Comparative pharmacokinetics of marbofloxacin after a single intramuscular administration at two dosages to camels (*Camelus dromedarius*)

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Marbofloxacin is a fluoroquinolone antimicrobial agent used exclusively in veterinary medicine. This agent has a broad-spectrum microbial activity including most aerobic Gram-negative and some aerobic Gram-positive bacteria. Its spectrum of activity and pharmacokinetic profile suggest good tissue penetration making this drug a suitable second choice treatment especially for dermatological and pulmonary infections. Marbofloxacin is mainly eliminated in urine in its active form making it a suitable alternative for the treatment of urinary tract infections (Schneider *et al.*, 1996). A previous study has shown that the main clinical problems in adult dromedaries are dermatological and pulmonary infections whereas in young dromedaries infectious diarrhoea is of major clinical importance (Bengoumi & Faye, 2002). Marbofloxacin might be a suitable antimicrobial agent for the treatment of these diseases in the camel. The pharmacokinetics of marbofloxacin are well documented in bovine species, but not in camels. The purpose of the present study was to investigate the disposition of this fluoroquinolone in camels following administration of a single dose at a dosage of 2 and 4 mg/kg b.w. intramuscularly (i.m.).

The study was carried out on five healthy male camels, 5–13 years old and ranging in body weight from 291 to 535 kg. They were individually stabled and were fed barley (2 kg/day each) and had free access to hay and water. No drugs had been administered previously to these animals.

All the camels were administered a 10% aqueous solution of the base form of marbofloxacin (Vétoquinol, Lure, France) at a dose of 4 mg/kg b.w., i.m., in the right thigh. After a wash-out period of 2 weeks, the same animals were administered the same solution at a dose of 2 mg/kg b.w. i.m. in the right thigh. Blood samples (10 mL) were collected from the right jugular vein just before drug administration and at 5, 10, 15, 30, 45 min, 1, 2, 3,

4, 6, 8, 12, 16, 24, 36, 48, 72 and 96 h after administration. Blood samples were centrifuged (2600 *g* for 10 min) and plasma was stored at −20 °C until analysis.

The plasma concentration of marbofloxacin were determined by a reverse phase high-performance liquid chromatography with UV detection (295 nm) using the method described by Schneider *et al.* (1996). The standard curve of marbofloxacin in camel plasma was linear between 0.1 and 5 µg/mL with a determination coefficient (r^2) of 99.8%. The recovery measured on linear dosage interval was 96%. The intra- and inter-assay coefficients of variation were below 5%. The limit of quantification was established at 0.1 µg/mL.

Both compartmental and statistical moment approaches were used to analyse the plasma concentration–time data for marbofloxacin in camels using a nonlinear regression analysis program (Winonlin 4.01; Pharsight Inc., Mountain View, CA, USA). One- and two-compartment open models were tested using first-order absorption with and without a lag time. The best fitting model was selected using Akaike's Information Criterion (Yamaoka *et al.*, 1978). Classical pharmacokinetic parameters were calculated using standard equations (Gibaldi & Perrier, 1982). The observed maximum concentration (C_{maxobs}) and the time when these concentrations occurred (t_{max}) have also been indicated.

The relative bioavailability (*F*) was calculated using the equation:

$$F(\%) = \frac{AUC_{\text{i.m.4(0−inf)}}}{AUC_{\text{i.m.2(0−inf)}}} \frac{\text{Dose}_{\text{i.m.2}}}{\text{Dose}_{\text{i.m.4}}} \times 100.$$

Statistical analyses were performed using Systat software (Version 7.0; SPSS Inc., Chicago, IL, USA). The arithmetic mean

and standard deviation were calculated for all parameters excepted for half-life values where harmonic mean values and standard deviation were calculated according to Lam *et al.* (1985). The parameters were compared using a paired *t*-test. A level of significance was set at 0.05.

The mean marbofloxacin plasma concentration–time profiles following i.m. administration are shown in Fig. 1. The plasma disposition of marbofloxacin after i.m. administration at 2 and 4 mg/kg b.w. could be described by a bi-compartmental open model with first-order absorption without lag time.

Following i.m. administration of 2 mg/kg b.w., peak plasma concentrations (C_{max} = 2.50 ± 0.42 µg/mL) were reached at 1.0 ± 0.56 h, the area under the curve (AUC_{0-inf}) was 18.71 ± 3.86 µg·h/mL, the mean residence time (MRT_{inf}) was 8.90 ± 0.49 h, and the terminal half-life ($t_{1/2\beta}$) was 7.16 ± 1.32 h.

The *MRT*, the half-life of absorption ($t_{1/2}ka$) and terminal half-life ($t_{1/2\beta}$) did not differ significantly with dosage (Table 1), but the C_{max} and the *AUC* obtained for 4 mg/kg b.w. did not appear to be linear; the *AUC* of the 4 mg/kg b.w.
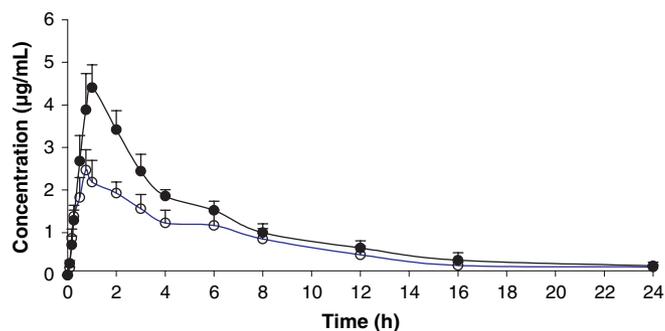

Fig. 1. Marbofloxacin plasma concentration in five camels (mean ± SD) after i.m. administration of 4 mg/kg b.w. (●) or i.m. administration of 2 mg/kg b.w. (○).

Table 1. Pharmacokinetic parameters of marbofloxacin after a single intramuscular administration (i.m.) at two dosages in camels ($n = 5$)

Parameters	Units	Route of administration/dosage (mg/kg b.w.)	
		i.m./(2)	i.m./(4)
t_{maxobs}	h	1.0 ± 0.56	0.9 ± 0.14
C_{maxobs}	µg/mL	2.50 ± 0.42	4.55 ± 0.48
AUC_{0-inf}	µg·h/mL	18.71 ± 3.86	28.37 ± 5.51
$t_{1/2}ka$	h	0.42 ± 0.075	0.69 ± 0.10
$t_{1/2}\lambda_3$	h	7.16 ± 1.32	7.98 ± 3.03
MRT_{inf}	h	8.90 ± 0.49	7.78 ± 1.98
$F_{relative}$	%		71.95 ± 6.41

t_{maxobs}, occurring time of maximum observed plasma concentration (C_{maxobs}); AUC_{0-inf}, area under the plasma concentration–time curve between 0 and infinity; $t_{1/2}ka$, absorption half-life; $t_{1/2}\lambda_3$, half-life; MRT_{inf}, mean residence time between 0 and infinity; *F*, relative bioavailability. Data are expressed as arithmetic mean ± SD except for $t_{1/2}$ which are expressed as harmonic mean ± SD.

dose was 28.37 µg/mL which is about 1.5 times the 2 mg/kg b.w. *AUC* and C_{max} of the 4 mg/kg b.w. is about 1.8 times of the 2 mg/kg b.w. C_{max}. This difference could be explained by the volume of injection. For 2 mg/kg b.w., using a 10% aqueous marbofloxacin solution, the volume of injection for an animal weighting 500 kg was 10 mL and for 4 mg/kg b.w. the volume was 20 mL. A high injection volume may produce local oedema with an inflammatory response, such as has been described in the bovine species (Anonymous, 1999) and consequently a reduced absorption.

The relative bioavailability between the two dosage regimens was 71.95%, which is in accordance with the *AUC* and C_{max} values. There was a significant difference between absorption half-life ($t_{1/2}ka$) of the two dosages denoting a marked variation in absorption of marbofloxacin between the two dosages administered.

The C_{max} and *AUC* of marbofloxacin were higher in the camel than in the bovine (Thomas *et al.*, 1993) while C_{max} was reached more quickly (t_{max} = 0.79 h) in the bovine than in the camel (t_{max} = 1.0 h). The mean terminal half-life was higher in the camel ($t_{1/2\beta}$ = 7.16 ± 1.32 h) than in the bovine ($t_{1/2\beta}$ = 5.72 ± 1.17 h, *t*-test, $0.05 < P < 0.10$) indicating a slower elimination in camel.

The minimum inhibitory concentration (*MIC*) of marbofloxacin has not been determined in isolates from the camel. However, an MIC_{90} of 0.03–0.21 µg/mL has been reported for susceptible bacteria isolated from bovine and equine species (Drugeon *et al.*, 1997; Bousquet-melou *et al.*, 2002). Based on this, a dosage of 2 mg/kg b.w. in camels should produce a C_{max} of 2.50 µg/mL that is about 12 ± 2 to 83 ± 14 times the MIC_{90} of these susceptible bacteria. For a dosage of 4 mg/kg b.w. a C_{max}/MIC_{90} range of 22 ± 3 to 152 ± 16 was calculated. For quinolones a second surrogate marker of efficacy *AUIC* (AUC/MIC_{90}), the area under the curve that the concentrations were above the *MIC*, was used and generally values between 75 and 125 h are recommended (Dalla Costa & Derendof, 1996). In our study, *AUIC* varied between 623 ± 128 h (MIC_{90}: 0.03 µg/mL) and 89 ± 18 h [MIC_{90}: 0.21 µg/mL (*Staphylococcus aureus*)] for the dosage of 2 mg/kg b.w. and, 945 ± 183 and 135 ± 26 h respectively for 4 mg/kg b.w. Based on the calculated C_{max}/MIC_{90} and *AUIC*, a dosage of 3 or 4 mg/kg b.w. might be recommended to treat infections caused by bacteria with *MIC* above 0.2 µg/mL.

The pharmacokinetic of marbofloxacin in the camel, compared with the bovine is characterized by a high C_{max} and *AUC*, rapid absorption following i.m. administration and longer terminal half-life. Once-a-day administration may achieve good tissue concentrations for the treatment of most sensitive bacterial infections in this species. However for good absorption and to minimize an any local reactions, it is advised that the volume of administration should not exceed 10 mL per injection site. For bacteria with *MIC* above 0.2 µg/mL a higher dosage than 2 mg/kg may be recommended. Further studies on tissue distribution and specific determination of the *MIC* of this antimicrobial agent for the major bacteria responsible for respiratory and cutaneous diseases in

camels should be performed to achieve a complete efficacy data of marbofloxacin in this species.

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