Turkish Journal of Veterinary and Animal Sciences

http://journals.tubitak.gov.tr/veterinary/

Research Article

Turk J Vet Anim Sci
(2015) 39: 168-173
© TÜBİTAK
doi:10.3906/vet-1411-57

Influences of flunixin and tenoxicam on the pharmacokinetics of florfenicol in lipopolysaccharide-induced endotoxemia

Feride KOÇ[1,*], Alptuğ ATİLA[2], Emre KARAKUŞ[3], Kamil ÜNEY[4]

[1]Department of Pharmacology and Toxicology, Faculty of Veterinary Medicine, Erciyes University, Kayseri, Turkey
[2]Department of Analytical Chemistry, Faculty of Pharmacy, Atatürk University, Erzurum, Turkey
[3]Department of Pharmacology and Toxicology, Faculty of Veterinary Medicine, Atatürk University, Erzurum, Turkey
[4]Department of Pharmacology and Toxicology, Faculty of Veterinary Medicine, Selçuk University, Konya, Turkey

Received: 26.11.2014 • **Accepted:** 05.02.2015 • **Published Online:** 01.04.2015 • **Printed:** 30.04.2015

Abstract: The purpose of this study was to investigate the influences of flunixin (FM) and tenoxicam (TN) on the pharmacokinetics of florfenicol (FF) after coadministration in lipopolysaccharide (LPS)-induced endotoxemic rabbits. Fifteen male rabbits were used in this study. FF (20 mg/kg), FM (2 mg/kg), and TN (1 mg/kg) were coadministered via intravenous injection to the animals. The concentrations of FF were determined by high-performance liquid chromatography with diode-array detection from 0.08 to 12 h in plasma. The plasma concentration-time profile of FF was described using a noncompartmental open model. In this study, terminal half-life, area under the curve, mean residence time, and volume of distribution at steady state were significantly increased, whereas total body clearance was decreased in coadministered groups. In conclusion, FM and TN have effects on the pharmacokinetics of FF in coadministered endotoxemic rabbits. When FF is coadministered with FM and TN, it can be given at a dose of 20 mg/kg b.w. every 8 h for treatment of infections caused by susceptible pathogens with a minimum inhibitory concentration (MIC) of ≤2 µg/mL or 12 h for treatment of infections caused by susceptible pathogens with MIC of ≤1 µg/mL in critically ill rabbits. Further studies are necessary to determine variations in dosage regimens.

Key words: Pharmacokinetics, florfenicol, rabbit, flunixin, tenoxicam, lipopolysaccharide

1. Introduction

Lipopolysaccharide (LPS) is an endotoxin present in the cell walls of gram-negative bacteria and an immune stimulant that induces the release of proinflammatory cytokines. Administration of LPS causes the acute phase response to be produced in the host and can also induce multiorgan dysfunction, fever, hypotension, disseminated intravascular coagulation, septic shock, and death (1,2). LPS, *Escherichia coli*-derived, has been widely used to cause an endotoxemic animal model in experiments (3,4).

Florfenicol (FF) is a synthetic broad-spectrum antibiotic that acts against both gram-negative and gram-positive organisms in the veterinary treatment of infectious diseases. It is an antibiotic that belongs to the chloramphenicol (CP) family, but it is used only in animals. The drug inhibits peptidyl transferase activity and affects bacterial protein synthesis at the 50S and 70S subunits ribosomes. Consequently, FF has more antibacterial activity than other drugs (chloramphenicol and thiamphenicol). Due to these advantages, FF has been supposed to be an ideal replacement for these two drugs in veterinary clinics to treat bacterial diseases since the early 1990s (5). It has also been reported that FF has a protective effect on acute lung injury induced by LPS in mice (6).

Flunixin meglumine (FM) and tenoxicam (TN) are nonsteroidal antiinflammatory drugs (NSAIDs). They also have analgesic and antipyretic properties. Antibiotics and NSAIDs are usually coadministered in therapy (7,8). Drug interaction is a common phenomenon in which a drug affects the activity of another drug when coadministered. This situation may be the result of various processes that may include alterations in the pharmacokinetics of the drug (9). Until now, the pharmacokinetic disposition of FF has been extensively documented in healthy and infected animal species only when FF was administered alone (10–14). Interactions of FF with some drugs (anthelmintics, polyether ionophores, and tylosin) have been reported in previous studies (15–17). However, there has been no pharmacokinetic report about the effects of FM and TN on the pharmacokinetics of FF in endotoxemic rabbits.

* Correspondence: feridekoc@yahoo.com

The purpose of this study was to determine the effects of FM and TN on the pharmacokinetic disposition of FF after intravenous coadministration in LPS-induced endotoxemic rabbits.

2. Materials and methods

2.1. Animals

A total of 15 healthy, adult, male rabbits (New Zealand White), approximately 6–12 months old and with a body weight of 3.18 ± 0.15 kg, were used in the present study. The rabbits were obtained from the Experimental Research Center of Atatürk University. They were housed there for 2 weeks before use. They were fed with pelleted feed (antibacterial-free) and water ad libitum. Animal experiments were performed in an ethically proper way, following guidelines set by the Ethics Committee of Atatürk University (Report No. 77/2014).

2.2. Drugs, chemicals, and instruments

FF (99.6% assay purity) and CP (99.7% assay purity) analytical standards were purchased from Schering-Plough (Segre, France). FF (Nuflor, 300 mg/mL, Sanofi), TN (Oksamen-L, 20 mg, Mustafa Nevzat), and FM (Fluvil, 50 mg/mL, Vilsan) were sourced from Turkey. Ammonium acetate, acetonitrile, and methanol were purchased from J.T. Baker (Merck, Ari Medical, Erzurum, Turkey). A high-performance liquid chromatography (HPLC) Prominence LC-20 A Series with diode array detector (DAD) and reverse phase Inertsil ODS-3V column (250 × 4.6, i.d. 5 µm) was from Shimadzu (Tokyo, Japan).

2.3. Experimental design and sample collection

The animals were randomly divided into 3 groups (n = 5, each group). Before intravenous (i.v.) administrations, restraint devices were applied to the auricular vein of each animal. LPS (*E. coli* 0111:B4, Sigma) was then administered to the 3 groups as a bolus i.v. injection (100 µg/kg b.w.). After 1 h, the blood samples (2 mL) were collected from the restraint devices for the control (at 0 min). FF (Nuflor) was then dissolved in an organic solvent (dimethyl formamide) and FF (20 mg/kg b.w.) was injected in the auricular vein of animals via bolus i.v. in Group I (FF-LPS). FF (20 mg/kg b.w.) and FM (2 mg/kg b.w.) were administered to Group II (FF-FM-LPS). FF (20 mg/kg b.w.) and TN (1 mg/kg b.w.) were administered to Group III (FF-TN-LPS) via the same routes, simultaneously. Blood samples (2 mL) were taken from each rabbit and collected in tubes containing heparin as the anticoagulant at 5, 10, 15, 30, 45, 60, and 90 min and 2, 4, 6, 8, and 12 h after drug administrations. They were centrifuged within 1 h after the collection and plasma was separated after centrifugation for 10 min at 2000 rpm. Plasma samples were stored at –20 °C until analysis. All of the samples were analyzed within 1 week of the experiments.

2.4. Analytical procedure

FF was determined in plasma samples by HPLC (Shimadzu 20A Prominence System) with DAD (224 nm) using a previously published method (18). CP was used as the internal standard. Samples were analyzed by an Inertsil ODS-3V column (250 × 4.6, i.d. 5 µm). The mobile phase consisted of a mixture of acetonitrile-ammonium acetate at a ratio of 20:80 (v/v). The injection volume was 100 µL, the monitoring wavelength was 224 nm, the flow rate was 1.5 mL/min, and the oven temperature was 35 °C.

2.5. Extraction procedure

The procedure was performed as described by Koc et al. (18). Briefly, the frozen plasma samples (0.25 mL) were thawed at a room temperature, and then 0.75 mL of water and 0.5 mL of internal standard (CP) were added to spike the samples. These samples were extracted by a solid phase extraction cartridge (C_{18}, 3 mL, 500 mg, Bond Elut, Agilent). The cartridge was conditioned with methanol and water (v/v, 3 mL/3 mL). The mixture was vortexed and transferred to a C_{18} cartridge. The cartridge was then washed with a mixture of acetonitrile-water (2 mL, 15/85) and 3 mL of hexane. An eluate was collected with acetonitrile (3 mL). The eluate was evaporated at 50 °C under a stream of nitrogen. The residue was dissolved in the mobile phase and 100 µL of it was injected into the HPLC system for analysis.

2.6. Validation

The validation parameters (linearity, precision [relative standard deviation (RSD)], accuracy, limit of detection (LOD), limit of quantitation (LOQ), recovery, and reproducibility) were determined for the method. For linearity, a calibration curve was calculated from 6 different levels (0.1–25.0 µg/mL) of FF automatically using software. The inter- and intraday precisions were calculated with 6 replicated analyses of spiked samples with 3 different levels (0.1, 5, and 10 μg/mL) of FF on the same and separate days. LOD was calculated to be 3 times the signal-to-noise ratio in the plasma samples when spiking at low concentrations. LOQ was calculated to be 10 times the signal-to-noise ratio. The recoveries and the inter- and intraday reproducibility were determined after spiking from 0.1 to 10 µg/mL with 3 different levels of FF.

The calibration curve provided excellent linearity with correlation coefficients (r^2) of >0.9998 in the present study. The inter- and intraday precision levels (RSD) were <7.0. The mean recovery was 91.2 ± 5.13% and LOD and LOQ were 0.01 and 0.03 µg/mL, respectively. There was a high degree of reproducibility for FF.

2.7. Pharmacokinetic analysis

The noncompartmental model independent analysis, based on the statistical moment theory, was applied to determine the pharmacokinetic parameters for each individual rabbit using a computerized program, WinNonlin version 4.01 (Pharsight Corporation, Scientific Consulting Inc., Raleigh, NC, USA).

To verify the time when the plasma drug concentration stayed above or was equal to the minimal inhibitory concentration (MIC) value, the following formula was applied:

$$\%T > MIC = ln\left(\frac{D}{Vd_{area}\ x\ MIC}\right) x \left(\frac{t_{1/2}}{\ln(2)}\right)\ x\ \left(\frac{100}{DI}\right),$$

where T > MIC is the time interval (in percent) during which the plasma concentration is above or equal to MIC values, D is the proposed dose, Vd_{area} is the volume of distribution (L), $t_{1/2}$ is the terminal elimination half-life (h), and DI is the dose interval (h) (19).

MIC_{90} values (0.25–2 µg/mL) reported for the most relevant pathogens (*Pasteurella multocida* and *Bordetella bronchiseptica*) that cause infection in rabbits were compared with the plasma-concentration time curves and kinetic parameters obtained in order to establish optimal dosing regimens (20,21).

2.8. Statistical analysis

Data were analyzed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Mean residence time (MRT) and terminal half-life ($t_{1/2\lambda z}$) were compared between groups by means of the Mann–Whitney U test. The other pharmacokinetic data were analyzed using one-way analysis of variance, followed by the Duncan test. Results are given as mean ± SD.

3. Results

The plasma concentration-time profile of FF was described using a noncompartmental open model in LPS-induced endotoxemic rabbits. After i.v. administrations to animals at a single dose (20 mg/kg b.w.) of FF in the FF-LPS (alone), FF-FM-LPS, and FF-TN-LPS groups, pharmacokinetic data and plasma concentration-to-time curves of FF were obtained as depicted in Table 1 and the Figure, respectively.

The $t_{1/2\lambda z}$, the area under the curve ($AUC_{(0-12)}$), the MRT and the volume of distribution at steady state (Vss) of FF were significantly increased, whereas total body clearance (Cl_T) was decreased in both the FF-FM-LPS and FF-TN-LPS groups (coadministered) compared to the FF-LPS (alone) group (P < 0.05, Table 1).

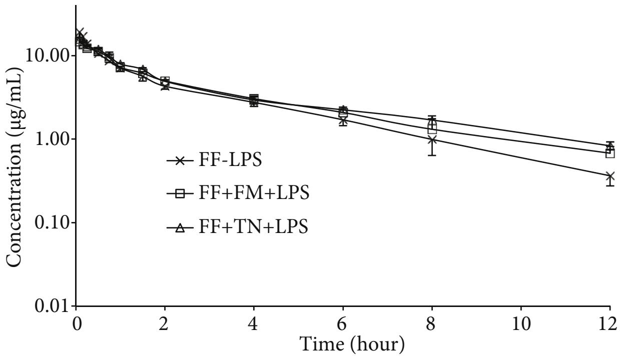

Figure. Plasma concentrations of florfenicol (20 mg/kg b.w.) following intravenous single administration and coadministration with flunixin meglumine and tenoxicam in LPS-induced endotoxemic rabbits.

Table 1. Mean ± SD pharmacokinetic parameters of florfenicol (20 mg/kg b.w.) following intravenous single administration and coadministration with flunixin meglumine and tenoxicam in LPS-induced endotoxemic rabbits.

Parameter	Unit	FF-LPS	FF-FM-LPS	FF-TN-LPS
λ_z	1/h	0.26 ± 0.03[a]	0.19 ± 0.03[b]	0.16 ± 0.01[b]
$t_{1/2\lambda z}$ (HM)	h	2.69 ± 0.38[b]	3.61 ± 0.56[a]	4.26 ± 0.32[a]
$AUC_{(0-12)}$	h × µg/mL	34.44 ± 2.62[b]	37.75 ± 2.24[a]	40.38 ± 1.94[a]
Cl_T	mL h^{-1} kg^{-1}	559.76 ± 44.66[a]	483.48 ± 22.51[b]	440.47 ± 26.68[b]
$AUMC_{(0-12)}$	h × h × µg/mL	96.37 ± 15.51[b]	120.76 ± 12.41[a]	135.43 ± 9.74[a]
MRT (HM)	h	2.77 ± 0.24[b]	3.19 ± 0.20[a]	3.35 ± 0.10[a]
V_{ss}	L/kg	1.85 ± 0.12[b]	2.16 ± 0.26[a]	2.21 ± 0.06[a]
V_d	L/kg	2.20 ± 0.28b	2.57 ± 0.40ab	2.71 ± 0.13a

[a, b, c]: Different letters in the same line are statistically significant (P < 0.05). FF-LPS, florfenicol alone; FF-FM-LPS, florfenicol coadministrated with flunixin meglumine; FF-TN-LPS, florfenicol coadministrated with tenoxicam; λz, the first-order rate constant associated with the terminal portion of the curve; $t_{1/2\lambda z}$, terminal half-life; $AUC_{(0-12)}$, area under the curve from time 0 to the last detectable concentration; Cl_T, total body clearance; $AUMC_{(0-12)}$, area under the first moment curve; MRT, mean residence time; Vss, volume of distribution at steady state; HM, harmonic mean.

Calculated %T > MIC results using the MIC values and the calculated kinetic data (PK) are presented in Table 2. At 8-, 12-, and 24-h intervals, FF following i.v. injection at a dose of 20 mg/kg b.w. for bacteria with MIC values of ≤2 μg/mL maintained a T > MIC value of or above 73%, 49%, and 24%, respectively, in all groups.

4. Discussion

In the present study, the plasma pharmacokinetic profile for FF was described by a noncompartmental open model. Until now, the best described models for this drug in rabbits was noncompartmental (11,12) except in only one study (13). The obtained result was in agreement with previous reported studies in rabbits.

In published studies, the Cl_T of FF was reported from 0.56 to 0.63 L kg^{-1} h^{-1} (13,12). In the present study, this value was 559.76 ± 44.66 L kg^{-1} h^{-1} in the FF-LPS (alone) group. The obtained value was similar to the above reports for administration of FF alone in healthy rabbits. In this study, the Cl_T of the FF-LPS group was higher than in the FF-FM-LPS (483.48 ± 22.51 L kg^{-1} h^{-1}) and FF-TN-LPS (440.47 ± 26.68 L kg^{-1} h^{-1}) groups. These differences in the Cl_T may be related to both the prostaglandin inhibitory effects of NSAIDs (FM and TN) and LPS-induced endotoxemia. It is known that NSAIDs have an influence on the kinetic disposition of some drugs. They may alter renal excretion via prostaglandin inhibitory effects (9). This is because the prostaglandins have a vasodilatory effect on blood vessels. Renal blood flow is thus slowed and renin release is altered by renal prostaglandins in the kidneys (22). In addition, endotoxin has some negative effects on the kidneys, such as direct vascular damage (endothelium and platelet aggregation) in renal glomerular capillaries. Tubular cell damage may be the result of effects of LPS. It also produces some functional changes, including a slow in the renal blood flow and glomerular filtration, and changes in the

Table 2. Calculated %T > MIC for florfenicol based on the pharmacokinetic parameters obtained after intravenous single administration and coadministration of florfenicol (20 mg/kg b.w.) with flunixin meglumine and tenoxicam in LPS-induced endotoxemic rabbits for 8-, 12-, and 24-h dosing intervals.

%T > MIC	Dose interval		
	8 h	12 h	24 h
MIC 0.25 μg/mL			
FF-LPS	174	116	58
FF-FM-LPS	224	149	75
FF-TN-LPS	260	173	87
MIC 0.5 μg/mL			
FF-LPS	141	94	47
FF-FM-LPS	179	119	60
FF-TN-LPS	207	138	69
MIC 1 μg/mL			
FF-LPS	107	71	36
FF-FM-LPS	134	89	45
FF-TN-LPS	153	102	51
MIC 2 μg/mL			
FF-LPS	73	49	24
FF-FM-LPS	88	59	29
FF-TN-LPS	100	67	33

%T > MIC has been calculated for MICs of 0.25, 0.5, 1, and 2 μg/mL on the basis of reported MIC_{90s} (0.25–2 μg/mL) for *Pasteurella multocida* and *Bordetella bronchiseptica* (20,21). MIC: Minimal inhibitory concentration.

hemodynamics in the kidney. As a result, endotoxin has an important role in the decrease of the body clearance of drugs that are widely eliminated by the renal route (23,24). It has been reported that FF was excreted in urine as the parent form (64%) and as component parts of FF (5).

In the present study, $t_{1/2\lambda z}$ was 2.69 ± 0.38 h, 3.61 ± 0.56 h, and 4.26 ± 0.32 h in the FF-LPS, FF-FM-LPS, and FF-TN-LPS groups, respectively. The obtained results were significantly increased in the FF-FM-LPS (3.61 ± 0.56 h) and FF-TN-LPS (4.26 ± 0.32 h) groups (coadministered) when compared with the FF-LPS group (alone) in the present study. In addition, these parameters were significantly increased and inconsistent with the results of reported studies (11–13) in healthy rabbits. In the present study, the $AUC_{(0-12)}$ was somewhat similar to that of a previous study (13) after administration of FF in healthy rabbits. However, this value slightly increased in coadministration of FF-FM-LPS and FF-TN-LPS when compared with FF-LPS in animal groups. As a result, increasing the $AUC_{(0-12)}$ and lengthening the $t_{1/2\lambda z}$ may be related to decreasing the Cl_T of FF in coadministered groups in endotoxemic rabbits. In our study, the V_{ss} of FF was large (from 1.85 ± 0.12 to 2.21 ± 0.06 L/kg). These results were inconsistent with the results (from 0.57 ± 0.85 to 0.98 ± 0.05 L/kg) of previous studies (11–13) in healthy rabbits. The V_{ss} significantly altered in coadministration of LPS-induced rabbits. The large size of the V_{ss} may be related to both the lipophilicity of the drug and endotoxemia. The MRTs of FF in the present study were not similar to those of previous studies (11–13) in healthy rabbits. The MRT was longer in coadministered endotoxemic rabbits. The greater lengths of the $t_{1/2\lambda z}$ and the MRT are important due to the residues of drugs in coadministration. In further studies, the withdrawal time of FF may be altered in coadministered animals.

Drug interaction is a common phenomenon in pharmacology. There are many reports about this phenomenon in different species. In previous studies, the pharmacokinetics of FF were altered by the combination of FF and tylosin in dogs (16), FF-anthelmintics combination in goats (15), and FF-polyether ionophore combination in broilers (17). The result of our study was in agreement with the results of the above reported studies. Liu et al. (25) reported that there was no statistically significant difference between the pharmacokinetic profiles of FF for pigs infected with *Actinobacillus pleuropneumoniae* and healthy pigs. On the other hand, it was reported that there was a decrease in the elimination half-life and the apparent volume of distribution of FF in healthy and *Escherichia coli*-infected broiler chickens (26).

FF acts as a time-dependent bactericidal drug (27). The most important pharmacodynamic/pharmacokinetic parameter for a time-dependent drug is the length of the time above the MIC_{90} value (19,28,29). It is generally recommended that T > MIC should be at least 40% of the dosage interval. It has also been reported that plasma concentrations of drugs in critically ill patients should exceeded MIC_{90} values for 80% of the time between two consecutive applications (30). The MICs of FF for bacteria isolated from rabbits have not yet been determined. The in vitro efficacy of FF against *Pasteurella multocida* and *Bordetella bronchiseptica* isolated from pigs and cattle has been demonstrated by various studies (20,21). Considering the reported MIC_{90} (0.25–2 μg/mL) for *Pasteurella multocida* and *Bordetella bronchiseptica* (20,21), which cause infection in rabbits, the T > MIC has been calculated for MICs of 0.25, 0.5, 1, and 2 μg/mL. Results show that at 8-, 12-, and 24-h intervals, FF following i.v. injection at a dose of 20 mg/kg b.w. for bacteria with MIC values of ≤2 μg/mL maintains T > MIC above 73%, 49%, and 24%, respectively, in all groups. In this study, because the rabbits are critically ill, T > MIC for FF should be above 80% in the time between two consecutive applications. When the experimental data presented here are evaluated according to T > MIC above 80%, the results show that FF at a dose of 20 mg/kg b.w. intravenously administered is sufficient to maintain T > MIC at above 88% for bacteria with MIC values of ≤2 μg/mL at 8-h intervals and above 89% for bacteria with MIC values of ≤1 μg/mL at 12-h intervals with the administration of FM and TN, and above 87% for bacteria with MIC values of ≤0.25 μg/mL at 24-h intervals with the administration of TN only.

In conclusion, FM and TN affected the pharmacokinetic profile of FF when FF, FM, or TN were coadministered in endotoxemic rabbits. Due to their effects, the adjustment of the dosage regimens of FF should be considered. Because the dose regimen suggested in the present study meets the pharmacokinetic/pharmacodynamic criteria in predicting a successful therapy for susceptible bacteria with an MIC of ≤2 μg/mL, it may be considered for clinical use in critically ill rabbits. However, the dosage regimen of FF may be altered according to the pharmacodynamic parameters determined from the pathogens of rabbit origin, the pharmacokinetic parameters obtained in large populations, and the replacement therapy in critically ill rabbits. Further studies are necessary to determine variations in dosage regimens.

Acknowledgment
We thank Atatürk University, Erzurum, Turkey (Veterinary Faculty and Experimental Research Center) for its support.

References

1. Mayeux PR. Pathobiology of lipopolysaccharide. J Toxicol Environ Health 1997; 51: 415–435.
2. Annane D, Bellissant E, Cavaillon JM. Septic shock. Lancet 2005; 365: 63–78.
3. Redl H Bahrami S, Schlag G, Traber DL. Clinical detection of LPS and animal models of endotoxemia. Immunobiology 1993; 187: 330–345.
4. Elmas M, Yazar E, Uney K, Er Karabacak A. Pharmacokinetics of flunixin after intravenous administration in healthy and endotoxaemic rabbits. Vet Res Commun 2006; 30: 73–81.
5. Papich MG, Riviere JE. Chloramphenicol and derivatives, macrolides, lincosamides and miscellaneous antimicrobials. In: Adams HR, editor. Veterinary Pharmacology and Therapeutics. 8th ed. Ames, IA, USA: Iowa State University Press; 2001. pp. 868–897.
6. Zhang X, Song K, Xiong H, Li H, Chu X, Deng X. Protective effect of florfenicol on acute lung injury induced by lipopolysaccharide in mice. Int Immunopharmacol 2009; 9: 1525–1529.
7. Anderson KL, Smith AR, Shanks RD, Davis LE, Gustafsson BK. Efficacy of flunixin meglumine for the treatment of endotoxin-induced bovine mastitis. Am J Vet Res 1986; 47: 1366–1372.
8. Van Donkersgoed J, Berg J, Hendrick S. A comparison of florfenicol-flunixin meglumine versus tulathromycin for the treatment of undifferentiated fever in fall-placed feedlot calves. Vet Ther 2009; 10: 78–85.
9. Verbeeck RK. Pharmacokinetic drug interactions with nonsteroidal anti-inflammatory drugs. Clin Pharmacokinet 1990; 19: 44–66.
10. Li JZ, Fung KF, Chen ZL, Zhang J. Tissue pharmacokinetics of florfenicol in pigs experimentally infected with *Actinobacillus pleuropneumoniae*. Eur J Drug Metab Pharmacokinet 2002; 27: 265–271.
11. El-Aty AM, Goudah A, El-Sooud KA, El-Zorba HY, Shimoda M, Zhou HH. Pharmacokinetics and bioavailability of florfenicol following intravenous, intramuscular and oral administrations in rabbits. Vet Res Commun 2004; 28: 515–524.
12. Park BK, Lim JH, Kim MS, Hwang YH, Yun HI. Pharmacokinetics of florfenicol and its major metabolite, florfenicol amine, in rabbits. J Vet Pharmacol Ther 2007; 30: 32–36.
13. Koc F, Ozturk M, Kadioglu Y, Dogan E, Yanmaz LE, Okumus Z. Pharmacokinetics of florfenicol after intravenous and intramuscular administration in New Zealand White rabbits. Res Vet Sci 2009; 87: 102–105.
14. Koc F, Uney K, Ozturk M, Kadioglu Y, Atila A. Pharmacokinetics and bioavailability of florfenicol in the plasma of Japanese quails. New Zeal Vet J 2009; 57: 388–391.
15. Atef M, El-Gendi AY, Amer AM, El-Aty AM. Effect of three anthelmentics on disposition kinetics of florfenicol in goats. Food Chem Toxicol 2010; 48: 3340–3344.
16. Kim EY, Gebru E, Lee JS, Kim JC, Park SC. Pharmacokinetics of a florfenicol-tylosin combination after intravenous and intramuscular administration to beagle dogs. J Vet Med Sci 2011; 73: 463–466.
17. Wang G, Tu P, Chen X, Guo YG, Jiang SX. Effect of three polyether ionophores on pharmacokinetics of florfenicol in male broilers. J Vet Pharmacol Ther 2013; 36: 494–501.
18. Koc F, Atila A, Karakus E, Cetin N. Determination of florfenicol in plasma of rabbits by high-performance liquid chromatography after solid phase extraction. J Vet Pharmacol Ther 2012; 35: 89–89.
19. Turnidge JD. The pharmacodynamics of beta-lactams. Clin Infect Dis 1998; 27: 10–22.
20. Priebe S, Schwarz S. In vitro activities of florfenicol against bovine and porcine respiratory tract pathogens. Antimicrob Agents Chemother 2003; 47: 2703–2705.
21. Kehrenberg C, Mumme J, Wallmann J, Verspohl J, Tegeler R, Kühn T, Schwarz S. Monitoring of florfenicol susceptibility among bovine and porcine respiratory tract pathogens collected in Germany during the years 2002 and 2003. J Antimicrob Chemother 2004; 54: 572–574.
22. Dunn MJ, Hood VL. Prostaglandins and the kidney. Am J Phys Ren Phys 1977; 233: 169–184.
23. Hasegawa T, Takagi K, Kitaichi K. Effects of bacterial endotoxin on drugs pharmacokinetics. Nagoya J Med Sci 1999; 6: 11–28.
24. Yang KH, Lee MG. Effects of endotoxin derived from *Escherichia coli* lipopolysaccharide on the pharmacokinetics of drugs. Arch Pharm Res 2008; 31: 1073–1086.
25. Liu J, Fung KF, Chen Z, Zeng Z, Zhang J. Pharmacokinetics of florfenicol in healthy pigs and in pigs experimentally infected with *Actinobacillus pleuropneumoniae*. Antimicrob Agents Chemother 2003; 47: 820–823.
26. Shen J, Wu X, Hu D, Jiang H. Pharmacokinetics of florfenicol in healthy and *Escherichia coli*-infected broiler chickens. Res Vet Sci 2002; 73: 137–140.
27. AliAbadi FS, Lees P. Antibiotic treatment for animals: effect on bacterial population and dosage regimen optimisation. Int J Antimicrob Agents 2000; 14: 307–313.
28. Craig WA. Interrelationship between pharmacokinetics and pharmacodynamics in determining dosage regimens for broad-spectrum cephalosporins. Diagn Microbiol Infect Dis 1995; 22: 89–96.
29. McKellar QA, Sanchez Bruni SF, Jones DG. Pharmacokinetic/pharmacodynamic relationships of antimicrobial drugs used in veterinary medicine. J Vet Pharm Therap 2004; 27: 503–514.
30. Toutain PL, Del Castillo JRE, Bousquet-Melou A. The pharmacokinetic-pharmacodynamic approach to a rational dosage regimen for antibiotics. Res Vet Sci 2002; 73: 105–114.