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PHARMACOKINETICS OF CEFQUINOME IN CAMELS

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SUMMARY

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 hour. 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 (AUC0-∞) was 20.37 μg mL^{-1} h^{-1}. The serum concentrations of cefquinome along 24 hours 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.

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., 1997; 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.

MATERIAL 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 minutes, 1,2,4,6,8,10 and 24 hour after drug administration. The blood was allowed to clot at room temperature and then the serum was separated by centrifugation at 3000 r.p.m for 15 minutes 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

serum samples were fortified with 0.01, 0.06, 0.08, 0.2, 0.6 and 1 ug 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 hours. 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 the animals prior to the experiment. Standard 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 ug ml^{-1} was achieved at (t_{max}) 4.25 hour. 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 (AUC0-∞) was 20.37 µg mL^{-1} h^{-1}(table 1).

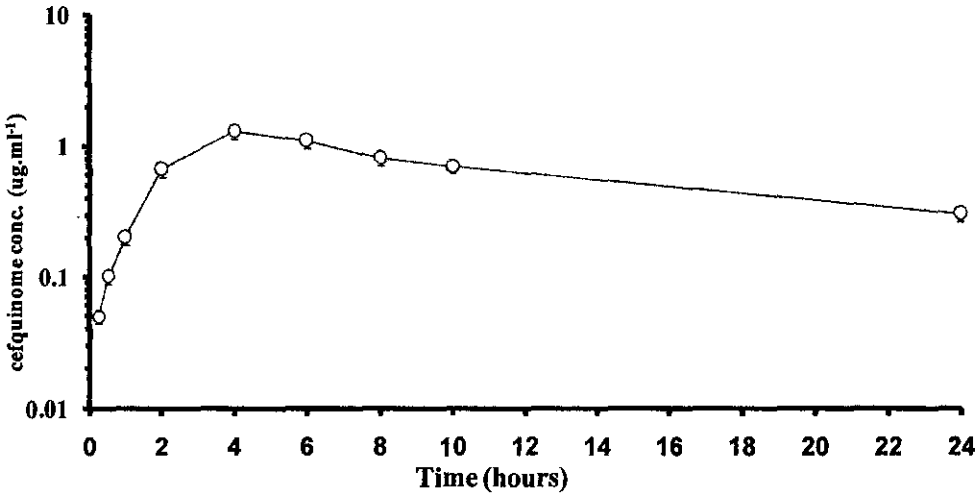

Fig 1 :Mean (± SE) serum concentrations of cefquinome vs time after a dose of 1 mg/kg of body weight given intramuscularly

Table 1: Mean ± SE kinetic parameters of cefquinome following a single i.m. injection of 1 mg/kg 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
$AUC_{0-\infty}$	$\mu g\ mL^{-1}\ h^{-1}$	20.37 ± 1.1
MRT	H	16.74 ± 0.9
C_{max}	$\mu g\ mL^{-1}$	1.23 ± 0.08
T_{max}	H	4.25 ± 0.1

Kab, first-order absorption rate constant; t½ab, absorption half-life;Kel, first-order elimination rate constant; t½el, elimination half-life; AUC0-∞, area under curve from zero time to infinity; MRT, mean residence time; Cmax, maximum serum concentration after intramuscular administration; Tmax, 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 of 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 (Bindu et al., 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 μg ml^{-1} (0.0625-2 μg ml^{-1}), 0.07 μg ml^{-1} 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 μg ml^{-1} (0.06-4 μg ml^{-1}) and 0.5 μg ml^{-1} (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 μg $ml^{-1}$and 0.03-0.06 μg ml^{-1}, respectively (Chin et al., 1992; Murphy et al., 1994).

E. coli are 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 spp., Pasteurella multocida and Klebsiella spp., 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).

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 hours 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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المسار الحركى لدواء سيفكينوم فى الجمال

عبد الله الطاهر

كلية الطب البيطري والثروة الحيوانية جامعة الملك فيصل ، الأحساء

أجريت هذه الدراسة على عدد خمس جمال حيث تم إعطاء كل حيوان دواء سيفكينوم 1 مجم/ كجم كجرعة واحدة عن طريق الحقن العضلى. تم تجميع عينات من الدم فى اوقات مختلفة من ربع ساعة-24 ساعة من بداية الحقن وتم فصل مصل الدم وحفظه الي ان تم تحليله باستخدام الطريقة الميكروبيولوجية لقياس المضادات الحيوية . و قد أظهرت الدراسة أن أقصى تركيز للدواء فى الدم هو 1,23 ميكروجرام/مللى بعد زمن قدره 4,25 ساعه وكان معدل امتصاص الدواء عن طريق الحقن العضلي هو 4,35 ساعة . وكانت فتره عمر النصف لأخراج الدواء هي 10,24 ساعه. وقد اوضحت الدراسة ايضا بأن مستوي الدواء بالدم قد تجاوز التركيز اللازم لقتل الميكروبات الحساسة لمدة 24 ساعة. وتفيد نتائج هذه التجربة بأن دواء السيفكينوم هو من الأدوية الجيدة للأستخدام لعلاج حالات العدوي الميكروبية في الجمال المسببه بالميكروبات الحساسه لهذا الدواء عند استخدامه بالجرعة المستخدمه بهذه التجربة.