Steady-State Pharmacokinetics and Sputum Penetration of Lomefloxacin in Patients with Chronic Obstructive Pulmonary Disease and Acute Respiratory Tract Infections

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Oral doses of 400 mg of lomefloxacin were administered once daily prior to breakfast to 10 middle-aged to elderly hospitalized patients with chronic obstructive pulmonary disease during treatment for bronchopulmonary infections. Serial plasma and sputum samples and fractional urine samples were obtained over a steady-state dosing interval. Lomefloxacin concentrations were determined in duplicate by a validated agar well diffusion microbiological assay. The maximum plasma lomefloxacin concentration (4.5 ± 1.8 mg/liter), the time of occurrence of the maximum concentration (1.7 ± 1.6 h), and the apparent volume of distribution associated with the terminal phase (2.19 ± 1.05 liter/kg) were comparable to the values reported for healthy, young volunteers. Compared with the data reported for young adults, the elimination half-life (12.7 ± 4.67 h) was longer and the apparent total body clearance (132 ± 36.6 ml/min/1.73 m2) was lower in middle-aged to elderly patients. These differences were most likely attributable to age-related decreases in renal function, as evidenced by the lower lomefloxacin renal clearance (70.3 ± 33.5 ml/min) in patients. The presence of acute respiratory infection per se did not appear to alter lomefloxacin pharmacokinetics. The peak lomefloxacin concentration in purulent, expectorated sputum samples of 4.3 ± 1.2 mg/liter occurred 3.1 ± 1.7 h after dose administration and subsequently declined to 1.7 ± 0.5 mg/liter at the end of the 24-h dosing interval. The percent penetration into sputum, as assessed by comparing the area under the curve for sputum and plasma samples, was 120 ± 39.8 (range, 70 to 185). The steady-state lomefloxacin concentrations in plasma and sputum samples from ill, older patients were in excess of the MICs for 90% of the strains tested of common, susceptible respiratory pathogens over most of the dosing interval.

Because the fluoroquinolones exhibit broad-spectrum activity against gram-positive and -negative bacteria, they have become a valuable addition to the antimicrobial armamentarium against a wide variety of infections (15). In the treatment of respiratory tract infections, however, concern about their use against streptococcal and pseudomonal pathogens has been expressed (7, 14, 20). In general, fluoroquinolone MICs against Strepptococcus pneumoniae and Pseudomonas aeruginosa are higher than those against other common respiratory pathogens and may indeed be higher than antibiotic concentrations in sputum and bronchial tissue (7). The desirability of achieving inhibitory or bactericidal sputum antibiotic concentrations in the treatment of acute episodes of chronic bronchitis and bronchiectasis has been underscored by several clinical trials (17). The ability of quinolones to penetrate the blood-bronchus barrier and be distributed considerably has therefore attracted considerable attention. It appears that some variation exists in the bronchopulmonary disposition of currently available quinolones (7, 10). The concentration of lomefloxacin in bronchial mucosal tissue has been assessed in patients undergoing bronchoscopy; the median steady-state concentration was 177% that of serum (1). Its penetration into purulent infected sputum, however, has not been evaluated.

An additional consideration during antimicrobial therapy is the effect of the acute infectious process itself on pharmacokinetics. Some investigators have identified this effect as a factor which can significantly alter the systemic disposition of antibiotics (8, 9, 13). Pneumonia in elderly patients (19) and changes in arterial oxygenation associated with pulmonary disease (6), for instance, have been correlated with altered drug metabolism. This investigation was therefore designed to characterize the steady-state disposition and sputum penetration of lomefloxacin in middle-aged to elderly hospitalized patients with chronic obstructive pulmonary disease during treatment for bronchopulmonary infections. (This work was presented in part at the 30th Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlanta, Ga., 21 to 24 October 1990.)

MATERIALS AND METHODS

Patients. Patients with moderate to severe acute lower respiratory tract infections (complicating chronic obstructive pulmonary disease) which warranted hospitalization were enrolled in this study. Subjects were excluded if they were known to exhibit hypersensitivity to the quinolone class of antibiotics, had received concomitant antimicrobial therapy within 48 h prior to enrollment, had impairment of renal function (serum creatinine level of >1.8 mg/dl or >150 μmol/liter) or hepatic function (alanine transaminase, aspartate transaminase, or bilirubin level greater than twice the upper limit of normal), or required oral antacid therapy during the study. All patients received lomefloxacin under a clinical efficacy and safety investigational protocol approved by the Medical Ethics Committee of the Military Hospital Dr
TABLE 1. Demographic and pharmacokinetic characteristics of patients receiving lomefloxacin

| Patient | Age (yr) | Wt (kg) | CLCR* (mL/min/1.73 m²) | Cmax (mg/liter) | Cmin (mg/liter) | Tmax (h) | t1/2 (h) | AUC (mg h/liter) | Vd/f (liter/kg) | CLf/ (mL/min/1.73 m²) | CLR (mL/min/1.73 m²) | CLRg/ (mL/min/1.73 m²) | Sputum |
|---------|----------|---------|------------------------|----------------|----------------|----------|---------|----------------|----------------|--------------------|-------------------|-------------------|-----------------|--------|
| 1       | 74       | 45.4    | 52.6                   | 7.3            | 0.9            | 2        | 7.49    | 79.3          | 1.20           | 100                | 58.8             | 41.2             | 4.0               | 6     | 85     |
| 2       | 69       | 39.6    | 46.8                   | 7.4            | 2.0            | 2        | 11.91   | 90.4          | 1.91           | 102                | 46.0             | 56.0             | 5.7               | 3     | 70     |
| 3       | 61       | 75      | 60                     | 5.1            | 1.0            | 1        | 13.41   | 55.2          | 1.91           | 111                | 51.9             | 59.1             | 3.7               | 1     | 103    |
| 4       | 84       | 86      | 47.9                   | 4.9            | 1.2            | 1        | 15.07   | 66.5          | 1.52           | 82.4               | 47.5             | 34.9             | 4.0               | 6     | 103    |
| 5       | 66       | 80      | 96.7                   | 3.2            | 0.3            | 1        | 7.48    | 31.4          | 1.72           | 181                | 145              | 36.0             | 2.5               | 3     | 114    |
| 6       | 79       | 57      | 40.2                   | 3.0            | 1.2            | 6        | 14.09   | 46.8          | 3.05           | 154                | 41.1             | 113              | 5.8               | 3     | 170    |
| 7       | 77       | 60.3    | 55                     | 5.0            | 1.2            | 2        | 11.51   | 63.0          | 1.75           | 109                | 76.6             | 32.4             | 4.0               | 3     | 111    |
| 8       | 52       | 81.5    | 90.3                   | 4.5            | 0.5            | 0.75     | 7.74    | 42.5          | 1.29           | 137                | 87.8             | 49.2             | 3.7               | 2     | 93     |
| 9       | 89       | 86      | 47.4                   | 2.4            | 0.6            | 0.5      | 13.49   | 28.7          | 2.98           | 186                | 103              | 83               | 3.6               | 3     | 168    |
| 10      | 87       | 88.2    | 35.3                   | 2.5            | 1.0            | 1        | 23.03   | 37.0          | 4.60           | 161                | 45.0             | 116              | 6.0               | 1    | 185    |

| Mean    | 74       | 69.9    | 57.2                   | 4.5            | 1.0            | 1.7      | 12.7    | 54.1          | 2.19           | 132                | 70.3             | 62.1             | 4.3               | 3.1   | 120    |
| Standard deviation | 12       | 17.9    | 20.4                   | 1.8            | 0.5            | 1.6      | 4.67    | 20.6          | 1.05           | 36.6               | 33.5             | 31.4             | 1.2               | 1.7   | 39.8   |

* CLCR estimated by the formula of Cockroft and Gault (5).

A Matthijsen. Informed consent was granted by all patients prior to enrollment.

Study design. A medical history, physical examination, laboratory screening profile (hematology, serum chemistry, and urinalysis), and determination of the theophylline concentration in serum were completed for each patient before participation in the study, once between days 3 to 5 during therapy, and again between 3 to 5 days after the last lomefloxacin dose. For patients receiving an oral theophylline preparation, the serum theophylline concentration was measured 4 h after the morning dose had been administered. Lomefloxacin was supplied by G. D. Searle Nederland BV, Maarssen, The Netherlands. Each subject received 400 mg (two 200-mg capsules) orally 1.5 h prior to breakfast each morning.

Pharmacokinetic sampling. On one occasion between days 4 to 6 of therapy, multiple plasma, urine, and sputum samples for drug analysis were collected over one dosing interval. Patients fasted overnight until 1.5 h after administration of the lomefloxacin dose. Blood samples were collected from an indwelling heparinized catheter into glass collection tubes (Becton Dickinson, Rutherford, N.J.) containing lithium heparin before the dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 h after dose administration. Samples were protected from exposure to light; plasma was separated from blood by centrifugation and frozen at -70°C until analysis. Total urine output was collected over the time intervals 0 to 4, 4 to 8, 8 to 12, and 12 to 24 h. After quantitation, a portion of each sample was stored at -70°C. Expectorated sputum was collected over the following intervals: predose, 0 to 2, 2 to 4, 4 to 8, 8 to 12, and 22 to 24 h. Samples were frozen without further preparation at -70°C.

Sample analysis. The concentrations of lomefloxacin in plasma, urine, and sputum samples were measured in duplicate by an agar well diffusion microbiological assay (3) with Escherichia coli ATCC 25922 (American Type Culture Collection, Rockville, Md.) as the test organism on Iso-Sensitest agar (Oxoid). Plasma samples were assayed directly, urine was diluted 100-fold in phosphate-buffered saline (PBS) (pH 7.4), and sputum was homogenized by sonication (Sonifer B12; Branson Sonic Power Co., Danbury, Conn.) for 2 min until fluid. Lomefloxacin standards ranging from 0.25 to 5 mg/liter were prepared in normal human plasma, PBS, and normal, homogenized sputum. The assay was linear over the range of quality control concentrations used; patient samples in which the concentration of lomefloxacin exceeded 5 mg/liter were redetermined after dilution with the appropriate substance. The lower limit of sensitivity was 0.1 mg/liter for all three substances. The inter- and intraassay coefficients of variation over the concentration range tested were ±7.5%.

Data analysis. Lomefloxacin pharmacokinetics were analyzed by noncompartmental methods (11). The terminal elimination rate constants (β) were determined by weighted nonlinear regression analysis. The last four or five lomefloxacin concentrations (sample collection times, 6 to 24 h) were chosen on the basis of visual inspection of the loglinear concentration-time plots; concentrations were weighted as follows: 1/β². The elimination half-life (t1/2β) was calculated as ln 2 divided by β. The peak plasma and sputum lomefloxacin concentrations (Cmax) and time to peak concentration (Tmax) were compiled from the concentration-time data. The apparent total body clearance (CLf), renal clearance (CLR), and apparent volume of distribution in the terminal phase (Vd/f) were calculated by the following equations: CLf = dose/AUC0-24, CLR = X1-2/AUC1-2, and Vd/f = dose/(AUC0-24 × β). In these equations, the dose is the oral lomefloxacin dose administered, AUC0-24 is the total area under the plasma lomefloxacin concentration-versus-time curve from 0 to 24 h obtained by the trapezoidal rule, AUC1-2 is the area under the curve over the urine collection interval r1 to r2, and X1-2 is the amount of lomefloxacin excreted in urine over the collection interval between t1 and t2.

Cerebral clearance (CLCR) was calculated from the formula of Cockroft and Gault (5). Apparent nonrenal clearance (CLRg/f) was determined as the difference between CLf and CLR. Penetration of lomefloxacin in sputum was calculated as the ratio of sputum lomefloxacin AUC0-23 to plasma lomefloxacin AUC0-23. Data are presented as means ± standard deviations.

RESULTS

Clinical results. Twelve patients were enrolled in this study. Two were withdrawn from the study prior to the pharmacokinetic analysis because their sputum production had diminished, rendering them unable to fulfill the required sampling protocol. Demographic characteristics of the 10 evaluable participants are shown in Table 1. Subjects (9 males and 1 female) ranged in age from 52 to 89 years (mean
age, 74 ± 12 years), with a mean weight of 69.9 ± 17.9 kg and a mean height of 172 ± 11 cm. Patients were hospitalized with acute episodes of chronic bronchitis (9), or cardiac decompensation (3), and/or bronchopneumonia (6). Bacterial pathogens were isolated from the pretherapy sputum sample in 7 of the 10 participants. The maximum oral temperature was 38.0 ± 0.6°C, and the pretherapy leukocyte count was (12.8 ± 7.1) 10^9/mm^3. All patients used theophylline plus β-sympathomimetic agents (either salbutamol or terbutaline in eight patients), and five patients used prednisolone. Diuretics were prescribed for five patients. Lomefloxacin therapy was well tolerated by all subjects. No adverse reactions with probable or highly probable relationship to drug administration were observed. In patients concurrently receiving theophylline preparations, no significant elevation in serum theophylline concentration during coadministration of lomefloxacin was noted: 8.4 ± 8.5 mg/liter prior to entry in study, 9.8 ± 4.8 mg/liter during trial, and 8.8 ± 4.0 mg/liter after participation in study.

**Pharmacokinetics.** Plasma lomefloxacin concentration (mean ± standard deviation) versus time data are illustrated in Fig. 1. The mean plasma lomefloxacin $C_{\text{max}}$ of 4.5 ± 1.8 mg/liter occurred 1.7 ± 1.6 h after oral administration; at 12 h, the concentration had fallen to 2.1 ± 0.8 mg/liter. The minimum plasma lomefloxacin concentration ($C_{\text{min}}$) 24 h after the dose was 1.0 ± 0.5 mg/liter. The $t_{1/2 \text{b}}$, AUC, $V_{\text{d}}$, and CL/f values were 12.7 ± 4.67 h, 54.1 ± 20.6 mg h/liter, 2.19 ± 1.05 liter/kg, and 132 ± 36.6 ml/min/1.73 m², respectively, as shown in Table 1. The mean urine lomefloxacin concentrations (in milligrams per liter) per collection interval were 240 ± 116 (0 to 4 h), 235 ± 120 (4 to 8 h), 236 ± 98.3 (8 to 12 h), and 187 ± 65.3 (12 to 24 h). A total of 214 ± 67.6 mg of lomefloxacin, or 53.5% of the administered dose, was recovered in urine over 24 h. CL_R was 70.3 ± 33.5 ml/min/1.73 m². The peak lomefloxacin concentration in purulent, expectorated sputum of 4.3 ± 1.2 mg/liter occurred 3.1 ± 1.7 h after dose administration and subsequently declined to a $C_{\text{min}}$ of 1.7 ± 0.5 mg/liter at 23 h (Fig. 1). The mean percent lomefloxacin penetration into sputum, as assessed by AUC comparison was 120 ± 39.8 (range, 70 to 185 [Table 1]).

**DISCUSSION**

Compared with data derived from studies of young adult volunteers receiving multiple doses of lomefloxacin (12), the elimination half-life and AUC_{0-24} in our study population were increased (12.7 ± 4.67 versus 6.20 ± 0.75 h; 54.1 ± 20.6 versus 37.0 ± 10.7 mg h/liter), with a corresponding decrease in CL/f (2.02 ± 0.47 versus 3.16 ± 0.81 ml/min/kg). These differences are most likely attributable to age-related decreases in renal function, as evidenced by the markedly lower CL_R in patients (70.3 ± 33.5 versus 134 ± 11.7 ml/min). $C_{\text{max}}$, $T_{\text{max}}$, and $V_{\text{d}}$ were similar for older patients and young adults (4.5 ± 1.8 versus 4.7 ± 1.3 mg/liter, 1.7 ± 1.6 versus 1.9 ± 1.2 h, and 2.19 ± 1.05 versus 1.71 ± 0.55 liter/kg, respectively). Inasmuch as these data in infected older patients agree with that from noninfected elderly volunteers (21), the presence of acute respiratory infection does not appear to be associated with altered lomefloxacin pharmacokinetics in older individuals. The lack of influence of lomefloxacin on theophylline disposition corroborates the findings of a controlled, cross-over investigation in healthy young adults (16).

Sputum represents an appropriate substance for assessing antibiotic penetration in chronic bronchial infections, since the bacteria involved are most often located in the bronchial lumen (2). Also, pathologic alterations in bronchopulmonary anatomy and host defenses which are peculiar to purulent bronchitis may be important components in determining whether adequate antibiotic concentrations are achieved at the infection site (17). These considerations underscore the relevance of assessing sputum antibiotic penetration in patients at steady state during treatment for a bronchopulmonary infection. In this group of acutely ill bronchitis patients, the steady-state lomefloxacin $C_{\text{max}}$ in purulent sputum was similar but slightly delayed compared with that occurring simultaneously in plasma. The elevated sputum lomefloxacin $C_{\text{min}}$ relative to that in plasma observed in our study participants may support the finding that patients with chronic bronchitis are prone to slower clearance of intrabronchial antibiotics (18). Certain methodological difficulties inherent in the collection of sputum samples (2) must be considered in interpreting these results. It is possible that saliva may have contaminated or diluted the expectorated samples, since the concentration of lomefloxacin in saliva is slightly lower than that in serum (21). Additionally, the pooling of sputum samples over 2- or 4-h intervals (designed to facilitate collection and accommodate the diminished production usual for bronchitis patients in the afternoon hours) may have reduced the observed sputum lomefloxacin $C_{\text{max}}$ and/or increased the $T_{\text{max}}$.

The MICs of lomefloxacin for 90% of the strains tested of Haemophilus influenzae, Klebsiella pneumoniae, Moraxella catarrhalis, E. coli, Enterobacter spp., and Legionella spp. range from ≤0.06 to 2 mg/liter (4, 22). These concentrations were exceeded in both plasma and sputum samples over most of the dosing interval. If the attainment of bactericidal antibiotic concentrations in sputum is essential for the treatment of pulmonary infections, then lomefloxacin's marginal activity against S. pneumoniae may limit its use in community-acquired respiratory tract infections, as has been previously described for other fluoroquinolones (7, 14, 20).

On the basis of its activity against common gram-negative respiratory pathogens and its steady-state pharmacokinetic properties, lomefloxacin is potentially effective given once daily in the treatment of bronchopulmonary infections caused by susceptible microorganisms. Controlled efficacy trials are warranted to fully define lomefloxacin's role in these indications.
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REFERENCES