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Penetration of Ofloxacin into Human Lung Tissue following a Single Oral Dose of 200 Milligrams

FRANCIS SEROUR,[1] MICHAEL DAN,[2]* ALFRED GOREA,[3] ALON YELLIN,[1] YAIR LIEBERMAN,[1] AND STEPHEN A. BERGER[3]

Department of Thoracic Surgery, The Sheba Medical Center, Tel Hashomer,[1] Infectious Diseases Unit, The E. Wolfson Medical Center, Holon,[2] and Department of Microbiology, Tel Aviv Medical Center, Tel Aviv,[3] Israel

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The penetration of ofloxacin into lung tissue was studied in 10 patients subjected to pulmonary surgery. Samples of blood and lung tissue were obtained 3 to 8 h (mean, 5 h) after oral administration of 200 mg. The mean level in tissue was 2.17 ± 0.5 μg/g, while the mean level in serum was 0.85 ± 0.23 μg/ml. The mean lung tissue/serum concentration ratio was 2.55 ± 0.30. The achievable levels of ofloxacin in lung tissue are above the MICs for most pulmonary pathogens.

Gram-negative bacillary (GNB) pneumonia is a severe infection, the treatment of which is hampered by the poor tissue penetrability of some of the antibacterial agents commonly used against these organisms (1).

A recently introduced fluoroquinolone group is characterized by broad antibacterial activity, including activity against gram-negative bacilli (5). Adequate levels in serum are obtained after oral administration, and a good concentration is achieved in most of the body tissues (4, 5).

In an attempt to evaluate the suitability of the fluoroquinolones in the treatment of pneumonia, we have studied the penetration of ofloxacin into the lung parenchymas of patients undergoing elective pulmonary surgery.

Ten adult patients (four males and six females) scheduled for elective pulmonary surgery were studied. The mean patient age was 52 years (range, 33 to 65 years), and the mean body weight was 64.2 kg (range, 47 to 94 kg). Creatinine concentrations in serum were normal in all instances, and none of the patients had received antimicrobial agents or antacids in the preceding 72 h. None of the patients had evidence of pulmonary or pleural infection.

A single dose of ofloxacin (200 mg) was administered orally 3 to 8 h (mean, 5 h) prior to surgery. At the time of surgery, a normal tissue sample was excised from the lung and rinsed in nonbacteriostatic saline to eliminate contaminating blood. A blood sample was obtained concomitantly, and serum was separated from blood by centrifugation. All specimens were frozen and stored at −70°C until the time of assay. Tissue samples were homogenized in a microhomogenizer with phosphate-buffered saline (pH 6.2). All specimens were assayed for ofloxacin activity by a standard bioassay by using 6-mm paper disks (Difco Laboratories, Detroit, Mich.) and Iso-Sensitest agar (pH 7.1 to 7.2; Oxoid, Ltd, London, U.K.) seeded with a clinical isolate of *Enterobacter cloacae* known to be susceptible to ofloxacin (MIC, 0.015 to 0.030 μg/ml). The minimal concentration detectable in the assay was 0.1 μg/ml. Standards for serum and tissue assays were prepared with antibiotic-free pooled human serum and phosphate-buffered saline (pH 6.2), respectively. Standard curves for serum and lung parenchyma assays were prepared in quadruplicate, each with five antibiotic concentrations. All points on the standard curve fell in proximity to a straight line (Pearson correlation coefficient, >0.45). In each instance, control curves were identical and exhibited coefficients of variation of ≤5.0% at minimal and maximal concentrations. All assays were performed in 1 day at a single session.

The concentrations of ofloxacin in the lung tissue and concomitant serum samples are shown in Table 1. Levels of ofloxacin in the lung tissue ranged from 0.53 to 5.7 μg/g (mean, 2.17 ± 0.50 μg/g). The mean concomitant level in serum was 0.85 ± 0.23 μg/ml (range, 0.3 to 2.28 μg/ml). The mean lung tissue/concomitant serum concentration ratio was 2.55 ± 0.30. Further analysis of the results has suggested some relationship between the time of sampling and concentrations in serum and tissue; this correlation, however, could not be definitely demonstrated, possibly because of the low number of subjects studied. High levels in tissue (1.3 μg/g) were detected as long as 8 h after drug administration.

Ofloxacin is a new fluoroquinolone active against most bacterial species associated with pulmonary infections. Gram-negative organisms including *Pseudomonas aeruginosa* and *Haemophilus influenzae* show the highest susceptibility with the MIC for 50% of the isolates ranging between 0.05 and 0.8 μg/ml. *Legionella pneumophila* is also quite susceptible to ofloxacin, while *Streptococcus pneumoniae* and *Mycoplasma pneumoniae* are less susceptible, although the MIC for 50% of the isolates is within the range of levels achievable in lung tissue (8).

Data on penetration of ofloxacin into lung tissue are scarce, and only two studies on this subject have been published. Couraud et al. (2) have studied 17 patients who received 200 mg of ofloxacin twice a day during 48 h. The mean concentration in lung tissue determined by high-pressure liquid chromatography (HPLC) was 6.7 ± 1.0 μg/g 1 h after the last dose was administered; the mean tissue/concomitant serum concentration ratio was 3.5 ± 0.4. The higher levels in tissue observed in this study, compared with our findings, may be explained by drug accumulation in tissue after repetitive dosing and/or the shorter interval between administration of the last dose and tissue sampling. The difference in methods of concentration determination (bioassay versus HPLC) is probably less determinant, as only a small proportion (6%) of ofloxacin is metabolized (5).

Wijnands et al. (6) have measured the concentrations of

* Corresponding author.

TABLE 1. Concentrations of ofloxacin in lung tissue and in serum after a single oral dose of 200 mg

Patient	Time of sample (h)	Concurrent concn in:		Tissue/serum concn ratio
		Lung tissue (μg/g)	Serum (μg/ml)	
1	4	0.53	0.5	1.06
2	7	1.33	0.3	4.43
3	6	4.0	0.34	11.76
4	3	0.6	2.14	0.28
5	4	5.7	0.6	9.5
6	4	2.3	0.36	6.38
7	5	1.0	1.12	0.89
8	6	1.9	0.4	4.75
9	8	1.3	0.44	2.95
10	3	3.0	2.28	1.91

ofloxacin in the lung tissue of 11 subjects after a single oral dose of 600 mg. Although the levels that they achieved in serum and tissue were higher, the increased dosage had no influence on the tissue/serum concentration ratio.

Our finding of high concentrations of ofloxacin in lung tissue, amply exceeding those in serum, is thus in accordance with earlier reports (2, 6). The same phenomenon of accumulation in lung tissue has been demonstrated for ciprofloxacin (3) and enoxacin (7).

Although it might be argued that drug levels in the pulmonary interstitium are relevant to intraalveolar infection, levels in tissue are still the first defense against systemic invasion by intraalveolar pathogens.

We conclude that ofloxacin penetrates well into the lung tissue, with a concentration well above the MIC for 50% of the isolates for most respiratory pathogens. This is particularly important in case of gram-negative bacillary pneumonia, since some of the other antibacterial agents used for gram-negative bacterial infections show inconsistent activity in the bronchial mucosa. In addition, ofloxacin offers the convenience of oral administration, which is particularly advantageous for patients treated for exacerbation of chronic obstructive lung disease.

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