This assay method measure the activity of the drug in serum rather than estimation of the drug itself. However, the reported value was higher than that reported for cefquinome in dogs (0.14 ± 0.05h) (Zhou *et al,* 2015).

The reported maximum serum concentration (C_{max}; 3.2 ± 0.39 µg/ml) was higher than (C_{max}; 1.23 ± 0.08 µg/ml) that reported in camel (Al-Taher, 2010) and was achieved at short time (T_{max}; 0.82 ± 0.06 hours) than that reported previously (T_{max}; 4.25 ± 0.1 h). This is probably due to the use of different assay method. The reported Cmax and time to maximum concentration in this study was nearly similar to

those reported in crossbred wild boars (C_{max} 3.89 ± 0.51 µg/mL and Tmax 0.66 ± 0.07 h) (Liu *et al,* 2012). However, the reported C_{max} was higher than that reported in cattle (C max 2.34 ± 0.12 µg/ml) receiving cefquinome at similar dosage rate (Shan *et al,* 2014), although, it was attained after similar T_{max} (0.78 ± 0.32 h). On the contrary, the obtained results were lower than that reported in goat (C_{max} 4.84 ± 0.23 µg/ml, Tmax 1.50 ± 0) (Dumka *et al,* 2013) and dogs (C_{max} 4.83 ± 0.79 µg/ml, Tmax 0.43 ± 0.11 h) (Zhou *et al,* 2015) following IM administration of cefquinome at double doses. The differences could be attributed to the differences in doses in addition to species difference. The bioavailability of cefquinome in normal camels, which assesses the per cent of the dose, entered the systemic circulation after IM injection was 85.52 ± 11%. This indicates proper absorption of cefquinome after IM injection. This value was similar to those recorded in pigs (85.13 ± 9.93%) (Lu *et al,* 2007) and in sheep (89.31 ± 6.06 %) (Uney *et al,* 2011) but it was higher than that reported in goat (Dumka *et al,* 2013). However, higher values were reported in dogs (Zhou *et al,* 2015).

Since cefquinome is a β-lactam antimicrobial and acts as a time-dependent bactericidal drug (Thomas *et al,* 2006), the most suitable PK–PD parameter to describe drug efficacy is the time during which the drug's concentration exceeds the minimum inhibitory concentration (T > MIC) (Zonca *et al,* 2011).

The lower values of A, α, B, β, k_{10}, k_{12}, k_{21} after intramuscular injection were expected because when drug is absorbed from outside the systemic circulation, as with intramuscular doses, the peak plasma drug concentration occurs sometime after time zero rather than at time zero, as with an IV drug injection. The peak plasma concentration occurs at the point where the amount eliminated and the amount absorbed is equal. When a drug is absorbed more slowly, such as after an intramuscular injection, it will have a smaller peak concentration and a slightly longer duration of action than the IV administration of the same drug. The slow intramuscular absorption allows significant drug elimination to occur before absorption is complete. This could explain the relatively lower value of AUC after an intramuscular injection. Both physicochemical and physiologic factors influence the rate of drug absorption from the site of an intramuscular injection that explains the delayed distribution half-life and explain the longer elimination half-life. One potential determinant is the drug's partition between aqueous and lipid phases. Lipophilic drugs can diffuse directly through the membranes in contrast to cefquinome, which is characterised by low fat solubility. The concentration of the injected solution can also affect the rate of absorption. Another factor that influences the rate of absorption is the total surface area available for diffusion with which the injected solution is in contact (Koch-Weser and Greenblatt, 1976).

The results of this study indicate that a dosage regimen of 1 mg /kg body weight at 12 h intervals following IV or IM injection of cefquinome would maintain the plasma levels between 0.28 and 0.18 µg/ml which is ≤ MIC for susceptible bacterial pathogens particularly *S. agalactiae, S. dysgalactiae, P. multocida, E. coli* and Enterobacteriaceae. The IM route exhibited longer elimination half-life.

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