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Plasma disposition of enrofloxacin and its metabolite ciprofloxacin following intravenous and drinking water route administration in emu (*Dromaius novaehollandiae*) birds

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Abstract
Disposition of enrofloxacin was characterized following intravenous and drinking water route administration at a dose of 10mg/kg in emus birds. Blood samples were collected from jugular vein at assigned time intervals. The plasma concentration of enrofloxacin and its active metabolite ciprofloxacin were measured by HPLC. Plasma concentration-time data and relevant parameters were best described by non-compartmental analysis. Following i.v. administration, $t_{1/2\beta}$, $AUC_{0-\infty}$, MRT, V_{darea} and CL_B was 4.364±0.179h, 20.085±3.493µg.h/mL, 5.105±0.216h, 3.921±1.005L/kg and 0.629±0.164 L/h.kg, respectively. After drinking water route administration, $t_{1/2\beta}$, $AUC_{0-\infty}$, MRT, V_{darea} and CL_B was 4.066±0.295h, 14.807±1.766µg.h/mL, 6.942±0.572h, 3.130±0.264, 0.713±0.064L/h.kg, respectively. The mean absolute bioavailability for enrofloxacin was 73.723±8.792%, respectively. The ratio of AUC_{0-t}cipro/ AUC_{0-t}enro was 7.764% and 9.834%, respectively for i.v. and drinking water route administration of enrofloxacin. From the pharmacokinetic data and PK/PD indices, the recommended doses of enrofloxacin in emu birds were 10mg/kg body weight once daily for i.v. and drinking water route against organisms susceptible to 0.25µg/mL and 0.125µg/mL, respectively. There were no much differences between the pharmacokinetic parameters of i.v and drinking water route in emu birds. Hence, it can be concluded that drinking water route is suitable and practicable method for emus and it is also desirable method for mass medication.

Keywords: Enrofloxacin, emu, ciprofloxacin, pharmacokinetics, intravenous route, in-water route

1. Introduction
Enrofloxacin, a fluoroquinolone antimicrobial agent has the following properties which make it a useful compound in veterinary application; wide spectrum of bactericidal activity against a range of clinically relevant Gram-negative and Gram-positive pathogens as well *Mycoplasma* and *Chlamydiae;* bactericidal and mycoplasmicidal activity at low concentration; efficacy against organisms that are resistant to many other antibacterial substances and good tolerance and rapid absorption after parenteral and oral administration resulting in high blood and tissue concentrations [1]. Because of its spectrum of activity, enrofloxacin has potential therapeutic application for many types of bacterial infections in birds [2]. Pharmacokinetic studies offer highly relevant information on the time course of the drugs, their metabolites and facilitate the computation of optimal dosage regimens of drugs to maintain their therapeutic concentration at the biophase [3]. The pharmacokinetic behaviour of enrofloxacin has been investigated in various animal and bird species including wild animals and aquatic species.
The important causes of morbidity and mortality in domestic emu birds are bacterial infections [4]. Kumar *et al.* [5] isolated *E. coli* and *Salmonella spp.* in emu birds reared under captive conditions. Hence drug administration is important practices in rearing domestic emus. The computation of an optimal dosage regimen depends on the understanding of the drugs in the target species. The recommended doses of enrofloxacin in emu birds were published by the same author as 10 mg/kg body weight once daily for i.v. and oral routes against organisms susceptible to 0.25 and 0.125 lg/mL, respectively [6]. Because of restraining difficulties in emus, drug administration through the oral route is not easy. Drug administration through drinking water route is practically suitable method in emu birds. Hence, in the current study, it was proposed to investigate the disposition kinetics of enrofloxacin in emus following drinking water route administration.

2. Materials and Methods

2.1 Experimental Design

Apparently healthy 8 emu birds (4 male + 4 female) aged 18 to 24 months with a mean (±SE) body weight of 38.06±1.12 kg were selected. The birds were maintained at Emu Research Unit, TANUVAS-Regional Research Centre, Pudukkottai, Tamil Nadu, India. Birds were offered feed and water *ad libitum*. Previous to the study, each bird was examined clinically to rule out the possibility of any disease. No antibiotics and anthelmintics were administered two months prior to the start of experiment. All the experimental design and procedures were performed as per the guideline for animal experiments and approved by the Institutional Animal Ethics Committee (IAEC), TANUVAS, Chennai.

2.2 Drug Assay

A cross over design with a 15-day washout period was followed to study disposition kinetics of enrofloxacin and its active metabolite ciprofloxacin. The dose of enrofloxacin was determined as 10 mg/kg on the basis of earlier study on ostrich, greater rhea and emu [6-8] for i.v. and drinking water route of administration. Enrofloxacin was administered intravenously (bolus dose) through the jugular vein. Blood samples (2mL) were collected by jugular venipuncture into heparinized tubes immediately prior and at 0.083, 0.167, 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 8, 12, 18, 24 and 36h after dosing. After 2 weeks wash out period, the same batch was given enrofloxacin at 10mg/kg through drinking water. Drinking water was withdrawn 6h prior to drugs administration. During treatment, the total dose of enrofloxacin was dissolved in one fourth volume of the daily water intake of the bird and assured that it was consumed within 4h. After consumption of medicated water, the birds were provided drug free water for the rest of the day. Then, 2ml of blood samples were collected at 0.25, 0.50, 0.75, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48 and 60h after dosing. The collected blood samples were centrifuged at 950xg for 20min to separate the plasma. Because all the plasma samples were not analysed on the same day, the samples were stored at -40^{0}C until analysis.

The extraction method of enrofloxacin and ciprofloxacin in plasma was based on liquid-liquid extraction procedures as described by Nielsen and Hansen [9]. A 0.75mL of acetonitrile was added to 0.5mL of plasma, then vortex-mixed for 15sec. The mixture was centrifuged for 15min at 4^{0}C at a speed of 900xg. The clear supernatant was collected and twice the volume of HPLC grade water was added. The aliquot was then filtered through 0.2µ HNN nylon membrane filter and 20µL of filtrate was injected into the HPLC system.

The high performance liquid chromatography (Shimadzu Corporation, Japan) analysis was performed as method developed by Kung *et al.* [10] to determine enrofloxacin and ciprofloxacin. The HPLC system comprised of LC-20 AD double plunger pump, Rheodyne manual loop injector with a 20µL loop, column oven CTO-10 AS vp, SPD-M20A diode array detector and a software LC Solution for data analysis. A reverse phase C18 column (Hibar 250-4, 6 RP-18 endcapped, Particle size 5µm, 4.6x250 mm, Merck, Germany) was utilized to separate compound using as a stationary phase. A mixture containing acetonitrile, methanol and water (containing 0.4% phosphoric acid and adjusted to pH 3.0 using triethylamine) in the ratio of 17:3:80 was used as mobile phase at a flow rate of 1 mL/min. All samples were analysed for 10min at 40° C. The detection wavelength of PDA was 278nm. The mean (±SE) retention times for ciprofloxacin and enrofloxacin were 5.65±0.003min and 7.16±0.006min, respectively. The extraction recoveries from plasma for enrofloxacin was 97.78±5.45%, 99.58±4.87% and 101.75±40.01% and for ciprofloxacin 98.06±5.11%, 98.79±4.09%, 99.60±3.99% for 0.1, 0.5 and 1 µg/mL, respectively. The limit of detection (LOD) and quantification (LOQ) were 0.01 and 0.025 µg/mL for enrofloxacin and 0.025 and 0.05 µg/mL for ciprofloxacin, respectively. The intra-day and inter-day CV were within the limits (<10%) specified (enrofloxacin: 5.307 to 8.827%, ciprofloxacin; 4.757 to 8.632%).

2.3 Pharmacokinetic Analysis

Non-compartmental pharmacokinetic analysis was used to fit the plasma concentration of enrofloxacin and ciprofloxacin versus time curve for each emu using pharmacokinetic software *PK function* [11].

2.4 Pharmacokinetic/Pharmacodynamic (PK/PD) integration

The ratios C_{max}/MIC and AUC/MIC; C_{max} / MPC and AUC / MPC were calculated for hypothetical MIC_{90} (0.05, 0.125, 0.25 and 0.5µg/mL) and MPC (0.2, 0.5, 1.0 and 2µg/mL) values using the means of C_{max} and AUC obtained in this study.

2.5 Statistical Analysis

Statistical analysis of the pharmacokinetic parameters was carried out using SPSS 17.0 software. To find out difference between and among various groups, *t*-test and analysis of variance were applied, respectively [12]. Means of the different subgroups were compared by Duncan's multiple range tests as described by Kramer [13]. For the data not distributed normally, harmonic mean was used.

3. Results and Discussion

The pharmacokinetic parameters and mean plasma concentrations-time curve after enrofloxacin administration based on non-compartmental analysis are shown in Table 1 and Fig. 1. These findings indicated better absorption and bioavailability of enrofloxacin in emus after drinking water route administration. Sumano *et al.* [14] in domestic chicken reported lesser bioavailability compared to the present study. This finding is almost similar with findings of Kumar *et al.* [6] who observed bioavailability 79.94% in emu birds. Dorrestein [15] reported that the digestive system was shown important differences in the extend and rate of drug absorption. Herd and Dawson [16] found that particulate matter in the digestive tract of emus was retained for 5.5h. Wilson [17] described that some food items in the digestive tract of emus were retained one to two days, sometimes over one week. Slow intestinal transit and comparatively long intestinal tract might be the reasons for the better absorption of orally administered drugs in emu birds.

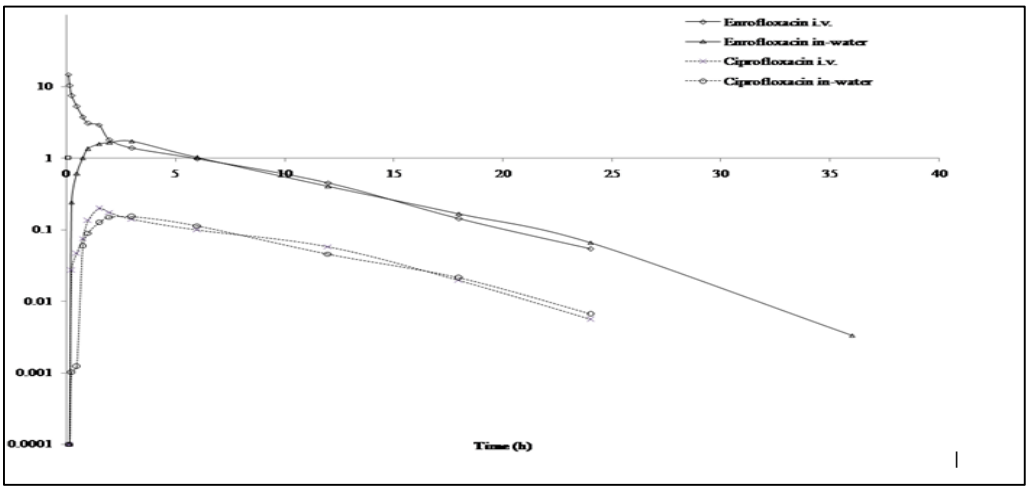

Fig 1: Semilogarithmic plot of mean plasma concentration of enrofloxacin and its active metabolite ciprofloxacin (µg/mL) vs. time in emus (n=8) following single intravenous and in water administration of enrofloxacin (10 mg/kg)

Table 1: Pharmacokinetic parameters of enrofloxacin and its metabolite ciprofloxacin following i.v. and in-water route administration of enrofloxacin (10mg/kg) in emus

Variable	Unit	Routes of administration			
		Intravenous		Drinking water	
		Enrofloxacin	Ciprofloxacin	Enrofloxacin	Ciprofloxacin
β.	h^{-1}	0.159±0.007	0.152±0.006	0.170±0.011	0.215±0.013
AUC_{0-t}	µg.h/mL	19.553 ±3.518	1.518±0.258	14.236±1.609	1.400±0.087
$AUC_{0-\infty}$	µg.h/mL	20.085 ±3.493	1.561±0.262	14.807±1.766	1.581±0.183
$AUMC_{0-t}$	µg.h^2/mL	90.670±19.068	10.591±2.058	96.980±22.926	9.9596±1.201
$AUMC_{0-\infty}$	µg.h^2/mL	104.619±19.920	11.889±2.058	107.427±22.695	10.350±1.167
MRT	h.	5.105 ±0.216	7.454±0.223	6.942±0.572	6.773±0.638
MAT	h.	-	-	1.837±0.572	-
$V_{d\ area}/F$	L/kg	-	-	4.177±0.275	-
V_{darea}	L/kg	3.921 ±1.005	-	3.130±0.264	-
V_{dss}/F	L/kg	-	-	4.773±0.196	-
CL_B	L/h.kg	0.629±0.164	8.256±2.385	-	-
CL_B/F	L/h.kg	-	-	0.713±0.064	6.687±0.646
$t_{1/2\beta}$	h.	4.364±0.179	4.595±0.163	4.066±0.295	3.277±0.185
C_{max}	µg/mL	-	0.197±0.029	2.015±0.062	
t_{max}	h.	-	1.417±0.834	2.583±0.375	
AF	%	-	-	73.723±8.792	-
AUC_{0-t} Cipro/ AUC_{0-t} Enro		7.764		9.834	

The $t_{1/2\beta}$ of enrofloxacin observed in the current study is longer compared to values of reported for turkey [18] and chicken [19]. Whereas, De Lucas *et al.* [7] observed shorter $t_{1/2\beta}$ in ostrich compared to present study. The $t_{1/2\beta}$ obtained in the present study indicates that emu tend to eliminate enrofloxacin faster than ostrich and slower than chickens and turkeys. It is in agreement with Baert and De-Backert [20] who suggested that the drug elimination half-life had the negative correlation with the body weight. The other possible reason might be variation in protein binding nature of drug with various species.

The hepatic conversion of enrofloxacin into ciprofloxacin in emu birds observed in this study was not in accordance with Helmick *et al.* [21], who reported inconsistent conversion in emus. Whereas, the ratio of AUC_{0-t} cipro/ AUC_{0-t} enro observed in this study was 7.764 and 9.711 after i.v. and drinking water route administration of enrofloxacin, respectively. This finding is in agreement with Kumar *et al.* [6] in emus and De-Lucas *et al.* [7] in ostrich after oral administration of enrofloxacin. However, high hepatic conversion of enrofloxacin to ciprofloxacin was noted in the chicken by Anadon *et al.* [19]. This result indicated limited, but rapid conversion of ciprofloxacin in the liver of emu birds.

Enrofloxacin has excellent tissue penetration [22] as reflected by high V_{darea} in the present study. Compared to the present value, Abd-El-Aziz *et al.* [23] found lesser V_{darea} (2.17L/kg) in chicken while De-Lucas *et al.* [8] observed higher values (5.01L/kg) in greater rheas. This result is in accordance with Bugyei *et al.* [24] who explained the variability might be due to differences in drug protein binding. The clearance and volume of distribution obtained in the current study are high compared to other avian species with less body weight. It is in agreement with Cox *et al.* [25] who suggested that the clearance and volume of distribution were proportional to body weight

The C_{max}, $t_{1/2\beta}$, AUC and V_{darea} variables found lower for drinking water route, while the elimination rate constant (β) and total body clearance were higher compared to the values obtained by Kumar *et al.* [6] for enrofloxacin administered after oral route in emus. It is in accordance with the pharmacokinetics variables reported in chickens by Sumano *et al.* [14] and Sumano *et al.* [26]. The MRT value obtained in the present study is higher for the enrofloxacin administered via drinking water compared to the findings observed by

Kumar *et al.* [6] in emus (6.616h) after administration via oral route. In the present study, the birds consumed the medicated water with various time intervals and hence, the intake of drug continued for long period. Enrofloxacin was force-placed in the gastrointestinal tract at one time by Kumar *et al.* [6] to study pharmacokinetics of enrofloxacin after oral route administration in emus. This might be the reason for the higher MRT values of enrofloxacin administered through drinking water than that administered through the oral route.

The pharmacokinetic parameters of the enrofloxacin at 10 mg/kg showed insignificant difference between drinking water route (observed in this study) and oral route (as reported by Kumar *et al.*, [6] in emus. In the field conditions of poultry farms, mostly drugs are administered through drinking water. The drug are not directly administered into the gastrointestinal tract, but administered as *ad libitum* via drinking water. This direct administration of enrofloxacin in the gastrointestinal tract might be the reason for the difference in the pharmacokinetic values of enrofloxacin administered through drinking water and oral route. Still, factors such as the relationship between environmental temperature and water consumption, soundness of the water system should be explored in commercial poultry houses.

The PK/PD integration parameters are given in Table 2 and 3. The parameter AUC/MIC and C_{max}/MIC ratios are the important indicators for good clinical outcome. Turnidge [27] reported that for efficient and optimal pharmacotherapy of enrofloxacin, C_{max}/MIC and AUC/MIC values should be more than 8 and more than100, respectively. The C_{max}/MIC and AUC/MIC ratios recorded in the present study indicated that enrofloxacin at 10mg/kg through i.v. route was effective against the organisms susceptible to MIC of 0.25µg/mL while, drinking water dosing was effective against the organisms susceptible to MIC of 0.125µg/mL. The C_{max}/MPC_{90} and AUC/MPC_{90} ratios of 1.4 and 39 were protective against resistant mutants of *E. coli* for enrofloxacin, respectively [28]. From the PK/PD parameters recorded in this study, administration of enrofloxacin through i.v. route was most useful in preventing resistance compared to drinking water route of administration. Whereas, the active metabolite ciprofloxacin was not taken into account in this study, and therefore underestimate enrofloxacin efficacy.

Table 2: Pharmacokinetic/pharmacodynamic parameters of enrofloxacin considering MICs of 0.05, 0.125, 0.25 and 0.5 µg/mL

Ratio	MIC (µg/mL)	Route of administration	
		Intravenous	In-water
C_{max}/MIC	0.05	295.11±44.52*	40.29±1.24
	0.125	118.04±17.81*	16.12±0.49
	0.25	59.02±8.90*	8.06±0.25
	0.5	29.51±4.45*	4.03±0.12
AUC_{0-24}/MIC	0.05	391.06±70.35	281.90±27.80
	0.125	156.42±28.14	112.76±11.12
	0.25	78.21±14.07	56.38±5.56
	0.5	39.11±7.03	28.19±2.78

*For $C_{max,}$ a value of 14.755 µg/mL (mean peak plasma concentration at 5 min) was used for the calculation

Table 3: Pharmacokinetic/pharmacodynamic parameters of enrofloxacin considering MPCs of 0.2, 0.5, 1.0 and 2µg/mL

Ratio	MIC (µg/mL)	Route of administration	
		Intravenous	In-water
C_{max}/MPC	0.2	73.78±11.13*	10.07±0.31
	0.5	29.51±4.45*	4.03±0.12
	1	14.76±2.23*	2.01±0.06
	2	7.38±1.11*	1.01±0.03
AUC_{0-24}/MPC	0.2	97.76±17.59	70.47±6.95
	0.5	39.11±7.03	28.19±2.78
	1	19.55±3.52	14.09±1.39
	2	9.78±1.76	7.05±0.70

*For $C_{max,}$ a value of 14.755 µg/mL (mean peak plasma concentration at 5 min) was used for the calculation

4. Conclusion

From the pharmacokinetic parameters and PK/PD indices, the recommended doses of enrofloxacin was 10mg/kg once daily for drinking water route against organisms susceptible to 0.125µg/mL. The pharmacokinetic parameters and PK/PD indices observed in this study after drinking water route administration is compared with values recorded by Kumar *et al.* [6] for oral rote administration of enrofloxacin at the same dose rate in emus. No significant difference was observed between drinking water and oral route of administration. Since restraining and drug administration is serious problem in emus, drinking water route is a suitable and practical method for emus and it is also desirable method for mass medication. Thus, it can be concluded that the drinking water route is much better to oral route for administration of enrofloxacin under field condition.

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Conflict of interest: The authors declare no conflict of interest.

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