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Pharmacokinetics of danofloxacin after single dose intravenous, intramuscular and subcutaneous administration to loggerhead turtles *Caretta caretta*

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ABSTRACT: The single-dose disposition kinetics of the antibiotic danofloxacin were determined in clinically normal loggerhead turtles (n = 6) after intravenous (IV), subcutaneous (SC) and intramuscular (IM) administration of 6 mg kg^{-1} bodyweight. Danofloxacin concentrations were determined by high performance liquid chromatography with fluorescence detection. The concentration–time data were analyzed by non-compartmental kinetic methods. Steady-state volume of distribution, and total body clearance of danofloxacin after IV administration were estimated to be 1.02 ± 0.17 l kg^{-1} and 0.11 ± 0.01 l h^{-1} kg^{-1}, respectively. Following IM and SC administration, danofloxacin achieved maximum plasma concentrations of 10.25 ± 4.59 and 10.35 ± 4.45 mg l^{-1} at 1.20 ± 0.52 and 1.46 ± 0.48 h, respectively. The absolute bioavailabilities after SC and IM routes were 98.72 ± 11.73 and 104.81 ± 14.97 %, respectively. Danofloxacin shows a favourable pharmacokinetic profile in loggerhead turtles reflected by parameters such as a long half-life and a high bioavailability following a single dose of 6 mg kg^{-1} by IM and SC routes; thus, it is likely that this treatment will be effective in loggerhead turtles with bacterial infections.

KEY WORDS: Danofloxacin · Pharmacokinetics · Loggerhead turtle · Bioavailability · *Caretta caretta*

INTRODUCTION

Safe and effective antibacterial dosage regimens are poorly established for many reptiles, including sea turtles. Most antibiotic dosage regimens for these animals are empirical or extrapolated from other species. Cross-species extrapolation is risky because of differences in antibiotic disposition between reptiles and mammals and even between species of reptiles.

Danofloxacin is a fluoroquinolone antibacterial drug that was developed specifically for veterinary use. This drug is active against many pathogens of veterinary importance, including most Gram-negative bacteria and some Gram-positive bacteria and mycoplasmas, but it has only limited activity against anaerobic organisms (Aliabadi et al. 2003a). Fluoroquinolones exhibit bactericidal action by targeting the bacterial DNA topoisomerases (gyrase) II and IV (Wolfson & Hooper 1989, Drlica & Zhao 1997). Principal advantages of fluoroquinolones include bactericidal activity at low tissue concentrations and good penetration into phagocytic cells (Giguere et al. 1996). They have a large volume of distribution combined with low plasma protein binding in most of the investigated species, which allows them to reach tissue concentrations often higher than concurrent serum concentrations (Prescott & Baggot 1993).

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Wild loggerhead turtles *Caretta caretta* may require antimicrobial therapy when brought into oceanariums and rehabilitation facilities for treatment and/or prevention of primary and secondary bacterial infections; however, few pharmacokinetic studies have been performed (Stamper et al. 1999, 2003, Harms et al. 2004, Jacobson et al. 2005, Manire et al. 2005). The pharmacokinetic properties of danofloxacin have been evaluated in several species (rabbits, Fernández-Varón et al. 2007; cows, Shem-Tov et al. 1998; and horses, Fernández-Varón et al. 2006), but not yet in sea turtles.

Thus, the purpose of the study reported here was to determine the pharmacokinetics of danofloxacin after intravenous (IV), intramuscular (IM), and subcutaneous (SC) administration to immature loggerhead turtles, and to investigate the bioavailability after the extravascular routes. This pharmacokinetic information is necessary to make empirical dosage regimens for clinical studies of danofloxacin's safety and efficacy in these species.

MATERIALS AND METHODS

Turtles. Six clinically healthy inmature loggerhead turtles (2 female and 4 male) weighing between 9 and 21 kg were obtained from the Wildlife Recuperation Center in Murcia (Spain). The animals were maintained in indoor pools with a recycled water system and water temperatures between 25 and 27°C (salinity 33 to 35 ppm). Turtles were fed ad libitum with fresh fish and squid under a 12:12 h light:dark cycle, and no antibiotics were administered for at least 30 d preceding the study. For each treatment period of the cross-over, they were observed daily for general health, and physical observations were made prior to injection, and at 2, 10 and 24 h post-injection.

Experimental design. A cross-over design ($2 \times 2 \times 2$) was used in 3 phases. Each turtle received single IV, SC and IM injections of danofloxacin 18% (Advocin 180, Pfizer Animal Health, Madrid, Spain) at a dose of 6 mg kg^{-1} with at least 30 d washout period.

For the IV administration, the solution was injected into the left cervical sinus and blood samples were collected from the contralateral cervical sinus into heparinized tubes. Subcutaneous injections were administered under the skin of the left shoulder between the dorsal forelimb and the carapace, and IM injections into the left deltoid muscle. Blood samples were collected at 0 (pre-treatment), 0.083, 0.25, 0.5, 1, 1.5, 3, 6, 12, 24, 48, 72, 96, 120 and 144 h post-dosing. Blood was collected each time using a 2 ml syringe with a 21 gauge needle. The syringe and needle interiors were rinsed before use with 0.1 ml of 5000 UI ml^{-1} sodium heparin solution (Heparina Mayne 5%, Mayne Pharma). Samples were centrifuged at $1500 \times g$ for 15 min and the plasma taken and stored in individual eppendorf tubes at −45°C until assayed (maximum 1 wk).

Analytical method. Plasma concentrations of danofloxacin were measured using a modified HPLC method previously reported (Siefert et al. 1999). The HPLC system was equipped with a model LC-10ASvp pump, a RF-10AXL Fluorescence Detector and a model SIL-10ADvp autoinjector (Shimadzu), and connected to a computer with a Shimadzu Class-VP™ Chromatography Data System programme.

Pure danofloxacin (Pfizer Animal Health) was used for quality controls. Ciprofloxacin (Vita Pharma) was used as an internal standard. After addition of 10 µl of the internal standard (1 mg l^{-1}) to 200 µl of plasma, 200 µl acetonitrile was added. Plasma proteins were precipitated at ambient temperature by shaking in an ultrasonic bath followed by centrifugation for 10 min at $1600 \times g$. The supernatant was diluted 4-fold with 0.067 M disodium hydrogen phosphate buffer pH 7.5 and transferred to HPLC autosampler vials. The HPLC separation was performed using a reverse-phase Discovery C_{18} column with an injection volume of 25 µl. Autosampler vials and column temperature was set at 5°C. The mobile phase consisted of acetonitrile (12%) and tetrabutylammonium hydrogensulphate solution (5 g l^{-1}) (88%) using an isocratic method with a flow rate of 1.0 ml min^{-1}. Danofloxacin eluted at approximately 9.1 min. The fluorescence detection was performed at an excitation wavelength of 280 nm and an emission wavelength of 440 nm.

Method validation. Quality controls were prepared from a pool of blank turtle plasma spiked with 9 concentrations of danofloxacin between 5 and 2000 µg l^{-1}. Plasma aliquots were stored at −45°C until assay. Aliquots of quality controls were extracted as above and 25 µl were injected into the chromatographic system. Standard curves were obtained by unweighted linear regression of danofloxacin peak areas versus known concentrations. Each point was established from an average of 5 determinations. Correlation coefficients (r) were > 0.97% for calibration curves. The percentage recovery was determined by comparing peak areas of plasma blank samples spiked with different amounts of drug and treated as any samples, with the peak areas of the same standards prepared in phosphate buffer. Each point was established from an average of 5 determinations. The mean percentage recovery of danofloxacin from plasma was 92.37 ± 1.21%. The assay precision (relative standard deviation, RSD) was assessed by expressing the standard deviation of repeated measurements as a percentage of the mean value. Intra-day precision was estimated from 6 replicates of 3 standard samples used for calibration curves (RSD < 10%). Inter-day precision was

estimated from the analysis of standard samples on 3 separate days (RSD < 10%). The limit of quantification (LOQ) was 5 µg l^{-1}.

Pharmacokinetic analysis. The values of the pharmacokinetic parameters were determined for each individual animal using noncompartmental analysis (WinNonlin Professional version 5.2, Pharsight).

Calculated values (Gibaldi & Perrier 1982) were area under the concentration–time curve (AUC), area under the plasma concentration–time curve from 0 to 24 h (AUC_{24}), area under the first moment curve (AUMC), using the linear trapezoidal rule with extrapolation to time infinity. Mean residence time was calculated as MRT = AUMC/AUC. Mean absorption time was calculated as $MAT = MRT_{SC,IM} - MRT_{IV}$. The systemic clearance was estimated as Cl = Dose/AUC. The apparent volumes of distribution at steady state were calculated as V_{ss} = (Dose · AUMC)/AUC^2. The apparent volume of distribution calculated by the area method as V_z = Dose/(AUC · λ_z). Elimination rate constant (λ_z) was calculated as the slope of the terminal phase of the plasma concentration curve that included a minimum of 3 time points, and half-life $t_{1/2\lambda z}$ = 0.693/λ_z.

Bioavailability (F) was calculated by the method of corresponding areas, which entails comparison of the total areas under the plasma concentration-time curves obtained after extravascular and intravenous administrations:

$$F = [(AUC_{SC,IM} / Dose_{SC,IM}) / (AUC_{IV} / Dose_{IV})] \cdot 100$$

All pharmacokinetic parameters of danofloxacin were calculated for individual animals and are presented as arithmetic means ± SD except for $t_{1/2\lambda z}$ values, which were calculated as harmonic mean.

Statistical analysis. Descriptive statistical parameters as mean, SD and coefficient of variation were calculated. Harmonic means were calculated for the half-lives of elimination. The Wilcoxon Rank Sum test and Student's t-test were used to test parameters for significant differences between IV, SC and IM administration (Powers 1990). The statistical software used was SPSS (Version 11.0).

RESULTS

Physical examination of all the turtles before and after each administration did not reveal any abnormalities. No local or systemic adverse reactions occurred after IV, IM and SC injection of danofloxacin.

The mean (±SD) plasma concentrations of danofloxacin following IV, SC and IM administration are plotted in Fig. 1. The mean (±SD) pharmacokinetic parameters based on non-compartmental pharmacokinetic analysis are presented in Table 1. Danofloxacin was detected in plasma up to 120 h after IV, IM and SC administrations.

DISCUSSION

Danofloxacin showed a wide distribution in turtles with a V_{ss} of 1.02 ± 0.17 l kg^{-1} suggesting good penetration through biological membranes and wide distribution, as with other fluoroquinolones. This V_{ss} is lower than those determined for danofloxacin in rabbits (V_{ss} = 3.16 l kg^{-1}; Fernández-Varón et al. 2007), horses (V_{ss} = 2.00 l kg^{-1}; Fernández-Varón et al. 2006), goats and sheep (V_{ss} = 2.44 and 2.19 l kg^{-1}, respectively; Escudero et al. 2007) and camels (V_{ss} = 2.53 l kg^{-1}; Aliabadi et al. 2003b).

The terminal half-life ($t_{1/2\lambda z}$) after IV dosing was 15.40 h; this value was longer than those reported for florfenicol (Stamper et al. 2003) and ticarcillin (Manire et al. 2005) in loggerhead turtles, showing advantages, in principle, over these 2 drugs. The mean $t_{1/2\lambda z}$ value following IM administration was 14.70 h. The fact that half-life value after IV dosing is longer than that after IM dosing has also been reported for danofloxacin and other fluoroquinolones in goats (Aliabadi & Lees 2001, Marín et al. 2007), sheep (Aliabadi et al. 2003a) and

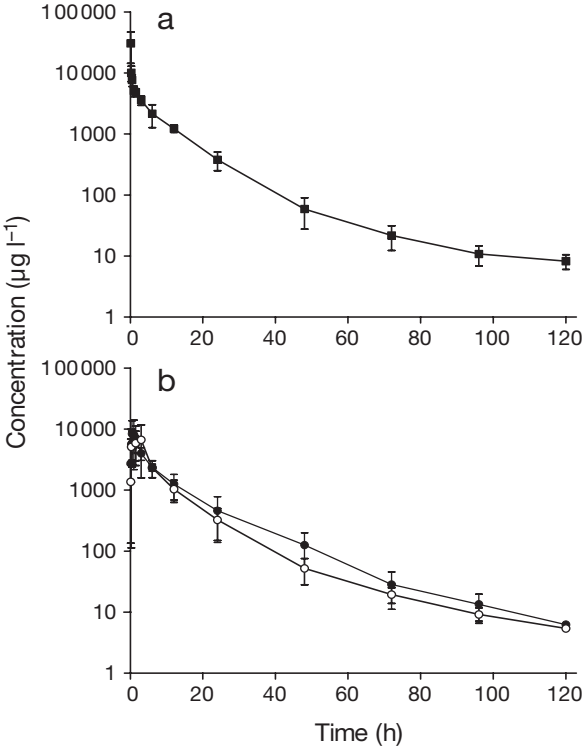

Fig. 1. Experimental plasma concentrations (mean ± SD) of danofloxacin in loggerhead turtles *Caretta caretta* following a single dose of 6 mg kg^{-1} bodyweight (n = 6). (a) Intravenous, (b) subcutaneous (○) and intramuscular (●) administration

Table 1. Pharmacokinetic parameters (mean ± SD) of danofloxacin in loggerhead turtles *Caretta caretta* after intravenous (IV), intramuscular (IM) and subcutaneous (SC) administration at a single dose of 6 mg kg^{-1} bodyweight (n = 6). λ_z: terminal slope of semilogarithmic concentration–time curve. $t_{1/2\lambda z}$: elimination half-life associated with terminal slope (λ_z) of semilogarithmic concentration–time curve (harmonic mean). V_{ss}: apparent volume of distribution at steady state. V_z: apparent volume of distribution calculated by the area method. Cl: total body clearance of drug from plasma. AUC: area under plasma concentration–time curve from zero to infinity. AUMC: area under the first moment curve. MRT: mean residence time. MAT: mean absorption time. *F*: fraction of administered dose systemically available (bioavailability). t_{max}: time to reach peak or maximum plasma concentration following extravascular administration. C_{max}: peak or maximum plasma concentration following extravascular administration. AUC_{24}: AUC from 0 to 24 h

Parameter	Unit	IV	IM	SC
λ_z	h^{-1}	0.05 ± 0.01	0.05 ± 0.01	0.04 ± 0.01
$t_{1/2\lambda z}$	h	15.40	14.70	18.71
V_{ss}	l kg^{-1}	1.02 ± 0.17	–	–
V_z	l kg^{-1}	2.41 ± 0.60	–	–
Cl	l h^{-1} kg^{-1}	0.11 ± 0.01	–	–
AUC	mg h l^{-1}	56.54 ± 7.20	59.82 ± 14.65	55.30 ± 11.53
AUMC	mg h^{-} l^{-1}	545.75 ± 148.66	694.67 ± 263.40	509.81 ± 157.68[a]
MRT	h	9.58 ± 1.70	11.27 ± 3.84	9.33 ± 2.21
MAT	h	–	1.78 ± 1.21	0.75 ± 0.48
C_{max}	mg l^{-1}	–	10.25 ± 4.59	10.35 ± 4.45
t_{max}	h	–	1.20 ± 0.52	1.46 ± 0.48
F	%	–	104.81 ± 14.97	98.72 ± 11.73
AUC_{24}	mg h l^{-1}	49.61 ± 5.88	50.01 ± 11.06	49.33 ± 11.18

[a]Significantly different from both IV and IM (both $p < 0.05$)

horses (Fernández-Varón et al. 2006). Therefore absorption processes do not appear to affect elimination of danofloxacin. After SC administration $t_{1/2\lambda z}$ was 18.71 h, this value was shorter than that reported for enrofloxacin, after oral administration, in the same species (Jacobson et al. 2005) however, the obtained maximum plasma concentration (C_{max}) was less than the values reported here, although the enrofloxacin dose was higher (10 mg kg^{-1}). This parameter is very important, because fluoroquinolones exhibit concentration-dependent killing. Significant differences were not found between IV, IM and SC administrations for $t_{1/2\lambda z}$ in this study ($p > 0.05$).

Elimination half-lives after IV, IM and SC administration in this study were longer than those described for danofloxacin in horses ($t_{1/2\lambda z}$ = 6.31 h IV and $t_{1/2\lambda z}$ = 5.36 h IM, Fernández-Varón et al. 2006), rabbits ($t_{1/2\lambda z}$ = 4.88 h IV, $t_{1/2\lambda z}$ = 6.70 h IM and $t_{1/2\lambda z}$ = 8.20 h SC, Fernández-Varón et al. 2007), sheep ($t_{1/2\lambda z}$ = 3.27 h IV and $t_{1/2\lambda z}$ = 3.07 h SC, Escudero et al. 2007) and camels ($t_{1/2\lambda z}$ = 5.37 h IV and $t_{1/2\lambda z}$ = 5.71 h IM, Aliabadi et al. 2003b). Consequently the systemic clearance of danofloxacin in our study (Cl = 0.11 ± 0.01 l h^{-1} kg^{-1}) was slower than those described in the cited studies. In principle, these long half-lives may allow dosing intervals in loggerhead turtles to be increased compared to those used in mammals.

High values of systemic availability have been obtained after extravascular administration of danofloxacin to loggerhead turtles. Similar high values have been obtained for this drug in other species (Aliabadi et al. 2003b, Escudero et al. 2007, Fernández-Varón et al. 2007). Bioavailability showed low variability after both extravascular routes of administration, which is an advantage for clinical use in sea turtles.

For concentration-dependent antibacterial agents such as fluoroquinolones, overall efficacy is related to AUC, and the AUC/MIC index (MIC = minimum inhibitory concentration) is the most important surrogate marker in determining efficacy (Vogelman et al. 1988). Aliabadi & Lees (2001) showed that C_{max} is important not only for determining the antibacterial effect in the postantibiotic phase but also for killing the more resistant subpopulations of bacteria. Therefore, C_{max}/MIC is important for determining overall efficacy, and it has a pronounced effect on the emergence of antibiotic resistance (Aliabadi & Lees 2001). Consequently, the ratios $C_{max}/MIC_{90\%}$ and $AUC_{24}/MIC_{90\%}$ are the best parameters for predicting the antimicrobial effect of fluoroquinolones (Lode et al. 1998). Craig (1998) showed that for fluoroquinolones $C_{max}/MIC_{90\%} > 3$ produced a 99% reduction in bacterial count and $C_{max}/MIC_{90\%} \geq 8$ prevented the emergence of resistant microorganisms. Furthermore, $AUC_{24}/MIC_{90\%} > 100$ h should be achieved to give maximum clinical and bacteriological efficacy (Toutain & Lees 2004).

The MIC data of danofloxacin against bacterial isolates from sea turtles have not yet been reported. Taking into account MICs of other veterinary fluoroquinolones against sensitive strains of various microorganisms isolated from other fields of veterinary importance (Hannan et al. 1997), and using the surrogate marker $C_{max}/MIC = 8$, danofloxacin could be effective by the SC and IM routes at 6 mg kg^{-1} against bacterial isolates with MIC ≤ 1.28 µg ml^{-1}. Using the index $AUC_{24}/MIC_{90\%} = 100$ h, IM and SC administration of danofloxacin would be effective against microorganisms with MIC ≤ 0.5 µg ml^{-1}. Levels of danofloxacin >0.05 µg ml^{-1} were maintained until 48 h after extravascular administrations. However, a multidose study would be necessary before a complete dosing regimen could be recommended, because the 6 mg kg^{-1} dose is only speculative with regard to clinical

dosing and further studies are needed to be sure that unexpected accumulations are not a problem.

Wild loggerhead turtles frequently require antimicrobial therapy when brought into oceanariums and rehabilitation facilities. Many have gastrointestinal infections associated with the ingestion of hooks and monofilament lines, and a wide range of Gram-negative and Gram-positive bacteria (including *Bacillus* spp., *Escherichia coli*, *Pasteurella* spp., *Proteus* spp., *Staphylococcus* spp., *Streptococcus* spp. and *Vibrio alginolyticus*) have been isolated from these lesions (Orós et al. 2004). Although MIC values of danofloxacin against bacterial isolates from sea turtles are unknown, MIC values reported for several bacteria ranged from 0.03 to 0.06 µg ml^{-1} (McKellar et al. 1999, Lauritzen et al. 2003, TerHune et al. 2005). Therefore, danofloxacin could be used for the treatment of diseases caused by various microorganisms in turtles.

It is concluded that, since general adverse reactions were not observed in any turtle of the study, and in light of the favourable pharmacokinetic properties such as long half-life and high bioavailability and volumes of distribution, danofloxacin administered at 6 mg kg^{-1} via IM or SC routes could be effective in loggerhead sea turtles. However, further studies are needed to establish a multiple dosage regimen and clinical efficacy.

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