

The influence of the site of drug administration on florfenicol pharmacokinetics in turkeys

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ABSTRACT Florfenicol is a broad-spectrum antibacterial drug used in the treatment of farm animals, including poultry. This drug is poorly soluble in water, therefore, administration in drinking water may lead to high variability of concentrations in treated individuals. The use of injection preparations, however, requires individual administration and may have a negative effect on the quality of the carcass. In addition, the renal portal system in birds may reduce the bioavailability of the drug administered in the caudofemoral region of the body. The aim of this study was to compare the pharmacokinetics of florfenicol in turkeys after a single intravenous, intramuscular, and subcutaneous administration at a dose of 15 mg/kg body weight. Additionally, to evaluate the effect of renal portal system on drug kinetics, the intramuscular administration was divided into pectoral and caudofemoral administration. The study showed that the area under the concentration-time curve (AUC) was similar regardless of the route of

administration. The mean values for clearance and volume of distribution were 0.33 L/kg/h and 0.92 L/kg, respectively. The mean residence time (MRT) was 2.87 h for an intravenous bolus, while for the extravascular administrations it was approx. 5.5 h. The elimination half-life was approx. 4 h regardless of the route of administration. The maximum plasma concentration did not differ statistically between intramuscular (approx. 6.8 mg/L) and subcutaneous (8.2 mg/L) administrations, while the time to appear for this concentration was the longest for caudofemoral administration (1.5 h). The bioavailability was 88.64% for subcutaneous administration, 77.95% for pectoral administration and 85.30% for caudofemoral administration. Overall, all 3 routes of extravascular administration allowed for efficient drug absorption. There was no evidence of an influence of the renal portal system on the kinetic parameters of the drug administered to the lower extremities of the body.

Key words: florfenicol, renal portal system, turkey, pharmacokinetics, site of drug administration

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INTRODUCTION

Florfenicol (FF) is a fluorinated synthetic derivative of thiamphenicol (TP) that also lacks the p-nitro group present in their parent compound chloramphenicol (CP). These drugs act by binding irreversibly to a receptor site on the 50S subunit of the bacterial ribosome, thereby inhibiting peptidyl transferase enzyme and preventing the amino acid transfer to growing peptide chains and subsequently inhibiting protein formation (Dowling, 2013). FF is considered more potent than CP and TP, and the substitution of hydroxyl group at C-3 with fluorine makes FF less susceptible to resistance

from bacteria expressing CP acetyl transferases (Schwarz et al., 2004). FF is bacteriostatic against a number of important bacterial pathogens of cattle and pigs including *Actinobacillus pleuropneumoniae*, *Histophilus somni*, *Mannheimia hemolytica*, *Trueperella pyogenes*, *Pasteurella multocida*, and *Streptococcus suis* (Dowling, 2013). In poultry, FF was proven to be effective against *Escherichia coli* and *Pasteurella multocida* in chickens (Shen et al., 2002; Lan et al., 2019), and *Ornithobacterium rhinotracheale* in turkeys (Watteyn et al., 2013). FF is considered a valuable antibacterial drug and a safe alternative to CP to be administered to food-producing animals because it is not associated with dose independent aplastic anemia in humans or any other species (Dowling, 2013). Because of its high lipophilicity, FF has shown good tissue penetration throughout the body (Anadon et al., 2008). Thus, FF has been applied gradually across the world since 1990. However, due to massive usage in veterinary

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settings, some resistance problems have also emerged (Li et al., 2020).

Pharmacokinetics (**PK**) and tissue depletion of FF have been extensively studied not only alone (Afifi and El-Sooud, 1997; Shen et al., 2003) but also together with other members of fenicol family (Świtała et al., 2007; Tikhomirov et al., 2019) in various species of poultry including chickens (Afifi and El-Sooud, 1997; Shen et al., 2002; Shen et al., 2003; Anadon, et al., 2008; Lohani, et al., 2010; Abu-Basha et al., 2012; Poźniak et al., 2017; Wang et al., 2018), ducks (El-Banna, 1998; Lan et al., 2019; Tikhomirov et al., 2019), geese (Tikhomirov et al., 2021), pigeons (Ismail and El-Kattan, 2009), quails (Koc et al., 2009), and in turkeys (Świtała et al., 2007; Watteyn et al., 2013; Tikhomirov et al., 2018; Watteyn et al., 2018).

There are obvious interspecies differences in the disposition of FF in birds (Ismail and El-Kattan, 2009) that may limit the extrapolation of drug dosage used in one species for another species (Vermeulen et al., 2002). These differences result from the variation in body anatomy, physiology, and behavior (Frazier et al., 1995; Toutain et al., 2010) and that contribute to the need of conducting studies in the target species to enable rational decisions for effective clinical drug use (Ismail and El-Kattan, 2009). However, even within a single species, drug disposition may be different depending on the route of administration or drug formulation (Toutain et al., 2010). Moreover, the renal portal system (**RPS**) in birds may further complicate bioavailability (**F**,%) of drugs administered in the different regions of the body (Frazier et al., 1995). In farm animals, the choice of the route and the formulation should focus on the optimization of pharmacotherapeutic effects and its practical feasibility. To our knowledge, only a few PK studies were conducted on FF in turkeys following a single bolus intravenous (**i.v.**) or oral administration (Switala et al., 2007; Watteyn et al., 2013; Tikhomirov et al., 2018; Watteyn et al., 2018). There is a paucity of information about PK profile of FF in turkeys using extravascular routes of administration. Therefore, the objectives of this study are to evaluate the PK characteristics of FF after subcutaneous (**s.c.**) administration at the chest region and intramuscular (**i.m.**) administration that was further divided into pectoral (**IMP**) and caudofemoral (**IMCF**) administration. This approach aimed at evaluating the influence of the RPS on the PK profile of FF in turkeys.

MATERIALS AND METHODS

Animals

The experiment was carried out using 24 healthy female turkeys (BUT-9) breed, 10 wk of age and with an average body weight of 9.03 ± 1.34 kg. They were housed in an isolated room with temperature ranging between 20 and 23°C. The birds were fed antibiotics-free commercial diets and provided with water and feed ad libitum for a period of 2 wk during which they were

allowed to acclimate to the environment before starting the experiment.

Drug

FF (pharmaceutical grade) was supplied by Vetos-Farma (Bielawa, Poland). The basic formulations consisted of the active substance (8%, w/v), N-methylpyrrolidone (9%, w/v), and N-dimethyl acetamide (83%, w/v). The 8% solution of FF was diluted with sterile saline (1:5) under aseptic conditions 2 h prior to administration.

Experimental Method

The turkeys were randomly allocated into 4 groups ($n = 6$), namely: **i.v.**, **s.c.**, **IMP** and **IMCF** group, and the experiment was performed using a parallel study design, which means that independent groups of animals were subjected to the treatment simultaneously. The experiment was approved by the Local Animal Experimentation Committee in Wrocław (permit number 85/2006). All procedures involving animals were performed in accordance with national and international guidelines and regulations and all efforts were made to maintain good animal welfare and to use the minimum number of turkeys possible. For the **i.v.** group, FF solution was administered as a single bolus at a dose of 15 mg/kg BW into the wing vein using a catheter. For **s.c.**, **IMP** and **IMCF** groups, the same dose was administered with a hypodermic needle subcutaneously (chest region), into the pectoral muscle or into the thigh muscle, respectively. Blood samples (1.5 mL) were collected from each turkey into a heparinized syringe and tube via the jugular. For the **i.v.** group, the sampling time points were: 0, 0.03, 0.5, 1, 2, 4, 6, 12, and 24 h and for the other groups (**s.c.**, **IMP** and **IMCF**): 0, 0.05, 0.5, 1, 2, 4, 6, 8, 12, and 24 h. The blood samples were centrifuged within 30 min after collection at 1,500 g revolution for 10 min. The plasma obtained was immediately separated and stored at -20°C until assayed.

Analytical Method

Plasma drug concentrations were determined using high-performance liquid chromatography (**HPLC**) and following the same procedure as previously described (Świtała et al., 2007). A Waters Alliance HPLC system (Milford, MA) equipped with a 2996 PDA detector and a Chromolith Performance RP-180 4.6–100 mm column (Merck KGaA Darmstadt, Germany) were used for the separation and quantification of the drug. The mobile phase was a mixture of acetonitrile and water (18:82) at a flow rate of 1 mL/min. The drug was detected by UV absorption at 224.1 nm. The limit of detection and limit of quantification for FF were 0.007 and 0.021 $\mu\text{g/mL}$, respectively. The intra- and interassay coefficients of variation (**CV**) for FF were 1.90 and 3.30%, respectively (at the

concentration of 1 $\mu\text{g}/\text{mL}$). The recovery rate was above 92.3%.

Pharmacokinetic Analysis

Pharmacokinetic data analysis was performed with a PK software ThothPro version 4.3.0 (ThothPro, Gdansk, Poland), where a noncompartmental approach was used to calculate the PK parameters. The area under the concentration-time curve extrapolated to infinity ($\text{AUC}_{0 \rightarrow \infty}$) was determined using the linear up/log down trapezoidal rule. Moreover, area under the first moment curve ($\text{AUCM}_{0 \rightarrow \infty}$), mean residence time (MRT), total body clearance (CL_B), apparent volume of distribution at steady state (V_{ss}), elimination half-life ($T_{1/2el}$), elimination rate constant (K_{el}), initial plasma concentration (C_0) for i.v. administration, the observed values for the maximal plasma concentration (C_{max}) and the observed time at maximum plasma concentration (T_{max}) were determined (the last 2 parameters were determined for extravascular administrations only). The estimation of $T_{1/2el}$ was based on at least three data points indicating the linear phase of elimination. Bioavailability (F, %) was calculated following the equation: $F (\%) = (\text{AUC}_{non\ IV} / \text{AUC}_{IV}) \times 100\%$. The mean absorption time (MAT) was calculated: $\text{MAT} = \text{MRT}_{non\ IV} - \text{MRT}_{IV}$. Due to the parallel study design, both F% and MAT were calculated only for the mean values and they lack the measure of variability.

Statistical Analysis

The data are presented as mean \pm standard deviation ($M \pm SD$) and their distribution was confirmed to be normal (Shapiro–Wilk test) except for the values of T_{max} which are presented as median with the range in brackets. One-way ANOVA with Tukey's post-hoc test was used to determine any statistically significant differences between the observed mean values of PK parameters, while Kruskal–Wallis test was used to analyze the T_{max} data (STATISTICA v.13.3, TIBCO, Palo Alto, CA). Differences were considered statistically significant when $P < 0.05$.

RESULTS

FF was well tolerated in all experimental subjects throughout the experiment with no adverse drug reaction observed. The mean plasma concentration-time profiles of FF after a single bolus i.v., s.c., IMP, and IMCF administration are presented in Figure 1. For the i.v. route, because of an error encountered at the 8-h sampling period, the data obtained was not included. No measurable concentration of FF was detected in any sample collected prior to drug administration. The mean values of the calculated PK parameters are presented in Table 1. The $\text{AUC}_{0 \rightarrow \infty}$ were found to be relatively similar irrespective of the route of administration used. The MRT for the i.v. route was shorter compared with those mean values obtained by other routes, and they were

statistically different ($P < 0.05$). The mean C_0 value for i.v. route is about 10 times of the mean C_{max} values obtained for all the extravascular administrations. No statistical differences ($P > 0.05$) were observed between the mean C_{max} values for the extravascular administration methods. The mean value obtained for $T_{1/2kel}$ was very similar irrespective of the route of administration, the same observation was made with the mean values of K_{el} and MAT . The calculated absolute values of F (%) for extravascular administration were found to be 77.95% for IMP, 85.30% for IMCF, and 88.64% for s.c. administration.

DISCUSSION

Antimicrobial agents are of great importance to the poultry industry where they are employed for metaphylactic, or therapeutic purposes (Watteyn et al., 2013). FF is an antimicrobial agent used extensively to treat respiratory conditions of bacterial origin in bovine and poultry species of animals (Watteyn et al., 2013; Toutain et al., 2019). In the present study, the pharmacokinetics of FF was investigated in healthy female turkeys, after administration via four different routes (i.v., s.c., IMP, and IMCF) at a dose of 15 mg/kg BW. For the s.c. route, based on the authors' best knowledge, this is the first report of FF PKs determined after using this method of administration in an avian species.

Following extravascular administration, FF was rapidly absorbed from all routes administered as reflected by similar values of MAT . Our findings in this study were lower than the mean MAT values previously reported in chickens, pigeons, and quails after i.m. administration of FF at 30 mg/kg BW (Ismail and El-kattan 2009; Koc et al., 2009). The AUC represents all the pharmacokinetic processes related to the changes in drug concentration occurring during its measurement. In this study, the AUC was found to be relatively similar regardless of the route of administration. This indicates that the majority of the administered dose reaches the general circulation. No significant differences were found between mean C_{max} values for all extravascular methods of administration. The mean C_{max} values obtained for i.m. administrations are in agreement with the mean values previously reported in healthy broiler chickens after i.m. administration (Shen et al., 2002). In contrast, our results are remarkably higher than the values obtained by (Affi and El-Sooud, 1997) using the same route of administration in chickens. The observed difference may result from either species differences in drug handling (Toutain et al., 2010), variation in the dose administered (15 vs. 30 mg/kg BW) (Houben et al., 2016) or analytical methods used. This is because Affi and El-Sooud (1997) used microbiological methods in estimating FF plasma concentration instead of HPLC.

Bioavailability (F, %) is an important PK parameter that denotes the rate and extent at which fraction of the administered dose of a drug becomes available in the systemic circulation (Toutain et al., 2010). Following

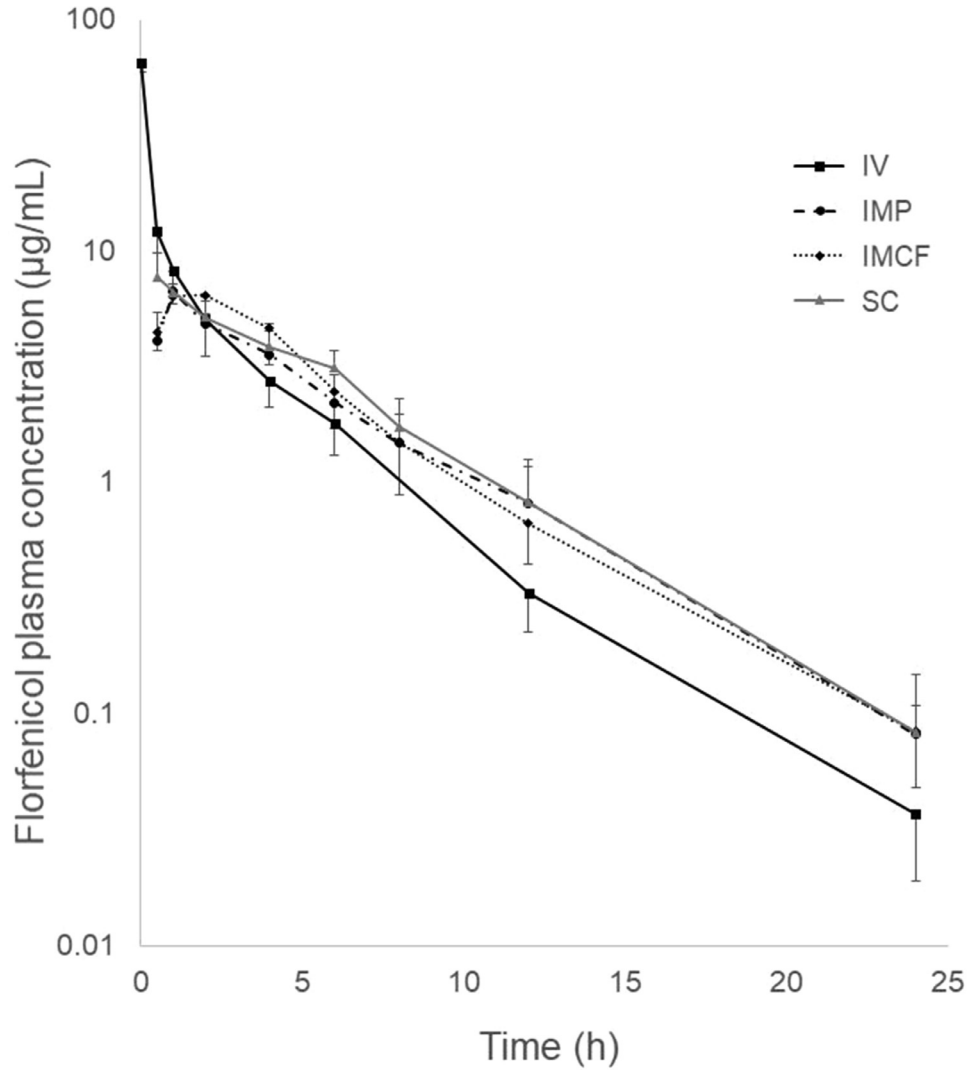


Figure 1. Plasma florfenicol concentrations (mean \pm SD) after single intravenous (IV), subcutaneous (SC) and intramuscular administrations at a dose of 15 mg/kg to turkeys. Intramuscular administration was performed in two groups: one received the drug into the femoral muscle (IMCF) and one into the pectoral muscle (IMP). $n = 6$ in each group.

Table 1. Pharmacokinetic parameters (mean \pm SD) after a single intravenous (i.v.), intramuscular pectoral (IMP), intramuscular caudofemoral (IMCF) and subcutaneous (s.c.) administration of florfenicol (FF) at a dose of 15 mg/kg BW in broiler Turkeys ($n = 6$).

Parameter	Units	i.v.	IMP	IMCF	s.c.
$AUC_{0 \rightarrow \infty}$	mg \cdot h/L	46.03 \pm 5.98	35.78 \pm 8.68	39.86 \pm 7.55	41.09 \pm 8.15
$AUMC_{0 \rightarrow \infty}$	mg \cdot h \cdot h/L	131.71 \pm 16.38	207.74 \pm 90.63	220.57 \pm 52.90	226.17 \pm 49.11
$MRT_{0 \rightarrow \infty}$	h	2.87 \pm 0.27 ^a	5.66 \pm 1.62 ^b	5.51 \pm 0.55 ^b	5.51 \pm 0.44 ^b
C_0	μ g/mL	64.72 \pm 6.09	-	-	-
C_{max}	μ g/mL	-	6.71 \pm 1.56	6.89 \pm 0.83	8.24 \pm 1.52
T_{max}	h	-	1.0 (0.5–1.0)	1.50 (1.0–2.0)	0.5 (0.5–1.0)
K_{el}	1/h	0.22 \pm 0.03	0.20 \pm 0.04	0.18 \pm 0.07	0.20 \pm 0.03
$T_{1/2kel}$	h	3.22 \pm 0.42	3.60 \pm 0.76	4.41 \pm 1.56	3.60 \pm 0.63
CL_B	L/kg/h	0.33 \pm 0.04	-	-	-
V_{ss}	L/kg	0.92 \pm 0.17	-	-	-
F	%	-	77.95	85.30	88.64
MAT	h	-	2.59	2.23	2.44

Abbreviations: AUC_0 , area under the concentration time curve; $AUMC_{0 \rightarrow \infty}$, area under first moment curve; C_0 , initial concentration observed after i.v. administration; C_{max} , observed values of maximal concentration; CL_B , clearance; F, bioavailability; MAT, mean absorption time; MRT, mean residence time; $T_{1/2kel}$, elimination half-life; K_{el} , elimination rate constant; T_{max} , observed time of maximal concentration; V_{ss} , apparent volume of distribution at steady state.

The calculated PK parameters for all routes of administration were presented as mean \pm SD except for T_{max} which is presented as median with range in brackets.

^{ab}Values within the same row sharing difference superscript letter differ significantly $P < 0.05$ and absence of superscript indicate lack of statistical significance.

extravascular administration of FF, a greater fraction of the administered dose of FF reached the general systemic circulation. Although, subcutaneous administration of drugs in birds is mostly associated with drug deposition in fat-depots, which leads to unfavorable absorption patterns due to slow release into the systemic circulation (Vermeulen et al., 2002), in this study, the s. c. route revealed the highest bioavailability (88.64%). This may be due to the fact that the drug was administered subcutaneously at the middle half of the pectoral region which has very little fat tissue. This could have prevented FF sequestration in fat and contributed to the rapid absorption via high surface area of tissues under loose and well perfused skin.

Volume of distribution at steady state (V_{ss}) is a clearance independent volume of distribution that is used to calculate the amount of drug in the body under equilibrium conditions (Toutain and Bousquet–Mélou, 2004a). Following i.v. administration, FF was widely distributed throughout the body, which was achieved in a short period of time. The result obtained in this study is in agreement with the previous mean value reported in turkeys (Świtłała et al. 2007), but it is lower than the mean value reported in chickens (Anadon et al., 2008) and quails (Koc et al., 2009) using the same route of administration. The reason for the differences observed in the V_{ss} may be explained due to the variability either in species of birds, body size, protein binding, dose administered, or difference in drug disposition (Ismail and El-Kattan, 2009; Toutain et al., 2010; Houben et al., 2016; Csikó et al., 2018).

Total body clearance (CL_B) is a pharmacokinetic parameter expressing the overall capacity of the body to eliminate the drug (Houben et al., 2016). It is well known that it is the most important pharmacokinetic parameter related to elimination processes (Toutain and Bousquet–Mélou, 2004b). FF was slowly cleared from the system following i.v. administration. The mean CL_B value obtained in this study was in agreement with previous values reported in turkeys (Świtłała et al. 2007). Comparatively similar value was also reported in ducks (Tikhomirov et al. 2019). In contrast to our findings, slightly higher values were reported in chickens, pigeons, and quails (Ismail and El-kattan, 2009) after i.v. administration. Differences in PK profile of administered drug between bird species exist as well (Houben et al., 2016). For instance, significant species differences in mean CL_B were reported between chickens and guinea fowl (Csikó et al., 2018). A comparative study in poultry has shown that the mean CL_B of FF was higher in small-body size birds than in those with larger body size (Koc et al., 2009). Moreover, the mean CL_B value of FF was compared across some species of poultry and was found that it follows power-law relationship (Poźniak et al., 2017). The present study has demonstrated that none of the extravascular routes studied affected the rate of elimination of FF as evidenced by the very similar elimination half-lives. The mean values of $T_{1/2_{kel}}$ obtained in this study were higher than the previous values reported in turkeys (Świtłała et al., 2007). A possible explanation

may be associated with the differences in body weight between the turkeys used in both studies. Additionally, our earlier study had revealed that an age-dependent increase in body weight was shown to have a significant influence in causing variability in PK and hemodynamic parameters within the same species of birds (Świtłała et al., 2016).

RPS is well developed in birds and reptiles (Palmore and Ackerman, 1985; Blackburn and Prashad, 1990; Frazier et al., 1995). This vascular system drains a fraction of blood flow from the caudal body region and extremities directly through the kidneys (Palmore and Ackerman 1985). The magnitude of the renal portal supply reaching the kidney appears to be controlled by an autonomically innervated smooth muscle valve called the renal portal valve (Blackburn and Prashad, 1990). Although the physiologic significance of the renal portal valve in controlling blood flow remains debatable, it was presumed that the opening or closure of the valve might be associated with blood flow required by the kidney (Frazier et al., 1995).

A study in turkeys revealed that administration of epinephrine or acetylcholine influenced the opening or closure of the valve, respectively (Palmore and Ackerman, 1985; Blackburn and Prashad 1990). The kidney is one of the 2 major active organs of drug elimination (Frazier et al., 1995). FF and its metabolite FF amine are primarily eliminated by the kidney through the process of glomerular filtration (Anadon et al., 2008; Dowling, 2013). In birds, drugs injected in the hind limb or caudal body may be carried in the blood through the RPS and perfuse the kidneys (Frazier et al., 1995; Vermeulen et al., 2002). Therefore, some portion of the administered drug may be affected by first-pass metabolism or may get excreted by the kidney without reaching the general systemic circulation (Toutain et al., 2010; Abo-El-Sooud et al., 2012; Houben et al., 2016). Concerning the renal biotransformation of administered drugs, relatively little is known about the characteristics of avian renal xenobiotic-metabolizing enzymes and their influence on PK characteristics of administered drugs (Vermeulen et al., 2002; Wang et al., 2018). However, FF gets metabolized by cytochrome P450 3A in the liver to FF amines and the same process is assumed to occur in the kidney (Anadon et al., 2008; Wang et al., 2018).

The glomerular filtration process is not constant but intermittent in birds (Frazier et al., 1995). It was observed that the body hydration status determines the possibility of renal portal blood flow toward the avian kidney and affects the glomerular filtration rate (Frazier et al., 1995; Vermeulen et al., 2002). In the present study, there was no difference ($P > 0.05$) observed between PK parameters when we administered FF into the pectoral or thigh muscles, with the latter being drained by blood vessels that eventually supply blood to the RPS. Despite the species difference, our finding is in agreement with the report by Holz et al. (1997) where they administered gentamicin into the hind limb of a reptile (red-eared slider) and observed no difference (P

> 0.05) between the PK profiles resulting from the administration to the hind limb as compared to that to the forelimb. In another study, gentamicin was injected into the thigh muscles of chickens and the RPS was found to have influenced the PK profile of the drug, which resulted in decreased internal exposure in comparison with pectoral administration. However, the difference was not considered clinically significant (Abo-El-Sooud et al., 2012). The absence of influence of the RPS in the present study may be associated with mild stress the turkeys were exposed to during blood sampling which triggered the release of adrenergic hormones that opened the valve (Blackburn and Prashad 1990). It may also be due to decreased body hydration status caused by fluid loss associated with the substantial blood sampling during the experiment. However, no sign of dehydration for example, panting was observed (Frazier et al., 1995; Vermeulen et al., 2002). Therefore, a thorough understanding of the regulation of the RPS and its influence on the PK of drugs administered in the lower extremities requires further studies.

FF has been classified as a time-dependent antibiotic with bacteriostatic antibacterial activity (Dowling, 2013). Antimicrobial dosage regimen recommendations for bacteriostatic drugs are typically based on maintaining free drug plasma concentrations above the minimum inhibitory concentration (MIC) values against the bacterial pathogens throughout a significant fraction of the dosing interval (Anadon et al., 2008). Recently, Toutain et al., (2019) recommended that the duration of plasma concentrations exceeding the MIC ($T > MIC$) should be maintained for a longer proportion of the dosing interval (at least 40% or higher) in 90% of the treated animals. Although the clinical breakpoints for FF in poultry isolates have not yet been established, for other species of mammals like calves, a breakpoint of 1 $\mu\text{g}/\text{mL}$ was established for 2 bacterial species of the bovine respiratory disease complex (*Pasteurella multocida* and *Mannheimia hemolytica*), which was approved as a PK/PD cut-off for both AUC/MIC and $T > MIC$ (Toutain et al., 2019). The protein binding was considered negligible and not included in these calculations. With these assumptions, in the present study, the $T > MIC$ for the cited MIC value was maintained for 5.5 h after a single dose administration for all extravascular routes studied. This suggest that FF should be given twice daily with a 12-h dosing interval giving the $T > MIC$ of ca. 50%.

It is concluded from the findings of the present study that FF has shown favorable PK characteristics after i.v. and extravascular administration. The RPS did not show any influence on the PK parameters of FF following IMCF administration as compared to the other routes. Among the extravascular routes of administration studied, the s.c. route revealed the best PK characteristics of FF. Although FF is typically administered orally, under some conditions an individual treatment may be required (e.g., in backyard poultry or valuable individuals/breeders). In such cases, FF should be administered to turkeys subcutaneously twice daily for

achieving effective drug concentration and therapeutic efficacy. An additional advantage for this route may be the lower risk of injection site-associated drug residues in the primary tissue of interest for consumers, the muscle. Further study is required to elucidate the PK-PD characteristics of FF in turkeys and other avian species to obtain an accurate and reasonable dosing regimen for treating various bacterial pathogens affecting bird species.

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DISCLOSURES

The authors declare no conflicts of interest.

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