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Pharmacokinetics of ceftiofur after single intravenous and intramuscular administration in camels (*Camelus dromedarius*)

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The Arabian camel (*Camelus dromedarius*) is an important domestic animal in arid and semi-arid zones. It is used in pastoral societies as a source of meat, hair, hides and milk and for draught and transport. In gulf countries, it is used in sport races, and in other countries, it is a popular zoo animal (Ali *et al.*, 1996). Antibacterial drugs are used in both treatment and prevention programmes for bacterial diseases of camel. Ceftiofur is a semisynthetic third generation cephalosporin, is a broad-spectrum antibiotic against both Gram-positive and Gram-negative bacteria including beta-lactamase-producing bacterial strains and some anaerobic bacteria and it is less active against *Pseudomonas aeruginosa* (Brown *et al.*, 1991; Prescott, 2000). Its antibacterial activity results from the inhibition of mucopeptide synthesis in the cell wall in a similar fashion to other cephalosporins. The thioester bond on ceftiofur is rapidly cleaved to give desfuroylceftiofur, which is further metabolized to a disulfide dimer and various desfuroylceftiofur-protein and amino acid conjugates (Jaglan *et al.*, 1990; Beconi-Barker *et al.*, 1995). Free desfuroylceftiofur is an active metabolite with the intact cephalosporin part of the molecule responsible for biological activity (Jacobson *et al.*, 2006). The pharmacokinetics of ceftiofur in various species was reviewed by Brown *et al.*, 1991, in cattle (Soback *et al.*, 1991; Halstead *et al.*, 1992; Erskine *et al.*, 1995; Brown *et al.*, 1996, 2000) and in sheep (Craigmill *et al.*, 1997). Potentially it will be of therapeutic value in many camel diseases. However, there is limited published information in the camel on the pharmacokinetics of antibacterial agents. In fact, there are no published data on the pharmacokinetics in camel of ceftiofur. The potential value of ceftiofur in the camel is indicated by previous studies describing its clinical efficacy and pharmacokinetics in ruminant species, horse, poultry and pig. This work was designed to study the pharmacokinetic parameters of ceftiofur in healthy adult female camels after intravenous (i.v.) and intramuscular (i.m.) administration routes at a dosage of 2.2 mg/kg b.w. in all animals.

Six healthy female camels, 6–7 years old ranging in body weight from 350 to 450 kg were used in this experiment. None had received any drug for at least 4 months. The camels were in optimal nutritional condition, were fed high quality lucerne (alfalfa) hay once daily and water was allowed *ad libitum*. The health of all animals was monitored prior to and throughout the experimental period. The Advisory Committee constituted by the Faculty approved the experiment protocol used. The study was performed in two phases, following a crossover design. Three animals were given a single i.m. dose of 2.2 mg/kg b.w. ceftiofur sodium (Excenel®; Upjohn Company, Kalamazoo, MI, USA) into the lower third region of the neck muscles, and the other three were injected with the drug into the left jugular vein at the same dose. Venous whole blood samples were taken by jugular venepuncture into 10 mL heparinized vacutainers (Becton Dickinson vacutainer Systems, Rutherford, NJ, USA). The sampling times were 0 (blank sample), 0.16, 0.33, 0.5, 0.75, 1, 2, 4, 6, 8, 10, 12, 24, 48 and 72 h after treatment. All blood samples were centrifuged at 1500 ***g*** for 15 min to separate the plasma. The plasma samples were frozen at −70 °C until analysed. After a washout period of 3 weeks, the animals that had been injected intravenously with the drug were injected intramusculary and *vice versa*. Blood samples were collected and processed as above.

Quantification of microbiologically active ceftiofur (parent and metabolites) in plasma and milk samples was accomplished by a modified agar diffusion bioassay method previously reported by Arret *et al.*, 1971, using *Micrococcus luteus* (ATCC 9341) as the reference organism. As the assay method fails to distinguish between ceftiofur and its active metabolites, the results relate to ceftiofur equivalent antimicrobial activities. To simplify the presentation, however, the term concentration is used throughout the text. Bioassay plates were prepared by using Mueller Hinton agar (Alkan Medical Division; Dokki, Giza, Egypt). The standard curve of ceftiofur in camel plasma was linear between 0.01 and 12.5 μg/mL with a determination coefficient (r^2) of 0.998. The mean percentage recovery of ceftiofur (measured by comparing the zone of inhibitions of the spiked samples with an external standards in phosphate buffer saline) was 90%. The intra- and inter-assay coefficients of variation were below 10%. The limit of quantification (LOQ) was 0.1 μg/mL of ceftiofur per millilitre of plasma and milk. The extent of protein binding was determined *in vitro* according to the method described previously by Craig and Suh (1980), using antimicrobial-naïve camels plasma fortified with a known concentration of ceftiofur. This method was based on the diffusion of free antibiotic into the agar medium. The differences in the diameters of the inhibition zones between the solutions of the drugs in the buffer and plasma samples were then calculated.

The determination of the best-fit compartmental model and initial estimates of the model-dependent pharmacokinetic

parameters were analyzed using a computerized curve-stripping program (R Strip; Micromath Scientific Software, version 5.0; Salt Lake City, UT, USA). This program also calculated noncompartmental parameters using the statistical moment theory (Gibaldi & Perrier, 1982; Martinez, 1998). The maximum plasma concentration (C_{max}) and time of maximum plasma concentration (t_{max}) were taken directly from the curve. The area under plasma concentration–time curve (*AUC*) and area under the first moment curve (*AUMC*) were calculated by the method of trapezoids, and extrapolation to infinity was performed. Mean residence time was calculated as $MRT = AUMC/AUC$. The systemic clearance as $Cl = \text{Dose}/AUC$. The absolute bioavailability was calculated as $(AUC_{\text{i.m.}}/AUC_{\text{i.v.}}) \times 100$. The mean plasma pharmacokinetic variables for ceftiofur were statistically compared by nonparametric analysis, using the Mann–Whitney test and Instant version 3.00 (GraphPad Software, San Diego, CA, USA). Mean values were considered significantly different at $P < 0.01$. Pharmacokinetic variables are reported as mean ± SD. The time concentrations remaining above 0.2 μg/mL ($t_{>0.2}$) were calculated using the following formula:

$$t_{>0.2} = \frac{\ln(B) - \ln(0.2)}{\beta}.$$

The mean ceftiofur plasma concentration–time profiles following i.v. and i.m. administration are shown in Fig. 1. A summary of pharmacokinetic parameters following i.v. and i.m. administration is presented in Table 1. The present investigation revealed that plasma ceftiofur concentrations vs. time decreased in a bi-exponential manner following i.v. injection, demonstrating the presence of distribution and elimination phases and justifying the use of two-compartmental open model for analysing data. This finding was previously reported for ceftiofur sodium in sheep (Craigmill *et al.*, 1997) and dairy goat (Courtin *et al.*, 1997). Although, Soback *et al.*, 1991 and Aziza *et al.*, 1998 found that one compartment open model would characterize ceftiofur sodium disposition in lactating cow and chicken, respectively. Ceftiofur sodium was rapidly distributed with half-life of distribution ($t_{1/2\alpha}$) of 0.48 ± 0.07 h; this result is consistent with that recorded in dairy goats 0.46 h at a dose of 1.1 mg/kg b.w. (Courtin *et al.*, 1997) and differs from that reported by Courtin *et al.*, 1997 in lactating and nonlactating goats at a dose of 2.2 mg/kg b.w. 0.69 and 0.8 h respectively. Ceftiofur elimination half-life ($t_{1/2\beta}$) was 3.18 ± 0.21 h; this value is consistent with that reported by Soback *et al.*, 1989 in lactating cow 3.6 h and Brown *et al.*, 1991 in calves and adult cows 3.5 h, Courtin *et al.*, 1997 in lactating goats 3.8, 2.8 at a dosage of 1.1 and 2.2 mg/kg b.w., and this value was shorter than that reported by Courtin *et al.*, 1997 in nonlactating goats 4.2 h, Craigmill *et al.*, 1997 in sheep 5.83 and 4.87 h at a dose of 1.1 and 2.2 mg/kg b.w. respectively. The $V_{d(ss)}$ is an indication of the diffusion of the drug into body tissues, the $V_{d(ss)}$ for ceftiofur was relatively small 0.13 ± 0.03 L/kg in camels indicating that the drug is only minimally distributed in extravascular tissues. However, this value is lower than that reported in lactating goats at a dose of 1.1 and 2.2 mg/kg b.w. and nonlactating goats at a dose of 2.2 mg/kg b.w. 0.26, 0.31 and 0.25 L/kg respectively (Courtin *et al.*, 1997). The total body clearance (Cl_{tot}) was 0.03 ± 0.001 L/h/kg, this value differ from that reported by Courtin *et al.*, 1997 in lactating goats at a dose of 1.1 and 2.2 mg/kg b.w. and nonlactating goats at a dose of 2.2 mg/kg b.w. 0.089, 0.082 and 0.066 L/h/kg respectively. The *AUC* value reported here was 70.53 ± 9.46 μg·h/mL and this value differ from that reported for sheep (Craigmill *et al.*, 1997), lactating and nonlactating goats at a dose of 2.2 mg/kg b.w. (Courtin *et al.*, 1997), were 38.1, 27.1 and 33.9 μg·h/mL respectively. Following single i.m. injection of ceftiofur sodium at a dose of 2.2 mg/kg b.w., the plasma concentration of ceftiofur exceeded the MIC_{90} for most sensitive pathogens for longer time than i.v. injection. The persistence of antibiotic concentrations in plasma and tissues above the *MIC* is the pharmacodynamic variable related to the clinical efficacy of ceftiofur (Toutain *et al.*, 2002). In this study, the peak plasma concentration (C_{max}) was 10.34 ± 1.24 μg/mL,

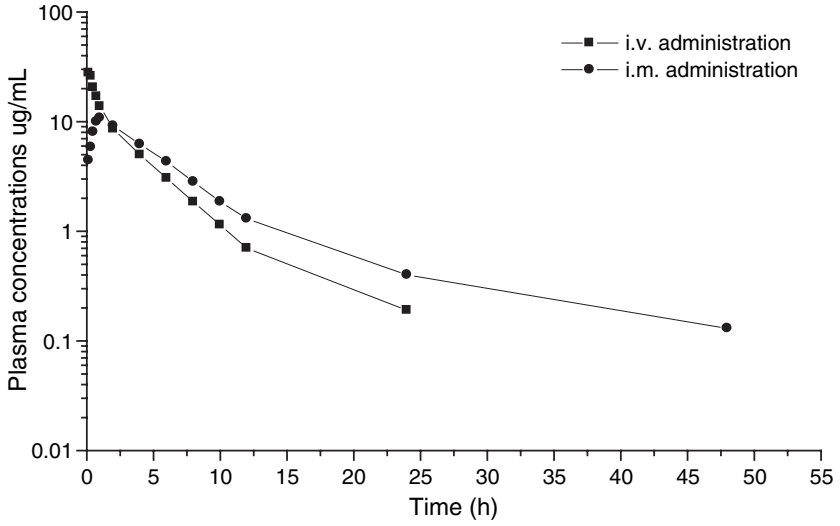

Fig. 1. Semilogarithmic graph depicting the concentrations of ceftiofur in the plasma of camels after i.v. and i.m. administration of 2.2 mg/kg b.w. ($n = 6$).

Table 1. Mean ± SD plasma pharmacokinetic parameters of ceftiofur in camels ($n = 6$) following intravenous (i.v.) and intramuscular (i.m.) administration at a dosage of 2.2 mg/kg b.w.

Parameters	Unit	i.v.	i.m.
α (k_{ab})	h^{-1}	1.45 ± 0.16	2.1 ± 0.21**
$t_{1/2\alpha}$ ($t_{1/2ab}$)	h	0.48 ± 0.07	0.34 ± 0.04*
B	μg/mL	11.13 ± 1.27	14.85 ± 1.67**
β (k_{el})	h^{-1}	0.22 ± 0.06	0.21 ± 0.06
$t_{1/2\beta}$ ($t_{1/2el}$)	h	3.18 ± 0.21	3.29 ± 0.20
$V_{d(ss)}$	L/kg	0.13 ± 0.03	–
Cl_{tot}	L/h/kg	0.03 ± 0.001	–
AUC	μg·h/mL	70.53 ± 9.46	68.70 ± 7.19
MRT	h	3.68 ± 0.2	5.21 ± 0.31**
C_{max}	μg/mL	–	10.34 ± 1.24
t_{max}	h	–	1.22 ± 0.11
$t_{>0.2}$	h	18.26 ± 2.93	20.51 ± 4.23
F	%	–	97.4 ± 18.41

β, elimination rate constant; $t_{1/2\alpha}$, distribution half-life; $t_{1/2ab}$, absorption half-life; $t_{1/2\beta}$, elimination half-life; $t_{1/2el}$, elimination half-life; B, zero time plasma drug concentration intercepts of elimination phase; $V_{d(ss)}$, volume of distribution; Cl_{tot}, total body clearance; *AUC*, area under the curve from zero to infinity by the trapezoidal integral; *MRT*, mean residence time; C_{max}, maximum plasma concentration; t_{max}, time to peak concentration; $t_{>0.2}$, the time concentrations remaining above 0.2 μg/mL; *F*%, bioavailability.

this result is lower than that reported by Brown *et al.*, 2000 in cattle 13.9 μg/mL, Brown *et al.*, 1999 in pigs at a dose of 3 and 5 mg/kg b.w., 15.8 and 28.3 μg/mL, respectively, and near that reported in sheep 8.44 μg/mL (Craigmill *et al.*, 1997). The *MIC* of ceftiofur against *Pasteurella haemolytica* (*Mannheimia* spp.), *Pasteurella multocida* and *Haemophilus somnus* was ≤ 0.06 μg/mL (Yancey *et al.*, 1987). A 0.2 μg/mL established in these studies afforded a conservative measure of clinical efficacy against these major pathogens in camel as reported by Brown *et al.*, 1999 for pigs and Brown *et al.*, 2000 for cattle. In addition, the value of 0.2 μg/mL is a value above the LOQ of the assay method and, therefore, is a reliable concentration when measured. The time of mean peak concentration (t_{max}) was 1.22 ± 0.11 h, this result is similar to that seen in goat 1.17 h (Courtin *et al.*, 1997), and higher than that seen in cattle 0.67 h (Brown *et al.*, 2000). Mean residence time (*MRT*) was longer in an extremely significant manner for i.m. administration compared with that for i.v. dosing, with an estimated time of 5.21 ± 0.31 h. This was expected as the *MRT* after i.m. administration depends on both the disposition and absorption rates. The elimination half-life ($t_{1/2el}$) following i.m. injection of ceftiofur sodium was 3.29 ± 0.20 h; this value was consistent with that reported in lactating cow 3.5 h (Soback *et al.*, 1989), in calves 3.1 h (Halstead *et al.*, 1992), in foal 3.26 h (Meyer *et al.*, 1992), but lower than that reported by Brown *et al.*, 2000 in cattle 10.7 h. The *AUC* values reported for sheep (Craigmill *et al.*, 1997), goats (Courtin *et al.*, 1997) and cattle (Brown *et al.*, 2000) were 33.7, 24.1 and 112 μg·h/mL, respectively, compared with that reported for camel 68.70 ± 7.19 μg·h/mL. The systemic bioavailability of ceftiofur sodium in camels after i.m. administration was complete 97.4%, this value indicates an excellent absorption of the drug from that site of injection. This value was nearly consistent with that reported in lactating cow (Soback *et al.*, 1989; Brown *et al.*, 1991) and sheep (Craigmill *et al.*, 1997) 100%. Ceftiofur could not be detected in milk of camels after i.v. and i.m. administration. This finding was recorded by Soback *et al.* (1989); Owens *et al.* (1990) and Jaglan *et al.* (1992) in cow. Moreover, Erskine *et al.* (2002) and Wenz *et al.* (2005) recorded that i.m. administration of ceftiofur has no beneficial effect on the outcome of systemically mild clinical mastitis. *In vitro* protein binding per cent of ceftiofur sodium in camel plasma was 87%; this finding is supported by that obtained by Robb *et al.* (1993) in dairy cattle 85–95%. Aziza *et al.* (1998) found that ceftiofur has a mean binding to chicken serum protein of 23.07%. The kinetic parameters of ceftiofur in camels in the present work differ from those in sheep and cattle. This variation may be due to species differences, the extent of period between blood sampling or the health status of the animal or the assay method used as by HPLC method, while I measured the drug using a microbiological method. It is known that the two methods may yield different results from the same species. It should be mentioned, however, that in this work some of the kinetic parameters were similar whether the measurement of the drug was carried out either microbiologically or by HPLC. Ceftiofur should be useful for treating a wide ra nge of bacterial infections in camels, based on pharmacokinetic analysis and the *MIC* of 0.2 μg/mL for most susceptible bacterial pathogens is recommended twice daily i.m. administration to ensure adequate plasma levels. Moreover, systemic administration of ceftiofur has no beneficial effect on the outcome of systemically mild clinical mastitis.

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