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PHARMACOKINETIC DISPOSITION OF MARBOFLOXACIN AND DANOFLOXACIN IN CAMEL (*Camelus dromedarius*)

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ABSTRACT

The pharmacokinetic disposition of marbofloxacin and danofloxacin was studied in camels following a high dosage administration as a single-dose (one shot) in a two-period crossover studies. Marbofloxacin was administred by intramuscular and intravenous routes @ 8mg/kg body weight. Danofloxacin was administred by sub-cutaneous and intravenous routes @ 6mg/kg body weight. Concentrations of both fluoroquinolones were measured by high-performance liquid chromatography and the data were subjected to kinetics analysis. The plasma disposition of marbofloxacin was best described by a tri-compartmental for intravenous and a bicompartmental open model with first-order for intramuscular dosing. The Peak plasma concentration (C_{max}) of 39.80 ± 11,29 mg/l was reached at (Tmax) 1,16 ± 0,460 h after intamuscular administration. The elimination half-life ($t_{1/2\,\beta}$) and area under curve of concentration (AUC) were 11.97 ± 3.84 h and 320.65 ± 67.93 mg h/l, respectively. Danofloxacin achieved maximum plasma concentration (C_{max}) after sub-cutaneous administration of 27.61 ± 5.00 mg /l at (T_{max}) 2.54 ± 1.51h. The distribution half-life (t1/2 β) value of 33.77 ± 32.68 h was obtained for danofloxacin. These data were used together with *in vivo* pharmacokinetic parameters; C_{max} and AUC to determine the surrogate markers of antimicrobial activity; C_{max}/MIC and AUC/MIC. Taking into account the values obtained for these markers, it was concluded that an intramuscular dose of 8 mg/kg of marbofloxacin and a sub-cutaneous dose of 6mg/kg of danofloxacin could be adequate for the treatment of infectious diseases caused by high susceptible bacteria such *Mannheimia haemolytica* and *Pasteurella multocida* in camels.

Key words: Camels, danofloxacin, fluoroquinolones, marbofloxacin, pharmacokinetic

The fluoroquinolones are antimicrobial drugs which generally have very good activities against a broad spectrum of aerobic bacteria, including *Pasteurella* spp and mycoplasma (Gutierrez *et al*, 1993; Hannan *et al*, 1997; Giles *et al*, 1991). Danofloxacin and Marbofloxacin are a synthetic antibacterial agent of the fluoroquinolone group, developed specifically for use in veterinary medicine. A formulation of marbofloxacin (Marbocyl 10%) and danofloxacin (Advocin 180) were developed to allow the delivery of a high dosage with bactericidal concentration dependent activity. The concept of the high dosage in a single injection (one shot) is that, after injection, the drug is available in sufficient concentrations to kill all the sensitive bacteria during a relatively short period of time (Mc Kellar *et al,* 2000). This may reduces the selection pressure for resistance and involve less handling which is of special importance for camel conducted in extensive mode of management.

The purpose of this study was to investigate the disposition kinetics of marbofloxacin and danofloxacin in the plasma of the dromedary camel at high dosage regimens, 8mg/kg for marbofloxacin and 6mg/kg for danofloxacin.

Materials and Methods

Marbofloxacin study: two-period cross-over study was undertaken in 6–8 years old healthy female camels (*Camelus dromedarius*), weighing 383.33 ± 58.23kg b.wt. Each animal received marbofloxacin (Marbocyl 10%, Vétoquinol, Lure, France) at 8mg/kg both by intravenous (i.v.) and intramuscular (i.m.) routes. In period 1, three camels received marbofloxacin i.v. into the right jugular vein, and three camels received the same dose rate into the

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neck muscle. In period 2, administration routes were reversed. An interval of 15 days was allowed between the two periods. Hay and water were provided *ad libitum,* and each animal received approximately 1kg of concentrate feed daily.

Danofloxacin study: It was undertaken in female camels of 5–7 years and weighing 291 .8 ± 19.72kg b.wt. receiving danofloxacin (Advocin, Pfizer Animal Health, AMM : UK- Vm 00057/4211 Sandwich, Kent, UK) at a dosage of 6 mg/kg both i.v. and subcutanous (s.c.) routes. Animals were maintained in the same condition as the marbofloxacin study.

Sampling Procedure

Blood samples (10 ml) for subsequent determination of marbofloxacin and danofloxacin in plasma concentrations were collected by jugular venipuncture into lithium-heparin beaded tubes (Venoject) just before drug administration and at 5, 10, 15, 30, 45 min, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72, 96 and 120 hours after marbofloxacin administration. Blood samples were centrifuged at 2600g for 10 min. Plasma was harvested, divided in two aliquots, and stored at - 20°C until analysis. The same sampling procedure was performed until 96h for danofloxacin.

HPLC analysis

The plasma concentrations of marbofloxacin were determined by reverse phase high-performance liquid chromatography (HPLC) according to the method described by Schneider *et al* (1996). The plasma concentration of danofloxacin was determined by HPLC using the method described by Friis (1993). The chromatographic system consisted of an LC Perkin Elmer 200 series Liquid Chromatograph Pump, a Merck Column, 250mm×4mm, 5µm Lichrospher RP-18 equipped with precolumn Guard filter RP-18, Merck. The column was maintained at a temperature of 30 ± 0.5°C using a LC Perkin Elmer 200 series column heater. A Perkin Elmer fluorescence detector was used at an excitation wavelength of 280nm and an emission wavelength of 440 nm for danofloxacin and a Perkin Elmer UV detector with 295nm wavelength for marbofloxacin.

The standard curve in camel plasma was linear between (0.5– 5 µg / mL) with correlation coefficient (r^2) of 0.99. The limit of quantification (LOQ) was established at 0.5 µg /ml and limit of detection (LOD) at 0.15 µg /ml for plasma analysis. Mean analytic recovery for marbofloxacin in plasma was 94.57 ± 6.61%. The coefficient of variation (CV) of inter-assay and intra-assay reproducibility were of 6.67% and 6.57%, respectively.

For danofloxacin, the standard curve in camel plasma was linear between (0.125– 1 µg / mL) with correlation coefficients (r^2) of 0.99. The LOQ was 0.125 µg /ml and LOD was 0.05 µg /ml for plasma analysis. The mean recovery for danofloxacin was 65.23 ± 2.84%, the intra-assay and inter-assay (CV) were 2.85% and 4.40%, respectively.

Results and Discussion

Marbofloxacin

No compartmental and compartmental open models were tested using first-order absorption. Classical pharmacokinetic parameters were calculated using standard equations (Gibaldi and Perrier, 1982). The mean marbofloxacin plasma concentration-time profiles following i.v. and i.m. administration are illustrated in Fig 1. The pharmacokinetic data associated with each route of drug administration are given in Table 1.

The plasma disposition of marbofloxacin was best described by a tri-compartmental open model for i.v. route and a bicompartmental open model with first-order absorption without Tlag time after i.m. dosing according to Akaike's Information Criterion (Yamaoka *et al,* 1978). The plasma of marbofloxacin profiles after the i.m. administration, evolved with a slow absorption phase. As compared with previous study of comparative pharmacokinetics of marbofloxacin after a single intramuscular administration at two dosages to camels (Laraje *et al,* 2006), there was a difference between absorption half-life ($t_{1/2\alpha}$) of the dosage 8mg/kg after i.m. administration ($t_{1/2\alpha}$=1.57 ± 1.10h) and the dosage 2mg/kg ($t_{1/2\alpha}$=0.42 ± 0.075h) denoting a marked variation in absorption of marbofloxacin between the two dosages regimens. The C_{max} (39.80±11.229 mg/l) and AUC (320.65 ± 67.93mg h/l) of marbofloxacin obtained with 8mg/kg after i.m. administration were higher than that obtained with 2mg/kg (C_{max}=2.50±0.42mg/l, AUC=18.71 ± 3.86 mg h/l) (Laraje *et al,* 2006), while Cmax was reached in slightly close time (T_{max}= 1.16 ± 0.46 h) for 8mg/kg, and (T_{max}=1.0±0.56h) for 2mg/kg. The mean residence time of 8mg/kg dosage by i.v. route was higher (MRT=11.06 ± 2.54h) as compared to values obtained by i.m. route in camel with 2mg/kg (MRT= 8.90±0.49h) (Laraje *et al,* 2006), as it would be slowly released from the site of injection, intramuscular administration of 8mg/kg can therefore, provide an extended period with approximately even

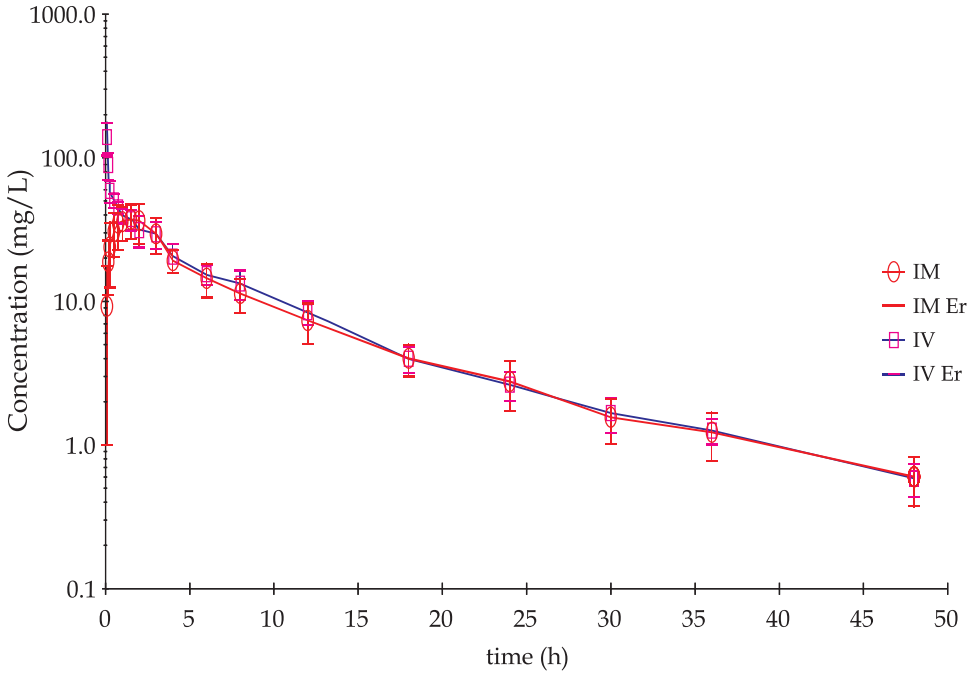

Fig 1. Mean (±SD) plasma concentration profiles of marbofloxacin following intravenous and intramuscular administration (8 mg/kg) to camels (n = 6).

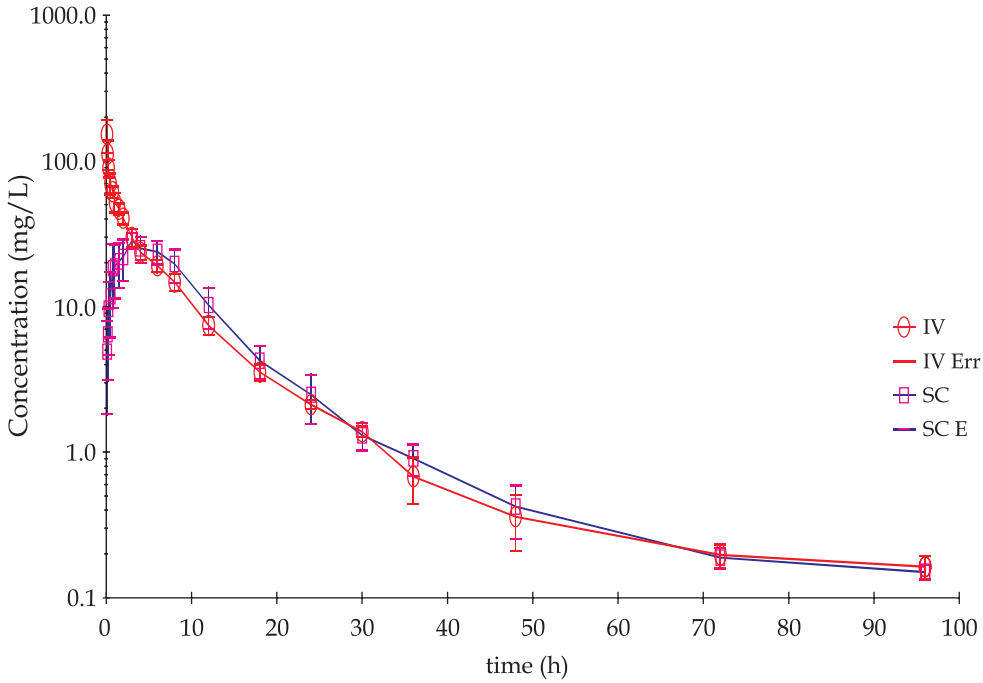

Fig 2. Mean (±SD) plasma concentration profiles of danofloxacin following intravenous and subcutaneous administration (6 mg/kg) to camels (n = 6).

concentrations of the drug in the blood. The mean terminal half-life obtained was similar for both administration routes with ($t_{1/2\,\beta}$ =11.97 ± 3.84 h) and ($t_{1/2\lambda z}$ = 11.64 ± 4.18 h) for i.m. and i.v., respectively. These elimination half lives are slightly higher than the values found in the same species with 2mg/kg ($t_{1/2\lambda z}$ =7.16±1.32h) (Laraje *et al,* 2006), higher than in the bovine ($t_{1/2\,\beta}$ = 5.72 ± 1.17 h) (Thomas *et al,* 1993), indicating a slower elimination in the camel. The difference in elimination could be explained by hydration status of the animals. Fluoroquinolones are mainly excreted through kidneys by glomerular

Table 1. Mean ± SD plasma pharmacokinetic parameters in camel (n = 6) of marbofloxacin administration @ 8 mg/kg b.wt. i.v. and i.m. and danofloxacin administration at 6 mg/kg b.wt. by i.v. and s.c. routes in camels.

Parameters	Marbofloxacin		Danofloxacin	
	i.v.	i.m.	i.v.	s.c.
$t_{1/2\alpha}$ (h)	0.052 ± 0.025	1.57 ± 1.10	0.15 ± 0.20	4.83 ± 1.38
$t_{1/2\beta}$ (h)	1.52 ± 1.37	11.97 ± 3.84	3.38 ± 2.43	33.77 ± 32.68
$t_{1/2\lambda z}$ (h)	11.64 ± 4.18	-	17.15 ± 21.05	-
AUC $_{(0-\infty)}$ (mg h/l)	372.79 ± 44.52	320.65 ± 67.93	403.26 ± 36.65	336.65 ± 59.79
Vc comp (l/kg)	0.03 ± 0.02	-	0.037 ± 0.019	-
Vss $_{noncomp\ (0-\infty)}$ (l/kg)	0.24 ± 0.05	-	0.155 ± 0.04	-
CLB $_{(0-\infty)}$ (l/h/kg)	0.022 ± 0.003	-	0.015 ± 0.002	-
MRT $_{(0-\infty)}$ (h)	11.06 ± 2.54	-	10.41 ± 3.09	-
$C_{(max)}$ (mg/l)	-	39.80 ± 11.29	-	27.61 ± 5.00
$T_{(max)}$ (h)	-	1.16 ± 0.46	-	2.54 ± 1.51
F (%)	-	87.22 ± 21.34	-	84.71 ± 20.62

$t_{1/2\alpha}$ absorption half-life (harmonic mean); $t_{1/2\beta}$, distribution half-life(harmonic mean); $t_{1/2\lambda z}$, elimination half-life (harmonic mean); Vc, volume of central compartment ; Vdss, volume of distribution at steady-state; Cl, clearance of drug; AUC, total area under the concentration time-curve; MRT, mean residence time; C_{max}, peak observed concentration; T_{max}, time at which peak plasma concentration is observed; F(%), bioavailability.

filtration and tubular secretion (Bregnate *et al,* 1999). Infact, the glomerular filtration rate of camels is about (0.55–0.65 mL/kg/min) (Wilson, 1984) and the low total body clearance of 0.022 ± 0.003L/ kg/h may be related to a low glomerular filtartion rate especially in a state of dehydration (Bengoumi, 1992). The influence of this low clearance produce a relatively long persistence of drug in the body as compared to bovines.

Bioavailiability (F%) of marbofloxacin (87.22 ± 21.34%) was slightly higher than the relative bioavailiability obtained in the same species (71.95%) (Laraje *et al,* 2006). This value is similar to that reported for mature horses with a dosage of 2mg/kg (F% = 87.9 ± 6.0%) (Carretero *et al,* 2002).

The interaction between pharmacokinetics and pharmacodynamics of fluoroquinolones can be assessed by measuring the area under the concentration time curve over 24 h, and divide this by the MIC value (AUC/MIC ratio) and the peak level divided by the MIC (Cmax/MIC) (Mouton *et al*, 2005). The value of >125 for AUC/MIC ratio and of 10 for Cmax/MIC has been recommended to achieve high efficacy for fluoroquinolones, according to the concept of concentration-dependent antibacterial activity of this class of antibiotics (Schentag, 2000; Schentag *et al*, 2001; Drusano, 2004).

Several species of microorganisms have been isolated from both apparently healthy and affected respiratory tract of camels as Staphylococci, Streptococci, Corynebacterium, *E. coli*, Pasteurella and Klebsiella (El Mosalami and Ghawi, 1983; Chauhan *et al*, 1987; Gobrial *et al*, 1991; Rana *et al*, 1993; Fatma *et al*, 2001; Seddek, 2002; Kane *et al,* 2005). There are no published data about antibacterial activity of marbofloxacin against camel isolates. However, an MIC of 0.016-0.56 µg/ml has been reported for susceptibile bacteria to marbofloxacin for bovine pathogenic strains (*Mannheimia haemolytica* and *Pasteurella multocida*) (Meunier *et al,* 2004). Based on this, the dose of 8 mg/kg b.wt. used in this study, showed Cmax of 39.80±11.29 mg/l and AUC of 320.65 ± 67.93 mg h/l. Using theses Cmax, AUC values and MIC of 0.56 µg/ml (*Pasteurella multocida*), the calculated ratio of Cmax/MIC was 71.07h for 8mg/kg b.wt. dosing, which was about seven time the recommended ratio. The calculated AUC/ MIC ratio of 572.59h represent about four times the recommended surrogate marker of fluoroquinolones efficacy. A dosage of 8 mg/kg b.wt. generated a high plasma concentration which may cover most of the bacteria with MIC less than 0.56 µg/ml and may be recommended to treat most of susceptible bacteria for the camelid species.

Danofloxacin

The bicompartmental is the best model to describe the kinetic of danofloxacin administered by i.v. route and tricompartmental model without Tlag

is the best model to describe the kinetic of s.c. route administration.

The pharmacokinetic data associated with both routes of drug administrations (i.v. and s.c.) are given in Table.1. The plasma danofloxacin profiles showed a slow absorption phase after s.c. administration ($t_{1/2\alpha}$ = 4.83 ± 1.38h). This value is slightly higher than the one obtained in the same species after i.m administration of 1.25mg/kg ($t_{1/2\alpha}$ = 0.12±0.01h) (Shojaee Alibadi *et al,* 2003b), this can be explained by a slow release of drug from the site of subcutaneous administration.

The mean terminal half-life after s.c. administration ($t_{1/2\beta}$ = 33.77 ± 32.68 h) is almost twice the value obtained for i.v. dosage ($t_{1/2\lambda z}$ = 17.15 ± 21.05h).

The slower elimination of danofloxacin after s.c. administration is in accordance with study conducted in lactating cows (Shem-Tov *et al,* 1998), which strongly supports a regimen of a single administration.

Toutain and Bousquet-Melou (2004) indicated breakpoint clearance values to classify drug clearance as high, medium or low as 28, 12 and 5.8 ml/kg/min, respectively. In this study, the danofloxacin clearance intravenously of 0.015 ± 0.002 l/ kg/h may be classified as low. This value is much less than that reported by (Shojaee Alibadi *et al,* 2003) (0.44±0.02 l/h/kg), while The MRT after i.v administration of 10.41 ± 3.09h is twice the value found in the same species (5.82 ±0.53h) with 1.25mg/kg b.wt. which suggest the low elimination process.

The pharmacokinetic disposition of danofloxacin is characterised by high AUC values obtained for i .v (403.26 ± 36.65mg h/l) and for s.c (336.65 ± 59.79 mg h/l). This high plasma drug exposure is in accordance with high C_{max} (27.61 ± 5.00 mg/l) over long period of time (MRT= 10.41 ± 3.09h and $t_{1/2\beta}$ = 33.77 ± 32.68 h). These relevant data obtained for danofloxacin administration @ 6mg/kg b.wt. may be recommended to obtain adequate clinical efficacy in camel infected with sensitive bacteria to danofloxacin.

In addition, minimal inhibitory concentration data of danofloxacin against camel bacterial isolates have not been previously reported, however, when extrapolating MIC data from bovine isolates results to camel, the range of MIC values for danofloxacin against *Mannheimia haemolytica* and *Pasteurella multocida* was 0.015-0.5 µg/ml and 0.015-0.06 µg/ml, respectively (Giles *et al,* 1991; Rowan *et al,* 2004). The administration of 6mg/kg b.wt. in our study generated a Cmax of 27.61 ± 5.00 mg/l and an AUC of 336.65 ± 59.79 mg h/l, using theses C_{max}, AUC values and MIC of 0.5 µg/ml (*Mannheimia haemolytica*) (Giles *et al,* 1991), the calculated ratio of C_{max}/MIC (55.22h) and AUC /MIC ratio (673.3h) which both represent about five times the recommended surrogate markers of fluoroquinolones efficacy. These values are largely beyond the predicted effective values referred above. It could be concluded that danofloxacin administration at 6mg/kg may be highly effective in the treatment of all camelid bacteria infections with MIC under 0.5 µg/ml.

Conclusion

The pharmacokinetic disposition of marbofloxacin (8mg/kg b.wt.) and danofloxacin (6mg/kgb.w) with a single dose injection in the camel (one shot), compared to other dose regimens are characterised by a high Cmax and AUC over long period of time (high MRT and long terminal half-life). It can be concluded that marbofloxacin and danofloxacin represents a good practical alternative for the treatment of infectious diseases in camel, involving less handling and a concurrent reduction in handling stress. Considering efficacy predictors, both marbofloxacin and danofloxacin would appear to be a good therapeutic tool for the treatment of the most pathogenic bacteria for camels. Further studies on tissue distribution and specific determination of the MIC of these antimicrobials agents for the major susceptible bacteria responsible for respiratory and cutaneous diseases in camels should be performed to achieve a complete efficacy data of marbofloxacin and danofloxacin in this species.

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