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Short communication

Differences in the pharmacokinetics of flumequine after single and continuous oral administration in non-fasted broiler chickens

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Abstract

The aim of this study was to determine the influence of feed on the pharmacokinetics of flumequine (FLU) administered to broiler chickens as follows: directly into the crop (10 mg/kg of BW) of fasted (group I/control) and non-fasted chickens (group II), or administered continuously with drinking water (1 g/L for 72 h) and with unlimited access to feed (group III). Plasma concentration of FLU was determined by high-performance liquid chromatography with fluorescence detection. In group II, a significant decrease in the maximum concentration (C_{max} = 2.13±0.7 μg/mL) and the area under the concentration curve from zero to infinity ($AUC_{0\to\infty}$ = 7.47±2.41 μg·h/mL) was noted as compared to the control group (C_{max} = 4.11±1.68 μg/mL and $AUC_{0\to\infty}$ = 18.17±6.85 μg·h/mL, respectively). In group III, the decrease in AUC was significant only in the first 3 hours ($AUC_{0\to3}$ = 5.02±1.34 μg·h/mL) as compared to the control group ($AUC_{0\to3}$ = 7.79±3.29 μg·h/mL). The results indicate that feed reduced the bioavailability of FLU from the gastrointestinal tract by at least 50% after the administration of a single oral dose. However, continuous administration of FLU with drinking water could compensate for the feed-induced decrease in absorption after single oral dose.

Key words: flumequine, HPLC, interactions with feed, broiler chickens

Introduction

Flumequine (FLU), a second-generation fluoroquinolone, is used for the treatment of systemic *Escherichia coli* infections in poultry and other infections caused mainly by Gram-negative bacteria (Maślanka and Jaroszewski 2009, Ferraresi et al. 2013). Fluoroquinolones, including FLU, are capable of interacting with feed, which decreases their bioavailability and efficacy (Ziółkowski et al. 2014). In poultry farms, FLU is administered continuously with water for several days. In pharmacokinetic (PK) studies, a single oral and/or parenteral dose is generally administered to determine PK parameters. However, this mode of administration

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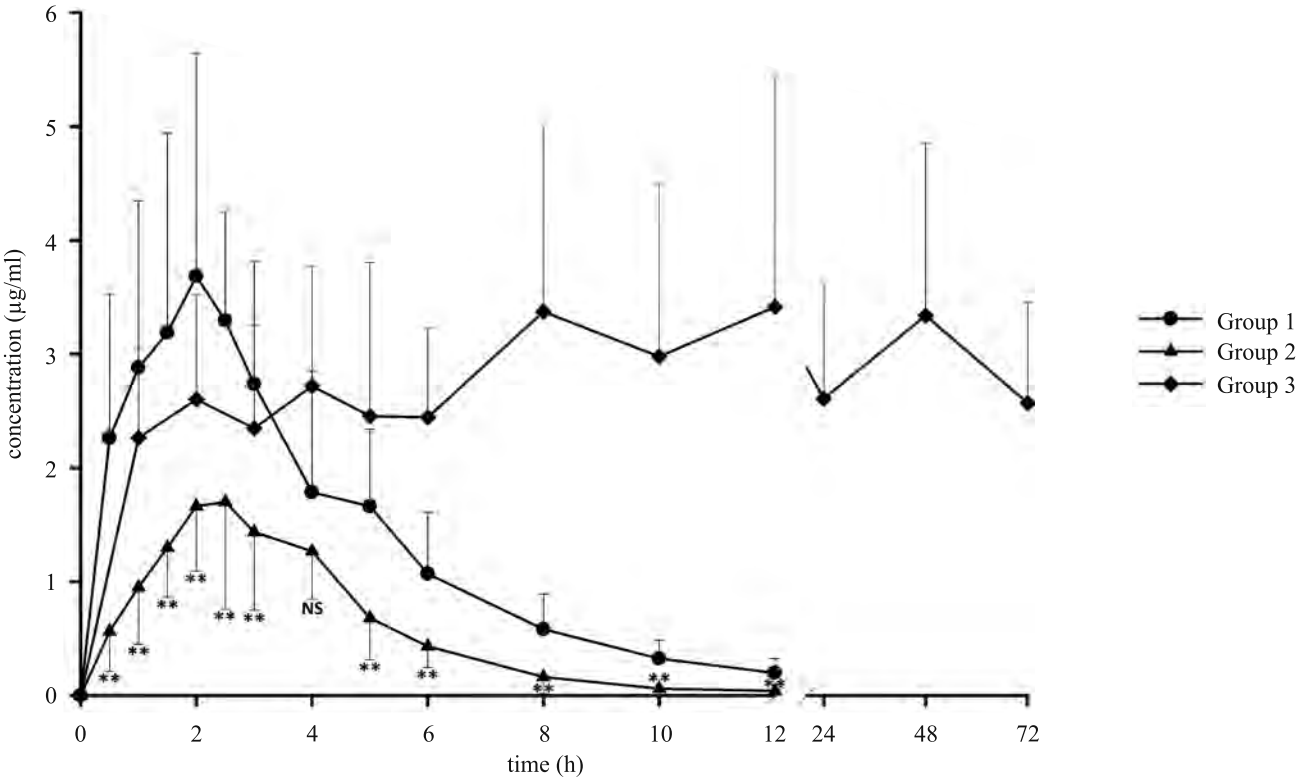

Fig. 1. Mean (± SD; n = 10) plasma concentration-time profiles of flumequine administered directly into the crop (10 mg/kg of BW) of fasted (Group I) and non-fasted chickens (Group II) or administered continuously with drinking water (1 g/L every 24 h for 72 h) and with unlimited access to feed (Group III). [a,b] – significant differences for the same time points between group I and II at ** $p<0.01$.

does not always reliably reflect the drug's concentration in the body during treatment in farm conditions. It should be noted that the PK profile of a drug is determined not only by the dose, but also by interactions with feed. To the best of our knowledge, the effect of feed on the PK profile of FLU in broiler chickens has never been described in the literature. Therefore, the aim of this study was to determine the influence of feed on the PK parameters of FLU administered in a single oral dose to fasted and non-fasted birds, and administered continuously with water to broiler chickens with unlimited access to feed.

Materials and Methods

The study was performed on thirty 4-week-old male and female broiler chickens randomly divided into 3 groups (n = 10 in each group). The birds were clinically healthy, and their housing conditions and treatment protocols had been approved by the Local Ethics Committee (decision No. 15/2013). Flumequine (Imequyl 10%, Biowet Drwalew, Poland) was administered in a single dose (10 mg/kg of BW) via a plastic tube directly into the crop of fasted birds (feed was withheld from 6 h before administration to 3 h after administration in group I – control) and non-fasted birds (group II) or was administered continuously with drinking water at a similar dose (1 g/L of water) for 72 h (simulation of farm conditions) with unlimited access to feed (group III). Blood samples were collected from the left brachial vein at 0, 0.5 (groups I and II), 1.0, 1.5 (groups I and II), 2.0, 2.5 (groups I and II), 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 24.0, 48.0 (group III) and 72.0 (group III) hours after drug administration. The plasma concentration of FLU was determined by high-performance liquid chromatography with fluorescence detection (HPLC/FLD) according to the method described previously by Ziółkowski et al. (2014) for enrofloxacin, with minor modifications (the mobile phase consisted of a mixture of 0.01M potassium phosphate and methanol with a 35:65 v/v ratio, pH was adjusted to 4.0 with 10% acetic acid, and the flow rate was 0.25 ml/min). HPLC/FLD was performed at an excitation wavelength of 233 nm and an emission wavelength of 338 nm. A non-compartmental PK analysis was carried out in the ThothPro v 4.1 program (ThothPro LLC, Gdańsk, Poland). Mean absorption time (MAT) and half-life in absorption phase ($t_{1/2kab}$) were calculated using one compartmental analysis. Pharmacokinetic parameters were expressed as mean values (±SD). A statistical analysis was performed in SigmaPlot v. 12.0 for Windows software (Systat Soft-

Table 1. Selected pharmacokinetic parameters of flumequine administered to broiler chickens in a single and continuous oral dose.

Pharmacokinetic parameters	Administration		
	Single dose (10 mg/kg BW)		Continuous dose (1 g/L of water)
	without feed (Group I)	with feed (Group II)	with feed (Group III)
k_{el}	0.29±0.11[a]	0.51±0.19[b]	-
$t_{1/2kel}$ (h)	2.74±1.26[a]	1.58±0.67[b]	-
k_{ab} (h^{-1})	2.19±0.95	1.49±0.97	-
$t_{1/2kab}$ (h)	0.37±0.15	0.59±0.38	-
t_{max} (h)	2.22±0.51[a]	2.39±0.82[b]	33.10±27.44[c]
t_{last} (h)	12	11.56±0.88	72
C_{max} (μg/mL)	4.11±1.68[a]	2.13±0.7[b]	4.25±1.53[a]
C_{last} (μg/mL)	0.20±0.13[a]	0.04±0.04[b]	2.57±0.88[c]
$AUC_{0\to3}$ (μg·h/mL)	7.79±3.29[a]	3.31±1.09[b]	5.02±1.34[c]
$AUC_{0\to12}$ (μg·h/mL)	17.24±6.76[a]	7.37±2.36[b]	30.87±10.85[c]
$AUC_{0\to\infty}$ (μg·h/mL)	18.17±6.85[a]	7.47±2.41[b]	-
$MRT_{0\to t}$ (h)	3.95±1.81[a]	2.28±0.97[b]	36.71±2.41[c]
MAT (h)	0.53±0.21	0.85±0.55	-
F_{rel} (%)	100.0[a]	42.73±13.67[b]	179.05±62.91[c]

k_{el} – elimination rate constant; $t_{1/2kel}$ – half-life in elimination phase; k_{ab} – absorption rate constant; $t_{1/2kab}$ – half-life in absorption phase; t_{max} – time to reach the maximum concentration, t_{last} – time of last measured concentration; C_{max} – maximum plasma concentration; C_{last} – last measured plasma concentration; $AUC_{0\to3}$ – area under the concentration curve vs. the time curve for 0 to 3 h; $AUC_{0\to12}$ – area under the concentration curve vs. the time curve for 0 to 12 h; $AUC_{0\to\infty}$ – area under the concentration curve vs. the time curve for 0 to infinity; $MRT_{0\to t}$ – mean residence time between 0 and t_{last}; MAT – mean absorption time; F_{rel} – relative bioavailability calculated from $AUC_{0\to12}$.

[a,b,c] significant differences between groups at $p<0.05$.

ware Inc., San Jose, CA, USA) using Student's t-test. Differences were regarded as significant with $p<0.05$.

Results and Discussion

The PK profile of FLU in all groups is presented in Fig. 1, and PK parameters are shown in Table 1. The PK parameters of FLU associated with the absorption rate (C_{max}, AUC_{0-3}, AUC_{0-12}, $AUC_{0-\infty}$, $t_{1/2kab}$,) were significantly ($p<0.05$) lower in group II than in group I, which indicates that feed inhibited the absorption of FLU from the gastrointestinal tract. In the group where FLU was administered continuously with water for three successive days, its concentration exceeded the C_{max} level noted in group II despite the fact that $AUC_{0\to3}$ was lower than in group I. The above suggests that continuous exposure to the drug could compensate the feed-induced decrease in absorption from the gastrointestinal tract. Different results were reported by Anadon et al. (2008) who administered FLU to fasted chickens in a single dose that was 20% higher and withheld of feed was longer than in our study. In our study C_{max} was higher in group I, lower in group II and was achieved later. Moreover, the mean residence time (MRT) was much lower, indicating faster clearance. The differences between our findings and the results reported by Anadon et al. (2008) could be attributed to somewhat different experimental conditions (the origin of birds, shorter feed withholding time in our study), as well as the effect of feed in group II. On the other hand Ferraresi et al. (2013) exposed turkeys to a single FLU dose that was 50% higher than in our study, and reported considerably higher values of C_{max}, $AUC_{0-\infty}$ and MRT than those observed in group I in our study. However, after continuous administration of higher doses of FLU to turkeys, the values of C_{max} and $AUC_{0-\infty}$ were similar and MRT was higher in our study. The observed discrepancies could be attributed to differences in experimental conditions (e.g. different drug doses and bird species, pulsed oral administration in turkeys), which indicates that a cautious approach should be adopted when extrapolating the results from one species to another.

The obtained results indicate that feed reduced the bioavailability of FLU from the gastrointestinal tract after the administration of a single oral dose. When FLU was administered continuously with drinking water over a period of several days, greater exposure to the drug could compensate the feed-induced decrease in absorption, resulting in concentrations that are sufficient to eliminate sensitive pathogens.

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