Interaction study between cephalexin and omeprazole after oral administration in dogs

Martin Pablo Lupi,[1] Sabrina Passini,[1] Laura Montoya,[1] Agustina Monfrinotti,[1] Luis Ambros[1,2]

[1]Department of Pharmacology, Faculty of Veterinary Sciences, University of Buenos Aires; [2]CONICET – UBA Institute of Animal Production Research, Faculty of Veterinary Sciences, University of Buenos Aires, Argentina

Abstract

Cephalexin, a widely used first-generation cephalosporin antibiotic, is frequently prescribed in veterinary medicine for various bacterial infections in canines. Concurrently, omeprazole, a proton pump inhibitor (PPI), is commonly used to manage gastric ulcers and related conditions. Understanding potential drug interactions is crucial for optimizing therapeutic outcomes. We conducted a study to assess the impact of omeprazole on the disposition of cephalexin in canines. Ten healthy mixed-breed dogs received cephalexin alone and after a 5-day pretreatment with omeprazole. Pharmacokinetic parameters were evaluated using high-pressure liquid chromatography (HPLC) analysis. The mean plasma concentration-time curves showed a relatively slow absorption phase with comparable peak plasma concentrations (C_{max}) of 17.32±4.21 µg/mL for cephalexin alone and 16.66±5.26 µg/mL when administered with omeprazole. Similarly, other pharmacokinetic parameters, including area under the plasma concentration-time curve (AUC), elimination half-life ($T_{1/2}$), absorption half-life ($T_{1/2a}$), and total body clearance (Cl/F), did not exhibit significant differences between treatments. Our results demonstrate that omeprazole did not significantly alter the pharmacokinetics of cephalexin in canines, allowing for their effective combination without the need for dosage adjustments.

Correspondence: Martin Pablo Lupi, Department of Pharmacology, Faculty of Veterinary Sciences, University of Buenos Aires, Av. Chorroarín 280, 1430 Buenos Aires, Argentina.
E-mail: mlupi@fvet.uba.ar

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Introduction

Cephalexin, a first-generation cephalosporin antibiotic, has played a significant role in antimicrobial therapy since its discovery. With its potent activity against Gram-positive bacteria, including Streptococcus and Staphylococcus species, cephalexin has become a valuable tool in the treatment of various bacterial infections. Its effectiveness, combined with its favorable pharmacokinetic profile and low toxicity, has contributed to its extensive use in both human and veterinary medicine.[1-5]

Clinical examples of the use of cephalexin and omeprazole in canines highlight their importance in veterinary practice. Cephalexin is commonly prescribed for various bacterial infections, including skin and soft tissue infections, urinary tract infections, and respiratory tract infections.[3,6,7]

To optimize therapeutic efficacy and combat the development of antibiotic resistance, it is crucial to gain a comprehensive understanding of cephalexin's antimicrobial spectrum, resistance mechanisms, and other relevant pharmacokinetic properties. This knowledge enables informed decision-making in clinical practice, ensuring effective treatment outcomes.

In the context of oral administration, proper gastrointestinal absorption is essential for cephalexin to achieve optimal pharmacokinetics and therapeutic efficacy. The gastric pH, which influences drug solubility and dissolution, plays a critical role in the absorption of orally administered medications. Therefore, it is important to consider potential interactions between cephalexin and concurrently administered drugs, particularly those that can modify gastric pH.[8,9]

One commonly used medication that can impact gastric pH is omeprazole, a proton pump inhibitor (PPI) frequently prescribed in veterinary medicine to treat upper gastrointestinal injuries in dogs. Omeprazole effectively reduces gastric acid production, reaching peak efficacy within 3 to 5 days of administration. Its bioavailabil-

ity also stabilizes over this period. Omeprazole is frequently used to manage gastric ulcers, gastroesophageal reflux disease (GERD), and other conditions related to excessive gastric acid production.[10-13] There is a real potential for clinically significant drug interactions in patients receiving PPIs and other drugs. These interactions may result from an increase in gastric pH induced by PPIs, which can reduce drug solubility or alter drug release from its pharmaceutical formulation.[14] Additionally, cephalexin absorption depends on PepT1, a proton-dependent intestinal transporter. Elevation of gastric pH by omeprazole disrupts the proton gradient essential for PepT1 function, potentially decreasing drug absorption.[15] Pharmacokinetic interactions between cephalexin and omeprazole have been studied in humans;[16] however, to our knowledge, no studies have been conducted on this topic in canines.

The concurrent use of omeprazole with other medications, such as cephalexin, requires caution. The increase in gastric pH induced by omeprazole can potentially affect the absorption and effectiveness of cephalexin.[16]

This study was conducted to evaluate the potential interaction between omeprazole and cephalexin in canines. Our objective was to evaluate the disposition of orally administered cephalexin in the presence of previously administered omeprazole and provide valuable insights into the pharmacokinetic profile of this antibiotic. The findings of this study will provide valuable information for veterinarians to make informed decisions about the appropriate use of cephalexin and omeprazole in canines. Understanding the potential impact of omeprazole on the disposition of cephalexin is essential for optimizing therapeutic outcomes and ensuring the safety and efficacy of these medications in clinical settings.

Materials and Methods

Experimental animals

For this study, ten mixed-breed dogs were included. The animals were housed in the kennels of the Faculty of Veterinary Medicine at the University of Buenos Aires. They were fed twice a day (8 am and 8 pm) with 100 g of premium commercial dry dog food per feeding. Water was provided *ad libitum*, and their body weights ranged between 14.5 and 28.2 kg. All animals were healthy as determined by clinical examination, complete blood and serum biochemical analysis, and urinalysis. All animal procedures were approved by the Institutional Animal Care and Use Committee, School of Veterinary, University of Buenos Aires, Argentina (protocol number 2012/30).

Experimental design

The study was conducted in two phases, with a two-week washout period. In the first phase, each dog received cephalexin monohydrate orally (500 mg tablet, Cefalexina®, Holliday-Scott, Buenos Aires, Argentina) at a dosage of 25 mg/kg, followed by an oral flush with 12 mL of tap water to ensure the tablet was swallowed. In a second phase, every dog received omeprazole orally (10 mg tablet, Nogastrol®, Mayors Laboratories, Buenos Aires, Argentina) at a dosage of 1 mg/kg every 24 hours for five days, preceding the cephalexin monohydrate administration. In both experiences, the dogs were deprived of access to food for 12 hours before each cephalexin administration and remained unfed for at least 4 hours after application.

Blood sampling

Blood samples (2 mL) were collected through a catheter placed in the cephalic vein before antibiotic administration and at 0, 0.16,

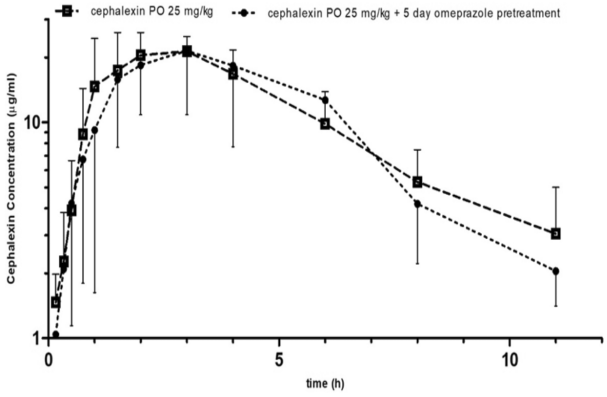

Figure 1. Mean plasma concentrations of cephalexin following a single oral 25 mg/kg administration (phase 1) and after 5 days pretreatment with 1 mg/kg omeprazole (phase 2) to ten dogs. Vertical bars represent standard error of the mean.

Table 1. Pharmacokinetic parameters calculated by one-compartment analysis after the oral administration of 25 mg/kg of cephalexin alone and after a 1 mg/kg omeprazole 5-day pretreatment to ten dogs. Data are presented as mean±SD.

Parameter	CFX	CFX+OMP
AUC_{inf} (h·ug/mL)	116.71±30.58	108.26±43.24
Cl/F (L/h/kg)	0.23±0.07	0.26±0.11
C_{max} (µg/mL)	17.32±4.21	16.66±5.26
T_{max} (h)	2.42±0.55	2.30±0.40
K_{01} (1/h)	0.55±0.22	0.52±0.19
$T_{1/2a}$ (h)	1.44±0.49	1.50±0.42
K_{10} (1/h)	0.35±0.10	0.40±0.07
$T_{1/2}$ (h)	2.12±0.60	1.78±0.26
MRT_{inf} (h)	5.11±1.4	4.60±0.81

SD, standard deviation; CFX, cephalexin; CFX+OMP, cephalexin+ omeprazole; AUC_{inf}, area under the plasma concentration time-curve from 0 to infinite; Cl/F, total body clearance/ bioavailability; C_{max}, peak plasma concentration; T_{max}, time to reach peak plasma concentration; K_{01}, absorption rate constant; $T_{1/2a}$, absorption half-life; K_{10}, elimination rate constant; $T_{1/2}$, elimination half-life; MRTinf, mean residence time.

0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, and 11 hours after administration. Heparinized tubes were used to collect the blood samples. After collection, the tubes were mixed and kept on ice to preserve the samples. Subsequently, the samples were centrifuged, and the resulting plasma was separated. The plasma samples were then stored at −20ºC until they were assayed. The blood sampling schedule was the same for the two phases of the study.

Chromatographic conditions

Plasma cephalexin concentrations were determined using a sensitive and accurate high-pressure liquid chromatography (HPLC) method based on the technique described by Al-Said *et al.* (2000).[17] The HPLC system utilized in the analysis consisted of a Thermo Scientific Dionex UltiMate, HPG-3200SD isocratic solvent delivery system, and a UV Visible Multi-Length 151 variable UV/Vis detector. The chromatograph employed a LiChroCART® RP C18 column (125×4 mm, 5 µm, Merck KGaA, Darmstadt, Germany). The mobile phase consisted of a mixture of acetonitrile and 0.05 M potassium dihydrogen phosphate buffer (pH 4) in a ratio of 10:90. The flow rate was maintained at 2.0 mL/min, and the detection wavelength was set at 280 nm. A 0.4 mL plasma sample was mixed with 20 µL of a 1000 µg/mL cefuroxime solution as the internal standard and 0.1 mL of 12.5% trichloroacetic acid. After centrifugation at 3500 g for 10 minutes, a 50 µL aliquot of the resulting mixture was injected into the HPLC system. The peak heights of the cephalexin were recorded to determine its concentration in each plasma sample. The standard curve was linear within the range of 0.5-50 µg/mL, the limit of quantification was 0.5 µg/mL, and the R^2 value was 0.99. The values of interday and intraday coefficients ranged from 1.34% to 7.97% and from 0.11% to 10.22%, respectively.

Pharmacokinetic analysis

The individual plasma concentration-time curves of cephalexin in both phases were analyzed using Phoenix WinNonlin 8.0 software (Certara, L.P., Princeton, NJ, USA). Initial estimates were obtained using the residual method,[18] and further refined through nonlinear regression. The number of exponents needed was determined by the Akaike criterion.[19] Pharmacokinetic parameters, including maximum concentration (C_{max}), elimination half-life ($T_{½}$), absorption half-life ($T_{½a}$), absorption rate constant (K_{01}), elimination rate constant (K_{10}), apparent volume of distribution divided by bioavailability (V/F), and total body clearance (Cl/F), were calculated using compartmental analysis equations. The area under the plasma concentration-time curve (AUC) was determined using the linear trapezoidal rule. The mean residence time (MRT_{inf}) was obtained as the area under the moment curve (AUMC)/AUC calculated by a non-compartmental model.

Statistical analysis

Main pharmacokinetic parameters from each treatment were compared using the Wilcoxon test, with a significance level of $p<0.05$.

Results

Adverse effects were not observed during or following both phases of the experiment in any of the dogs. The values of pharmacokinetic parameters are presented as mean ± standard deviation in Table 1. The time course of cephalexin alone or in combination with omeprazole in the serum of dogs treated by the oral route was best described by a one-compartment model.

In both phases, the mean plasma concentrations *versus* time curves (Figure 1) demonstrated a relatively slow absorption phase reflected by the time to reach peak plasma concentration (T_{max}) values (2.42±0.55 h and 2.30±0.40 h for phases 1 and 2, respectively). The drug remained detectable in plasma at all sampling times between 0.16 and 11 hours after administration. The $T_{½}$ values were 2.12±0.60 h (phase 1) and 1.78±0.26 h (phase 2). There were no statistically significant differences observed between the pharmacokinetic parameters of cephalexin obtained in both treatments.

Discussion and Conclusions

In this study, we reported the pharmacokinetic parameters of cephalexin administered alone or in combination with omeprazole to dogs. The doses administered for both drugs were those recommended by the manufacturers. Although the current recommendation for canine omeprazole dosing is every 12 hours,[12,13] we decided to follow the recommended dosages and dosing intervals as outlined by Boothe (2012), as these continue to be widely used in clinical practice.[10]

A comparison of the pharmacokinetic parameters obtained in our study with those from previous studies reveals similarities in the disposition of cephalexin in canines. When the absorption profiles of cephalexin were compared, the T_{max} ranged from approximately 1 to 2 hours. Prados *et al.* (2007) reported a T_{max} of 141±0.7 min following morning administration,[20] while Carli *et al.* (1999) observed a T_{max} of 90 min.[2] Silley *et al.* (1988) reported a T_{max} of 1.8 h (approximately 108 min).[5] In our study, the values were slightly longer, with 2.42±0.55 h in phase 1 and 2.30±0.40 h in phase 2. These findings indicate that our study exhibited a slightly delayed T_{max} compared to previous research.

When comparing the C_{max} values obtained in our study (17.32±4.21 µg/mL in phase 1 and 16.66±5.26 µg/mL in phase 2) with previous research, interesting observations arise. Carli *et al.* reported peak serum concentrations of 20.3±1.7 µg/mL after oral dosing with a 20 mg/kg dosage.[2] Prados *et al.* observed a cephalexin peak plasma concentration of 18.77±2.8 µg/mL following a 25 mg/kg dose.[20] Silley *et al.* reported peak serum concentrations of 18.6 µg/mL with a total dose of 150 mg.[5] These findings indicate that the C_{max} values obtained in our study are within a comparable range to the values reported in the aforementioned studies, highlighting consistency in the peak plasma concentrations achieved after administration of cephalexin.

Additionally, other pharmacokinetic parameters evaluated in our study were consistent with previous research where comparisons were possible. Parameters such as AUC, Cl/F, K_{01}, $T_{1/2a}$, $T_{1/2}$, and K_{10} showed similar trends and values compared to the respective studies. This consistency in pharmacokinetic parameters suggests similar absorption, distribution, and elimination patterns of cephalexin among these studies.

The therapeutic activity of antibiotics depends on their plasma concentrations, and changes in their pharmacokinetics may lead to variations in their clinical outcomes. Our results showed that none of the pharmacokinetic parameters calculated after the oral administration of cephalexin alone was statistically different from those calculated after animals were pretreated with omeprazole. Moreover, mean disposition curves were almost superimposable. Deppermann *et al.* (1989) investigated potential drug interactions with cephalexin.[8] In this case, the effects of antacids (aluminum magnesium hydroxide), antimuscarinic drugs (pirenzepine), and H2-blockers (ranitidine) on the bioavailability of various antibi-

otics, including cephalexin, were evaluated. It was found that antacids, pirenzepine, and ranitidine had no significant influence on the bioavailability of cephalexin, except for a significant reduction in the gastrointestinal absorption of doxycycline when coadministered with antacids. This resulted in subtherapeutic levels of doxycycline.

The study by Madaras-Kelly *et al.* also investigated the effect of acid-suppressing medications such as ranitidine and omeprazole on the pharmacokinetics of cephalexin.[16] It was found that coadministration of cephalexin with ranitidine or omeprazole resulted in relatively minor changes in pharmacokinetic parameters such as C_{max}, AUC, $T_{1/2}$, and Cl/F. However, unlike our results, a significant delay in time to reach T_{max} was observed when cephalexin was administered with ranitidine or omeprazole.

Prados *et al.* (2007) reported that the AUC and C_{max} of cephalexin were increased when the antimicrobial was administered in combination with metoclopramide.[21]

The presence of food may increase or decrease oral absorption; however, in a previous study, food did not affect cephalexin pharmacokinetics in dogs.[1] On the other hand, omeprazole did not modify the pharmacokinetic profile of levofloxacin in humans when both drugs were administered orally in combination.[22]

Specifically, our study showed no statistically significant differences in the pharmacokinetic parameters of cephalexin when administered with omeprazole. Although previous studies conducted in humans have shown that the pharmacokinetic interactions between cephalexin and omeprazole were not clinically significant, the widespread use of both drugs in various canine treatments, along with the pharmacokinetic differences of drugs across species, justified the conduct of this study. This aligns with the findings of previous research, indicating that omeprazole does not significantly alter the disposition of cephalexin in canines. In conclusion, due to the lack of interaction, both drugs can be effectively prescribed in combination without any alteration to their dosage regimens.

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