Concentrations of Oral Lomefloxacin in Serum and Bronchial Mucosa

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The bronchial mucosal concentrations of lomefloxacin were determined for specimens obtained by fiber-optic bronchoscopy and compared with simultaneous concentrations in serum. The 23 patients studied were given an oral dose of 400 mg once daily for 4 days to achieve steady-state levels. The median concentration in serum was 2.5 μg/ml (range, 1.0 to 5 μg/ml), and the median bronchial mucosal concentration was 5.0 μg/g (range, 0.7 to 18.6 μg/g). The median percent penetration was 177% (range, 69 to 541%). The concentrations in serum and mucosa exceeded the MIC for 90% of strains of organisms causing bronchial infections but not sufficiently to recommend lomefloxacin for the routine treatment of pneumococcal infections.

The likely clinical efficacy of antibiotics may be predicted from the concentrations of the agent in the tissues and secretions which are the usual sites of infection. In the respiratory tract, antibiotic concentrations in sputum have been determined, but these can be unreliable (1, 13). The bronchial mucosa is probably the main site of acute bacterial infection in patients with chronic bronchitis and bronchiectasis (5) and, therefore, it is reasonable to measure drug concentrations at this site. Several quinolones have been found to attain higher bronchial mucosal and lung tissue concentrations than simultaneous concentrations in serum (7, 9, 17). The aim of this study was, therefore, to assess the concentration of a new quinolone, lomefloxacin, in human bronchial mucosa.

Lomefloxacin is a fluoroquinolone with a broad spectrum of in vitro activity against clinically important gram-positive and gram-negative aerobes and anaerobes, including the majority of organisms responsible for lower respiratory tract infections, including Staphylococcus aureus (18). Like the other quinolones, it also has activity against Legionella pneumophila and Mycoplasma pneumoniae (6). It has a prolonged serum half-life, and it is therefore appropriately given as a once-daily dose (16).

MATERIALS AND METHODS

A total of 23 patients (14 male and 9 female) undergoing fiber-optic bronchoscopy for diagnostic purposes were studied. The indication for bronchoscopy was focal radiological abnormality in 19 patients and hemoptysis in 4 patients. The final diagnosis was squamous cell carcinoma in seven patients, and in the remainder, no abnormality was found. Ages ranged from 40 to 65 years (mean, 57 years). Lomefloxacin was self-administered in a dose of 400 mg once daily, in the morning, for 4 days, with the final dose of lomefloxacin given on the morning of the bronchoscopy, making a total of 4 doses. A standard premedication of 160 mg of 4% nebulized lignocaine, 0.6 mg of intramuscular atropine, and 2.5 to 5 mg of intravenous midazolam was used. Bronchial biopsies were taken from the subcarinae of macroscopically normal bronchi (absence of erythema, nodularity, or edema) and immediately placed in a humidity chamber. Any specimens macroscopically contaminated with blood were discarded. A serum sample for determination of lomefloxacin concentration and also for urea, creatinine, calcium, bilirubin, and electrolyte concentrations was taken at the same time as the bronchial biopsy. Also, aspartate transaminase and alkaline phosphate activities were measured. In addition, a hemoglobin determination and an automated count with a Coulter Counter were performed. Each patient underwent a clinical examination before and after taking the drug.

Exclusion criteria for this study were as follows: (i) clinical or radiological evidence of cardiac failure; (ii) disturbance of hepatic function (serum transaminase activity more than the upper limit of normal, bilirubin above the normal range); (iii) renal impairment (blood urea greater than 9 μmol/liter or creatinine greater than 140 mmol/liter); (iv) a hemoglobin determination of less than 10 g/liter; (v) a history of concomitant drug therapy, including any other investigational drug, antibiotics, antacids, theophylline, and drugs affecting the central nervous system other than sedatives; (vi) evidence of active lung infection; and (vii) child-bearing potential.

All patients provided full written informed consent, and the study was approved by the Hospital Ethical Committee. All samples were assayed within 1 h of collection by using a microbiological plate diffusion technique in which the indicator strain Escherichia coli (Bayer 4004) was inoculated onto prepoured plates of Iso-Sensitest agar (Oxoid, Basingstoke, United Kingdom). Assay plates were incubated at 30°C for 18 h. Standards were diluted in pooled human serum for the serum samples and in phosphate buffer at pH 7 for biopsy samples. Biopsy samples were weighed and, following the addition of 200 μl of cooled phosphate buffer, ultrasonicated on ice for 1 min prior to assaying (model W225; Ultrasonics Heat Systems; 50% duty cycle pulsed). The lower limit of sensitivity of the assay was 0.1 μg/ml, and the coefficient of variation was 7.9%. All samples and standards were shielded from the light. Results have been expressed as a percentage of the simultaneous concentration in serum.

RESULTS

Figure 1 shows the concentrations of lomefloxacin in serum and tissue plotted against time since final dose. The scatter of data points is small, suggesting good reproducibil-
ity. The mean concentration in serum was 2.8 μg/ml (standard deviation [SD], 1.0 μg/ml) and the mean biopsy concentration was 5.8 μg/g (SD, 3.7 μg/g). The mean percentage of biopsy concentration compared with the concentration in serum was 202% (SD, 94%). The medians were 2.5 μg/ml (range, 1.0 to 5 μg/ml), 5 μg/ml (range, 0.7 to 18.6 μg/ml), and 177% (range, 69 to 541%), respectively. There was no significant correlation between the time since the last dose of lomefloxacin and concentrations in either serum or tissue (Fig. 1). Table 1 shows the mean concentrations in serum and tissue and the mean percent penetration at different times. Data are also shown after excluding patients 20 and 21, and results show that these patients were responsible for the high mean percent penetration after 4 h. These two patients had chronic airflow limitation, and although the mucosa was macroscopically normal, it is possible that the tissue was inflamed. After exclusion of these two patients, the mean percent penetration was 177.5 (SD, 43%). Patients did not report any unusual symptoms during or 1 week after treatment, and none of the hematological or biochemical parameters specified above showed any significant difference before and after treatment in any patient.

### DISCUSSION

The concentration of an antibiotic at the site of infection is likely to be an important determinant of its effectiveness. The site of infection represents the area where bacteria are multiplying in sufficient numbers to produce tissue damage, either by direct action on the mucosal surface or by stimulating exuberant host defenses which themselves lead to damage (11, 15).

In the lungs, the sites of infection which have previously been investigated with regard to antibiotic penetration are sputum and bronchial secretions (10, 13, 17), bronchial mucosa (7, 9, 10) and alveolar fluid, and macrophages (2, 4, 12). It has been suggested (7, 9, 13) that the bronchial mucosal concentration of an antibiotic is a better indicator of its likely clinical efficacy than sputum, because sputum is difficult to collect, may be contaminated with saliva and blood, and is pooled in the lung over several hours. This is confirmed by the fact that concentrations in sputum have been shown to correlate poorly with concentrations in serum (1). Bronchial mucosal concentrations are also relevant, since infections of the bronchial mucosa may progress to direct invasion following adherence of bacteria to damaged mucosa. A high concentration of an antimicrobial agent would inhibit such adherence and invasion. Our data show that lomefloxacin concentrations in the bronchial mucosa are higher than concentrations in serum, indicating that the drug is concentrated by the bronchial mucosa. The mucosal concentrations are likely to represent a minimum value, because any microscopic blood contamination would reduce the overall concentration.

The 1.5- to 2-fold-greater concentrations of lomefloxacin in bronchial mucosa are similar to those found for other quinolones, including ciprofloxacin (147%) (7) and temafloxacin (178%) (D. R. Baldwin, R. Wise, and D. Honeybourne, unpublished data). Enoxacin has a far higher tissue/serum concentration ratio (previous studies show from 400 to 4,500% penetrations [9, 17]) than the other quinolones, but as yet there is no agreed-upon explanation for this and verification of these data should be undertaken.

The mechanisms of transport of drugs into tissues are difficult to study, but there has been much in vitro work on penetration of drugs into cells. The human cells used have been monocytes, macrophages, and polymorphonuclear leukocytes (4, 8, 14). It has been shown that drugs with a lipophilic character or those which are actively transported move rapidly into cells and tend to attain higher cellular concentrations. For example, the quinolones and macrolides (which are lipophilic and in some cases actively transported [3]) both attain high cellular concentrations, whereas β-lactams do not. Tissues differ from isolated cells, since the differentiation of the individual cells in a tissue can lead to the development of transport mechanisms and barriers which individual cells do not have (for instance, the mucous barrier). However, a similar situation may exist for tissues, since it appears that the same antibiotics that attain high cell

### TABLE 1. Concentrations in serum and tissue at different times

<table>
<thead>
<tr>
<th>Time since last dose (h)</th>
<th>Mean serum concn (SD) (μg/ml)</th>
<th>Mean tissue concn (SD) (mg/kg)</th>
<th>Mean % penetration (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1-3</td>
<td>3.3 (1.0)</td>
<td>6.1 (1.7)</td>
<td>189 (29)</td>
</tr>
<tr>
<td>&gt;3-4</td>
<td>2.1 (0.7)</td>
<td>3.7 (1.7)</td>
<td>173 (62)</td>
</tr>
<tr>
<td>&gt;4-7</td>
<td>3.0 (1.0)</td>
<td>8.2 (6.2)</td>
<td>259 (162)</td>
</tr>
<tr>
<td>&gt;4-7*</td>
<td>2.7 (0.5)</td>
<td>4.4 (1.0)</td>
<td>160 (10)</td>
</tr>
</tbody>
</table>

* Patients 20 and 21 were excluded from analysis.
concentrations also attain high tissue concentrations. This is a generalization, and there is a great deal of variation from tissue to tissue. Quinolones move quickly into isolated cells but also readily move out. This could be advantageous in bronchial mucosal infections, since a gradient of antibiotic concentration should be maintained from tissue to secretions, providing a greater half-life of the antimicrobial agent in sputum.

Our data show that the bronchial mucosal concentrations of lomefloxacin in a population of patients representative of those most likely to receive antibiotic therapy for infections of the bronchial mucosa are in excess of the MIC for 90% of strains of the common respiratory pathogens (Haemophilus influenzae, 0.03 μg/ml; Moraxella catarrhalis, 0.03 μg/ml) (6, 18). The MIC for 90% of strains of Streptococcus pneumoniae (1 μg/ml) was just exceeded in all serum samples and in all but one biopsy sample (Table 1); that for Pseudomonas aeruginosa (4 μg/ml) was not reliably exceeded. These data suggest that lomefloxacin would be effective against some common respiratory pathogens of the bronchial mucosa but that further studies in which higher doses are used are required before it can be recommended for clinical trials when pneumococcal infections are suspected. The high bronchial mucosal concentrations would favor the use of this agent in Mycoplasma and Legionella infections, since a high intracellular concentration is implied at the more peripheral sites which are involved in pneumonia.

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LITERATURE CITED