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Pharmacokinetic parameters and optimal dosage of a florfenicol and tylosin mixture in beagle dogs

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ABSTRACT: The aims of this study were to evaluate the *in vitro* antibacterial activity of a florfenicol and tylosin mixture and to determine the pharmacokinetic parameters of each drug following administration of the 2 : 1 florfenicol and tylosin mixture in beagle dogs. The antibacterial activity of the two antibiotics, both singly and as a mixture, was investigated in bacteria isolated from 119 beagle dogs. Minimum inhibitory concentrations were determined using the broth dilution method, whereas the checkerboard assay was used to evaluate the antibacterial effects of the combination of florfenicol and tylosin. The pharmacokinetic parameters of the two antibiotics were determined following administration of the mixture in beagle dogs. Serum concentrations of both drugs were analysed using high-performance liquid chromatography. Pharmacokinetics parameters such as area under the concentration-time curve, absolute bioavailability and systemic clearance were determined using non-compartmental analysis. The results showed that tylosin and florfenicol exerted varying degrees of antibacterial activity against the tested isolates. The combination of florfenicol and tylosin produced a synergistic and additive antibacterial effect. Analysis of the serum samples revealed a rapid and almost complete absorption of florfenicol and tylosin with mean bioavailabilities of 92.7% and 106.1%, respectively. The times needed to reach maximum concentration for florfenicol and tylosin were 1.5 and 3 h, respectively. Moreover, intramuscular injection of the mixture to beagle dogs resulted in serum concentrations that were higher than the corresponding minimum inhibitory concentrations in beagle dogs. This is the first study to report optimisation of florfenicol and tylosin doses following administration of a combination of the two drugs to beagle dogs.

Keywords: antibacterial activity; drug combination; serum concentration; synergistic interaction

Antimicrobial combinations are commonly used with the objectives of enhancing efficacy, safety and minimising resistance (Eliopoulos and Moellering 1991). Florfenicol is a derivative of thiamphenicol and chloramphenicol, with a better spectrum of activity (Sams 1994). Tylosin, a macrolide antibiotic, is widely used in veterinary medicine for the treatment of infectious diseases caused by Gram-positive bacteria (Gutierrez-Martin and Rodriguez-Ferri 1993). A combination of florfenicol and tylosin (2 : 1) (w/w) is currently marketed in Asia, especially in Korea, for bacterial diseases of dogs. The pharmacokinetic parameters of florfenicol (Ali et al. 2003; Liu et al. 2003; Park et al. 2008; Koc et al. 2009) and tylosin (Weisel et al. 1977; Prats et al. 2002; Ji et al. 2013) have been thoroughly studied in different animal species including dogs. These studies have shown that florfenicol has high bioavailability and good distribution into tissues. It is also known to be rapidly eliminated from the body, whereas tylosin is highly lipid-soluble with moderate binding to serum proteins and a wide range of distribution.

In spite of the widespread clinical use of two different doses each of florfenicol and tylosin as a mixture (FTD mixture) (tylosin 2.5 mg/kg and florfenicol 5 mg/kg body weight; tylosin 5 mg/kg and florfenicol 15 mg/kg body weight) in pigs and dogs in Korea, only limited information is available on the pharmacokinetic parameters of each drug

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following administration. In our previous studies, the pharmacokinetic variables of florfenicol and tylosin after intramuscular (*i.m.*) and intravenous (*i.v.*) administration of a mixture at a dose of 10–20 mg/kg of florfenicol and 5–10 mg/kg of tylosin were investigated in dogs (Kim et al. 2011) and pigs (Kim et al. 2008). However, the pharmacokinetic parameters and optimal doses of florfenicol and tylosin following administration of the mixture at 5 mg/kg of florfenicol and 2.5 mg/kg of tylosin, the most frequently used dose combination, have not been fully documented in dogs. From the above observations, we hypothesised that the combination of florfenicol and tylosin may have a synergistic effect against pathogenic bacteria from dogs in vitro, and that the combined administration of 5 mg/kg of florfenicol and 2.5 mg/kg tylosin would also possess sufficient pharmacokinetic properties in dogs. Therefore, the aims of this study were to investigate the antibacterial activity, pharmacokinetic parameters and the optimal doses of florfenicol and tylosin after administration of a mixture of 5 mg/kg of florfenicol and 2.5 mg/kg tylosin in beagle dogs.

MATERIAL AND METHODS

Minimum inhibitory concentrations. Specimens were collected from 119 adult and juvenile dogs of both sexes brought to the Gyeongbuk Veterinary Service Laboratory, Republic of Korea. The dogs had shown clinical signs of pyoderma, otitis externa, respiratory tract infections and diarrhoea. In addition, the animals had no records of prior antibiotic treatment. Faecal swabs and swab samples from skin, ears, throat and nose were collected from 119 dogs. Bacteria, including *Staphylococcus intermedius* (n = 11), *Staphylococcus aureus* (n = 10), *Pasteurella* spp. (n = 10), *Escherichia coli* (n = 11) and *Bordetella bronchiseptica* (n = 11) were isolated and characterised based on standard microbiological procedures (Isenberg 1995; Hoekstra and Paulton 2002; Pedersen et al. 2007). The minimum inhibitory concentrations (MICs) for florfenicol, tylosin and the FTD mixture were determined using the broth dilution method (CLSI 2012). MICs were determined as the minimum concentrations of antibiotics in which visible bacterial growth was inhibited after 24 h of incubation. For quality control purposes, *E. coli* ATCC 25922, *S. aureus* ATCC 29213, *S. intermedius* ATCC 29663 and *B. bronchsiptica* ATCC 10580 were used in all MIC assays. In addition, *Pasturella* spp. were included in every test run to confirm the final inoculum concentration of approximately 5×10^5 CFU/ml. The susceptibility of the bacterial isolates to the tested antibiotics was determined by comparing the MIC values with the breakpoints set by CLSI and/or published reports, when available (Vaara 1993; CLSI 2002; Ganiere et al. 2005; Pedersen et al. 2007; Scott et al. 2010; Awji et al. 2012, Pyorala et al. 2014).

Checkerboard assay. Fractional inhibitory concentration (FIC) index values were calculated to determine the antibacterial effects that resulted from the interaction of florfenicol and tylosin as follows:

FIC index = FIC (F) + FIC (T)

where: FIC (F) = minimum inhibitory concentration (F) in combination/minimum inhibitory concentration (F) alone; FIC (T) = minimum inhibitory concentration (T) combination/minimum inhibitory concentration (T) alone

FIC values less than 0.5, between 0.5 and 1, between 1 and 4 and greater than 4 were interpreted as synergistic, additive, indifferent and antagonistic effects, respectively (Meletiadis et al. 2010).

Animals and experimental design. One-to-two-year-old Beagle dogs (n = 6; males) weighing 8–10 kg were housed separately and provided with a commercial diet. Water was given *ad libitum*. Prior to the experiment and during the acclimation period, a clinical investigation was carried out and the animals were found to be healthy. In addition, the dogs did not have a history of treatment prior to the experiment. Experimental procedures were conducted in accordance with international guidelines. The study was approved by the bioethics committee of the College of Veterinary Medicine (CVM 200712), Kyungpook National University (Republic of Korea).

A randomised crossover design was conducted in six dogs allocated into two groups. Group 1 received 5 mg/kg of florfenicol and 2.5 mg/kg of tylosin through the jugular vein. Similar doses were given to the other group into the inner thigh muscle. A single dose of the FTD mixture (FTD-inj, Shinilbiogen Co.) that represents 5 mg/kg of florfenicol and 2.5 mg/kg of tylosin was calculated taking into account the 2 : 1 ratio of florfenicol

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(100 mg/ml) to tylosin tartrate (50 mg/ml) in the combined product into consideration. Most importantly, our previous study showed the absence of detectable levels of both drugs in serum taken randomly from dogs one week after administration through both routes. In addition, serum and tissue analysis from pigs slaughtered 14 days after *i.m.* injection did not reveal detectable levels of either florfenicol or tylosin. Therefore, after a washout period of 14 days the routes of administration were exchanged. Blood samples were then collected at 0, 0.25, 0.5, 1, 2, 4, 6, 8, 12 and 24 h after drug administration. The samples were kept at room temperature for clot retraction and centrifuged at 2000 × *g* for 10 min. Serum was separated and frozen at –20 °C pending analysis.

HPLC analysis. Tylosin, florfenicol and the FTD mixture containing florfenicol (100 mg/ml) and tylosin tartarate (50 mg/ml) were supplied by Shinilbiogen Co., Seoul, Republic of Korea. HPLC-grade chemicals and reagents (Sigma) were used for extraction of samples. Serum samples were analysed with a Hewlett Packard 1100 HPLC System using HP octadecyl silica columns (200 × 4.6 mm; particle size, 5 µm), a HPLC pump, an auto-injector and a UV lamp system. The HPLC methods, including the mobile phase, flow rate and detection wavelength were determined based on a previously established and validated method (Kim et al. 2011).

Pharmacokinetic analysis. The concentrations of florfenicol and tylosin obtained from analysis of serum samples taken from 0 to 24 h were analysed with WinNonlin software (Version 5.2, Pharsight Corporation, and USA). Non-compartmental analysis was used to determine parameters such as area under the concentration-time curve (AUC), absolute bioavailability ($AUC_{i.m.}/AUC_{i.v.} \times 100\%$) and systemic clearance (Cl = Dose/AUC). Data were analysed using SAS software (SAS Institute, Inc. version 9) and results were presented as mean ± standard deviation (SD).

RESULTS

The MICs of tylosin, florfenicol and the FTD mixture against bacterial isolates from dogs are shown in Table 1. The antibacterial activity of tylosin was limited to the Gram-positive bacteria with an MIC value of 0.5 µg/ml, whereas florfenicol demonstrated a relatively broad antibacterial activity with MIC values ranging between 0.5 and 2 µg/ml. The MICs of the FTD mixture were similar to those of florfenicol in all of the tested bacteria except *S. intermedius*. FICI values obtained from the checkerboard assay indicated that the FTD mixture exerted an additive antibacterial effect against all of the tested isolates except for *S. intermedius* and *S. aureus*, against which it exerted synergistic and indifferent responses, respectively.

Curves of serum concentrations of florfenicol and tylosin versus time following *i.v.* and *i.m.* administration of the florfenicol and tylosin mixture (2 : 1) to beagle dogs are shown in Figure 1A and 1B. The effects of concentration and time on the pharmacokinetic parameters of florfenicol and tylosin are displayed in Table 2. Intramuscular administration of the mixture to beagle dogs resulted in a mean bioavailability of 92.7% for florfenicol and 106.1% for tylosin. Maximum serum concentrations of florfenicol and tylosin were achieved after 1.5 and 3 h of administration, respectively. The volume of distribution of tylosin was higher than that of florfenicol. In contrast to tylosin, florfenicol was rapidly eliminated following *i.m.* administration as compared with the *i.v.* injection.

DISCUSSION

The clinical isolates of *S. aureus* in this study were susceptible to tylosin when compared with the MIC breakpoint of 1 µg/ml reported in a quality control strain (Odland et al. 2000) and clinical isolates (Bonnier et al. 2006). The MIC breakpoint for

Table 1. Minimal inhibitory concentration (µg/ml) and fractional inhibitory concentration (FIC) of florfenicol (FLO), tylosin (TYS) and florfenicol-tylosin mixture (FTD) against five bacterial species isolated from dogs

Antibiotics	*S. intermedius* (*n* = 11)	*S. aureus* (*n* = 10)	*E. coli* (*n* = 11)	*Pasturella* spp. (*n* = 10)	*B. bronchsiptica* (*n* = 11)
TYS	0.125–1 (0.25) [RB]	0.25–1 (1)	> 256	> 256	16–64
FLO	0.5–4 (2)	0.5–8 (8)	0.5–8 (8)	2–8 (2)	1–8 (2)
FTD	0.125–1	0.5–2	2–4	1–16	2–8
FIC	0.25–0.5	1–2	0.67–1	0.67–1	0.6–1

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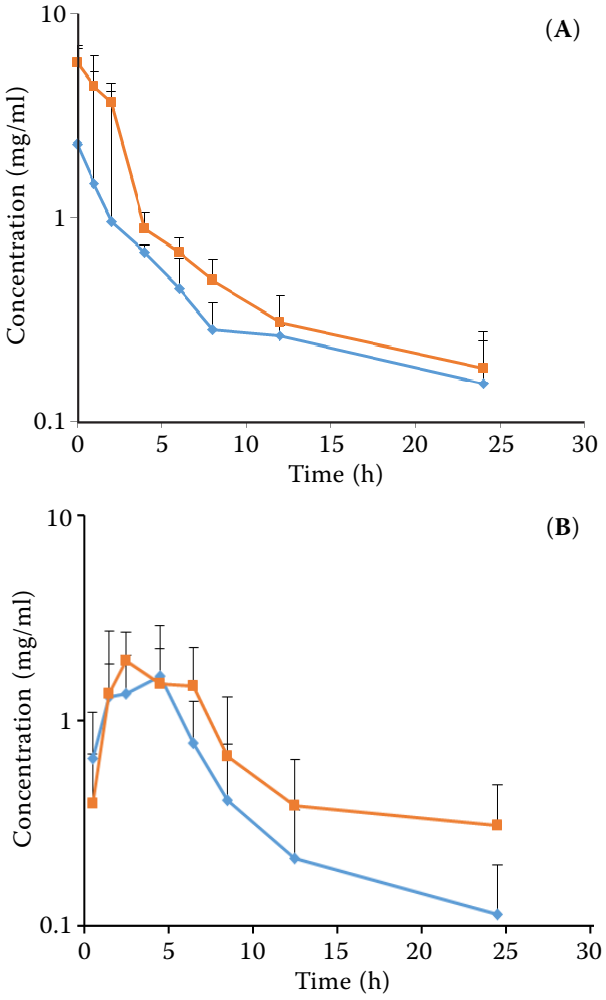

Figure 1. Semi-logarithmic plot of serum drug concentration versus time after intravenous (**A**) and intramuscular (**B**) administration of a combination of florfenicol and tylosin (2 : 1); values represent mean ± SD (n = 6)
= florfenicol (5 mg/kg), = tylosin (2.5 mg/kg)

tylosin is not available for *S. intermedius* in dogs; however; all the isolates had MICs of 0.5 µg/ml which are slightly different from what was reported previously (0.25 µg/ml) (Scot et al. 2010). The lower susceptibility of Gram-negative bacterial isolates to tylosin in this study was not surprising, because the drug has poor permeability across the bacterial wall (Vaara 1993) and hence, the bacteria are inherently resistant to its action (Pyorala et al. 2014).

The clinical *E. coli* and *S. aureus* isolates investigated in the current study were susceptible to florfenicol with an MIC breakpoint of 8 µg/ml (Pedersen et al. 2007; Awji et al. 2012). Meanwhile, the MIC values of florfenicol in *B. bronchseptica*, *S. intermedius* and Pasteurella species found in this study fall into the susceptible range with respect

Table 2. Pharmacokinetic parameters of florfenicol and tylosin (mean ± SEM) after intramuscular and intravenous administration of a combination of florfenicol and tylosin (2 : 1) to beagle dogs (n = 6)

Parameter	Florfenicol		Tylosin	
	i.v.	*i.m.*	*i.v.*	*i.m.*
Tmax (h)	–	1.5 ± 0.22	–	3.0 ± 0.44
Cmax (µg/ml)	–	2.18 ± 0.47	–	1.79 ± 0.26
AUC_{0-24} (µg.h/ml)	15.6 ± 4.62	14.5 ± 3.85	11.22 ± 2.16	9.24 ± 1.25
Ke (l/h)	0.17 ± 0.02	0.18 ± 0.01	0.09 ± 0.01	0.08 ± 0.01
T1/2el (h)	4.57 ± 1.07	3.9 ± 0.3	8.44 ± 1.38	9.95 ± 2.68
Vd (l/kg)	2.0 ± 0.65	–	2.72 ± 0.32	–
Cl (l/kg/h)	0.34 ± 0.08	–	0.35 ± 0.12	–
F (%)		92.7 ± 11.6		106.1 ± 36

Cmax and Tmax = peak serum concentration and time required to attain maximum concentration, respectively; AUC_{0-24} = area under the serum concentration time curve from time zero to 24 h; Ke = elimination rate constant; T1/2el = elimination half-life; Vd = volume of distribution; F = bioavailability; Cl = total body clearance

to the ≤ 2 µg/ml MIC breakpoint reported in the CLSI (2002) and by Ganiere et al (2005). Most importantly, our results indicate that the mixture of florfenicol and tylosin produces an additive and synergistic response against most of the tested bacterial isolates except *S. aureus*. Interestingly, tylosin acts as a potentiator of florfenicol in Gram-negative isolates. Thus, the clinical use of tylosin and florfenicol mixtures is advantageous to increase the antibacterial activity of both drugs.

The bioavailability of florfenicol after *i.m.* administration of the FTD mixture was lower than that reported in previous studies following high-dose injection of the mixture in beagle dogs (Kim et al. 2011) and after administration of florfenicol alone to dogs and other species of animals (Ali et al. 2003; Jiang et al. 2006; Park et al. 2008). Similarly, the average volume of distribution of florfenicol was slightly lower than our previous value of 2.6 l/kg, which was obtained after administering a high-dose FTD mixture to the same animal species. In addition, the elimination half-lives of florfenicol after *i.v.* and *i.m.* injections of the mixture were slightly shorter as compared with the findings following administration of high doses of a similar preparation (Kim et al. 2011). However, it was significantly longer compared to the 1.1-hour elimination half-

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life reported in dogs following 20 mg/kg *i.v.* administration of florfenicol only (Park et al. 2008). The variation in the pharmacokinetic parameters of florfenicol observed in this study might be due to differences in the dose and in the methods used for pharmacokinetic analysis.

The volume of distribution and prolonged terminal half-lives of tylosin found after administration of the mixture were comparable to our previous findings in beagle dogs (Kim et al. 2011). In contrast, other studies have shown that serum concentrations of tylosin fell rapidly after *i.m.* injection in different animal species (Duthu et al. 1985; Taha et al. 1999). The prolonged elimination half-lives of tylosin in the current study might have resulted from the interactions between the two drugs and the subsequent effects on metabolism and renal clearance (Kim et al. 2011).

Determining dosage regimens, dose, and frequency of administration of an antibacterial is dependent on how long blood or tissue concentration stays above the MIC. On the other hand, there is a paucity of data on the optimal doses of florfenicol and tylosin following administration of a combination of these drugs in beagle dogs. The current study demonstrates that the MIC of florfenicol ranges from 0.5–2 μg/ml. In addition, MIC values of less than 0.5 μg/ml were reported in most pathogenic bacteria (Priebe and Schwarz 2003). On the other hand, the MIC of tylosin against *S. intermedius* and *S. aureus* was 0.5 μg/ml, while values of below 2 μg/ml MIC were reported in canines for *Clostridium difficile* and *Clostridium perfringens* (Marks and Kather 2003). In determining the optimal dosage, we took into account previous reports and current data regarding MICs and pharmacokinetic parameters of florfenicol and tylosin. Average plasma florfenicol and tylosin concentrations of 0.5 mg/ml and 2 mg/ml, respectively, were considered as desired MIC values for common canine pathogens with a 12-h dosage interval. Accordingly, the recommended *i.m.* dosages in dogs was calculated from the following equations:

$$IDF = [(C_{ave} \times Vd_{ss} \times 12\ h/1.44)/T_{1/2}\beta] = [(0.5\ mg/l \times 2\ l/kg \times 12\ h/1.44)/3.9\ h] = 2.14\ mg/kg$$

i.m. dose of tylosin = [(2.0 mg/l × 2.72 l/kg × 12 h/1.44) /9.95 h] = 4.56 mg/kg

where: IDF = intramuscular dose of florfenicol, C_{ave} = average plasma concentration, Vd_{ss} = volume of distribution, $T_{1/2}\beta$ = elimination half-life

Therefore, combined *i.m.* injection of florfenicol and tylosin at a dose of 5 mg/kg florfenicol and 2.5 mg/kg tylosin could result in serum concentrations of florfenicol and tylosin greater than their corresponding minimum inhibitory concentrations.

In conclusion, combined administration of florfenicol-tylosin at 5 mg/kg and 2.5 mg/kg, respectively, to beagle dogs resulted in a significant absorption of florfenicol and tylosin without any noticeable side effects. The combination ensured a good distribution of both drugs with slow elimination rate. The results of this study indicate that lower doses of FTD mixtures (5 mg/kg florfenicol and 2.5 mg/kg tylosin) could be considered in beagle dogs as they can produce the same pharmacological effect as the routinely used high-dose mixture. Additional pharmacodynamic and toxicological studies are needed prior to clinical usage of the mixture in dogs.

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