Steady-State Plasma and intrapulmonary Concentrations of Levofloxacin and Ciprofloxacin in Healthy Adult Subjects*

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Study objectives: To determine the steady-state plasma, epithelial lining fluid (ELF), and alveolar macrophage (AM) concentrations of levofloxacin and ciprofloxacin.

Design: Multiple-dose, open-label, randomized pharmacokinetic study.

Participants: Thirty-six healthy, nonsmoking adult subjects were randomized either to oral levofloxacin, 500 or 750 mg once daily for five doses, or ciprofloxacin, 500 mg q12h for nine doses.

Interventions: Venipuncture, bronchoscopy, and BAL were performed in each subject at 4 h, 12 h, or 14 h after the last administered dose of antibiotic.

Measurement and results: Mean plasma concentrations of levofloxacin and ciprofloxacin were similar to those previously reported. For once-daily dosing of levofloxacin, 500 mg, the mean (± SD) steady-state concentrations at 4 h, 12 h, and 24 h in ELF were 9.9 ± 3.7 µg/mL, 6.5 ± 2.5 µg/mL, and 0.7 ± 0.4 µg/mL, respectively; AM concentrations were 97.9 ± 80.0 µg/mL, 36.7 ± 23.4 µg/mL, and 13.8 ± 16.0 µg/mL, respectively. For levofloxacin, 750 mg, the mean steady-state concentrations in ELF were 22.1 ± 14.9 µg/mL, 9.3 ± 5.3 µg/mL, and 1.5 ± 0.8 µg/mL, respectively; AM concentrations were 105.1 ± 60.5 µg/mL, 36.2 ± 26.1 µg/mL, and 15.1 ± 2.0 µg/mL, respectively. The concentrations of ciprofloxacin at 4 h and 12 h in ELF were 1.9 ± 0.9 µg/mL and 0.4 ± 0.1 µg/mL, respectively; AM concentrations were 34.9 ± 23.2 µg/mL and 6.8 ± 5.9 µg/mL, respectively. The differences in the ELF concentrations of the two levofloxacin groups vs those of the ciprofloxacin group were significant (p < 0.05) at each sampling time.

Conclusions: Levofloxacin was more extensively distributed into intrapulmonary compartments than ciprofloxacin and achieved significantly higher steady-state concentrations in plasma and ELF during the 24 h after drug administration. (CHEST 2000; 118:1114-1122)

Keywords: ciprofloxacin, fluoroquinolones, levofloxacin, penetration, pharmacokinetics, respiratory tract infection.

Abbreviations: AM = alveolar macrophage; ANOVA = analysis of variance; BAL = aspirates recovered from the second, third, and fourth instillations that were pooled; ELF = epithelial lining fluid; HPCL = high-performance liquid chromatography; MIC90 = minimum inhibitory concentration that inhibits 90% of isolates; VBAL = volume of aspirated BAL fluid; VL = volume of ELF sampled by the BAL.

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F luoroquinolones have a broad spectrum of in vitro antimicrobial activity against the pathogens commonly associated with lower respiratory tract infections.1,2 Pivotal clinical trials have established the bacteriologic and clinical effectiveness of these agents for the treatment of community-acquired pneumonia and acute bacterial exacerbation of chronic bronchitis caused by susceptible strains of Streptococcus pneu-

miciae, Haemophilus influenzae, Moraxella catarrhalis, Chlamydia pneumoniae, Legionella pneumophila, and Mycoplasma pneumoniae.3-7 In addition, these agents are well tolerated and have an incidence of drug-related adverse effects similar to those of β-lactam agents such as ceftriaxone or cefuroxime axetil.8,9

Clinical Investigations
Levodopa and ciprofloxacin have demonstrated extensive penetration into lung tissues. The concentrations in lung tissue samples have been reported to be two to five times higher than serum or plasma concentrations. However, these studies used homogenized tissue samples that averaged the various concentrations within the different compartments (eg, extracellular and intracellular) of the lung. Epithelial lining fluid (ELF) and alveolar macrophages (AMs) have been advocated as important infection sites for common extracellular and intracellular pathogens, respectively. In addition, intrapulmonary and lung penetration studies of levofloxacin have been limited to a dose level of 500 mg.

The purpose of this study was to determine and compare the steady-state plasma, ELF, and AM concentrations of levofloxacin and ciprofloxacin in healthy, nonsmoking adult subjects who had undergone bronchoscopy and BAL. Because clinical trials are currently evaluating a once-daily treatment regimen of levofloxacin, 750 mg, for the treatment of nosocomial lower respiratory tract infections (James Kahn, MD, Ortho-McNeil Pharmaceuticals, personal communication; March 7, 2000), the determination of the intrapulmonary penetration of levofloxacin at this dose level also was performed.

**Materials and Methods**

**Study Design and Subjects**

This was a randomized, open-label, single-center study of levofloxacin (Ortho-McNeil Pharmaceutical, Inc; Bartonsville, NJ) and ciprofloxacin (Bayer Corporation; West Mogram, CT). Non-smoking, healthy adult subjects who were 18-58 years of age were considered to be eligible for this study. Nonsmoking was defined as an absence from cigarette smoking for the previous 12 months before enrollment into the study. All subjects must have met the inclusion and exclusion criteria, and had to undergo screening procedures that included a medical history, a physical examination, and an assessment of clinical laboratory parameters (eg, clinical chemistry, hematology, urinalysis, and pregnancy test [female subjects]). Subjects were randomized to receive 100% of their acceptable range of weight according to height and frame tables of the Metropolitan Life Insurance Company. Exposure criteria included the following: evidence of significant organ dysfunction, history of conditions affecting drug absorption, known hypersensitivity or intolerance to benzodiazepines, lidocaine, or fluoroquinolones, concurrent treatment with drugs that might interact with fluoroquinolones (eg, theophylline or asthmatics), and pregnancy or breast-feeding for women. Women of childbearing potential who were using effective means of contraception were allowed to participate. The study was approved by the institutional review board, and written informed consent was obtained from each subject before subject entry.

Subjects randomized to levofloxacin received one of the following two drug regimens: 500 mg (two 250-mg tablets) or 750 mg (three 250-mg tablets) once daily for a total of five oral doses. Subjects randomized to ciprofloxacin received nine oral doses administered as 500-mg tablets every 12 h. Subjects received verbal and written instructions regarding the dosing schedule of their medication and were contacted daily by telephone to monitor compliance and to assess any adverse events.

**Bronchoscopy and BAL**

Each subject underwent one standardized bronchoscopy and BAL procedure in the outpatient surgical facility at 4 h, 12 h, or 24 h after the administration of the last dose of the fluoroquinolone. The sampling times were selected to provide concentration-time data over the entire dosing interval of each drug being studied (ie, 12 h for ciprofloxacin and 24 h for levofloxacin). The 4-h sampling time was selected to represent the maximum (peak) intrapulmonary concentration, whereas the 12- and 24-h sampling times were chosen to represent the minimum (trough) concentrations for ciprofloxacin and levofloxacin, respectively. In order to facilitate the scheduling of bronchoscopy, subjects randomized to the 4-h or 24-h sampling times took their medications between 6:30 AM and 3 PM. The subjects randomized to the 12-h sampling time took their medication in the evening between 9 PM and 10:30 PM.

A 4% concentration of topical lidocaine was applied to the upper airway to prepare subjects for bronchoscopy. If needed, a 1% concentration of lidocaine was used in the lower airway. A fiberoptic bronchoscope (model F-10; Olympus America Inc; Melville, NY) was inserted into a subsegment of the middle lobe. The bronchoscope was in place for an average length of time of 6 min (range, 4 to 13 min). Four 50-ml aliquots of sterile 0.9% normal saline solution were instilled into the middle lobe, and each specimen was immediately aspirated and pooled. Each aliquot was collected in the first 50-ml instillation was collected separately and discarded because of significant contamination with cells from the proximal airway was reported.

The aspirate recovered from the second, third, and fourth instillations were pooled (BAL 2). The volume of BAL 2 was measured and recorded. A 4-ml aliquot was removed from the BAL 2 and immediately sent to the laboratory for cell count and differential count. The remaining volume of BAL 2 was immediately centrifuged at 400 g for 5 min. The supernatant and cells were separated and frozen at -70°C until the assays were performed. A single aliquot of supernatant was separated and frozen for the assay assay.

BP, heart rate, respiratory rate, and pulse were recorded before, at the end of, and 30 to 60 min after the end of the bronchoscopy procedure. A blood sample to determine drug and drug concentrations was obtained just before the scheduled bronchoscopy procedure and was kept on ice until centrifuged. Blood samples were centrifuged at 1,000 g for 10 min, and plasma was separated and stored at -70°C until the analyses were performed. A physical examination and assessment of clinical laboratory parameters (eg, clinical chemistry, hematology, and urinalysis) were repeated in all subjects after the end of the bronchoscopy procedure.

**Sample Preparation Procedures**

Plasma samples were ultrafiltrated (Amicon Centrifree, WR Grace & Co; Beverly, MA) based on a previously established protocol. A displacing reagent containing the internal standard (DNA gpyrase inhibitor, 0.57544; Abbott Laboratories; Abbott Park, IL) was used to remove the fluoroquinolone from the protein-binding sites. The displacing reagent consisted of a mixture of acetonitrilewater (30:70 vol/vol) containing 0.5%
sodium dodecyl sulfate and 0.057 M phosphate. The ultraltratrons were injected into a high-performance liquid chromatography (HPLC) column with elution using an isopropyl mobile phase.

The sample preparation procedures for BAL fluid and AMs were based on the detailed descriptions reported by Coutts et al. and Patel et al. For the cell sample assays, cells were resuspended to a total of 10^9 of their recovered BAL fluid volume with a potassium buffer saline solution (pH 8.0) and were carried through three freeze-thaw cycles. After the third cycle, samples were sonicated (VibraCell sonicator; Sonics and Materials, Inc.; Danbury, CT) at 50% power for 1 min. Microphase samples were extracted using the same procedure as that for plasma samples. BAL fluid samples were filtered through a 0.45-μm filter (type HV syringe filter; Niskin Millipore Ltd.; Yorkeata, Japan) before being injected into the HPLC system.

The prepared plasma, macrophase, and BAL fluid samples were stored at -20°C until thawed and analyzed. All samples were assayed within 6 months (range, 2 to 6 months) from the time of their collection.

Drug and Urea Assays

All drug and urea assays were performed at the Clinical Research Laboratory of the University of Illinois at Chicago College of Pharmacy. Concentrations of levofloxacin and ciprofloxacin were measured by a reversed-phase HPLC method based on the previously established procedure reported by Cunningham and Varja. A modification of the original assay procedure involved a change in the analytical column and mobile-phase composition. These modifications were made to shorten the analysis time and to apply the assay procedure to BAL fluid and AMs.

Briefly, the HPLC system consisted of an adventisilic column (model M510; Waters Associates; Milford, MA), an automated sample processor system (WISP model 712i; Waters Associates), and a programmable fluorescence detector (Spectroflow 980; Applied Biosystems; Foster City, CA). The mobile phase was a mixture of acetonitrile-water (42:58 v/v) containing 0.04 mM phosphoric acid, 0.01 mM NaH₂PO₄, 0.6% sodium dodecyl sulfate, and 0.005 mM Na₂EDTA-citric acid. The 3-μL samples were injected through a column (Symmetry C₁₈; Waters Associates; particle size, 5 μm; με, 3.9 ± 0.05 mm) at a flow rate of 1.5 mL/min at ambient temperature. Fluorescence detection was performed at wavelengths of 280 nm (excitation) and 300 nm (emission). The retention times for levofloxacin, ciprofloxacin, and A-75704 (internal standard) were 3.9 min, 4.3 min, and 10.4 min, respectively, with a total run time of 13 min.

The standard curves of plasma and BAL fluid for levofloxacin were linear (r² ≥ 0.99) in the range of concentrations from 8.98 to 5.340 μg/mL and 2.54 to 300 μg/mL, respectively. The intraday coefficients of variation for replicate plasma samples (n = 5) within these concentration ranges varied from 2.4 to 4.1% for plasma and 1.4 to 2.5% for BAL fluid. The interday coefficients of variation ranged from 1.8 to 2.5% for plasma and 1.3 to 2.5% for BAL fluid. The lower limit of detection was 8.0 ng/mL for plasma and 2.55 μg/mL for BAL fluid.

The standard curves of plasma and BAL fluid for ciprofloxacin were linear (r² ≥ 0.99) in the range of concentrations from 8.98 to 5.340 μg/mL and 2.60 to 41.2 μg/mL, respectively. The intraday coefficients of variation for replicate plasma samples (n = 5) within these concentration ranges varied from 0.8 to 2.3% for plasma and 1.9 to 2.7% for BAL fluid. The interday coefficients of variation ranged between 1.9% and 2.7% for plasma and between 2.6% and 4.3% for BAL fluid. The lower limit of detection was 9.0 ng/mL for plasma and 2.60 ng/mL for BAL fluid.

The standard curves for cell suspension were linear (r² ≥ 0.99) in the range of concentrations from 2.59 to 300 μg/mL, for levofloxacin and from 2.60 to 41.2 μg/mL, for ciprofloxacin. The intraday coefficients of variation for replicate cell suspension quality control samples (n = 5) within the concentration range of the standard curves varied from 3.1 to 6.9% for levofloxacin and 4.4 to 7.9% for ciprofloxacin. The interday coefficients of variation for cell suspensions varied from 5.1 to 7.7% for levofloxacin and from 3.6 to 9.2% for ciprofloxacin. The lower limit of detection for macrophase samples was 2.55 μg/mL for levofloxacin and 2.60 μg/mL for ciprofloxacin.

The concentrations of urine in plasma and BAL fluid were determined with a commercially available assay kit (Urea Nitro- gen Procedure No. 640; Sigma Diagnostics; St. Louis, MO) and were spectrophotometric (Spectronic 70; Benchmark and Lovich, Analytical Systems Division; Rochester, NY). The standard curve for plasma was prepared as recommended by the manufacturer and ranged from 1.0 to 7.50 mg/dL. For BAL fluid samples, a modification of the manufacturer's procedure was made, and standard curves were prepared in normal saline solution over a range of concentrations from 11.5 to 4.50 mg/dL. For both assays, standard curves were linear (r² ≥ 0.99), interday coefficients of variations were < 5%, and the relative accuracy ranged from 97.4 to 101.9%.

Calculations of ELF Volume and Aqueous Concentration in ELF and AMs

The calculations of ELF volume and aqueous concentration in ELF and AM were performed with fluid from BAL fluid. The concentration of fluorescein in the ELF (ABx_3,FL) was determined as follows:

\[ ABx_3,FL = ABx_3,MAX \times \frac{Y_{FL,ELF}}{Y_{FL,ELF}} \]

where ABx_3,MAX is the measured concentration of the antimicrobial agent in BAL fluid, Y_{FL,ELF} is the volume of aspirated BAL fluid, and Y_{FL,ELF} is the volume of ELF sampled by the BAL fluid, derived from the following:

\[ Y_{FL,ELF} = Y_{FL,AM} \times \frac{ABx_3,MAX}{ABx_3,MIN} \]

where ABx_3,MIN is the concentration of urine in BAL fluid and ABx_3,MAX is the concentration of urine in plasma.

The concentration of fluorescein in the AM (ABx_3,AM) was determined as follows:

\[ ABx_3,AM = \frac{ABx_3,ELF}{Y_{FL,ELF}} \]

where ABx_3,ELF, is the measured concentration of the antimicrobial agent in the 1-mL cell suspension, and Y_{FL,ELF}, is the volume of abscise cells in the 1-mL cell suspension. A differential cell count was performed to determine the number of macrophages and monocytes present. A mean macrophage cell volume of 2.45 μL/10⁶ cells was used in the calculations for volume of abscise cells in the pellet suspension.

Statistical Analysis

All data analyses were performed using a statistical software package (PC SAS, version 6; SAS Institute Cary, NC). Tests for the normality and equality of variances were performed with Shapiro-Wilk's test for normality, respectively. Analysis of variance (ANOVA) methods were used to access significant differences among the three stress groups using computer software (SAS-
Table 1—Characteristics of 36 Study Subjects*  

<table>
<thead>
<tr>
<th>Drug Region (n = 12)</th>
<th>Sex</th>
<th>Age, yr</th>
<th>Height, inches</th>
<th>Weight, kg</th>
<th>Total Cell Count in BAL Fluid, cells</th>
<th>Monocytes/Macrophages, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levofloxacin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>500 mg</td>
<td>F</td>
<td>31.5 ± 8.1</td>
<td>65.7 ± 5.5</td>
<td>70.3 ± 16.7</td>
<td>1.04 × 10^6 ± 0.65 × 10^6</td>
<td>69.8 ± 19.1</td>
</tr>
<tr>
<td>750 mg</td>
<td>M</td>
<td>28.9 ± 9.0</td>
<td>66.3 ± 4.0</td>
<td>68.7 ± 13.4</td>
<td>1.04 × 10^6 ± 0.41 × 10^6</td>
<td>78.8 ± 16.5</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td></td>
<td>31.2 ± 6.7</td>
<td>66.6 ± 3.6</td>
<td>77.3 ± 12.5</td>
<td>1.34 × 10^6 ± 0.91 × 10^6</td>
<td>71.3 ± 12.9</td>
</tr>
<tr>
<td>500 mg</td>
<td></td>
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</table>

*F = Female; M = Male. Data are expressed as mean ± SD, unless otherwise indicated. The differences in patient characteristics were not significant (p > 0.05) among the three drug regimens.

PROC GLM, SAS Institute. The nonparametric analog to the standard parametric ANOVA was also used. This method involved ranking the data first (SAS-PROC RANKS, SAS Institute) and then using the ranked data as the response in the ANOVA model. For patient demographic and laboratory characteristics, parametric and nonparametric comparisons were performed by the Newman-Keuls (all pairwise) and Kruskal-Wallis (unbalanced data) tests, respectively. Fisher’s Exact Test was used to evaluate the patient variable of sex. For comparisons of drug concentrations, parametric and nonparametric testing were performed with the Newman-Keuls (all pairwise) test. Significance was determined at the p < 0.05 level.

RESULTS

Thirty-six healthy, nonsmoking adult subjects (14 men and 22 women) ranging in age from 21 to 45 years completed the study (Table 1). Compliance with medication schedules was confirmed in all subjects. One subject experienced mild-to-moderate anxiety before the bronchoscopy procedure for which a single dose of midazolam was administered. Renal function tests were within the normal range for all subjects during the pretest and poststudy laboratory tests. One subject had elevated liver transaminase levels (aspartate aminotransferase, 49 U/L; alanine aminotransferase, 78 U/L) during the poststudy evaluation, but these levels returned to baseline values (≤ 35 U/L) within 1 week.

Levofloxacin and ciprofloxacin were well tolerated, and no serious drug-related adverse effects were reported. Twelve subjects (4 subjects from each group) experienced one or more mild adverse effects. These effects included nausea (n = 2), insomnia (n = 2), and loose stools (n = 2) in the levofloxacin, 500 mg, group. Subjects receiving levo-

![Graph](https://via.placeholder.com/150)

FIGURE 1. Individual steady-state concentrations of levofloxacin and ciprofloxacin in plasma at 4, 12, and 24 h after the administration of the last dose. The y axis is on the log scale. The dotted lines are representative for minimum inhibitory concentration (MIC) values of 0.0625 μg/ml (eg. H influenzae or M catarrhalis) and 1.0 μg/ml (eg. S pneumoniae).
floucin, 750 mg, reported nausea (n = 2), shakiness (n = 2), insomnia (n = 1), dizziness (n = 1), and abdominal cramps (n = 1). For the ciprofloxacin, 500 mg, group, adverse effects comprised insomnia (n = 1), gastric upset (n = 1), taste perversion (n = 1), and drowsiness (n = 1). Seventeen of the 36 subjects (47%) were observed to have transient cracks or chest during chest examinations after the bronchoscopy procedure.

The (mean ± SD) numbers of cells recovered in the BAL 2 were 1.04 × 10^7 ± 0.65 × 10^7 cells/L in the levofloxacin, 500 mg, group, 1.04 × 10^8 ± 0.41 × 10^8 cells/L in the levofloxacin, 750 mg, group, and 1.34 × 10^8 ± 0.91 × 10^8 cells/L in the ciprofloxacin group (Table 1). The (mean ± SD) percentage of cells that were classified as monocytes and macrophages were 69.8 ± 18.9 in the levofloxacin, 500 mg, group, 71.8 ± 10.5 in the levofloxacin, 750 mg, group, and 71.3 ± 12.9 in the ciprofloxacin group.

All four subjects within each sampling period had detectable steady-state plasma concentrations of levofloxacin and ciprofloxacin at the time of bronchoscopy (Fig. 1). At 4 h and 12 h, the steady-state plasma concentrations of levofloxacin, 500 mg, were significantly (p < 0.05) higher than that of ciprofloxacin, 500 mg (Table 2), by 2.5 times and 5.6 times, respectively. The mean plasma concentrations of levofloxacin, 750 mg, were 1.3 to 2.8 times higher than that of levofloxacin, 500 mg. The 4-h plasma concentrations of levofloxacin, 750 mg, were significantly (p < 0.05) higher than those for levofloxacin, 500 mg.

The concentrations of levofloxacin and ciprofloxacin in ELF are displayed in Figure 2. The ELF concentrations of levofloxacin, 500 mg, and levofloxacin, 750 mg, were significantly (p < 0.05) greater than that of ciprofloxacin, 500 mg (Table 2). Similar to plasma, the mean ELF concentrations of levofloxacin, 750 mg, were 1.2 to 2.3 times higher than those for levofloxacin, 500 mg. The 24-h ELF concentrations of levofloxacin, 750 mg, were significantly (p < 0.05) higher than those for levofloxacin, 500 mg. The mean ratio of ELF to plasma concentrations during the 4-h and 12-h sampling periods ranged from 1.8 to 2.3 for levofloxacin and 0.77 to 0.87 for ciprofloxacin. The mean ELF to plasma ratio at the 24-h sampling period was approximately 1.1 for both treatment regimens of levofloxacin.

The concentrations of levofloxacin and ciprofloxacin in AMs are illustrated in Figure 3. The concentrations in AMs among the three drug regimens were significantly (p < 0.05) greater than concurrent plasma and ELF concentrations at the 4-h and 12-h sampling times (Table 2). The AM concentrations for

| Table 2: Concentrations of Levofloxacin and Ciprofloxacin in Plasma, ELF, and AMs^* |
|-----------------|------------------|------------------|------------------|
|                  | Levofloxacin     | Ciprofloxacin    |
|                  | 500 mg           | 750 mg           |
|                  | ELF              | AM               |
| Sampling (h)     | Levofloxacin     | Ciprofloxacin    |
| 0.5             | 0.2            | 0.2             |
| 4               | 0.5            | 0.2             |
| 12              | 0.5            | 0.2             |
| 24              | 0.5            | 0.2             |

*Data are expressed as mean ± SD. Differences in levofloxacin, 750 mg, and ciprofloxacin, 500 mg, levels were significant (p < 0.05) during the sampling times of the same body fluid.

Clinical Investigations
the two levofloxacin treatment regimens were not significantly different (p > 0.05).

DISCUSSION
Adequate penetration of fluoroquinolones into intrapulmonary regions is important because these agents are commonly recommended as treatment for lower respiratory tract infections.1,41 This is the first study to report the steady-state concentrations of levofloxacin and ciprofloxacin in ELF and AMs after multiple oral doses. The previous studies of levo-
floxacin and ciprofloxacin11-15,36 limited their investi-

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**Figure 2.** Individual steady-state concentrations of levofloxacin and ciprofloxacin in ELF at 4 h, 12 h, and 24 h after the administration of the last dose. The y-axis is in the log scale. The dotted lines are representative for minimum inhibitory concentration values of 0.0625 μg/ml (eg, H influenzae or M catarrhalis) and 1.0 μg/ml (eg, S pneumoniae). See the legend of Figure 1 for abbreviations not used in the text.

**Figure 3.** Individual steady-state concentrations of levofloxacin and ciprofloxacin in AMs at 4 h, 12 h, and 24 h after the administration of the last dose. The y-axis is in the log scale.
tigations to a single dose of 500 mg. In addition, a few reports have determined steady-state concentrations of ciprofloxacin in ELF and AM after multiple oral doses of 250 mg every 12 h.

In our study, the ELF concentrations of levofloxacin, 500 mg, were approximately twofold higher than concurrent plasma concentrations at the 4-h and 12-h sampling periods. These results are similar to ELF samples obtained between 1 h and 8 h after a single dose of levofloxacin, 500 mg, in patients undergoing fiberoptic bronchoscopy. However, Andrews et al observed that ELF samples between 12 h and 24 h after a single-dose administration were below the quantitative limits of detection in almost all subjects. This is in contrast to our study in which ELF concentrations of levofloxacin at 24 h were approximately the same magnitude (mean, 0.7 μg/mL) as concurrent plasma concentrations. Our findings suggest that the accumulation of levofloxacin in the ELF approaches that of plasma concentrations after multiple doses.

The detection of ciprofloxacin in the ELF also suggests that concentrations are increased after multiple doses. Schuler et al studied the single-dose intrapulmonary pharmacokinetics of ciprofloxacin, 500 mg, in 15 patients undergoing diagnostic bronchoscopy and BAL. The median concentrations in the ELF and plasma at 2.5 h were 2.1 μg/mL and 2.3 μg/mL, respectively. However, ELF concentrations at 5 h and 12 h were below the quantitative limits of detection despite the fact that median plasma concentrations of ciprofloxacin were reported as 1.13 μg/mL and 0.43 μg/mL, respectively. Conte et al also were unable to detect ELF concentrations between 6 h and 24 h after a single dose of ciprofloxacin, 500 mg. These single-dose studies are in contrast to the observations obtained in the steady state. Baldwin et al observed measurable ELF concentrations between 3 h and 6 h after the administration of a twice-daily dosing regimen of ciprofloxacin, 250 mg. In our study, ciprofloxacin concentrations were detectable in the ELF up to 12 h after multiple doses of 500 mg (Fig 2).

The ratio of peak concentration to minimum inhibitory concentration has been suggested as one of the predictive pharmacodynamic parameters for the bacteriologic and clinical responses of fluoroquinolones. The steady-state concentrations of ciprofloxacin in plasma and ELF were less than those for levofloxacin despite the dose being 500 mg for both agents. In addition, the concentrations of levofloxacin at the site of lower respiratory tract infections were higher than those in plasma. This is in direct contrast to our observations with ciprofloxacin in which the concentrations in ELF were lower than those in plasma. The superior drug concentra-

The one-dose dosing regimen of oral levofloxacin, 750 mg, is currently being investigated in clinical trials for safety and efficacy. Pharmacokinetic studies for single and multiple once-daily oral doses of levofloxacin, 750 mg, have been reported in healthy volunteers and HIV-infected patients. Our study is the first report to assess the intrapulmonary penetration of levofloxacin at the once-daily dose of 750 mg (Table 2). The observed higher plasma and ELF concentrations with levofloxacin, 750 mg, may be beneficial in maintaining and/or increasing the ratio of peak concentrations to minimum inhibitory concentrations against extracellular pathogens associated with higher than usual minimum inhibitory concentrations. However, an increase in the daily dose of levofloxacin from 500 to 750 mg did not significantly (p > 0.05) increase drug concentrations in AMs (Fig 3). This lack of increase in AM drug concentrations is not clinically significant because extremely high intracellular concentrations already are achieved with either dosing regimen in the ELF concentrations of levofloxacin were similar or higher than those in plasma, whereas the ELF concentrations of ciprofloxacin were lower than those in plasma. Levofloxacin and ciprofloxacin achieved significantly higher steady-state concentrations in AMs compared to simultaneous plasma and ELF concentrations throughout the 12-h period after drug administration. The once-daily treatment regimen of levofloxacin, 500 mg and 750 mg, produced AM concentrations that were not significantly different. The observed higher plasma and ELF concentrations with levofloxacin, 750 mg, may be beneficial against extracellular pathogens associated with a higher than usual minimum inhibitory concentration value. Further clinical studies are needed to assess the efficacy of this higher treatment regimen of levofloxacin, 750 mg, in the treatment of lower respiratory tract infections.

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