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

Mark H. Gotfried, MD, FCCP; Larry H. Danziger, PharmD; and Keith A. Rodvold, PharmD

Study objective: 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 24 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 ($\pm$ SD) steady-state concentrations at 4 h, 12 h, and 24 h in ELF were 9.9 ± 2.7 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, 9.2 ± 5.3 µg/mL, and 1.5 ± 0.8 µg/mL, respectively; AM concentrations were 105.1 ± 65.5 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 2001; 119:1114–1122)*

Key words: ciprofloxacin; fluoroquinolone; levofloxacin; penetration; pharmacokinetics; respiratory tract infection

Abbreviations: AM = alveolar macrophage; ANOVA = analysis of variance; BAL 2 = aspirates recovered from the second, third, and fourth instillations that were pooled; ELF = epithelial lining fluid; HPLC = high-performance liquid chromatography; MIC_{90} = minimum inhibitory concentration that inhibits 90% of isolates; V_{BAL} = volume of aspired BAL fluid; V_{ELF} = volume of ELF sampled by the BAL

Fluoroquinolones 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 pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydia pneumoniae*, *Legionella pneumophila*, and *Mycoplasma pneumoniae*.[1-7] 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]

Levofloxacin and ciprofloxacin have demonstrated extensive penetration into lung tissues.[10] The concentrations in lung tissue samples have been reported to be two to five times higher than serum or plasma concentrations.[11-27] However, these studies used homogenized tissue samples that averaged the various concentrations within the different compartments (eg, extravascular 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.[10,28-34] Thus far, a limited number of single-dose studies have evaluated the penetration of levofloxacin and ciprofloxacin in ELF and AMs.[10,11,35,36] In addition, intrapulmonary and lung penetration studies of levofloxacin have been limited to a dose level of 500 mg.[11,22]

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; Raritan, NJ) and ciprofloxacin (Bayer Corporation; West Morgan, CT). Nonsmoking, healthy adult subjects who were ≥ 18 years of age were considered to be eligible for this study. Nonsmoking was defined as an abstinence 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 only]). Subjects were required to be within 10% of their acceptable range of weight according to height and frame tables of the Metropolitan Life Insurance Company.[37] Exclusion criteria included the following: evidence of significant organ dysfunction; history of conditions affecting drug absorption; known hypersensitivity or intolerance to benzodiazepines, lidocaine, or fluoroquinolones; concomitant treatment with drugs that might interact with fluoroquinolones (eg, theophylline or antacids); 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 study 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-h 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 medication 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 P-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 8 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 placed in ice. The aspirate from the first 50-mL instillation was collected separately and discarded because a significant contamination with cells from the proximal airways was reported.[28,32,35,38,39] The aspirates 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 400g 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 urea 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 urea concentrations was obtained just before the scheduled bronchoscopy procedure and was kept on ice until centrifuged. Blood samples were centrifuged at 1,000g for 10 min, and plasma was separated and stored at −70°C until the assay was performed. A physical examination and an 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 ultrafiltered (Amicon Centrifree; WR Grace & Co; Beverly, MA) based on a previously established procedure.[40] A displacing reagent containing the internal standard (DNA gyrase inhibitor A-57084; Abbott Laboratories; Abbott Park, IL) was used to remove the fluoroquinolone from the protein binding site. The displacing reagent consisted of a mixture of acetonitrile/water (30:70 vol/vol) containing 0.5%

sodium dodecyl sulfate and 0.075 mol/L phosphate. The ultrafiltrates were injected into a high-performance liquid chromatography (HPLC) column with elution using an ion-pair mobile phase.

The sample preparation procedures for BAL fluid and AMs were based on the detailed descriptions reported by Conte et al[35] and Patel et al.[39] For the cell sample assay, cells were resuspended to a total of 10% 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 2 min. Macrophage samples were extracted using the same procedure as that for plasma samples. BAL fluid samples were filtrated through a 0.45-μm filter (type HV syringe filters; Nihon Millipore Ltd; Yonezawa, Japan) before being injected into the HPLC system.

The prepared plasma, macrophage, and BAL 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 reverse-phase HPLC method based on the previously established procedure reported by Granneman and Varga.[40] Modifications 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 a solvent delivery system (model M510; Waters Associates; Milford, MA), an automated sample processor system (WISP model 712; 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 vol/vol) containing 0.04 mol/L phosphoric acid, 0.01 mol/L NaH_2PO_4, 0.4% sodium dodecyl sulfate, and 0.005 mol/L N-acetohydroxamic acid. Prepared samples were pumped through a column (Symmetry C_{18}; Waters Associates) [particle size, 5 μm; size, 3.9 × 150 mm] at a flow rate of 1.5 mL/min at room temperature. Fluorescence detection was performed at wavelengths of 280 nm (excitation) and 389 nm (emission). The retention times for levofloxacin, ciprofloxacin, and A-57084 (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 ($r^2 \geq 0.99$) in the range of concentrations from 8.84 to 5,430 ng/mL and 2.58 to 300 ng/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 8.90 ng/mL for plasma and 2.55 ng/mL for BAL fluid.

The standard curves of plasma and BAL fluid for ciprofloxacin were linear ($r^2 \geq 0.99$) in the range of concentrations from 8.68 to 5,360 ng/mL and 2.60 to 41.2 ng/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 1.5% and 2.7% for plasma and between 2.6% and 4.3% for BAL fluid. The lower limit of detection was 8.90 ng/mL for plasma and 2.60 ng/mL for BAL fluid.

The standard curves for cell suspension were linear ($r^2 \geq 0.99$) in the range of concentrations from 2.58 to 300 ng/mL for levofloxacin and from 2.60 to 41.2 ng/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 6.8% for levofloxacin and 4.4 to 7.9% for ciprofloxacin. The interday coefficients of variation for cell suspensions varied from 7.1 to 7.7% for levofloxacin and from 3.6 to 9.2% for ciprofloxacin. The lower limit of detection for macrophage samples was 2.55 ng/mL for levofloxacin and 2.60 ng/mL for ciprofloxacin.

The concentrations of urea in plasma and BAL fluid were determined with a commercially available assay kit (Urea Nitrogen Procedure No. 640; Sigma Diagnostics; St. Louis, MO) and were measured on a spectrophotometer (Spectronic 70; Bausch and Lomb, Analytical Systems Division; Rochester, NY). The standard curve for plasma was prepared as recommended by the manufacturer and ranged from 1.50 to 7.50 mg/dL. For BAL fluid samples, a modification in the manufacturer's procedure was made, and standard curves were prepared in normal saline solution over a range of concentrations from 0.113 to 4.50 mg/dL. For both assays, standard curves were linear ($r^2 \geq 0.99$), interday coefficients of variations were < 5%, and the relative accuracy ranged from 97.4 to 101.8%.

Calculations of ELF Volume and Antibiotic Concentrations in ELF and AMs

The calculations of ELF volume and fluoroquinolone concentrations in ELF and AM were performed with fluid from BAL 2,[28,32,35,38,39] The concentration of fluoroquinolone in the ELF (ABX_{ELF}) was determined as follows:

$$ABX_{ELF} = ABX_{BAL} \times \frac{V_{BAL}}{V_{ELF}}$$

where ABX_{BAL} is the measured concentration of the antimicrobial agent in BAL fluid, V_{BAL} is the volume of aspirated BAL fluid, and V_{ELF} is the volume of ELF sampled by the BAL. V_{ELF} is derived from the following:

$$V_{ELF} = V_{BAL} \times \frac{urea_{BAL}}{urea_{SER}}$$

where $urea_{BAL}$ is the concentration of urea in BAL fluid and $urea_{SER}$ is the concentration of urea in plasma.

The concentration of fluoroquinolone in the AM (ABX_{AM}) was determined as follows:

$$ABX_{AM} = \frac{ABX_{PELLET}}{V_{AC}}$$

where ABX_{PELLET} is the measured concentration of the antimicrobial agent in the 1-mL cell suspension and V_{AC} is the volume of alveolar 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 2.42 μL/10^6 cells was used in the calculations for volume of alveolar cells in the pellet suspension.[10,38]

Statistical Analysis

All data analyses were performed using a statistical software package (PC SAS, version 8.0; SAS Institute; Cary, NC). Tests for the normality and equality of variances were performed with Shapiro-Wilks and Levene tests, respectively. Analysis of variance (ANOVA) methods were used to assess significant differences among the three study groups using computer software (SAS-

Table 1—*Characteristics of 36 Study Subjects**

Drug Regimen (n = 12)	Age, yr	Sex		Height, inches	Weight, kg	Total Cell Count in BAL Fluid, cells/L	Monocytes/Macrophages, %
		F	M				
Levofloxacin							
500 mg	31.5 ± 8.1	8	4	65.7 ± 5.5	70.3 ± 16.7	$1.04 \times 10^8 \pm 0.65 \times 10^8$	69.8 ± 19.1
750 mg	28.9 ± 8.0	8	4	66.3 ± 4.0	68.7 ± 13.4	$1.04 \times 10^8 \pm 0.41 \times 10^8$	71.8 ± 10.5
Ciprofloxacin 500 mg	31.2 ± 6.7	6	6	66.6 ± 3.6	77.3 ± 12.5	$1.34 \times 10^8 \pm 0.91 \times 10^8$	71.3 ± 12.9

*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 also was used. This method involved ranking the data first (SAS-PROC RANK; 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 (unblocked 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 48 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 prestudy 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 ($\leq$ 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-
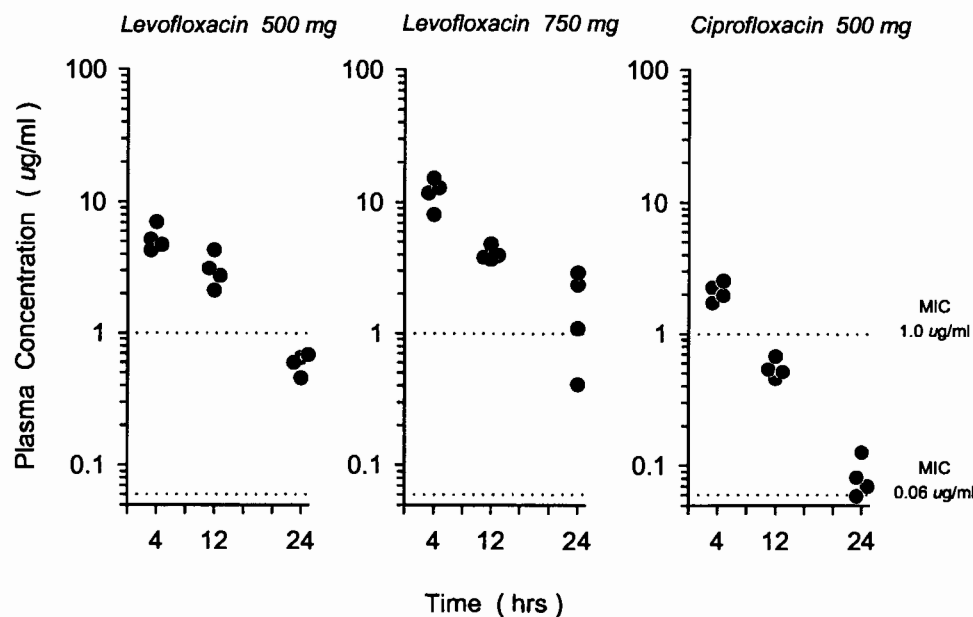

FIGURE 1. Individual steady-state concentrations of levofloxacin and ciprofloxacin in plasma at 4 h, 12 h, and 24 h after the administration of the last dose. The y-axis is in the log scale. The dotted lines are representative for minimum inhibitory concentration (MIC) values of 0.0625 μg/mL (eg, *H influenzae* or *M catarrhalis*) and 1.0 μg/mL (eg, *S pneumoniae*).

floxacin, 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 crackles or rhonchi during chest examinations after the bronchoscopy procedure.

The (mean ± SD) numbers of cells recovered in the BAL 2 were $1.04 \times 10^8 \pm 0.65 \times 10^8$ cells/L in the levofloxacin, 500 mg, group; $1.04 \times 10^8 \pm 0.41 \times 10^8$ cells/L in the levofloxacin, 750 mg, group; and $1.34 \times 10^8 \pm 0.91 \times 10^8$ cells/L in the ciprofloxacin group (Table 1). The (mean ± SD) percentage of cells that were classified as monocytes and macrophages were 69.8 ± 19.1 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*

Sampling Time (n = 4)	Plasma, µg/mL			ELF, µg/mL			AMs, µg/mL		
	Levofloxacin 500 mg	Levofloxacin 750 mg	Ciprofloxacin 500 mg	Levofloxacin 500 mg	Levofloxacin 750 mg	Ciprofloxacin 500 mg	Levofloxacin 500 mg	Levofloxacin 750 mg	Ciprofloxacin 500 mg
4 h	5.29 ± 1.23†	11.98 ± 2.99†§	2.11 ± 0.35	9.94 ± 2.74†**	22.12 ± 14.92†	1.87 ± 0.91	97.9 ± 80.0‖¶#	105.1 ± 65.5¶#	34.9 ± 23.2¶#
12 h	3.07 ± 0.93†	4.06 ± 0.51†	0.55 ± 0.09	6.46 ± 2.48†**	9.17 ± 5.34†	0.41 ± 0.10	36.7 ± 23.4†¶#	36.2 ± 26.1¶#	6.8 ± 5.9‖¶#
24 h	0.60 ± 0.10†	1.69 ± 1.14†	0.08 ± 0.03	0.70 ± 0.40†	1.45 ± 0.75†§	0.0**††	13.8 ± 16.0‖¶#	15.1 ± 2.0¶#	2.3 ± 2.8‖††#

*Data are expressed as mean ± SD.
†Differences in levofloxacin, 500 mg, and ciprofloxacin, 500 mg, were significant ($p < 0.05$) during this sampling time ($p < 0.05$) during this sampling time of the same body fluid.
‡Differences in levofloxacin, 750 mg, and ciprofloxacin, 500 mg, were significant ($p < 0.05$) during this sampling time of the same body fluid.
§Differences in levofloxacin, 750 mg, and levofloxacin, 500 mg, were significant ($p < 0.05$) during this sampling time of the same body fluid.
‖Three of four subjects had adequate samples available for drug assay.
¶Differences in AMs and plasma were significant ($p < 0.05$) during this sampling time for the same drug regimen.
#Differences in AMs and ELF were significant ($p < 0.05$) during this sampling time for the same drug regimen.
**Differences in ELF and plasma were significant ($p < 0.05$) during this sampling time for the same drug regimen.
††None of four subjects had concentrations equal to or above the quantitative limit of detection.
‡‡Three of four subjects had concentrations equal to or above the quantitative limit of detection.
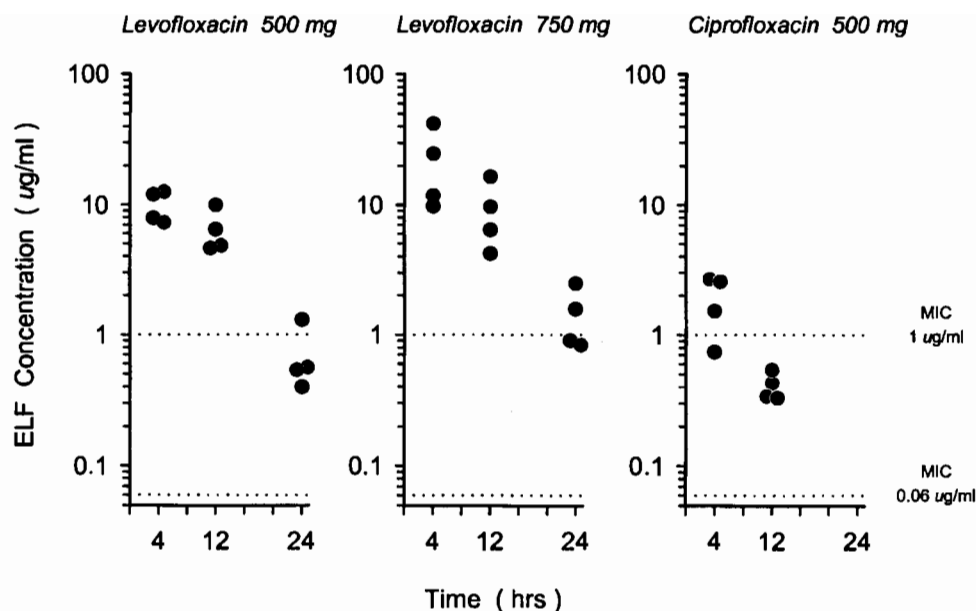
FIGURE 2. Individual steady-state concentrations of levofloxacin and ciprofloxacin in ELF at 4 h, 12 h, and 24 h after the administration of the last dose. The *y*-axis is in the log scale. The dotted lines are representative for minimum inhibitory concentration values of 0.0625 μg/mL (*eg, H influenzae* or *M catarrhalis*) and 1.0 μg/mL (*eg, S pneumoniae*). See the legend of Figure 1 for abbreviations not used in the text.

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 levofloxacin and ciprofloxacin[11,35,36] limited their inves-
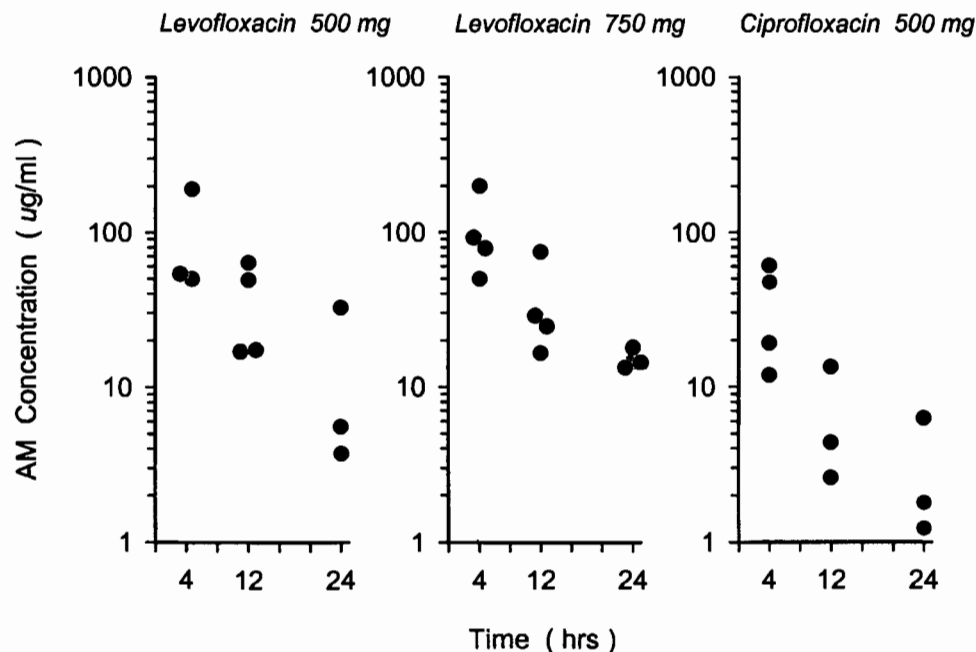

FIGURE 3. Individual steady-state concentrations of levofloxacin and ciprofloxacin in AMs at 4 h, 12 h, and 24 h after the administration of the last dose. The *y*-axis is in the log scale.

tigations to a single dose of 500 mg. In addition, a few reports[34,42,43] 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.[11] However, Andrews et al[11] 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[36] 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 2.33 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[35] 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[34] 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.[44,45] 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-

tions of levofloxacin in plasma and ELF are important for the treatment of extracellular pathogens such as S pneumoniae. The higher drug concentrations of levofloxacin allow the optimization of pharmacodynamic parameters in plasma and ELF because the minimum inhibitory concentrations that inhibit 90% of isolates (MIC_{90}) of S pneumoniae are similar to those for ciprofloxacin (MIC_{90}, 1 to 2 μg/mL) and levofloxacin (MIC_{90}, 1 μg/mL).[46,47]

The once-daily 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.[48,49] 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 treatment regimen of levofloxacin.

In summary, the steady-state plasma and ELF concentrations of levofloxacin, 500 mg and 750 mg, were significantly higher than that for ciprofloxacin, 500 mg, during the entire 24-h study time period. The mean 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 regimens 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.

References

1 Bartlett JG, Breiman RF, Mandell LA, et al. Community-acquired pneumonia in adults: guidelines for management. Clin Infect Dis 1998; 26:811–838

2 Pryka R, Kowalsky S, Haverstock D. Efficacy and tolerability of twice-daily ciprofloxacin 750 mg in the treatment of patients with acute exacerbations of chronic bronchitis and pneumonia. Clin Ther 1998; 20:141–155

3 DeAbate CA, Russell M, McElvaine P, et al. Safety and efficacy of oral levofloxacin versus cefuroxime axetil in acute bacterial exacerbations of chronic bronchitis. Respir Care 1997; 42:206–213

4 File TM, Segreti J, Dunbar L, et al. A multicenter, randomized study comparing the efficacy and safety of intravenous and/or oral levofloxacin versus ceftriaxone and/or cefuroxime axetil in treatment of adults with community-acquired pneumonia. Antimicrob Agents Chemother 1997; 41:1965–1972

5 Fogarty CM, Sullivan JG, Chattman MS, et al. Once a day levofloxacin in the treatment of mild to moderate and severe community-acquired pneumonia in adults. Infect Dis Clin Pract 1998; 7:400–407

6 Habib MP, Gentry LO, Rodriguez-Gomez G, et al. Multicenter, randomized study comparing efficacy and safety of oral levofloxacin and cefaclor in treatment of acute bacterial exacerbations of chronic bronchitis. Infect Dis Clin Pract 1998; 7:101–109

7 Shah PM, Maesen FPV, Domann A, et al. Levofloxacin versus cefuroxime axetil in the treatment of acute exacerbation of chronic bronchitis: results of a randomized, double-blind study. J Antimicrob Chemother 1999; 43:529–539

8 Lipsky BA, Baker CA. Fluoroquinolone toxicity profile: a review focusing on newer agents. Clin Infect Dis 1999; 28:352–364

9 Rodvold KA. Clinical safety profile of newer fluoroquinolones. J Crit Illness 1999; 14(suppl):S28–S40

10 Nix DE. Intrapulmonary concentrations of antimicrobial agents. Infect Dis Clin North Am 1998; 12:631–646

11 Andrews JM, Honeybourne D, Jevons G, et al. Concentrations of levofloxacin (HR 355) in the respiratory tract after a single oral dose in patients undergoing fiber-optic bronchoscopy. J Antimicrob Chemother 1997; 40:573–577

12 Bacracheva N, Scholl H, Gerova Z, et al. The distribution of ciprofloxacin and its metabolites in human plasma, pulmonary and bronchial tissues. Int J Clin Pharmacol Ther Toxicol 1991; 29:352–356

13 Bergogne-Bérézin E, Berthelot G, Even P, et al. Penetration of ciprofloxacin into bronchial secretions. Eur J Clin Microbiol 1986; 5:197–200

14 Birmingham MC, Guarino R, Heller A, et al. Ciprofloxacin concentrations in lung tissue after a single 400 mg intravenous dose. J Antimicrob Chemother 1999; 43(suppl A):43–48

15 Dan M, Torssian K, Weissberg D, et al. The penetration of ciprofloxacin into bronchial mucosa, lung parenchyma, and pleural tissue after intravenous administration. Eur J Clin Pharmacol 1993; 44:101–102

16 Fabre D, Bressolle F, Gomeni R, et al. Steady-state pharmacokinetics of ciprofloxacin in plasma from patients with nosocomial pneumonia: penetration of the bronchial mucosa. Antimicrob Agents Chemother 1991; 35:2521–2525

17 Forst H, Ruckdeschel G, Unertl K, et al. Lung tissue concentrations of ciprofloxacin after intravenous administration in patients. Arzneimittelforschung 1989; 39:618–619

18 Fraschini F, Braga PC, Cosentina R, et al. Ciprofloxacin: multiple-dose pharmacokinetic and clinical results in patients with hypercrinic bronchopulmonary diseases. Int J Clin Pharmacol Res 1987; 7:63–71

19 Honeybourne D, Andrews JM, Ashby JP, et al. Evaluation of the penetration of ciprofloxacin and amoxycillin into the bronchial mucosa. Thorax 1988; 43:715–719

20 Honeybourne D, Wise R, Andrews JM. Ciprofloxacin penetration into lungs [letter]. Lancet 1987; 1:1040

21 Hopf G, Bocker R, Estler CJ, et al. Concentration of ciprofloxacin in human serum, lung and pleural tissues and fluids during and after lung surgery [letter]. Infection 1988; 16:29–30

22 Lee LJ, Sha X, Gotfried MH, et al. Penetration of levofloxacin into lung tissues after oral administration to subjects undergoing lung biopsy or lobectomy. Pharmacotherapy 1998; 18:35–41

23 Reid TMS, Gould IM, Golder D, et al. Brief report: respiratory tract penetration of ciprofloxacin. Am J Med 1989; 87(suppl 5A):60S–61S

24 Rohwedder R, Bergan T, Caruso E, et al. Penetration of ciprofloxacin and metabolites into human lung, bronchial and pleural tissue after 250 and 500 mg oral ciprofloxacin. Chemotherapy 1991; 37:229–238

25 Scaglione F, Mezzetti M, Arcidiacono MM, et al. Penetration of pefloxacin and ciprofloxacin into lung tissue [letter]. J Antimicrob Chemother 1995; 35:557–559

26 Schlenkfhoff D, Dalhoff A, Knopf J, et al. Penetration of ciprofloxacin into human lung tissue after intravenous injection [letter]. Infection 1986; 14:299–300

27 Winter J, Sweeney G. Reproducibility of the measurement of ciprofloxacin concentration in bronchial mucosa. J Antimicrob Chemother 1991; 27:329–333

28 Baldwin DR, Honeybourne D, Wise R. Pulmonary disposition of antimicrobial agents: methodologic considerations. Antimicrob Agents Chemother 1992; 36:1171–1175

29 Baldwin DR, Honeybourne D, Wise R. Pulmonary disposition of antimicrobial agents: observations and clinical relevance. Antimicrob Agents Chemother 1992; 36:1176–1180

30 Baldwin DR, Wise R, Andrews JM, et al. Concentrations of antimicrobials in the pulmonary alveolar epithelial lining. Res Clin Forum 1990; 12(suppl 4):95–102

31 Bergogne-Bérézin E. Interpretation of pharmacologic data in respiratory tract infections. Int J Antimicrob Agents 1993; 3:S3–S14

32 Rodvold KA, Gotfried MN, Danziger LH, et al. Intrapulmonary steady-state concentrations of clarithromycin and azithromycin in healthy adult volunteers. Antimicrob Agents Chemother 1997; 41:1399–1402

33 Siegel RE. The significance of serum vs tissue levels of antibiotics in the treatment of penicillin-resistant Streptococcus pneumoniae and community-acquired pneumonia: are we looking in the wrong place? Chest 1999; 116:535–538

34 Baldwin DR, Wise R, Andrews JM, et al. Comparative bronchoalveolar concentrations of ciprofloxacin and lomefloxacin after oral administration. Respir Med 1993; 87:595–601

35 Conte JE, Golden J, Duncan S, et al. Single-dose intrapulmonary pharmacokinetics of azithromycin, clarithromycin, ciprofloxacin, and cefuroxime in volunteer subjects. Antimicrob Agents Chemother 1996; 40:1617–1622

36 Schuler P, Zemper K, Borner K, et al. Penetration of sparfloxacin and ciprofloxacin into alveolar macrophages, epithelial lining fluid, and polymorphonuclear leukocytes. Eur Respir J 1997; 10:1130–1136

37 Metropolitan Life Insurance Company. Metropolitan height and weight tables. Stat Bull 1983; 1983:64:2–9

38 Baldwin DR, Wise R, Andrews JM, et al. Azithromycin concentrations at the sites of pulmonary infection. Eur Respir J 1990; 3:886–890

39 Patel KB, Xuan D, Tessier PR, et al. Comparison of bronchopulmonary pharmacokinetics of clarithromycin and azithromycin. Antimicrob Agents Chemother 1996; 40:2375–2379

40 Granneman GR, Varga LL. High-performance liquid chromatographic procedures for the determination of temafloxacin in biological matrices. J Chromatogr 1991; 568:197–206

41 Niederman MS, Bass JB Jr, Campbell GD, et al. Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. Am Rev Respir Dis 1993; 148:1418–1426

42 Wise R. Comparative penetration of selected fluoroquinolones into respiratory tract fluids and tissues. Am J Med 1991; 91(suppl 6A):67S–70S

43 Wise R, Baldwin DR, Andrews JM, et al. Comparative pharmacokinetic disposition of fluoroquinolones in the lung. J Antimicrob Chemother 1991; 28(suppl C):65–71

44 Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 1998; 26:1–12

45 Preston SL, Drusano GL, Berman AL, et al. Pharmacodynamics of levofloxacin: a new paradigm of early clinical trials. JAMA 1998; 279:125–129

46 Thornsberry C, Ogilvie P, Kahn J, et al. Surveillance of antimicrobial resistance in *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* in the United States in 1996–1997 respiratory season: the Laboratory Investigator Group. Diagn Microbiol Infect Dis 1997; 29:249–257

47 Thornsberry C, Jones ME, Hickey ML, et al. Resistance surveillance of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* isolated in the United States, 1997–1998; J Antimicrob Chemother 1999; 44:749–759

48 Chien SCC, Wong FA, Fowler CL, et al. Double-blind evaluation of the safety and pharmacokinetics of multiple oral once-daily 750-mg and 1-gram doses of levofloxacin in healthy volunteers. Antimicrob Agents Chemother 1998; 42:885–888

49 Piscitelli SC, Spooner K, Baird B, et al. Pharmacokinetics and safety of high-dose and extended-interval regimens of levofloxacin in human immunodeficiency virus-infected patients. Antimicrob Agents Chemother 1999; 43:2323–2327