Pharmacokinetics of marbofloxacin in Japanese quails (*Coturnix japonica*) after different routes of administration

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Abstract: In this study the disposition kinetics and plasma availability of marbofloxacin in Japanese quails after single intravenous (IV), intramuscular (IM) and oral (PO) administrations of 5 mg/kg BW were investigated. Following IV injection, elimination half-life ($t_{1/2\beta}$), mean value of distribution at steady state (V_{dss}), total body clearance (Cl_{tot}) and mean residence time (MRT) of marbofloxacin were 4.03 h, 1.24 l/kg, 0.19 l/h/kg and 5.89 h, respectively. Following IM and PO administration of marbofloxacin at the same dose, the peak plasma concentration (C_{max}) were 3.86 and 3.59 µg/ml, respectively, which was obtained at 1.58 and 1.60 h, the time to peak concentration (t_{max}) for both routes. Elimination half-lives ($t_{1/2el}$) were 6.70 and 6.19 h, respectively, and mean absorption time (MAT) was 1.79 and 1.19 h, respectively. The systemic bioavailability following IM and PO administration were 98.72 and 87.94%, respectively. *In vitro* protein binding percent was 26.38%. Analysis of pharmacokinetic data obtained in this study reveals that a dosage of 5 mg/kg BW given by IM or PO routes every 24 h in Japanese quails might be recommended for a successful clinical effect in quails.
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Introduction

Fluoroquinolones have some characteristics such as a wide spectrum of bactericidal activity, a large volume of distribution, low plasma protein binding and relatively low MICs against susceptible target microorganisms (Spreng *et al*., 1995; Brown, 1996). Marbofloxacin is a third generation fluoroquinolone developed exclusively for veterinary use (Schneider *et al*., 1996). It possesses a wide spectrum of antimicrobial activity that includes Mycoplasmas, most Gram-negative bacteria and some Gram-positive organisms (Brown, 1996; Schneider *et al*., 1996; Thomas *et al*., 2003). Its action is bactericidal and it kills most sensitive pathogens by a concentration - dependent mechanism (Aliabadi and Lees, 2002). As with the other fluoroquinolones, marbofloxacin is a lipid soluble organic acid with good tissue penetration (Anon, 2003).

The pharmacokinetic properties of marbofloxacin have been reported in several poultry species like broiler chickens (Anadon *et al*., 2002), ostriches (De Lucas *et al*., 2005), turkey (Haritova *et al*., 2006), Muscovy ducks (Goudah and Hasabelnaby, 2011; Yuan *et al*., 2011) and Mallard ducks (Garcia-Montijano *et al*., 2012). However, species differences in absorption and disposition of drugs can occur, pharmacokinetic studies in each target species are needed to identify the required dosage for that particular species (Intorre *et al*., 1997).

The aim of this study was to investigate the plasma kinetics of marbofloxacin in quails after single IV, IM and PO administrations.

2. Materials and Methods
Drugs and chemicals:

Marbofloxacin was used as 10% injectable aqueous solution purchased from Veterinary Pharmaceutical Laboratories, France (Marbocyl®, Vetoquinol, Lure, France) and diluted to 0.25% with sterile distilled water for an accurate dosing. Mueller–Hinton agar was obtained from Mast Group Ltd., Merseyside, UK.

Experimental birds:

A total of 60 clinically healthy adult male and female Japanese quail, weighing an average of 190±21 g, were used to determine the pharmacokinetic parameters of marbofloxacin. Birds were housed in groups of 5 in cages and fed on a commercial drug-free quail diet along with water *ad libitum*. They were acclimatized for 2 weeks before the experiment began and were physically examined to establish they were healthy. The experiment was performed in accordance with the guidelines set by the Ethical Committee of Faculty of Veterinary Medicine.

Experimental design:

Quails were individually weighed before drug administration and doses were calculated precisely. A three-period sequential design was used, with a wash-out period of 3 weeks between the different routes of

administration of marbofloxacin. The birds were randomly divided into 12 groups of 5 birds. Each bird was blood-sampled only once, i.e. at only one time-point, to ensure that the volume that could be safely drawn from each did not exceed 1% of BW. Before administration of the drug, blood samples (0.75 ml) were collected from each group of birds one week prior to drug administration (time 0) as controls. Marbofloxacin was then administrated in a single IV dose into the right brachial vein, at 5 mg/kg BW. After a 3-week interval, birds injected the same dose through the leg muscles by means of a syringe. After another 3-week interval, birds dosed via 1- cc syringe directly into the crop at the same dose rate. Blood samples from all previous groups were collected from the left wing vein at 10, 20, 30 and 45 minutes, and 1, 2, 4, 6, 8, 12, 18 and 24 hours later (n=5 birds per time-point), into tubes containing heparin. Plasma was separated after centrifugation at 2000 g for 10 minutes. The plasma was decanted, labeled, and frozen at -20°C until the assays were performed.

Analytical method:

The concentration of marbofloxacin in plasma samples was estimated by a standard microbiological assay using *Escherichia coli* ATCC 25922 as test micro-organism (Tsai and Kondo, 2001). Standard curves were constructed using antibacterial free plasma collected from quails. Six wells, 8 mm in diameter were cut at equal distances in standard Petri dishes containing 25 ml seeded agar. The wells were filled with 100μl of either the test samples (plasma) or marbofloxacin standards. The plates were kept at room temperature for 2 h before being incubated at 37°C for 18 h. Zones of inhibition were measured using micrometers, and the marbofloxacin concentrations in the test samples were calculated from the standard curve. The method was validated in terms of linearity, sensitivity, recovery, intra-day and inter-day precision. Semi-logarithmic plots of the inhibition zone diameter, versus standard marbofloxacin concentrations in plasma, were linear between 0.05 and 10 μg ml^{-1}, with a typical correlation coefficient of 0.983 (for the standard curve). The limit of quantification of the marbofloxacin assay was 0.05 μg ml^{-1}. The percentage recoveries were determined by comparing the inhibition zones of blank samples spiked with different amounts of drug and treated as any sample, with the inhibition zones of the same standards prepared in phosphate buffer (n = 6). The mean percentage recovery of marbofloxacin from plasma was 93.29 ± 4.81%. Intra-assay variations were determined by measuring six replicates (n = 6) of three standard samples used for calibration curves. An inter-assay precision was determined by assaying the three standard samples on three separate days. The intra-assay variation coefficient was <5.41 and the inter-assay variation coefficient was <5.69 for plasma. The intra- and inter-day precision and accuracy of the assay were determined by percent coefficient of variation (CV). The coefficient of variation was calculated as follows:

CV (%) = (standard deviation/mean) x100.

The extent of protein binding was determined *in vitro* according to the method described previously by Craig and Suh (1991). This method was based on the diffusion of free antibiotic into the agar medium. To estimate the protein binding of marbofloxacin, the drug was dissolved in phosphate buffer (pH 7.2) and antibiotic free quail's plasma at different concentrations. This estimation was based on the facts that free unbound part of marbofloxacin only capable to diffuse through agar. The differences in the diameters of the inhibition zones between the solutions of the drug in the buffer and plasma samples were then calculated according to the following equation:

$$\text{Protein binding \%} = \frac{\text{Zone of inhibition in buffer - Zone of inhibition in plasma}}{\text{Zone of inhibition in buffer}} \times 100$$

Pharmacokinetic analysis

Plasma concentrations of marbofloxacin after IV, IM and PO administrations were subjected to a compartmental analysis. The analysis was done with the help of a computerized program WinNonlin 4.1 (Pharsight, Mountain View CA, USA) was used to analyze the concentration-time curves for each individual quail after the administration of marbofloxacin by different routes. Following IV administration, the plasma concentration vs time data of marbofloxacin in quails were fitted to a two-compartment open model system according to the following bi-exponential equation (Baggot, 1978):

$$C_p = Ae^{-\alpha t} + Be^{-\beta t}$$

where C_p is the concentration of drug in the plasma at time t, A and B are the zero-time drug intercepts of the distribution and elimination phase expressed as μg ml^{-1}, α and β are the distribution and elimination rate constants expressed in units of reciprocal time (h^{-1}), and e is the natural logarithm base.

For the IV data, the appropriate pharmacokinetic model was determined by visual examination of individual concentration-time curves and by application of Akaike's Information Criterion (AIC) (Yamaoka *et al*., 1978). The volume of distribution at steady state (V_{dss}), the total body clearance (Cl) and mean residence time (MRT) were computed according to standard equations (Gibaldi and perrier, 1982). Following IM and PO administration, plasma concentration data in quails were analyzed by compartmental and non-compartmental methods based on the statistical moment theory (Gibaldi and perrier, 1982). In compartmental analysis, best fitting of the data was accomplished using the one compartment open model. The area under the concentration time curve (AUC), and area under the first moment curve (AUMC), was calculated by the method of trapezoids. Mean residence time (MRT) was calculated as MRT =AUMC/AUC and the systemic clearance as Cl=Dose/AUC. The absolute bioavailability was calculated as F =$AUC_{IM \text{ or } PO}$/AUC_{IV}x100. Mean absorption time was calculated as MAT =$MRT_{IM \text{ or } po}$-MRT_{IV}. The pharmacokinetic parameters were reported as mean ± SD. Data obtained throughout the study were analysed using SPSS (16) software (SPSS Inc., Chicago, USA) and differences between the averages were examined by Duncan's multiple-range test. Mean values within a row with different superscript letters are significantly different (P< 0·05).

3. Results

Clinical examination of all birds before and after each trial did not reveal any abnormalities. No local or adverse reactions to marbofloxacin occurred after IV, IM or PO administration. The mean plasma concentration-time profiles of marbofloxacin following a single IV, IM and PO administrations of 5 mg/kg BW were presented graphically in the Figure 1. Mean ± SD values of pharmacokinetics parameters estimated from the curve fitting were shown in Table (1). After IV injection, the $t_{1/2\alpha}$ and $t_{1/2\beta}$ were 0.25 and 4.03 h, respectively. Following IM and PO administrations the corresponding pharmacokinetic variables are shown in Table 1, marbofloxacin was rapidly absorbed with a $t_{1/2ab}$ of 0.66 and 0.71 h, the maximum plasma concentration (C_{max}) 3.86 and 3.58 µg/ml were attained at 1.58 and 1.60 h, the time to peak concentration (t_{max}), the $t_{1/2el}$ of marbofloxacin were 6.70 and 6.19 h, marbofloxacin bioavailability were 98.72 and 87.94%, respectively. In vitro plasma protein binding percent of marbofloxacin in plasma was 26.38%.

Table 1. Mean ± SD plasma pharmacokinetic parameters of marbofloxacin in quails following IV, IM and PO administration of 5 mg/kg BW (n=5).

Parameter	Unit	IV	IM	PO
α (k_{ab})	h^{-1}	2.85 ± 0.37^a	1.06 ± 0.11^b	0.99 ± 0.16^b
$t_{1/2\alpha}$ ($t_{1/2ab}$)	h	0.24 ± 0.03^b	0.66 ± 0.05^a	0.71 ± 0.11^a
β (k_{el})	h^{-1}	0.17 ± 0.003^a	0.10 ± 0.005^c	0.11 ± 0.001^b
$t_{1/2\beta}$ ($t_{1/2el}$)	h	4.03 ± 0.08^c	6.70 ± 0.34^a	6.19 ± 0.08^b
AUC	µg ml^{-1} h^{-1}	26.03 ± 1.97	25.66 ± 2.51	22.78 ± 2.67
AUMC	µg ml^{-1} h^{-2}	153.75 ± 18.22	198.96 ± 31.79	162.01 ± 25.67
MRT	h	5.89 ± 0.25^b	7.72 ± 0.52^a	7.09 ± 0.28^a
MAT	h	—	1.79 ± 0.31	1.19 ± 0.39
Vd_{ss}	l kg^{-1}	1.24 ± 0.04	—	—
Cl_{tot}	l kg^{-1} h^{-1}	0.19 ± 0.01	—	—
C_{max}	µg ml^{-1}	—	3.86 ± 0.18	3.59 ± 0.24
t_{max}	h	—	1.58 ± 0.02	1.60 ± 0.04
F	%	—	98.72 ± 8.97	87.94 ± 12.78
C_{max}/MIC	Ratio	—	19.31 ± 0.90	17.94 ± 1.19
AUC/MIC	Ratio	—	128.28 ± 12.54	113.89 ± 13.35

α; **β** hybrid rate constant representing the slope of distribution and elimination phase after IV injection; **K_{ab}**; **K_{el}** absorbtion and elimination rate constant after IM and PO administratin; **$t_{0.5(\alpha)}$** distribution half-life after IV injection; **$t_{0.5(ab)}$** absorption half-life after IM and PO administration; **$t_{0.5(\beta)}$** elimination half-life after IV injection; **$t_{0.5(el)}$** elimination half-life after IM and PO administration; **AUC** area under plasma concentration-time curve; **AUMC** area under moment curve; **MRT** mean residence time; **MAT** mean absorption time; **Vd_{ss}** volume of distribution at steady state; **Cl** total body clearance. **C_{max}** maximum plasma concentration; **T_{max}** time to peak serum concentration; **F** fraction of drug absorbed systemically after oral

injection **C$_{max}$/MIC** maximum serum concentration/minimum inhibitory concentration ratio; **AUC/MIC** area under the plasma concentration-time curve/MIC ratio.

[a, b, c] Mean values having different letters in raw differ significantly (P<0.05).
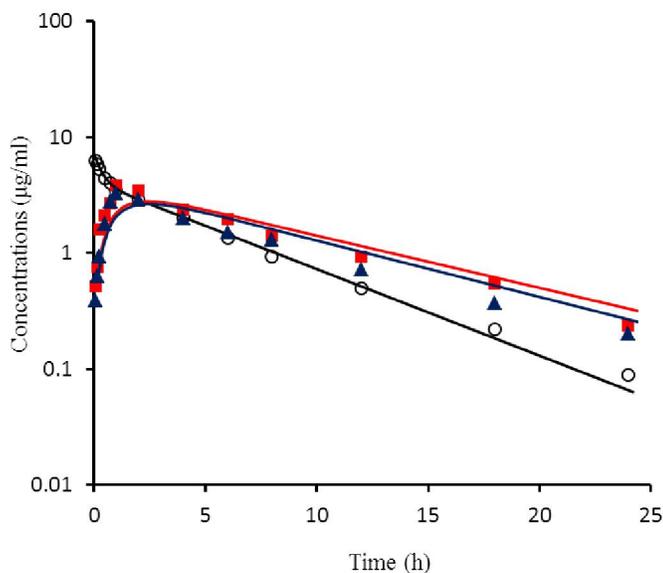

Figure 1. Semi-Logarithmic graph depicting the time-concentration of marbofloxacin in plasma of quails after a single IV (○), IM (■) and PO (▲) administration of 5 mg/kg BW (n=5).

4: Discussion

The present investigation revealed that, plasma marbofloxacin concentrations versus time decreased in a bi-exponential manner following IV injection, demonstrating the presence of distribution and elimination phases and justifying the use of two compartment open model. This finding is in agreement with other pharmacokinetic study of marbofloxacin in Muscovy ducks (Goudah and Hasabelnaby, 2011). Plasma concentration profiles showed a rapid initial distributive phase, followed by a slower elimination phase with an estimated mean distribution half-life ($t_{0.5\alpha}$) of 0.25 h. this result was longer than marbofloxacin (0.12 h) in chicken (Anadon et al., 2002) and shorter than marbofloxacin (1.58 h) in Mallard ducks(Garcia-Montijano et al., 2012). The elimination half-life ($t_{0.5\beta}$) was 4.03 h. This observation agreed with the data reported for difloxacin (4.10 h) in chickens (Inui et al. 1998), longer than orbifloxacin and levofloxacin (1.57, 2.52 h) in quails (Hawkins et al., 2011; Aboubakr, 2012), respectively and marbofloxacin (2.81 h) in Mallard ducks (Garcia-Montijano et al, 2012), and shorter than marbofloxacin (5.26 h) in chicken (Anadon et al., 2002). In this respect, fluoroquinolones have a long half-life making them suitable for once or twice a day administration (Vancutsem et al., 1990). Such differences are relatively common and frequently

related to inter-species variation, assay methods used, the time between blood samplings, and / or the health status and age of the animals (Haddad et al., 1985).

The Vd$_{ss}$ for marbofloxacin was 1.24 l/kg, suggesting good penetration through biological membranes and tissue distribution after IV administration in quails. The obtained value was similar to that recorded for orbifloxacin (1.27 l/kg) in quails (Hawkins et al., 2011), marbofloxacin (1.25 l/kg) in Muscovy ducks (Yuan et al., 2011), lower than marbofloxacin (3.22 l/kg) in ostrich (De lucas et al, 2005), enrofloxacin and danofloxacin (5.36, 8.67 l/kg) in quails (Haritova et al., 2013) and higher than marbofloxacin (0.77 l/kg) in chicken (Anadon et al., 2002). The total body clearance (CL$_{tot}$) was 0.19 l/h/kg, this value was nearly the same as marbofloxacin (0.17, 0.16, 0.23 l/h/kg) in chicken, turkeys and Muscovy ducks (Anadon et al., 2002; Haritova et al., 2006; Yuan et al., 2011), respectively and lower than marbofloxacin (2.19 l/h/kg) in ostrich (De lucas et al., 2005), orbifloxacin and levofloxacin (0.59, 0.40 l/h/kg) in quails (Hawkins et al, 2011; Aboubakr, 2012), respectively.

Following IM administration, marbofloxacin was rapidly absorbed in quails as the absorption half-life ($t_{0.5ab}$) was (0.66 h). The obtained value was longer than marbofloxacin (0.27 h) in Muscovy ducks (Goudah and Hasabelnaby, 2011). The rapid oral

absorption also reflected by low MAT (mean absorption time) value (1.79 h). This value was nearly similar to that reported for danofloxacin (1.35 h) in Muscovy ducks (Goudah and Mounier, 2009). The pharmacokinetic properties of fluoroquinolones include rapid absorption to the result of continued absorption of marbofloxacin from the site of IM administration during the elimination phase, thereby, prolonging the $t_{0.5el}$ of the drug. Absorption limits drug elimination (Gibaldi and Perrier, 1982). The drug was eliminated at a slow rate with an elimination half-life ($t_{0.5el}$) of (6.70 h).this value was longer than marbofloxacin (1.96, 2.82 h) in ostrich and Muscovy ducks (De Lucas *et al.*, 2005; Goudah and Hasabelnaby, 2011), respectively. Also, this result supported by longer MRT of 7.72 h. The (C_{max}) was 3.86 µg/ml achieved at (t_{max}) of 1.58 h. This value was nearly the same as marbofloxacin (3.11 µg/ml at 1.02 h) in Muscovy ducks (Goudah and Hasabelnaby, 2011) and higher than marbofloxacin (1.13 µg/ml at 0.61 h) in ostrich (De Lucas *et al.*, 2005). The systemic bioavailability of marbofloxacin in quails following IM administration was 98.72 %, which almost the same as marbofloxacin (95.03 %) in ostrich (De Lucas *et al.*, 2005). and higher than marbofloxacin (81.03 %) in Muscovey ducks (Yuan *et al.*, 2011).

Following PO administration, marbofloxacin was rapidly and efficiently absorbed through gastrointestinal tract of quails as the absorption half-life ($t_{0.5ab}$) was (0.71 h). This value was nearly the same as orbifloxacin (0.59) in quails (Hawkins *et al.*, 2011), longer than marbofloxacin (0.36 h) in Muscovy ducks (Goudah and Hasabelnaby, 2011) and shorter than levofloxacin (1.07 h) in quails (Aboubakr, 2012). The rapid oral absorption also reflected by low MAT (1.19 h). This value was nearly similar to that of enrofloxacin (1.20 h) in chickens (Knoll *et al.*, 1999). The elimination half-life ($t_{0.5el}$) was (6.19 h) was longer than marbofloxacin (4.61 h) in Muscovy ducks (Yuan *et al.*, 2011) and shorter than marbofloxacin (8.69, 7.73h) in chicken and turkeys (Anadon *et al.*, 2002; Haritova *et al.*, 2006), respectively. Maximal plasma concentration (C_{max}) was 3.59µg/ml achived at (t_{max}) of 1.60 h. These values were lower than orbifloxacin (5.22µg/ml at 1 h) in quails (Hawkins *et al.*, 2011). Following PO administration, the systemic bioavailability was (87.94 %) which almost the same with oral bioavailability reported for marbofloxacin (87.75 %) in Muscovy ducks (Yuan *et al.*, 2011), higher than marbofloxacin (56.82 %) in chicken (Anadon *et al.*, 2002) and lower than orbifloxacin (102.01 %) in quails (Hawkins *et al.*, 2011).

In this study, the *in vitro* plasma protein binding experiment showed that marbofloxacin displayed a low level of binding to plasma proteins (26.38%) to quails plasma. The low protein binding of marbofloxacin in quails plasma proteins is in agreement with reported value for levofloxacin (23.52%) in quails (Aboubakr, 2012) and higher than marbofloxacin (18.4%) in Muscovy ducks (Goudah and Hasabelnaby, 2011). This difference may reflect species differences in the number of plasma protein binding sites or their affinity for these drugs (Lin, 1995). As low protein binding generally enables rapid and extensive distribution into the intra and extracellular space to exert its high antibacterial activity.

Based on many *in vitro* and *in vivo* studies performed in humans and animals, it has been established that for concentration dependant antibacterial agents, such as fluoroquinolones, the AUC/MIC ratio is the most important factor in predicting efficacy, with the rate of clinical cure being greater than 80% when this ratio is higher that 100–125 (Forrest *et al.*, 1993; Madaras-Kelly *et al.*, 1996; Lode *et al.*, 1998). A second predictor of efficacy for concentration dependent antibiotic is the ratio C_{max}/MIC, considering that values above 8–10 would lead to better the clinical results, as well as, to avoid bacterial resistance emergence (Dudley, 1991; Drusano *et al.*, 1993; Madaras-Kelly *et al.*, 1996; Walker, 2000). Marbofloxacin has excellent potency *in vitro* against most pathogens that affect poultry and the MIC_{90} of marbofloxacin are generally ≤ 0.20 µg/ml for gram-negative bacteria, except for *P aeruginosa* (Spreng *et al.*, 1995). In quails, marbofloxacin results in potentially therapeutic plasma concentrations against gram-negative bacteria pathogens such as *E coli*, *P multocida*, and *Salmonella* spp. Following IM and PO administrations, the AUC/MIC ratio of (128.28, 113.89) and C_{max}/MIC ratio of (19.31, 17.94), respectively, indicates potential clinical and bacteriological efficacy of marbofloxacin in quails (calculated by use of an MIC_{90} value of 0.20 for general pathogens).

In conclusion, good bioavailability, the large volume of distribution, a high C_{max} and AUC and pharmacokinetic-pharmacodynamic hybrid efficacy predictors for marbofloxacin indicate that administration of marbofloxacin at 5 mg/kg BW by different routes may be highly efficacious against susceptible bacteria in quails. Further studies on tissue distribution and specific determination of the MIC of marbofloxacin for the major bacteria responsible for respiratory diseases in quails are warranted to further evaluate the efficacy of marbofloxacin in poultry.

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