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Original Research Article

PHARMACOKINETICS OF THE LONG-ACTING CEFTIOFUR CRYSTALLINE-FREE ACID IN ARABIAN SHE-CAMELS (*Camelus Dromedarius*)

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Abstract: Ceftiofur is an important broad-spectrum 3rd generation cephalosporin antibiotic. Owing to its time-dependent antimicrobial actions, the length of time of being above bacterial MIC is the critical point in using ceftiofur for chemotherapy rather than its peak of concentration. Consequently, this experiment was carried out to evaluate, for the first time, the pharmacokinetics of the long-acting ceftiofur crystalline acid-free form (ceftiofur-CAF) in camels. Ceftiofur-CAF 200 mg/ml suspension sterile solution was injected i/m at a dose 6.6 mg/kg. Blood samples were collected from the jugular vein in vacutainer tubes at 0, 0.13, 0.25, 0.5, 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, and 144 hours after administration of the drug. Ultrahigh Performance Liquid Chromatography-Mass Spectrometry (UPLC MS/MS) was used to measure serum concentration. Pharmacokinetic modeling was by a two-compartment model. Pharmacokinetics of ceftiofur-CAF after single i/m injection in she-camels was best modeled in the two-compartment model, where the drug slowly distributed to a second compartment with poor tissue penetration and high preference to the central compartment. In this study, the maximum plasma concentration (C_{max}) was 9.29±0.42 µg/ml at T_{max} equals 9.41±1.35 h. The area under the curve ($AUC_{0-\infty}$) was 354.1±57.22 µg/ml*h. The distribution and elimination half-lives were 7.42 and 46.13 h, respectively. The mean residence time (MRT) was 42.01 h. Compared with the rapidly absorbed form of ceftiofur (ceftiofur-RAF) in camels, there was almost similar maximal serum concentration but with delayed time to maximal concentration (T_{max}), longer means residence time (MRT) and higher distribution and elimination half-lives. In terms of antibacterial efficacy, ceftiofur-CAF stayed above a previously recommended level of 0.2 µg/ml for 7 days, which can be achieved after a single i/m injection of 6.6 mg/kg. The obtained pharmacokinetics data in camels recommends repeated administration of 2 days apart for bacteria requiring MIC levels above 2 µg/ml.

Key words: Ceftiofur; pharmacokinetics; camel; cephalosporins

Introduction

Ceftiofur is a semisynthetic 3rd generation cephalosporin with broad-spectrum antibacterial efficiency by inhibition of essential enzymes in cell wall biosynthesis resulting in a strong bactericidal effect (1, 2). It has been approved for veterinary medical uses in various animal species including equines, bovines, swine, sheep, and goats (3). The crystalline-free acid form of ceftiofur at a dose rate of 6.6 mg/kg can be used in two consecutive injections to cover a treatment course of 10 days (1). This is more beneficial than the laborious single daily dosing strategy.

Recently, camels have been reported to acquire serious respiratory infections caused by various bacterial and viral causative agents as middle east respiratory syndrome coronavirus (MERS CoV) or bacterial pneumonia (4, 5). Owing to the emerging nature of camel pathogens and their public health impact, proper therapeutic protocols have to be achieved.

Ceftiofur is an excellent choice in treating respiratory infections in horses, cattle, and swine (1).

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The usage of a long-acting formula of ceftiofur is thought to deliver significant-high serum concentration of ceftiofur for at least 4 days after a single i/m injection in horses and other animals (1, 3, 6-9). This will be beneficial in creating antimicrobial coverage in treating camel pathogens and during mass treatment of respiratory infections in camels. Moreover, a single long-acting dose minimizes handling and avoid stresses on camels during restraining and repeated daily injections. Despite the availability of such long-acting ceftiofur preparation, its pharmacokinetics and drug disposition parameters in camels is not well understood. This study investigates for the first time the pharmacokinetics of ceftiofur crystalline acid-free form (Ceftiofur-CAF) in Arabian she-camels. The obtained pharmacokinetic parameters were compared with that of the previously published results of ceftiofur immediate-release form (ceftiofur-IRF) in camels. This study will aid in designing dose frequencies and the proper design of antibacterial programs.

Materials and methods

Animals, facilities, and instruments

Three Arabian non-lactating 8 years old she-camels were used in this study. The she-camels were housed in the facilities of the camel research center, King Faisal University. Camels did not receive any previous treatments at least three months before the start of the experiment. Water was freely available during all experimental courses. She-camels were fed on alfalfa hay according to the camel center feeding schemes. The ethics committee of King Faisal University (no. 1811013) approved all experimental procedures and animal experiments. Waters Acquity Ultra-high performance liquid chromatography Mass-mass (UPLC–MS-MS) system equipped with an autosampler, C18 column, and Acquity Micromass triple-quadrupole was used to measure the serum concentration of injected Ceftiofur.

Drug administration

Ceftiofur-CAF 200 mg/ml suspension (Excede, Zoetis Inc, NJ, USA) sterile solution was injected i/m at a dose 6.6 mg/kg.

Collection of samples

Blood samples were collected from the left jugular vein in vacutainer tubes at 0, 0.13, 0.25, 0.5, 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, and 144 hours after administration of the drug Administration. Blood samples were inverted briefly for three times and kept in insulated refrigerated boxes to clot. After 15 min, the tubes were centrifuged at room temperature at 2000 g for 15 min. Aliquots of serum were stored at - 80 °C until chromatographic analysis.

Sample preparation and extraction

The sample preparation was performed as described by (10, 11) with slight variations. A standard stock solution at different concentrations was prepared by dilution in MilliQ water starting from 150 to 3.125 ng/ml concentrations. Within this range, six different concentrations were used to plot the standard curve. All tubes were stored at - 30°C and melted just before the experiment.

Sample preparation included deproteinization, evaporation of the solvent, and final dissolving of the mobile phase. Serum was deproteinized in acetonitrile 1:7 (v/v). After vortexing, the denatured protein was removed by centrifugation for 13,000 rpm for 10 min. the supernatant was evaporated under a nitrogen stream and the pellet was redissolved in the mobile phase. Twenty microliters of the solution were injected into the UPLC–MS-MS system.

Chromatographic conditions

UPLC-MS/MS was performed using a Waters Acquity UPLC system (Waters Corp., MA, USA). The system is composed of Waters Acquity Micromass triple-quadrupole MS quadrupole with electrospray source, Waters Acquity BEH C18 column, autosampler, quaternary solvent management system. The system was operated under the control of MassLynx 4.1 software. The mass multi-reaction-monitoring (MRM) mode was as described previously (10, 12, 13). The running solution contained solution (A): UPLC grade water containing 0.1% formic acid, and solution (B): methanol containing 0.1% formic acid. Half mM ammonium acetate was added for both solutions A and B. The gradient elution program (14) comprised a gradual increase in

solution B until 85:15 (v/v). validations of runs and limits of detection quantification were performed as described previously (15). The method was validated for selectivity, sensitivity, linearity, precision, accuracy, and stability. The blanc and drug samples were compared to assign the chromatographic selectivity. LLOQ (lower limit of quantification) was used as a measure of sensitivity by measuring the area of the curve that was at least five times higher than the blanc values. Drug concentrations of 0.195 ppb to 150 ppb were used for linearity checking. Intra and inter-day precision was carried out by measuring LLOQ, LOC, middle-quality control (MQC), and high-quality control (HQC) levels. Accuracy was assigned by estimation of the amount extracted after the addition of known amounts of the drug. The chromatograms for LOD and LOQ are given in the supplementary materials (Supplementary files 1 and 2).

Pharmacokinetic analysis

The pharmacokinetic analysis was performed by nonlinear curve fitting analysis. The data were fitted with the aid of PKsolver Excel add-on software (16).

Results

Both non-compartment and compartment pharmacokinetic models were used to fit the obtained data. Fig.1 shows the relation between the serum concentrations of ceftiofur-CAF concerning time. The best-fitting was determined to be by a two-compartment model to deliver the pharmacokinetic parameters (Table 1): α and β: the apparent rate constants of the distribution and elimination phases, the distribution and elimination half-lives ($t_{1/2\alpha}$ and $t_{1/2\beta}$), the rate constant for equilibration between the central and peripheral compartment (k_{12}), return to the central compartment (k_{21}), elimination from central component (k_{10}) and the volume of distribution (V_F). The rate constant for distribution to the peripheral compartment was 0.03 h^{-1} indicating slow transfer of drug from the central to peripheral compartment. The values of k_{12} and k_{21} indicate low and slow tissue penetration and a general preference for central compartment or serum. The area under the concentration curve ($AUC_{0\text{-}inf}$) was 354.1 µg/ml h^{-1} and mean residence time (MRT) 42.01 h.

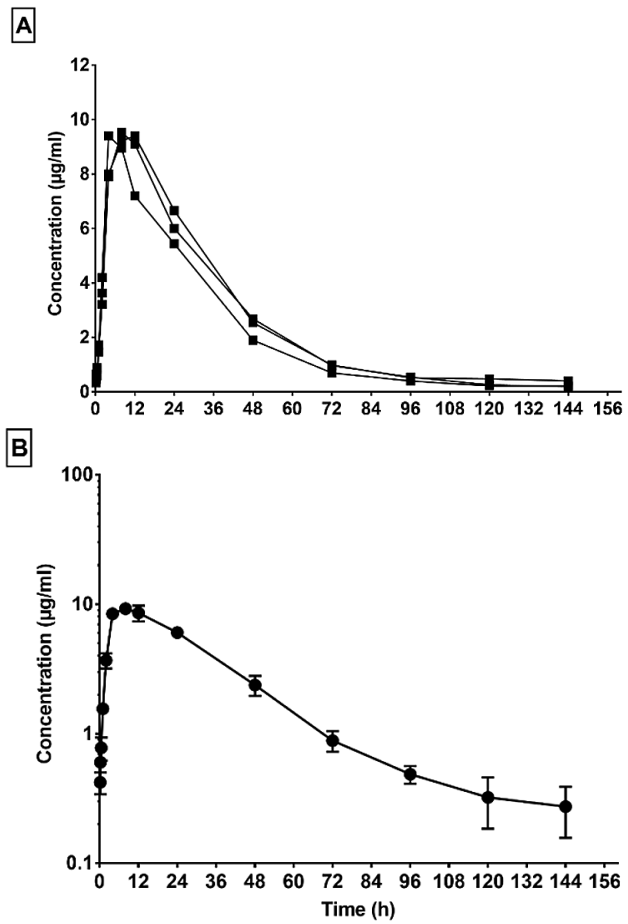

Figure 1: The relation between the serum concentrations of ceftiofur-CAF concerning time. A) the concentration (Y-axis) is plotted against time (X-axis). The values of each she-camel are plotted separately. B) semi-logarithmic plot of concentration-time relation. The values represent mean ± SD

Table 1: Pharmacokinetic parameters of single i/m injection of 6.6 mg/kg of ceftiofur-CAF in she-camels (n = 3)

Parameter	Unit	Average	SD
A	µg/ml	140.89	109.01
α	1/h	0.11	0.05
B	µg/ml	5.77	4.39
β	1/h	0.02	0.01
ka	1/h	0.15	0.02
Parameter	**Unit**	**Average**	**SD**
k_{10}	1/h	0.05	0.01
k_{12}	1/h	0.03	0.02
k_{21}	1/h	0.05	0.04
$t_{1/2\alpha}$	h	7.42	4.24
$t_{1/2\beta}$	h	46.13	37.75
$t_{1/2ka}$	h	4.64	0.75
V/F	(mg/kg)/(µg/ml)	0.35	0.04
CL/F	(mg/kg)/(µg/ml)/h	0.02	0.001
V_2/F	(mg/kg)/(µg/ml)	0.29	0.15
CL_2/F	(mg/kg)/(µg/ml)/h	0.01	0.01
T_{max}	h	9.41	1.35
C_{max}	µg/ml	9.29	0.42
AUC_{0-t}	µg/ml*h	335.55	36.25
AUC_{0-inf}	µg/ml*h	354.10	57.22
MRT	h	42.01	15.64

Discussion

This study investigated the pharmacokinetics of ceftiofur long-acting preparation in camels. This will help in the design of a suitable dosing program. Hibbard et al. (2002) reported that a single s/c injection of ceftiofur-CAF produced plasma levels of ceftiofur remained above 0.2 µg/ml for more than 7 days (7). In this study, ceftiofur-CAF injection in camels resulted in slow absorption from the injection site to reach a C_{max} and T_{max} of 9.41 µg/ml and 9.29 hours, respectively (Table 1). This indicates about 8 folds increase in the absorption time from the i/m injection site compared with immediate-release ceftiofur in camels, which was 1.22 h (17). Additionally, the C_{max} of ceftiofur-CAF was 9.29, which is highly comparable to the previously reported C_{max} of ceftiofur-IRF, 10.34 µg/ml (17).

The obtained C_{max} in she-camels (9.29 µg/ml) was prominently higher than 2.248 µg/ml in nonlactating goats (6), 1.458 in lactating goats (6), 6.39 µg/ml in beef cattle (6), 4.44 µg/ml in dairy cow, 2.45 µg/ml in sheep and 0.785 µg/ml in equine (1). The s/c injection in dairy cows, sheep, and goats, compared with i/m injection in this study might affect the peak of serum concentration. However, the several folds higher serum concentration in camels suggests the delayed absorption and camel specific factors in ceftiofur disposition. The obtained T_{max} in she-camels (9.41 h) is to be described as an earlier peak of ceftiofur concentration compared with 26.67 h in nonlactating goats (6) 46 h in lactating goats (6), 23 h in sheep (18), and 22 h in equine (1). The absorption half-life (t1/2βka) of ceftiofur-CAF in she-camels was 4.64 h, this is lower than the estimated value of 5.67 in nonlactating goats (6).

The distribution half-life ($t_{1/2\alpha}$) was 7.42 h indicating slow distribution. The $t_{1/2\alpha}$ obtained in ceftiofur-IRF was recording less than 1 h in cattle, sheep, and goats and about 0.34 h in camels (17). Similarly, the estimated elimination half-life ($t_{1/2\beta}$) was 46.13 h that is greatly higher than the average recorded value for ceftiofur-IRF, which was in the range of 3.18-5.83 h in cattle,

sheep, calves, or goats (17). Thus, ceftiofur-CAF produced a prominent long-lasting slow-release form in camels by showing delayed T_{max} and longer distribution and elimination half-lives. The elimination half-life ($t_{1/2\beta}$) of ceftiofur-CAF in she-camels was 46.13 h, which is more or less similar to 47.31 h in nonlactating goats (6) and 100 h in equine (1). This implies species-specific differences in $t_{1/2\beta}$ in animal species. The administration of ceftiofur-IRF in domestic and exotic birds showed wide variability in pharmacokinetic parameters with T_{max} = 0.83-2.67 h, C_{max} = 0.86-10.99 µg/ml, $t_{1/2\alpha}$ = 0.28-3.8 h and $t_{1/2\beta}$ = 2.5-8.65 h (19). This indicates the wide variability of ceftiofur pharmacokinetics.

The model for fitting ceftiofur-CAF pharmacokinetics was best explained by using a non-compartmental model in neonatal foals (3), equine (1), cattle egrets (9), guineafowl (20), American flamingos (21), ball python (22), and Rhesus macaques (8), one-compartment model in sheep (18) and goat (6) and two-compartment model in swine (23). The present data were fitted by a two-compartment model. This model was used to fit the pharmacokinetics data in pigs injected with commercial ceftiofur HCl suspension at a dose rate of 5 mg/kg (23). Compared with pigs data, she-camels pharmacokinetic parameters showed a 6-folds increase in distribution half-live, 10.45-folds increase in absorption half-life, 5.9-folds increase in T_{max}, 3.8 times lower C_{max}, and 3.36-folds increase in elimination half-life. This indicates delayed absorption, distribution, and elimination time in camels. Additionally, the drug levels fall below the recommended level of 0.2 µg/ml in pigs in less than 96 h, compared with 144 h in camels.

The analysis of the relation between the drug concentration and bacterial susceptibility was based on MIC levels for susceptible respiratory pathogens in cattle (7, 17). The obtained pharmacokinetic parameters revealed that one dose of i/m injection of ceftiofur-CAF at a dose rate of 6.6 mg/kg achieved serum levels above 0.2 µg/ml for 7 days in she-camels. In our study, the concentration of ceftiofur remained above 0.2 µg/ml for an average time of 119.833 h. Moreover, for proper antibacterial efficiency, achieving serum concentrations about 10-times the MIC values (24) or a serum level of 2 µg/ml is required. Based on pharmacokinetic parameters, the level of ceftiofur falls below 2 µg/ml after 48 h of injection. Therefore, a single injection is sufficient to cover 7 days for highly susceptible bacteria and it is recommended to administer a second dose of ceftiofur-CAF after 2 days from the first injection for less susceptible bacteria. The estimated ceftiofur levels were above 0.2 µg/ml for 9.1 days in beef cattle (6.6 mg/kg), 6.7 days in nonlactating goats, 8.5 days in dairy cows, and 7.5 days in lactating goats (6). This indicates a shorter duration in she-camels compared with other animals. Taking into consideration the "flip-flop" pharmacokinetics of slow-release preparations, the terminal phase of elimination of the drug is complicated by its slow release from the injection site. However, the impact of "flip-flop" pharmacokinetics is underscored in this camel experiment, as the half-life of absorption (4.64 h) is much lower than the elimination half-life ($_{t1/2\beta}$).

Conclusion: Ceftiofur-CAF achieved long-lasting serum levels in camels above the recommended level of 0.2 µg/ml for 4 days following a single i/m injection at a dose rate of 6.6 mg/kg. Careful dose adjustment depending on MIC values could be practiced by comparing its value with the provided concentration-time relation. Camels showed a higher peak of serum concentration with markers of slow excretion and longer persistence in the body compared with other animals.

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The authors declare that they have no conflict of interest.

All animals' procedures were approved by the ethics committee of King Faisal University (approval no: 1811013). Informed consent not apply to this work.

Authors' contributions, MK, WE, and MF designed the experiment, MK, WE, MF, IG performed the experiment, MK, WE, MF analyzed the results, MK, WE, and MF wrote the manuscript, MK, WE, MF, IG approved the submission.

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FARMAKOKINETIKA DOLGODELUJOČE CEFTIOFURNE KRISTALINIČNE PROSTE KISLINE PRI SAMICAH ARABSKIH KAMEL (*Camelus dromedarius*)

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Izvleček: Ceftiofur je pomemben širokospektralni antibiotik 3. generacije cefalosporinov. Zaradi njegovih časovno odvisnih protimikrobnih učinkov je čas, ko je raven ceftiofura nad bakterijskim MIC in ne pri njegovem vrhu koncentracije kritična točka pri uporabi tega antibiotika. Poskus je bil izveden z namenom ovrednotenja farmakokinetike dolgo delujoče ceftiofurjeve kristalinične brezkislinske oblike (ceftiofur-CAF) pri kamelah. Ceftiofur-CAF v koncentraciji 200 mg/ml suspenzije sterilne raztopine smo injicirali i/m v odmerku 6,6 mg/kg. Vzorci krvi so bili zbrani iz vratne vene v vakuumskih epruvetah ob injiciranju antibiotika in nato 8, 15 in 30 minut po injiciranju ter 1, 2, 4, 8, 12, 24, 48, 72, 96, 120 in 144 ur po injiciranju antibiotika. Za merjenje serumske koncentracije je bila uporabljena tekočinska kromatografija ultra visoke ločljivosti (UPLC MS/MS). Farmakokinetično modeliranje je bilo izvedeno z dvokomponentnim modelom. Farmakokinetiko ceftiofur-CAF-a po enkratnem i/m injiciranju v kamele je bilo najbolje modelirati v modelu z dvema predelkoma, kjer se je zdravilo počasi razdeljevalo v drugi predelek s slabo penetracijo v tkiva in veliko prednostjo do osrednjega predelka. Najvišja koncentracija antibiotika v plazmi (C_{max}) je bila 9,29 ± 0,42 µg/ml pri T_{max} 9,41 ± 1,35 ure. Površina pod krivuljo (AUC0-∞) je bila 354,1 ± 57,22 µg/ml*h. Razpolovni čas razporeditve in izločanja je bil 7,42 oziroma 46,13 ure. Povprečni čas prisotnosti antibiotika (MRT) je bil 42,01 h. V primerjavi s hitro absorbirano obliko ceftiofurja (ceftiofur-RAF) pri kamelah je bila skoraj podobna največja koncentracija v serumu, vendar z zakasnjenim časom do največje koncentracije (T_{max}), daljšim časom zadrževanja (MRT) in večjim razpolovnim časom porazdelitve in izločanja. Ceftiofur-CAF ostal dni nad predhodno priporočeno ravnijo učinkovitosti 0,2 µg/ml kar 7 dni, kar je bilo mogoče doseči po enkratni i/m injekciji 6,6 mg/kg. Pridobljeni podatki o farmakokinetiki v kamelah priporočajo večkratno dajanje v razmaku 2 dni za bakterije, ki potrebujejo ravni MIC nad 2 µg/ml.

Ključne besede: Ceftiofur; farmakokinetika; kamela; cefalosporini