Asian Journal of Pharmacology and Toxicology 02 (05); 2014; 01-06

Asian Journal of Pharmacology and Toxicology

RESEARCH ARTICLE

Received on: 02-09-2014
Accepted on: 09-10-2014
Published on: 20-10-2014

Corresponding author
Sara Melisa Arciniegas Ruiz
Departamento de Fisiología y Farmacología, Facultad de Medicina Veterinaria y Zootecnia, Universidad Nacional Autónoma de México. México.
Tel.: 52 (55) *5622-5908 y 80 ext. 110*
Email dinorah.vestrada@gmail.com

QR Code for Mobile users

Conflict of Interest: None Declared !

Pharmacokinetics of A New Oral Controlled-Release Formulation of Doxycycline Hyclate for Dogs

Sara Melisa Arciniegas Ruiz[a], Lilia Gutierrez Olvera[a], Maria Josefa Bernad Bernad[b], Dinorah Vargas Estrada[a]*

[a] Departamento de Fisiología y Farmacología, Facultad de Medicina Veterinaria y Zootecnia, Universidad Nacional Autónoma de México. México.
[b] Departamento de Farmacia. Facultad de Química, Universidad Nacional Autónoma de México, México

ABSTRACT

The aim of this study was to develop an oral drug formulation of doxycycline hyclate that maintain longer therapeutic levels than conventional forms. A polymethacrylate and acrylic acid based matrix were used in different proportions to obtain controlled-release formulations; DOX1, DOX2 and DOX-C (without excipients). Serum concentrations vs. time profile were investigated after their oral administration in healthy dogs. DOX1 and DOX2 showed therapeutic concentrations for 60 hours, while DOX-C only 24 hours. The pharmacokinetic values obtained were K½el, Cmax, Tmax, AUC, AUC∞, AUCt, AUMC, RT, Kel, Vdss, Clb and Frel. DOX1 did not differ significantly from DOX-C but showed significant differences in all variables with DOX2 ($p<0.05$). In conclusion DOX1 had the best pharmacokinetics-pharmacodynamics relationship for time-dependent drug and longer release time (60 hours), thereby reducing the frequency of administration, the patient's stress, the occurrence of adverse effects and the cost of treatment.

Keywords: canine, carbopol, eudragit, long-acting.

Cite this article as:
Sara Melisa Arciniegas Ruiz[a], [a] Departamento de Fisiología y Farmacología, Facultad de Medicina Veterinaria y Zootecnia, Universidad Nacional Autónoma de México. México.[b] Asian Journal of Pharmacology and Toxicology 02 (05); 2014; 01-06.

1. INTRODUCTION

Doxycycline (DOX) is a semi-synthetic drug derivative of oxytetracycline, has a broad-spectrum activity against a wide variety of microorganisms, including aerobic and anaerobic, Gram-positive and Gram-negative bacteria, chlamydiae, rickettsiae and mycoplasmas. DOX has bacteriostatic effect by inhibiting protein synthesis (1); recently has been discovered anti-inflammatory and anti-neoplastic roles for DOX (2, 3). In dogs, DOX is used for controlling infections caused by Staphylococus spp, Streptococcus spp (4), Haemophilus spp, Bordetella bronchiséptica (5), Mycoplasma spp, Borrelia burgdorferi, Campylobacter jejuni, Fusobacterium spp (1,6) and is the choice for treatment of infections caused by Leptospira spp (7), Brucella canis (1), Haemobartonella canis and numerous tick-borne diseases, been the most important Erhlichia canis (8). However, suitable treatment with DOX requires administration twice a day during prolonged periods ranging from 21 days to years even (9). Treatment could generate adverse reactions, like esophagus and stomach irritation, with the risk of ulcerations and vomits after the oral administration and tissue-irritation following subcutaneous or intramuscular injection (10, 11). These side effects are a limiting factor to the treatments which DOX is the only alternative, like Ehrlichia canis and carrier phase of Leptospira spp., which have importance not only in the dogs' health also on public health (8).

Controlled-release oral drug of doxycycline may reduce the gastrointestinal side effects and improve the efficacy in lengthy periods of treatment and reduce interruptions in the therapy. In Veterinary, a long acting injectable formulation of doxycycline has been evaluated for cattle (12), small ruminant (13) and dogs (14), and oral formulation for horses (15). The injection form showed increase in the half-life in dogs but caused inflammation in the injection site during 30 days, that aspect caused refusal of the dogs owners (14).

Considering the above, the objectives of this study were to develop and to determine pharmacokinetics values of new oral pharmaceutical presentation of doxycycline for dogs using acrylic acid polymer (Carbopol®) and polymethacrylate (EUDRAGIT® RL 100) to increase the duration time of therapeutic concentrations in blood, reducing the administration frequency over the existing products.

2. MATERIALS AND METHODS

Doxycycline hiclate (Indukern, México), EUDRAGIT RL100® (Evonik, Germany) and Carbopol® 971 P NF polymer (Lubrizol, México) were donated by the manufacturing companies.

Pre-formulation stage. Physical and chemical features of the doxycycline hiclate powder were obtained by Scanning Electron Microscopy (SEM) particle size distribution (PSD), Infrared Spectroscopy (Spectrometer FTIR Perkin-Elmer RX-I model), X-Ray diffraction (Siemens D5000 powder diffractometer with copper anticathode) and Differential Scanning Calorimetry (DSC 321 METTLER TOLEDO). Furthermore, rheological properties were determined, included bulk, tapped and true density, Carr's compressibility index, Hausner's ratio, porosity percentage, angle of repose and flow velocity. Powder's wet percentage was measured using OHAUS MB 2000 thermobalance. All techniques were performed according to the United States Pharmacopeia (16).

For controlled release drug preparations, doxycycline hiclate, Eudragit RL 100® and Carbopol® were mixed different ratios, DOX1 was mixed at 1:0.25:0.0037 ratios and DOX2 contained 1:1.5:0.0225 ratios of the above mentioned components. After mixture, preparations were granulated manually by wet granulation process (17). Control drug was doxycycline without excipients (DOX-C). For oral administration, the granules were inserted in a conventional gelatin capsule according the body weight of dogs in a dose of 20 mg/Kg. Proportions of excipients were based in (18, 19, 20) and considering recommendations of manufacturing enterprise (21).

This study was approved by the Institutional Subcommittee of Research, Care and Use of Experimental Animals (SICUAE) of Universidad Nacional Autonóma de México, according to the Mexican Official Regulation NOM-062-ZOO-1999 (22). The animals included in this research must have signed previous authorization by the owners.

Twenty-one healthy dogs (2 – 8 years) of different breeds, both sexes with a mean bodyweight of 15.4 Kg (12 to 35 Kg) were used in this trial. All animals were vaccinated, dewormed and assessed as clinically healthy after physical examination. During trials all animals received water ad libitum and fed commercial diet (Pedigree® dry food) twice daily. Dogs were not receiving other treatments. The same animals were used throughout and received all three treatments according to a three-way crossover model, randomly assigning the dogs to a given treatment and with two washout periods of 30 days.

The animals were assigned randomly in three groups. The first group was medicated with DOX1 (1:0.25:0.0035), the second group with DOX2 (1:1.5:0.0225) and the third group as control group, medicated with doxycycline without excipients (DOX-C). In all groups the administration was orally with a

single dose of 20 mg/Kg. Blood samples were obtained from each animal at 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 96 and 120 hours by vein puncture into eppendorf® tubes. Serum was immediately separated by centrifugation and store at - 18°C until analysis.

Serum doxycycline concentrations were determined by modified agar diffusion analysis (23) with Bacillus cereus (ATCC 11778) as a test organism in Mueller-Hinton dehydrated growth medium (BIOXON® Becton Dickinson, Mexico). Standard curve of DOX was strewn into agars (200, 20, 10, 5, 2.5, 1.25, 0.625, 0.3125 and 0.1562 µg/mL). Cultures were kept in incubator (RedLine, binder) during 24 hours at 37°C, then, the inhibition halos were measured with electronic digital caliper TRUPPER®. The concentrations values were determined using ORIGIN PRO 8.6® software (OriginLab Corporation, Massachussets, USA) and these values were used to determine the pharmacokinetics values.

Pharmacokinetics analysis. A computerized curve-stripping program (PKAnalyst, Micromath Scientific Software, Salt LakeCity, UT, USA) was used to analyze the concentration–time curve for each individual dog after the administration of doxycycline by oral route.

Akaike's information criterion (24) and graphical analysis of weighted residuals were used to determine the optimal pharmacokinetic model (25). For the oral administration the fitted curves of doxycycline that expressed the decline in drug concentration as a function of time was approximated to one compartment with first order input and first order output using model 3 ($r \geq 0.95$), with the following formula:

Pharmacokinetic variables obtained with PKAnalyst were: K½el = elimination half rate; Cmax = calculated maximum plasma concentration; AUC = area under the curve; AUCt = area under the concentration-time curve calculated by the trapezoidal method; AUMC = area under the first moment of the concentration-time curve; RT = retention time; Kel = elimination rate. The Tmax = time of peak plasma concentration, was determined by inspecting the individual drug plasma concentration-time profiles. The apparent volume of distribution at steady state (Vdss) was determined as follows: $(Dose*AUMC)/AUC^2$. The total body clearance (Clb) of oral doxycycline was estimated with the following formula: (Dose/AUC). The area under the concentration-time curve from zero up to ∞ with extrapolation of the terminal phase (AUC∞) was calculated with the following formula: AUC + (/Kel). Where is the last measurable concentration and Kel is the elimination rate. The relative bioavailability (Frel%) was obtained using the following equation:

Doxycycline serum concentrations and pharmacokinetics parameters of the three formulations were calculated for each dog and data were reported as mean ± standard error (SE). Normality and uniformity of the data were determined by Shapiro-wilks tests, differences between groups were obtained by ANOVA test and Tukey test for comparison of means.

3. RESULTS

The pharmacokinetics parameters are summarize in Table 1. The best fit for all formulations was a first order mono-compartmental model. Table 1 shows AUC, AUC ∞, RT and half-life (K½el) did not show statistically differences between DOX1 and DOX-C, but both differed significantly with regard to DOX2. The bioavailability (F%) of DOX2 was higher than DOX1 and DOX-C ($p<0.05$). The apparent volume of distribution (Vdss) between DOX-C and DOX1 did not differ statistically, while DOX2 was different than other groups ($p<0.05$). Maximum plasma concentration (Cmax) for DOX2 was 4.11 ± 0.21 µg/mL, while DOX-C and DOX1 were 2.03 ± 0.28 µg/mL and 2.63 ± 0.106 µg/mL respectively. Statistically DOX2 was larger in comparison with DOX-C and DOX1 ($p<0.05$). Significant differences were found for total body clearance (Clb) between the three groups ($p<0.05$).

After sixty hours of the drug administration both DOX1 and DOX2 had detectable plasma concentrations, both lasted longer than DOX-C, which during only 24 hours (Figure 1). However, DOX2 showed higher concentrations during the 60 hours compared with DOX1, which had similar plasma concentrations to DOX-C.

Animals did not show any unusual sign of discomfort, they did not present vomits or diarrhea during the study or afterwards.

4. DISCUSSION

Few pharmacokinetics studies of oral doxycycline in dogs have been published (26,27) and none of those studies consist of controlled-release oral formulations for dogs. In other species exist for this via report for perioral long-acting formulation for horse (15), perioral gel for periodontitis treatment in humans (28, 29) and subgingival system for local effect for periodontitis treatment in beagle dogs (30, 31) and humans (30, 32). In this study were obtained two oral long-acting formulations for systemic effect of doxycycline hiclate with 60 hours approximately duration in blood.

The differences between the two formulations were in pharmacokinetics values, but both had similar duration time (60 hours) into the body. DOX1 had a concentration peak of 2.63 ± 0.28 µg/mL, while DOX2

reached 4.11 ± 0.21 μg/mL, nevertheless like doxycycline is time-dependent drug is not necessary it has huge peaks while the concentration is over the minimal inhibitory concentration (MIC) specific for the treated microorganism (33). DOX shows best clinical efficacy with low concentrations, 2 to 4 times the MIC, in this case the inhibition of the microorganisms occurs in a time-dependent way, but at higher concentrations, 8 to 16 times the MIC, doxycycline exhibits concentration-dependent killing (33).

After Cmax, serum concentrations of DOX2 declined slowly (K½el 15.21 ± 0.99 hours) statistically larger than DOX1 (K½el 8.5 ± 0.46 hours). Predictably for a highly lipid soluble drug, a high apparent volume of distribution at steady state was achieved after oral administration of the drug for the two formulation and DOX-C and would be expected to have widespread tissue distribution (34). Body clearance (Clb) is a measure of drug elimination from the body, it indicates the volume of plasma from which the drug is completely removed, or cleared, in a given time period, the obtained clearance of the two formulations and DOX-C were very low, that indicates that the organism is very efficient removing the drug (35). Then, the high volume of distribution and the low total body clearance indicate that DOX is quickly absorbed, widely distributed and slowly eliminated in the body, the two long-acting formulations (DOX1 and DOX2) show better values in these parameters than DOX-C, and however this last has similar behavior. The Area under the curve (AUC) was 32.46 ± 0.66 and 88.6 ± 5.05 for DOX1 and DOX2 respectively, while was 22.1 ± 2.52 for DOX-C, those values were expected, because the AUC is inversely proportional to Clb, then patients with low clearance have high AUC (35).

In the sustained-release formulation is predictable than the absorption rate is lower than the elimination rate (36), in DOX2 the elimination rate was very slowly but was greater than the absorption rate. This finding is not unusual for long-acting preparations that exhibit flip-flop kinetics and may also explain the relative bioavailability which reaches an unusual 422.93 ± 26.04% and 146.89 ± 2.98 % for DOX2 and DOX1 respectively. In turn, to demonstrate flip-flop pharmacokinetics, the overall appearance of the serum concentration vs. time profile of the drug must be accounted for. If a much longer apparent elimination half-life following extravascular dosing is observed compared with the IV route, it suggests that flip-flop pharmacokinetics is occurring (36). However this is not possible with Doxycycline considering that IV administration of this drug is not recommended (31, 37, 38). For the same reason, the absolute bioavailability of doxycycline was not determined.

The benefits of the controlled release of drugs include the maintenance of serum drug concentration at an optimal therapeutic level for a more prolonged time interval, reduction in animal handling and consequently, a possible improvement in drug-administration compliance (33,34). In this context, both DOX1 and DOX2 preparation here described were capable of providing useful serum concentrations of this antibacterial drug for approximately 60 hours.

The quantitative/qualitative microbiological agar diffusion technique used in this trial to determine serum concentrations of doxycycline has been regarded as sufficiently reliable to replace analytical conclusions derived from high performance liquid chromatography (39). Furthermore, because it determines the active fraction(s) of the drug, it offers more clinically meaningful data than concentration values derived from purely chemical methods.

Summarizing, DOX1 presents ideal pharmacokinetics for time-dependent drug, either DOX1 or DOX2 are preparations that optimize the use of doxycycline in dogs in terms of duration time, pharmacokinetic values and PK/PD ratio, these could be advantages which likely may improve medical prescription compliance; although, the determination to use one or the other drug depends the microorganism in treatment. Nevertheless, clinical trials and toxicological studies are needed to assess if this preparation can be regarded as potentially useful in this species.

5. ACKNOWLEDGEMENTS

We would like to thank to MC MVZ Diana Perez Covarrubias of the Department of Small Animal Medicine and Surgery in Facultad de Medicina Veterinaria y Zootecnia, Universidad Nacional Autonóma de México as well as the dog's owners for their help and cooperation providing the patients and facilitating the blood collection and follow-up visits.

6. References

1.Holmes N, Charles P. Safety and efficacy review of doxycycline. Clin Med insights Ther 2009, 1:471–482.

2.Lee H, Park JW, Kim SP, et al. Doxycycline inhibits matrix metalloproteinase-9 and laminin degradation after transient global cerebral ischemia. Neurobiol Dis 2009, 34:189–198.

3.Zeng S, Zhou X, Tu Y, et al. Long-Term MMP inhibition by doxycycline exerts divergent effect on ventricular extracellular matrix deposition and systolic performance in stroke-prone spontaneously hypertensive rats. Clin Expl Hypertens 2011, 33(5):316–324.

4.Ross J, Jones R. MIC quality control guidelines for doxycycline when testing grampositive control strains by the reference methods. Diagn Microbiol Infect Dis 2004, 50:295–297.

5.Speakman A, Dawson S, Corkill J, et al. Antibiotic susceptibility of canine Bordetella bronchiseptica isolates. Vet Microbiol 2000, 71:193–200.

6.Cunha B, Sibley C, Ristuccia A. Doxycycline. Ther Drug Monit 1982, 4(2):115-135.
7.Levett P, Edward C. Leptospirosis. In: Bacterial infections of human: epidemiology and control. 4th ed. Edited by Evans AS, Brachman PS. New York: Springer; 2009;439-456.
8.McClure JC, Crothers ML, Schaefer JJ, et al. Efficacy of a doxycycline treatment regimen initiated during three different phases of experimental Ehrlichiosis. Antimicrob agents chemother. 2010, 54(12):5012–5020.
9.Bharti AR., Nally JE., Ricaldi JN, et al. Leptospirosis: a zoonotic disease of global importance. Lancet Infec Dis 2003, 3:757–771.
10.Smith K., Leyden JJ. Safety of doxycycline and minocycline: a systematic review. Clin Ther 2005, 27(9):1329-1342.
11.Xiao SY, Zhao L, Hart J, et al. Gastric mucosal necrosis with vascular degeneration induced by doxycycline. Am J Surg Pathol 2013, 37:259-263.
12.Vargas-Estrada D, Gracia-Mora J, Sumano H. Pharmacokinetic study of an injectable long-acting parenteral formulation of doxycycline hyclate in calves. Res Vet Sci 2008, 84:477–482.
13.Vargas D, Gutiérrez L, Juárez I, et al. Pharmacokinetics of an injectable long action parenteral formulation of doxycycline hyclate in goats. Am J Vet Res 2008, 69(8);1-6.
14.Gutiérrez L, Velasco Z, Vázquez C, et al. Pharmacokinetics of an injectable long-acting formulation of doxycycline hyclate in dogs. Acta Vet Scand 2012, 54: 35-43.
15.Zozaya H, Gutierrez L, Bernad M, et al. Pharmacokinetics of a peroral single dose of two long-acting formulations and an aqueous formulation of doxycycline hyclate in horses. Acta Vet Scand 2013, 55:21-28.
16.United States pharmacopeia and national formulary (USP 30-NF 25). Volume 2. Rockville: United States Pharmacopeia Convention. 2007:1553-1554.
17.Faure A., York P., Rowe R. Process control and scale-up of pharmaceutical wet granulation processes: a review. Eur J of Pharm Biopharm 2001, 52:269-277.
18.Karthikeyini C, Jayaprakash S, Abirami A, et al. Formulation and evaluation of aceclofenac sodium bilayer sustained release tablets. Int J ChemTech Res 2009, 1(4):1381-1385.
19.Kulkarni S., Kumar R, Shankar M., et al. Formulation and in vitro evaluation of sustained release matrix tablet of stavudine. Asian J of Pharm Clin Res 2010, 3(3), 215-217.
20.Rowe R. Handbook of pharmaceutical excipients. London: Pharmaceutical Press. 2012.
21.Evonik Industries AG. EUDRAGIT® application guidelines. 12th edition. Germany: Darmstadt. 2013.
22.NOM-062-ZOO-1999. Norma Oficial Mexicana, Especificaciones técnicas para la producción, cuidado y uso de los animales de laboratorio. Secretaría de Agricultura, Ganadería, Desarrollo Rural, Pesca y Alimentación. Estados Unidos Mexicanos. 1999. On line: http://www.senasica.gob.mx/?doc=743
23.Okerman S, Croubels M, Cherlet K, et al. Evaluation and establishing the performance of different screening tests for tetracycline residues in animal tissues. Food Addit Contam 21 (2), 145–153.
24.Yamaoka K., Nakagawa T., Uno T. Application of Akaike's information criterion (AIC) in the evaluation of linear pharmacokinetic equations. J Pharmacokinet Biopharm 1978, 6(2):165-175.
25.Gabrielsson J., Weiner, D. Parameter estimation. In: Pharmacokinetic and pharmacodynamic data analysis, concepts and applications. 4th edition. Edited by Gabrielsson, J., Weiner, D. & Swedish Pharmaceutical Society. Sweden: Swedish Pharmaceutical Press. 2007;21 - 44.
26.Michel G, Mosser J, Fauran F. Serum kinetics of doxycycline polyphosphate in dogs. Eur J Drug Metab Pharmacokinet 1979, 4(1):43–48.
27.Van Gool F, Santoul C,Giuseppin-Huet A. Doxycycline: pharmacokinetics and suggested dosage in dogs and cats. Tijdschrift Diergeneeskunde, 1988, 13:1189–1193.
28.Mundargi R, Srirangarajan S, Agnihotri S, et al. Development and evaluation of novel biodegradable microspheres based on poly(d,l-lactide-co-glycolide) and poly(epsilon-caprolactone) for controlled delivery of doxycycline in the treatment of human periodontal pocket: in vitro and in vivo studies. J Control Release 2007, 119(1):59-68.
29.Chadha V, Bhat K. The evaluation of doxycycline controlled release gel versus doxycycline controlled release implant in the management of periodontitis. J Indian Soc Periodontol 2012, 16(2):200-206.
30.Polson AM, Southard GL, Dunn RL, et al. Periodontal pocket treatment in beagle dogs using subgingival doxycycline from a biodegradable system. I. Initial clinical Responses. J periodontol 1996, 67:1176-1184.
31.Zetner K, Rothmueller G. Treatment of periodontal pockets with doxycycline in beagles. Vet Ther 2002, 3(4):441-452.
32.Polson A.M., Garrett S., Stoller N., et al. Multi-center comparative evaluation of subgingivally delivered sanguinarine and doxycycline in the treatment of periodontitis. II. Clinical results. J Periodontol 1997, 68(2):119-26.
33.Cunha B, Domenico P, Cunha C. Pharmacodynamics of doxycycline. Clin Microbiol Infect 2000, 6(5):270–273.
34.Abd El-Aty AM, Goudah A, et al. Pharmacokinetics of doxycycline after administration as a single intravenous bolus and intramuscular doses to non-lactating Egyptian goats. Pharmacol Res 2004, 49:487–491.
35.Jambhekar S., Breen P. Basic pharmacokinetics. USA: Pharmaceutical Press; 2009: 53-56.
36.Yáñez J, Remsberg C, Sayre C, et al. Flip-flop pharmacokinetics – delivering a reversal of disposition: challenges and opportunities during drug development. Ther Deliv 2001, 2(5):643–672.
37.Riond J, Riviere J, Duckett W, et al. Cardiovascular effects and fatalities associated with intravenous administration of doxycycline to horses and ponies. Equine Vet J 1992, 24(1):41–45.
38. El-Neweshy MS. Experimental doxycycline overdose in rats causes cardiomyopathy. Int J Exp Pathol 2013, 94:109-114.
39.Bocker R. Analysis and quantitation of a metabolite of doxycycline in mice, rats, and humans by high-performance liquid chromatography. J Chromatogr 1983, 274:255–262.

Figure 1. Mean ± SD plasma concentrations after single oral administration of Doxycycline hiclate (20 mg/kg) to dogs treated with formulations varying in their proportions of excipients. Control (without excipients), Dox1 (1:0.25:0.0037) and Dox2 (1:1.5:0.0225).

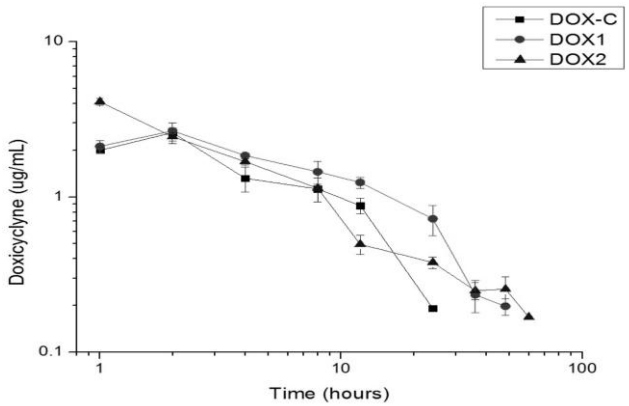

Table 1. Pharmacokinetic variables after oral administration of Doxycycline Hiclate (20 mg/kg) to dogs treated with formulations varying in their proportions of carbopol and polymethacrylate; Control, Dox1 and Dox2. [a b c] *The values within a row with no common superscript differ significantly (p<0.05).*

Mean ± SE	CONTROL DOX-C	DOX1 (1:0.25:0.0037)	DOX 2 (1:1.5:0.0225)
K½el (h)	7.54 ± 0.17[a]	8.5 ± 0.46[a]	15.21 ± 0.99[b]
Cmax (µg/mL)	2.03 ± 0.28[a]	2.63 ± 0.106[a]	4.11 ± 0.21[b]
T Cmax (h)	2	2	3.5 ± 1.1
AUC (µg*h/mL)	22.1 ± 2.52[a]	32.46 ± 0.66[a]	88.6 ± 5.05[b]
AUC ∞ (µg*h/mL)	24.18 ± 2.47[a]	34.54 ± 0.75[a]	94.04 ± 5.43[b]
AUCt (µg*h/mL)	18.65 ± 2.06[a]	37.91 ± 1.15[a]	84.08 ± 3.84[b]
AUMC (µg*h²/mL)	239.92 ± 21.793[a]	403 ± 29.01[a]	2018.95 ± 29.01[b]
RT (h)	10.82 ± 0.25[a]	12.37 ± 0.66[a]	22.01 ± 1.42[b]
Kel (h^{-1})	0.09 ± 0.002[a]	0.08 ± 0.004[a]	0.05 ± 0.003[b]
Vdss (L/Kg)	10.003 ± 1.37[a]	7.61 ± 0.29[a]	5.02 ± 0.27[b]
Clb (mL/min/Kg)	0.91 ± 0.1[a]	0.61 ± 0.12[b]	0.23 ± 0.013[c]
F (%)	-	146.89 ± 2.98[a]	422.93 ± 26.04[a]

K½el = elimination half rate; Cmax = calculated maximum plasma concentration; Tmax = time of maximum plasma concentration; AUC= area under the curve; AUC∞ = area under the concentration-time curve from zero up to ∞ with extrapolation of the terminal phase; AUCt = area under the concentration-time curve calculated by the trapezoidal method; AUMC = area under the first moment of the concentration-time curve; RT = retention time; Kel = elimination rate; Vdss = apparent volume of distribution at steady state; Clb = Total body clearance; F = bioavailability.