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# DISPOSITION KINETICS, BIOAVAILABILITY AND TISSUE RESIDUES OF MARBOFLOXACIN IN MOLAR DUCKS

**Saber El-Hanbally[1]*, Hanem El-Gendy[1] and Amera Abd El Latif[2]**

[1]Department of Pharmacology, Faculty of Veterinary Medicine, University of Sadat City, Egypt.
[2]Department of Pharmacology, Faculty of Veterinary Medicine, Kafrelsheikh University, Egypt.

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***Corresponding Author**
**Saber El-Hanbally**
Department of Pharmacology, Faculty of Veterinary Medicine, University of Sadat City, Egypt.
elhanbally@yahoo.com,

## ABSTRACT

The present study was designed to determine the pharmacokinetics, bioavailability and tissue residues of marbofloxacin (10mg/kg.b.wt.) in ducks. Forty Molar ducks were divided into two groups. Blood samples were collected at 5, 15, 30 minutes, 1,2,4,6,8,12 and 24 hours after marbofloxacin administration. Serum marbofloxacin concentrations were determined by using high performance liquid chromatography (HPLC) technique. The serum concentration-time curve indicated a two compartment open model. Following a single intravenous injection, distribution half-life ($t_{0.5\alpha}$) was 1.04 ± 0.16h, volume of distribution ($V_{dss}$) was 6.71 ± 0.46 L/kg, elimination half-life ($t_{0.5\beta}$) was 5.51 ± 0.61h and total body clearance ($CL_{tot}$) was 0.66±0.02l/kg/h. Following a single oral administration, marbofloxacin had a peak serum concentration ($C_{max}$) 1.60±0.03µg/ml at a time ($t_{max}$) of 1.69±0.03 h, elimination half-life ($t_{0.5el}$) was 2.73±0.07h indicating the tendency of ducks to eliminate marbofloxacin in slow rate. Oral bioavailability was 79.68± 2.62% indicating good absorption of marbofloxacin after oral administration. Tissue residues of marbofloxacin in slaughtered ducks were high in those tissues; lung, kidneys and liver tissues so ducks should not be slaughtered before 3 days of stopping of marbofloxacin administration.

**KEYWORDS:** Kinetic, marbofloxacin, tissue residues, ducks, bioavailability.

## 1. INTRODUCTION

Fluoroquinolones are synthetic antibacterial agents that have enjoyed extensive interest and rapid acceptance in both human and veterinary medicine; they are bactericidal with concentration-dependent efficacy (**Ihrke *et al.*, 1999**). They were banned from use in food producing animals such as poultry and ducks (**Wispelwey, 2005**). They are the derivatives of quinolones which are fluorinated at C-6 position of the quinolone ring. They act by frustration of DNA gyrase enzyme and transcription leading to cell death (**Somasundaram and Manivannan, 2013**). Marbofloxacin is a fluoroquinolone with a similar bactericidal spectrum to that enrofloxacin, but offers some advantages such as a longer elimination half-life, greater tissue penetrating ability and higher bioavailability. The pharmacokinetics of marbofloxacin have been investigated in a variety of avian species, most recently in ducks (**Guzman, 2014**). It has a broad of bactericidal activity against gram-negative, some gram-positive microscopic organisms (*Staphylococcus aureus, Staphylococcus intermedius, Escherichia coli, Klebsiella sp., Pasteurella multocida, Pasteurella haemolytica,* and *Haemophilus somnus*) and Mycoplasma (**Spreng *et al.*, 1995; Yuan *et al.*, 2011**). Similar to other fluoroquinolones; marbofloxacin has low plasma protein binding (**Ismail and El-Kattan, 2007**), large volume of distribution with good concentrations in tissues and body fluids (**Aliabadi and Lees, 2002; Anadon *et al.*, 2002**) and activity at extremely low concentrations (**Ding *et al.*, 2013**).

The kinetic profile of marbofloxacin has been studied in some avian species like broiler chickens (**Anadon *et al.*, 2002; Ding *et al.*, 2013**), ostriches (**De Lucas *et al.*, 2005**), turkey (**Haritova *et al.*, 2006**) Muscovy ducks (**Goudah and Hasabelnaby, 2010; Yuan *et al.*, 2011**) and Mallard ducks (**Garcia- Montijano *et al.*, 2012**). The aim behind the present study was to look at bioavailability, pharmacokinetics of marbofloxacin (10mg/kg.b.wt.) after both single intravenous and single oral administration in Molar ducks and to determine its tissue residues after repeated oral administration for five consecutive days.

## 2. MATERIAL AND METHODS

### 2.1. Drugs

It was obtained as injectable watery solution 10% under trade name (Marbocyl)® from Falcon`s Care Center, K.S.A. It manufactured by Vétoquinol S.A. (France).

### 2.2. Birds

Forty healthy Molar ducks of both sexes at 10 weeks of age weighing from 1800-2000 gm were used. Ducks

were obtained from a private farm. Ducks were housed in hygienic floor system chambers and were fed on a balanced antibiotics free ration and water was offered to birds as *ad-libitum.* Birds were kept under observation for 2 weeks before the start of experiments to withdraw any antibiotic residues. The experiment was performed in accordance with the guidelines set by the Ethical Committee of Faculty of Veterinary Medicine, University of Sadat City, Egypt.

**2.3. Experimental design**

**Group I:** It included five healthy ducks; each duck was given a single intravenous dose of marbofloxacin (10mg/kg.b.wt.) to determine its serum concentrations and pharmacokinetics, then after fifteen days the same birds were given a single oral dose of marbofloxacin (10mg/kg.b.wt.) to determine its serum concentrations, pharmacokinetics and its bioavailability.

**Group II:** It included twenty five apparently healthy ducks, each duck was given a repeated oral dose of marbofloxacin (10mg/kg.b.wt.) for five consecutive days for determination of its tissue residues using HPLC (**Atef *et al.*, 2017**), three ducks were randomly selected and slaughtered at 2hours, 1st, 2nd, 3rd, 4th, 5th and 6thday after the last dose of drug administration. Tissues samples (liver, kidney, lung, spleen, fat, thigh muscle) and sera were collected from all slaughtered birds.

**2.4. Samples**

**Blood samples**: One ml blood was collected from the right wing vein of each bird at 5,15 and 30 minutes and 1, 2, 4, 6, 8, 12 and 24 hours after both single intravenous and single oral administration. All blood samples were left to clot for 30 min., centrifuged at 3000 rpm for 15 min. and the obtained clear sera were transferred to eppendorf's tubes and kept in deep freeze (-20°C) till assayed.

**Tissue samples**: One gram of tissue samples (liver, kidney, lung, spleen, fat and thigh muscle) was added to 1ml of distilled water and thoroughly homogenized. Tissue sedimentation allowed for settling and the supernatant was transferred to sterilized eppendorf's tubes which kept at -80 $^{o}$C until assayed.

**2.5. Analytical methods**

Serum and tissue concentrations of marbofloxacin were determined using a high performance liquid chromatographic (HPLC) method. Sample analysis, solutions and HPLC conditions were carried out according to (**Lina, 2008**). 0.5 ml of serum or supernatant of tissues was added to 3 ml of Acetonitrile in centrifugation tubes and was mixed for 1 min by vortex, samples was centrifuged at 3000 rpm for 20 min, then the supernatant was transferred to other centrifuge tube and was evaporated under nitrogen flow to dryness, then 150 µl of mobile phase and 400 µl of Hexane was added to dry sample and mixed for 1 min by vortex, samples were centrifuged at 3000 rpm for 20 min, the supernatant was discarded and 50 µl was injected to HPLC (**Salman *et al.*, 2016**).

**2.6. Pharmacokinetic analysis**

Serum concentrations of marbofloxacin versus time curve were generated, and best fitted by the aid of computer poly-exponential curve stripping program, (R-Strip Micromath, software, USA). Data from each duck was fitted individually, and the pharmacokinetic variables were computed by the aid of the software programs. The hybrid rate constants of the distribution and elimination phase (α and β), and the first order absorption and elimination rate constants ($K_{ab}$ and $K_{el}$) and corresponding extrapolated zero time intercepts (A and B), absorption, distribution and elimination half-lives ($t_{0.5ab}$, $t_{0.5\alpha}$, $t_{0.5\beta}$, $t_{0.5el}$), transfer rate constants ($K_{12}$ and $K_{21}$). The area under the curve from zero to infinite time ($AUC_{0-\infty}$), mean residence time (MRT), maximum serum concentration ($C_{max}$) and time to be achieved ($T_{max}$) were calculated. The other pharmacokinetic parameters as total body clearance, the volume of the central compartment ($V_c$), the volume of distribution at steady state ($V_{dss}$) and the bioavailability (F%) were calculated by standard methods (**Baggot, 1978**). The results were expressed as mean±SE and the obtained data statistically using Student "t" test as described by (**Snedecor, 1969**).

## 3. RESULTS

**After a single intravenous administration**

The mean serum concentrations of marbofloxacin in ducks following a single intravenous dose of 10 mg/kg.b.wt. were (3.90±0.05 µg/ml) at 0.083 h and (0.14±0.002 µg/ml) at 24h after administration and presented in (Table 1). The serum drug concentrations declined in a biphasic pattern that can be described by a two-compartment open model (figure 1). The pharmacokinetic analysis of serum concentration versus time plot after a single intravenous injection of marbofloxacin was illustrated in (table 2). It was shown that the drug was rapidly distributed with a distribution half-life ($t_{0.5\alpha}$) of 1.04±0.16 h. The mean elimination half-life ($t_{0.5\beta}$) was 5.51±0.61 h and the total body clearance of the drug ($CL_{tot}$) was 0.66±0.02 l/kg/h. The apparent volume of distribution ($V_c$) of marbofloxacin in the central compartment showed a low value (2.69±0.01 L/kg) as compared with the apparent volume of distribution of the peripheral compartment ($V_{dB}$) of (7.93±0.93 L/kg) and the total volume of distribution at the steady state ($V_{dss}$) (6.71±0.46 L/kg).

**After a single oral administration**

The mean serum concentrations of marbofloxacin at different time intervals following a single oral administration of 10 mg/kg.b.wt. in ducks were (0.45±0.016µg/ml) at 0.083h and (0.076±0.0005µg/ml) at 24h after administration as mentioned in (Table 1) and depicted in (figure1). The pharmacokinetic parameters of marbofloxacin following its oral administration are tabulated in (table 3). The peak concentration ($C_{max}$) was

(1.60±0.03 µg/ml) and the calculated value of $T_{max}$ was (1.69±0.03 h). The drug was absorbed from duck s gut with absorption half-life ($t_{0.5ab}$) of 0.65±0.02 h and eliminated with a mean half-life ($t_{0.5el}$) of 2.73±0.07 h. The calculated bioavailability (F%) of marbofloxacin following its single oral administration of 10 mg/kg b.wt. in ducks was 79.68 ± 2.62% in (Table 4).

**Tissue residues after repeated oral administration**

Mean serum and tissue concentrations of marbofloxacin (µg/ml or µg/gm) assayed by HPLC following oral administration of 10 mg/kg.b.wt. once daily for 5 consecutive days were tabulated in (Table 5).Lung had the highest concentration of marbofloxacin followed by kidney and liver, while the lowest concentration was determined in thigh muscle, fat and spleen. Marbofloxacin still detected in 3rd day after last administration at lung, kidney, liver, spleen and thigh muscles in a concentration of 15.48, 7.40, 2.30, 2.22 and 0.85 µg/ml, respectively.

**Table 1: Serum concentrations of marbofloxacin (µg/ml) in Molar ducks after a single intravenous injection and a single oral administration of 10 mg/kg.b.wt. (n=5).**

| Time (h) | Single IV (X±S.E.) | Single oral (X±S.E.) |
|---|---|---|
| 0.083 | 3.90±0.05 | 0.45±0.016 |
| 0.25 | 3.00±0.04 | 0.71±0.009 |
| 0.5 | 2.74±0.07 | 0.95±0.014 |
| 1 | 2.54±0.07 | 1.44±0.05 |
| 2 | 1.64±0.07 | 1.78±0.037 |
| 4 | 1.04±0.07 | 0.97±0.005 |
| 6 | 0.62±0.01 | 0.63±0.011 |
| 8 | 0.414±0.007 | 0.42±0.006 |
| 12 | 0.26±0.007 | 0.32±0.004 |
| 24 | 0.14±0.002 | 0.076±0.0005 |

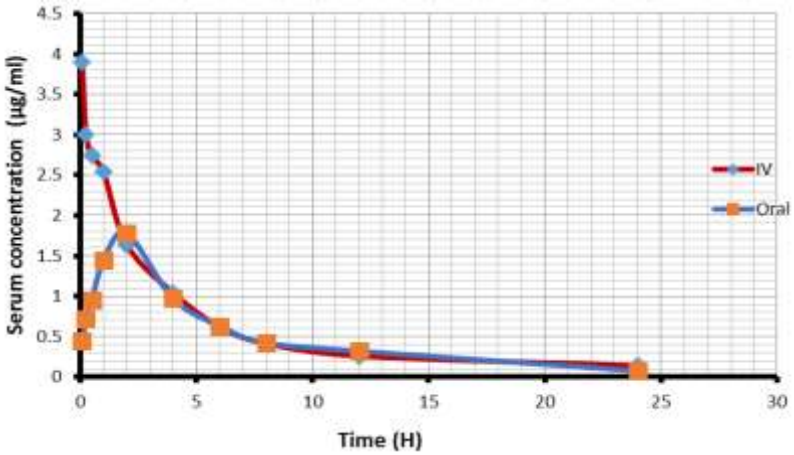


**Fig. 1: Semilogarithmic graph depicting the serum concentrations of marbofloxacin (µg/ml) in Molar ducks after a single intravenous injection & a single oral administration of 10 mg/kg.b.wt. (n=5).**

**Table 2: Pharmacokinetic parameters of marbofloxacin in Molar ducks after a single intravenous injection of 10 mg/kg.b.wt. (n=5).**

| Parameter | Units | X ± S.E. |
|---|---|---|
| $C_o$ | µg/ml | 3.72 ± 0.02 |
| A | µg/ml | 1.94 ± 0.15 |
| α | $h^{-1}$ | 0.74 ± 0.12 |
| $T_{0.5\ (\alpha)}$ | H | 1.04 ± 0.16 |
| B | µg/ml | 1.34 ± 0.16 |
| β | $h^{-1}$ | 0.13 ± 0.02 |
| $T_{0.5\ (\beta)}$ | H | 5.51 ± 0.61 |
| $AUC_{(0-\infty)}$ | µg/h/ml | 15.23 ± 0.57 |
| MRT | H | 4.38 ± 0.20 |
| $K_{12}$ | $h^{-1}$ | 0.50 ± 0.05 |
| $K_{21}$ | $h^{-1}$ | 0.39± 0.10 |
| $K_{el}$ | $h^{-1}$ | 0.28 ± 0.02 |
| $V_{d\beta}$ | L/kg | 7.93± 0.93 |
| $V_c$ | L/kg | 2.69 ± 0.01 |
| $V_{darea}$ | L/kg | 5.12 ± 0.41 |
| $V_{dss}$ | L/kg | 6.71 ± 0.46 |
| $Cl_{tot}$ | L/kg/hr | 0.66 ± 0.02 |

**Table 3: Pharmacokinetic parameters of marbofloxacin in Molar ducks after a single oral administration of 10 mg/kg.b.wt. (n=5).**

| Parameter | Units | X ± S.E. |
|---|---|---|
| A | µg/ml | 3.03 ±0.13 |
| $K_{ab}$ | $h^{-1}$ | 1.07±0.039 |
| $T_{0.5\ (ab)}$ | h | 0.65 ±0.02 |
| B | µg/ml | 3.24 ±0.13 |
| $K_{el}$ | $h^{-1}$ | 0.26±0.005 |
| $T_{0.5\ (el)}$ | H | 2.73 ±0.07 |
| $C_{max}$ | µg/ml | 1.60±0.03 |
| $T_{max}$ | h | 1.69 ±0.03 |
| $AUC_{(0-\infty)}$ | µg/h/ml | 12.08 ±0.11 |
| MRT | h | 4.80 ±0.08 |
| IBD | h | 11.93±0.13 |

**Table 4: Systemic bioavailability of marbofloxacin in Molar ducks following a single oral administration of 10 mg/kg.b.wt. (n=5).**

| Bird's No. | AUC | | Bioavailability (F %) |
|---|---|---|---|
| | Oral(µg/h/ml) | Intravenous(µg/h/ml) | |
| **1** | 12.13 | 16.55 | 73.29 |
| **2** | 12.17 | 14.01 | 86.87 |
| **3** | 12.19 | 15.02 | 81.16 |
| **4** | 11.63 | 14.01 | 83.01 |
| **5** | 12.26 | 16.55 | 74.08 |
| **X± S.E.** | 12.08 ± 0.11 | 15.23 ± 0.57 | 79.68 ± 2.62 |

**Table 5: Mean serum and tissues concentrations of marbofloxacin (µg/ml or µg/gm) in Molar ducks following oral administration of 10mg/kg.b.wt. once daily for 5 consecutive days.(n = 3).**

| Tissues | Time of slaughter after the last dose | | | | | | |
|---|---|---|---|---|---|---|---|
| | 2h | 1st day | 2nd day | 3rd day | 4th day | 5th day | 6th day |
| **Serum** | 4.60± 0.29 | 2.99±0.14 | 2.46±0.078 | 0.62±0.02 | --- | --- | --- |
| **Liver** | 12.32±0.46 | 6.03±0.27 | 4.65±0.14 | 2.30±0.05 | 1.04±0.03 | 0.53±0.03 | --- |
| **Kidney** | 38.17±1.85 | 22.53±0.02 | 11.07±0.30 | 7.40±0.02 | 3.08±0.11 | 1.45±0.07 | --- |
| **Lung** | 65.00±1.68 | 35.20±1.54 | 20.11±1.09 | 15.48±0.56 | 10.03±0.4 | 8.37±0.11 | 5.45±0.2 |
| **Spleen** | 9.30±0.04 | 6.05±0.26 | 4.25±0.06 | 2.22±0.09 | 1.58 ±0.04 | 0.65±0.03 | --- |
| **Fat** | 7.60±0.04 | 5.66±0.04 | 3.11±0.20 | --- | --- | --- | --- |
| **Thigh muscle** | 6.45±0.25 | 4.11±0.11 | 2.32±0.11 | 0.85±0.06 | --- | --- | --- |

## 4. DISCUSSION

Disposition kinetics of marbofloxacin after intravenous and oral administration in Molar ducks were best described by use of a two-compartment model (**Goudah and Hasabelnaby, 2010**). In this study marbofloxacin was given at dose rate 10 mg/kg.b.wt. (**El-Sheikh *et al.*, 2010**) as enrofloxacin in ducks (**Bratoev *et al.*, 2017**).Our results showed that marbofloxacin was rapidly and widely distributed after IV administration with a distribution half-life($t_{½\alpha}$) of 1.04± 0.16 h and $V_{dss}$ of 6.71±0.46L⁄kg, suggesting a good tissue penetration. This ($V_{dss}$) was in agreement with values recorded in ostriches (**De Lucas *et al.*, 2005**). But a low ($V_{dss}$) was observed after i.v. administration of marbofloxacin in Muscovy ducks1.25 ± 0.22 L⁄kg, Therefore, volume of distribution was allometrically related to body weight for marbofloxacin (**Cox, 2007**). When broiler chicken was dosed intravenously with 2 mg ⁄ kg, lower ($V_{dss}$) was achieved even after recalculation based on the dosage (**Anadon *et al.*, 2002**).

The $t_{1/2\beta}$value of marbofloxacin in our study was 5.51 ± 0.61h relatively similar with enrofloxacin in ducks 4.62±0.62h (**Bratoev *et al.*, 2017**) and longer than those previously reported in Muscovy ducks 3.28h (**Yuan et *al.*, 2011**) that may attributed to different doses. The clearance value obtained in our study was 0.66±0.02 L/h/kg, which is higher than that reported in chickens 0.19±0.02 L ⁄h/ kg (**Huang *et al.*, 2002**), while it is almost about one-fourth of the value in ostriches 2.19 ± 0.27 L ⁄h/kg (**De Lucas *et al.*, 2005**). Fluoroquinolones are excreted by renal tubular secretion and biliary or hepatic metabolic pathways (**Neuman, 1988**).

When given orally; marbofloxacin was rapidly and efficiently absorbed in ducks. The reported short half-life of absorption ($t_{0.5ab}$) 0.65±0.02 h was similar to previously reported in chickens 0.62±0.05 h (**Atef *et al.*, 2017**) following administration of 5mg/kg.b.wt. and to that reported in chickens 0.60±0.05h;following administration of 2mg/kg.b.wt. (**Anadón *et al.*, 2002**) but shorter than that reported in turkey 7.73 h; following administration of marbofloxacin in a dose of 2mg/kg (**Haritova *et al.*, 2006**).

Marbofloxacin achieved a maximum concentration ($C_{max}$) of 1.60±0.03µg/ml at ($t_{max}$) of 1.69±0.03 h which is nearly slightly higher than that reported in Mallard ducks; 1.34±0.27 µg/ml (**Garcia-Montijano *et al.*, 2012**) following administration of 2 mg/kg.b.wt. and higher than that reported in chickens; 1.05ug/ml (**Anadón *et al.*, 2002**) following administration of 2 mg/kg.b.wt.

It has been shown that ($C_{max}$) was increased by increasing the dose in dogs ranged from0.831±0.263 µg/ml after oral administration of 1 mg/kg.b.wt. to 2.927±0.581 µg/ml following oral dose of 4 mg/kg.b.wt. (**Schneider *et al.*, 1996**).

Oral bioavailability of marbofloxacin was was 79.68% similar to that reported in chickens; 80.2% (**Atef *et al.*, 2017**) and nearly similar to that reported in turkey; 84.34% (**Haritova *et al.*, 2006**) but it was higher than that recorded in broiler chickens; 56.82% (**Anadón, *et al.*, 2002**) and quails; 50.1% (**Lashev *et al.*, 2015**). The high oral bioavailability reflects the rapid rate and efficient extent of absorption of marbofloxacin.

Following repeated oral administration of 10 mg/kg.b.wt. of marbofloxacin once daily in ducks for five consecutive days, tissues residues of marbofloxacin in slaughtered ducks were high in those tissues lung, kidneys, and liver tissues and ducks should not be slaughtered before 3 days of stopping of drug administration. In particular point; the high clearance of marbofloxacin indicated the reduced possibility of finding residues of marbofloxacin in ducks a few days after treatment and necessity of shorter withdrawal time for this antimicrobial.

## 5. CONCLUSION

The causative agents of septicemia and air sacculitis include *Salmonella spp.*, *Escherichia coli*, *staphylococci* and *Pasteurella spp*. Antimicrobial therapy is an important tool in reducing both the incidence and mortality associated with these diseases (Watts *et al.*, 1993). It could be concluded that oral administration of marbofloxacin at 10 mg/kg.b.wt. achieved good serum concentrations covering the sensitive bacteria to it, which may be highly efficacious against susceptible bacteria in Molar ducks. The highest concentration of marbofloxacin in lung & kidney tissue, suggest that marbofloxacin is suitable for treatment of respiratory & urinary infections in Molar ducks. Ducks should not be slaughtered before 3days of stopping marbofloxacin administration.

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