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Pharmacokinetics of levofloxacin in Japanese quails (Coturnix japonica) following intravenous and oral administration

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Pharmacokinetics of levofloxacin in Japanese quails (*Coturnix japonica*) following intravenous and oral administration

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Abstract 1. The pharmacokinetics of levofloxacin were investigated in Japanese quails after a single dose of 10 mg/kg BW, given either intravenously or orally.
2. Following intravenous administration, the mean value of distribution at steady state (Vd_{ss}), total body clearance (Cl_{tot}) and mean residence time (MRT) of levofloxacin were 1·25 l/kg, 0·39 l/h/kg and 2·72 h, respectively.
3. Following oral administration of levofloxacin, the peak plasma concentration (C_{max}) was 3·31 μg/ml and was achieved at a maximum time (T_{max}) of 2 h. Mean residence time (MRT), mean absorption time (MAT) and bioavailability were 4·26 h, 1·54 h and 69·01%, respectively. *In vitro* plasma protein binding of levofloxacin was 23·52%.
4. Based on pharmacokinetic and pharmacodynamic integration, an oral dose of 10 mg/kg levofloxacin for every 12 h is recommended for a successful clinical effect in quails.

INTRODUCTION

Levofloxacin is a third-generation fluoroquinolone and possesses excellent activity against Gram-positive, Gram-negative and anaerobic bacteria (Davis and Bryson, 1994; North *et al*., 1998), as well as atypical pathogens such as *Mycoplasma* and *Chlamydia* (Eliopoulos *et al*., 1996). Compared to other fluoroquinolones, ofloxacin and ciprofloxacin, it also has more pronounced bactericidal activity against organisms such as *Pseudomonas, Enterobacteriaceae* and *Klebsiella* (Klesel *et al*., 1995).

The bactericidal effect of levofloxacin is achieved through reversible binding to DNA gyrase and subsequent inhibition of bacterial DNA replication and transcription (Fu *et al*., 1992). Levofloxacin distributes well to target body tissues and fluids in the respiratory tract, skin, urine and prostrate, and its uptake by cells makes it suitable for use against intracellular pathogens. Several studies have presented levofloxacin as a safe and effective treatment for community acquired pneumonia, and have indicated it to be at least equivalent to cephalosporins like ceftriaxone and cefuroxime (Norrby *et al*., 1998; Shah *et al*., 1999).

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

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intravenous (IV) and oral (PO) administration of 10 mg/kg BW.

MATERIALS AND METHODS

Drugs and chemicals

Tavanic® (100 ml vial of solution of levofloxacin hemihydrate equivalent to 500 mg (5 mg/ml) levofloxacin), and Levofloxcin oral tablets (Tavanic® 500 mg) were purchased from Sanofi-Aventis, Pharmaceutical Ltd, Egypt, and Mueller–Hinton agar from Mast Group Ltd., Merseyside, UK.

Experimental birds

A total of 60 clinically healthy adult male and female Japanese quail, weighing an average of 185 ± 23 g, were used to determine the pharmacokinetic parameters of levofloxacin. The birds were obtained from the quail farm at the Faculty of Agriculture, Benha University, Egypt. Birds were housed in groups of 5 in cages and fed a commercial drug-free quail diet (Al Sharkia Company, Zagazig, Egypt) along with water *ad libitum*. They were acclimatised 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 Benha University, Egypt.

Experimental design

A two-period sequential design was used, with a wash-out period of 2 weeks between the different routes of administration of levofloxacin. The birds were randomly divided into 12 groups of five 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 (1 ml) were collected from each group of birds one week prior to drug administration (time 0) as controls. Levofloxacin was then administrated in a single IV dose into the right jugular vein, at 10 mg/kg BW, and blood samples were collected from the opposite vein of each bird at 5, 15, 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 min. After a 2-week interval, birds were dosed using a 1 cc syringe directly into the crop at the same dose rate and blood samples were collected from the jugular vein, as described above for the IV route. The plasma was decanted, labelled, and frozen at −20°C until the assays were performed.

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. Standard curves were constructed using antibacterial free plasma collected from quails. The medium was prepared by dissolving 9·5 g Mueller–Hinton agar in 250 ml distilled water in a 0·5 l flat-bottomed flask, which was autoclaved for 20 min. After cooling to 50°C in a water bath, 0·4 ml of the diluted suspension of reference organism was added to the media. 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 100 µl of either the test samples or levofloxacin 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 levofloxacin concentrations in the test samples were calculated from the standard curve. The lower detectable limit of the levofloxacin assay was 0·05 µg/ml. Semi-logarithmic plots of the inhibition zone diameter, versus standard levofloxacin concentrations in serum, were linear between 0·05 and 25 µg/ml, with a typical correlation coefficient of 0·994 (for the standard curve).

The extent of protein binding was determined *in vitro* according to the method described previously by Craig and Suh (1991) based on the diffusion of free antibiotic into the agar medium. To estimate the protein binding of levofloxacin, the drug was dissolved in phosphate buffer (pH 6·2) and antibiotic free quail's plasma at different concentrations. The differences in the diameter of the inhibition zones between the solutions of the drug in the buffer and plasma samples were then used to calculate protein binding according to the following equation:

$$\text{Protein binding}(\%) = \frac{\left\{\begin{array}{l}\text{Zone of inhibition in buffer} \\ \quad -\text{Zone of inhibition in serum}\end{array}\right\}}{\text{Zone of inhibition in buffer}} \times 100$$

Pharmacokinetic analysis

Pharmacokinetic parameters were determined for each individual bird. Plasma concentrations of levofloxacin after IV 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). Values calculated following the IV administration were: area under the plasma concentration vs time curve (AUC), area under

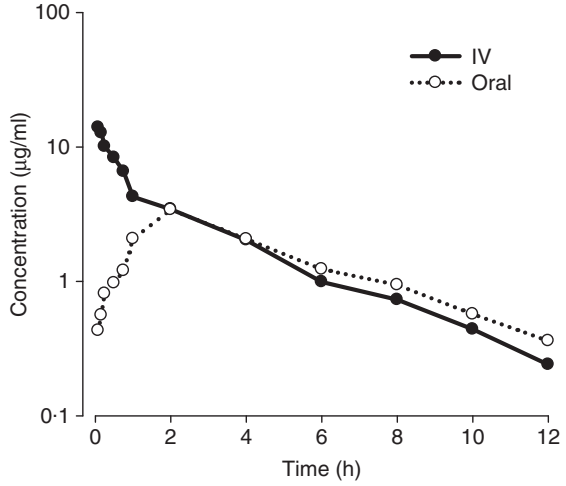

Figure. *Concentration of levofloxacin over time in plasma of quails after a single intravenous (●) and oral (○) administration of 10 mg/kg BW. The Y-axis is logarithmic.*

the first moment curve (AUMC); mean residence time (MRT, where MRT = AUMC/AUC), plasma clearance (Cl, where Cl = Dose/AUC), apparent volume of distribution at steady state (Vd_{ss}, where Vd_{ss} = Cl.MRT), elimination rate constant (β, calculated as the slope of the terminal phase of the plasma concentration curve) and terminal half-life ($t_{0.5}$, where $t_{0.5} = 0{\cdot}693/\beta$). After PO administration, the following parameters were determined as above: AUC, AUMC, MRT, K_{el}, mean absorption time (MAT, where MAT = $MRT_{PO} - MRT_{IV}$), $t_{0.5ab}$ = MAT.0·693 and bioavailability (F), where $F = [AUC_{PO}/AUC_{IV}]$ 100. The AUC and AUMC were calculated using trapezoidal rules. Each individual curve of levofloxacin over time was analysed to determine the peak concentration C_{max} (extrapolated from the curve), and the time to peak concentration T_{max} was read from the data.

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 intravenous or oral administration. The mean plasma concentration-time profiles of levofloxacin following a single intravenous and oral administration of 10 mg/kg BW is presented graphically in the Figure. Mean ± SD values of pharmacokinetics parameters estimated from the curve fitting is shown in the Table.

After intravenous injection, the elimination half-life ($t_{0.5\beta}$) was 2·52 h, volume of distribution at steady state (Vd_{ss}) was 1·25 l/kg and clearance (Cl) was 0·39 l/h/kg.

Following oral administration, levofloxacin was rapidly absorbed; $t_{0.5ab}$ was 1·07 h, maximum plasma concentration (C_{max}) 3·31 µg/ml was obtained at 2 h, and the time to peak concentration (T_{max}) and levofloxacin oral bioavailability (F) was 69·0%. *In vitro* plasma protein binding of levofloxacin was 23·5%.

Table. *Plasma pharmacokinetic parameters of levofloxacin in quails following intravenous and oral administration of 10 mg/kg BW (mean ± SD,* N = *5).*

Parameter[1]	Unit	Intravenous	Oral
C^o	µg ml^{-1}	15·06 ± 0·57	–
β	h^{-1}	0·27 ± 0·01	–
k_{el}	h^{-1}	–	0·25 ± 0·03
$t_{0.5(\beta)}$	h	2·52 ± 0·07	–
$t_{0·5(ab)}$	h	–	1·07 ± 0·03
$t_{0.5(el)}$	h	–	2·83 ± 0·30
AUC	µg ml^{-1} h^{-1}	24·03 ± 1·86	16·60 ± 1·62
AUMC	µg ml^{-1} h^{-2}	65·44 ± 7·37	70·81 ± 8·24
MRT	h	2·72 ± 0·09	4·26 ± 0·08
MAT	h	–	1·54 ± 0·05
Vd_{ss}	l kg^{-1}	1·27 ± 0·06	–
Cl	l kg^{-1} h^{-1}	0·40 ± 0·03	–
C_{max}	µg ml^{-1}	–	3·31 ± 0·21
t_{max}	h	–	2 ± 0·00
F	%	–	69·01 ± 1·81
C_{max}/MIC	Ratio	–	33·06 ± 2·89
AUC/MIC	Ratio	–	166·02 ± 16·18

[1]C^o concentration at zero time (immediately after single IV injection); β hybrid rate constant representing the slope of elimination phase after IV injection; K_{el} elimination rate constant after oral administratin; $t_{0.5(\beta)}$ elimination half-life after IV injection; $t_{0.5(ab)}$ absorption half-life; $t_{0.5(el)}$ elimination half-life after oral 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.

DISCUSSION

The elimination half-life ($t_{0.5\beta}$) of levofloxacin in quails following IV administration was 2·52 h. This observation agreed with the data reported in stallions (2·58 h, Goudah *et al.,* 2008) and male camels (2·92 h, Goudah, 2009*a*), longer than that reported in calves (1·61 h, Dumka and Srivastava, 2007) and shorter than that reported in rabbits (7·5 h, Destache *et al*., 2001) and sheep (3·29 h, Goudah and Hasabelnaby, 2010).

The Vd_{ss} is a clearance-independent volume of distribution that is used to calculate the drug amount in the body under equilibrium conditions (Toutain and Bousquet-Melou, 2004). The Vd_{ss} for levofloxacin was 1·25 l/kg, suggesting good penetration through biological membranes and tissue distribution after IV administration in quails. The value was close to that recorded in male camels (1·01 l/kg, Goudah, 2009*a*), longer than those reported in lactating goats and sheep (Goudah and Abo-El-Sooud, 2009 and Goudah and Hasabelnaby, 2010) (0·86, and 0·73 l/kg, respectively) and shorter than that

reported for other fluoroquinolones in chickens (Anadon *et al*., 2001; Ding *et al*., 2001; Anadon *et al*., 2011).

The total body clearance (CL_{tot}) was 0·39 l/h/kg. This value is consistent with that reported for enrofloxacin in female turkeys (0·38 l/h/kg, Dimitrova *et al*., 2007), levofloxacin in calves (0·32 l/h/kg, Dumka and Srivastava, 2007), difloxacin in chickens (0·37 l/h/kg, Ding *et al*., 2008) and moxifloxacin in chickens (0·36 l/h/kg, Goudah, 2009*b*).

The high value of AUC (24·54 $\mu g ml^{-1} h^{-1}$) indicates that a large area of the body was covered by the drug concentration. Similarity to the present study, high values of AUC of levofloxacin have also been reported in rabbits (29·7 $\mu g ml^{-1} h^{-1}$, Destache *et al*., 2001) and lactating goats (23·94 $\mu g ml^{-1} h^{-1}$, Goudah and Abo-El-Sooud, 2009).

Following oral administration, levofloxacin was rapidly and efficiently absorbed through the gastrointestinal tract of quails as the absorption half-life ($t_{0.5ab}$) was found to be 1·07 h. This was higher than reported by Anadon *et al*. (2011) for difloxacin in chickens (0·37 h) and Yuan *et al*. (2011) for marbofloxacin in ducks (0·34), but lower (1·19 h) than that reported for pefloxacin in chickens by Pant *et al*. (2005). The rapid oral absorption was also reflected by a low MAT (mean absorption time) value (1·54 h). This value was similar to that reported by Knoll *et al*. (1999) for enrofloxacin and danofloxacin in chickens (1·20 and 1·44 h, respectively).

The elimination half-life ($t_{0.5el}$: 2·91 h) was slower following oral compared with IV administration. The value in quails was lower than reported by Ding *et al*. (2001) for sarafloxacin in chickens (3·89 h), Tohamy (2011) for orbifloxacin in ducks (4·18 h) and Yuan *et al*. (2011) for marbofloxacin in ducks (4·61 h), but higher than for moxifloxacin in chickens (1·69 h) reported by Goudah (2009*b*).

Maximal plasma concentration (C_{max}) was 3·37 $\mu g/ml$ achived at (T_{max}) 2 h. These values were higher than reported by Anadon *et al*. (2011) for difloxacin in chickens (2·34 $\mu g/ml$ at 1·34 h) and Yuan *et al*. (2011) for marbofloxacin in ducks (1·13 $\mu g/ml$ at 1·41 h). In contrast, this value was lower than 3·78 $\mu g/ml$ at 3·33 h reported for pefloxacin in chicken by Pant *et al*. (2005).

Bioavailability is the fraction of a drug administered by any nonvascular route that gains access to the systemic circulation. Following oral administration, the systemic bioavailability of levofloxacin in quails was (69·5%) comparable with oral bioavailability reported by Anadon *et al*. (2001) for ciprofloxacin in chickens (69·1%), Dimitrova *et al*. (2007) for enrofloxacin in turkey (69·20%) and Goudah and Hasabelnaby (2011) for marbfloxacin in ducks (72·4%), higher than (54·2%) reported for difloxacin in chickens by Ding *et al*. (2008) and lower than reported for marbofloxacin in ducks (87·8%, Yuan *et al*., 2011) and moxiflxacin in chickens (90·0%, Goudah, 2009*b*).

Protein binding has long been considered one of the most important physicochemical characteristics of drugs, playing a potential role in distribution, excretion, and therapeutic effectiveness as a low protein binding generally enables a rapid and extensive distribution into the intracellular and extracellular space (Turnidge, 1999). In this study, the *in vitro* plasma protein binding experiment showed that levofloxacin displayed a low level of binding to quail plasma proteins (23·5%). This low protein binding of levofloxacin in quail is in agreement with the reported value of 27% for danofloxacin in turkey (Haritova *et al*., 2006).

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 will lead to better clinical results, as well as reducing the risk of bacterial resistance emergence (Dudley, 1991; Drusano *et al*., 1993; Madaras-Kelly *et al*., 1996; Walker, 2000).

The values for the AUC/MIC ratio and C_{max}/MIC ratio after oral administration were calculated using documented MIC values against Gram-positive and Gram-negative organisms. An average plasma concentration of 0·032–0·5 $\mu g/ml$ was reported as minimum therapeutic concentration (MIC_{90}) for levofloxacin against most bacteria (Chulavatnatol *et al*., 1999). An average MIC_{90} of 0·1 $\mu g/ml$ of levofloxacin has been taken into consideration for calculation of efficacy predictors. The AUC/MIC ratio of 166·02 and C_{max}/MIC ratio of 33·06 indicates potential clinical and bacteriological efficacy of levofloxacin in quails.

The concentration of levofloxacin in plasma samples was based on the level of antibacterial activity, without differentiating between the parent drug and its active metabolites. The reason why we selected the bioassay was that the bioassay measures the total activity which could be more practical for pharmacodynamic evaluations than HPLC (McKellar *et al*., 1999). As there is no report of significant active metabolites in rats or human beings, the application of

microthe biological assay for measuring levofloxacin concentration was considered to be the most suitable for our purposes.

In conclusion, lack of local reaction or any other adverse effect, good bioavailability, the large volume of distribution, a high C_{max} and AUC and pharmacokinetic-pharmacodynamic hybrid efficacy predictors for levofloxacin indicate that oral administration of levofloxacin at 10 mg/kg may be highly efficacious against susceptible bacteria in quails. Further studies on tissue distribution in quails should be conducted.

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