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# Penetration of Fleroxacin into Breast Milk and Pharmacokinetics in Lactating Women

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**Fleroxacin was administered to seven lactating women as a single oral dose of 400 mg. Plasma, urine, and milk samples were collected for up to 48 h after administration. Drug concentrations were determined by a reversed-phase high-pressure liquid chromatography method and were used for the pharmacokinetic evaluation. At approximately 2 h after oral administration, a maximum concentration of 5.6 mg/liter was determined in plasma; the area under the plasma concentration-time curve (AUC) amounted to 70.3 mg · h/liter, and the elimination half-life in the postdistributive phase was 8 h. Total systemic clearance was 97.3 ml/min, and urinary excretion was 38% of the dose within 48 h. In addition, 8.6% of the *N*-demethyl metabolite and 4.4% of the *N*-oxide metabolite were recovered from urine. In comparison with previous results obtained with healthy male volunteers, the time to reach maximum concentrations in plasma was twice as long in the nursing women, and total clearance as well as urinary elimination were reduced by 25%. In breast milk, the mean maximum concentration was 3.5 mg/liter, which was reached 2.6 h after drug administration. The elimination half-life of fleroxacin in milk was identical to that in plasma, and the AUC reached 43.3 mg · h/liter. On the basis of the comparison of the AUC in milk versus the AUC in plasma, the proportion of fleroxacin penetration into milk was 62%. The cumulative excretion in milk amounted to only 0.219 mg within 48 h. On the basis of an average daily intake of milk of a breast-fed child of 150 ml/kg of body weight, the maximum daily ingested fleroxacin dose would not exceed 10 mg. However, quinolones are known to induce arthropathy in juvenile animals, and therefore, administration of fleroxacin to breast-feeding women cannot be allowed.**

Arthropathy in juvenile animals has been observed after administration of all quinolones tested so far (2). Although the significance of this inadvertent finding for humans remains unclear, the toxic potential has led to the contraindication of quinolones in children and in women during pregnancy and lactation (18).

Despite the extensive use of fluoroquinolones, little is known about their excretion into human breast milk (7, 10, 13). More accurate data on the passage of these compounds into breast milk will allow for the establishment of better recommendations for their use in lactating women.

Fleroxacin is a newly developed trifluorinated quinolone that exhibits high in vitro activity against both gram-negative and gram-positive bacteria. Its favorable pharmacokinetic properties include complete absorption from the gastrointestinal tract when given orally, a long half-life, and rapid penetration into biological fluids, tissues, and cells (12, 16). The initial clinical studies have furnished promising results (14, 15).

In the study described here, we investigated the pharmacokinetics of fleroxacin in the plasma and breast milk of seven healthy nursing women who received a single oral dose of 400 mg.

## MATERIALS AND METHODS

Seven healthy women who had lactated for at least 2 days (2 to 5 days) and who were willing to abstain from breast-feeding for at least 48 h were recruited from the Obstetric Department of the E. Wolfson Hospital in Holon, Israel. The mean age of the subjects was 27 years (range, 22 to 35 years), and their mean weight was 75 kg (range, 68 to 82 kg). All women had normal renal and liver functions, and none had received antimicrobial agents within 48 h prior to entry into the study.

Upon entry into the study, a medical history was taken, and a physical examination was performed; the physical examination was repeated on day 3 after drug administration. Blood samples of 10 ml were collected for determination of laboratory values before and on day 3 after drug administration.

**Drug administration.** Two tablets of fleroxacin corresponding to 400 mg of active substance were taken as a single dose on an empty stomach.

**Sample collection.** Blood samples of 5 ml were collected in potassium-ammonium-oxalate Vacutainers before drug administration and at 30 min and 1, 2, 4, 6, 8, 12, 24, 36, and 48 h after dosing. Plasma was separated by centrifugation, transferred to glass tubes, and stored at −20°C until analysis. A predosing sample and all secreted milk in the intervals from 0 to 4, 4 to 8, 8 to 12, 12 to 24, and 24 to 48 h after drug administration were collected with an automatic pump. After the volumes were recorded and the pHs determined, aliquots of 10 ml were stored in glass tubes at −20°C. The complete urine volume was collected before dosing and following drug administration at intervals of 0 to 4, 4 to 8, 8 to 12, 12 to 24, and 24 to 48. After the volumes were recorded and the pHs determined, aliquots of 10 ml of urine were stored in glass tubes at −20°C.

Because fleroxacin is light sensitive, appropriate precaution was taken during sample collection and analysis by using brown glassware or protecting tubes from light by using aluminum foil.

**Assay procedure.** The fleroxacin concentrations in plasma, milk, and urine and the concentrations of the *N*-demethyl and *N*-oxide metabolites in urine were determined by a

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TABLE 1. Pharmacokinetic parameters of fleroxacin in plasma following oral administration of 400 mg[a]

| Subject no. | $t_{1/2}$ (h) | AUC (mg · h/liter) | $CL_S$ (ml/min) | $T_{max}$ (h) | $C_{max}$ (mg/liter) | $V_\beta$ (liter/kg) |
|---|---|---|---|---|---|---|
| 1 | 9.6 | 63.5 | 105.0 | 4.0 | 4.87 | 1.06 |
| 2 | 6.8 | 69.0 | 96.6 | 1.0 | 6.80 | 0.76 |
| 3 | 7.9 | 60.3 | 110.6 | 1.1 | 5.25 | 1.11 |
| 4 | 9.3 | 100.3 | 66.5 | 6.0 | 5.13 | 0.76 |
| 5 | 7.2 | 63.1 | 105.7 | 1.0 | 6.49 | 0.83 |
| 6 | 7.7 | 69.5 | 95.9 | 2.0 | 5.64 | 0.94 |
| 7 | 8.8 | 66.2 | 100.7 | 2.0 | 5.06 | 1.13 |
| Mean ± SD | 8.2[b] | 70.3 ± 13.6 | 97.3 ± 14.5 | 2.4 ± 1.9 | 5.61 ± 0.75 | 0.94 ± 0.16 |

[a] $t_{1/2}$, half-life; AUC, area under the concentration-time curve; $CL_S$, systemic clearance; $T_{max}$, time to maximum concentration in plasma; $C_{max}$, maximum concentration in plasma; $V_\beta$, volume of distribution by the β method.
[b] Harmonic mean.

reversed-phase high-pressure liquid chromatography (HPLC) method (6).

Aliquots of plasma were mixed with trichloroacetic acid, and the precipitated protein was subsequently removed by centrifugation. An aliquot of the supernatant was diluted with the mobile phase and chromatographed. Urine samples, to which pipemidic acid (internal standard) was added, were diluted with the mobile phase and chromatographed.

Milk, to which pipemidic acid and phosphate buffer were added, was extracted with a mixture of dichloromethane and isopropanol (7/3; vol/vol). After centrifugation and removal of the aqueous supernatant, an aliquot of the organic phase was transferred to a conical glass tube and evaporated to dryness under a stream of $N_2$. The dry residue was dissolved in the mobile phase, and *n*-hexane was added to remove the fat. After thorough mixing, centrifugation, and removal of the *n*-hexane, an aliquot of the aqueous phase was chromatographed. Recovery from milk was 79.9% (relative standard deviation, 6%) over the range of 0.02 to 5 mg/liter.

The HPLC system consisted of the following components: a Toyo Soda ODS-120T 5-μm column (250 by 4.6 mm), a Merck L 6000 pump (flow rate, 0.8 ml/min), a Merck/Hitachi F 1000 fluorescence spectrophotometer (excitation at 290 nm, emission at 450 nm), a Kontron MSI 6000 T autoinjector, and a Spectra Physics 4200 computing integrator. The mobile phase was a mixture of 5 mM tetrabutylammonium hydrogen sulfate (aqueous solution) and methanol (72/28; vol/vol).

In each analytical run, a number of quality control samples (spiked plasma, urine, or milk samples) covering the complete range of quantification were analyzed to ensure precision and reproducibility. The coefficient of variation for unchanged fleroxacin was 4% for the plasma samples (range, 0.02 to 10 mg/liter), 7% for the milk samples (range, 0.1 to 10 mg/liter), and ranged from 3 to 10% for the urine samples (range, 1 to 200 mg/liter. Recovery from plasma was 81% (relative standard deviation, 10%) over the range of 0.01 to 5 mg/liter.

**Pharmacokinetic evaluation.** The plasma and milk concentration-versus-time curves were plotted semilogarithmically for each subject, the terminal elimination was determined by nonlinear least-squares regression analysis by using a weighting factor of $1/y$. Peak concentrations in plasma and the times of their occurrence were read directly from the observed data. The area under the concentration-versus-time curve (AUC) for plasma ($AUC_{plasma}$) and milk ($AUC_{milk}$) was obtained by the trapezoidal rule method to the last datum point and was extrapolated to infinity ($AUC_{0-\infty}$).

The ratio $AUC_{milk}/AUC_{plasma}$ was taken as a measure of the percentage of penetration of fleroxacin into human breast milk. Other pharmacokinetic parameters were calculated by conventional methods (8). The total systemic clearance ($CL_{TS}$) was calculated by $CL_{TS}/F$ = dose/$AUC_{0-\infty}$, in which $F$ is the fraction of the administered dose absorbed unchanged. On the basis of previous experiments, $F$ can be assumed to be 1 (17).

Renal clearance ($CL_R$) was determined by the following equation: $CL_R = f_e \cdot CL_{TS}$, in which $f_e$ is the fraction of dose excreted with urine.

The pharmacokinetic parameter values are presented as means ± standard deviations. The average elimination half-life was calculated as an harmonic mean.

**Safety parameters.** Vital signs were recorded predose and daily for up to 3 days following fleroxacin administration. Laboratory tests for the evaluation of safety were performed at the baseline and on day 3 following drug administration. All adverse events that occurred during the study were recorded on the case report form.

The study protocol was approved by the E. Wolfson Hospital Ethical Committee.

## RESULTS

Following a single oral dose of 400 mg of fleroxacin, a mean maximum concentration of 5.6 mg/liter was determined in plasma after 2.4 h (Table 1). The mean plasma concentration-versus-time profile is shown in Fig. 1. The AUC was 70.3 mg · h/liter, and the elimination half-life in the postdistributive phase was 8.2 h. Total systemic clearance was 97.3 ml/min, and 51% of the dose was excreted in urine within 48 h: 38% as unchanged drug, 8.6% as the *N*-demethyl metabolite, and 4.4% as the *N*-oxide metabolite (Fig. 2). The volume of distribution amounted to approximately 1 liter/kg of body weight and reflects the good penetration of fleroxacin into body fluids and tissues (Table 1).

In urine, fleroxacin reached maximum levels of between 100 and 400 mg/liter (median, 142 mg/liter) within the first 12 h after administration.

In breast milk, a maximum fleroxacin concentration of 3.5 mg/liter was reached in general in the first sampling interval (0 to 4 h) (Fig. 1; Table 2). The elimination half-life of the drug in milk was identical to that in plasma (8 h), and the AUC amounted to 43.3 mg · h/liter. The AUC ratio $AUC_{milk}/AUC_{plasma}$ was 63% and indicated the extent of penetration of fleroxacin into breast milk. The cumulative excretion in breast milk reached only 0.219 mg within 48 h, which corresponded to 0.05% of the oral dose. Apparent total clearance from milk was 0.056 ml/min.

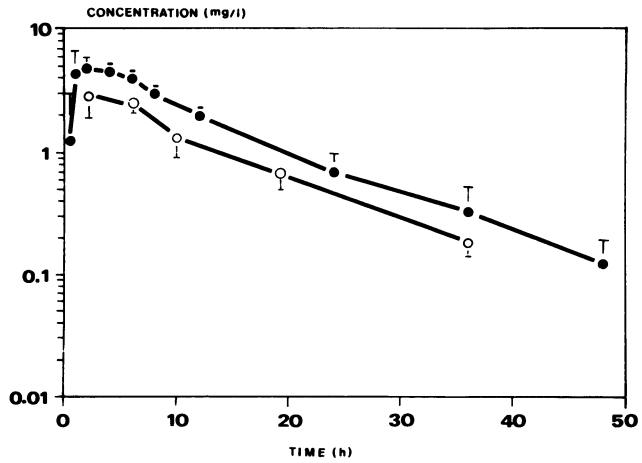


FIG. 1. Mean ± standard deviation fleroxacin concentration in plasma (●) and milk (○) versus time after a single 400-mg oral dose. Each point represents the mean of seven determinations, and the bars show standard errors.

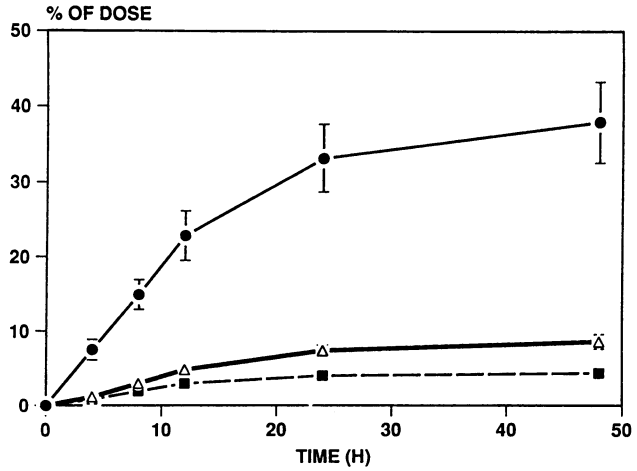


FIG. 2. Mean ± standard error cumulative urinary secretion of fleroxacin (●), *N*-demethylfleroxacin (△), and the *N*-oxide metabolite (■) versus time after a single 400-mg dose. Each point represents the means of seven determinations.

A single oral dose of 400 mg of fleroxacin was well tolerated in the present study. Headaches remotely or possibly related to the trial drug were reported by two subjects, but no other adverse events were reported. There was one potentially clinically relevant laboratory abnormality, thrombocytosis, that was considered to be remotely related to the trial medication. In another patient, slight elevations of liver enzymes were observed (108% of the upper limit of the normal value for alkaline phosphatase, 160% for serum glutamic oxalacetic transaminase, and 120% for serum glutamic pyruvic transaminase), and the elevations persisted for up to 13 days postadministration, when they were last tested.

## DISCUSSION

The extent of excretion of antimicrobial agents into breast milk depends mainly on the pH of the milk and plasma and the $pK_a$ of the drug (11). Most drugs enter the mammary alveolar cells in the nonionized, non-protein-bound form (1). Under normal conditions, the pH of breast milk, which averages 6.8 to 7.0, is lower than that of plasma (3). Thus, weakly basic antibiotics are less ionized in maternal plasma, and more nonionized molecules are available to pass from plasma into milk. Such agents tend to reach higher concentrations in breast milk and lower concentrations in maternal serum (9). Once inside the alveolar milk-secreting cells, antibiotics readily enter the milk, primarily by diffusion and occasionally by active transport or apocrine secretion. Lipid-soluble agents appear to reach higher peak levels in milk after shorter intervals than do the less lipid-soluble agents (3).

The high $pK_a$, lipid solubility, and low protein binding of the fluoroquinolones should predict increased excretion in breast milk. The penetrability of these agents into maternal milk has been incompletely investigated in only a few cases. Takase et al. (13) studied four lactating women who received a single subtherapeutic dose of norfloxacin (200 mg). The concentration of norfloxacin in the milk at 1 to 4 h after drug administration was <0.05 mg/liter. Muth et al. (10) measured ofloxacin concentrations in the milk of a breast-feeding woman 44 to 75 h after the completion of a 10-day course of 400 mg of fleroxacin per day. The levels of drug ranged between 0.034 and 0.006 mg/liter.

The present study is the first one to thoroughly investigate the pharmacokinetics of a fluoroquinolone in human breast milk. As predicted on the basis of the physicochemical properties of the drug (high $pK_a$, lipid solubility, and low protein binding), our data show a substantial penetration of

TABLE 2. Pharmacokinetic parameters of fleroxacin in milk following oral administration of 400 mg[a]

| Subject no. | $t_{1/2}$ (h) | AUC (mg · h/liter) | $CL_S$ (ml/min) | $T_{max}$ (h)[b] | $C_{max}$ (mg/liter)[c] |
|---|---|---|---|---|---|
| 1 | 7.50 | 45.5 | 0.114 | 2.0 | 4.50 |
| 2 | 8.97 | 42.7 | 0.055 | 2.0 | 3.64 |
| 3 | 7.97 | 48.8 | 0.080 | 2.0 | 3.62 |
| 4 | 8.79 | 46.2 | 0.026 | 2.0 | 2.91 |
| 5 | 8.94 | 39.4 | 0.049 | 6.0 | 2.60[d] |
| 6 | 7.18 | 43.2 | 0.022 | 2.0 | 3.92 |
| 7 | 8.73 | 37.3 | 0.048 | 2.0 | 3.17 |
| Mean ± SD | 8.24[e] | 43.3 ± 4.0 | 0.056 ± 0.032 | 2.6 ± 1.5 | 3.48 ± 0.64 |

[a] See footnote *a* of Table 1 for abbreviation definitions.
[b] Midpoint of sampling interval.
[c] Concentration in the sampling interval from 0 to 4 h.
[d] Sampling interval from 4 to 8 h.
[e] Harmonic mean.

fleroxacin into milk, with 63% penetrability on the basis of the AUC in milk in comparison with the AUC in plasma. On the basis of an average daily intake of milk of a breast-fed child (150 ml/kg of body weight), the daily fleroxacin intake was calculated. Within 48 h the mean cumulative amount excreted with milk was 0.219 mg (range, 0.086 to 0.445 mg). The milk volume secreted during that time ranged from 65 to 735 ml (median, 194 ml). These low and varying milk volumes can be regarded as normal during the first and second weeks postpartum until milk production is greater and steadier. The daily milk intake of an infant can be assumed to be 150 ml/kg of body weight (4), and in general, it might not exceed 1.5 to 2 liters/day. Taking the highest fleroxacin concentration determined in milk (4.5 mg/liter), the maximum daily dose ingested by a breast-fed infant would not exceed 10 mg. This corresponds to approximately 1 mg/kg of body weight, which is lower than the daily dose administered to adults (3 to 5 mg/kg).

Data on the pharmacokinetics of fleroxacin in plasma obtained in the present study were somewhat different from the data obtained previously in healthy volunteers (16). The time to reach the maximum concentration in plasma was twice as long in nursing women, and total clearance as well as the cumulative concentration in urine were reduced by approximately 25%. These differences might be related to an impaired bioavailability of fleroxacin ($F < 1$) and the reduced gastrointestinal motility, delayed gastric emptying, and increased volume of distribution observed during pregnancy (5) and probably in the immediate postpartum period.

We conclude that although drug intake through the mother's breast milk would be moderate for the infant, when the toxicological findings of arthropathy in juvenile animals are applied to humans, administration of the drug to breast-feeding women should not be allowed.

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