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Pharmacokinetics of Cefquinome in Camels

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Abstract: The Pharmacokinetic characters of cefquinome were studied in camels following single intramuscular administration of 1 mg kg^{-1} b.wt. Cefquinome concentrations in serum were determined by microbiological assay using *Micrococcus luteus* (ATCC 9341) as test organism. After intramuscular administration, the mean peak serum Concentrations (C_{max}) was 1.23 μg mL^{-1} and achieved after (t_{max}) 4.25 h. The absorption half life ($t_{1/2(ab)}$) was 4.35 h and the elimination half-life ($t_{1/2(el)}$) was 10.24 h. The Mean Residence Time (MRT) was 16.74 h and area under curve from zero time to infinity ($AUC_{0-\infty}$) was 20.37 μg/mL/h. The serum concentrations of cefquinome along 24 h post-injection in this study was exceeding the MICs of different susceptible micro-organisms responsible for serious disease problems. These findings indicate the suitability of successful use of this antibiotic in camels. A recommended single daily dose of 1 mg kg^{-1} of cefquinome given intramuscularly can achieve quite therapeutic concentrations in serum, that exceeding the minimal inhibitory concentrations against different susceptible pathogens.

Key words: Serum, intramascular, camels, *in vitro*, micrococcus luteus, Saudi Arabia

INTRODUCTION

Cephalosporins antibiotics are a well tolerated member of antibiotics in human and animals (Preston, 1992). Among this member of antibiotics, third-generation cephalosporins (aminothiazolyl cephalosporins) have a major advance in antibacterial therapy because of their broad antibacterial spectrum, resistance to enzymatic hydrolysis by beta-lactamases and improved pharmacokinetic properties (Qadri *et al*., 1993). In addition, fourth-generation cephalosporins show marked resistance to β-lactamases and increased outer membrane permeability, when compared with third-generation cephalosporins (Hancock and Bellido, 1992).

Cefquinome is the first member of fourth-generation cephalosporin developed for use in veterinary medicine. The *in vitro* and *in vivo* efficacy of this drug against a wide range of Gram-negative and Gram-positive bacterial pathogens has been demonstrated by Limbert *et al*. (1991).

Additionally, cefquinome has a good activity against causative agents of respiratory tract infections, diarrhea and mastitis in cattle (Kikuchi *et al*., 1995; Wilson *et al*., 1996; Barkema *et al*., 1998; Shpigel and Schmid, 1997; Schmid and Thomas, 2002).

Pharmacokinetics of the long acting formulation of cefquinome (Cobactan) have been studied in calves, cattle and goats following (i.m.) administration (Tohamy *et al*., 2006). No data for pharmacokinetics of cefquinome in camels is available. The purpose of the present study is to determine pharmacokinetic profile of cefquinome in camel following intramuscular administration of long acting preparation of this drug in order to establish adequate dose regimen for potential clinical use in camel diseases caused by susceptible micro-organisms.

MATERIALS AND METHODS

Antimicrobial agent: Cefquinome was obtained from Intervet International Company, as 2.5% cefquinome suspension in ethyl oleate (Cobactan). Standard of cefquinome was generously provided by Intervet International Company.

Animals: Five healthy male camels (weighing 350-425 kg b.wt), were used. Animals were kept under good hygienic condition, feed on hay, concentrated mixture and green fodder and water was provided *ad-libitum*. None of the animals were treated with antibiotics for one month prior to the trial.

Experimental protocol: Each animal was given a single intramuscular (i.m.) dose of 1 mg kg^{-1} cefquinome (Schimmel *et al*., 1990; Shpigel *et al*., 1997; Ehinger *et al*., 2006) into the deep gluteal muscle of hindquarter. Blood samples of 10 mL each were collected from the jugular vein just before dosing and at 15 and 30 min, 1, 2, 4, 6, 8, 10 and 24 h after drug administration. The blood was

allowed to clot at room temperature and then the serum was separated by centrifugation at 3000 rpm for 15 min and stored at -20°C until assayed.

Drug bioassay: Cefquinome concentrations in serum samples were determined by microbiological assay method described by Arret *et al.* (1971) using *Micrococcus luteus* (American Type Culture Collection ATCC 9341) as an indicator organism (San-Martin *et al.*, 1998). Standard curves were processed using antibacterial-free pooled sera collected from the animals prior to the experiment. Standard serum samples were fortified with 0.01, 0.06, 0.08, 0.2, 0.6 and 1 μg mL^{-1}. Six wells were made at equal distances in standard petri-dishes containing 25 mL 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 lower detectable limit of the cefquinome assay was 0.01 ug mL^{-1}. Semi-logarithmic plots of the inhibition zone diameter versus standard cefquinome concentrations in serum were linear with typical correlation coefficient of 0.990 (for the standard curve).

Pharmacokinetic analysis: Serum concentrations versus time curve were generated and best fitted by the aid of computer poly-exponential curve stripping program (R-strip, Micromath, Scientific software, USA). Data from each animal were fitted individually and the pharmacokinetic variables were computed by the aid of the software program. The hybrid rate constants of the first order absorption and elimination rate constants (K_{ab} and K_{el}), absorption and elimination half lives ($t_{1/2(ab)}$ and $t_{1/2(el)}$), Area Under the Curve from zero to infinity (AUC), Mean Residence Time (MRT), maximum serum concentration (C_{max}) and time to be achieved (t_{max}) were calculated.

RESULTS

Following intramuscular administration of cefquinome, the drug was detected in serum after 15 min and for 24 h post i.m. administration (Fig. 1). A peak serum concentration (C_{max}) of 1.23 μg mL^{-1} was achieved at (t_{max}) 4.25 h. The absorption half life ($t_{1/2(ab)}$) was 4.35 h and the elimination half-life ($t_{1/2(el)}$) was 10.24 h. The Mean Residence Time (MRT) was 16.74 h and area under curve from zero time to infinity ($AUC_{0-\infty}$) was 20.37 μg/mL/h (Table 1).

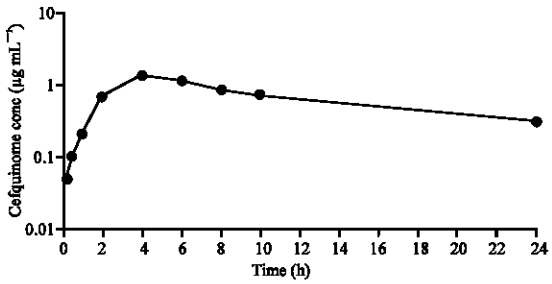

Fig. 1: Mean±SE serum concentrations of cefquinome vs. time after a dose of 1 mg kg^{-1} of body weight given intramuscularly

Table 1: Mean±SE kinetic parameters of cefquinome following a single i.m. injection of 1 mg kg^{-1} bw in camels (n = 5)

Parameters	Unit	Mean±SE
K_{ab}	h^{-1}	0.16±0.001
$t_{1/2ab}$	h	4.35±0.27
K_{el}	h^{-1}	0.067±0.002
$t_{1/2el}$	h	10.24±0.8
$AUC_{0-\infty}$	μg/mL/h	20.37±1.1
MRT	h	16.74±0.9
C_{max}	μg mL^{-1}	1.23±0.08
T_{max}	h	4.25±0.1

K_{ab}: first-order absorption rate constant; $t_{½ab}$: absorption half-life; K_{el} first-order elimination rate constant; $t_{½el}$: elimination half-life; $AUC_{0-\infty}$: Area under Curve from zero time to infinity; MRT: Mean Residence Time; C_{max}: maximum serum concentration after intramuscular administration; T_{max}: Time to peak serum concentration

DISCUSSION

The incorporation of a methoxyimino-aminothiazolyl moiety in the acyl side chain of cephalosporins brought about significant enhancement of activity, extension of the antibacterial spectrum, especially against Gram negative bacteria and high resistance to inactivation by β-lactamases (Neu, 1983; Durckheimer *et al.*, 1988). Cefquinome is highly resistant to hydrolysis by plasmid encoded β-lactamases from *Escherichia coli*, *Klebsiella pneumoniae* or *Pseudomonase aeruginosa*, as well as by chromosomal-encoded β lactamases from *Citrobacter* species, *Enterobacter cloacae* and *Klebsiella oxytoca* (Limbert *et al.*, 1991).

Because of little literatures on pharmacokinetics of cefquinome and availability of one literature for long acting preparation of cefquinome in ruminants (Tohamy *et al.*, 2006) so we used literatures of other members of cephalosporins in this discussion. Following intramuscular injection (i.m.) of cefquinome in a single dose of 1 mg kg^{-1} b.wt., peak serum Concentrations (C_{max}) was 1.23 μg mL^{-1}. These concentrations in serum were achieved after (t_{max}) 4.25 h. This result indicates the slow absorption o f this formula. These results differ from those recorded for cefquinome in mice, pigs and calves (C_{max}) 3.6-26.1 μg mL^{-1} at (t_{max}) 0.38-2 h (Limbert *et al.*,

1991), Coho Salmon (C_{max}) 3.35 μg mL^{-1} at 12 h (San-Martin *et al*., 1998) and bovine (C_{max}) 1.88 μg mL^{-1} (Ehinger *et al*., 2006) this difference could be attributed to the use of cefquinome as long acting preparation in the present study additionally, the dose of cefquinome used in the present study was 10-20 times lower than that used in mice, pigs, calves in work done by Limber *et al.* (1991) and Coho Salmon (San-Martin *et al*., 1998). However, studies conducted to determine the efficacy of cefquinome in the treatment of respiratory diseases in cattle (Gibbs *et al*., 1994) and in the experimental *Escherichia coli* mastitis in dairy cows (Shpigel *et al*., 1997) had used dose levels (0.5-1.0 and 2.0 mg kg^{-1}) close to the dose used in this study. Also doses of 0.5 and 1.0 mg kg^{-1} were used in sows (Schimmel *et al*., 1990). The reported t_{max} for cefquinome in camels in this study was close to those reported in cattle calves and cattle in a previous study by other researchers using the same long acting formulation (Tohamy *et al*., 2006).

Cefquinome was absorbed in camels at slower rate than that in cattle calves, buffalo calves and cattle as indicated by long absorption half-life $t_{1/2(ab)}$ of 4.35 h, however, this value was close to those reported in gaots (Tohamy *et al*., 2006). The recorded value is longer than that recorded for ceftriaxone in goals 0.138 h (Ismail, 2005). Differences in kinetic parameters are relatively common and are frequently related to interspecies variation, age, breed, health status of the animals, the assay method used as well as the formulation of the drug used (Haddad *et al*., 1985).

Cefquinome showed long elimination half-life ($t_{1/2(el)}$) after i.m administration in camels 10.24 h. Prolonged $t_{1/2(el)}$ has been reported for cefquinome in buffalo calves, cattle calves, cows and goats 12.86, 13.46, 7.102 and 8.680 h, respectively (Tohamy *et al*., 2006) and for other cephalosporin: ceftriaxone in calves 6.54 h (Srivastava and Johal, 1998).

Cefquinome had shown a potent *in vitro* activity against Gram-positive and Gram-negative bacteria isolated from pigs and calves (Schimmel *et al*., 1990; Murphy *et al*., 1994; Bottner *et al*., 1995). Cefquinome Minimum Inhibitory Concentration (MIC_{90}) for pathogenic organisms isolated from other animal species such as *Escherichia coli* (*E. coli*) are between the ranges of 0.03-1 μg mL^{-1} and *Klebsiella pneumoniae* are between the ranges of 0.03-0.5 μg mL^{-1} (Deshpande *et al*., 2000). For *E. coli* strains isolated from diarrheic calves, cattle and pigs, these concentrations (MIC_{90}) are 0.125 (0.0625-2), 0.07 and 0.06 μg mL^{-1}, respectively (Orden *et al*., 1999; Sheldon *et al*., 2004; Wisselink *et al*., 2006). *Pasteurella* species (*P. haemolytica* and *P. multocida*) and *Salmonella* species were inhibited by (MIC_{90}) 0.12 (0.06-4) and 0.5 (0.06-1 μg mL^{-1}), respectively (Bottner *et al*., 1995). *Haemophilus infleunza* and *Streptococcus* species appear to be the most sensitive organisms with MIC values ranging between 0.06-1 and 0.03-0.06 μg mL^{-1}, respectively (Chin *et al*., 1992; Murphy *et al*., 1994).

E. coli are an important cause of diarrhea in many animal species (Holland, 1990). Members of Enterobacteriace constitutes the major causes of fatal diseases (coliform septicemia, pneumonia, colibacillosis and meningitis) especially in newborn animals. Among the infective agents thought to be associated with such disease conditions, *Escherichia coli*, *Salmonella* sp., *Pasteurella multocida* and Klebsiella sp., assume a dominant role (Bastianello and Jonker 1981; Contrepois *et al*., 1986; Butler and Clarke 1994; Tegtmeier *et al*., 1999). Nevertheless, few antibiotics can provide safe and effective therapy for such conditions, especially those caused by strains resistant to the most commonly used antibiotics (Mevius and Hartman, 2000; Orden *et al*., 2000).

CONCLUSION

Integration of Pharmacokinetic data for cefquinome reported in camel in the present study and its pharmacodynamic properties reported in previous literature indicates favorable pharmacokinetics characters of this antibiotics in such species. The serum concentrations of cefquinome along 24 h post-injection in this study was exceeding the MICs of different micro-organisms responsible for serious disease problems in most animal species as mentioned before, these findings indicates the suitability of successful use of this antibiotics in camels. A recommended single daily dose of 1 mg kg^{-1} of cefquinome given intramuscularly can achieve quite therapeutic concentrations in serum exceeding the minimal inhibitory concentrations against different susceptible pathogens infecting this animal species.

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