doi: 10.17221/8247-VETMED

Pharmacokinetics of florfenicol following intravenous and intramuscular administration in dogs

Y.O. Birdane, F.M. Birdane

Faculty of Veterinary Medicine, University of Afyon Kocatepe, Afyonkarahisar, Turkey

ABSTRACT: Florfenicol is a synthetic broad-spectrum antibiotic used to treat infectious diseases in veterinary medicine. Limited information is available on the pharmacokinetics and bioavailability of florfenicol in dogs. This study was conducted in six healthy dogs to determine the bioavailability and pharmacokinetics of florfenicol following a single intravenous (*i.v.*) and intramuscular (*i.m.*) dose of 30 mg/kg body weight (b.w.). Blood samples were taken over the course of 24 h post-treatment and the recovered plasma was extracted and analysed using high-performance liquid chromatography (HPLC). Pharmacokinetic analysis was performed using a two-compartment open model. After *i.v.* administration of florfenicol, elimination half-life ($t_{½b}$), volume of distribution at steady state (V_{dss}), total body clearance (Cl_T) and area under curve (AUC_{0-24}) were 3.09 ± 0.13 h, 1.19 ± 0.15 l/kg, 0.37 ± 0.04 l/h/kg, and 59.44 ± 5.27 μg/h/ml, respectively. The peak plasma concentration (C_{max}), time to maximum concentration (t_{max}) and bioavailability (F) were 3.05 ± 0.43 μg/ml, 1.50 ± 0.35 h, and 44.70 ± 6.75%, respectively, following *i.m.* administration. In this study the time that plasma concentration exceed the concentration of 1 μg/ml was approximately 8 h. Therefore, florfenicol should be given twice daily at a dosage of 30 mg/kg b.w. to maintain therapeutic concentration. The pharmacokinetic profile of florfenicol in dogs reveals that it may be therapeutically useful against susceptible microorganisms involved in most common infections in dogs.

Keywords: pharmacokinetics; florfenicol; bioavailability; dogs

Florfenicol is a broad-spectrum, primarily bacteriostatic antibiotic with a range of activity similar to that of chloramphenicol, and is effective against many Gram-negative and Gram-positive organisms (Syriopoulou et al. 1981; Cannon et al. 1990). Florfenicol, a structural analogue of thiamphenicol, is a broad spectrum antibiotic with activity not only against chloramphenicol-sensitive pathogens such as *Pasteurella multocida*, *Pasteurella haemolytica and Haemophilus somnus*, but also against certain chloramphenicol- and thiamphenicol-resistant strains of *Escherichia coli*, *Salmonella typhimurium*, *Shigella dysenteriae*, *Klebsiella pneumoniae*, *Proteus vulgaris and Staphylococcus aureus* (Marshall et al.1996; Booker et al.1997; Varma et al.1998; Ayling et al. 2000). The substitution of a fluorine atom in florfenicol for the hydroxyl group at C-3 site of thiamphenicol prevents acetylation by acetyltransferase (Sams 1994). Although florfenicol is not used in human medicine, the same advantages as those in veterinary medicine would presumably apply, including an efficacy comparable to that of chloramphenicol, lower toxicity and less development of resistance (Decraene et al. 1997).

The pharmacokinetics of florfenicol have been extensively investigated in veal calves (Varma et al. 1986; Adams et al. 1987), cows (Bretzlaff et al. 1987; Soback et al. 1995), horses (McKellar and Varma 1996), goats (Atef et al. 2001), broiler chickens (Shen et al. 2002), pigs (Liu et al. 2003), camels (Ali et al. 2003) North American elk (Alcorn et al. 2004), sheep (Lane et al. 2004; Jianzhong et al. 2004), catfish (Park et al. 2006) and rabbits (Park et al. 2007). However, florfenicol pharmacokinetics in dogs have scarcely been documented (Park et al. 2008, Kim et al.2011). In both of these studies, the analytical methods used and the doses (20 mg/kg and 10 mg/kg) were different than in our study. It is understood that pharmacokinetic parameters of florfenicol in dogs differ from each other. Besides,

doi: 10.17221/8247-VETMED

Park et al. (2008) used pure florfenicol at a dose of 20 mg/kg, and the time of plasma concentration above 2 µg/ml was approximately 4 h. For this reason, they suggested that a dose higher than 20 mg/kg needed to be used. With this recommendation in mind, we decided to assess the dose of 30 mg/kg in dogs. The pharmacokinetic parameters and daily usage dose of a commercial florfenicol preparation in dogs was not known. Without this knowledge, the development of species-specific dosage regimens and evaluation of clinical efficacy is not possible. Therefore the purpose of this study was to determine the kinetic disposition of florfenicol (commercial preparation, 30 mg/kg b.w.) in plasma and its bioavailability after *i.m.* and *i.v.* administration in dogs.

MATERIAL AND METHODS

Chemicals. A commercial formulation of florfenicol containing 300 mg florfenicol per ml (Nuflor®) obtained from CEVA-DIF (Istanbul, Turkey) was used in the study. Pure analytical standards of florfenicol and chloramphenicol were purchased from Sigma (St. Louis, MO, USA). High-performance liquid chromatography (HPLC) grade ethyl acetate and acetonitrile were purchased from Merck® (Darmstadt, Germany).

Animals. Six healthy male crossbred Turkish sheep dogs, aged two to three years and weighing 17–21 kg, were used in this study. The dogs were kept in individual shelters at the Faculty of Veterinary Medicine and fed a commercial diet once a day. Water was available *ad libitum*. All animals were clinically healthy and had not received any drug in the five weeks prior to the study. The Ethics Committee of the Faculty of Veterinary Medicine (086, 29-07, University of Afyon Kocatepe, Afyonkarahisar, Turkey) approved the study protocol.

Experimental design.The study was conducted using a cross-over design with a two weeks interval between each experiment to ensure complete elimination of any residual drugs. Florfenicol was injected intravenously into the right cephalic vein for 20 s. and intramuscularly into the right semimembranosus muscle at a dose of 30 mg/kg b.w. Neither pain nor irritations were observed at the site of injection after the treatment.

Blood samples (5 ml) were collected into tubes with heparin from the catheterised left cephalic vein at 0, 10, 15, 20, 30, 45 min and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 18, 24 h after florfenicol administration. The catheter was flushed with heparinised saline between time points. All the samples were promptly centrifuged at 3000 × *g* for 15 min and the plasma samples were stored at –20 °C until analysis.

Determination of florfenicol concentrations

High performance liquid chromatography (HPLC) was used to measure the plasma concentration of florfenicol. The Dionex HPLC system (Dionex Corporation, Germering, Germany) consisted of a P 680 gradient pump with an ASI-100 autosampler and a Photodiode Array detector (PDA 100). Chromeleon 6.60 chromatography management software (Dionex, Germering, Germany) was used for system control and data processing.

The extraction procedures and HPLC method were modified from a previously published method (Varma et al. 1986). Florfenicol was detected by UV-VIS absorption at 223 nm. The used column was a Dionex C_{18} (5 µm, 4.6 × 150 mm) column. The mobile phase was prepared by mixing 27% acetonitrile and 73% de-ionised water and the flow rate was 1.0 ml/min.

Chloramphenicol was used as an internal standard in the analytical method. Frozen plasma samples were thawed at room temperature and then 0.5 ml plasma were added to tubes containing 10 µl of a 5 µg/ml internal standard. After mixing each sample, 0.5 ml of 0.1M phosphate buffer (pH 7) was added and then the tubes were spun. Four ml of ethyl acetate were added to this mixture, after which tubes were capped and centrifuged spun for 15 min. The samples were then centrifuged at 3000 × *g* for 10 min. The plasma sample was extracted twice with 4 ml ethyl acetate. The organic layer was collected and dried under a stream of nitrogen at 45 °C. After evaporation, each residue was reconstituted in 200 µl of the mobile phase and 50 µl was injected into the HPLC system for analysis.

Pharmacokinetic analysis. The plasma concentration of drug versus time curves for each individual animal were analysed using the PKCALC computer programme (Shumaker 1986) using a least-squares regression analysis. Selection of the compartmental pharmacokinetic model that best fitted the data was made on the basis of the coefficient of determination (r^2) and Akaike information criterion (AIC) (Yamaoka et al. 1978).

doi: 10.17221/8247-VETMED

Following *i.v.* and *i.m.* administrations, a two-compartment open model was found to best fit the data suggesting the use of the following exponential equations:

$$C = A_1e^{-at} + A_2e^{-bt} \qquad (i.v.)$$

$$C = A_1e^{-at} + A_2e^{-bt} - A_3e^{-kat} \qquad (i.m.)$$

where:

C = plasma concentration of florfenicol
A_1, A_2, A_3 = mathematical coefficients
α = hybrid rate constant for the distribution phase
β = hybrid rate constant for the terminal elimination phase
k_a = the first-order absorption rate constant
e = mathematical coefficient
t = time

After *i.v.* and *i.m.* administrations, the area under the concentration time curves (AUC) was calculated using the trapezoidal method.

The systemic bioavailability F(%) is the fraction of the intramuscular dose absorbed and is calculated as $(AUC_{0-24\,i.m}/AUC_{0-24\,i.v}) \times 100$. Pharmacokinetic variables were also calculated using compartmental analysis based on the equations described by Wagner (1975). From these data, the half-life of the a phase ($t_{½a}$), the half-life of the b phase ($t_{½b}$), mean residence time (MRT), volume of distribution in steady state (V_{dss}), total plasma clearance (Cl_T), bioavailability [F(%)], maximum plasma concentration (C_{max}) and time to reach C_{max} (t_{max}) were estimated. C_{max} and t_{max} were determined directly from the data. All results are presented as mean ± SD.

RESULTS

The calibration curve prepared from dog plasma spiked with known amounts of drugs was linear between 0.030–15 µg/ml florfenicol. Correlation coefficients of calibration curves were more than 0.999. Intra-day and inter-day coefficients of variation were average 3.6% and 5.4%, respectively. The lower quantitation limit of florfenicol was approximately 0.030 µg/ml. The mean analytical recovery for florfenicol in plasma samples was more than 98%. Retention time for florfenicol was about 7 min.

All animals were clinically healthy throughout the experiment and no adverse effects were observed in any of the dogs. The plasma concentration–time data and pharmacokinetic parameters for florfenicol after single *i.v.* and *i.m.* administrations of 30 mg/kg b.w. in dogs are presented in Figure 1 and Table 1, respectively. Obtained data were best fitted to a biexponential equation (two compartment open model). The plasma concentration of florfenicol at 10 min after *i.v.* and *i.m.*

Table 1. Pharmacokinetic parameters of florfenicol following intravenous and intramuscular injection at a single dose (30 mg/kg) in dogs (mean ± SD, n = 6)

Parameters	Intravenous	Intramuscular
AUC_{0-24} (µg/h/ml)	59.44 ± 5.27	26.43 ± 3.62
$t_{½a}$ (h)	0.10 ± 0.03	2.09 ± 0.88
$t_{½b}$ (h)	3.09 ± 0.13	8.57 ± 1.65
MRT (h)	3.52 ± 0.17	11.95 ± 1.68
C_{max} (µg/ml)	NA	3.05 ± 0.43
t_{max} (h)	NA	1.50 ± 0.35
V_{dss} (l/kg)	1.19 ± 0.15	NA
Cl_T (l/h/kg)	0.37 ± 0.04	NA
F (%)	NA	44.70 ± 6.75

AUC = areas under the concentration time curves; $t_{½a}$ = the half-life of the a phase; $t_{½b}$ = the half-life of the b phase; MRT = mean residence time; C_{max} = maximum concentration; t_{max} = time to maximum concentration; V_{dss} = volume of distribution at steady-state; Cl_T = total plasma clearance; F = bioavailability, NA = not applicable

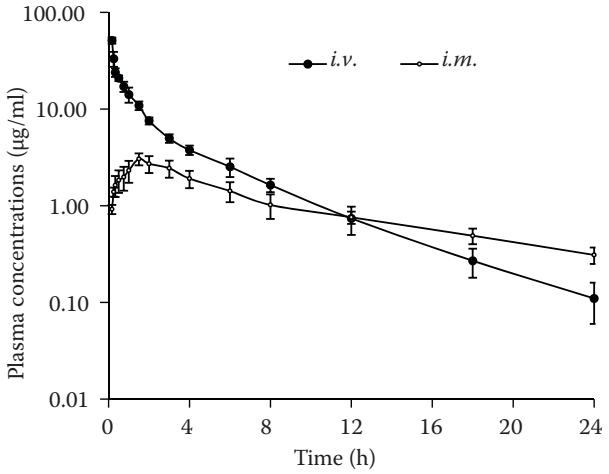

Figure 1. Semi-logarithmic plot of plasma concentrations-time curves of florfenicol after intravenous (*i.v.*) and intramuscular (*i.m.*) administrations at a dose of 30 mg/kg b.w. to dogs (n = 6)

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administration was 51.22 ± 3.72 µg/ml and 0.92 ± 0.1 µg/ml, respectively. The level of florfenicol was quantifiable 24 h after *i.v.* dosing (0.10 ± 0.08 µg/ml) and after *i.m.* dosing (0.31 ± 0.07 µg/ml).

Following *i.v.* injection the total body clearance was 0.37 ± 0.04 l/kg/h, with the volume of distribution at steady-state being 1.19 ± 0.15 l/kg. Elimination half-life was 3.09 ± 0.13 h. The value indicates a rapid elimination of the drug following *i.v.* administration in dogs.

After *i.m.* administration, observed C_{max} values (3.05 ± 0.43 µg/ml) were at 1.50 ± 0.35 h (t_{max}). The bioavailability (*F*) of florfenicol after *i.m.* administration was 44.70 ± 6.75%.

DISCUSSION

This study shows that florfenicol plasma concentration values after both types of administration (*i.m.* and *i.v.*) in dogs were best fitted to a two compartment open model. These results are in agreement with the findings of previous studies on florfenicol performed in sheep (Ali et al. 2003; Lane et al. 2004), goats (Atef et al. 2001; Ali et al. 2003), calves (Varma et al. 1986; Adams et al. 1987; Decraene et al. 1997) and broiler chickens (Shen et al. 2003). However, Lobell et al. (1994), Soback et al. (1995) and Jianzhong et al. (2004) found that the disappearance of florfenicol from the plasma after *i.v.* administration was described adequately by a three compartment term. These differences are unlikely to be of clinical importance.

After *i.v.* injection of florfenicol, the elimination half-life ($t_{½b}$) of the drug in the plasma of dogs was calculated in the present study to be 3.09 h. This finding was in agreement with the time of 3.2 h reported in cattle (Bretzlaff et al.1987), 2.87–3.18 h in calves (Varma et al. 1986; Adams et al. 1987; Decraene et al. 1997), 2.61 h in goats (Atef et al. 2001) and 3.02 h in broiler chickens (Shen et al. 2003). However, this value (3.09 h) was also much longer than those reported in several previous studies: 1.1 h in dogs (Park et al. 2008), 1.49 h in camels (Ali et al. 2003), 1.31–1.09 h in sheep (Ali et al. 2003; Lane et al. 2004), 1.80 h in equines (McKellar and Varma 1996) and 1.54–0.90 h in rabbits (Abd El-Aty et al. 2004; Park et al. 2007). Differences in kinetic parameters are relatively common, and frequently related to interspecies variation, age, breed, health status of the animals and/or the assay method used. The value of AUC (59.44 l/kg/h) after *i.v.* administration of florfenicol in our study was similar to that recorded in sheep (Jianzhong et al. 2004), camels (Ali et al. 2003), and higher than goats (Atef et al. 2001), chickens (Shen et al. 2003), rabbits (Park et al. 2007) and dogs (Kim et al. 2011), which showed that florfenicol was distributed rapidly in dogs.

Our results demonstrated that florfenicol is quickly and widely distributed after *i.v.* administration in dogs with a half-life ($t_{½a}$ h) of 0.10 h and a V_{dss} of 1.19 l/kg, which suggests good penetration through biological membranes into the body tissues. The V_{dss} was similar to the 1.20 l/kg reported in pigs (Liu et al. 2003), 1.45 l/kg in dogs (Park et al. 2008) and 1.51 l/kg in chickens (Shen et al. 2002). However, this value differs from those reported in sheep (V_{dss} = 0.50 l/kg, Lane et al. 2004; V_{dss} = 1.71 l/kg, Jianzhong et al. 2004) and goats (V_{dss} = 1.69 l/kg, Atef et al. 2001; V_{dss} = 0.69 l/kg, Ali et al. 2003). In the present study, florfenicol was more widely distributed than what has been reported for thiamphenicol in dogs (0.66 l/kg; Castells et al. 1998). Florfenicol is a lipophilic drug and the V_{dss} may be related to the physiochemical characteristics of the drug.

The total body clearance (0.37 l/kg/h) after *i.v.* administration was shorter than the 1.03 l/kg/h for florfenicol reported in beagle dogs (Park et al. 2008). However, the value was similar to those reported in veal camels, sheep (Ali et al. 2003), rabbits (Abd El-Aty et al. 2004), pigs (Liu et al. 2003) and dogs (Kim et al. 2011). The Cl_T was similar to that reported for thiamphenicol in dogs (Castells et al. 1998). Bretzlaff et al. (1987) suggested that the small Cl of florfenicol in animals is due to the replacement of – OH in chloramphenicol and thiamphenicol by – *F* in the structure florfenicol, which thereby prevents the conjugation with glucuronic acid and delays its excretion. These little differences may be related to differences in metabolism, analytical methods or the metabolic body size of the animals under study.

After *i.m.* injection of florfenicol, a maximum plasma concentration (C_{max}) of 3.05 µg/ml was attained post administration. The t_{max} value (1.5 h) was consistent with values recorded in goats (Atef et al. 2001), sheep (Jianzhong et al. 2004), and camels (Ali et al. 2003).

The bioavailability of florfenicol after *i.m.* administration of 30 mg/kg (b.w.) was 44.70 ± 6.75%. The

doi: 10.17221/8247-VETMED

value was similar to that recorded for florfenicol in lactating cows (38%; Soback et al. 1995), while higher than that for chloramphenicol in cattle (19%; Sanders et al. 1988) and lower than that recorded for florfenicol in rabbits (Abd El-Aty et al. 2004), sheep (Jianzhong et al. 2004), goats (Atef et al. 2001). This difference in bioavailability from the intramuscular site might be due to differences in regional blood flow from muscle tissues.

The MRT of florfenicol was 3.52 and 11.95 h after *i.v.* and *i.m.* administration, respectively. The plasma concentration – time curve after *i.m.* administration can be considered as representing a 'flip-flop' situation. The commercially available formulation of florfenicol is long-acting, so that "flip-flop" kinetics occurred, where elimination is prolonged due to slow absorption from the injection site (Abd El-Aty et al. 2004; Switala et al. 2007). The absorption of florfenicol after intramuscular administration appeared slow and the kinetic parameters and serum concentration time curve were suggestive of absorption rate-dependent elimination (Soback et al. 1995).

Pharmacokinetic/pharmacodynamic properties of the main classes of antibiotics need to be taken into account in order to optimise their efficacy (MacGowan and Bowker 1997; Andes and Craig 2002; Tautain et al. 2002). Florfenicol is a time-dependent antimicrobial agent that shows strong bactericidal activity at MICs for *Pasteurella multocida*, *Actinobacillus* p*leuropneumoniae*, *Mannheimia haemolytica*, and *Histophilus somni* and bacteriostatic activity at the MIC for *Staphylococcus aureus* (Pasmans et al. 2008). For bacteriostatic antibiotics, T > MIC is the most important parameter. In this regard, additional work is needed for florfenicol. The minimum inhibitory concentrations (MICs) of florfenicol for bacterial isolates from dogs have not yet been determined. Based on the MIC data for bacteria from fish, swine, calves and cows, 1–2 µg/ml florfenicol showed high efficacy against most bacteria (Varma et al. 1986; Bretzlaff et al. 1987; Ueda et al. 1995; Ho et al. 2000). In this study, the time of plasma concentration above 1 µg/ml was approximately 8 h. Therefore, florfenicol should be given twice daily at a dosage of 30 mg/kg b.w. to maintain therapeutic concentration. The pharmacokinetic profile of florfenicol in dogs reveals that it may be therapeutically useful against susceptible microorganisms involved in most common infections in dogs. Clinical use in dogs should be approached carefully before efficacy is determined and toxicological studies are conducted.

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Received: 2014–07–02
Accepted after corrections: 2015–04–28

Corresponding Author:

Assoc. Prof. Dr. Yavuz Osman Birdane, University of Afyon Kocatepe, Faculty of Veterinary Medicine, Department of Pharmacology and Toxicology, 03200 Afyonkarahisar, Turkey
E-mail: ybirdane@aku.edu.tr