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Original Contribution

COMPARATIVE PHARMACOKINETICS OF PEFLOXACIN IN CHICKENS, PHEASANTS AND PIGEONS

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SUMMARY

The drug disposition of pefloxacin was studied in 10 broiler chickens (crossbreed Cornish X White Plymouth Rock), 10 pheasants (Phasianus colchicus) and 9 homing pigeons (Columba livia) after intravenous and via croup administration at a dose rate of 10 mg/kg body weight. Serum concentrations of pefloxacin were determined by microbiological assay procedure using *Escherichia coli* Bay 14 as test microorganism. Selected pharmacokinetic parameters were calculated. There were found significant differences in disposition kinetics of pefloxacin in the experimental bird species. These differences occurred with regard to absorption, distribution and elimination.

Key words: comparative pharmacokinetics, pefloxacin, chickens, pheasants, pigeons.

INTRODUCTION

Pefloxacin (PFL) is a member of quinolone group. It is a synthetic antimicrobial agent, belonging to 3^{rd} generation fluoroquinolones. Pefloxacin has broad spectrum of activity against most gram-negative and gram-positive bacteria and it can be used successfully in a variety of specific infections (1-10).

Pefloxacin is a bactericidal compound (11). It inhibits bacterial DNA synthesis. 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, 11, 12, 13). Pefloxacin has a good absorption with high bioavailability, a long half-life, excellent tissue and body fluid penetration (14-21). It is metabolised extensively and its main metabolites are N-demethyl pefloxacin (norfloxacin), pefloxacin N-oxide (with some antibacterial activity) and the oxo metabolites (2, 11, 22, 23).

There are data for the pharmacokinetics of PFL in different bird species (17, 18, 22-25). However, no information is available on the comparative drug disposition of this chemotherapeutic agent in the fowl.

Therefore, the aim of the present study were to compare the pharmacokinetic properties of PFL after intravenous (i.v.) and via crop (v.c.) administrations at a dose of 10 mg/kg body weight in chickens, pheasants and pigeons.

MATERIAL AND METHODS

Animals: Experiments were performed on 10 broiler chickens (crossbreed Cornish X White Plymouth Rock), 10 pheasants (Phasianus colchicus) and 9 homing pigeons (Columba livia) (mature birds, both sexes, with average body weight between 300.0 g and 1800.0 g). The birds were housed under conventional conditions (e.g. appropriate temperature and humidity) for each species. They 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 μ g/mg activity) was obtained from NIHFI, Sofia.

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Drug administration: Pefloxacin was given to the birds at 10 mg/kg body weight i.v. as a single bolus dose and v.c. with 2 weeks interval between experiments.

Blood sampling

Blood samples were collected by venopuncture from the brachial vein at predetermined intervals: after i.v. administration - 0, 0.08, 0.17, 0.33, 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 h; after v.c. treatment -0.0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 h, respectively.

Blood sampling for 10 h and 12 h were performed only in chickens and pigeons (at 10 h – for chickens and pigeons and at 12 h – only for chickens). Blood was allowed to clot at room temperature and was centrifuged at 1500 x g for 10 min (within 2 hours). Serum was stored at –20 °C until analysed.

Drug analysis

Bioassay

Serum concentrations of PFL were determined by microbiological assay procedure (measures the antibacterial activity of the parent drug and its active metabolites) using *Escherichia coli* Bay 14 as test microorganism.

The Nutrient agar (Merck Art. 5450) was supplemented with 0.1 % KH_2PO_4 , then cooled to 50 °C and inoculated with 24-h incubated *E. coli* culture (0.1 ml/100 ml agar). After the solidification holes of 10 mm were punched out of the agar. Subsequently the

punch-holes were filled with 100 μ l of serum in duplicate for calibrators and samples. After the incubation at 37 °C (about 18 h), the inhibition zones were measured and the concentrations calculated. The limit of quantification was 0.015 μ l/ml serum.

Pharmacokinetic analysis

Selected pharmacokinetic parameters of PFL were determined as follows: for i.v. administration – elimination half-life $(t_{1/2\beta})$, distribution half-life ($t_{1/2\alpha}$), apparent volume of distribution $(V_{d(area)})$, area under the serum concentration-time curve (AUC), mean residence time (MRT) and clearance body (Cl_B); for v.c. treatment – elimination half-life $(t_{1/2\beta'})$, absorption half-life $(t_{1/2abs})$, peak serum concentration ($C_{p max}$), time to reach $C_{p max}$ AUC, and $(t_{max}),$ MRT systemic bioavailability (F).

All kinetic parameters were calculated according to the compartmental methods (26, 27). Statistical analysis was performed using nonparametric (Mann-Whitney) two sample test.

RESULTS

After i.v. administration a two-compartment open model best described the decrease of PFL concentrations in serum of chickens, pheasants and pigeons (**Figure 1**). Lower PFL levels were found in pigeons and pheasants (after 1 h) than in chickens.



Figure 1: Pefloxacin concentrations in serum of chickens, pheasants and pigeons after i.v. administration at a dose rate of 10 mg/kg body weight

Selected pharmacokinetic parameters of PFL are presented on **Table 1**.

Following v.c. administration of PFL concentration-time data in all experimental

bird species were best fitted to an onecompartment open model with absorption (Figure 2). Serum concentrations of PFL were higher in chickens than in pheasants and (except Pefloxacin pigeons 0.25 h). disappeared rapidly in the serum of pheasants.

Selected pharmacokinetic parameters of PFL are presented on Table 2.

The drug was detectable in serum of all bird species more than 24 h (Figure 1 and Figure 2).

Table 1: Selected pharmacokinetic parameters (mean ± SEM) of pefloxacin (PFL) in chickens, pheasants and pigeons after i.v. administration at dose rate of 10 mg/kg body weight

Parameter	Unit	Bird species		
		Chickens	Pheasants	Pigeons
t _{1/2β}	h	4.67 ± 0.27	5.00 ± 0.06	$3.33 \pm 0.11 **$
$t_{1/2\alpha}$	h	0.42 ± 0.02	$0.46 \pm 0.01*$	0.35 ± 0.06
V _{d(area)}	l/kg	1.736 ± 0.138	$3.537 \pm 0.061 *$	$2.279 \pm 0.091 **$
$AUC_{0>?}$	µg.h/ml	36.28 ± 1.43	$23.82 \pm 0.82*$	$22.29 \pm 0.18 **$
MRT	h	5.39 ± 0.25	$4.61 \pm 0.28*$	$4.35 \pm 0.08 **$
Cl _B	l/h.kg	0.283 ± 0.012	$0.445 \pm 0.015*$	$0.475 \pm 0.004 **$

*Significant difference between chickens and pheasants at p<0.05

**Significant difference between chickens and pigeons at p<0.05

Table 2: Selected pharmacokinetic parameters (mean ± SEM) of pefloxacin (PFL) in chickens, pheasants and pigeons after v.c. administration at dose rate of 10 mg/kg body weight

Parameter	Unit	Bird species		
		Chickens	Pheasants	Pigeons
$t_{1/2\beta'}$	h	6.45 ± 0.09	$5.07 \pm 0.42*$	6.68 ± 0.18
t _{1/2abs}	h	0.11 ± 0.00	$0.42 \pm 0.04*$	0.17 ± 0.01 **
t _{max}	h	0.90 ± 0.02	$1.78 \pm 0.09*$	$1.16 \pm 0.02 **$
C _{p max}	µg/ml	5.35 ± 0.11	$2.75 \pm 0.05*$	$2.90 \pm 0.02 **$
V _{d(area)}	l/kg	1.749 ± 0.037	$3.006 \pm 0.029 *$	$3.125 \pm 0.019 **$
$AUC_{0>?}$	µg.h/ml	56.48 ± 1.59	$24.14 \pm 0.41*$	$32.83 \pm 0.72 **$
MRT	h	9.71 ± 0.13	$7.25 \pm 0.23*$	10.10 ± 0.25
F	%	89.63 ± 4.61	$104.20 \pm 2.19*$	73.42 ± 3.23**

*Significant difference between chickens and pheasants at p<0.05 **Significant difference between chickens and pigeons at p<0.05



Figure 2. Pefloxacin concentrations in serum of chickens, pheasants and pigeons after v.c. administration at a dose rate of 10 mg/kg body weight

DISCUSSION

There are marked species differences in disposition kinetics of PFL after i.v. and v.c. administration in the experimental birds. Pefloxacin concentrations are usually higher in chickens. After i.v. application the drug is widely distributed within the body of all birds, especially in pheasants ($V_{d(area)} = 3.537 \pm 0.061 \text{ l/kg}$).

Pefloxacin shows almost complete and a rapid absorption following v.c. administration of 10 mg/kg body weight (faster in pheasants). The drug is retained longer in serum of chickens than in pheasants (the values of MRT in chickens and in pheasants are 9.71 ± 0.13 h and 7.25 ± 0.23 h, respectively). Our data are in agreement with these of other authors (23, 24).

The information obtained from the experiments is useful. On the basis of this data it is possible to optimize the dosage of pefloxacin.

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