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Pharmacokinetic variables of moxifloxacin in healthy male camels following intravenous and intramuscular administration

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Moxifloxacin is a fourth generation fluoroquinolone with a methoxy group in the C-8 position and C-7 side chain. Moxifloxacin has *in vitro* activity similar to that of older (fluoro)quinolones against Gram-negative bacteria, but shows improved activity against Gram-positive cocci, aerobic, anaerobic intracellular bacteria, as well as atypical organisms, such as *Mycoplasma* and *Chlamydia,* compared with older (fluoro) quinolones (Betriu *et al.*, 2000). As a member of the fluoroquinolone group, moxifloxacin acts on bacterial DNA topoisomerases II and IV (Wolfson & Hooper, 1989; Drlica & Zhao, 1997). The fluoroquinolones are characterized by concentration-dependent bactericidal activity and the ability to induce a postantibiotic effect against both Gram-positive and Gram-negative bacteria (Odenholt & Bengtsson, 1994; Spreng *et al.*, 1995). The fluoroquinolones have some additional characteristics, such as a wide spectrum of bactericidal activity, a large volume of distribution and relatively low minimal inhibitory concentrations (*MIC*s) against target micro-organisms (Spreng *et al.*, 1995; Brown, 1996). The extent of plasma protein binding was in a range of 60–93% for the gyrase inhibitors of the first generation and newer agents, such as rosoxacin, trovafloxacin and rufloxacin, and 20–40% for all other 'fluoroquinolones' of the third generation (Zlotos *et al.*, 1998). In humans, moxifloxacin pharmacokinetic properties are characterized by high bioavailability (approximately 91%) and rapid penetration into target tissues (Stass & Kubitza, 1999).

The pharmacokinetics of moxifloxacin are well documented in humans (Siefert *et al.*, 1999; Stass & Kubitza, 1999; Stass *et al.*, 2005; Pea *et al.*, 2006); a few reports have also been conducted in animals including horses (Gardner *et al.*, 2004), lactating goats (Fernandez-Varon *et al.*, 2006; Carceles *et al.*, 2007) and rabbits (Fernandez-Varon *et al.*, 2005; Carceles *et al.*, 2006). However, data on the pharmacokinetics of fluoroquinolones in camels, llama and alpaca are limited (Gavrielli *et al.*, 1995; Christensen *et al.*, 1996; Aliabadi *et al.*, 2003; Gandolf *et al.*, 2005; Laraje *et al.*, 2006).

The dromedary camel is a species that survives and reproduces in high air temperatures despite the lack of drinking water and feed supply as result of physiological and behavioural adaptation. A previous study has shown that the main clinical problems in adult dromedaries are dermatological and pulmonary infections, whereas infectious diarrhoea is of major clinical importance in young dromedaries (Bengoumi & Faye, 2002). Moxifloxacin might be a suitable antimicrobial agent for the treatment of these diseases in camels. Indeed, the physiological and biochemical peculiarities that differentiate the dromedary from other species may influence drug disposition, pharmacodynamic activity and residues in edible tissues. Differences were previously observed between camels and cattle in terms of the kinetic dispositions of ivermectin and moxidectin (Oukessou *et al.*, 1999). To date, full studies on moxifloxacin pharmacokinetics in camels have not been presented. This report describes the disposition kinetics and absolute bioavailability of moxifloxacin in the serum of healthy dromedary camels following intravenous (i.v.) and intramuscular (i.m.) administrations of a single dose of the drug at a dose rate of 5 mg/kg body weight.

Moxifloxacin hydrochloride (purity 96.1% on anhydrous basis) was kindly provided by Bayer Korea Ltd, Seoul, Korea. Stock solutions were prepared according to the British Society of Antimicrobial Chemotherapy Guidelines (British Society for Antimicrobial Chemotherapy Working Party, 1991) and stored at −20 °C. The working standard solutions for bioassays were prepared daily from the moxifloxacin stock solution by serial dilution with phosphate-buffered saline (PBS) to yield final

concentrations of 0.019, 0.039, 0.078, 0.156, 0.312, 0.625, 1.25, 2.5, 5 and 10 μg/mL. Quality control standards were prepared by the addition of different concentrations of moxifloxacin to a pool of blank camel sera to obtain similar concentrations.

The study was carried out on six male one-humped camels (*Camelus dromedarius*) weighing 350–500 kg and aged from 6 to 8 years old. Camels were determined to be clinically healthy before the study based on physical examination. The animals were kept in a camel herd in Imbaba (in the South of Giza, Egypt) under the normal day length and temperature. The camels were fed on barley, alfalfa hay and wheat straw, with free access to food and water. The animals did not receive any drug treatment before the study. The study was approved by the Bioethics Committee of the Faculty of Veterinary Medicine, Cairo University.

All animals received moxifloxacin by the i.v. and i.m. routes according to a cross-over design (3 × 3) with a 15-day washout period between the two phases. Moxifloxacin solution was administered by the i.v. and i.m. routes as a single dose of 5 mg/kg body weight. For i.v. administration, the solution was injected into the left jugular vein, and blood samples (5 mL) were collected from the contralateral jugular vein into sterilized plastic tubes immediately before administration (0 min), and then at 10, 20, 30, 45 min, and 1, 2, 4, 6, 8, 10, 12, 24, 36 and 48 h after the start of the i.v. bolus. For the i.m. administration, the drug was injected into the semimembranous muscle and blood samples were collected at the same sampling points of the i.v. injection. The blood was kept undisturbed (for 30 min) at room temperature, and was then centrifuged at 1500 ***g*** for 10 min. The recovered serum was transferred to plastic vials and stored at −20 °C until it was assayed. The samples were analyzed within a week of sampling.

The concentrations of moxifloxacin in serum were determined by a modified agar diffusion bioassay method that was previously described by Bennett *et al.* (1966) using *Escherichia coli* (ATCC 25922) as the test organism (Odenholt *et al.*, 2002). Bioassay plates were prepared by placing 9.5 g Mueller Hinton agar (Alkan Medical Division, Dokki-Giza, Egypt) and 250 mL distilled water into a 0.5-L flat-bottomed flask, which was autoclaved for 20 min. After cooling to 50 °C in a water bath, 0.4 mL of the diluted suspension of reference organism was added to the media. After pouring (25 mL) and solidifying of the media, six wells were cut into the solidified bioassay plates at equal distances. Triplicate serum samples and standard concentrations (0.312 μg/mL) of the drug in pooled sera were placed directly into the wells. A mid-range dilution (0.312 μg/mL) of moxifloxacin was placed in the same location on all plates to compensate for any plate-to-plate variations. The plates were kept at room temperature for 2 h prior to incubation at 37 °C for 18 h. The mean zone diameter was used to calculate the concentration in each sample. Calibration graphs were constructed by plotting the diameters of the inhibition zones against the logarithm of moxifloxacin concentrations. All of the standard curves were linear from 0.019 to 10 μg/mL with correlation coefficients in excess of 0.975. The assay precision [relative standard deviation (RSD)] was assessed by expressing the standard deviation (SD) of repeated measurements as a percentage of the mean value, and was <10%. The intra-assay coefficients of variation for the two lowest (0.019 and 0.039 μg/mL) and the two highest (5 and 10 μg/mL) standard concentrations used for the curves that were employed to determine i.v. and i.m. concentrations in serum were <15%.

The extent of protein binding was determined *in vitro* according to the method described previously by Craig and Suh (1980). 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 serum samples were estimated.

Experimental serum concentration vs. time profiles were fitted to a three-compartment open model with i.v. bolus input and linear first-order elimination from the central compartment using iterative weighted nonlinear least squares regression with the MULTI program (RUNGE) (Yamaoka *et al.*, 1981). Model selection was guided by visual inspection of the observed serum profiles and Akaike's information criterion (AIC) (Yamaoka *et al.*, 1978) general polyexponential equation:

$$C_p = A^{-\alpha t} + B^{-\beta t} + C^{-\lambda t},$$

where C_p is the serum concentration of moxifloxacin; A, B and C are the zero-time drug concentration intercepts of the disposition curve; α, β and λ are the hybrid rate constants of distribution, elimination phase and terminal elimination slope respectively; and t is the time after moxifloxacin injection. λ (the apparent terminal log-linear disposition rate constant) was derived from the terminal slope of the logarithmic serum concentration vs. time profile.

Classical pharmacokinetic parameters were calculated using standard equations (Gibaldi & Perrier, 1982). The absorption and disposition half-lives were calculated as $t_{1/2kab} = \ln 2/k_{ab}$, $t_{1/2\beta} = \ln 2/\beta$ and $t_{1/2\lambda} = \ln 2/\lambda$ respectively.

Following i.m. injection of moxifloxacin values of the pharmacokinetics parameters were based on a two-compartment open model with first-order absorption. A noncompartmental model (moment analysis) was used to determine the area under the concentration–time curve (*AUC*) and the area under the first moment curve (*AUMC*), using the linear trapezoidal rule with extrapolation of infinity. Mean residence time was calculated as $MRT = AUMC/AUC$, mean absorption time was calculated as $MAT = MRT_{i.m.} - MRT_{i.v.}$ and systemic clearance was calculated as $Cl = \text{Dose}/AUC$. Bioavailability (F) was calculated by the method of corresponding areas:

$$F(\%) = \frac{AUC_{i.m.}}{AUC_{i.v.}} \times 100.$$

The descriptive data are presented as mean ± SD values. The Wilcoxon rank sum test was used to test parameters for significant differences ($P < 0.05$) between i.v. and i.m. administrations (Powers, 1990). The software used was PRISM

Version 4.03, 2005 (GraphPad software Inc., San Diego, CA, USA).

Semilogarithmic plots of the mean serum concentration vs. time profiles of moxifloxacin (±SD) following single i.v. administration at a dosage of 5 mg/kg are shown in Fig. 1. The mean serum concentrations after i.v. administration were higher than those following i.m. administration until 2 h postadministration, and were generally detectable up to 36 h. The serum concentration–time curves were best resolved into a three-compartment open model (Fig. 1) following i.v. bolus injection. The corresponding mean compartmental and noncompartmental PK parameters of moxifloxacin in camels following i.v. administration are presented in Table 1. Serum concentration profiles showed a rapid initial distributive phase, followed by a slower β-phase and a prolonged λ-phase with an estimated mean terminal elimination half-life of 12.26 ± 5.83 h. The serum moxifloxacin clearance (Cl_{tot}) was 0.34 ± 0.02 L/h·kg, the mean value for the volume of distribution at steady-state ($V_{d(ss)}$) was 1.78 ± 0.79 L/kg, and the area under the serum concentration–time curve from zero to infinity ($AUC_{0-\infty}$) was 14.72 ± 0.69 μg·h/mL. The value obtained for *MRT* was 5.77 ± 1.83 h.

The disposition of i.m.-administered moxifloxacin in camels was best fitted to a two-compartment open model with first-order absorption (Fig. 1). The mean serum concentrations after i.m. injection were higher than those following i.v. administration at 6 h postinjection and onwards. After injection, moxifloxacin was rapidly absorbed, with a time of maximum concentration (t_{max}) of 1.04 ± 0.14 h. The mean peak serum concentration (C_{max}) and $AUC_{0-\infty}$ were 2.16 ± 0.13 μg/mL and 12.17 ± 0.78 μg·h/mL respectively. The terminal half-life ($t_{1/2\beta}$) was 11.95 ± 4.61 h. Compared with i.v. administration, moxifloxacin had a relatively high bioavailability (F) of 82.10 ± 5.50% after i.m. administration (Table 1). There were statistically significant differences when the α (k_{ab}), $t_{1/2\alpha}$ ($t_{1/2ab}$), $t_{1/2\beta}$ ($t_{1/2el}$), and $AUC_{0-\infty}$ pharmacokinetic parameters were compared.

Table 1. Single-dose pharmacokinetic parameters of moxifloxacin in serum following intravenous bolus administration and intramuscular injection in camels (n = 6)

Parameters	Unit	i.v.	i.m.
A	μg/mL	4.21 ± 0.59	–
α (k_{ab})	h^{-1}	2.83 ± 0.29	1.72 ± 0.27*
$t_{1/2\alpha}$ ($t_{1/2ab}$)	h	0.25 ± 0.03	0.41 ± 0.06*
B	μg/mL	3.47 ± 0.16	2.39 ± 1.75
β (K_{el})	h^{-1}	0.37 ± 0.03	0.34 ± 0.02
$t_{1/2\beta}$ ($t_{1/2el}$)	h	1.87 ± 0.16	2.07 ± 0.13*
C	μg/mL	0.18 ± 0.07	–
λ	h^{-1}	0.06 ± 0.02	0.07 ± 0.02
$t_{1/2\lambda}$	h	12.26 ± 5.83	11.95 ± 4.61
V_c	L/kg	0.64 ± 0.04	–
V_p	L/kg	0.61 ± 0.04	–
$V_{d(ss)}$	L/kg	1.78 ± 0.79	–
Cl_{tot}	L/h·kg	0.34 ± 0.02	–
$AUC_{0-\infty}$	μg·h/mL	14.72 ± 0.69	12.17 ± 0.78*
AUMC	μg·h^2/mL	79.04 ± 39.15	89.24 ± 20.67
MRT	h	5.77 ± 1.83	7.29 ± 1.32
MAT	h	–	1.99 ± 2.55
C_{max}	μg/mL	–	2.16 ± 0.13
t_{max}	h	–	1.04 ± 0.14
F	%	–	82.10 ± 5.50

$A + B + C$, zero-time drug concentration intercepts of the disposition curve; α (k_{ab}), β (K_{el}) and λ: hybrid rate constants at the distribution (absorption), elimination and slope elimination phases respectively; $t_{1/2\alpha}$ ($t_{1/2ab}$), $t_{1/2\beta}$ ($t_{1/2el}$), $t_{1/2\lambda}$: half-life of the distribution (absorption), elimination and terminal phase elimination respectively; V_c, V_p and $V_{d(ss)}$: the apparent distribution volumes of the central compartment, peripheral compartment and at steady-state respectively; Cl_{tot}, total body clearance of drug from the serum; $AUC_{0-\infty}$, the area under the serum concentration–time curve from zero to infinity; *AUMC*, area under the moment curve; *MRT*, mean residence time; *MAT*, mean absorption time; C_{max} and t_{max}, maximum serum concentration and time to peak concentration respectively; F (%), the fraction of the administered dose systemically available (bioavailability).
*Significantly different from i.v.

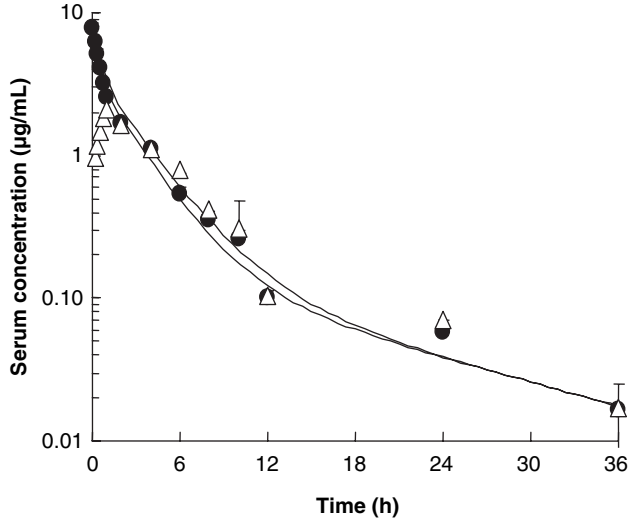

Fig. 1. Experimental (semi-logarithmic plot) serum concentrations of moxifloxacin following a single intravenous (●) and a single intramuscular (△) injection of 5 mg/kg body weight in camels. Each point plots the mean level of six camels each ±SD at that time-point.

The *in vitro* serum protein binding of moxifloxacin ranged from 33% (at a concentration of 0.65 μg/mL) to 38% (at a concentration of 0.156 μg/mL). The proportion increased to 40–40.9% when estimated from high concentrations of 5 or 10 μg/mL respectively.

No adverse effects were observed in any of the camels following i.v. and i.m. administrations of moxifloxacin at 5 mg/kg.

After data analysis, the three-compartment model described following i.v. dosing in our study was found to be in agreement to that reported by Aliabadi *et al.* (2003) for danofloxacin in camels, and contrasts that reported by Fernandez-Varon *et al.* (2006) for moxifloxacin in lactating goats.

Serum concentration profiles showed a rapid initial distributive phase, followed by a slower β-phase and a prolonged λ-phase with an estimated mean terminal elimination half-life of 12.26 ± 5.83 h. This finding was similar to that recorded for moxifloxacin in humans (12–13 h) (Siefert *et al.*, 1999; Pea *et al.*, 2006), but was much longer than the value reported in lactating goats (1.94 ± 0.41 h) (Fernandez-Varon *et al.*, 2006). On the other hand, Siefert *et al.* (1999) reported a half-life for moxifloxacin in several species, ranging from 1.2 h in rats to 8.6 h in dogs after i.v. dosing. Although the aforementioned studies measured moxifloxacin by high-performance liquid chromatography (HPLC), it appeared that the analytical method was not sensitive enough to estimate moxifloxacin serum concentrations in the terminal portions of the curves. From the apparent half-life of elimination obtained in our study, moxifloxacin seems to offer advantages in camels over the finding reported in lactating goats (Fernandez-Varon *et al.*, 2006) as well as other fluoroquinolones, such as danofloxacin (terminal half-life 5.71 h, Aliabadi *et al.*, 2003).

Moxifloxacin exhibits a relatively high volume of distribution at steady-state (1.78 L/kg), which exceeded the volume of the central compartment (0.64 L/kg) and total body water of the camel (Wilson, 1984), thus suggesting an extensive tissue distribution. The total water content of the camel decreases from 75% of body weight during hot dry periods to around 50% during the cold winter period (Schmidt-Nielsen *et al.*, 1956; Wilson, 1984), but this is expected to have little effect on moxifloxacin kinetics, as the drug has a high volume of distribution. The estimated value was considerably higher than that recorded for moxifloxacin in lactating goats (0.79 ± 0.08 L/kg) (Fernandez-Varon *et al.*, 2006), but approximately half that reported for danofloxacin in camels ($V_{d(ss)}$ = 3.43 L/kg). The clearance modelled as a function of dose was relatively rapid (0.34 L/kg/h) after i.v. administration, and was consistent with the value reported for danofloxacin in camels (0.44 L/kg/h) (Aliabadi *et al.*, 2003).

In the present experiment, the estimated C_{max} (2.16 ± 0.13 μg/mL) is slightly lower than that reported for moxifloxacin in lactating goats (2.82 ± 0.58 mg/L) (Carceles *et al.*, 2007). The maximum time of absorption of moxifloxacin in the camel (t_{max} = 1.04 ± 0.14 h) is close to that observed for marbofloxacin in the same animal species (1.0 ± 0.56 h) (Laraje *et al.*, 2006), and was higher than that recorded for moxifloxacin in lactating goats (1.7 ± 1.20 h) (Carceles *et al.*, 2007).

The *MRT* (7.29 ± 1.32 h) was higher than that reported for moxifloxacin following subcutaneous (s.c.) (6.15 ± 0.92 h) and i.m. (3.27 ± 0.85 h) administration in lactating goats (Fernandez-Varon *et al.*, 2006; Carceles *et al.*, 2007). The exposure level of camels to moxifloxacin was estimated by the serum *AUC* (12.17 ± 0.78 μg·h/mL), which was slightly lower than that reported for moxifloxacin following s.c. (11.28 ± 1.16 mg·h/L) and i.m. (10.95 ± 3.56 mg·h/L) administrations to lactating goats (Fernandez-Varon *et al.*, 2006; Carceles *et al.*, 2007). These differences might be due to the physiological particularities of the camel.

High bioavailability was achieved after i.m. administration of moxifloxacin to camels (82.1%). The present finding was lower than that recorded for danofloxacin in camels (114.5%) (Aliabadi *et al.*, 2003), as well as that for moxifloxacin administered to lactating goats by the s.c. route (96.87%) (Fernandez-Varon *et al.*, 2006). Conversely, the present value was higher than that reported after i.m. administration of marbofloxacin in camels (71.95%) (Laraje *et al.*, 2006). Moxifloxacin was well absorbed, a finding that is supported by its high bioavailability. From the *MAT* (1.99 ± 2.55 h) and k_{ab} (1.72 ± 0.27 h^{-1}), the absorption from the injection site was rapid, with a t_{max} of 1.04 ± 0.14 h. In contrast Fernandez-Varon *et al.* (2006) observed slow absorption of moxifloxacin following s.c. administration to lactating goats.

The *in vitro* serum protein binding of moxifloxacin ranged from 33% to 38% at concentrations observed in clinical studies (i.e. from 0.156 to 0.65 μg/mL) (Woodcock *et al.*, 1997). However, the proportion increased to 40.9% at higher concentrations (i.e. 5 or 10 μg/mL). The mechanism for this atypical pattern of increased protein binding at higher concentrations is unknown, but may be partly attributable to the ability of moxifloxacin to form metal ion complexes, which has been previously documented with tetracycline (Chin & Lach, 1975; Gabler, 1991). The present finding was quite a bit lower than that recorded in humans (55%) and dogs (71%) (Siefert *et al.*, 1999). A low protein binding generally enables a rapid and extensive distribution into the intracellular and extracellular space. However, the highest unbound fraction in dogs is probably due to the lower albumin concentration in dog plasma, as the drug mainly bound to albumin and the binding was fully reversible (Siefert *et al.*, 1999).

For a concentration-dependent drug, such as moxifloxacin, successful treatment usually correlates with AUC_{24}/MIC and C_{max}/MIC, and high ratios of the latter have also been associated with a lower incidence of the development of resistance (Drusano *et al.*, 1993; Lode *et al.*, 1998). Animal models with different quinolones showed that an AUC_{24}/MIC ratio of about 100 h or a C_{max}/MIC ratio of 10 should be achieved to give maximum clinical and microbial efficacy (Turnidge, 1999). However, it should be noted that the numerical values of AUC_{24}/MIC, C_{max}/MIC and $T > MIC$, used as a surrogate marker to predict optimal dosage, have been generated in experimental infections in laboratory animals and in human clinical trials (Toutain & Lees, 2004), and these numerical values may or may not be applicable in relation to camel infections. Nothing is known of moxifloxacin *MIC*s against the most important pathogens that affect camels, but *MIC*s against sensitive strains of different micro-organisms range from 0.01 to 0.5 μg/mL (Woodcock *et al.*, 1997). Therefore, using the above surrogate markers, it was determined that when administered by the i.m. route at 5 mg/kg, moxifloxacin is likely to be effective against bacterial isolates with $MIC \leq 0.1$ μg/mL (Aliabadi *et al.*, 2003).

Taken together, the favourable PK properties such as the long half-life and high bioavailability, moxifloxacin administered at 5 mg/kg is likely to be effective in camels.

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