Pharmacokinetics of Cefquinome in Camels

A. Y. Al-Taher
Department of Physiology, Biochemistry and Pharmacology,
College of Veterinary Medicine and Animal Resources, King Faisal University,
Postal Code, 1757 AL-Ahsa, 31982, Saudi Arabia

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 1/2a) was 4.35 h and the elimination half-life (t 1/2e) 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, intramuscular, 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 beta-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-straint, 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 (Kₐ and K₋), absorption and elimination half lives (t₁/₂ₐ and t₁/₂₋), Area Under the Curve from zero to infinity (AUC), Mean Residence Time (MRT), maximum serum concentration (Cₘ₉₉) and time to be achieved (t₉₉₉) 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 (Cₘ₉₉) of 1.23 μg mL⁻¹ was achieved at (t₉₉₉) 4.25 h. The absorption half life (t₁/₂ₐ) was 4.35 h and the elimination half-life (t₁/₂₋) was 10.24 h. The Mean Residence Time (MRT) was 16.74 h and area under curve from zero time to infinity (AUCₜₐ) was 20.37 μg/mL/h (Table 1).

![Graph showing the mean ± SE serum concentrations of cefquinome vs. time after a dose of 1 mg kg⁻¹ of body weight given intramuscularly.](image)

**DISCUSSION**

The incorporation of a methoxyimino-aminothiazol 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 *Pseudomonas 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 literate for long acting preparation of cefquinome in ruminants (Tohany 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 (Cₘ₉₉) was 1.23 μg mL⁻¹. These concentrations in serum were achieved after (t₉₉₉) 4.25 h. This result indicates the slow absorption of this formula. These results differ from those recorded for cefquinome in mice, pigs and calves (Cₘ₉₉) 3.6-26.1 μg mL⁻¹ at (t₉₉₉) 0.38-2 h (Limbert et al.,...
Cefquinome (Cenova) 3.35 µg mL⁻¹ at 12 h (San-Martin et al., 1998) and bovine (Cenova) 1.88 µg mL⁻¹ (Elanger 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 t₁/₂ for cefquinome in calves 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 (Tolnay et al., 2006).

Cefquinome was adsorbed in calves at slower rate than that in cattle calves, buffalo calves and cattle as indicated by long absorption half-life t₁/₂(α) of 4.35 h, however, this value was close to those reported in goats (Tolnay et al., 2006). The recorded value is longer than that recorded for ceftriaxone in goats 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 (t₁/₂(β)) after i.m administration in calves 10.24 h. Prolonged t₁/₂(β) has been reported for cefquinome in buffalo calves, cattle calves, cows and goats 12.86, 13.46, 7.102 and 8.680 h, respectively (Tolnay et al., 2006) and for other cephalosporin: ceftriaxone in calves 6.54 h (Srivasatava 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 (MIC₅₀) 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 (MIC₅₀) were 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 (MIC₅₀) 0.12 (0.06-4) and 0.5 (0.06-1 µg mL⁻¹), respectively (Bottner et al., 1995). Haemophilus influenzae 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 Enterobacteriaceae constitute the major causes of fatal diseases (coli form 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 Jorker 1981; Contrepois et al., 1986; Butler and Clarke 1994; Tegtmeyer et al., 1999). Nevertheless, few antibiotics can provide safe and effective therapy for such conditions, especially those caused by strains resistant to the 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.

REFERENCES


