PHARMACOKINETIC STUDY OF ENROFLOXACIN IN TIANFU GEESE

F. Shi[1,2], H. Tang[2], W. Xie[1], A. Anees[1], Z. Yang[2] and X. Zhang[1,]

[1]College of Veterinary Medicine, Northwest A&F University, Yangling 712100, China
[2]College of Veterinary Medicine, Sichuan Agricultural University, Ya'an 625014, Sichuan province, China
Corresponding author E-mail: zhang.xy@nwsuaf.edu.cn

ABSTRACT

The pharmacokinetic behavior of enrofloxacin (EF) was investigated in geese after oral (*p.o.*) and intravenous (*i.v.*) administrations of a single dose of 20 mg/kg body weight. Plasma concentrations of EF and its active metabolite, ciprofloxacin, were determined by high performance liquid chromatography fluorescence method. Plasma concentrations versus time were analyzed by non-compartmental method. The elimination half-life and area under drug concentration-time curve from zero to infinity of EF after *i.v.* administration were 3.32 ± 0.43 h and 45.73 ± 5.74 mg/L·h, respectively. After *p.o.* administration, EF was absorbed fast and the maximum plasma concentration of 3.86 ± 0.36 mg/L reached at 2.14 ± 1.10 h. The concentration-time profile of EF showed a double peak-shaped curve, indicating the possibility of enterohepatic recirculation of EF in geese. The bioavailability for EF after *p.o.* administration was $78.09 \pm 25.76\%$. Seldom ciprofloxacin was detected in the plasma both after *i.v.* and *p.o.* administrations, indicating low transformation rate from EF to ciprofloxacin in geese. Taking into account the efficacy indices obtained, a single *p.o.* dose of 20 mg/kg of EF would be adequate for treating infections caused by highly susceptible bacteria in geese.

Key words: pharmacokinetics; enrofloxacin; geese; intravenous administration; oral administration.

INTRODUCTION

China is in a dominating position with a share of over 75% of global waterfowl production, while the geese population accounts for about 90% of the entire world's geese (Liu and Wang, 2012). A Tianfu goose is one of the most popular breeds of domestic goose (Wang, 2002). Enrofloxacin (EF), an exclusive veterinary antibiotic, is a member of fluoroquinolones which can effectively protect against a broad spectrum of Gram-positive and Gram-negative bacteria. EF is commonly used in the geese industry to control the infection caused by *Pasteurella multocida*, *Staphylococcus aureus*, *Escherichia coli* and *Salmonella ssp*. The pharmacokinetics of EF have been investigated in poultry including young domestic *ostriches* (de Lucas *et al*., 2004), chickens (da Silva *et al*., 2006), turkeys (Dimitrova *et al*., 2006), greater *rheas* (de Lucas *et al*., 2008), as well as in other animals. However, the pharmacokinetics of EF in geese has not been reported. To provide a good contribution for further study and to assess the clinical efficacy of EF in geese, the pharmacokinetic profile of EF in geese was investigated after intravenous (*i.v.*) and oral (*p.o.*) administrations. Pharmacokinetic characteristics of EF in different animal species were summarized and further analyzed to provide a comprehensive understanding of EF pharmacokinetics.

MATERIALS AND METHODS

Reagents and chemicals: EF powder (96.28% purity) was kindly provided by Dingjian Co. Ltd. (Sichuan, China). EF control powder (100.0% purity) and Ciprofloxacin hydrochloride control powder (99.8% purity) was supplied by the China Institute of Veterinary Drug Control (Peking, China). High performance liquid chromatography (HPLC)-grade methanol and acetonitrile were purchased from Guangdong Guanghua Chemical Factory Co. Ltd. (Guangdong, China). Hydrochloric acid EF injection (Baytril 5%, Bayer) was obtained from Bayer Co. Ltd. (Sichuan, China). Ultra-pure water was collected from Milli-Q Water Purification System (MILLIPORE, France). Citric acid, ammonium acetate and lactose are all analytical reagents.

Animals: Ten 230-day male geese weighting 4.13 ± 0.25 kg and ten 210-day female geese weighting 3.46 ± 0.29 kg were obtained from Sichuan Agricultural University geese farm. All animals were provided water and ration *ad libitum*. The geese were acclimatized for 7 days to the experimental conditions before the commencement of the experiment. All animal procedures were performed in accordance with the local and universities' guidelines for care and use of laboratory animals.

Experimental design: Experimental animals were randomly distributed to two equal groups of 10 geese each. EF powder was made by adding 5 g EF powder (96.28%) into 20 g lactose and mixed thoroughly. The concentration of the EF powder was determined as

19.26%. Capsules containing exact amount of EF powder (19.26%) for individual goose were prepared. The first group was given single *p.o.* administration and another group was given single injection into the right brachial vein. Blood samples of 1.5 milliliter (mL) each were collected at 5, 15, 30, 45 min and 1, 2, 4, 6, 8, 12, 24, 36, 48 hours after each administration using intravenous catheter fixed into the left brachial vein. The samples were immediately transferred to clean heparinized polyethylene tube and mixed slightly. The plasmas were collected after the blood samples were centrifuged at 2500 r/min for 15 min at 4 ℃ and stored at -20 ℃. All the plasma samples were analyzed within two weeks.

Analytical method: EF Plasma concentrations were determined by HPLC-Fluorescence detection according to previous reports (Idowu and Peggins, 2004; Garcés *et al.*, 2006). In brief, 0.5 mL plasma sample and 1.0 mL methanol were added into polyethylene tube, vortexed for 3 min and centrifuged at 14000 r/min for 15 min. Each 0.9 mL supernatant was decanted into another tube and blown dry under nitrogen gas. After the residue was dissolved by 0.3 mL of the mobile phase, the solution was filtered through a 0.2 μm nylon syringe filter. Each 10 μL solution was then injected into the HPLC system (LC-2010C$_{HT}$, Shimadzu, Japan) coupled to a fluorescence detector (RF-10A$_{XL}$, Shimadzu) and a SCL-10AVP system controller. The HPLC was achieved by a reverse phase C$_{18}$, 5μm, 250mm×4.6mm, analytical column (Hypersil BDS, serial: E2212708, Dalian Elite Analytical Instruments Co., Ltd.). The flow rate was 1.0 mL/min. Excitation wavelength and emission wavelength was 278 nm and 465 nm, respectively. The mobile phase was consisted of acetonitrile and buffer (17:83). The buffer contained of Citric acid (0.10 mol/L), ammonium acetate (0.05 mol/L) and ultra-pure water. The column temperature and the room temperature were both set at 25ºC.

Calibration curve: A stock solution including both 1.0 mg/mL of EF and 1.0 mg/mL of ciprofloxacin was prepared by dissolving 50.0 mg EF control powder and 58.3 mg ciprofloxacin control powder in 50.00 mL sodium hydroxide solution (0.01mol/L). Standard working solutions (0.02, 0.05, 0.10, 0.20, 0.50, 1.00, 2.00, 5.00, 10.00 and 15.00 mg/L) were prepared by diluting the stock solution in ultra-pure water. Standard curves were plotted by the peak areas against the corresponding concentrations of EF. The analytical method was validated by assessing extraction efficiencies, recoveries

inter-day and intra-day precision values at levels of 0.02, 1.00 and 15.00 mg/L.

Data analysis: Model fitting and evaluation of the pharmacokinetic parameters were executed with Drug and Statistics 2.0 (DAS 2.0; Drug Clinical Research Center of Shanghai University of Traditional Chinese Medicine, Shanghai, China). Pharmacokinetic parameters were determined using the noncompartmental method based on statistical moment theory. All pharmacokinetic parameters were calculated for individual goose according to the standard equations (Gibaldi and Perrier, 1982) and presented as mean ± SD.

RESULTS

The chromatograms of EF in chicken plasma were sharp, showing no interference in matrix, and the retention time was about 9 min. Both standard curves of EF and ciprofloxacin were linear between 0.02 and 15.00 mg/L (r^2>0.999). In plasmas fortified at concentrations of 0.02, 1.0 and 15.0 mg/L, all the recoveries of EF and ciprofloxacin were larger than 90.0% (n=5); all the intra-day and inter-day coefficients of variation were 12% (n=5).

No signs of adverse reactions were observed after both *i.v.* and *p.o.* administrations of EF to geese. The plasma concentration-time data showed a clear double peak-shaped curve after *p.o.* administration. The mean ± SD plasma concentrations of EF vs. time following *p.o.* and *i.v.* administration were plotted in Fig. 1. Ciprofloxacin, as a metabolite of EF, was detected in most of the plasma samples; however most of the outcomes were below the limit of quantization (0.020 mg/L).

The mean pharmacokinetic parameters for EF after *p.o.* and *i.v.* administrations to TIANFU geese, analyzed by non-compartmental method, were presented in Table 1. After *i.v.* administration, the area under drug concentration-time curve from zero to infinity (AUC$_{0-∞}$), elimination half-life (t$_{1/2z}$), total body clearance (CL$_z$) and apparent volume of distribution (V$_z$) were 45.73 ± 5.74 mg/L·h, 3.32 ± 0.43 h, 0.44 ± 0.06 L/h/kg and 2.12 ± 0.35 L/kg, respectively. Following *p.o.* administration, the peak plasma EF concentration (C$_{max}$), time peak plasma EF concentration reached (T$_{max}$) and absolute bioavailability (F) were 3.86 ± 0.36 mg/L, 2.14 ± 1.10 h and 78.09 ± 25.76%, respectively.
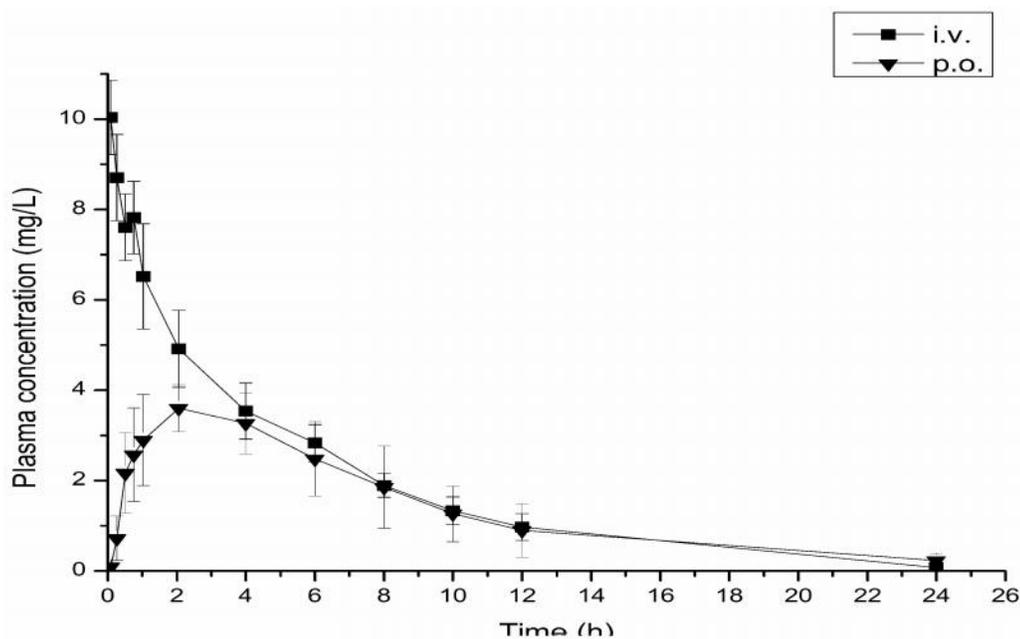
Fig. 1 Plasma EF concentration-time profiles in TIANFU geese after single dosage of 20 mg/kg b.w. (n=10)

Table 1 Pharmacokinetic parameters of EF in geese after a single dose of dosage of 20 mg/kg b.w. (n=10)

Parameter	Unit	*i.v.* Mean ± SD	*p.o.* Mean ± SD
$AUC_{(0-t)}$	mg/L·h	45.36 ± 5.62	33.49 ± 11.06
$AUC_{(0-\infty)}$	mg/L·h	45.73 ± 5.74	33.90 ± 10.93
$MRT_{(0-t)}$	H	5.11 ± 0.46	6.78 ± 2.03
$MRT_{(0-\infty)}$	H	5.29 ± 0.57	7.11 ± 1.94
$t_{1/2z}$	H	3.32 ± 0.43	4.35 ± 1.48
T_{max}	H	0.08 ± 0	2.14 ± 1.10
CL_z	L/h/kg	0.44 ± 0.06	N/A
CL_z/F	L/h/kg	N/A	0.65 ± 0.22
V_z	L/kg	2.12 ± 0.35	N/A
V_z/F	L/kg	N/A	3.80 ± 1.1
C_{max}	mg/L	N/A	3.88 ± 0.36
F	%	N/A	74.13 ± 23.90

N/A: not available; MRT: the mean residence time

DISCUSSION

Pharmacokinetics of EF has been investigated in a variety of bird species; however, there are few reports (Intorre *et al*., 1997; Wack *et al*., 2012) concerning waterfowl, in which EF is used widely.

In our study the V_z of EF in geese was 2.12 ± 0.35 L/kg. As a lipid-soluble drug, the values of V_z were reported ranged from 1.1 L/kg to 4.8 L/kg, indicating EF's wide distribution in the body tissues.

As illustrated in Table 2, after *i.v.* administration, EF had a quick $t_{1/2z}$ of 3.32 ± 0.43 h in geese; similar to those of the mammals and birds including chickens (1.5 ± 0.2 h), greater *rheas* (2.66 ± 0.46 h), angora rabbits (3.0 h), lactating sheep (3.30 h), sheep (4.31 h), houbara bustards (5.63 ± 0.54 h), turkeys (6.64 ± 0.90 h) and mares (6.7 h); smaller than those of the fish, reptiles and crabs including catfish (17.44 h), brown trouts (19.14 h), *Eriocheir sinensis* (21.3 h), American alligators (21.05) and *carassius auratus gibelios* (63.5 h). The reasons may be the differences of hepatic renal function between them. The difference of $t_{1/2z}$ between sheep (4.31 h) and lactating sheep (3.30 h) may be induced by the different physiological status. The $t_{1/2z}$ of foals (17.1 h) was larger than that of mares (6.7 h) may be due to the difference of hepatic renal function caused by age.

The Cl_z after *i.v.* in geese (0.44 ± 0.06 L/ h/kg) is close to that of turkeys (0.41 L/ h/kg). The Cl_z in higher animals including greater *rheas* (3.95 ± 1.07 L/ h/kg), angora rabbits (1.7 L/ h/kg), goats (1.33 L/ h/kg),

geese, turkeys, mares (0.22 L/ h/kg) and gorals (0.19 L/ h/kg) were larger than those of lower animals including catfish (0.17 L/ h/kg), brown trouts (0.14 L/ h/kg), American alligators (0.047 L/ h/kg) and carassius auratus gibelios (0.04 L/ h/kg); to the contrary, the $t_{1/2z}$ of higher animals were less than that of lower animals. The Cl_z in mares (0.22 L/ h/kg) was larger than that of foals (0.104 L/ h/kg), while the $t_{1/2z}$ of mares was less than that of foals. The differences of Cl_z and $t_{1/2z}$ between higher and lower animals are consistent. As the results of evolution and growth, the liver and kidney of higher and mature animals are more dynamic than those of lower and younger animals. In clinic, the dose should be less and interval between administrations should be longer in lower animals and the young.

As illustrated in Table 3, the concentration of EF in plasma reached the peak at 2.14 ± 1.10 h after *p.o.* in geese and the bioavailability (F) was $74.13 \pm 23.9\%$. It indicates that EF was absorbed rapidly and thoroughly in geese after *p.o.* administration. The reported T_{max} varied from 0.66 h to 3.44 h, and the relevant F varied from 62.7% to 86% except foals (42%). It indicates EF was absorbed thoroughly in most animals after *p.o.* administration. Moreover, T_{max} after *p.o.* in American alligators was 55 ± 29 h, which could be caused by the physiological feature of decreasing gut blood flow in rest.

The possibility of enterohepatic circulation of EF was indicated by the double peak-shaped curve of the plasma concentration-time data following *p.o.* administration in geese, which is in agreement with the common mechanism of fluoroquinolones elimination. It was observed in tilapias (Chang, 2009), silver crucian carps (Fang *et al.*, 2012). The values of $t_{1/2z}$, CL_z and V_z become larger while enterohepatic recirculation occurs. Because of first pass effect, more sections of EF were trapped in enterohepatic recirculation. It may be the reason of larger $t_{1/2z}$, CL_z/F and V_z/F values observed after *p.o.* than *i.v.*. It was accordant to the report EF accumulated readily in bile (Chang, 2009).

Table 2. Pharmacokinetic parameters of EF after *i.v.* administration in different animal species

Species	Dose (mg/kg)	$AUC_{(0-24)}$ (mg /L·h)	$MRT_{(0-\infty)}$ (h)	$T_{1/2z}$(h)	Cl_z(L/h/ kg)	V_z(L/ kg)	Reference
Geese	20	45.36± 5.62	5.29± 0.57	3.32± 0.43	0.44± 0.06	2.12± 0.35	The present study
Turkeys	10	25.91± 5.12	8.96± 1.18	6.64± 0.90	0.41± 0.07	3.82± 0.73	(Dimitrova, Lashev *et al.*, 2007)
Carassius auratus Gibelios	10	239.6	N/A	63.5	0.04	N/A	(Fang, Liu *et al.*, 2012)
Sheep	2.5	9.24	N/A	4.31	N/A	1.1	(Otero, Mestorino *et al.*, 2009)
Brown trouts	10	70.87± 4.02	N/A	19.14± 1.51	0.14± 0.01	3.40± 0.18	(Koc, Uney *et al.*, 2009)
Angora rabbits	5	3.2±0.80	N/A	3.0± 0.95	1.7± 0.52	4.8± 0.84	(Elmas, Uney *et al.*, 2007)
Mares	5	N/A	N/A	6.7± 2.9	0.22± 0.10	1.9± 0.4	(Papich, Van Camp *et al.*, 2002)
Alpacas	5	55.5	N/A	11.2	N/A	N/A	(Gandolf, Papich *et al.*, 2005)
American alligators	5	N/A	N/A	21.05	0.047± 0.02	1.88± 0.96	(Helmick, Papich *et al.*, 2004)
Lactating sheep	5	4.19± 0.18	N/A	3.30± 0.36	N/A	2.91± 0.17	(Haritova, Lashev *et al.*, 2003)
Foals	5	48.5± 10.46	N/A	17.10± 0.09	0.104	2.49± 0.43	(Bermingham, Papich *et al.*, 2000)
Catfish	10	60.34± 19.83	23.58±7.0	17.44± 4.66	0.17± 0.05	3.93± 0.12	(Kim, Lim *et al.*, 2006)
Gorals	5	N/A	N/A	13.3	0.19± 0.14	2.15-1 .01	(Gandolf, Papich *et al.*, 2006)
Greater *rheas*	15	3.57± 1.54	1.23±0.21	2.66± 0.46	3.95± 1.07	2.22± 0.61	(de Lucas, Rodriguez *et al.*, 2005)
Houbara bustards	10	N/A	N/A	5.63± 0.54	N/A	N/A	(Bailey, Sheen *et al.*, 1998)
Goats	N/A	1.916± 0.140	0.97±0.05	0.73± 0.047	1.33± 0.09	1.38± 0.045	(Rao, Ramesh *et al.*, 2002)
African penguins	15	N/A	N/A	13.67	0.182	3	(Wack, KuKanich *et al.*, 2012)

N/A: not available

Table 3 Pharmacokinetic parameters of EF after *p.o.* administration in different animal species

Species	Dose (mg/kg)	$AUC_{(0-24)}$ (mg /L·h)	$MRT_{(0-\infty)}$ (h)	$T_{1/2z}$ (h)	T_{max} (h)	C_{max} (mg/L)	F (%)	Reference
Geese	20	33.49 ± 11.06	7.11 ± 1.95	4.35 ± 1.48	2.14 ± 1.10	3.86 ± 0.36	74.13 ± 23.90	The present study
Carassius auratus gibelios	10	205.9	N/A	62.7	N/A	4.5	86	(Fang, Liu *et al.*, 2012)
Scyllaserratas	30	1628.6	83.72	65.09	2	30.53	N/A	(Fang, Zhou *et al.*, 2007)
Brown trouts	10	54.95 ± 1.42	N/A	22.09 ± 2.02	8	2.30 ± 0.08	78 ± 4	(Koc, Uney *et al.*, 2009)
Turkeys	10	18.11 ± 3.33	11.91 ± 1.87	6.92 ± 0.97	6.33	1.23 ± 0.3	69.2 ± 0.43	(Dimitrova, Lashev *et al.*, 2007)
Chickens	10	N/A	15.64	1.5 ± 0.2	9.0 ± 2.0	1.5 ± 0.2	N/A	(da Silva, Reyes *et al.*, 2006)
American alligators	5	N/A	N/A	77.73	55 ± 29	0.50 ± 0.27	N/A	(Helmick, Papich *et al.*, 2004)
Catfish	10	38.43 ± 10.21	39.72 ± 6.24	34.13 ± 11.50	3.44 ± 0.81	1.02 ± 0.41	64.59 ± 4.58	(Kim, Lim *et al.*, 2006)
Muscovy ducks	N/A	6.65 ±0.44	6.01 ± 0.54	N/A	1.38	0.99 ± 0.08	N/A	(Intorre, Mengozzi *et al.*, 1997)
Houbara bustards	10	N/A	N/A	6.80 ± 0.79	0.66 ± 0.05	1.84 ± 0.16	62.7 ± 11.1%	(Bailey, Sheen *et al.*, 1998)
African penguins	15	N/A	N/A	N/A	4.8	4.38	N/A	(Wack, KuKanich *et al.*, 2012)

Ciprofloxacin is the major metabolite formed by the de-ethylation of EF in many animal species, and it possesses stronger antibacterial activity than that of EF. The transformation rates from EF to ciprofloxacin in birds were 12.6% in chickens (Guo *et al*., 2010), 4.2-6.4% in turkeys (Dimitrova *et al*., 2006), 10% in Muscovy ducks (Intorre *et al*., 1997), 14% in greater *rheas* (de Lucas *et al*., 2005; de Lucas *et al*., 2008), < 10% in young domestic ostriches (de Lucas *et al*., 2004). The concentration of ciprofloxacin was too little to be quantified though it was detected in most of the plasmas, indicating just a small part of EF has been converted to ciprofloxacin in geese.

The transformation rate of EF to ciprofloxacin in dogs was 43% (Kung *et al*., 1993), while Tang (Tang *et al*., 2007) reported that the ciprofloxacin concentration in dogs' plasma was too low to calculate the transformation rate. The transformation rates in other mammals vary from 20.6% (sheep) to 64% (steers) (Sharma *et al*., 2003; Davis *et al*., 2007; de Lucas *et al*., 2008; Otero *et al*., 2009; Idowu *et al*., 2010) and those in birds were less than 14%. But for lower animals the transformation rates were less than 3.8%, such as brown trouts and mud crabs (*Scylla serrata*) (Fang *et al*., 2007; Koc, Uney *et al*., 2009). It was concluded that the transformation rate was gradually reduced with the decrease of animal level.

As a concentration-dependent antibiotic, EF's ratios of C_{max}/MIC and AUC_{0-24}/MIC should be larger than 8 to 10 and 100 to 125, respectively (Lode *et al*., 1998). Mean MICs of EF inhibiting common geese pathogens were 0.008 mg/L for *Pasteurella multocida*,

0.12mg/L for *Staphylococcus aureus*, (Grobbel, *et al*., 2007), 0.25 mg/L for *Escherichia coli* (Grobbel *et al.,* 2007; Ozawa et al., 2010) and *Salmonella ssp* (Haines *et al*., 2000). With the MICs above, AUC_{0-24}/MIC for EF after a single dosage of 20 mg/kg b.w. by *i.v.* and *p.o.* were larger than 181 h and 134 h respectively. The C_{max}/MIC for EF were larger than 15.44 after a single dosage of 20mg/kg b.w. by *p.o.* As a result, the regimens of a single dosage of 20mg/kg by *i.v.* or *p.o.* would be adequate for the infections in geese by *Pasteurella multocida*, *Staphylococcus aureus*, *Escherichia coli* and *Salmonella ssp*.

Conclusion: Moderate F with good pharmacokinetic profile and pharmacokinetic-pharmacodynamic efficacy predictors for EF indicate that single oral administration of EF at 20 mg/kg may be highly effective against susceptible bacteria in geese.

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