Pharmacokinetics of sarafloxacin in pigs and broilers following intravenous, intramuscular, and oral single-dose applications

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Pharmacokinetics of sarafloxacin, a fluoroquinolone antibiotic, was determined in pigs and broilers after intravenous (i.v.), intramuscular (i.m.), or oral (p.o.) administration at a single dose of 5 (pigs) or 10 mg/kg (broilers). Plasma concentration profiles were analysed by a noncompartmental pharmacokinetic method. Following i.v., i.m. and p.o. doses, the elimination half-lives ($t_{1/2\beta}$) were 3.37 ± 0.46, 4.66 ± 1.34, 7.20 ± 1.92 (pigs) and 2.53 ± 0.82, 6.81 ± 2.04, 3.89 ± 1.19 h (broilers), respectively. After i.m. and p.o. doses, bioavailabilities (F) were 81.8 ± 9.8 and 42.6 ± 8.2% (pigs) and 72.1 ± 8.1 and 59.6 ± 13.8% (broilers), respectively. Steady-state distribution volumes ($V_{d(ss)}$) of 1.92 ± 0.27 and 3.40 ± 1.26 L/kg and total body clearances (Cl_B) of 0.51 ± 0.03 and 1.20 ± 0.20 L/kg/h were determined in pigs and broilers, respectively. Areas under the curve (*AUC*), mean residence times (*MRT*), and mean absorption times (*MAT*) were also determined. Sarafloxacin was demonstrated to be more rapidly absorbed, more extensively distributed, and more quickly eliminated in broilers than in pigs. Based on the single-dose pharmacokinetic parameters determined, multiple dosage regimens were recommended as: a dosage of 10 mg/kg given intramuscularly every 12 h in pigs, or administered orally every 8 h in broilers, can maintain effective plasma concentrations with bacteria infections, in which MIC_{90} are <0.25 μg/mL.

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INTRODUCTION

Sarafloxacin is a fluoroquinolone exclusively used in preventive and therapeutic treatments in animals. It has high antimicrobial activity *in vitro* against a wide variety of Gram-negative and Gram-positive bacterial and mycoplasma such as *Staphylococcus aureus*, *Streptococcus*, *Escherichia coli*, *Klebsiella* sp., *Salmonella* sp., etc. (Eliopoulos *et al.*, 1985; Fernandes *et al.*, 1986; Smith *et al.*, 1986; Bansal & Thadepalli, 1987; Digranes & Dibb, 1988). In veterinary medicine, sarafloxacin seems to have a great potential for treating infections caused by bacteria (Zeng *et al.*, 2000). With its broad spectrum of antibacterial activity and good distribution in most tissues and body fluids as well as low incidence of adverse effects, sarafloxacin has been used in many types of infections. Successful therapeutic application of sarafloxacin requires detailed information on pharmacokinetic properties in those food-producing animals. To date, several studies have been published regarding pharmacokinetics of sarafloxacin in Atlantic salmon (Martinsen *et al.*, 1993a,b, 1994; Gingerich *et al.*, 1995). However, there is a paucity of information in the literature regarding pharmacokinetics of sarafloxacin in pigs or broilers. The objective of this paper is to describe and compare the absorption, distribution and elimination of sarafloxacin after intravenous (i.v.), intramascular (i.m.), or oral (p.o.) administration in pigs and broilers. With the pharmacokinetic parameters determined from the studies, reasonable multiple dosage regimens for sarafloxacin can be designed, which can be recommended for clinical treatment.

MATERIALS AND METHODS

Animals

Two-month-old castrated cross-bred (Duroc × Landrace × Yorkshire) pigs ($n = 7$) were used for the studies. The average body weight of the pigs was 22.7 ± 3.6 kg (range of 18–29 kg). Pigs were housed indoor and fed daily with drug-free commercial pellet diet. Pigs had free access to drinking water.

A total of 30 broilers were also used in the studies. The average body weight was 1.63 ± 0.16 kg (range of 1.48–1.96 kg). The broilers were provided a drug-free pelleted diet and given water *ad libitum*. All the pigs and chickens were in good health as determined by physical examination before drug administration. The animals were humanely handled according to the approved IACUC protocols in South China Agricultural University.

Drugs and chemical agents

Sarafloxacin (Standard, 99.9% or 2.5% injectable, Lot # 971107 or 971101) was donated by Guangzhou Huihua Animal Health Products Co. Ltd. (Guangzhou, China). Enrofloxacin (99.9%, Lot # 9406) was donated by Veterinary Bioproduct and Drug Control Office of China (Beijing, China). Other agents were A.R. grade and purchased in China.

Drug application/kinetic sampling

Pigs. The pharmacokinetic study of sarafloxacin in pigs was carried with a Latin Square design, which eliminates the effect of the body weight on the pharmacokinetic parameters. Over the study period, each pig received an i.v., an i.m. and a p.o. administration of sarafloxacin at a dosage of 5 mg/kg. A 7-day washout period was allowed between different treatments. The i.v. bolus doses of sarafloxacin were administered via the ear vein, and the i.m. doses of sarafloxacin were injected into the neck muscle. Blood samples were collected from the superior vena cava by venipuncture into tubes containing heparin before drug application and at 0.1, 0.25, 0.5, 0.75, 1, 2, 4, 6, 9, 12, 16 and 24 h after i.v. or i.m. administration. The p.o. administrations were carried out by gavage and blood samples were collected into tubes containing heparin prior to and at 0.1, 0.25, 0.5, 1, 2, 3, 4, 6, 9, 12, 16 and 24 h after sarafloxacin administration. All blood samples were centrifuged at $930 \times \boldsymbol{g}$ for 10 min at room temperature (25 °C). The separated plasma samples were kept at −20 °C until HPLC analysis.

Broilers. All broilers were weighed on the day of drug administration (at a dosage of 10 mg/kg b.w.) and randomly assigned to one of the three treatment (i.v., i.m., p.o.) groups. Ten animals were used in each group. Each individual broiler was administrated the drug only once and there was no significant difference between the average body weight of different groups. The i.v. injections of sarafloxacin were administered into the brachial vein of the birds in group I; the i.m. doses of sarafloxcin were injected into the pectoral musculature of birds in group II. Two millilitres of blood samples were taken from the brachial vein into tubes containing heparin at the following preset time points: 0, 0.083, 0.25, 0.5, 0.75, 1, 2, 4, 6, 9, 12, 16 and 24 h after i.v. or i.m. administration. Sarafloxacin was administered to birds in group III orally by gavage. Blood samples were collected and heparinized at the following preset time points: 0, 0.083, 0.25, 0.5, 1, 2, 3, 4, 6, 9, 12, 16 and 24 h after sarafloxacin administration. All blood samples were centrifuged at $930 \times \boldsymbol{g}$ for 10 min at room temperature (25 °C) and the collected plasma samples were stored at −20 °C until HPLC analysis as described below.

HPLC analysis. Sarafloxacin plasma concentrations were determined with an HP 1100 HPLC system using a method adapted from Nilsson-Ehle (1987). An aliquot of 0.5 mL plasma (spiked with 10 μL of 50 μg/mL enrofloxacin as an internal standard) was deproteinized with 0.5 mL methanol, vigorously vortexed for 2 min, and then followed by centrifugation ($20620 \times \boldsymbol{g}$). Fifty microlitres of the supernatant was injected into the HPLC system (Hewlett Packard 1100, Palo Alto, CA, USA) for analysis. Chromatography was carried out using a Nova-Pak C_{18} Column (4 μm, 4.6 × 25 mm); the mobile phase consisted of acetenitrile and 0.0174 mol/L tetrabutylammonium bromide solution (14:86, v/v, pH 3.0) at 1 mL/min flow rate. The fluorescence detector operated at an excitation wavelength of 278 nm and an emission wavelength of 460 nm. Chromatogram peak areas were quantitated using internal standard technique. The limit of quantitation, quantitation linearity and recovery of sarafloxacin from plasma were determined in pigs and broilers. Coefficients of variation (CV %) within and between HPLC runs were also calculated.

Pharmacokinetic analysis

Pharmacokinetic parameters were determined using a model-independent method (Notari, 1987). The area under the curve (*AUC*) was calculated using the trapezoidal rule during the sampling period with addition of the extrapolated-to-infinity area, which was calculated by dividing the last experimental concentration by terminal slope (β). Statistic moment theory was applied to calculate the *AUMC* and other main pharmacokinetic parameters with the following equations:

$$t_{1/2\beta} = \frac{\ln 2}{\beta}$$

β is the slope of terminal phase of the plasma concentration–time curve, determined by regression with the method of least squares from the last 4–7 concentration–time data points.

$$AUC = \int_0^{+\infty} c\,\mathrm{d}t = \int_0^{t^*} c\,\mathrm{d}t + \frac{c^*}{\beta}$$

c^* is the last observed drug concentration, and t^* is the time of the last observed drug concentration.

$$AUMC = \int_0^{+\infty} tc\,\mathrm{d}t = \int_0^{t^*} tc\,\mathrm{d}t + \frac{c^*}{\beta^2} + \frac{t^* c^*}{\beta}$$

$$MRT = \frac{AUMC}{AUC}$$

$$Cl_{\mathrm{B}} = \frac{D}{AUC}$$

D is the dose rate of administration, 5 mg/kg for pigs and 10 mg/kg for broilers.

$$V_{d(ss)} = \frac{D \times MRT}{AUC}$$

$$MAT = MRT_{ev} - MRT_{iv}$$

MRT_{ev} is mean residence time (*MRT*) for extra vascular administration; and MRT_{iv} is *MRT* for i.v. administration.

$$F = \frac{AUC_{ev}}{AUC_{iv}} \times 100\%$$

AUC_{ev} is *AUC* for extra vascular administration; AUC_{iv} is *AUC* for i.v. administration.

The *AUC* was previously defined; and *AUMC* is the area under the curve of the product of time and drug concentration vs. time from time 0 to ∞ (Gibaldi & Perrier, 1982). The pharmacokinetic parameters are reported as group mean ± SD. The mean for each pharmacokinetic variable were determined by averaging the calculated parameters for drug disposition in each animal.

RESULTS

Excellent HPLC separation of the test drug (Sarafloxcin, peak $t_R = 5.50$ min) and the internal standard (Enrofloxcin, peak $t_R = 3.99$ min) was achieved using the method refined in this study. The limit of quantitation was 0.05 μg/mL for sarafloxacin. Sarafloxcin quantitation was linear within a range of 0.05–10 μg/mL. The recoveries of sarafloxacin from plasma samples were 96.4 and 97.3% for pigs and broilers, respectively. Coefficients of variation were <5% for both within runs and between runs.

The pharmacokinetic parameters calculated from the plasma data are listed in Table 1 for pigs and Table 2 for broilers. The plasma concentration vs. time curves and log-concentration vs. time curves of sarafloxacin are shown in Fig. 1a and b for pigs and Fig. 2a and b for broilers, respectively.

After i.v. administration, the pharmacokinetic parameters for pigs and broilers were, respectively, determined as the elimination half-life ($t_{1/2\beta}$) 3.37 ± 0.46 and 2.53 ± 0.82 h; volume of distribution at steady-state ($V_{d(ss)}$) 1.92 ± 0.27 and 3.40 ± 1.26 L/kg; and total body clearance (Cl_B) 0.51 ± 0.03 and 1.20 ± 0.20 L/kg/h.

Following i.m. administration, the kinetic parameters in pigs and broilers were determined as: $t_{1/2\beta}$ 4.66 ± 1.34 and 6.81 ± 2.04 h; bioavailabilities (*F*) 81.8 ± 9.8 and 72.1 ± 8.1%, respectively.

Table 1. Pharmacokinetic parameters (mean ± SD) obtained from plasma concentrations of sarafloxacin after single intravenous (i.v.), intramuscular (i.m.) or oral (p.o.) administration in pigs (5 mg/kg, $n = 7$)

Pharmacokinetic parameters	i.v.	i.m.	p.o.
AUC (mg/L/h)	9.83 ± 0.60	8.05 ± 1.15	4.22 ± 1.02
MAT (h)		1.82 ± 1.16	7.54 ± 2.73
MRT (h)	3.76 ± 0.34	5.58 ± 0.99	11.29 ± 2.85
$t_{1/2\beta}$ (h)	3.37 ± 0.46	4.66 ± 1.34	7.20 ± 1.92
Cl_B (L/kg/h)	0.51 ± 0.03		
$V_{d(ss)}$ (L/kg)	1.92 ± 0.27		
F (%)		81.8 ± 9.8	42.6 ± 8.2

**AUC*: area under plasma concentration time curve extrapolated to infinity; *MAT*: mean absorption time; *MRT*: mean residence time; $t_{1/2\beta}$: elimination half-life; Cl_B: total body clearance; $V_{d(ss)}$: volume of distribution at steady state; *F*: bioavailability.

Table 2. Pharmacokinetic parameters (mean ± SD) obtained from plasma concentrations of sarafloxacin after single intravenous (i.v.), intramuscular (i.m.), or oral (p.o.) administration in broilers (10 mg/kg, $n = 10$)

Pharmacokinetic parameters	i.v.	i.m.	p.o.
AUC (mg/L/h)	8.59 ± 1.75	6.20 ± 0.69	5.12 ± 1.19
MAT (h)		4.40 ± 1.82	2.87 ± 1.11
MRT (h)	2.83 ± 0.88	7.23 ± 1.82	5.70 ± 1.11
$t_{1/2\beta}$ (h)	2.53 ± 0.82	6.81 ± 2.04	3.89 ± 1.19
Cl_B (L/kg/h)	1.20 ± 0.20		
$V_{d(ss)}$ (L/kg)	3.40 ± 1.26		
F (%)		72.1 ± 8.1	59.6 ± 13.8

**AUC*: area under plasma concentration time curve extrapolated to infinity; *MAT*: mean absorption time; *MRT*: mean residence time; $t_{1/2\beta}$: elimination half-life; Cl_B: total body clearance; $V_{d(ss)}$: volume of distribution at steady state; *F*: bioavailability.

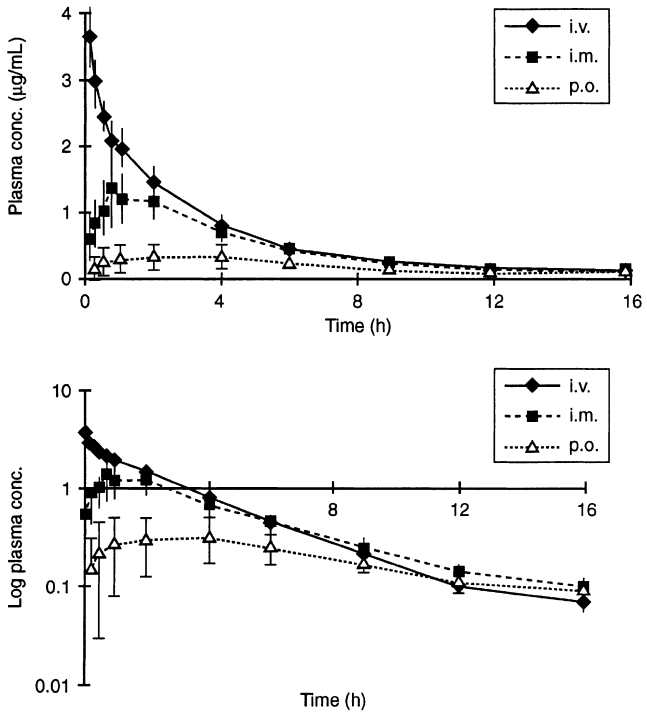

Fig. 1. Plasma concentration (a) or log-concentration (b) vs. time curves of sarafloxacin in pigs ($n = 7$) after intravenous (i.v.), intramuscular (i.m.), or oral (p.o.) administration at a single dose of 5 mg/kg.

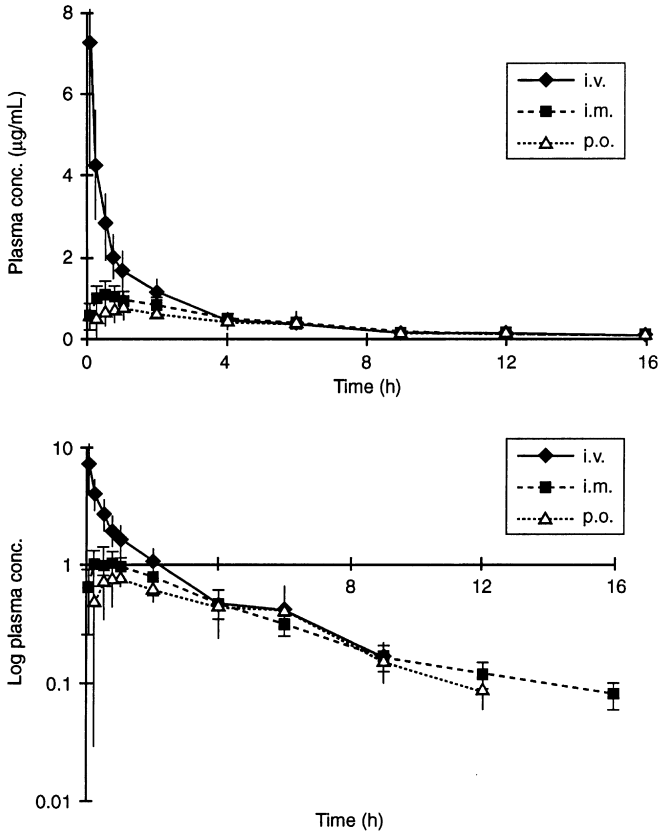

Fig. 2. Plasma concentration (a) or log-concentration (b) vs. time curves of sarafloxacin in broilers ($n = 10$) after intravenous (i.v.), intramuscular (i.m.), or oral (p.o.) administration at a single dose of 10 mg/kg.

After p.o. administration, the kinetic parameters were determined as: $t_{1/2\beta}$ 7.20 ± 1.92 and 3.89 ± 1.19 h; F 42.6 ± 8.2 and 59.6 ± 13.8% in pigs and broilers, respectively.

DISCUSSION

During the last decade, several fluoroquinolones such as enrofloxacin, danofloxacin, sarafloxacin and marbofloxacin have been carefully investigated for veterinary application in the treatment of a variety of bacterial infections. There are many papers published on the pharmacokinetics of these antimicrobial agents in various animal species. Although the pharmacokinetics of sarafloxacin has been described in Atlantic salmon (Martinson *et al.*, 1993a,b, 1994; Gingerich *et al.*, 1995), no pharmacokinetic studies of sarafloxacin in pigs or broilers has been reported in the literature. Our results from the i.v., i.m., and p.o. administrations of sarafloxacin in pigs and broilers show that sarafloxacin had quite similar pharmacokinetic characteristics as other fluoroquinolones.

In pigs, the $t_{1/2\beta}$ after i.v. administration of sarafloxacin was estimated to be 3.37 h, similar to that of enrofloxacin and ciprofloxacin (Zeng & Fung, 1997; Fang *et al.*, 1999), but apparently shorter than that of danofloxacin (Richez *et al.*, 1997). Distribution volume at steady-state was 1.92 L/kg. This large distribution volume indicates that sarafloxacin was well distributed into the tissues in pigs. Total body clearance was 0.51 L/kg/h. Maximum concentration (C_{max}) of 1.34 μg/mL after i.m. administration of sarafloxacin in this study was observed at 0.75 h. The bioavailability was calculated to be 81.8%, which is lower than that of enrofloxacin (Zeng & Fung, 1997), but higher than that of ciprofloxacin and norfloxacin in the pig (Anadón *et al.*, 1994; Fang *et al.*, 1999). The $t_{1/2\beta}$ of sarafloxacin was determined to be 4.66 h, which is similar to that of enrofloxacin and norfloxacin (Anadon *et al.*, 1994; Zeng & Fung, 1997), longer than that of ciprofloxacin, but shorter than that of danofloxacin in the pig (Richez *et al.*, 1997; Fang *et al.*, 1999). The $t_{1/2\beta}$ is also longer than that of i.v. sarafloxacin because of the confounding presence of the absorption process. The results of the analysis after p.o. administration showed that sarafloxacin was slowly and partially absorbed, with a C_{max} of 0.34 g/mL achieved at 3 h. Bioavailability of the oral sarafloxacin was 42.6%, less than that for enrofloxacin and ciprofloxacin in the pig (Zeng & Fung, 1997; Fang *et al.*, 1999).

In broilers, sarafloxacin was rapidly and extensively distributed into body fluids and tissues after i.v. administration. Distribution volume at steady-state in broilers was calculated to be 3.40 L/kg, which is much higher than that in pigs. The $t_{1/2\beta}$ after i.v. administration of sarafloxacin was estimated to be 2.53 h, much less than that of ofloxacin, norfloxacin, enrofloxacin, danofloxacin and ciprofloxacin (Chen *et al.*, 1994; Atta & Sharif, 1997; Kietzmann *et al.*, 1997; Liu & Fung, 1997; Hu & Fung, 1999), indicating that sarafloxacin was eliminated more rapidly than other fluoroquinolones. Therefore, sarafloxacin may offer the advantage of shorter withdrawal time than other fluoroquinolones in broilers for food-animal tissue drug residue considerations. A C_{max} of 1.11 μg/mL after i.m. administration of sarafloxacin in broilers was achieved at 0.5 h. The bioavailability was calculated to be 72.1%, which is similar to that of norfloxacin (Chen *et al.*, 1994). The $t_{1/2\beta}$ was 6.81 h, which is much longer than that following i.v. (2.53 h) or p.o. administration (3.89 h). The causes for this may be the continued and delayed absorption process after i.m. administration. Oral administration gave the observed C_{max} of 0.79 μg/mL at 0.75 h. Bioavailability was 59.6%, which is similar to that of norfloxacin (Chen *et al.*, 1994), but less than those of enrofloxacin, ciprofloxacin, ofloxacin and danofloxacin (Atta *et al.*, 1997; Kietzmann *et al.*, 1997; Liu & Fung, 1997; Hu & Fung, 1999). The $t_{1/2\beta}$ was estimated to be 03.89 h, which is much less than those of other fluoroquinolones such as enrofloxacin, ofloxacin, norfloxacin and danofloxacin (Chen *et al.*, 1994; Kietzmann *et al.*, 1997; Liu & Fung, 1997; Hu & Fung, 1999).

In conclusion, this study demonstrated a major interspecies difference in the pharmacokinetics of sarafloxacin between pigs and broilers. Sarafloxacin was completely absorbed after single i.m. administration and slowly eliminated after p.o. administration in healthy pigs. In healthy broilers, the drug was incompletely absorbed after single p.o. administration and

slowly eliminated after single i.m. administration. Sarafloxacin was demonstrated to be more rapidly absorbed, more extensively distributed, and more quickly eliminated in broilers than in pigs. Because of the larger distribution volume of this drug in broilers than in pigs, the effective administration of sarafloxacin in broilers should be higher than that in pigs in order to achieve a comparable peak plasma concentration.

Based on the pharmacokinetic parameters determined through this study, a sarafloxacin i.m. dosage of 10 mg/kg applied every 12 h in the pig could provide sufficient plasma concentrations to inhibit bacteria with MIC_{90} <0.25 μg/mL. In contrast, a dosage of 10 mg/kg administered orally every 8 h could maintain effective plasma concentrations in broilers with bacterial infections, in which MIC_{90} are less than 0.25 μg/mL. Such multiple dosing regimens should be suggested and followed.

An alternative dosage regimen was also provided. As the *AUC* to *MIC* ratio and C_{max} to *MIC* ratio were considered to be critical for fluoroquinolone efficacy recently (Brown, 1996; Shojaee Aliabadi & Lees, 1997), C_{max}/*MIC* ratio and *AUC*/*MIC* ratio can be used in designing reasonable dose regimens. According to this study, for pigs, a sarafloxacin dosage of 5 mg/kg i.m. with a 12-h dosing interval will provide effective plasma concentration to inhibit bacteria with *MIC* less than 0.1 μg/mL such as *S. aureus*, *E. coli* and *Salmonella* sp. In contrast, a dosage of 10 mg/kg administered orally at 12-h intervals could provide effective plasma concentration in chickens with bacteria infection in which *MIC* are <0.1 μg/mL such as *Mycoplasma gallisepticum* infection, *Salmonellosis avium* and *Colibacillosis*.

The issues of antimicrobial resistance should be carefully considered when applying drugs such as fluoroquinolones because of the economic trend towards globalization. As there was a paucity of *MIC* data for sarafloxacin and bacteria isolated from pigs and broilers, collected cultures and sensitivities is of practical importance in determining the optimal treatment regimens, and thus should deserve further investigations.

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