

## The effect of ketoprofen on the plasma concentration and pharmacokinetic parameters of ciprofloxacin in chickens

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### ABSTRACT

Ciprofloxacin (CFX) and ketoprofen (KPN) are used widely in combination in veterinary interventions for bacterial infections, so in this study the effect of KPN was studied on the efficacy of CFX, by measuring its plasma concentration and pharmacokinetic parameters in 7-10 day-old chickens. The analgesic median effective dose ( $ED_{50}$ ) of KPN was determined to be 1.62 mg/kg, IM, in the chickens. The preferable analgesic dose of KPN to be used with CFX was 4 mg/kg, IM, which differs significantly from KPN 2 mg/kg, IM. The CFX plasma concentrations alone (8 mg/kg, IM) measured at different times (0.5, 1, 2, 4 and 24 hours) were 3.31, 3.60, 3.21, 2.70 and 0.17  $\mu\text{g/mL}$  while its concentration was elevated by 53, 54, 90, 107 and 418 % when coadministered with KPN (4 mg/kg, IM) to 5.05, 5.53, 6.10, 5.59 and 0.88  $\mu\text{g/mL}$  in the chickens, respectively. CFX pharmacokinetic parameters, such as the area under the curve (AUC), the area under the moment curve (AUMC), mean residence time (MRT), half-life ( $t_{1/2p}$ ),  $T_{\max}$ , and  $C_{\max}$  increased when KPN was coadministered with CFX by 129, 289, 70, 49, 100 and 69 %, whereas the elimination rate constant ( $K_{el}$ ), the volume of distribution at steady state ( $V_{ss}$ ) and clearance (Cl) decreased by 36, 34 and 58 %, respectively. It was concluded that coadministration of KPN alters the plasma concentration and the pharmacokinetic parameters of CFX, suggesting that the CFX dose can be reduced when used with KPN to achieve the desired concentration of CFX in the plasma, as an antibacterial for treatment of infected animals.

**Key words:** chickens; ciprofloxacin; ketoprofen; pharmacokinetics; plasma concentration

### Introduction

CFX is a fluoroquinolones antibiotic used to treat many bacterial infections, especially of the respiratory, renal, and gastrointestinal systems in chickens, other animal species, and humans (HORI et al., 2003; KHAN et al., 2015; IVANOVA et al., 2017). It is considered to be a bactericidal antibiotic

that inhibits DNA replication by suppressing bacterial DNA topoisomerase and DNA-gyrase, which is effective against gram-negative bacteria and some gram-positive bacteria (SAMAREI 2014; FIEF et al., 2019). CFX as a metabolite of enrofloxacin antibiotics, its pharmacokinetic profile

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in chickens differs from enrofloxacin approximately by half (OVANDO et al., 1999; GOUVEA et al., 2015; HOOPER and JACOBY, 2016). CFX leads to the improvement of veterinary treatment through therapeutic and prophylactic use, causing chickens to attain efficient production enhancement (ATTA and SHARIF, 1997; BILLAH et al. 2014). KPN, a nonsteroidal anti-inflammatory drug (NSAID), produces anti-inflammatory, antipyretic, and analgesic actions through its mode of action by inhibiting the cyclooxygenase (COX) enzyme, thus preventing prostaglandin (a chemical mediator responsible for producing the inflammatory process, fever and nociception) biosynthesis (MEEK et al., 2010; ZARGHI and ARFAEI, 2011; WALLER and SAMPSON, 2018). The usual concurrent use of medications composed of KPN and CFX in veterinary medicine has tremendous benefits also through the elimination of the inflammatory process (LOCKWOOD et al., 2003; DAUNDKAR et al., 2015). Moreover, the inflammatory state is usually accompanied by the presence of fever and pain, and it contributes to reducing or eliminating these and the use of KPN (a powerful protein-bound > 99%) (LASCELLES et al., 2007; NAIDOO et al., 2010) may lead to drug interaction and a fall or increase in the CFX concentration in the plasma and change its pharmacokinetic profile, thus leading to a decrease or increase in the therapeutic efficacy of CFX. This causes therapeutic issues in chickens, as well as an increase in the risk of CFX toxicity.

Thus, the aim of this study was to examine the possible changes in CFX plasma concentration and its pharmacokinetic parameters (which is a crucial factor which directly influences CFX efficacy) following intramuscular (IM) administration of KPN in chickens because these two drugs are widely used for management of bacterial infection in poultry.

## Materials and methods

*Birds and drug administration.* Seven to ten-day old broiler chickens of both genders were used in all the trials (19 of them in analgesic experiments whereas the other 50 chickens were used in the pharmacokinetic study) with regular bodyweight (70-115 g). They were kept at 32-35 °C, with

constant light, with litter derived from shreds of wood, and water and feed provided freely. CFX (pure powder obtained from General Company for Drugs and Medical Supplies, Samarra, Iraq) and KPN (10%, Razaq Laboratories, Iran) were diluted in a physiological saline solution (0.9% NaCl) to obtain the desired dose for each drug to be injected at 5 mL/kg, IM separately into the pectoral muscle of the chickens.

*Ethics.* This research and the use of experimental birds was authenticated by monitoring by the scientific members of the ethics committee of the Department of Physiology, Biochemistry and Pharmacology, Veterinary Medicine College, Mosul University.

*Analgesic ED<sub>50</sub> of KPN in the chickens.* The analgesic ED<sub>50</sub> value of KPN was estimated according to the up-and-down routine designed by (DIXON, 1980) as the first step for the use of an accurate dose of KPN in experiments on chickens. The first dose of KPN was at 4 mg/kg, IM depends solely on an introductory study. The chickens were assessed independently before and 30 minutes after the KPN injection using an electro-stimulator device (Harvard apparatus, USA) (the presence of distress indicating perception of pain in the chickens) (MOUSA, 2019; 2020; MOUSA and MOHAMMAD, 2012; MOUSA and AL-ZUBAIDY, 2019). At that point, the dosage of KPN was reduced or raised by 1 mg/kg according to whether there was an excess or lack of analgesia (the decrease or increase in dosage was adjusted so it did not exceed 30% of the first dose of KPN used in this experiment for accurate results).

*The analgesic effect of two doses of KPN in the chickens.* To select the preferable doses in the next experiment, two doses of KPN 2 and 4 mg/kg, IM (which approximately resembles the ED<sub>50</sub> and ED<sub>100</sub> of KPN, respectively, determined by the previous experiment) were used to compare their analgesic efficiency. The pain-threshold voltages were documented pre- and post-injection (after 30 minutes) of KPN for 6 chickens per dosing group. The delta voltage and the analgesic percentages for each dosing group were also recorded.

*Drugs administration and the process of plasma sampling for pharmacokinetic analysis.*

One group was treated with CFX alone at 8 mg/kg, IM (ANADON et al., 2001) while the other group was injected with CFX (8 mg/kg, IM) and KPN (4 mg/kg, IM). Blood samples (About 5 mL) were collected from the jugular vein from each chicken separately (5 chickens for each measuring time after 0.5, 1, 2, 4, and 24 hours of administration) for both the groups that received CFX alone or CFX plus KPN. Then, plasma was obtained by adding heparin (B. Braun Medical Inc, USA) (used as 1:10 v/v) to the blood samples with centrifugation (Chalice, UK) 3000 rpm for 15 minutes. Finally, the plasma samples were frozen at -18 °C for 72 hours until analysis using spectrophotometric apparatus (Lovibond, Germany) supplied with an ultra-violet detector.

*Determination of CFX plasma concentration in the chickens and its alteration following KPN administration.*

*Preparation of CFX standards.* The standards of CFX consisted of 1.25, 2.5, 5, 10, 20, and 40 µg/mL (ANADON et al., 2001; KHAN and KHAN, 2008; NATRAJ et al., 2013) formed by dilution of the pure ciprofloxacin powder in distilled water, and they were vortexed for 5 minutes then centrifuged at 3000 rpm for 15 minutes. The solution was then filtered using filter paper, and the net solution was finally analyzed in three replicates using a spectrophotometer device at a wavelength of 335 nm (NATRAJ et al., 2013). The following equation for the simple linear regression of the CFX standards was used to estimate CFX concentration in the plasma samples, calculated for both groups of chickens (consisting of CFX with and without KPN administration).

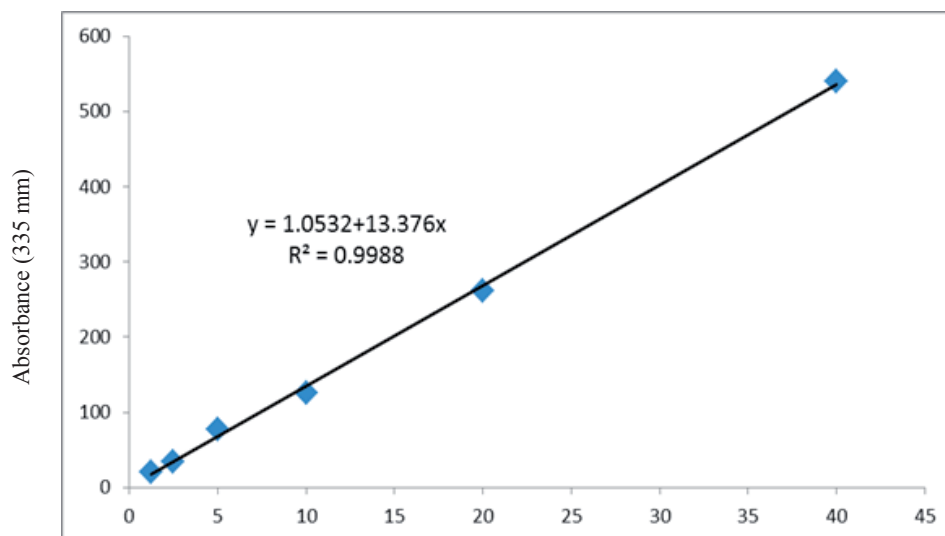


Fig. 1. Simple linear regression for CFX standards (1.25, 2.5, 5, 10, 20 and 40 µg/mL) and their absorbance (335 nm) with LOD and LOQ are 0.45 and 1.36 µg/mL, respectively

$y = a + b x$  (simple linear regression equation of CFX standards with  $R^2 = 0.9988$ )

where:

$y$  = absorbance of plasma samples (335 nm);  
 $a$  = intercept (1.0532);  $b$  = slope (13.376) and  
 $x$  = concentration of CFX (anonymous) in the plasma specimen.

The limit of detection (LOD) and the limit of quantitation (LOQ) of the ciprofloxacin standards were determined by the following formula (PANDEY et al., 2012):

$$\text{LOD} = 3.3 \sigma / b = 0.45 \mu\text{g/mL}$$

$$\text{LOQ} = 10 \sigma / b = 1.36 \mu\text{g/mL}$$

Where  $\sigma$  is the standard deviation.

*Extraction of CFX from the plasma samples.* A simple, validated and accurate method for extraction of plasma samples was applied according to KHAN and KHAN (2008). The technique consisted of adding 0.5 mL of acetonitrile to 0.5 mL of plasma specimen (1:1 v/v), then the mixture was transferred to a tube and vortexed for five minutes. After that, the mixture was centrifuged (3000 rpm for 15 minutes) and the resultant aliquot solution was filtered through filter paper. The net resultant specimen was examined by the spectrophotometer apparatus (using UV-chromatographic detection at 335 nm) (NATRAJ et al., 2013).

*Determination of CFX pharmacokinetic parameters in the chickens and their alteration with KPN administration.* The non-compartmental model of pharmacokinetic analysis was applied to reveal the pharmacokinetic parameters of CFX alone or its combination with KPN by using a PKSolver program compact as an add-in with the Excel program (ZHANG et al., 2010), which involved AUC ( $\mu\text{g}\cdot\text{h} / \text{mL}$ ), AUMC ( $\mu\text{g}\cdot\text{h}^2 / \text{mL}$ ), MRT (AUMC / AUC)(h),  $t_{1/2\beta}$  (h),  $T_{\text{max}}$  (h),  $C_{\text{max}}$

( $\mu\text{g}$ ),  $K_{\text{el}}$  ( $0.693 / t_{1/2\beta}$ )( $\text{h}^{-1}$ ),  $V_{\text{ss}}$  [dose.AUMC / (AUC)<sup>2</sup>](L / kg) and Cl (dose / AUC)(L / h / kg). Any increase or reduction in the percentages of these pharmacokinetic data was calculated for both dosage groups of chickens treated with CFX with or without KPN.

*Statistics.* The analysis of parametric statistics was conducted using paired and unpaired student T-tests to relate the means of the two groups and the non-parametric data were analyzed using the Fisher (percentages) and Mann Whitney U-tests (delta voltages) (KVAM and VIDAKOVIC, 2007; KATZ, 2011; PETRIE and WATSON, 2013). The level of significance was set at  $P < 0.05$ .

### Results

*The analgesic ED<sub>50</sub> value of KPN in chickens.* The analgesic ED<sub>50</sub> of KPN necessary to cause analgesia in 50% of the chickens was found to be 1.62 mg/kg, IM, which is stated here for the first time in chicken, and Table 1 shows the results obtained from this trial.

Table 1. Analgesic ED<sub>50</sub> of KPN in the chickens

Parameter	Result
ED <sub>50</sub> value*	1.62 mg/kg, IM
The range of the doses used	1-4 mg/kg
Initial dose	4 mg/kg
Last dose (x)	2 mg/kg
Table value (k) (Dixon, 1980)	-0.380
± Dosage (d)	1 mg/kg
Quantity of chickens	7 (XXXOXXX)

\* ED<sub>50</sub> value= x + (k × d)

X= result (antinociception), O= no result (nociception)

Volts recorded preinjection and after 30 minutes of KPN injection

*Analgesic effect of two doses of KPN in chickens.* There are significant differences between the groups of chickens treated with KPN at 4 mg/kg, IM (ED<sub>100</sub> of KPN) and KPN at 2 mg/kg, IM

(ED<sub>50</sub> of KPN) in terms of the percentages of analgesic efficacy, post-injection analgesia and the delta voltage estimated, as shown in Table 2.

Table 2. Analgesic effect of two doses of KPN in the chickens

KPN mg/kg, IM	Analgesic efficacy %	Voltage (volt) preinjection	Voltage (volt) postinjection	Delta Voltage
2	50 (3/6)	12.17 ± 0.31	13.33 ± 0.67	1.17 ± 0.54
4	100* (6/6)	12.00 ± 0.47	16.67 ± 0.71* <sup>a</sup>	4.67 ± 0.76*

Result denoted to Mean ± Std.Error for 6 chickens per dosing group

Voltages recorded preinjection and 30 minutes after KPN injection

\* significantly different from KPN group (2 mg/kg, IM) (P < 0.05)

<sup>a</sup> differ significantly from preinjection of the similar group (P < 0.05)

Plasma concentrations of CFX alone or in combination with KPN in the chickens at different times. Table 3 and Fig. 2 show a significant elevation in the CFX plasma concentration when administered with KPN in comparison to the group treated with CFX alone. The plasma concentrations of CFX alone (8 mg/kg, IM) measured at different

times (0.5, 1, 2, 4 and 24 hours) were 3.31, 3.60, 3.21, 2.70 and 0.17 µg/mL, respectively, while the plasma concentrations after CFX and KPN administration (8 and 4 mg/kg, IM respectively) was greater than before by 53, 54, 90, 107 and 818 %, to become 5.05, 5.53, 6.10, 5.59 and 0.88 µg/mL, respectively.

Table 3. Plasma concentrations of CFX with or without KPN in the chickens at different measuring times

Measuring time (Hour)	Groups		Effect of KPN on plasma concentration of CFX (%) <sup>+</sup>
	CFX alone	CFX plus KPN	
0.5	3.31 ± 0.16	5.05 ± 0.22*	3
1	3.60 ± 0.15	5.53 ± 0.13*	54
2	3.21 ± 0.14	6.10 ± 0.18*	90
4	2.70 ± 0.32	5.59 ± 0.28*	107
24	0.17 ± 0.04	0.88 ± 0.13*	418

Data denoted to Mean ± Std. Error in µg/ml for 5 chickens per measuring time

\* significantly different from the CFX alone group (P < 0.05)

CFX was injected at 8 mg/kg, IM alone or with KPN at 4 mg/kg, IM

<sup>+</sup> % of the effect of KPN on plasma concentration of CFX = (CFX plus KPN - CFX alone) / CFX alone × 100

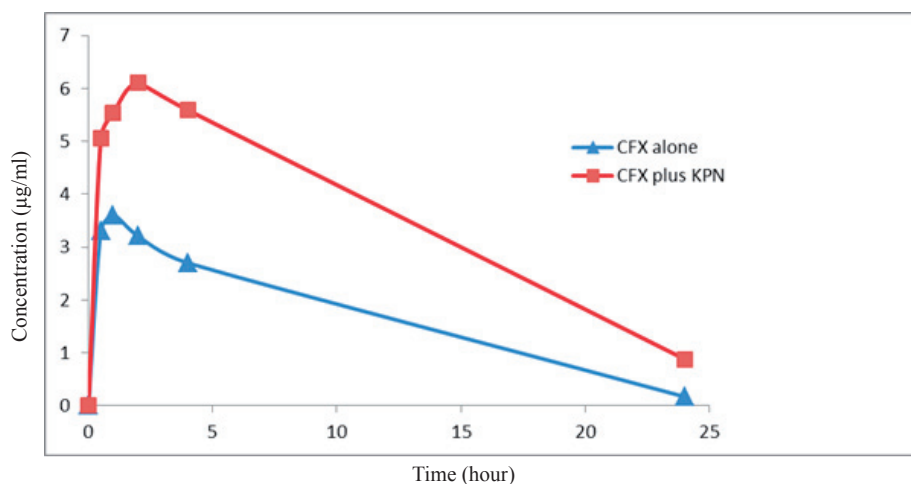


Fig. 2. Plasma concentrations of CFX with and without KPN in the chickens at different measuring times

*Pharmacokinetic parameters of CFX with or without KPN in the chickens.* Injection of CFX with or without KPN revealed the pharmacokinetic profile as illustrated in Table 4.

Table 4. Pharmacokinetic parameters of CFX alone or in combination with KPN in the chickens

Pharmacokinetic data	Groups		Effect of KPN (%)*
	CFX alone	CFX plus KPN	
AUC ( $\mu\text{g}\cdot\text{h}/\text{mL}$ )	41.82	95.91	(+) 129
AUMC ( $\mu\text{g}\cdot\text{h}^2/\text{mL}$ )	212.14	825.17	(+) 289
MRT = AUMC/AUC (h)	5.07	8.60	(+) 70
$t_{1/2\beta} = 0.693 \times V_{ss}/\text{CL}$ (h)	5.17	7.72	(+) 49
$T_{\max}$ (h)	1	2	(+) 100
$C_{\max}$ ( $\mu\text{g}$ )	3.60	6.10	(+) 69
$K_{el} = 0.693/t_{1/2\beta}$ ( $\text{h}^{-1}$ )	0.14	0.09	(-) 36
$V_{ss} = \text{dose}\cdot\text{AUMC}/(\text{AUC})^2$ (L/kg)	1.41	0.93	(-) 34
Cl = dose/AUC (L/h/kg)	0.19	0.08	(-) 58

CFX was injected at 8 mg/kg, IM alone or with KPN at 4 mg/kg, IM

Pharmacokinetic data obtained using a non-compartmental model estimated by using the PKSolver program as an add-in in Excel program

\* % of the effect of KPN on plasma concentrations of CFX= CFX plus KPN - CFX alone / CFX alone  $\times$  100

The values of AUC, AUMC, MRT,  $t_{1/2\beta}$ ,  $T_{\max}$ , and  $C_{\max}$  in the chickens that were given CFX with KPN increased to become 95.91, 825.17, 8.60, 7.72, 2, and 6.10, by percentages of 129, 289, 70, 49, 100, and 69 %, respectively. The other pharmacokinetic parameters, including  $K_{el}$ ,  $V_{ss}$ , and Cl, decreased in percentages to become 0.09, 0.93, and 0.08, by 36, 34, and 58 %, respectively, in comparison to the group that received CFX alone (Table 4).

## Discussion

The aim of this study was to examine possible changes in CFX plasma concentrations and its pharmacokinetic parameters (which is a crucial factor that directly influence CFX efficacy) when administered with KPN to chickens, because these two drugs are widely used for management of bacterial infections in poultry and other animal species (KHAN et al., 2015; IVANOVA et al., 2017). CFX is mostly used to manage respiratory, renal and gastrointestinal bacterial infections in chickens and other animal species (HORI et al., 2003; KHAN et al., 2015; IVANOVA et al., 2017). It also leads to an improvement in veterinary

treatment through its therapeutic and prophylactic use by leading to improvements in production efficiency in chickens (ATTA and SHARIF, 1997; BILLAH et al. 2014). CFX is given orally or parenterally for clinical and research purposes to treat broiler chickens (DEVREESE et al., 2014). The advantage of parenteral application over the oral route in chickens is that it decreases the wide range of deleterious effects of CFX on the microflora present in the gastrointestinal lumen, and reduces the development of bacterial resistance (DEVREESE et al., 2014). The usual concurrent use of medications composed of KPN and CFX in veterinary medicine has tremendous benefits because of their synergistic effect causing the elimination of the inflammatory process, besides relieving the fever and pain caused by bacterial infection (LOCKWOOD et al., 2003; LASCELLES et al., 2007; NAIDOO et al., 2010; DAUNDKAR et al., 2015). The optimal therapeutic dose of CFX was used here in this trial according to a previous study (ANADON et al., 2001), while the dose of KPN was given according to the first and second experiments described above (due to the lack of

relevant studies) which resembles the dose of KPN necessary to produce its therapeutic (analgesic) effect in all tested chickens. Here, we used a precise, efficient, and valuable method for estimation of CFX concentration in specimens with LOD (0.45 µg/ml) and LOQ (1.36 µg/mL) that was discussed and linked to previous literature (PANDEY et al., 2012). The results of this study showed that the plasma concentration of CFX increased when it was administered with KPN in the chickens, which may be due to the ability of KPN to bound readily to plasma proteins (> 99%) (LASCELLES et al., 2007; NAIDOO et al., 2010). This increases the binding sites available on the plasma protein for CFX binding and thus increasing the amount of free drug concentrations of CFX in the plasma, with a concurrent increase in its concentration in the plasma. This kind of pharmacokinetic interaction between KPN and CFX can cause changes in the pharmacokinetic profile of CFX, as shown in this study, thus leading to an increase in the therapeutic efficacy of CFX (GRILL and MAGANTI, 2011). Other relevant studies suggest that KPN increases the plasma concentration and the therapeutic efficacy of cefepime antibacterial action in sheep (PATEL et al., 2012), which is in accordance with what was found in this study. As estimated in the pharmacokinetic profile, KPN decreases the excretion and the metabolism of CFX, which prolongs the persistence of CFX in the body, by increasing both the elimination half-life and the mean residence time besides decreasing the clearance and elimination rate constant of CFX (HOSSAIN et al., 2016). These are all reasons that indicate the effects of this combination that may enhance its therapeutic efficacy, but perhaps also its adverse effects especially if it is given continuously for the appropriate therapeutic period. Another effect of KPN, resulting from the fact that it diminishes the apparent volume of distribution (GROVER and BENET, 2009) of CFX over estimated time intervals, is indicated by the alterations in the quantity of CFX available at tissue sites which are necessary for its bactericidal action, since low concentrations (below the minimum inhibitory concentration-MIC) at the tissue sites may affect its bacterial resistance and tolerance.

The results of this trial concluded that administration of KPN modifies the plasma concentration and pharmacokinetic parameters of CFX, suggesting that the CFX dose can be reduced when used with KPN to achieve the desired concentration of CFX in the plasma as an antibacterial for treatment of infected animals. Other future studies are necessary to show this relevant interaction in other animals.

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**MOUSA, Y. J., S. M. AMIN, D. H. ABDULRAZZAQ, F. K. IBRAHIM: Učinak ketoprofena na koncentraciju u plazmi i farmakokinetičke pokazatelje ciprofloksacina u pilića. *Vet. arhiv* 92, 171-179, 2022.**

### SAŽETAK

Kombinacija ciprofloksacina (CFX) i ketoprofena (KPN) u širokoj je upotrebi u veterinarskom liječenju bakterijskih infekcija. Ovo je istraživanje provedeno kako bi se ustanovio utjecaj KPN-a na učinkovitost CFX-a mjerenjem njegove koncentracije u plazmi i farmakokinetičkih pokazatelja u pilića starih između 7 i 10 dana. Procijenjeno je da je prosječna doza analgetičke učinkovitosti ( $ED_{50}$ ) KPN-a u pilića 1,62 mg/kg, intramuskularno. Poželjna analgetička doza KPN-a bila je 4 mg/kg, intramuskularno, što se znakovito razlikuje od doze KPN-a od 2 mg/kg, intramuskularno, koja se daje s CFX-om. Koncentracije CFX-a u plazmi (8 mg/kg, im.) u različitim vremenima mjerenja (0, 5, 1, 2, 4 i 24 sata) bile su 3,31, 3,60, 3,21, 2,70 i 0,17  $\mu\text{g/mL}$ , a primijenjene zajedno s KPN-om (4 mg/kg, im) porasle su za 53, 54, 90, 107 i 418 % i iznosile 5,05, 5,53, 6,10, 5,59 i 0,88  $\mu\text{g/mL}$ . Farmakokinetički pokazatelji CFX-a, koji uključuju područje ispod krivulje (AUC), područje ispod krivulje momenta (AUMC), prosječno vrijeme zadržavanja (MRT), poluživot ( $t_{1/2\beta}$ ),  $T_{\max}$ , i  $C_{\max}$ , porasli su kad je KPN primijenjen s CFX-om za 129, 289, 70, 49, 100 i 69 %, dok su se konstanta brzine eliminacije ( $K_{el}$ ), volumen distribucije u stabilnom stanju ( $V_{ss}$ ) i klirens (Cl) smanjili za 36, 34 i 58 %. Zaključeno je da zajednička primjena KPN-a i CFX-a mijenja koncentraciju u plazmi i farmakokinetička svojstva CFX-a. Navedeno upućuje na to da bi se doza CFX-a mogla smanjiti kad se primjenjuje u kombinaciji s KPN-om, pri čemu se postigla željena koncentracija CFX-a u plazmi kao antibakterijskog lijeka za zaražene životinje.

**Ključne riječi:** pilići; ciprofloksacin; ketoprofen; farmakokinetika; koncentracija u plazmi

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