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Short Communication

Pharmacokinetics of enrofloxacin in meat pigeons after a single intramuscular and oral administration

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Abstract

The pharmacokinetic properties of enrofloxacin were investigated after a single intra-muscular (i.m.) and oral administration of 10 mg/kg b.w. to 12 healthy adult pigeons. Twelve pigeons were randomly divided to two groups. Blood samples were collected at different time points following drug administration. Plasma enrofloxacin concentrations were determined by reverse-phase high-performance liquid chromatography. Pharmacokinetic analysis was conducted using non-compartmental methods via the ncappc package in R. The mean concentration area under curve (AUC_{last}) for enrofloxacin was determined to be 21.75±5.67 μg·h/mL for i.m., administration and 17.30±4.94μg·h/mL for oral administration. The elimination half- life ($T_{1/2\lambda z}$) was 9.51±5.72 and 6.87±1.81 h for the i.m., and oral route, respectively. The mean maximum plasma concentration (C_{max}) after i.m., administration was 2.50±0.27 μg/mL at 0.67±0.20 h, whereas after oral administration C_{max} was 0.98±0.45μg/mL at 6.33±2.66 h. Mean residence time (*MRT* last) following i.m., injection was 11.02±2.28 and 14.85±1.78 h after oral administration. There are some discrepancies in part of the pharmacokinetics parameters of enrofloxacin between meat pigeons and other poultry.

Keywords: Enrofloxacin, Pigeon, Pharmacokinetics, Intramuscular and oral administration

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Introduction

The pigeon is an important agricultural economic animal. Pigeon meat has long been considered a delicacy and is popular among consumers in China, Europe and the US (Pomianowski *et al*., 2009). However, the use of most medicines for meat pigeons lacks the support of direct pharmacokinetic data.

Enrofloxacin is a fluorinated quinolone antimicrobial agent developed specifically for veterinary use. Also, enrofloxacin exhibits the properties of a broad antibacterial spectrum, a low host toxicity and high bactericidal activity (Lopez-Cadenas *et al*., 2013). Accordingly, enrofloxacin is widely used in poultry production (Chrzastek *et al*., 2012). The pharmacokinetics of enrofloxacin has been investigated in poultry like geese (Shi *et al*., 2014), young domestic ostriches (de Lucas *et al*., 2004), chickens (da Silva *et al*., 2006), turkeys (Dimitrova *et al*., 2007), as well as in other animals(Kim et al., 2006; Rahal *et al*., 2006; Elmas *et al*., 2007). However, limited information is reported about the pharmacokinetics of enrofloxacin in meat pigeons. This study aimed to measure the plasma enrofloxacin concentrations and characterize its pharmacokinetics in meat pigeons following a single oral and intramuscular administration of 10 mg/kg, to provide the basis for its rational application in veterinary clinical practice.

Materials and Methods

Animal Ethics Statement: All animal experiments were performed according to the Regulations for the Administration of Affairs Concerning Experimental Animals (Ministry of Science and Technology, China, revised in June 2004) and approved by the Institutional Animal Care and Use Committee in the College of Animal Science and Technology, Sichuan Agricultural University, Sichuan, China under permit No. DKY-13316-2019002.

Experimental animals: Twelve White King pigeons aged 22-24 months and of 502.3-585.5g body weight were used. They were housed individually and were fed with a mixed-grain diet. Drinking water was available *ad libitum*.

Drug administration and blood sampling: Enrofloxacin was administered as either a powder (Purity 96.28%; pharmaceutical grade; Dingjian Co., Ltd. China) or i.m., formulation (Bayer Co., Ltd. Germany). Enrofloxacin powder was dispersed in normal saline and administered by intragastric gavage. Injection formulations were administered by intramuscular injection. The dosage was 10 mg/kg b.w., for both oral and injection routes. Blood samples (about 1.0 mL each) were collected via the brachial vein into heparinized glass tubes at 0 (pretreatment), 5, 15, 30, 45 min and 1, 2, 4, 8, 12, 24 and 48 h after drug administration. Subsequently, blood samples were centrifuged at 2000 rpm for 10 mins to harvest plasma stored at -20 ℃ until assayed.

Drug analysis: Frozen plasma samples were thawed and vortexed, 0.5 mL plasma was mixed with 0.1mL internal standard (2 μg/mL Dafloxacin) and 2 mL phosphate buffer, followed by vortex-mixing for 2 mins. The samples were purified on a C18 SPE column. In particular, C18 SPE columns were conditioned with 2mL methanol and phosphate buffer (pH 7.0). Then, the samples were passed through the SPE column for cleanup using 1.0 mL of ultra-pure water and then eluted out using 1.0 mL of the mobile phase. The eluates were filtered through a 0.2 μm nylon syringe filter. The sample was transferred to a clean autosampler injection vial and a 5 μL sample was injected into HPLC system for analysis. The concentrations of enrofloxacin in plasma were estimated by RP-HPLC system (LC-2010CHT; Shimadzu,,Japan). The mobile phase was 0.05 M phosphoric acid-triethylamine buffer solution/acetonitrile (83/17, v/v)) and the flow rate was set at 1.0 mL/min. Chromatographic assay was performed at ambient temperature and the excitation wavelength and emission wavelength was 278 nm and 465 nm, respectively. Peak areas were used for quantification of the concentration of the enrofloxacin. Calibration curves were established using the areas of the chromatographic peaks measured at six enrofloxacin concentrations ranging from 0.1 to 3.0 μg/mL.

Pharmacokinetic analysis: Enrofloxacin time–concentration data was analyzed by non-compartment methods (Acharya *et al*., 2016) using the ncappc package for R (version 0.3.0).

Results and Discussion

Good linearity was obtained for all analytes throughout the concentration range and the regression equations were obtained: Y = 0.1505X + 0.0436(R^2=0.9991). Assay precision was assessed by use of three quality-control samples at three concentrations (0.10, 0.40, 1.5 μg/mL). The inter- and intra-day coefficients of variation at three different concentrations were below 3.0% (n=5). The recoveries were all larger than 82.14% (n=5). The limit of quantification was 0.025 μg/mL.

The mean ± SD plasma concentrations vs. time curves of enrofloxacin following 10 mg/kg i.m., and per os (p.o.) doses in pigeons are plotted on a semilogarithmic scale in Figure 1. The various pharmacokinetic parameters are presented in Table 1.

The oral value of MRT_{last} (14.85h) is significantly higher than the intra-muscular MRT_{last} value(11.02h) (*p*-value:0.0088, *t*-test). The MRT following oral administration of 10mg/kg b.w. enrofloxacin is similar to turkeys (11.91h) (Dimitrova *et al*., 2007) and chickens (15.64) (da Silva *et al*., 2006) and obviously longer than that in geese (7.11h) (Shi *et al*., 2014), ostrich(1.5h) (de Lucas *et al*., 2004) and duck(6.01h) (Intorre *et al*., 1997). After intramuscular administration, the drug reached mean C_{max} (2.50μg/mL) in 0.67h, while oral administration exhibited a lower mean C_{max} (0.98 μg/mL) and longer T_{max} (6.33h). Compared with the other poultry, the oral T_{max} value(6.33h) of the pigeon is similar to turkeys' (6.33h) (Dimitrova *et al*., 2007) and is longer than geese's (2.14h) (Shi *et al*., 2014) and Muscovy ducks' (1.38h) (Intorre *et al*., 1997), but shorter than chicken's (9.0h) (da Silva *et al*., 2006). The oral

mean C_{max} value (0.98 µg/mL) of the pigeon is much closer to Muscovy ducks' (0.99µg/mL) (Intorre *et al*., 1997) and turkeys' (1.23µg/mL) (Dimitrova *et al*., 2007), and is lower than chicken's (1.5µg/mL) (da Silva *et al*., 2006) and Houbara bustards' (1.84µg/mL) (Bailey *et al*., 1998) under the same dosage. The intra-muscular mean C_{max} value (2.50 µg/mL) of the pigeon lies between Muscovy ducks' (1.67µg/mL) (Intorre *et al*., 1997) and Houbara bustards'(2.75µg/m) (Bailey *et al*., 1998). The relative bioavailability of enrofloxacin for the oral administration routine was 76.10% when compared to the intramuscular administration routine in this study. It is slightly higher than that previously reported in Houbara bustards (64.08%) (Bailey *et al*., 1998) and Muscovy ducks (65.78%) (Intorre *et al*., 1997). The apparent volumes of distribution (Vz) for i.m., and p.o. in pigeons are 5.83 and 6.36L/kg, respectively, which suggests good tissue penetration. Pharmacokinetics researches in Houbara bustards (Bailey *et al*., 1998) and Muscovy ducks (Intorre *et al*., 1997) indicate that Vz values for i.m., and p.o., range between 3.09 - 8.89 L/kg. The Vz values obtained in this study are in the above range. These results indicated that there are some discrepancies in part of the pharmacokinetic parameters of enrofloxacin between meat pigeons and other poultry. It may be associated with marked differences in the anatomy and physiological features of the various birds. For example, the storage function and emptying pattern of the pigeon's crop resulted in an irregular availability of the drug from tablets when compared with capsules, suspensions or solutions (Dorrestein, 1991).

In summary, we elucidated the pharmacokinetic profiles of enrofloxacin in meat pigeons, which enables the establishment of a reasonable dosage regimen and estimate the withdrawal time of enrofloxacin.

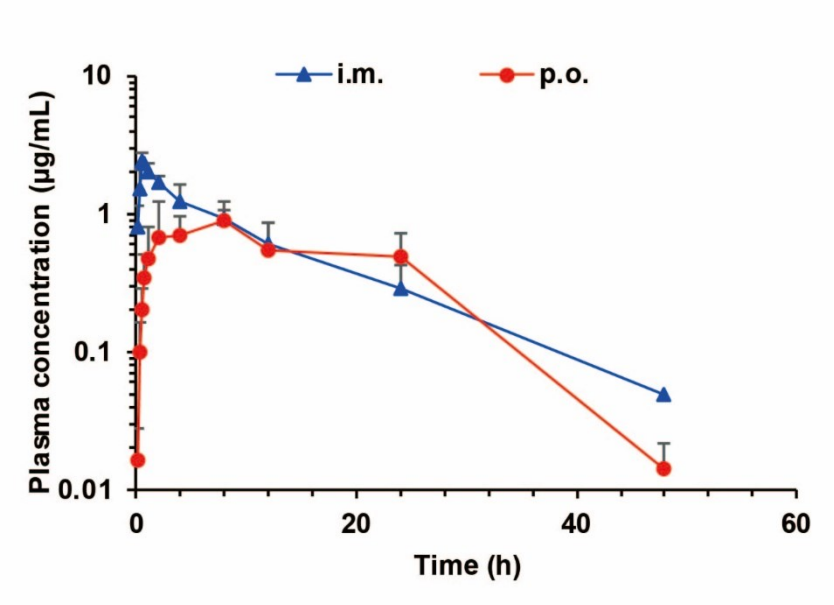

Figure 1

Table 1 Plasma pharmacokinetic parameters after a single i.m. and p.o. administration of 10 mg/kg b.w. enrofloxacin. (n=6)

Parameter	Route of administration	
	i.m.	p.o.
λz (1/h)	0.09 ± 0.03	0.11 ± 0.03
$T_{1/2\lambda z}$ (h)	9.51 ± 5.72	6.87 ± 1.81
T_{max} (h)	0.67 ± 0.20	6.33 ± 2.66
C_{max} (µg/mL)	2.50 ± 0.27	0.98 ± 0.45
AUC_{last} (µg·h/mL)	21.75 ± 5.67	17.30 ± 4.94
AUC_{INF_obs} (µg·h/mL)	22.93 ± 7.27	17.45 ± 4.87
Vz (L/kg)	5.83 ± 1.78	6.36 ± 3.23
***Cl* (L/h/kg)**	0.47 ± 0.13	0.61 ± 0.16
MRT_{last} (h)	11.02 ± 2.28	14.85 ± 1.78
Relative Bioavailability (%)	–	76.10

Data are expressed as mean ± SD. λz, the elimination rate constant; $T_{1/2\lambda z}$, terminal half-life. AUC last, area under the concentration versus time curve from the first observed to last measurable concentration; AUC_{INF_obs} , area under the concentration versus time curve from the first sampled data extrapolated to infinity; C_{max} , the value of maximum observed concentration; *Cl*, total body clearance; T_{max}, the time of maximum observed concentration; Vz, apparent volume of distribution; MRT_{last} , mean residence time from the first observed to last measurable concentration.

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