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Research Article

Influence of *Aeromonas hdrophilia* Infection on the Disposition Kinetic of Norfloxacin in Goldfish (*Carassius auratus auratus*)

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Abstract

The pharmacokinetic of norfloxacin (10 mg kg^{-1}) following single intravenous (IV) and oral administration (PO) in healthy goldfish were investigated. Also, repeated (PO) administration of norfloxacin in healthy and experimentally *Aeromonas hydrophilia* infected goldfish was studied. Following IV administration, norfloxacin obeyed a two compartments open model, distribution half-life ($t_{1/2(\alpha)}$) equal to 0.12 h, volume of distribution (V_{dss}) was 1.01 L kg^{-1}, elimination half-life ($t_{1/2(\beta)}$) was 4.30 h and total body clearance (CL_{tot}) was 0.17 L kg^{-1}h^{-1}. Following PO administration, norfloxacin was rapidly and efficiently absorbed through gastrointestinal tract as the absorption half-life ($t_{1/2(ab)}$) was 0.84 h. Maximum serum concentration (C_{max}) 4.10 µg ml^{-1}, was achieved its maximum time (t_{max}) at about 2 h post administration and the elimination half-life ($t_{1/2(el)}$) was 3.91 h. Oral bioavailability was 57.63% indicating moderate absorption of norfloxacin from oral site. Serum concentrations of norfloxacin following repeated PO administration of 10 mg kg^{-1} BW once daily for 5 consecutive days, were significantly lower in experimentally *Aeromonas hydrophilia* infected goldfish than in healthy ones. Based on these pharmacokinetics parameters determined, a dosage of 10 mg kg^{-1} BW given orally every 24 h in goldfish can maintain effective plasma concentrations with *Aeromonas hydrophilia* infection with (minimum inhibitory concentration) MIC$_{90}$ ≤ 0.25 µg ml^{-1}. Therefore, norfloxacin may be an effective therapy for goldfish diseases.

Keywords

Norfloxacin; Pharmacokinetics; Goldfish; Infection

Introduction

The world of fish pharmacology is now changing quickly. As aquaculture continues to expand, there is a need for greater knowledge of medicinal treatments both for the prevention and treatment of diseases, and for the economic husbandry of fish. A wide variety of experiments and the use of drugs in fish have been elucidated in various literature. Fish has now been considered as the model organism for conducting different experimental studies, including those of pharmacology and toxicology [1]. At the same time, increased incidence of disease, also due to intensive aquaculture, requires a more intense use of veterinary drugs and chemicals [2]. Nonetheless, relatively few drugs have been approved for use in aquaculture, so fish farmers might use unapproved or unidentified active substances.

Several antimicrobial agents have found application in the treatment of bacterial diseases of fish. The most important groups in this respect are the tetracyclines, quinolones, sulphonamides, aminopyrimidines and amphenicols [3]. Quinolones are bactericidal broad-spectra antibacterial agents that act especially against gram-negative bacteria; inhibit bacterial growth by interfering with the enzyme DNA gyrase [4]. Due to their low minimum inhibitory concentration (MIC) value for most susceptible fish pathogens and effective systemic distribution in fish when administered orally via medicated feed, quinolones have been widely used to treat systemic bacterial infections in fish [5,6]. The antimicrobial spectrum of norfloxacin makes this drug attractive in veterinary therapy [7]. The aim of this study is to investigate the pharmacokinetics profile of norfloxacin following single intravenous, oral administration in healthy goldfish and multiple oral administrations in healthy and experimentally *Aeromonas hydrophilia* infected goldfish.

Materials and Methods

Drug (Norfloxacin)

Norfloxacin was obtained as an oral solution from ATCO Pharma for pharmaceutical industries, Egypt, under a trade name (Atonor®). Each ml contains 300 mg of norfloxacin base.

Experimental design

Three hundred goldfish were used in this investigation, weighing an average of 40 ± 5 g and obtained from local farm in El-Ismallia government, Egypt. It was fed on pelleted feed twice daily (25% proteins, 8% fat) from El-Abassa farm, El-Sharkia, Egypt. The fishes were divided into 4 groups; Group (1): 30 goldfish, divided in 5 glass aquaria and each fish was injected intravenously in the caudal vein with 10 mg kg^{-1} BW of norfloxacin. Group (2): 30 goldfish were divided into 5 glass aquaria and each fish was administered 10 mg kg^{-1} BW of norfloxacin by oral cannula to calculate the bioavailability of norfloxacin in goldfish. Group (3): 120 goldfish were administrated orally with 10 mg kg^{-1} BW of norfloxacin once daily for 5 consecutive days, to determine the blood concentrations of norfloxacin in healthy fishes. Group (4): 120 goldfish were intraperitoneally injected with *Aeromonas hydrophilia*. After the appearance of signs of infection as hemorrhage all over the skin especially under the base of the fins and erosion in fins, each fish was orally administrated with 10 mg kg^{-1} BW of norfloxacin once daily for 5 consecutive days, to determine the blood concentrations of norfloxacin in infected fishes. Before the experiment blood samples were taken, negative control samples (non-treated) showed no bacterial inhibition, indicating no intrinsic antibacterial activity of the samples. The experiment was performed in accordance with the guidelines set by the Ethical Committee of Benha University, Egypt.

Blood samples

Blood samples (0.75 ml) were collected from heart following IV

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or PO administration in normal and experimentally infected goldfish. Each Fish was blood-sampled only once, i.e. at only one time-point. Blood samples were collected after 5 min, 10 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, 8 hr, 12 hr and 24 hours after drug administration in single study (IV and PO), and after 15 min, 30 min, 1 hr, 2 hr, 4 hr, 8 hr, 12 hr and 24 hr in repeated PO administration. All blood samples were collected in sterilized centrifuged tubes and allowed to clot. Serum was separated by centrifugation for 10 minutes at 3000 r.p.m. The serum was decanted, labeled, and frozen at -20°C until the assays were performed.

Analytical procedures

The concentration of norfloxacin in serum samples was estimated by a standard microbiological assay using *Escherichia coli* ATCC 25922 as test micro-organism [8]. This method estimated the level of drug having antibacterial activity, without differentiating between the parent drug and its active metabolites. Standard curves were constructed using antibacterial free serum collected from goldfishes. The medium was prepared by dissolving 9.5 g Mueller–Hinton agar in 250 ml distilled water in a 500 ml 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 norfloxacin 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 norfloxacin concentrations in the test samples were calculated from the standard curve. The method was validated in terms of linearity, sensitivity, recovery, intra-day and inter-day precision. Semi-logarithmic plots of the inhibition zone diameter, versus standard norfloxacin concentrations in serum, were linear between 0.05 and 20 μg ml^{-1}, with a typical correlation coefficient of 0.990 (for the standard curve). The limit of quantification of the norfloxacin assay was 0.05 μg ml^{-1}. The percentage recoveries were determined by comparing the inhibition zones of blank samples spiked with different amounts of drug and treated as any sample, with the inhibition zones of the same standards prepared in phosphate buffer (n=6). The mean percentage recovery of norfloxacin from serum was 96.17 ± 6.79%. Intra-assay variations were determined by measuring six replicates (n=6) of three standard samples used for calibration curves [low (0.1 μg ml^{-1}), medium (1 μg ml^{-1}), and high (10 μg ml^{-1})] on the same day. The intra-assay variation coefficient was 3-5% for serum. An inter-assay precision was determined by assaying the three standard samples on three separate days. The inter-assay variation coefficient was 5-8% for serum. The intra- and inter-day precision and accuracy of the assay were determined by percent coefficient of variation (CV). The coefficient of variation was calculated as follows: CV (%) = (standard deviation/mean) ×100.

Pharmacokinetic analysis

Pharmacokinetic parameters were determined for each individual fish. Plasma concentrations of norfloxacin after IV and PO administrations were subjected to a compartmental and non-compartmental analysis using computerized program, WinNonlin 4.1 (Pharsight, Mountain View CA, USA). Following IV administration, the plasma concentration vs time data of norfloxacin in goldfishes were fitted to a two-compartment open model system according to the following bi-exponential equation [9]: $C_p = Ae^{-\alpha t} + Be^{-\beta t}$

where C_p is the concentration of drug in the plasma at time t,

A and B are the zero-time drug intercepts of the distribution and elimination phase expressed as μg ml^{-1}, α and β are the distribution and elimination rate constants expressed in units of reciprocal time (h^{-1}), and e is the natural logarithm base.

For the IV data, the appropriate pharmacokinetic model was determined by visual examination of individual concentration-time curves and by application of Akaike's Information Criterion (AIC) [10]. The volume of distribution at steady state (V_{dss}), the total body clearance (Cl) and mean residence time (MRT) were computed according to standard equations [11]. Following PO administration, plasma concentration data in fishes were analyzed by compartmental and non compartmental methods based on the statistical moment theory [11]. In compartmental analysis, best fitting of the data was accomplished using the one compartment open model. The area under the concentration time curve (AUC), and area under the first moment curve (AUMC), was calculated by the method of trapezoids. Mean residence time (MRT) was calculated as MRT=AUMC/AUC and the systemic clearance as Cl=Dose/AUC. The absolute bioavailability was calculated as F=AUC$_{IM\ or\ PO}$/AUC$_{IV}$×100. Mean absorption time was calculated as MAT=MRT$_{po}$-MRT$_{IV}$.

The data were analyzed using SPSS (16) software (SPSS Inc., Chicago, USA) and differences between the averages were examined by Duncan's multiple-range test. Mean values within a row with different superscript letters are significantly different (P< 0.05).

Results and Discussion

Following a single IV injection of 10 mg kg^{-1} BW in healthy goldfishes, norfloxacin could be detected therapeutically for 24 hours. The serum concentration – time curve of norfloxacin following IV injection showed that the drug obeyed a two compartments open model. The disposition kinetics of norfloxacin following a single IV and PO administration were recorded in (Tables 1 and 2) and shown in (Figure 1). Oral administration of 10 mg kg^{-1} BW every 24 hours for 5 doses in healthy and *Aeromonas hydrophilia* infected goldfishes,

Table 1: Pharmacokinetics parameters of norfloxacin in goldfish (*Carassuys auratus Linnaeus*) after a single IV administration of 10 mg kg^{-1} BW (n=3).

| Parameter	Unit	Mean ± S.D.
C°	μg ml^{-1}	13.95 ± 0.77
A	μg ml^{-1}	4.28 ± 0.68
B	μg ml^{-1}	9.67 ± 0.26
α	h^{-1}	5.76 ± 0.50
β	h^{-1}	0.16 ± 0.01
K$_{12}$	h^{-1}	1.65 ± 0.44
K$_{21}$	h^{-1}	4.03 ± 0.08
K$_{12}$/ K$_{21}$	Ratio	0.41 ± 0.11
t$_{1/2(α)}$	h	0.12 ± 0.01
t$_{1/2(β)}$	h	4.30 ± 0.33
V$_{dss}$	L kg^{-1}	1.01 ± 0.02
Cl$_{(tot)}$	L kg^{-1}h^{-1}	0.17 ± 0.01
AUC	μg ml^{-1}h^{-1}	67.05 ± 4.89
AUMC	μg ml^{-1}h^{-2}	448.08 ± 39.32
MRT	h	6.68 ± 0.13

C°: concentration at zero time (immediately after single IV administration); **A, B**: zero-time intercepts of the biphasic disposition curve; **α, β**: hybrid rate constants representing the slopes of distribution and elimination phases, respectively; **K$_{12}$**: first-order constant for transfer from central to peripheral compartment; **K$_{21}$**: first-order constant for transfer from peripheral to central compartment; **t$_{1/2(α)}$**: distribution half-life; **t$_{1/2(β)}$**: elimination half-life; **V$_{dss}$**: volume of distribution at steady state; **Cl$_{(tot)}$**: total body clearance; **AUC**: area under serum concentration-time curve; **AUMC**: area under moment curve; **MRT**: mean residence time.

Table 2: Pharmacokinetics parameters of norfloxacin in goldfish after a single PO administration of 10 mg kg^{-1} BW (n=3).

Parameter	Unit	Mean ± S.D.
K_{ab}	h^{-1}	0.82 ± 0.06
K_{el}	h^{-1}	0.18 ± 0.02
$t_{1/2(ab)}$	h	0.84 ± 0.06
$t_{1/2(el)}$	h	3.91 ± 0.33
C_{max}	µg ml^{-1}	4.10 ± 0.11
t_{max}	h	2.00 ± 0.00
AUC	µg ml^{-1}h^{-1}	38.54 ± 1.03
AUMC	µg ml^{-1}h^{-1}	326.47 ± 5.05
MRT	h	8.47 ± 0.15
MAT	h	1.79 ± 0.26
F	%	57.63 ± 3.17

k_{ab}: first-order absorption rate constant; K_{el}: elimination rate constant; $t_{1/2(ab)}$: absorption half-life;
$t_{1/2(el)}$: elimination half-life; C_{max}: maximum serum concentration; t_{max}: time to peak serum concentration; **MAT**: mean absorption time; **F**: fraction of drug absorbed systemically after PO administration.
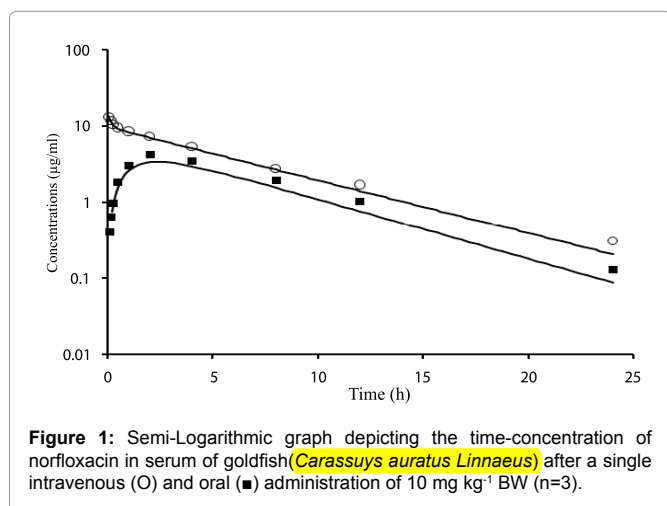
Figure 1: Semi-Logarithmic graph depicting the time-concentration of norfloxacin in serum of goldfish(*Carassuys auratus Linnaeus*) after a single intravenous (O) and oral (■) administration of 10 mg kg^{-1} BW (n=3).

revealed a lower significant serum norfloxacin concentration at all-time sampling in *Aeromonas hydrophilia* infected goldfishes than in healthy ones (Figure 2). The pharmacokinetic parameters of norfloxacin after repeated PO administration in healthy goldfishes were compared to those in *Aeromonas hydrophilia* infected ones as shown in (Table 3).

In the present investigation, IV administration of 10 mg kg^{-1} BW of norfloxacin in healthy goldfish showed that the drug disposition best fitted a two-compartments- open model; a compartment of plasma and rapid equilibrating tissues, and a deeper slower compartment. The obtained result was consistent with those reported for norfloxacin in broiler chicken [12] and horses [13]. Also, this result was similar to other fluoroquinolones in other fish species as enrofloxacin in brown trout and crucian carp [14,15]. Elimination half-life ($t_{1/2(\beta)}$) of norfloxacin in goldfish following IV administration was 4.30 h. This observation agreed with the data reported for norfloxacin (3.93 h) in rabbits [16], longer than norfloxacin (2.1 h) in swine [17] and shorter than norfloxacin (8h) in chicken [12], flumequine (24.6 h) in catfish [18] and enrofloxacin (63.5 h) in crucian carp [15]. Variation in biology (age, condition, and size), method (dose and route of administration), and environment (pH, ion content, and temperature), each of these variables affects the pharmacokinetic parameters, so the results do not solely reflect species differences [19].
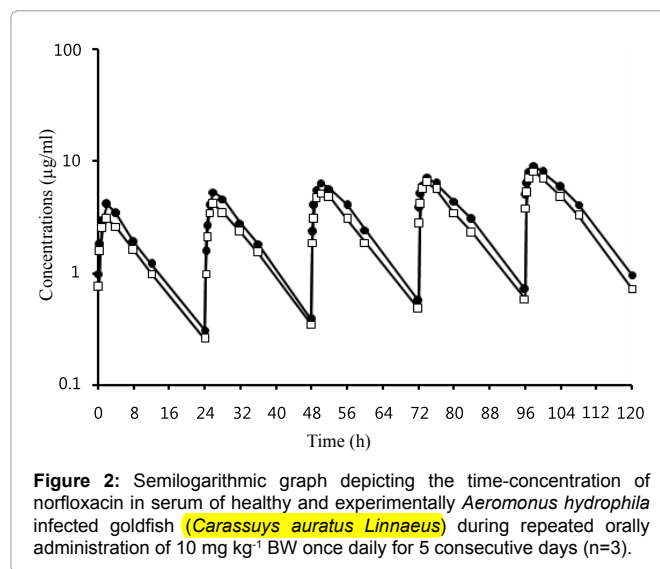
Figure 2: Semilogarithmic graph depicting the time-concentration of norfloxacin in serum of healthy and experimentally *Aeromonus hydrophila* infected goldfish (*Carassuys auratus Linnaeus*) during repeated orally administration of 10 mg kg^{-1} BW once daily for 5 consecutive days (n=3).

The V_{dss} for norfloxacin was 1.01 L kg^{-1}, suggesting good penetration through biological membranes and tissue distribution after IV administration in goldfish. The obtained value was longer to that recorded for flumequine (0.52 L kg^{-1}) in catfish [18] and enrofloxacin (0.38 L kg^{-1}) in cuttlefish [20] and shorter than enrofloxacin (3.93, 3.40 L kg^{-1}) in Korean catfish and brown trout, respectively [14,21]. The total body clearance (CL_{tot}) was 0.17 L kg^{-1}h^{-1}, this value was close to other fluoroquinolones as flumequine (0.14 L kg^{-1}h^{-1}) in catfish [18] and enrofloxacin (0.14 L kg^{-1}h^{-1}) in brown trout [14], shorter than enrofloxacin (0.28 L kg^{-1}h^{-1}) in cuttlefish [20] and longer than enrofloxacin (0.04 L kg^{-1}h^{-1}) in crucian carp [15].

Following PO administration, norfloxacin was rapidly and efficiently absorbed through gastrointestinal tract of goldfish as the absorption half-life ($t_{1/2(ab)}$) was 0.84 h. The obtained value was longer than marbofloxacin (0.36 h) in crucian carp [22], difloxacin (0.20 h) in crucian carp [23] and shorter than flumequine (4.94 h) in catfish [18]. The elimination half-life ($t_{1/2(el)}$) was 3.91 h, this value was longer than enrofloxacin (1.81 h) in cuttlefish [20] and shorter than flumequine (21.8 h) in catfish [18], enrofloxacin (22.09 h) in brown trout [14] and difloxacin (26.01 h) in crucian carp [23].

Maximal plasma concentration (C_{max}) was 4.10 µg ml^{-1} achieved at (t_{max}) 2 h. These values were similar to enrofloxacin (4.5 µg ml^{-1}) achieved at 2 h in crucian carp [15]. The (C_{max}) obtained in present study was higher than those reported for enrofloxacin (1.2 µg ml^{-1}) in Korean catfish [21] and lower than enrofloxacin (10.95 µg ml^{-1}) in cuttlefish [20].

The bioavailability of norfloxacin in healthy goldfish was 57.63%. This value referred to a moderate absorption of norfloxacin from gastrointestinal tract. This value was in agreement with that previously reported for enrofloxacin (55.5% & 54%) in Atlantic salmon and seabream in seawater [24,25], lower than enrofloxacin (78%) in brown trout [14] and higher than flumequine (44%) in catfish [18]. These differences in bioavailability may be related to water chemistry (pH, ion content) that have been identified as important factors in the stability of drugs [26]. The bioavailability of quinolones is lower in seawater than in freshwater because ionization at higher pH causes chelation with cations [19,21].

The obtained blood levels of norfloxacin in *Aeromonas*

Table 3: Non compartmental pharmacokinetics parameters of norfloxacin in healthy (H) and experimentally *Aeromonus hydrophila* infected (I) goldfish (*Carassuys auratus Linnaeus*) following repeated oral administration of 10 mg kg^{-1} BW every 24 hours for 5 consecutive doses (n=3).

Parameters	Unit	1st dose		3rd dose		5th dose	
		(H) Mean ± SD	(I) Mean ± SD	(H) Mean ± SD	(I) Mean ± SD	(H) Mean ± SD	(I) Mean ± SD
K_{el}	h^{-1}	0.110 ± 0.004^c	0.111 ± 0.03^c	0.117 ± 0.002^b	0.108 ± 0.002^c	0.119 ± 0.004^{ab}	0.124 ± 0.002^a
$t_{1/2(el)}$	h	6.27 ± 0.23^a	6.20 ± 0.17^a	5.90 ± 0.09^b	6.38 ± 0.09^a	5.79 ± 0.18^{bc}	5.57 ± 0.09^c
C_{max}	µg ml^{-1}	4.15 ± 0.13^e	3.90 ± 0.04^f	5.62 ± 0.10^c	4.61 ± 0.07^d	6.70 ± 0.11^a	5.85 ± 0.07^b
t_{max}	h	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00
AUC	µg ml^{-1}h^{-1}	37.36 ± 1.04^e	34.20 ± 0.69^f	52.75 ± 1.49^c	41.67 ± 0.98^d	68.87 ± 2.27^a	58.02 ± 1.94^b
AUMC	µg ml^{-1}h^{-2}	337.43 ± 9.59^c	299.89 ± 12.31^e	480.94 ± 19.04^c	384.44 ± 13.97^d	646.02 ± 35.62^a	523.16 ± 26.74^b
MRT	h	9.03 ± 0.19^{bc}	8.77 ± 0.18^c	9.12 ± 0.11^{ab}	9.22 ± 0.12^{ab}	9.38 ± 0.22^a	9.01 ± 0.16^{bc}
Cl$_{(tot)}$	L kg^{-1}h^{-1}	0.27 ± 0.007^b	0.29 ± 0.005^a	0.19 ± 0.005^d	0.24 ± 0.006^c	0.15 ± 0.004^f	0.17 ± 0.005^e

^{a,b,c,d,e,f} Mean values having different letters in column differ significantly (P<0.05).

hydrophilia infected goldfish were significantly lower than those in healthy one following repeated oral administrations. These lower blood concentrations in infected goldfish might be attributed to the higher penetrating power of norfloxacin to the diseased tissues [27]. The relative higher plasma concentrations of norfloxacin after the last dose compared to the first doses indicated the accumulation of norfloxacin in blood during multiple dosing at 24 hours intervals for 5 consecutive days. These observations agreed with the progressive daily increase in the mean serum concentrations following the intramuscular injection of ciprofloxacin in lactating goats given a daily dose of 5 mg kg^{-1} BW for 5 consecutive days [28].

The MIC values of fluoroquinolones for pathogens infecting fish range from 0.0064 to 0.032 µg ml^{-1} for most susceptible organisms [29]. The required C_{max}/MIC and AUC/ MIC for quinolones are 8-10 and 125, respectively [26,30]. Following PO administration of 10 mg kg^{-1} BW in goldfish, the peak plasma concentration was 4.10 µg ml^{-1} achieved at 2 h and the mean plasma concentration was 0.29 µg ml^{-1} at 24 h. This concentration is above the MIC for most fish pathogens and above the MIC$_{90}$ of *Aeromonas hydrophilia*; the effectiveness of quinolones may also be enhanced by a post-antibiotic effect [30].

Conclusions

This study indicates that it is possible to obtain therapeutic blood concentrations of norfloxacin at a single dose (10 mg kg^{-1} BW) after oral administration in goldfish (*Carassuys auratus Linnaeus*); therefore, it may be an effective therapy for goldfish's diseases. Also, accumulation of norfloxacin in blood during multiple dosing was recorded.

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