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The Veterinary Journal 170 (2005) 364–368
The Veterinary Journal
www.elsevier.com/locate/tvjl

Pharmacokinetics of marbofloxacin after intravenous and intramuscular administration to ostriches

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Accepted 22 June 2004

Abstract

The pharmacokinetics of marbofloxacin was investigated after intravenous (IV) and intramuscular (IM) administration, both at a dose rate of 5 mg/kg *BW*, in six clinically healthy domestic ostriches. Plasma concentrations of marbofloxacin was determined by a HPLC/*UV* method. The high volume of distribution (3.22 ± 0.98 L/kg) suggests good tissue penetration. Marbofloxacin presented a high clearance value (2.19 ± 0.27 L/kg h), explaining the low AUC values (2.32 ± 0.30 μg h/mL and 2.25 ± 0.70 μg h/mL, after IV and IM administration, respectively) and a short half life and mean residence time ($t_{1/2\beta}$ = 1.47 ± 0.31 h and 1.96 ± 0.35 h; MRT = 1.46 ± 0.02 h and 2.11 ± 0.30 h, IV and IM, respectively). The absorption of marbofloxacin after IM administration was rapid and complete (C_{max} = 1.13 ± 0.29 μg/mL; T_{max} = 0.36 ± 0.071 h; MAT = 0.66 ± 0.22 h and *F* (%) = 95.03 ± 16.89).

Keywords: Pharmacokinetics; Fluoroquinolones; Marbofloxacin; Ostrich; Avian

1. Introduction

Marbofloxacin is a fluoroquinolone antimicrobial agent developed exclusively for veterinary use. It differs from enrofloxacin by an oxadiazine ring, which may provide some pharmacokinetic advantages such as long elimination half-life and high bioavailability after intramuscular (IM) and oral administration, at least in dogs (Scheneider et al., 1996; Heinen, 2002). In ruminants, however, (Shojaee Aliabadi and Lees, 2002; Waxman et al., 2001) and birds of prey (García Montijano et al., 2001; García Montijano et al., 2003) marbofloxacin is reported to have a shorter elimination half life. Marbofloxacin exhibits high bactericidal activity against a broad spectrum of aerobic Gram-negative and some Gram-positive bacteria, and also against *Mycoplasma* spp. (Hannan et al., 1997).

Enteric infections occur commonly in ostrich chicks and can cause significant morbidity and death. Pathogenic organisms frequently isolated include *Clostridium* spp., *Escherichia coli*, *Campylobacter* spp. and *Proteus* spp. (Shane, 1998). The absence of pharmacokinetic studies in ostriches obliges the clinician to practice empirical assays based on allometric calculations or to extrapolate dosage from other species (Jensen, 1998). Previous studies carried out with other drugs, have however shown differences in pharmacokinetic behaviour between ostriches and other avian species (Helmick et al., 1997; Clarke et al., 2001; Baert and De Backert, 2003). Pharmacokinetic studies are therefore necessary in order to design rational therapeutic dosage schedules for the ostrich. Extrapolation of marbofloxacin data from other species or allometric calculations could lead

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doi:10.1016/j.tvjl.2004.06.012

to subtherapeutic or toxic levels of the drug, bacterial resistance and pose a possible risk of unacceptable residues in meat.

The aim of this study was to determine the pharmacokinetic behaviour of marbofloxacin after single intravenous (IV) and IM administration to domestic ostriches.

2. Materials and methods

2.1. Animals

The experiment was performed in six healthy ostriches ranging in age from six to seven months and weighing 43.48 ± 6.02 kg *BW*, obtained from a breeding farm. No antibiotics or anthelmintics were administered for at least two months prior to the start of the study. A complete clinical evaluation was performed each day throughout the study.

The ostriches were placed in a ratite shelter with facilities for drinking and eating; pelleted, antibiotic-free food concentrate and water were available ad libitum.

The study was approved by The Ethics in Animal Experimentation Committee (CEEA) of the School of Veterinary from Universidad Complutense de Madrid (UCM).

2.2. Drugs

The marbofloxacin formulation Marbocyl 10% injectable solution (batch 84923: Vétoquinol) was used for the pharmacokinetic study. Marbofloxacin (Vétoquinol: batch: L98002390), and ofloxacin (Sigma: batch 58H0572; internal standard) were used as reference standards for high performance liquid chromatography (HPLC) analyses.

2.3. Drug treatment

Ostriches were randomly allocated to two treatment groups. Using a two-period crossover design, the IV and IM pharmacokinetics of marbofloxacin in ostriches were determined at the 5 mg/kg *BW* dose level. A two-week washout period was allowed.

Marbofloxacin was administered IM into the iliotrochanteric muscle and IV (as a bolus) through a catheter placed in the brachial vein. Blood samples (1.5 mL) were collected from the right jugular vein at 0, 5, 10, 15, 30, 45, 60 and 90 min, 2, 3, 4, 6, 8, 10, 12, 24, 48 and 72 h after dosing. Heparin was used as the anticoagulant. Plasma was separated and stored at −20 °C until assay.

2.4. Drug assay

Plasma marbofloxacin concentrations were quantified using HPLC/*UV* according to a method previously described by Waxman et al. (2001). The extracted samples were injected directly into the HPLC system (Spectra System, Thermo Separation Products) where the separation was accomplished using an ion-pairing reverse-phase column (PR C-18 5 μm 150 × 4.6 mm. Precolumn: PR C-18 5 μm 15 × 4.6 mm.). The mobile phase comprised buffer pH 2.7: methanol:acetonitrile:acetic acid:triethylamine (74:20:4:1:1, v:v:v:v:v). The buffer pH 2.7 was a 0.4% aqueous solution of tetrabutylammonium hydrogen sulphate (p/v) and diammonium hydrogen phosphate (p/v).

Marbofloxacin was detected using ultraviolet spectrophotometry at 295 nm and the flow rate was 0.6 mL/min. Samples were run in duplicate. The limit of quantification was 0.017 μg/mL for marbofloxacin and the method was linear up to 10 μg/mL The recoveries of marbofloxacin from plasma samples were 91.7 ± 4.1 %. The inter-assay coefficients of variation for 0.025 and 2.5 μg/mL were 8.3% and 5.1%, respectively. The intra-assay coefficients of variation for 0.025 and 2.5 μg/mL were 5.2% and 3.6%, respectively.

2.5. Pharmacokinetic analysis

Pharmacokinetic parameters were determined for each individual animal. Plasma concentrations of marbofloxacin after IV and IM administrations were subjected to a non-compartmental analysis using a PCnonlin V 4.0 software package (Statistical Consultants Inc.).

Values calculated following the IV administration were: area under the plasma concentration vs time curve (AUC), area under the first moment curve (AUMC); mean residence time (MRT, where MRT = AUMC/AUC), plasma clearance (Cl, where Cl = Dose/AUC), apparent volume of distribution at steady state (V_{ss}, where V_{ss}=Cl × MRT), elimination rate constant (k_{el}, calculated as the slope of the terminal phase of the plasma concentration curve that included a minimum of four points) and terminal half-life ($t_{1/2}$, where $t_{1/2} = 0.693/k_{el}$).

After IM administration, the following parameters were determined as above: AUC, AUMC, MRT, mean absorption time (MAT, where $MAT = MRT_{IM} - MRT_{IV}$) and bioavailability ($F$), where $F = [AUCIM/AUCIV] \times 100$. The AUC and AUMC were calculated using trapezoidal rule with extrapolation to infinity (∞). The extrapolated area did not exceed 6% of the total area.

2.6. Statistical analysis

The statistical analysis was performed using the SPSS 10.0 software package (SAS). The results are presented as means ± standard deviation (SD). The non-parametric Wilcoxon test was used to compare the parameters obtained after IV and IM administrations. A value of $P < 0.05$ was considered significant.