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Original Contribution

PHARMACOKINETICS OF PEFLOXACIN IN BIRDS

R. Moutafchieva[1]*, D. Yarkov[2]

[1]Department of Pharmacology, Physiology of Animals &Physiological Chemistry;
[2]Department of Animal Science, Faculty of Veterinary Medicine,
Trakia University, Stara Zagora, Bulgaria

ABSTRACT

Serum drug disposition of pefloxacin was studied for 3 consecutive days in 20 broiler chickens and 9 homing pigeons (*Columba livia*) following drinking water medication with pefloxacin sodium salt at 125 mg/l and co-medication with maduramycin (only in chickens). The coccidiostatic drug was given with the fodder at 5 ppm for 1 week before and during the experiment. Subsequent serum concentrations of pefloxacin were determined by microbiological assay procedure using *Escherichia coli* Bay 14 as test microorganism. Study state levels of pefloxacin for chickens (1.8 µl/ml) and for pigeons (0.6 µl/ml) were obtained within one day. Pefloxacin levels in chickens were decreased after co-administration with maduramycin. We conclude that drinking water medication of pefloxacin at 125 mg/l in chickens and pigeons (Columba livia) might ensure serum concentrations therapeutically effective for most pefloxacin-sensitive pathogens (such as Gram-negative aerobes, Gram-positive aerobes and anaerobes).

Key Words: pharmacokinetics, pefloxacin, maduramycin, drug interactions, water medication, birds

INTRODUCTION

Pefloxacin (PFL) is a synthetic broad-spectrum fluoroquinolone antibacterial agent. It has an excellent antibacterial activity against most gram-negative and gram-positive bacteria (1-7). Pefloxacin is a bactericidal compound (8). This action results from interference with the activity of DNA gyrase and topoisomerase IV, which are needed for the transcription and replication of bacterial DNA. As a result DNA replication and transcription are inhibited (2, 8, 9, 10). The chemotherapeutic agent has a high potency and it is successfully used in humans (2, 8). Pefloxacin shows a good absorption with high bioavailability, a long half-life, excellent tissue and body fluid penetration (11-18). It is metabolised extensively and main metabolites are N-demethyl pefloxacin (norfloxacin), which is itself licensed for use in human and veterinary medicine; pefloxacin N-oxide with some antibacterial activity and the oxo metabolites (2, 8, 19, 20). There are data for the pharmacokinetics of pefloxacin in fowl by different route of administration (14, 15, 19-21). Little is known about disposition kinetics of this antibacterial agent in birds after medication via water and about its drug interactions (14, 22, 23).

The aims of the present study were to establish the pharmacokinetics of pefloxacin and some drug interactions of this agent following drinking water medication in birds.

MATERIAL AND METHODS

Animals: Studies were performed on 20 broiler chickens (crossbreed Cornish X White Plymouth Rock, age 2 months, both sexes, equally divided, average body weight 1.9 kg) and 9 homing pigeons (Columba livia) (both sexes, with average body weight 300 g).

The animals were housed in cages (for broilers – battery cages) situated in a climate rooms. The temperature and the humidity were optimal for both species. The broilers were divided at random into 2 groups, each of 10 chickens (of equal sexes). The cages were separately equipped with drinking water and

* **Correspondence to**: *Rumyana Moutafchieva, Department of Pharmacology, Physiology of Animals & Physiological Chemistry, Faculty of Veterinary Medicine, Trakia University, Student Town, 6000 Stara Zagora, Bulgaria; Tel: ++359.42/699 621; Fax: +359.42/670 624; E-mail: rmoutafchieva@uni-sz.bg*

feed supply. The fowls received water and food *ad libitum* (the food was specially prepared without additives, such as antibiotics and growth promoters).

Experimental design:

Drugs: Pefloxacin (as pefloxacin sodium salt, with 1000 µg/mg activity) was obtained from NIHFI, Sofia and maduramycin (Jumamycin – 10 UI/mg) – from Biovet, Peshtera.

Drug administration: The birds received medicated drinking water with pefloxacin 125 mg/l tape water for 3 consecutive days. Maduramycin was given only to chickens through the fodder at 5 ppm for 1 week before and during the experiment. The intended medication was as follows:

- Group I - chickens (Control group, n = 10): pefloxacin in drinking water at a dose rate of 125 mg/l;
- Group II - chickens (Experimental group, n = 10): pefloxacin in drinking water at a dose rate of 125 mg/l + maduramycin 5 ppm through the fodder;
- Group III - pigeons (n = 9): pefloxacin in drinking water in a dose of 125 mg/l.

The medicated water was supplied via a separate drinker for each cage. The water consumption was determined daily. At the end of the treatment period, the drinking water was replaced by drug-free water and the equipment was thoroughly cleaned to remove drug residuals.

Blood sampling: Blood samples were taken by venopuncture from the wing vein at selected intervals: for chickens - 0, 2, 6, 8, 24, 28, 32, 48, 52 and 56 h and for pigeons - 0, 2, 4, 8, 24, 28, 32, 48, 52 and 56 h. Blood sampling was also performed after cessation of the medication - 70 and 96 h (after start of the medication) for chickens and 72 and 96 h – for pigeons, respectively. The blood was allowed to clot at room temperature and was centrifuged for 10 min at 1500 g as soon as possible after collection (within 2 hours). Serum was stored at –20 ºC until analysed.

Drug analysis:

Bioassay: An agar diffusion method was used to determine the concentrations of pefloxacin (measures the antibacterial activity of the parent drug and its active metabolites) in the serum utilizing *Escherichia coli* Bay 14 as test microorganism.

The Nutrient agar (Merck Art. 5450), supplemented with 0.1 % KH_2PO_4, was cooled to 50 ºC, inoculated with 24-h incubated *E. coli* culture (0.1 ml/100 ml agar). After solidification holes of 10 mm were punched out of the agar. Subsequently the punch-holes were filled with 100 µl of serum in duplicate for calibrators and samples. After the incubation overnight (about 18 h) at 37 ºC, the inhibition zones were measured and the concentrations calculated. The limit of quantification was 0.015 µg/ml serum. The calculations were carried out according curve-fitting by means of unweighted regression analysis. The correlation coefficients of the curves used for both species exceeded 0.99.

Pharmacokinetic analysis:

Selected pharmacokinetic parameters of pefloxacin were determined: area under the serum concentration-time curve (AUC), half-life ($t_{1/2}$) and mean residence time (MRT).

All kinetic parameters were calculated according to the well-known methods (24, 25) Study state levels and the time to reach them were estimated from the observed data.

For an analysis of variance we used nonparametric (Mann-Whitney) two-sample test.

RESULTS

Serum concentrations (mean ± SE) of PFL in birds (chickens and pigeons) are presented on **Table 1.** They are depicted in **Figure 1-3.** Following oral drinking water medication a study state level (about 1.8 µg/ml) of PFL in chickens (control group) was obtained within one day (**Table 1, Figure 1**).

It was found that PFL concentrations are decreased after co-administration with maduramycin (the experimental group) (**Table 1, Figure 2**). A study state level was about 1.6 µg/ml. After cessation of the medication a fast decline in serum drug concentration of PFL was observed. Analysis of variance utilizing nonparametric (Mann-Whitney) two-sample test revealed significant differences between the control and the experimental group.

The PFL concentrations in serum of pigeons varied between 0.47 – 0.86 µg/ml (**Table 1, Figure 3**). We observed a study state level of approximately 0.6 µg/ml within one day. Pefloxacin disappeared rapidly in the serum after cessation of the medication. The level of PFL at 72 h was 0.07±0.01 µg/ml. The drug was not detectable in serum at 96 h.

Selected pharmacokinetic parameters of PFL are presented on **Table 2.**

Table 1. *Pefloxacin concentrations (µg/ml) in serum of chickens and pigeons after drinking water medication at a dose rate of 125 mg/l tap water during 3 days*

Time after start of the medication (h)	***Group I – chickens (Control group, n = 10) (mean±SE)***	***Group II - chickens (Experimental group, received maduramycin 5 ppm; n = 10) (mean±SE)***	***Group III - pigeons (n = 9) (mean±SE)***
2	0.56±0.02	0.48±0.02*	0.47±0.14**
4			0.77±0.15
6	0.80±0.03	0.68±0.03*	
8	1.04±0.04	0.81±0.08*	0.57±0.12**
24	1.77±0.04	1.35±0.09*	0.59±0.06**
28	1.84±0.03	1.58±0.05*	0.82±0.10**
32	1.86±0.05	1.58±0.04*	0.62±0.11**
48	1.94±0.14	1.64±0.04*	0.50±0.05**
52	1.92±0.03	1.69±0.08*	0.86±0.06**
56	1.92±0.06	1.68±0.07*	0.63±0.05**
70	0.54±0.04	0.39±0.05*	
72			0.07±0.01
96	0.03±0.02	0.02±0.00*	not detected

** Significant difference between group I and group II at p<0.05*
*** Significant difference between group I and group III at p<0.05*

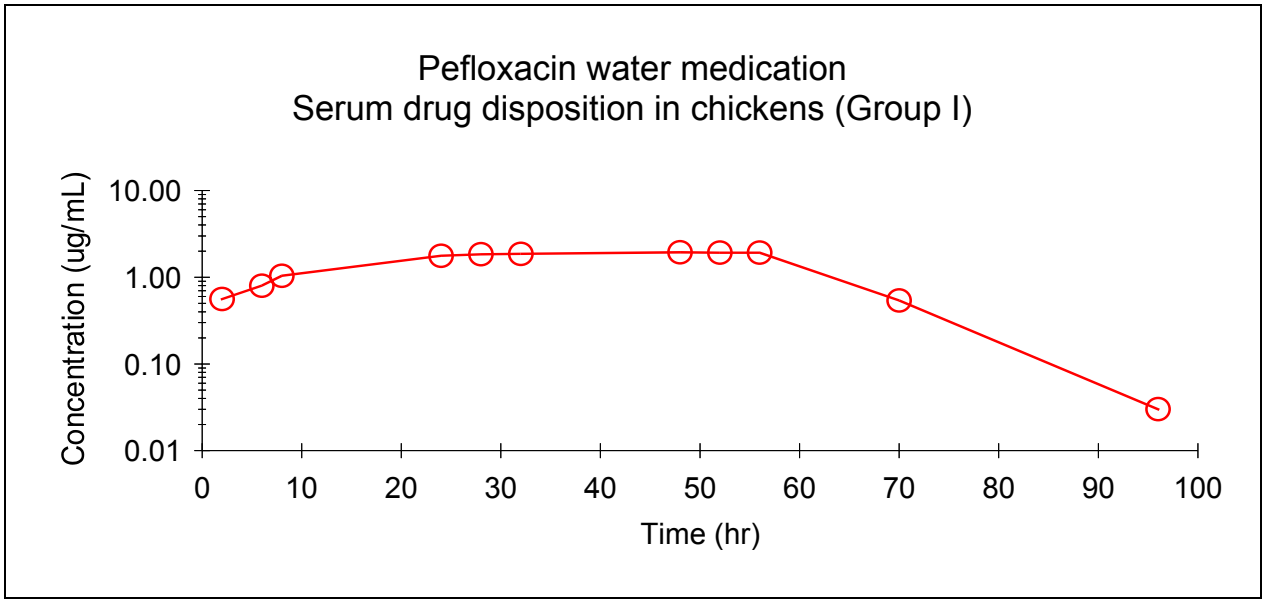

Figure 1. *Pefloxacin concentrations in serum of chickens after drinking water medication at a dose rate of 125 mg/l tap water during 3 days*

DISCUSSION

There are differences in serum disposition of PFL after water medication in studied birds. Pefloxacin concentrations are higher in chickens (approximately 2- bis 3-times) and the drug is retained longer than in pigeons (the values of MRT in chickens and in pigeons are 9.55±0.11 h and 6.11±0.20 h, respectively). We obtained similar data in these two species in our previous experiments (14, 15). The elimination rate of PFL in pigeons is more rapid.

The data obtained in this study are in agreement with other authors (20, 21), however relatively slow elimination is reported too (23).

Co-medication with maduramycin affects the serum disposition of PFL in chickens after its water medication. The present data are very close to those we found for PFL in chickens treated simultaneously with maduramycin (14). A two-week prior administration of maduramycin with fodder caused changes in the pharmacokinetics of PFL, administered intravenously and via the crop (14). The drug interactions between PFL and other drugs (such as ionophores, malathion) have been reported (22, 23).

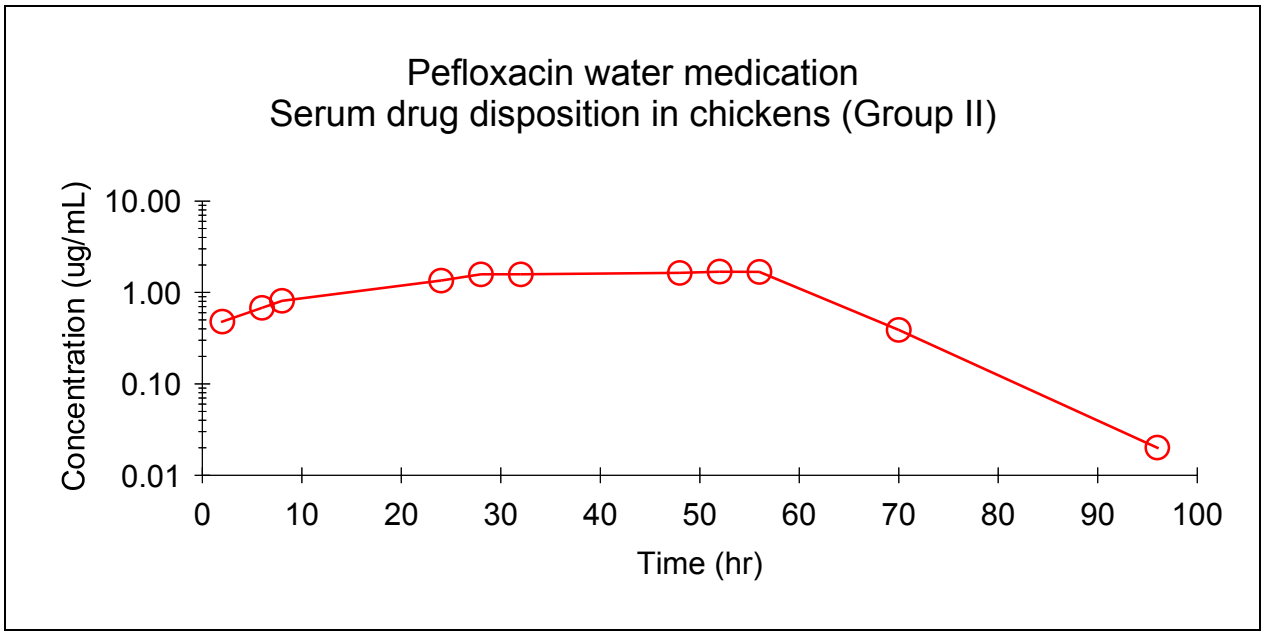

Figure 2. *Pefloxacin concentrations in serum after drinking water medication at a dose rate of 125 mg/l tap water during 3 days in chickens treated with maduramycin 5 ppm through the fodder*

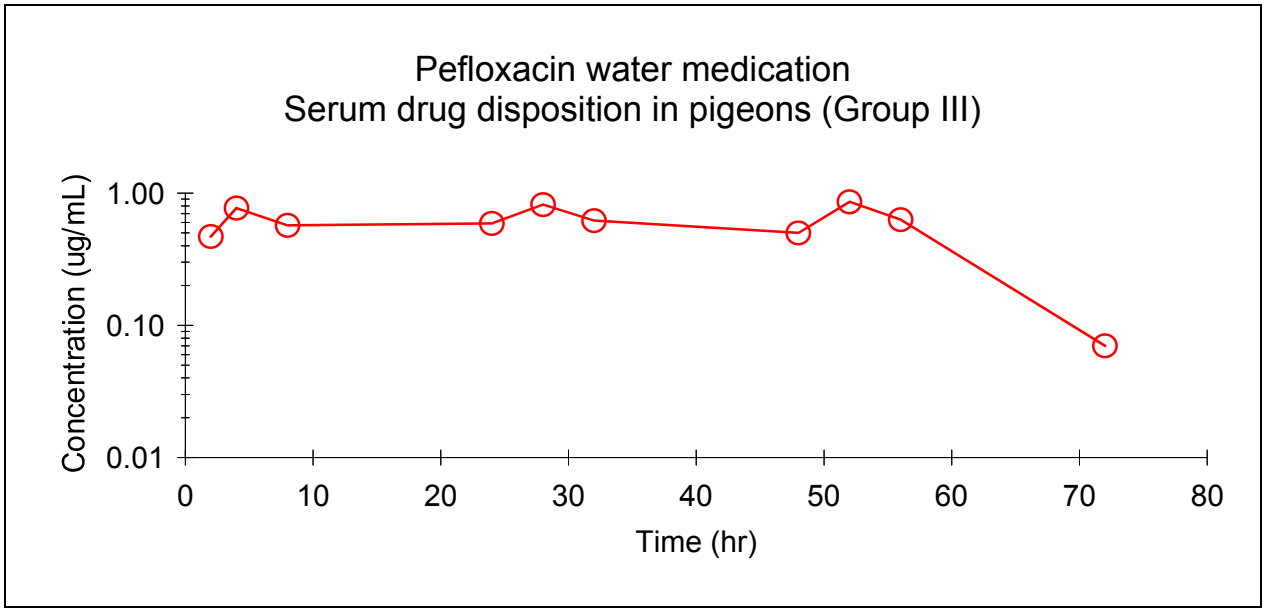

Figure 3. *Pefloxacin concentrations in serum of pigeons after drinking water medication at a dose rate of 125 mg/l tap water during 3 days*

Table 2. *Selected pharmacokinetic parameters of pefloxacin after drinking water medication at a dose rate of 125 mg/l tap water during 3 days in chickens and pigeons*

Parameter	Unit	Group I – chickens (Control group, n = 10) (mean±SE)	Group II - chickens (Experimental group, received maduramycin 5 ppm; n = 10) (mean±SE)	Group III - pigeons (n = 9) (mean±SE)
AUC	µg.h/ml	112.70±2.50	92.73±1.70*	42.58±0.52**
$t_{1/2}$	h	6.62±0.07	6.30±0.06*	4.23±0.16**
MRT	h	9.55±0.11	9.09±0.10*	6.11±0.20**

** Significant difference between group I and group II at p<0.05*
*** Significant difference between group I and group III at p<0.05*

The information obtained from the experiment is useful. On the basis of this data (put it together with average concentration greater than *MIC* for the most sensitive bacteria) (3), we would suggest as appropriate a dosage of PFL 125 mg/l for drinking water medication in chickens and in pigeons. The dose rate will be successful for the treatment of common infectious diseases in these two species.

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