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PHARMACOKINETICS PROFILE OF DANOFLOXACIN IN FEBRILE CAMELS WITH *E. COLI* ENDOTOXEMIA

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ABSTRACT

Camels are one of the most sensitive animals to *E. Coli* endotoxin and their pathophysiological effects on the body. In this work, pharmacokinetics of danofloxacin was studied in normal and febrile camels after single intravenous (i.v.) and intramuscular (i.m.) administration of 1.25 mg kg^{-1}. Plasma concentrations of the drug were determined by high performance liquid chromatography (HPLC). Following i.v. administration plasma danofloxacin curves were declined bi-physically in normal and febrile camels that characterised two compartment open model. The distribution pattern ($t_{1/2\alpha}$ and V_{dss}) of the drug was not altered by endotoxaemia. Danofloxacin was rapidly cleared from febrile camels, total body clearance CL_B, 0.16 l h^{-1} kg^{-1} versus 0.31 l h^{-1} kg^{-1} in normal camels. Plasma concentrations of danofloxacin, AUC and elimination half life ($t_{1/2\beta}$) following both routes were significantly higher in febrile camels than in normal ones. Fever significantly increased the MAT and absorption half-life of danofloxacin but did not alter the systemic bioavailability.

Key words: Camels, danofloxacin, *E. coli*, endotoxin, fever, pharmacokinetics

Danofloxacin is a synthetic fluoroquinolone antimicrobial drug, developed for veterinary use (McGuirk *et al,* 1992). It is bactericidal, has a broad spectrum of activity and acts by a concentration-dependent killing mechanism (Aliabadi and Lees, 2001; Sarasola *et al,* 2002). It is active against a wide range of bacteria including Gram-negative, Gram positive and *Mycoplasma* (Walker, 2000). Pharmacokinetic properties have been extensively examined in a variety of domestic animal species including camels (Giles *et al,* 1991; Mann & Frame, 1992; Friis, 1993; McKellar *et al,* 1998; Aliabadi & Lees, 2001; Aliabadi *et al,* 2003). Pathophysiological changes accompanying acute phase response have modified the pharmacokinetic behaviour of several drugs as well as danofloxacin in different species. Fever is a common sign for acute phase response associated with many infectious diseases (Anika *et al,*1986; Knoppert *et al,* 1988; Kumar and Malik, 1999; Monshouwer and Witkam, 2000) and following administration of *Escherichia coli* endotoxin in the domestic animals including camels (van Miert *et al,* 1983; van Gogh *et al,* 1984; van Miert *et al,* 1988; ; Al-Dughaym, 2004) . However, from the previous work in camels, it was showed that camels are highly sensitive to endotoxin than other domestic animals and this was apparent in their biochemical and pathophysiological response to such toxins (Al-Dughaym, 2004). To date, the impacts of such alteration on drug disposition in such species are still lacking. Although, alterations in the pharmacokinetics of fluoroquinolones has been reported in many animal species (Jha *et al,* 1996; Rao *et al,* 2000; Waxman *et al,* 2003; Ismail, 2006). The aim of the present investigation was to determine the pharmacokinetic properties of danofloxacin in normal and febrile camels.

Materials and Methods

Drug

Danofloxacin was purchased from Pfizer (Advocin, Riyadh, Saudi Arabia) as an injectable solution of of danofloxacin mesylate.

Animals

Ten camels of majaheem breed, which ranged in age from 2-4 years and weighed 350-450 kg, were used. All camels were considered healthy by clinical examination, complete blood picture, biochemical blood analysis and urinalysis. Each camel was housed in an individual well-ventilated hygienic pen. Feed consisted of alfalfa hay, concentrate and green fodder,

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and drinking water was provided *ad libitum*. The protocol of this study was reviewed and approved by Institutional Animal Care and Use Committee of King Faisal University.

Induction of febrile state

Fever was induced by i.v. injection of 0.2 µg kg^{-1} b.wt. of *E. coli* endotoxin (Difco laboratories, MI, USA) prepared in pyrogen free normal saline. Another 2 doses of *E coli* endotoxin (0.1 and 0.05 µg kg^{-1} b.wt.) were given, 8 and 16 hours after the first dose to maintain the febrile response up to 24 hours.

Drug administration and sampling

The study was performed in two phases. In the first phase animals were divided into 2 groups each of 5 camels. Animals in the first group received danofloxacin at a dose of 1.25 mg kg^{-1} b.wt. intravenously into the right jugular vein. Animals in the second group received the same dose intramuscularly injected deep into the gluteal muscle.

In the second phase of the study, separated by 2 weeks washout period, the study was repeated after inducing the febrile state in the same animals. The same dose of the drug was administered by both routes in febrile animals one hour after the first dose of endotoxin. Blood samples (3 ml each) were collected in heparinised tubes just prior to administration and at 5, 10, 15, 30 minutes and 1, 2, 4, 6, 8, 10, 12, 24, 36 and 48 hours post administration. Blood samples were centrifuged at 1000 g for 5 minutes and the plasma was decanted and frozen at -70°C until assayed.

Danofloxacin assay

Plasma concentrations of danofloxacin were analysed by reverse phase high performance liquid chromatography according to the method of Kung *et al* (1993). The chromatographic system used (Shimadzu LC -10 model) composed of 2 pump solvent delivery system, an automatic injector and Shimadzu fluorescence detector was set at an excitation wavelength of 280 nm and an emission wavelength of 440 nm.

Plasma (0.5 ml) samples were prepared by addition of ofloxacin solution as internal standard. Plasma protein was precipitated by addition of acetonitrile, the mixture was vortexed for 10 s, and 10 µl of the supernatant was injected into the HPLC system.

The chromatographic separation for plasma assays was accomplished on reverse phase, Phenomenex C18 (150 X 4.6 mm ID, particle size, 5 µm).

Calibration curves of danofloxacin standard concentrations versus peak height ratios (peak height of danofloxacin/peak height of internal standard) were established by the use of linear regression. Best linearity for the method used was accomplished in the range of 0.01 to 5 ug/ml with a correlation coefficient (*r*) of 0.99.

Intra-assay precision and accuracy were determined by measuring 5 replicates of each of 3 standard concentrations (0.01, 2.5 and 5 µg/ml) prepared in plasma together with standard used to construct a standard curve. Interassay precision and accuracy were estimated by assaying 3 plasma concentrations on 4 occasions.

The intra-assay and interassay coefficients of variation for the method were < 5 %. The intra-assay and interassay accuracies were > 97 %, respectively. A recovery of danofloxacin from plasma was found to be 97.5 %. The lower limit of quantitation (LOQ) in plasma was determined to be 0.01µg/ml.

Pharmacokinetic analysis

A pharmacokinetic computer program (Winnonlin, Pharsight Corporation. Mountain View, California, USA) was used to determine the least squares best-fit curve for danofloxacin concentration versus time data. Choice of appropriate pharmacokinetic model was made on the basis of the lowest weight sum of squares and lowest Akaike's information criterion value for the individual data (Yamaoka *et al,* 1978).

Following intravenous administration a two-compartment open model (Baggot, 1978) was found to best fit the data. The parameters calculated include A and α (intercept and slope of the distribution phase), B and β (intercept and slope of the elimination phase). The distribution and elimination half lives ($t_{1/2\alpha}$ and $t_{1/2\beta}$), the volume of distribution at steady-state (V_{dss}), the volume of the central compartment (Vc) and the total body clearance (Cl_B) were computed according to standard equations (Gibaldi and Perrier, 1982).

Following i.m. administration, plasma concentration data was analysed by both compartmental and non-compartmental methods based on the statistical moment theory (Gibaldi and Perrier, 1982). The terminal elimination half-life ($t_{1/2el}$) and absorption half-life ($t_{1/2ab}$) were calculated as ln $2/k_{el}$ or ln $2/k_{ab}$, respectively where k_{el} and k_{ab} are the elimination rate constant and absorption rate constant, respectively. The area under the plasma concentration-time curve ($AUC_{0-\infty}$) and the area under the first moment curve ($AUMC_{0-\infty}$) were calculated

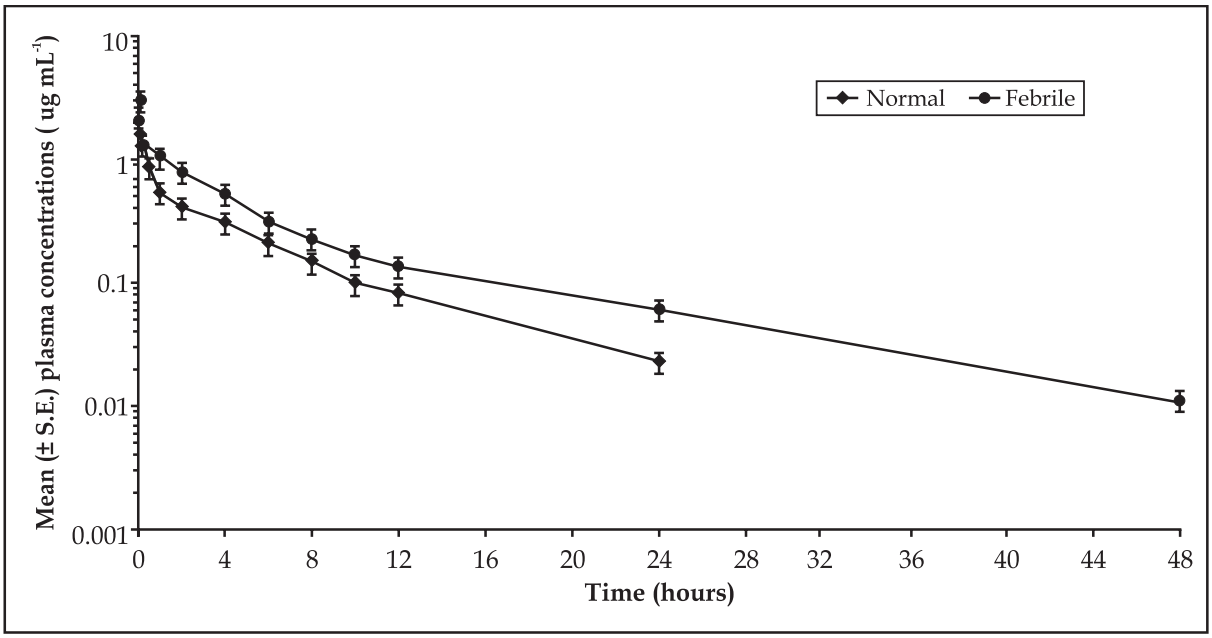

Fig 1. Semilogarethmic graph depicting the plasma concentrations of danofloxacin versus time in normal and febrile camels following i.v. administrtion of 1.25 mg/kg b.wt.(n=5).

by the trapezoidal rule for all measured data with extrapolation to infinity. The mean residence time (MRT) was calculated as MRT= $AUMC_{0-\infty}/AUC_{0-\infty}$. Mean absorption time was calculated as MAT= MRTi.m.- MRTi.v. The peak plasma concentration (C_{max}) and time to maximum concentration (t_{max}) were taken from the plot of each camels's plasma concentration-time curve. Bioavailability (F; fraction of drug absorbed systemically) was calculated as follows: $F = AUC_{i.m.} / AUC_{i.v} \times 100$.

Statistical Analysis

The statistical analysis was performed using the SPSS ® 6.1.3 software package (SAS, Cary, NC, USA). Results were expressed as mean ± S.E. Analysis of variance was performed by one-way analysis of variance (ANOVA) procedures. Significant differences between results reported in normal camels and those in febrile ones were determined by the method of least significant difference (LSD). A P-value <0.05 was considered to be significant.

Results

A significant rise in body temperature of at least 1.7°C was noted half an hour post injection of *E coli* endotoxin in all camels and maintained for 30 hours. The plasma concentrations were significantly higher in febrile camels than in normal ones all over the sampling times following both routes of administration (Fig 1 and Fig 2). Pharmacokinetic parameters following i.v. administration of the drug in febrile and normal camels are presented in table 1. The elimination half life, MRT and AUC were significantly higher and total body clearance was significantly lower in febrile camels than in normal ones. The distribution half life and volume of distribution were not altered by febrile condition.

Pharmacokinetic parameters following i.m. administration of the drug are shown in table 2,

Table 1. Pharmacokinetic parameters of danofloxacin in normal and febrile camels following single intravenous administration of 1.25 mg kg^{-1} b. wt. (Mean ± SE, n=5).

Parameters	Units	Mean ± S.E.	
		Normal	Febrile
$t_{1/2\alpha}$	(h)	0.32 ± 0.02	0.48 ± 0.015
$t_{1/2\alpha}$	(h)	5.5 ± 0.2	8.9 ± 0.1[B]
V_c	(l kg^{-1})	0.61 ± 0.08	0.54 ± 0.07
V_{dss}	(l kg^{-1})	2.0 ± 0.31	1.7 ± 0.21
Cl_B	(l h^{-1} kg^{-1})	0.31 ± 0.022	0.16 ± 0.01[C]
$AUC_{0-\infty}$	(µg h ml^{-1})	4.2 ± 0.25	8.6 ± 0.36[C]
$AUMC_{0-\infty}$	(µg h^2 ml^{-1})	27.3 ± 0.8	68.8 ± 3.5[C]
MRT	(h)	6.4 ± 0.8	7.99 ± 0.4[C]

[B]P<0.01; [C]P<0.001.

α, β, hybrid rate constants representing the slopes of distribution and elimination phases, respectively; $t_{½\alpha}$, distribution half-life; $t_{1/2\beta}$, elimination half-life, Vc, apparent volume of the central compartment; V_{dss}, volume of distribution at steady state; Cl_B, total body clearance; $AUC_{0-\infty}$, area under curve from zero time to infinity; $AUMC_{0-\infty}$, area under the first moment curve from zero time to infinity; MRT, mean residence time.

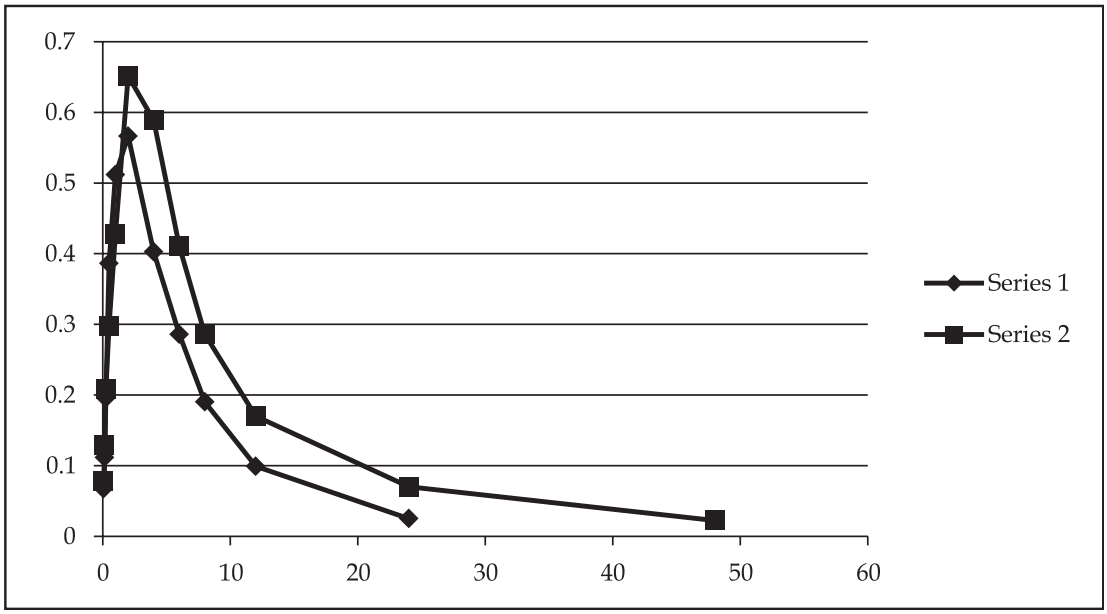

Fig 2. Semilogarethmic graph depicting the plasma concentrations of danofloxacin versus time in normal and febrile camels following i.m. administration @ 1.25 mg/kg b.wt.(n=5).

the elimination half life, MRT, AUC and C_{max} were significantly higher and $t_{1/2ab,}$ MAT and T_{max} were significantly lower in febrile camels than in normal ones. The systemic bioavailability following i.m. administration of the drug was not significantly altered in febrile camels.

Discussion

Following i.v. administration of danofloxacin in normal camels at a dose of 1.25 mg kg^{-1}, the time course of the drug in plasma was best described by a two compartment open model with an initial rapid distribution phase with a distribution half life of 0.13 hour and elimination half life of 5.1 hours. After i.m. administration of the same dose in normal camels, the drug was rapidly absorbed with a short absorption half life and a peak plasma concentration of 0.56 µg mL^{-1} was attained after 2.0 hour. The pharmacokinetics parameters reported in normal camels in this study are close to findings previously reported by Aliabadi *et al* (2003).

A significant increase in elimination half life was reported following i.v. and i.m. administration of the drug in camels intravenously injected with *E coli* endotoxin. Previous studies (van Miert, 1990; Roth *et al,* 1997; Ahmed *et al,* 1999; Hasegawa *et al,* 1999) have shown that *E. coli* endotoxin exert a pronounced inhibitory effect on the hepatic drug metabolising capacity *in vivo*. It also produces a significant reduction in glomerular filtration rate and it is likely to impair the excretion process of organic anions at the stage of transport from intracellular stage to bile via canalicular membrane (Hasegawa *et al,* 1999). These could also be an explanation to the reduced overall total body clearance of danofloxacin in febrile camels as compared to normal ones. As a consequence of the reduced total body clearance of the drug in febrile camels, the area under the plasma concentration versus time curve and MRT were increased significantly. In accordance with our findings, a significant increase in elimination half

Table 2. Pharmacokinetic parameters of danofloxacin in normal and febrile camels following single intramuscular administration of 1.25 mg kg^{-1} b. wt. (Mean ± SE, n=5).

Parameters	Units	Mean ± S.E.	
		Normal	Febrile
$t_{1/2ab}$	(h)	0.13 ± 0.02	0.34 ± 0.04[A]
$t_{1/2el}$	(h)	5.1 ± 0.4	10.2 ± 0.3[B]
C_{max}	(µg ml^{-1})	0.56 ± 0.03	0.65 ± 0.01[B]
t_{max}	(h)	2.0 ± 0.05	2.0 ± 0.03
$AUC_{0-\infty}$	(µg h ml^{-1})	4.35 ± 0.4	8.22 ± 0.5[C]
$AUMC_{0-\infty}$	(µg h^2ml^{-1})	15.87 ± 2.6	43 ± 2.3[C]
MRT	(h)	7.3 ± 0.7	12.15 ± 0.9[B]
MAT	(h)	0.9 ± 0.02	4.15 ± 0.06[B]
F	(%)	101 ± 13.5	96 ± 11.2

[A]P<0.05; [B]P<0.01; [C]P<0.001.

K_{ab}, absorption rate constant; K_{el}, first-order elimination rate constant; $t_{½el}$, elimination half-life; $t_{½ab,}$ absorption half-life; Cmax, peak drug concentration; tmax, time to peak concentration; $AUC_{0-\infty}$, area under curve from zero time to infinity; $AUMC_{0-\infty}$, area under the first moment curve from zero time to infinity; MRT, mean residence time; MAT, mean absorption time; F, systemic bioavailability following intramuscular administration.

life, AUC and MRT of norfloxacin and enrofloxacin have been reported in febrile goats (Jha *et al,* 1996; Rao *et al,* 2000). Induced endotoxaemia in the present study did not alter the volume of distribution of danofloxacin in camels. The effect of the disease on the distribution of drugs is dependant upon their degree of ionisation (Baggot, 1980). Fever significantly increased V_{dss} for basic drugs, gentamicin (pKa; 8.2) in rabbits (Hillel *et al,* 1980) and amikacin (pKa; 8.1) in goats (Agrawal *et al,* 2001). On the contrary, Marier *et al* (2001) recorded a significant reduction on V_{dss} of acidic drug, amoxicillin (pKa; 2.7) in febrile dogs injected with *E coli* endotoxin. Similarly to our result, endotoxaemia did not alter the distribution character of norfloxacin or enrofloxacin (Jha *et al,* 1996; Rao *et al,* 2000). Result of the present study could be attributed to the zwitterionic nature of danofloxacin (pKa; 6.0 and 8.8) so endotoxaemia would minimally affect their distribution characters.

A significant increase in absorption half life, mean absorption time following IM route was reported in febrile camels. These findings in addition to the longer elimination half life following this route of administration versus intravenous routé indicated the extension of absorption phase into the elimination phase in a flip flop manner. This finding could be attributed to the effect of endotoxaemia on cardiac output and blood flow to the different body compartments (Blatteis *et al,* 1988; van Miert, 1990).

The plasma concentration, C_{max} and AUC were significantly higher in febrile camels than in normal ones. The MIC_{90} of danofloxacin to most susceptible bacteria has been reported to be 0.015 μg ml^{-1} (Walker *et al,* 2000). It has been suggested for fluoroquinolones that a C_{max}/ MIC_{90} ratio of 10 or greater is predictive of a successful clinical outcome (Sullivan *et al,* 1993) or alternatively, that an AUC or 24 hour dosing period divided by the MIC_{90} of 125 or greater is predictive of bacterial eradication in pneumonic patients (Forrest *et al,* 1993). With these predictive models and by incorporating C_{max} and AUC data obtained following i.m. administration of the drug in the present study with an MIC_{90} of 0.015 μg ml^{-1}, the C_{max}/ MIC_{90} and AUC/ MIC_{90} (43 & 548) were double tin febrile camels than in normal ones (37& 290), respectively.

In conclusion, the present study indicated that endotoxin induced febrile state in camels altered the overall clearance of the drug from the body and resulted in a significant increase in plasma concentrations, AUC and MRT of danofloxacin following both routes of administration. The findings of the present work emphasis the previous findings that camels has their own profile regarding pharmacokinetics of most medicines.

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