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The influence of propionic acid pre-treatment on the oral pharmacokinetics of marbofloxacin in broiler chickens

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ABSTRACT

Propionic acid, an organic acid commonly utilized as a feed additive in broiler chickens, serves as an acidifier. Its application can impact the oral pharmacokinetics of marbofloxacin, a promising antimicrobial drug exclusive to veterinary use, extensively employed in poultry farming. Consequently, this present investigation was conducted to examine the influence of pre-treatment with propionic acid (4 g/L in drinking water for 10 days) on the pharmacokinetics of marbofloxacin after its oral administration (5 mg/kg body weight) in broiler chickens. A single oral dose of marbofloxacin was administered to broiler chickens both without (Group-I) and with propionic acid pre-treatment (Group-II). Blood sampling at pre-determined time points was done for both groups, and plasma marbofloxacin concentrations were quantified using ultra high-performance liquid chromatography with UV detection. The pharmacokinetic parameters were determined using non-compartmental modeling through the 'PK solver 2.0' software. To compare the mean differences between the two groups, an independent sample t-test was employed. A statistically significant difference was observed in the marbofloxacin concentrations obtained from the two groups at the time points of 0.0833 hours (5 minutes) and 4 hours ($P \leq 0.01$). Group I displayed a higher maximum plasma drug concentration (C_{max}) of 2.43 µg/mL in comparison to Group II, which exhibited a C_{max} of 2.08 µg/mL. The mean elimination half-life ($t_{½\beta}$) of marbofloxacin was extended by 1.1 hours in Group-II compared to Group-I. However, none of the pharmacokinetic parameters exhibited statistically significant differences between the two groups, indicating that there is no necessity for dosage adjustment of marbofloxacin in broiler chicken flocks receiving propionic acid as a growth promoter.

Key words: broiler chickens; marbofloxacin; pharmacokinetics; propionic acid pretreatment

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Introduction

Chickens account for about 90 percent of global poultry meat production and are a major source of quality protein used to meet nutritional requirements in developed as well as developing nations. The global protein availability from poultry meat is projected to undergo a substantial increase of 16% by 2031, as predicted by the Food and Agriculture Organization (FAO) in 2022. Notably, organic acids, including propionic acid, have demonstrated their efficacy as viable alternatives to antibiotic growth promoters due to their growth promoting, health enhancing, and antibacterial effects (KWON and RICKE, 2003; ÇELIK et al., 2003; HAQUE et al., 2009; PALUPI et al., 2020). Hence they are commonly used as a feed additive. Propionic acid ($C_3H_6O_2$) is a naturally occurring short-chain mono-carboxylic acid. The growth-promoting effect of propionic acid is mediated through multiple mechanisms, including the reduction of the pathogenic burden via gut pH modulation, enhancement of digestibility, improvement of intestinal mucosa permeability, and the consequent elevation of nutrient absorption and utilization rates (HAQUE et al., 2009). In broiler chickens, the addition of buffered propionic acid (BPA) at a concentration of 3% has been observed to significantly reduce the growth of Salmonella as well as anaerobic microbes in the intestinal tract by lowering the pH from 7 to 5. This decrease in pH was found to have a maximum inhibitory effect on microbial growth (KWON and RICKE, 2003). Incorporating propionic acid into poultry feed at a concentration of up to 0.75% has been found to enhance the percentage of live weight in broiler chickens, without adversely affecting the condition of their internal organs or the length of the small intestine (PALUPI et al., 2020). In a study on turkey chicks, ÇELIK et al. (2003) observed that supplementing with propionic acid led to an improved feed conversion ratio (FCR), in comparison with the group that did not receive propionic acid supplementation.

The emergence of resistance to existing antimicrobial drugs in poultry medicine has created a gap in the arsenal against bacterial infections (ROTH et al., 2019). Therefore, there is a demand for newer antibacterial drugs that should be used cautiously for treating bacterial infections, including colibacillosis in broiler chickens. However, considering the issue of drug residues in chicken tissues, the new drug must ensure safety, have a short withdrawal period, and preferably be restricted to veterinary medicine. Marbofloxacin, a third-generation fluoroquinolone, exclusively used in veterinary practice, meets these requirements. Marbofloxacin is categorized as a Category B antibiotic by the Antimicrobial Advice ad hoc Expert Group (AMEG) of the European Medicines Agency (EMA). Category B antibiotics are classified as "Restricted" group antibiotics. They are recommended for use when there are no antibiotics in Categories C or D that could be clinically effective, and their use should be based on antimicrobial susceptibility testing whenever possible. Marbofloxacin is a broad-spectrum antimicrobial drug of the fluoroquinolone class which acts in a concentration-dependent manner, demonstrating a significant post-antibiotic effect (PAE). It effectively eliminates bacteria during both the static and growth phases of bacterial replication (SINGH et al., 2023).

The potential impact of propionic acid, as an acidifier and feed additive, on the pharmacokinetics of promising antimicrobial drugs such as marbofloxacin is currently a subject of investigation. We hypothesized that using propionic acid might lead to changes in the disposition kinetics of marbofloxacin, ultimately affecting its therapeutic efficacy, either by enhancement or reduction. However, there was no literature available regarding the pharmacokinetic behavior of marbofloxacin in broiler chickens that have been pre-treated with propionic acid, which could provide evidence to support this hypothesis. Therefore, the present study aimed to evaluate the influence of propionic acid pre-treatment on the pharmacokinetics of marbofloxacin in broiler chickens.

Materials and methods

Experimental birds and study design. The Institutional Animal Ethics Committee (IAEC) of the College of Veterinary Science and Animal Husbandry, Kamdhenu University, Sardarkrushi-

nagar, Gujarat, India, granted approval for the experiment under Protocol No.: VETCOLL/IAEC/2022/19/PROTOCOL-12. Sixteen, healthy male broiler chickens (*Gallus gallus domesticus*) of the Ven-cobb strain, aged between 3-6 weeks, and weighing more than 1 Kg, were procured from a registered commercial poultry farm, Palanpur, Gujarat, India. These chickens underwent a 10-day observation period before the commencement of the experiment to preclude any existing diseases. All sixteen birds were randomly divided into two groups, i.e. groups I and II, each group containing eight birds. In group I there was no pre-treatment with propionic acid, whereas in group II all the eight birds were pre-treated with propionic acid (4 g/L) once a day for 10 days in their drinking water. A single oral dose of marbofloxacin at 5 mg/kg body weight was administered to both group I (without any pre-treatment) and group II on the last day of the propionic acid pre-treatment. A 12-hour fasting period was implemented, during which the feed was withheld from the birds, before the oral administration of the drug for conducting the pharmacokinetic study.

Drug standard and chemicals. The standard marbofloxacin drug powder was sourced from Nexia Enterprise, Mumbai, India. The required HPLC-grade chemicals and buffers were purchased from S.D. Fine Chemicals Ltd., Mumbai, India. AR grade propionic acid, with 99.5% purity, was obtained from Sisco Research Laboratories Pvt. Ltd., Mumbai, India.

UHPLC analysis. Ultra high-performance liquid chromatography (UHPLC) apparatus (Dionex ultimate 3000®, Thermofisher, Germany), consisting of an ultraviolet (UV) detector, a gradient solvent delivery pump and a manual injector, were used in the present study. Chromatographic separation was performed using a reverse phase C-18 column (GL Science Inc., Japan, 25 cm × 4.6 mm ID, ODS-3V, 5 µm) at room temperature (28-32°C). The loop used for sample injection had 50 µl capacity. The data integration was performed using 'Chromeleon™ software version 6.8'. The chromatographic conditions used for UHPLC quantification of marbofloxacin were adopted from previous work by CARPENTER et al. (2006) and SINGH et al. (2023). The mobile phase comprised of a mixture of 0.01 M formic acid (pH 3.7) and acetonitrile in a ratio of 82:18. In isocratic run mode, the mobile phase flowed at a rate of 1.0 mL/minute, and the effluents were UV-monitored at a wavelength of 297 nm. For plasma drug extraction, liquid-liquid extraction of plasma samples (150 µl) was performed using an equal volume of 20% perchloric acid. After vertex and then centrifugation at 10,000 rpm for 10 minutes at 4°C, 50 µl of the extracted supernatant was manually injected into the UHPLC system. The UHPLC assay demonstrated both sensitivity and reproducibility. Linearity was observed over the concentration range of 0.0390 to 10 µg/mL, with a mean correlation coefficient (R^2) value of 0.9993. Precision and accuracy were assessed by analyzing three replicates at three different plasma standard concentrations: 0.10, 1.00, and 10.00 µg/mL. The intra-day and inter-day coefficients of variation for the three samples were satisfactory, with relative standard deviations (RSD) not more than 5%.

Pharmacokinetic analysis. Non-compartmental analysis (NCA) of the plasma concentration-time curves of individual birds was employed, using "PK Solver 2.0," an add-in program for Microsoft Excel, to determine the targeted pharmacokinetic (PK) parameters of marbofloxacin (ZHANG et al., 2010).

Statistical analysis. The PK parameters were presented as the mean ± standard error (SE). The independent sample t-test to compare the oral PK parameters of marbofloxacin derived for group I and group II broiler chickens was used at a significance level of $P \leq 0.05$ (statistically significant) and $P \leq 0.01$ (statistically highly significant) using IBM SPSS software version 20.

Results

The marbofloxacin peak in the UHPLC chromatogram appeared at an average retention time of 5.6 (±0.4) minutes. The figure depicts a comparison of the mean plasma marbofloxacin concentrations (n=8) after a single oral dose (5.0 mg/Kg body weight) between group I (broiler chickens without pre-treatment) and group II (broiler chickens

pre-treated with propionic acid at a concentration of 4 g/L in drinking water for 10 days). A significant difference was observed at 4 h ($P \leq 0.01$), when comparing the respective marbofloxacin concentrations in the two groups. However, apart from this time point, there were no statistically significant differences between group I and group II observed in the concentrations. The mean values of various pharmacokinetic parameters were also compared between group I and group II broiler chickens, and none of the pharmacokinetic parameters exhibited any statistically significant differences.

In group I and group II broiler chickens, the mean peak plasma concentrations of marbofloxacin were 2.43±0.16 and 2.08±0.09 µg/mL, respectively, after oral administration of marbofloxacin at a dose rate of 5.0 mg/kg body weight. These concentrations were achieved at T_{max} values of 1.75±0.16 and 2.00±0.00 hours, respectively. Furthermore, in group I and group II birds, the mean plasma concentrations of marbofloxacin remained at 0.10 and 0.13 µg/ml, respectively, up to 24 hours after drug administration (as shown in the Fig. 1).

Discussion

The pharmacokinetics of marbofloxacin have been studied previously in broiler chickens (ANADON et al., 2002; EL-KOMY et al., 2016; ATEF et al., 2017; PATEL et al., 2018; SINGH et al., 2023) but the present investigation focused on the impact of propionic acid pre-treatment on the pharmacokinetics of marbofloxacin in broiler chickens and addressed the significant gap in the scientific literature in this aspect. The outcome of the study has the potential to contribute to a better understanding of the possible interactions between propionic acid and marbofloxacin, thereby guiding poultry veterinarians in the development of effective treatment strategies in this context.

The oral dose of marbofloxacin (5.0 mg/kg body weight) used in the present study was selected on the basis of a review of the literature, and the findings of other experiments related to the dosage derivation of marbofloxacin in broiler chickens (PATEL et al., 2018; SINGH et al., 2023). The dose rate of propionic acid used (4 g/L drinking water) was in accordance with the recommendations of the European Food Safety Authority (EFSA, 2011). Throughout the en-

Table 1. Comparison of the pharmacokinetic parameters of marbofloxacin following a single dose oral administration (5.0 mg/kg b.w.) in group I and II broiler chickens

Pharmacokinetic parameters	Unit	Values of PK parameters (Mean ± S.E.)	
		Group I (n=8)	Group II (n=8)
C_{max}	µg/ml	2.43 ± 0.16	2.08 ± 0.09
T_{max}	h	1.75 ± 0.16	2.00 ± 0.00
b	Per h	0.12 ± 0.01	0.10 ± 0.005
$t_{1/2\beta}$	h	5.84 ± 0.43	6.94 ± 0.35
AUC	µg·h/ml	15.79 ± 1.47	16.37 ± 1.08
AUMC	µg·h^2/ml	111.76 ± 12.50	150.35 ± 10.49
MRT	h	7.07 ± 0.33	9.19 ± 0.28
$V_{d(area)}/F$	L/kg	2.78 ± 0.29	3.17 ± 0.28
Cl_B/F	L/h/kg	0.33 ± 0.03	0.31 ± 0.02

[#] No pharmacokinetic parameter showed any statistical difference at $P \leq 0.05$ or $P \leq 0.01$

Abbreviations used: C_{max}: Observed peak plasma concentration; T_{max}: Time at which C_{max} was observed; β: Elimination rate constant; $t_{1/2\beta}$: Elimination half-life; $AUC_{0-\infty}$: Area under the curve; AUMC: Area under the first moment of the plasma drug concentration; MRT: Mean Resident Time; $V_{d(area)}/F$: Apparent volume of distribution (scaled by bioavailability); Cl_B/F: Total body clearance (scaled by bioavailability)

Table 2. Values of AUC/MIC and C_{max}/MIC calculated for marbofloxacin (5.0 mg/kg body weight) following oral administration in groups I and II broiler chickens

Sr. No.	Group I (n=8)				Group II (n=8)			
	AUC (µg.h/mL)	AUC/ MIC	C_{max} (µg/mL)	C_{max}/ MIC	AUC (µg.h/mL)	AUC/ MIC	C_{max} (µg/mL)	C_{max}/ MIC
B1	14.78	118.24	1.97	15.76	16.14	129.12	2.15	17.20
B2	24.57	196.56	3.10	24.80	21.74	173.92	2.49	19.92
B3	17.89	143.12	2.98	23.84	18.12	144.96	2.08	16.64
B4	12.99	103.92	2.46	19.68	16.44	131.52	2.07	16.56
B5	17.64	141.12	2.63	21.04	18.52	148.16	2.36	18.88
B6	12.14	97.12	1.89	15.12	12.87	102.96	1.80	14.40
B7	12.99	103.92	2.15	17.20	13.12	104.96	1.67	13.36
B8	13.34	106.72	2.28	18.24	14.02	112.16	2.01	16.08
Mean	15.79	126.34	2.43	19.46	16.37	130.97	2.08	16.63

(Reference MIC: 0.125 µg/ml)

Abbreviations used: AUC: Area under the curve; MIC: Minimum Inhibitory Concentration; C_{max}: Observed peak plasma concentration; B1 to B8 represents the bird numbers of the respective groups

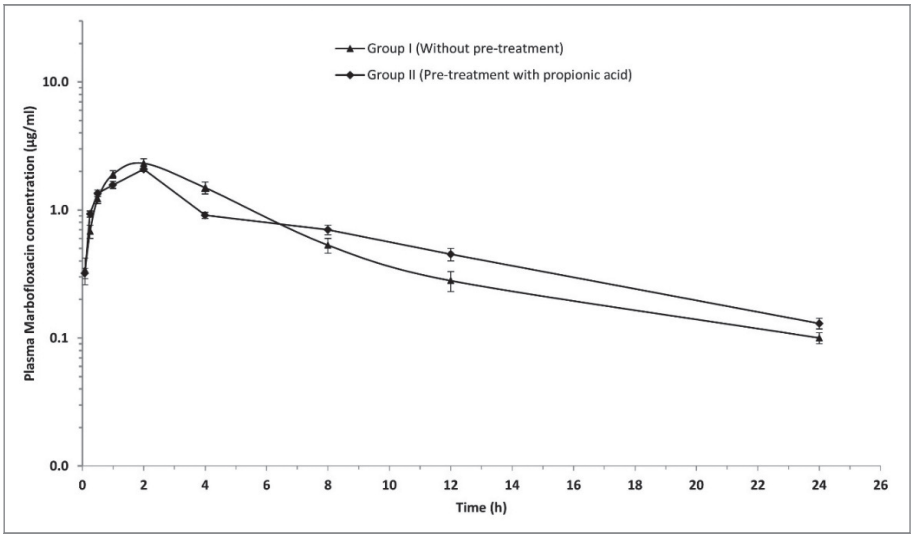

Fig. 1. Comparison of semi-logarithmic plot of plasma marbofloxacin concentration versus time in group I and II broiler chickens (n=8)

tire experimental period, the physical demeanor of all the treated broiler chickens remained normal; no atypical clinical indications or symptoms of adverse medication reactions were seen. There was no abnormality observed in their appetite, water or feed intake, feces, or alertness. The growth rates of all the treated birds were normal in terms of body weight gain. Other studies had similar findings (EL-KOMY et al., 2016; TUKRA et al., 2024), indicating that marbofloxacin is safe for broiler chickens.

In both groups I and II, no plasma drug concentrations were detectable in any of the plasma

samples collected beyond 24 hours, specifically at 36 and 48 hours. A comparison of mean marbofloxacin concentrations in group I and group II broiler chickens at all sample collection time-points up to 24 hours only showed a statistically significant difference at 4 hours (1.49 µg/ml and 0.91 µg/ml, respectively). However, when analysed, this difference did not translate into a statistically significant difference in any of the pharmacokinetic parameters between the two groups (Table 1). The assumption was that propionic acid pretreatment, as an acidifier, could potentially impact the gastrointestinal pH, and consequently influence the pharmacokinetic behavior of marbofloxacin. However, previous reports (IZAT et al., 1990; TAWFEEQ and AL-MASHHDANI, 2020) have indicated that propionic acid does not have any long-term effect on the pH of the gastrointestinal tract in broiler chickens. This could be a reason why no statistically significant effect was observed after propionic acid pre-treatment on the pharmacokinetics of marbofloxacin in this study.

The peak plasma drug concentration (C_{max}) is of significant importance for concentration-dependent antimicrobial drugs such as marbofloxacin. Consequently, monitoring and optimizing C_{max} levels plays a crucial role when using these drugs, in order to ensure therapeutic success while minimizing the risk of treatment failure and the emergence of resistance. Following oral administration of marbofloxacin at a dose rate of 5.0 mg/kg body weight, the mean C_{max} values of marbofloxacin in group I and group II broiler chickens were 2.43±0.16 and 2.08±0.09 µg/ml, respectively. These concentrations were achieved at a T_{max} of 1.75±0.16 and 2.00±0.00 hours, respectively. Thus, there was a decrease of 0.35 µg/ml in C_{max} in group II (propionic acid treated birds) compared to group I broiler chickens, along with an average delay of 0.25 hours in achieving the peak concentration. The reduction in the average C_{max} value observed in group II as compared to group I was not statistically but numerically significant (Table 1). In order to optimize therapeutic outcomes and mitigate the development of resistance, achieving a higher and faster C_{max} of marbofloxacin, a concentration-dependent antibacterial drug, is imperative. The attainment of a C_{max} /MIC ratio above 10, a pivotal pharmacodynamic-pharmacokinetic index, is crucial for eliciting bactericidal effects. In the present investigation, although C_{max} levels were lower in group II birds, both groups I and II exhibited C_{max}/MIC values surpassing 10 (Table 2). This suggests that the administration of marbofloxacin in propionic acid-pretreated birds could result in optimal bactericidal activity, thereby mitigating the emergence of resistance.

The mean elimination half-life was determined to be 5.84 and 6.94 hours, for group I and group II birds, respectively. A shorter $t_{1/2\beta}$ value of 4.62 hours was observed in broiler chickens following the oral administration of marbofloxacin at the same dose (PATEL et al., 2018), whereas in other avian species, such as Japanese quails, a similar elimination half-life ($t_{1/2\beta}$) of 6.19 hours was reported by ABOU-BAKR and ABDELAZEM (2015). In dogs, marbofloxacin showed longer half-lives of 9.07 hours (HEINEN, 2002) and 22.14 hours (LEI et al., 2018). The increase in the elimination half-life of marbofloxacin in mammalian species such as dogs could be attributed to the continued absorption of the drug from the site of oral administration, even during the elimination phase (LEI et al., 2018).

The marbofloxacin drug molecules stayed for a substantial time of period in the bodies of the broiler chickens belonging to both groups I and II in the present study, as indicated by the high mean residence time (MRT) (7.07 and 9.19 h, respectively). A longer mean residence time (MRT) indicates that the drug remains in the body for an extended duration, resulting in sustained exposure to therapeutic concentrations. Prolonged drug exposure is associated with enhanced bacterial killing and decreased emergence of drug resistance. The extended presence of the drug increases the likelihood of complete eradication of the bacteria, and reduces the potential for the survival and proliferation of resistant strains (DRLICA and ZHAO, 2007).

After oral administration of marbofloxacin, the average apparent volume of distribution ($V_{d(area)}$/F) was 2.78 L/kg in group I birds, and 3.17 L/kg in group II birds. High V_d values after oral administration reflect the extensive tissue penetration of the drug, which is a basic requirement for treating respiratory infections in poultry, where the adequate pulmonary tissue penetration of the drug is

desired. In our study, the values of mean total body clearance (Cl_B/F) observed were similar in both the groups, measuring 0.33 and 0.31 L/h/kg. These values were higher than the previously reported range of 0.18-0.20 L/h/kg in broiler chickens (ANADON et al., 2002; PATEL et al., 2018). Having a moderate to high clearance rate is desirable for drugs intended for use in food-producing animals or birds, as it indicates their efficient elimination from the body. The findings from this study highlight the favorable clearance rates of marbofloxacin in broilers, in order to avoid the persistence of drug residue in edible tissues.

It is noteworthy that the propionic acid pre-treated group exhibited plasma concentrations consistently above the minimum inhibitory concentration (MIC) of 0.125 µg/ml, up to 24 h. This MIC value effectively targets a wide range of susceptible Gram-negative bacterial isolates of veterinary species (SPRENG et al., 1995; HARITOVA et al., 2006; KROEMER et al., 2012). Concentration-dependent antimicrobial drugs, such as fluoroquinolones, rely on the AUC/MIC ratio as a predictor of efficacy. A ratio greater than 100-125 h is associated with a clinical cure rate exceeding 80% for Gram-negative bacteria. Another predictor of efficacy for concentration-dependent drugs is the C_{max}/MIC ratio, with a value of ≥10 indicating successful clinical outcomes, which are also beneficial in reducing the risk of bacterial resistance (NIELSEN and FRIBERG, 2013). Thus, the AUC/MIC and the C_{max}/MIC ratio are the two important pharmacokinetic-pharmacodynamic (PK-PD) indices used to predict the efficacy of marbofloxacin. The efficacy prediction for the dosage used in the study was conducted for groups I and II on the basis of the PK-PD indices presented in Table 2. The MIC value for PK-PD integration, used as 0.125 µg/mL, would cover common gram-negative pathogenic bacteria in poultry species (HARITOVA et al., 2006). Table 2 presents the calculated mean values of the AUC/MIC ratio, which were 126.34 and 130.97, and the C_{max}/MIC ratio, which were 19.46 and 16.63, for groups I and II, respectively. These values indicate that an oral dose of marbofloxacin at 5 mg/kg body weight would be effective in treating bacterial infections in broiler chickens caused by susceptible pathogens with a MIC below 0.125 µg/mL, as the AUC/MIC ratio exceeds 120 and the C_{max}/MIC ratio exceeds ten. It is also evident that the PK-PD indices for both groups of oral treatment exhibit identical values, indicating that there is no requirement to modify the dosage regimen of marbofloxacin for the treatment of susceptible bacterial infections in broiler chickens when using propionic acid as a growth promoter at the recommended level.

From the results of present investigation, we have ascertained that pre-treatment with propionic acid indeed imparts an arithmetic influence on the pharmacokinetics of marbofloxacin in broiler chickens. Nevertheless, the disparities noted in our observations did not attain a level of significance that would necessitate any adjustment in the marbofloxacin dosage for chickens administered propionic acid as a growth promoter. As a result, poultry veterinarian and farmers can confidently continue to use propionic acid as a feed additive, with the assurance that it will not impede the efficacy of marbofloxacin.

Etichs approval

The Institutional Animal Ethics Committee (IAEC) of the College of Veterinary Science and Animal Husbandry, Kamdhenu University, Sardarkrushinagar, Gujarat, India, granted approval for the experiment under Protocol No.: VETCOLL/ IAEC/ 2022/19/PROTOCOL-12.

Declaration of competing interest

No potential conflicting interest was reported by the authors

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SAŽETAK

Propionska kiselina, organska kiselina koja se obično upotrebljava kao dodatak obroku za tovne piliće, služi kao zakiseljivač hrane. Njena upotreba može utjecati na farmakokinetiku oralno primijenjenog marbofloksacina, obećavajućeg antimikrobnog lijeka isključivo u veterinarskoj medicini, koji ima široku primjenu u peradarstvu. U radu se istražuje utjecaj prethodnog liječenja propionskom kiselinom (4 g/L u vodi za piće tijekom 10 dana) na farmakokinetiku marbofloksacina nakon njegove oralne primjene (5 mg/kg tjelesne mase) u tovnih pilića. Jednokratna peroralna doza marbofloksacina primijenjena je u tovnih pilića bez prethodne terapije (skupina I) i u onih kojima je prethodno davana propionska kiselina (skupina II). U objema je skupinama provedeno uzorkovanje krvi u određenim vremenskim točkama, a koncentracije marbofloksacina u plazmi kvantificirane su primjenom tekućinske kromatografije ultravisoke učinkovitosti s UV detekcijom. Farmakokinetički pokazatelji određeni su primjenom nesegmentnog modeliranja pomoću računalnog programa PK solver 2.0. Kako bi se analizirale razlike između srednjih vrijednosti skupine I i skupine II, primjenjen je t-test za nezavisne uzorke. Uočena je statistički znakovita razlika u koncentracijama marbofloksacina kvantificiranog u vremenskim točkama od 0,0833 sati (5 minuta) i 4 sata ($P \leq 0,01$). U skupini I uočena je veća maksimalna koncentracija lijeka u plazmi (C_{max}), od 2,43 µg/mL, u uporedbi sa skupinom II, u kojoj je zapažena koncentracija (C_{max}) od 2,08 µg/mL. Srednja vrijednost poluvijeka eliminacije ($t½\beta$) marbofloksacina produljena je za 1,1 sat u skupini II u usporedbi sa skupinom I. Ni jedan farmakokinetički pokazatelj, međutim, nije pokazao statistički znakovite razlike između dviju skupina, što upućuje na to da nema potrebe za prilagodbom doze marbofloksacina u tovnih pilića koji su dobivali propionsku kiselinu kao pospješivač rasta.

Ključne riječi: tovni pilići; marbofloksacin; farmakokinetika; prethodno liječenje propionskom kiselinom