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Research Article

Pharmacokinetics of Marbofloxacin in Dogs After Single Intravenous and Oral Administration, and its Interaction with Sucralfate

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Abstract

The study aims to establish plasma pharmacokinetic parameters of marbofloxacin in dogs, at a 2 mg/kg single dose, intravenously, orally only and orally with sucralfate pre-treatment (1g per animal), to evaluate its influence on antimicrobial absorption. Concentrations of marbofloxacin in plasma were determined using high-performance liquid chromatography (HPLC) with fluorescence detection. After intravenous application of marbofloxacin, the mean (± SD) of AUC0-24, Vd, Clt and MRT, were 13.5 ± 3.4 µg-h/mL, 2.45 ± 0.9 L/kg, 157.3 ± 47.9 mL/h/kg and 14.6 ± 1.3 hours, respectively. After oral administration, the Cmáx, t½ abs and bioavailability were 1.1 ± 0.5 µg/mL, 0.5 ± 0.3 hours and 107.5 ± 11.7%, respectively. In animals given an oral dose of marbofloxacin with sucralfate pre-treatment, delay absorption and there was a significant decrease in Cmax (< 53.5 ± 18.6%) and AUC (< 42.6 ± 10.7%).

Keywords: *Marbofloxacin; Dog; Pharmacokinetic*

Introduction

Marbofloxacin is a third-generation fluoroquinolone, developed for Veterinary Medicine use only. Provided with a broad antimicrobial spectrum [1,2], it develops concentration-dependent bactericidal activity; Area Under the Curve (AUC)/MIC and Maximum Concentration (Cmax)/MIC ratios greater than 125 and 10 are considered predictors of clinical efficacy for all fluoroquinolones [2-4].

The structural modifications introduced in marbofloxacin molecule, improved it kinetics characteristics: long elimination half-time (t½β) and wide volume of distribution (Vd) [2,3].

Kinetic background in dogs for intravenous administration, indicates that marbofloxacin exhibits immediate tissue diffusion, based on the reported mean time of distribution (t½α) of 0.3 hours [5]. Reported Vd of 1.9 [6] up to 2.3 L/kg [5], corresponds to high tissues passage. Total clearance (Clt) ranges oscillate between 0.10 [6] and 0.23 L/h/kg [5]; t½β values for intravenous application have been reported in ranges from 8.08 ± 6.2 [5] to 12.4 ± 2.6 hours [6] and mean residence time (TMR) was 9.8 ± 7.8 hours [5].

Oral administration determined rapid absorption [7], optimal bioavailability (F), Cmáx of 1.4 µg/mL obtained at 2.5 hours [6] and a t½β of 9.1 hours [7]. Sucralfate is an aluminum hydroxide with sulfated sucrose complex, that after oral application, quickly forms a strong physical barrier that protects the gastrointestinal tract for 6 hours, being indicated in the treatment of ulcers in humans [8-10] and in animals [11].

Concomitant use with sucralfate affects or postpones the absorption of fluoroquinolones [2,12]. In humans, the interaction significantly reduces the AUC and Cmax of some fluoroquinolones [8,13,14]. The effects differ depending on the drug and the time elapsed between the application of sucralfate and fluoroquinolone [8,13,15]. Fluoroquinolones are important clinical tools that must be preserved to minimize the chances of therapeutic failure, maximize the chances of clinical cure and avoid the development of resistance [2,14], this study was carried out to establish plasmatic kinetic parameters in dogs after single application by intravenous and oral routes with the purpose of providing tools that facilitates the rational use of the drug and simultaneously determine the influence of pretreatment with sucralfate on the oral absorption of the antimicrobial.

Materials and Methods

Animals

Six adult dogs of different sex, undefined breeds, clinically healthy, with no history of pharmacological treatment in the last 3 weeks and weighing 24.5 ± 10.4 kg, randomly selected from a shelter of 45 animals in the city, were used. from Río Cuarto, Argentina.

In trial A, canines received 2 mg/kg of marbofloxacin (Marbofloxacin 2% injectable solution, Laboratorio Río de Janeiro, Argentina) intravenously. In trial B, carried out two weeks later, the experiment was repeated orally, the same animals received the same dose using tablets (ad hoc formulation of 28 mg marbofloxacin tablets (Laboratorio Río de Janeiro, Argentina) after fasting for 12 and 3 hours before and after application, respectively. In trial C, with the same animals two weeks later, the experiment was repeated orally under identical conditions, except that two hours before the administration of marbofloxacin the animals were pretreated orally with 1g of sucralfate (Sucravet®, suspensión x 100 ml).

Sample treatment

After administration, blood samples were obtained from the left jugular vein (3 - 4 ml) in heparinized tubes at 15, 30, 45 minutes and 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours, centrifuged at 1200g for 10 minutes and plasma was stored at -20°C until analysis. The samples were pre-treated using 150 µL of plasma to which 150 µL of 25% trichloroacetic acid (1:1) was added; the preparative assay consisted of liquid-liquid extraction of the analyte using 150 µL of the supernatant, 150 µL of water, 600 µL of methanol and 20 µL of enrofloxacin as internal standard [16]. The whole was subjected to vortex agitation for 30" and centrifugation at 13,500 rpm at 4°C for 25 minutes.

Separation and quantification were performed by HPLC using an isocratic elution in reverse phase with a flow rate of 0.8 mL/minute, 100 µL of sample injection volume, pre-column and octadecylsilane column (C-18), reading in a fluorescence detector established at 295 nm excitation and 490 nm emission, using mobile phase composed of water, acetonitrile and triethylamine (79:20:1 v/v/v) adjusted to pH 3.0 with orthophosphoric acid [16]. The elution generated peaks in the chromatogram corresponding to marbofloxacin and the internal standard, enrofloxacin. Experimental protocol was approved by the Ethics Committee of the National University of Río Cuarto included in the project 083/2020.

Concentration calculations

With the chromatogram obtained in the run the plasma samples separately and with the known concentration standard, a quotient was obtained taking the value of the peak area of the drug and the corresponding internal standard. A quotient of both was obtained and used for the preparation of the calibration curve to establish plasma concentrations of marbofloxacin by simple linear regression (r^2= 0.99) [17].

Pharmacokinetic analysis

Together with the applied dose, weight and plasma concentration values versus time of each animal in each experience, were analyzed with the non-compartmental pharmacokinetic program PK Solution v 2.0 [18] with the purpose of estimating robust pharmacokinetic parameters, essential to assess the disposition of marbofloxacin. Oral bioavailability (F) was determined using the equation: $F = AUC_{oral} / AUC_{EV}$. The detection and quantification limits of the assay were 0.0121 and 0.0363 µg/mL, respectively.

Statistical analysis

A non-parametric Mann-Whitney test was performed to assess significant differences ($p < 0.05$) between the pharmacokinetic parameters of marbofloxacin in each of the dogs by oral application and those of oral administration in conjunction with sucralfate. Statistical tests were performed by Graph Pad Prism Software [19].

Results

Figure 1 indicates the disposition curves after the single application of marbofloxacin in the different experiences. Table 1 indicates the kinetic parameters (± SD) obtained in each test.

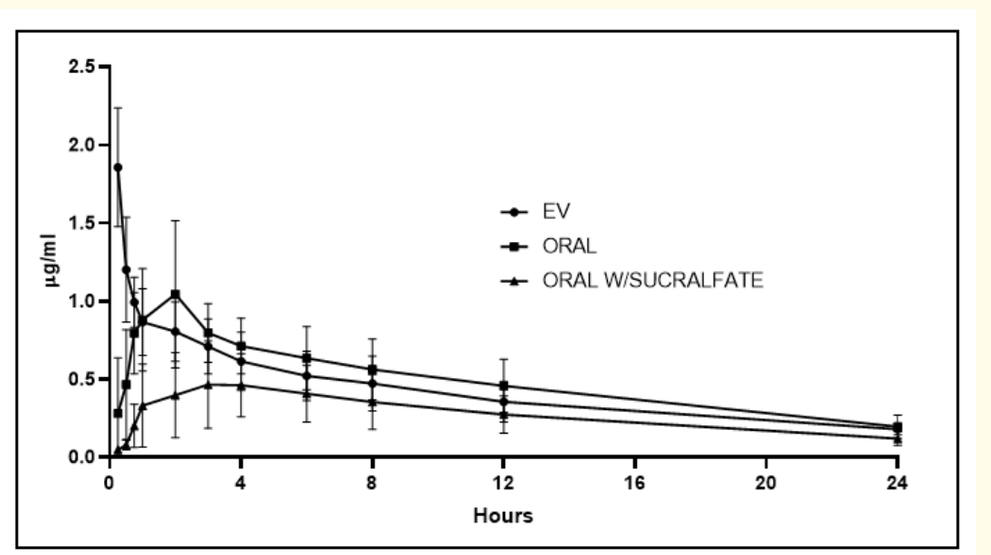

Figure 1: *Disposition curves after the single application of marbofloxacin in different experiences.*

Parameters	Experience 1 EV	Experience 2 Oral	Experience 3 Oral + Sucralfate
Cmax (µg/ml)	-	1,1 ± 0,5	0,5 ± 0,3
Tmax (h)	-	1,5 ± 0,6	3,5 ± 0,5
t½abs (h)	-	0,5 ± 0,3	1,3 ± 0,6
t½α (h)	0,24 ± 0,21	1,7 ± 1,0	2,0 ± 0,8
Vd (L/kg)	2,45 ± 0,9	-	-
AUCarea(µg-h/ml)	13,55 ± 3,4	14,7 ± 4,8	8,6 ± 3,4
t½β (h)	10,73 ± 0,9	10,7 ± 2,1	11,5 ± 2,7
TMR (h)	14,63 ± 1,3	15,1 ± 2,5	17,6 ± 4,7
Cl (ml/h/kg)	157,30 ± 47,9		
F (%)	-	107,5 ± 11,7	62,0 ± 13,8
Weight (Kg)	24,5 ± 10,4	24,5 ± 10,4	24,5 ± 10,4

Table 1: *Pharmacokinetic parameters (± SD) obtained in each experience*

References: Cmax: Maximal Concentration; Tmax: Time to Reach Cmax; t½abs: Absorption Half-Life; t½α: Distribution Half-Life; AUCarea: Area Under Curve; t½β: Elimination Half-Life; TMR: Average Residence Time; Cl: Clearance; F: Bioavailability.

Discussion

After intravenous application, marbofloxacin diffuses rapidly from the central compartment, similar to that reported in other experiences [5], it exhibits wide distribution in tissues according to the volume of distribution (Vd= 2.4 ± 0.9 L/kg), value higher than that reported by Schneider., *et al*. 1996 [6] and similar to 2.3 L/kg [5], a result that corresponds to the high passage to tissue as a result of the low ionization of the molecule at physiological pH associated with its lipophilic character and limited binding plasma proteins (9%), characteristics that promote diffusion to tissues [2,3]. Similar to other experiences [5,6], marbofloxacin shows long permanence in the body, according to the values obtained in the elimination half-life and TMR parameters established at 10.7 ± 0.9 and 14.6 ± 1.3 hours, respectively, and limited Clt value [5,6].

Similar to what has been reported in other experiences, oral application determines prompt absorption [7] (absorption half-life of 0.5 ± 0.3 hours), Cmax of 1.1 ± 0.5 µg/mL was established at 1.5 ± 0.6 hours, it offers optimal bioavailability (F = 107.5 ± 11.7%) [6,7] and long permanence in the organism (t½β= 10.7 ± 2.1 hours) higher than reported with enrofloxacin, difloxacin and orbifloxacin in this specie [7]. These results are consistent with the modifications made to the marbofloxacin molecule that give it greater persistence and tissue distribution [2,3,20].

Oral administration provides levels comparable to intravenous administration that persist up to 24 hours after application. The profile of the plasmatic curves generated in the different tests indicates that the drug achieves concentrations up to 24 hours after application and suggests its oral application with intervals of 24 hours, however the plasmatic levels established at 24 hours are insufficient to control most relevant pathogen microorganisms [1], in addition, efficacy predictors (PK-PD) are not sufficient to ensure adequate clinical responses, so that a dosage adjustment is necessary [3].

The interaction of sucralfate and fluoroquinolones in dogs has been extrapolated from results obtained in humans, considering all anatomical differences [14,21], since there is only one study in dogs on this interaction [21], in which only enrofloxacin and ciprofloxacin were evaluated. Administration of sucralfate at least two hours before is recommended to avoid interfering with the absorption of fluoroquinolones [8,13].

Pretreatment with sucralfate, two hours before oral administration of marbofloxacin, delay absorption and significantly affects some pharmacokinetic parameters of marbofloxacin, decreasing AUC and Cmax by 42.6 ± 10.7 and 53.5 ± 18.6%, respectively ($p < 0.05$); higher than that reported for ciprofloxacin in dogs, applied simultaneously with sucralfate, a reduction of Cmax and AUC of 48 and 52%, respectively, and in animals that were applied sucralfate two hours after ciprofloxacin, the reduction of both pharmacokinetic parameters was 14% [21].

However, in the present study, a significant interaction of sucralfate on marbofloxacin absorption was observed in dogs [2,12], one of the fluoroquinolones that is starting to be used as a treatment in pets [6].

Conclusion

Results obtained are similar to those observed with this antimicrobial in other domestic species and agree with the kinetic profile of fluoroquinolones in domestic animals. The pharmacokinetic characteristics promote the clinical use of marbofloxacin in canines by intravenous and oral routes, with appreciable advantages over other fluoroquinolones, such as very good tissue diffusion and long recorded permanence, which suggests application every 24 hours, although simultaneous use with sucralfate should be avoided. It is also necessary, consider a dosage adjustment to ensure effective clinical therapy.

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