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# Comparative Single-Dose Pharmacokinetics of Four Quinolones, Oxolinic Acid, Flumequine, Sarafloxacin, and Enrofloxacin, in Atlantic Salmon (*Salmo salar*) Held in Seawater at 10°C

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**Quinolones are currently the most commonly used group of antimicrobial agents in Norwegian aquaculture. The aims of this study were to examine and compare the pharmacokinetic properties of the quinolones oxolinic acid, flumequine, sarafloxacin, and enrofloxacin after intravascular and oral administration to Atlantic salmon (*Salmo salar*) by using identical experimental designs. The study was performed in seawater at 10.2 ± 0.2°C with Atlantic salmon weighing 240 ± 50 g (mean ± standard deviation). The bioavailability varied considerably among the four quinolones. Following oral administration of medicated feed, the bioavailabilities of oxolinic acid, flumequine, sarafloxacin, and enrofloxacin were 30.1, 44.7, 2.2, and 55.5%, respectively. Taking the different dosages (25 mg/kg of body weight for oxolinic acid and flumequine and 10 mg/kg for sarafloxacin and enrofloxacin) into account, enrofloxacin showed the highest maximum concentration in plasma, followed by flumequine, oxolinic acid, and sarafloxacin. Following intravenous administration, the volumes of distribution at steady state of oxolinic acid, flumequine, sarafloxacin, and enrofloxacin were 5.4, 3.5, 2.3, and 6.1 liters/kg, respectively. Hence, all the quinolones showed good tissue penetration in Atlantic salmon. The elimination half-life of three of the quinolones, oxolinic acid, flumequine, and sarafloxacin, was less than or equal to 24 h, with oxolinic acid showing the shortest (18.2 h). On the other hand, the elimination half-life of enrofloxacin was estimated to be 34.2 h, almost twice that of oxolinic acid. This study showed that flumequine and enrofloxacin had better pharmacokinetic properties, compared with those of oxolinic acid, in Atlantic salmon held in seawater.**

In recent years, the quinolones oxolinic acid and flumequine have been the most frequently used antimicrobial agents in Norwegian aquaculture (17). Sarafloxacin, enrofloxacin, and other fluoroquinolones have showed enhanced in vitro activities compared with those of older quinolones, such as oxolinic acid and flumequine, against fish pathogenic bacteria (2, 21). Studies have also revealed better bactericidal activity (3, 16), as well as promising clinical efficacy in treatment of bacterial fish diseases (6, 14, 29). The chemical structures of oxolinic acid, flumequine, sarafloxacin, and enrofloxacin are shown in Fig. 1.

The pharmacokinetic properties of quinolones have not been extensively studied in fish. However, there are several single reports indicating that their pharmacokinetic properties vary considerably from one compound to another (7, 11, 19, 24). It is therefore important to clarify the pharmacokinetic properties of the different quinolones in fish, so as to be able to select the most beneficial compound for the treatment of bacterial fish diseases.

Some data concerning the pharmacokinetic properties of oxolinic acid and flumequine in Atlantic salmon (*Salmo salar*) are available (11, 12, 24). As regards sarafloxacin and enrofloxacin in Atlantic salmon, one paper on the kinetics of sarafloxacin in Atlantic salmon held in seawater at 8.5°C has been published (19).

The aims of the present study were to examine and compare the pharmacokinetic properties of the quinolones oxolinic acid, flumequine, sarafloxacin, and enrofloxacin after intravascular and oral administration to Atlantic salmon (*S. salar*) held in seawater, using identical experimental designs, and to calculate and compare bioavailability based on the pharmacokinetic parameters. For flumequine, two different oral formulations were investigated so that any pharmacokinetic differences between the two formulations would be revealed.

## MATERIALS AND METHODS

**Antimicrobial agents.** Enrofloxacin was obtained from Bayer A.G., Leverkusen, Germany; sarafloxacin was obtained from Abbott Laboratories, North Chicago, Ill; and flumequine and oxolinic acid to make intravenous (i.v.) solutions were purchased from Sigma Chemical Co., St. Louis, Mo. Flumequine and oxolinic acid for the oral formulations were obtained from Apothekernes Laboratorium A/S, Oslo, Norway (flumequine), and Ewos Aqua A/S, Skårer, Norway (flumequine and oxolinic acid).

**Antimicrobial formulations.** Each solution for i.v. administration of oxolinic acid, flumequine, and sarafloxacin was prepared by dissolving the drug in question in 0.1 M NaOH, regulating the pH to 11.0 with 6 M HCl, and adjusting the final volume with 0.9% saline. The solution of enrofloxacin for i.v. administration was made by diluting Baytril (25 mg of enrofloxacin per ml) in 0.9% saline. The final quinolone concentration for i.v. administration of the oxolinic acid and flumequine solutions was 25 mg/ml, while the corresponding concentration of the sarafloxacin and enrofloxacin solutions was 10 mg/ml. Check analysis of the solutions used for i.v. administration showed 25.8 mg of oxolinic acid per ml, 23.8 mg of flumequine per ml, 10.1 mg of sarafloxacin per ml, and 11.2 mg of enrofloxacin per ml.

The drugs for oral administration were mixed into ordinary fish feed by Ewos Aqua A/S, utilizing the double coating technique, at concentrations of 2 g of enrofloxacin and sarafloxacin and 5 g of oxolinic acid and flumequine per kg of feed. For flumequine, Aqualets (9) containing 5 g of flumequine per kg were made by Apothekernes Laboratorium A/S. Check analysis of the medicated feed administered showed 4.7 mg of oxolinic acid per g of feed, 4.7 mg of flumequine per g of feed, 2.0 mg of sarafloxacin per g of feed, and 2.0 mg of enrofloxacin per g of feed. Check analysis of the Aqualets administered showed them to contain 4.8 mg of flumequine per g.

**Test facilities and test fish.** The study was conducted at NIVA Marine Re-

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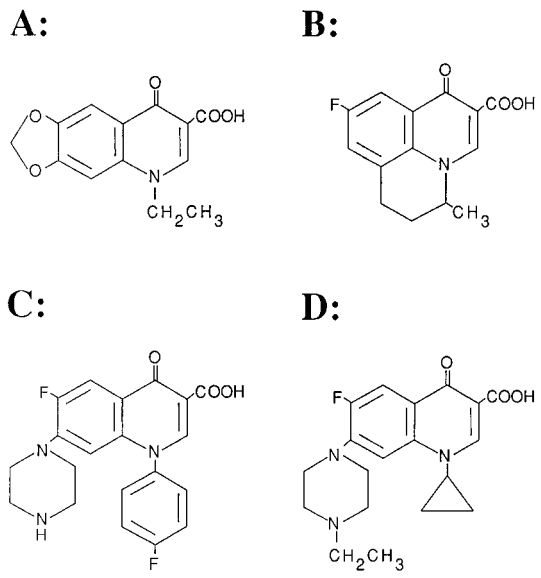


FIG. 1. Chemical structures of oxolinic acid (A), flumequine (B), sarafloxacin (C), and enrofloxacin (D).

search Station, Drøbak, Norway. The fish were held in fiberglass tanks of 1-$m^3$ capacity supplied with running seawater with a salinity of about 33‰. The study was performed at a water temperature of 10.2 ± 0.2°C.

Three hundred sixty experimental fish were obtained from NIVA Marine Research Station. The test fish were Atlantic salmon (*S. salar*) postsmolts, weighing 240 ± 50 g (mean ± standard deviation).

The fish were randomly divided into nine groups of 40 each 14 days prior to the start of the study and transferred to the test tanks for adaptation. They were fed a commercial pelleted fish diet (T. Skretting A/S, Stavanger, Norway) ad libitum once a day during the adaptation period. On the day prior to drug administration and during the experimental period, the fish were not fed.

**i.v. administration.** Four groups of test fish were given the different drugs i.v., administered by bolus into the caudal vein as described by Martinsen et al. (20). If the injection needle translocated during the injection, the fish was excluded and replaced. The four fish groups were given either oxolinic acid or flumequine at a dose rate of 25 mg/kg of body weight or sarafloxacin or enrofloxacin at a dose rate of 10 mg/kg.

**Oral administration.** The other five groups received the different drugs orally, as medicated feed or Aqualets, via a premade and preloaded syringe introduced into the esophagus (20). All four antimicrobial drugs were administered orally as medicated feed, one drug to each of four fish groups. In addition, flumequine was administered orally as Aqualets to the fifth group. The oral doses were as follows: enrofloxacin and sarafloxacin, 10 mg/kg; flumequine and oxolinic acid, 25 mg/kg. After administration, each orally dosed fish was transferred to an individual tank for observation of regurgitation before being transferred to the experimental tank. Any fish which regurgitated during the 5 min in the observation tank was excluded from the study.

**Sampling.** Five fish from each group were killed at each time point by a blow to the head. Blood samples were taken from each fish by caudal venipuncture with a 21-gauge, 1.5-in. (ca. 3.8-cm) needle and heparinized Vacutainers (5 ml) (Venoject; Terumo Europe N.V., Leuven, Belgium). Blood samples from fish given the drug i.v. were collected at least 2 cm anterior to the injection site. Blood was sampled before drug administration and 3, 6, 12, 24, 48, 72, and 120 h postadministration.

After centrifugation of the blood at 2,000 × *g* for 10 min, the plasma was collected and frozen at −20°C in plastic vials until analyzed.

After blood sampling, each fish in the orally administered groups was examined for possible traumatic rupture of the stomach.

**Analytical procedures.** The plasma samples of all four quinolones were cleaned up by solid-phase extraction on a column of the Bond Elute type, size 1 ml, with $C_2$ sorbent material, according to previously published methods (23, 25, 28). The concentrations of the four quinolones in plasma were determined by means of high-performance liquid chromatography using a fluorescence detector (23, 25, 28). The detector was operated at an excitation wavelength of 278 nm and emission wavelength of 440 nm when enrofloxacin and sarafloxacin were analyzed (25, 28). When analyzing for oxolinic acid and flumequine, the detector was operated at an excitation wavelength of 260 nm and emission wavelength of 380 nm (23). The lower limits of quantitation of the methods were 5 ng/ml for enrofloxacin and oxolinic acid and 10 ng/ml for flumequine and sarafloxacin. The analytical methods were linear over a range of 25 to 4,000 ng/ml for all four quinolones, and the linear correlation coefficients of the assays were >0.9986 for all the drugs. The recovery was >92% at concentrations of both 400 and 3,000 ng/ml, and the coefficient of variation determined for those two concentrations was less than 8.2% for intraday variation and less than 6.9% for interday variations for all assays. Seeded controls were also analyzed with the unknown study samples. Data were deemed acceptable if the accuracy of each seeded control was within 12% of its theoretical value.

**Pharmacokinetic analysis.** In the i.v. dosed groups, pharmacokinetic evaluation was performed by using the computer program PCNONLIN, version 4.0 (Statistical Consultants Inc., Lexington, Ky.), in a least-squares nonlinear regression analysis. For all four quinolones, standard pharmacokinetic parameters were calculated from the best fitting relationship between mean plasma drug concentration and time, according to a two-compartment model (1). The proper model was chosen by minimum Akaike's information criterion estimation (31), in which all data were weighed to produce the best curve fit during the elimination phase (interval from 24 to 120 h postadministration).

In the orally dosed groups, estimated plasma drug concentration-time curves were computed according to a two-compartment model for sarafloxacin and enrofloxacin, while a one-compartment model gave the best estimation of the corresponding curves for oxolinic acid and flumequine (minimum Akaike's information criterion). The pharmacokinetic parameters, maximum concentration ($C_{max}$), time to reach $C_{max}$, area under the plasma drug concentration-time curve (trapezoidal method from 0 to 120 h and log trapezoidal method from 120 h to infinity), and the bioavailability, were calculated on the basis of the mean of observed plasma drug concentrations at each time point.

## RESULTS

The mean plasma drug concentration and the standard deviation at each time point for each quinolone are given in Table 1, while the estimated pharmacokinetic parameters are shown in Table 2.

Absorption following oral administration of all the four quinolones was fairly rapid but incomplete. The time to $C_{max}$ was 6 h for flumequine and enrofloxacin and 12 h for oxolinic acid and sarafloxacin following oral administration of medicated feed, while the time to $C_{max}$ for flumequine following oral administration of Aqualets was 12 h.

Bioavailability varied considerably among the four quinolones. Following oral administration of medicated feed, the bioavailabilities of oxolinic acid, flumequine, sarafloxacin, and enrofloxacin were 30.1, 44.7, and 2.2, and 55.5%, respectively. The bioavailabilities of flumequine in each of the two oral formulations were nearly identical, the Aqualet formulation showing a bioavailability of 44.6% compared to the 44.7% bioavailability of the medicated feed formulation.

Taking the different dosages (25 mg/kg for oxolinic acid and flumequine and 10 mg/kg for sarafloxacin and enrofloxacin) into account, enrofloxacin showed the highest mean $C_{max}$, followed by flumequine, oxolinic acid, and sarafloxacin. In the medicated feed groups, the mean $C_{max}$s of oxolinic acid, flumequine, sarafloxacin, and enrofloxacin were 0.61, 1.42, 0.08, and 1.54 μg/ml, respectively. In the group given flumequine in the form of Aqualets, the mean $C_{max}$ was 1.75 μg of flumequine per ml of plasma.

Following i.v. administration, the apparent volumes of distribution at steady state ($V_{ss}$s) of oxolinic acid, flumequine, sarafloxacin, and enrofloxacin were 5.4, 3.5, 2.3, and 6.1 liters/kg, respectively.

The total body clearance ($CL_T$) following i.v. administration was highest for oxolinic acid, followed by flumequine, enrofloxacin, and sarafloxacin. Three of the quinolones—oxolinic acid, flumequine, and sarafloxacin—had an elimination half-life of less than or equal to 24 h, with oxolinic acid showing the shortest (18.2 h). On the other hand, the elimination half-life of enrofloxacin was estimated to be 34.2 h, almost twice that of oxolinic acid.

Figure 2 depicts the observed concentrations of the four quinolones in plasma after i.v. and oral administration. The estimated plasma drug concentration-time curves calculated by PCNONLIN are also shown.

TABLE 1. Mean plasma quinolone concentrations in Atlantic salmon (*S. salar*) at different times following a single i.v. or single oral administration[a]

| Antimicrobial agent (dose, mg/kg) and administration | Mean plasma drug conc (μg/ml)[b] at (h): | | | | | | |
|---|---|---|---|---|---|---|---|
| | 3 | 6 | 12 | 24 | 48 | 72 | 120 |
| Oxolinic acid (25) | | | | | | | |
| i.v. | 5.20 (0.37) | 3.54 (0.90) | 2.22 (0.44) | 1.01 (0.24) | 0.34 (0.25) | 0.26 (0.16) | 0.02 (0.01) |
| Oral, medicated feed | 0.18 (0.08) | 0.46 (0.15) | 0.61 (0.21) | 0.46 (0.10) | 0.24 (0.15) | 0.11 (0.07) | 0.01 (<0.01) |
| Flumequine (25) | | | | | | | |
| i.v. | 9.51 (1.55) | 5.46 (1.05) | 3.11 (0.71) | 1.15 (0.34) | 0.55 (0.05) | 0.25 (0.13) | 0.06 (0.03) |
| Oral, medicated feed | 0.50 (0.17) | 1.42 (0.44) | 1.13 (0.27) | 1.05 (0.54) | 0.47 (0.17) | 0.29 (0.17) | 0.07 (0.06) |
| Oral, Aqualets | 0.36 (0.23) | 1.72 (0.51) | 1.75 (0.52) | 0.71 (0.39) | 0.43 (0.22) | 0.36 (0.10) | 0.03 (0.03) |
| Sarafloxacin (10) | | | | | | | |
| i.v. | 5.73 (1.10) | 2.50 (0.65) | 1.51 (0.36) | 0.94 (0.21) | 0.56 (0.21) | 0.22 (0.05) | 0.06 (0.02) |
| Oral, medicated feed | 0.02 (<0.01) | 0.06 (0.02) | 0.08 (0.04) | 0.03 (0.01) | 0.01 (<0.01) | <0.01 (<0.01) | <0.01 (<0.01) |
| Enrofloxacin (10) | | | | | | | |
| i.v. | 2.17 (0.65) | 1.35 (0.11) | 1.04 (0.24) | 0.80 (0.14) | 0.50 (0.22) | 0.33 (0.14) | 0.11 (0.05) |
| Oral, medicated feed | 0.65 (0.08) | 1.39 (0.25) | 0.82 (0.37) | 0.52 (0.30) | 0.26 (0.08) | 0.15 (0.09) | 0.05 (0.03) |

[a] Salmon were kept at 10.2 ± 0.2°C in running seawater.
[b] Values in parentheses are standard deviations.

## DISCUSSION

Some pharmacokinetic information has been published for oxolinic acid (11, 12, 24), flumequine (24), and sarafloxacin (18, 19) in Atlantic salmon held in seawater, while such information is lacking for enrofloxacin. The only comparative study published is that of Rogstad et al. (24), in which oxolinic acid and flumequine were compared. In the present study, four quinolones were compared by identical study protocols, including fish from the same fish population and identical tanks with identical water temperatures and other water quality parameters. By standardizing the study as much as possible in this way, it is much more likely that the pharmacokinetic differences revealed are real and not apparent differences attributable to different study designs.

In the present study, the bioavailability of oxolinic acid in Atlantic salmon was calculated to be 30.1%, which is higher than the 19.9 and 21.4% previously reported at 7.5 and 9.0°C, respectively (11). In contrast to Hustvedt et al. (11), Rogstad et al. (24) reported dose-dependent bioavailability of oxolinic acid in Atlantic salmon at 5°C, as they estimated 25 and 40% bioavailabilities at doses of 50 and 25 mg/kg, respectively. In rainbow trout held in freshwater, Cravedi et al. (8) also reported dose-dependent bioavailability of oxolinic acid, as they estimated 14.3 and 38.1% bioavailabilities at doses of 100 and 20 mg/kg, respectively.

The bioavailability of flumequine dosed as Aqualets in Atlantic salmon held in seawater at 5°C has previously been estimated to be 39 and 46% for doses of 50 and 25 mg/kg, respectively (24). This is in accordance with our study, which showed a bioavailability of 44.6% for flumequine dosed as Aqualets. There was no difference in the bioavailability of flumequine between the medicated feed formulation and the Aqualets used in this study.

In this study, the bioavailability of sarafloxacin dosed as medicated feed was calculated to be 2.2%, which is lower than the 3.6 and 7.4% previously reported for homogeneously mixed and coated medicated feeds, respectively (19). The reason for the lower bioavailability might be differences in drug formulation, as none of the formulations tested in the previous study (19) were identical to the formulation in this study. Another reason for the lower bioavailability obtained in the present study might be that the last sampling time point in this study was 120 h after administration compared to 48 h in the other study (19). This means that the slower terminal excretion

TABLE 2. Pharmacokinetic parameters[a] of four quinolones in Atlantic salmon held in running seawater at 10.2°C following i.v. or oral administration

| Quinolone (dose, mg/kg) and administration | α ($h^{-1}$) | β ($h^{-1}$) | $V_{SS}$ (liters/kg) | $CL_T$ (liter/h/kg) | $t_{1/2\alpha}$ (h) | $t_{1/2\beta}$ (h) | AUC (μg · h/ml) | $C_{max}$ (μg/ml) | $T_{max}$ (h) | $F$ (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Oxolinic acid (25) | | | | | | | | | | |
| i.v. | 0.147 | 0.038 | 5.4 | 0.28 | 4.7 | 18.2 | 89.1 | | | |
| Oral, medicated feed | | | | | | | 26.8 | 0.61 | 12 | 30.1 |
| Flumequine (25) | | | | | | | | | | |
| i.v. | 0.224 | 0.030 | 3.5 | 0.18 | 3.1 | 22.8 | 140.2 | | | |
| Oral, medicated feed | | | | | | | 62.7 | 1.42 | 6 | 44.7 |
| Oral, Aqualets | | | | | | | 62.5 | 1.75 | 12 | 44.6 |
| Sarafloxacin (10) | | | | | | | | | | |
| i.v. | 0.485 | 0.029 | 2.3 | 0.10 | 1.4 | 24.0 | 100.7 | | | |
| Oral, medicated feed | | | | | | | 2.2 | 0.08 | 12 | 2.2 |
| Enrofloxacin (10) | | | | | | | | | | |
| i.v. | 0.496 | 0.020 | 6.1 | 0.14 | 1.4 | 34.2 | 72.4 | | | |
| Oral, medicated feed | | | | | | | 40.2 | 1.54 | 6 | 55.5 |

[a] α, distribution rate constant; β, elimination rate constant; $t_{1/2\alpha}$, distribution half-life; $t_{1/2\beta}$, elimination half-life; AUC, area under plasma drug concentration-time curve; $T_{max}$, time to reach $C_{max}$; $F$, bioavailability.

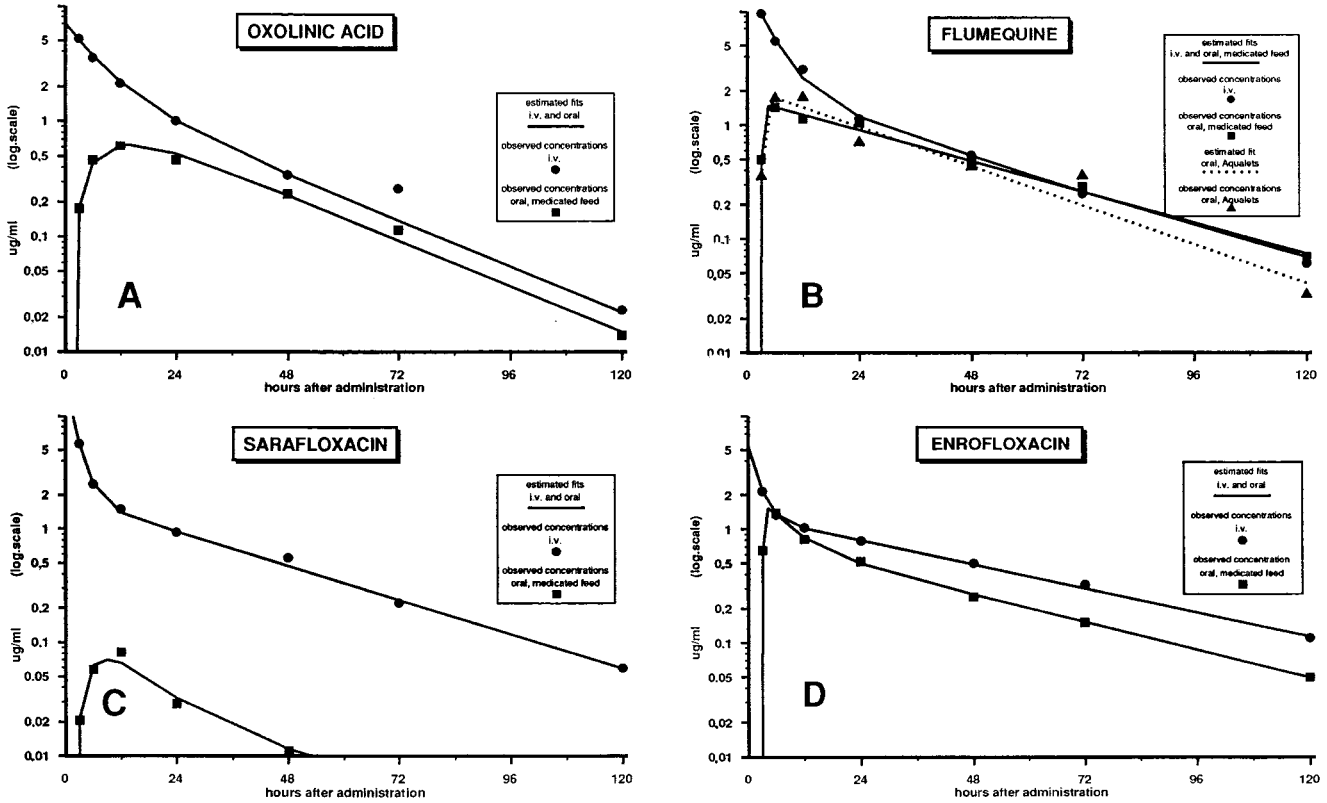


FIG. 2. Estimated (by PCNONLIN) plasma drug concentration-time curves and observed mean plasma drug concentrations after i.v. and oral administration.

phase commonly described for drugs in fish (5, 24, 26) was more correctly revealed in this study. The terminal elimination rate in the previous study (19) might have been overestimated, and the area under the curve for i.v. administration would thus be underestimated. This would in turn result in overestimation of the bioavailability.

No previous information on the bioavailability of enrofloxacin in Atlantic salmon held in seawater is available. The 55% bioavailability of enrofloxacin calculated in the present study was, however, higher than the 25% previously reported for enrofloxacin in fingerling rainbow trout dosed at 10 mg/kg in freshwater at 10°C (7). This might be explained by either species differences, variations related to the two different water types of freshwater (7) and seawater (as examined in this study), or a combination of the two factors.

The reported 55% bioavailability of enrofloxacin is much lower than that of quinolones in humans and domestic animals. It is also much lower than that of florfenicol (20) and trimethoprim (unpublished data) in Atlantic salmon held in seawater. Nevertheless, the bioavailability of enrofloxacin is the highest reported for a quinolone in Atlantic salmon held in seawater.

All the quinolones are well distributed to different tissues of Atlantic salmon, as they show an apparent $V_{SS}$ greater than 2.3 liters/kg. This is in accordance with similar large $V_{SS}$s reported in domestic animals (30) and humans (27). The differences in the $V_{SS}$ between individual quinolones in domestic animals (30) and humans (27) are also valid for Atlantic salmon, as the $V_{SS}$s of the four quinolones varied between 2.3 and 6.1 liters/kg. The reason for and the significance of these differences are still unclear (27).

The $CL_T$ after i.v. administration of oxolinic acid was calculated to be 0.28 liter/h/kg, which is higher than the $CL_T$s of the other three quinolones studied. A quite similar $CL_T$ of 0.21 liter/h/kg for oxolinic acid has been previously described by Rogstad et al. (24). Hustvedt et al. (12) reported a $CL_T$ of 0.03 liter/h/kg for oxolinic acid in cannulated Atlantic salmon held at 9°C in seawater. The main reason for this comparatively large discrepancy is probably that cannulated fish typically demonstrate altered pharmacokinetic properties compared with those of noncannulated fish (15, 22).

The $CL_T$ after i.v. administration of enrofloxacin was calculated to be 0.14 liter/h/kg in the present study. Bowser et al. (7) reported a $CL_T$ of 0.06 liter/h/kg after administration of a single i.v. dose of 10 mg of enrofloxacin per kg to rainbow trout. The main reason for this apparent discrepancy is probably that quinolones are eliminated more slowly from salmonids held in freshwater than from those held in seawater (10, 13). However, the fact that the two studies were carried out on two different species, rainbow trout and Atlantic salmon, might also be relevant (18).

The elimination half-lives of oxolinic acid, flumequine, and sarafloxacin were rather short, calculated to be 24.0 h or less. The elimination half-life of enrofloxacin was considerably longer, being estimated to be 34.2 h. The longer elimination half-life of enrofloxacin was mainly due to a very large $V_{SS}$ (6.1 liters/kg). However, the $CL_T$ (0.14 liter/h/kg) was in the same range as those of flumequine and sarafloxacin.

The elimination half-life of oxolinic acid was calculated to be 18.2 h, which is longer than the 10 h reported by Rogstad et al. (24) but shorter than the 60.3 h reported for cannulated Atlantic salmon by Hustvedt et al. (12).

The elimination half-life of flumequine at 10.2°C was estimated to be 22.8 h. This is identical to that previously reported

for Atlantic salmon held in seawater at 5°C (24). However, this should not be taken as a demonstration of non-temperature-dependent elimination, as the two studies were not conducted under identical conditions.

The elimination half-life of sarafloxacin was calculated to be 24.0 h, which is longer than the 15.9 h previously reported (19). The elimination half-life previously reported for sarafloxacin (19) may have been somewhat underestimated, as no sampling time points were later than 48 h after administration. The plasma drug concentration-time curve following i.v. administration was best described by a one-compartment model, and hence, the slower terminal excretion phase commonly described for drugs in fish (5, 24, 26) would not have been revealed. Therefore, the elimination half-life in this study, based on a two-compartment kinetic model, will probably be more correct than that estimated by a one-compartment model in the previous study.

Enrofloxacin showed a significantly longer elimination half-life in Atlantic salmon than did the other quinolones. The reason for this longer elimination half-life is not known. However, significant differences in half-life between quinolones are also commonly obtained in humans (27) and domestic animals (30).

The MICs of oxolinic acid, flumequine, and sarafloxacin for susceptible strains of *Aeromonas salmonicida*, *Vibrio salmonicida*, *Vibrio anguillarum*, and *Yersinia ruckeri* have been reported to range from 0.005 to 0.5 μg/ml (for most strains, <0.1 μg/ml) (2, 21). The corresponding MICs of enrofloxacin have been reported to range from 0.001 to 0.1 μg/ml (for most strains, <0.05 μg/ml) (2, 21). The MICs of enrofloxacin for quinolone-resistant *A. salmonicida* strains have been reported to be 1.28 μg/ml or less, while the corresponding MICs of oxolinic acid, flumequine, and sarafloxacin have been reported to be up to 12.8, 8.0, and 5.12 μg/ml, respectively (21).

Blaser et al. (4) reported that bacterial regrowth occurred in vitro unless the peak concentration/MIC ratio exceeded 8:1 for the fluoroquinolone enoxacin. In this study, both flumequine and enrofloxacin exceed this peak concentration/MIC ratio in plasma at doses of 25 and 10 mg/kg, respectively. In addition, the peak enrofloxacin concentration also surpassed the highest MIC reported for quinolone-resistant strains of *A. salmonicida.*

In summary, this study showed that flumequine and, even more so, enrofloxacin have better, and sarafloxacin has poorer, pharmacokinetic properties in Atlantic salmon held in seawater than does oxolinic acid. Taking previously reported in vitro properties into account (2, 21), enrofloxacin appears to be even more promising for evaluation in clinical trials, compared with flumequine and oxolinic acid.

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