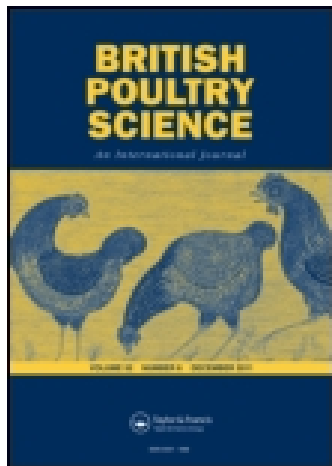


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## British Poultry Science

Publication details, including instructions for authors and subscription information:  
<http://www.tandfonline.com/loi/cbps20>

### Bioavailability and pharmacokinetic profile of levofloxacin following intravenous, intramuscular and oral administration in turkeys

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Accepted author version posted online: 01 Nov 2013. Published online: 16 Apr 2014.

To cite this article: M. Aboubakr, K. Uney & M. Elmas (2014) Bioavailability and pharmacokinetic profile of levofloxacin following intravenous, intramuscular and oral administration in turkeys, *British Poultry Science*, 55:1, 115-119, DOI: [10.1080/00071668.2013.860214](https://doi.org/10.1080/00071668.2013.860214)

To link to this article: <http://dx.doi.org/10.1080/00071668.2013.860214>

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## Bioavailability and pharmacokinetic profile of levofloxacin following intravenous, intramuscular and oral administration in turkeys

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**Abstract** 1. The pharmacokinetics and bioavailability of levofloxacin in turkeys were investigated after a single intravenous (IV), intramuscular (IM) and oral (PO) administration of 10 mg/kg body weight. 2. The concentrations of levofloxacin in plasma samples were assayed using a microbiological assay method and pharmacokinetic parameters were calculated by non-compartmental analysis. 3. Following IV administration, the elimination half-life ( $t_{0.5(\beta)}$ ), volume of distribution at steady state ( $V_{d_{ss}}$ ) and total body clearance (Cl) were 4.49 h, 1.31 l/kg and 0.23 l/h/kg, respectively. 4. After single IM and PO administrations at the same dose, levofloxacin was rapidly absorbed as indicated by an absorption half-life ( $t_{0.5_{ab}}$ ) of 1.02 and 0.76 h, respectively; maximum plasma concentrations ( $C_{max}$ ) of 5.59 and 5.15 µg/ml were obtained at a maximum time ( $T_{max}$ ) of 2 h for both routes and levofloxacin bioavailability (F) was 96.5% and 79.9% respectively after IM and PO administration. *In vitro* plasma protein binding of levofloxacin was 24.3%. 5. Based on these pharmacokinetic parameters, a dose of 10 mg/kg body weight given intramuscularly or orally every 24 h in turkeys can maintain effective plasma concentrations with bacterial infections with (minimum inhibitory concentration)  $MIC_{90} > 0.1$  µg/ml.

### INTRODUCTION

Levofloxacin is a third-generation fluoroquinolone with excellent broad-spectrum activity against Gram-positive, Gram-negative and anaerobic bacteria as well as atypical pathogens such as *Mycoplasma* and *Chlamydia* (see Aboubakr, 2012).

The pharmacokinetics of levofloxacin has been investigated in many animal species including rabbits, rats, cats, calves, stallions, male camels, lactating goats, sheep and quails (Destache *et al.*, 2001; Cheng *et al.*, 2002; Albarellos *et al.*, 2005; Dumka and Srivastava, 2006, 2007; Goudah *et al.*, 2008; Goudah, 2009a; Goudah and Abo-El-Sooud, 2009; Goudah and Hasabelnaby, 2010; Aboubakr, 2012). However, there is no available information on the kinetics of levofloxacin in turkeys. The

present study was planned to determine the disposition kinetics and bioavailability (F) of levofloxacin in turkeys following a single intravenous (IV), intramuscular (IM) and oral (PO) administration of 10 mg/kg body weight. Based on its pharmacological profile, levofloxacin is a promising therapeutic tool for several bacterial infections in turkeys.

### MATERIALS AND METHODS

#### Drugs and chemicals

Tavanic (100 ml solution of levofloxacin hemihydrate equivalent to 500 mg (5 mg/ml) levofloxacin) and Levofloxacin oral tablets (Tavanic

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Accepted for publication 10 September 2013.

500 mg) were purchased from Sanofi-Aventis, Pharmaceutical Ltd, Egypt, and Mueller–Hinton agar from Mast Group Ltd., Merseyside, UK.

### Experimental birds

Fifteen clinically healthy broiler turkeys, 7–8 month old (8 males and 7 females), weighing between 6–8 kg, were provided from a commercial farm. The birds were housed in groups of 5 per cage; the house was maintained at room temperature (20°C) and 65% relative humidity. Acclimatisation lasted at least two weeks before starting the experiment to ensure the complete withdrawal of any residual drugs. Standard commercial feed (without antibiotics and coccidiostats) and water were supplied *ad libitum*. Their health status was checked by daily observations and no clinical signs of diseases were seen. The experiment was performed in accordance with the guidelines set by the Ethical Committee of Benha University, Egypt.

### Experimental design

Turkeys were individually weighed before drug administration and doses were calculated precisely. This study was performed as a parallel design to avoid the physiological changes in young and rapidly growing birds which may alter the pharmacokinetics between the first and second period as in case of cross-over design. The turkeys were allocated to three equal groups of 5 each. Birds in group 1 were given a single IV dose of levofloxacin at 10 mg/kg body weight into the left brachial vein. Birds in other groups were given the same dose by IM injection into the leg muscle and PO directly into the crop using a thin plastic tube attached to a syringe. Food, but not water, was withheld for 12 h before oral dosing until 8 h after drug administration. All dosages were given between 07.00 and 08.00. Blood samples (each of 1.5 ml) were collected immediately prior to medication (time = 0), and then at 0.08, 0.17, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 10, 12, 18 and 24 h after treatment, from the right brachial vein, into tubes containing heparin. Plasma was separated after centrifugation at 500 g for 10 min. The plasma was decanted, labelled and frozen at –20°C until assayed.

### Analytical method

The concentration of levofloxacin in plasma samples was estimated by a standard microbiological assay (Bennett *et al.*, 1966) using *Escherichia coli* ATCC 10536 as test micro-organism. The analytical method was the same as that reported for the pharmacokinetics of levofloxacin in quails (Aboubakr, 2012).

### Pharmacokinetic analysis

Pharmacokinetic parameters were determined for each individual bird. Plasma concentrations of levofloxacin after IV, IM and PO administrations were subjected to a non-compartmental analysis based on the statistical moment theory (Gibaldi and Perrier, 1982) using a computerised program, WinNonlin 4.1 (Pharsight, Mountain View, CA, USA). The pharmacokinetic analysis was the same as that reported for pharmacokinetics of levofloxacin in quails (Aboubakr, 2012).

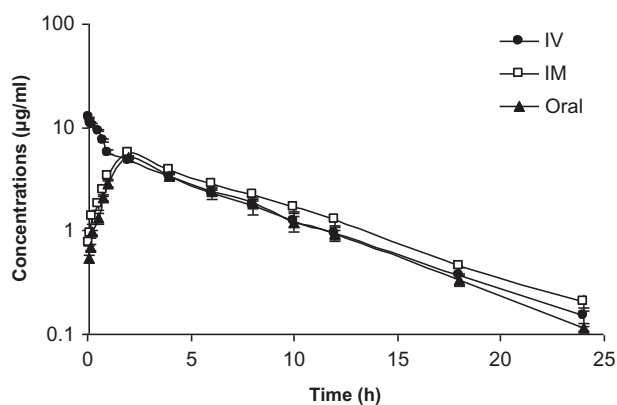
The data were analysed using SPSS software (SPSS Inc., Chicago, USA) pocket program and differences between the averages were examined by multiple-range test. Mean values within a row with different superscript letters are significantly different ( $P < 0.05$ ).

## RESULTS

Clinical examination of all birds before and after each trial did not reveal any abnormalities. No local or adverse reactions to levofloxacin occurred after IV, IM and PO administrations. The mean plasma concentration–time profiles of levofloxacin following a single IV, IM and PO administrations of 10 mg/kg body weight are presented graphically in the Figure. Mean  $\pm$  SD values of pharmacokinetic parameters estimated from the curve fitting are shown in the Table.

After IV injection, the elimination half-life ( $t_{0.5\beta}$ ) was 4.49 h, volume of distribution at steady state ( $V_{d_{ss}}$ ) was 1.31 l/kg and clearance (Cl) was 0.23 l/h/kg.

Following IM and PO administration, levofloxacin was rapidly absorbed and ( $t_{0.5ab}$ ) was 1.02 and 0.76 h, respectively. Maximum plasma concentrations ( $C_{max}$ ) of 5.59 and 5.15  $\mu\text{g/ml}$ , respectively, were obtained at 2 h, the time to peak serum concentration ( $T_{max}$ ) for both routes was 96.5 h and levofloxacin bioavailability (F) was



**Figure.** Semi-logarithmic graph depicting the time–concentration of levofloxacin in plasma of turkeys after a single IV (●), IM (□) and PO (▲) administration of 10 mg levofloxacin/kg body weight.

**Table.** Plasma pharmacokinetic parameters of levofloxacin in turkeys (n = 5) following intravenous (IV), intramuscular (IM) and oral (PO) administration of 10 mg/kg body weight (mean ± SD)

Parameter <sup>1</sup>	Unit	IV	IM	PO
C <sup>0</sup>	µg ml <sup>-1</sup>	13.93 ± 0.44	–	–
β	h <sup>-1</sup>	0.15 ± 0.004	–	–
k <sub>el</sub>	h <sup>-1</sup>	–	0.15 ± 0.01	0.17 ± 0.01
t <sub>0.5(β)</sub>	h	4.49 ± 0.12	–	–
t <sub>0.5(ab)</sub>	h	–	1.02 ± 0.11	0.76 ± 0.13
t <sub>0.5(el)</sub>	h	–	4.60 ± 0.22	4.07 ± 0.17
AUC	µg ml <sup>-1</sup> h <sup>-1</sup>	43.15 ± 4.18 <sup>a</sup>	41.58 ± 3.86 <sup>a</sup>	34.40 ± 2.51 <sup>b</sup>
AUMC	µg ml <sup>-1</sup> h <sup>-2</sup>	225.43 ± 34.56 <sup>b</sup>	278.22 ± 33.04 <sup>a</sup>	217.06 ± 20.21 <sup>b</sup>
MRT	h	5.20 ± 0.30 <sup>c</sup>	6.68 ± 0.17 <sup>a</sup>	6.30 ± 0.13 <sup>b</sup>
MAT	h	–	1.48 ± 0.16	1.10 ± 0.19
Vd <sub>ss</sub>	l kg <sup>-1</sup>	1.31 ± 0.04	–	–
Cl	l kg <sup>-1</sup> h <sup>-1</sup>	0.23 ± 0.03	–	–
C <sub>max</sub>	µg ml <sup>-1</sup>	–	5.59 ± 0.26	5.15 ± 0.12
T <sub>max</sub>	h	–	2 ± 0.00	2 ± 0.00
F	%	–	96.45 ± 4.00	79.89 ± 2.74
C <sub>max</sub> /MIC	Ratio	–	55.92 ± 2.58	51.46 ± 1.18
AUC/MIC	Ratio	–	415.78 ± 38.64	344.02 ± 25.14

Notes: –Not available.

<sup>1</sup>C<sup>0</sup>: concentration at zero time (immediately after single IV injection); β: hybrid rate constant representing the slope of elimination phase after IV injection; K<sub>el</sub>: elimination rate constant after PO administration; t<sub>0.5(β)</sub>: elimination half-life after IV injection; t<sub>0.5(ab)</sub>: absorption half-life; t<sub>0.5(el)</sub>: elimination half-life after PO administration; AUC: area under plasma concentration–time curve; AUMC: area under moment curve; MRT: mean residence time; MAT: mean absorption time; Vd<sub>ss</sub>: volume of distribution at steady state; Cl: total body clearance; C<sub>max</sub>: maximum plasma concentration; T<sub>max</sub>: time to peak serum concentration; F: fraction of drug absorbed systemically after PO injection; C<sub>max</sub>/MIC: maximum serum concentration/minimum inhibitory concentration ratio; AUC/MIC: area under the plasma concentration–time curve/MIC ratio.

<sup>a</sup>, <sup>b</sup>, <sup>c</sup>Within a column, values not sharing a common superscript letter are significantly different ( $P \leq 0.05$ ).

79.9% following IM and PO administrations. *In vitro* plasma protein binding of levofloxacin in turkeys was 24.3%.

## DISCUSSION

The elimination half-life (t<sub>0.5β</sub>) of levofloxacin in turkeys following IV administration was 4.49 h, which agrees with the data reported for levofloxacin (4.44 h) in chickens (Kalaiselvi *et al.*, 2006), longer than marbofloxacin (2.83 h) in Muscovy ducks (Goudah and Hasabelnaby, 2011) and shorter than danofloxacin (8.62 h), marbofloxacin (7.37 h) and enrofloxacin (6.92 h) in turkeys (Dimitrova *et al.*, 2007; Haritova *et al.*, 2006a, 2006b). Such differences are relatively common and frequently related to inter-species variation, assay methods used, the time between blood samplings, health status and age of the animals (Haddad *et al.*, 1985).

The Vd<sub>ss</sub> for levofloxacin was 1.31 l/kg, suggesting good penetration through biological membranes and tissue distribution after IV administration in turkeys. The value was close to that recorded for marbofloxacin (1.41 l/kg) in turkeys (Haritova *et al.*, 2006b), longer than marbofloxacin (0.57 l/kg) in Muscovy ducks (Goudah and Hasabelnaby, 2011) and shorter than danofloxacin and enrofloxacin (6.59 and 3.57 l/kg) in turkeys (Dimitrova *et al.*, 2007; Haritova *et al.*, 2006a), respectively.

The total body clearance (CL<sub>tot</sub>) was 0.23 l/h/kg: the same as marbofloxacin (0.23 l/h/kg) in

Muscovy ducks (Yuan *et al.*, 2011), but shorter than danofloxacin (0.59 l/h/kg) in turkeys (Haritova *et al.*, 2006a).

Following IM administration, levofloxacin was rapidly absorbed in turkeys (absorption half-life t<sub>0.5ab</sub>: 1.02 h). This value was higher than danofloxacin and marbofloxacin (0.31, 0.27 h) in Muscovy ducks (Goudah and Hasabelnaby, 2011; Goudah and Mouneir, 2009). Rapid oral absorption is also reflected by low MAT (mean absorption time) value (1.48 h), similar to danofloxacin (1.35 h) in Muscovy ducks (Goudah and Mouneir, 2009) but lower than sarafloxacin (4.40 h) in chickens (Ding *et al.*, 2001).

Elimination half-life (t<sub>0.5el</sub>: 4.60 h) in turkeys was lower than difloxacin (5.64 h) in chickens (Ding *et al.*, 2008) but higher than both danofloxacin and marbofloxacin (2.91, 2.82 h) in Muscovy ducks (Goudah and Hasabelnaby, 2011; Goudah and Mouneir, 2009).

The C<sub>max</sub> was 5.59 µg/ml, achieved at (T<sub>max</sub>) 2 h: lower than marbofloxacin (3.11 µg/ml at 1.02 h) in Muscovy ducks (Goudah and Hasabelnaby, 2011) and moxifloxacin (2.23 µg/ml at 1.56 h) in chickens (Goudah, 2009b). The systemic bioavailability of levofloxacin in turkeys (96.5%) was similar to moxifloxacin (97.1%) in chickens (Goudah, 2009b) and higher than sarafloxacin (72.1%) in chickens (Ding *et al.*, 2001).

Following PO administration, levofloxacin was rapidly and efficiently absorbed through the gastrointestinal tract of turkeys with an absorption half-life (t<sub>0.5ab</sub>: 0.76 h). This value was higher than



marbofloxacin (0.36 h) in Muscovy ducks (Goudah and Hasabelnaby, 2011) but lower than difloxacin (1.74 h) in chickens (Anadon *et al.*, 2011). This rapid oral absorption is also reflected by low MAT (1.10 h), similar to enrofloxacin (1.20 h) in chickens (Knoll *et al.*, 1999) but lower than the 2.76 h reported for enrofloxacin in turkeys (Dimitrova *et al.*, 2007).

The elimination half-life ( $t_{0.5el}$ : 2.91 h) was similar to marbofloxacin (4.61 h) in Muscovy ducks (Yuan *et al.*, 2011) but lower than for norfloxacin, danofloxacin, marbofloxacin and enrofloxacin (9.07, 9.74, 7.73, 6.92 h, respectively) in turkeys (Dimitrova *et al.*, 2007; Haritova *et al.*, 2006a, 2006b; Laczay *et al.*, 1998).

Maximal plasma concentration ( $C_{max}$ ) was 5.15 µg/ml achieved at ( $T_{max}$ ) 2 h, higher than that for difloxacin (4.34 µg/ml at 1 h) in chickens (Ding *et al.*, 2008). Following PO administration, the systemic bioavailability of levofloxacin in turkeys was 79.9%, almost the same as the oral bioavailability reported for enrofloxacin (77.8, 79.6%) in female and male turkeys (Dimitrova *et al.*, 2006), danofloxacin and marbofloxacin (78.4, 84.4%) in turkeys (Haritova *et al.*, 2006a, 2006b).

For concentration-dependent 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 exceeds 100–125 (Forrest *et al.*, 1993; Lode *et al.*, 1998; Madaras-Kelly *et al.*, 1996). A second predictor of efficacy for such antibiotics is the ratio  $C_{max}/MIC$ : values above 8–10 lead to better clinical results, as well as avoid bacterial resistance emerging (Drusano *et al.*, 1993; Dudley, 1991; Madaras-Kelly *et al.*, 1996; Walker, 2000).

The values for AUC/MIC ratio and  $C_{max}/MIC$  ratio after IM and PO administrations were calculated using documented MIC values against Gram-positive and Gram-negative organisms. An average plasma concentration of 0.032–0.5 µg/ml was reported as the minimum therapeutic concentration ( $MIC_{90}$ ) for levofloxacin against most bacteria (Chulavatnatol *et al.*, 1999). An average  $MIC_{90}$  of 0.1 µg/ml of levofloxacin has been taken into consideration for calculation of efficacy predictors. Following IM and PO administrations, the AUC/MIC ratio of 415.8, 334.0 and  $C_{max}/MIC$  ratio of 55.9, 51.5, respectively, indicate potential clinical and bacteriological efficacy of levofloxacin in turkeys.

In conclusion, the lack of local reaction or any other adverse effects, good bioavailability, the large volume of distribution, a high  $C_{max}$  and AUC and pharmacokinetic–pharmacodynamic hybrid efficacy predictors for levofloxacin indicate that administration of levofloxacin at 10 mg/kg by different routes may be highly efficacious against

susceptible bacteria in turkeys. Further studies on tissue distribution in turkeys should be conducted.

## ACKNOWLEDGEMENT

The authors wish to thank Prof. Dr Ashraf Elkomy (Department of Pharmacology, Faculty of Veterinary Medicine, Benha University, Egypt) for his comments on the manuscript.

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