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Penetration of Ciprofloxacin into Human Pleural Fluid

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The concentrations of ciprofloxacin (1.5 mg/kg of body weight) in serum and in uninfected pleural exudates were studied after one and three intravenous injections had been given at 8-h intervals. The drug was assayed in serum and in pleural fluid by high-performance liquid chromatography. The peak concentrations in pleural fluid 1.5 h after one and three injections were (mean ± standard error of the mean) 0.52 ± 0.09 and 0.77 ± 0.15 mg/liter, respectively; the corresponding 8-h concentrations were 0.19 ± 0.05 and 0.39 ± 0.10 mg/liter. At 1 and 8 h, the ratios of mean concentrations in pleural fluid to mean concentrations in serum were 112 and 158%, respectively, after one injection and 77 and 122% after three injections. This study suggested that there is a satisfactory pleural penetration of ciprofloxacin after intravenous injection.

Ciprofloxacin is a new fluoroquinolone with high in vitro activity against aerobic gram-negative bacteria, including members of the family *Enterobacteriaceae* and *Pseudomonas aeruginosa*, and, to a lesser degree, against gram-positive cocci (5). This broad antimicrobial activity makes this drug suitable for the treatment of nosocomial pleural infections if its pleural diffusion is of sufficient magnitude. Therefore, the penetration of intravenously injected ciprofloxacin was studied in pleural exudates.

(These results were presented in part at the 25th Interscience Conference on Antimicrobial Agents and Chemotherapy, Minneapolis, Minn., October 1985 [abstr. no. 1001].)

The patients that we studied were hospitalized in the Thoracic Surgery Department at the Erasmus University Hospital. Patient clinical features and pleural fluid data are shown in Table 1. Patients underwent either a lobectomy (nine patients) or a pneumectomy (one patient) 1 to 3 days (mean, 2.2 days) before the investigation. All patients had postoperative pleural drainage with a chest tube on continuous aspiration. All had normal renal function (serum creatinine, ≤1.1 mg/dl). Only patients with low blood contamination of the pleural fluid (blood contamination was defined as low if the ratio of pleural fluid to blood hemoglobin multiplied by 100 was lower than 10%) were included in this study. Gram stains and aerobic and anaerobic cultures of the pleural fluids were all negative. Informed consent was obtained from every patient. The study was approved by the ethical review committee of the hospital.

Ten patients were studied. The first five patients were given a single dose of 1.5 mg of ciprofloxacin per kg of body weight (mean dose, 109 mg; range, 80 to 125 mg), and the other five received three injections of the same dose (mean dose, 98 mg; range, 75 to 108 mg) at 8-h intervals. The drug was injected intravenously over 3 min. Ciprofloxacin was supplied by Bayer AG, Wuppertal, Federal Republic of Germany.

Blood samples were taken just before and 0.08, 0.25, 0.5, 1, 2, 4, 6, and 8 h after the intravenous (i.v.) administration. Pleural samples were collected through the chest tube just before and during intervals of 0.05 to 1 (0 to 0.5 and 0.5 to 1

TABLE 1. Clinical characteristics of patients

Patient no[a]	Age (yr)	Wt (kg)	Creatinine (mg/dl)	Delay after surgery (day)	Blood contamination of pleural fluid (%)	Total proteins in pleural fluid (g/dl)	Leukocyte count of pleural fluid (mm^{-3})
1	65	80	0.9	3	9	3.6	140
2	46	52	0.7	2	9	2.6	1,500
3	56	75	0.9	3	5	4.0	500
4	59	83	0.7	2	2	2.9	100
5	71	72	0.8	2	3	2.7	600
6	29	65	0.6	2	5	4.0	460
7	75	65	0.8	2	2	2.9	1,000
8	52	72	0.7	3	9	3.6	3,800
9	52	50	0.5	1	2	3.0	300
10	73	71	0.7	2	3	2.6	240

[a] All patients were male.

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TABLE 2. Concentrations of ciprofloxacin in serum and in pleural fluid after one dose[a]

Patient no.	Concn (mg/liter) in serum/concn in pleural fluid at following time (h) after dose[b]:							
	0.08	0.25	0.5	1	2	4	6	8
1	2.72/ND[c]	1.42/ND	1.07/ND	0.72/0.31	0.52/0.58	0.37/0.41	0.26/0.28	0.18/0.22
2	3.16/ND	1.36/ND	0.77/ND	0.47/0.49	0.28/0.37	0.18/0.19	0.09/0.12	0.08/0.08
3	2.26/ND	1.10/ND	0.68/ND	0.50/0.32	0.33/0.36	0.22/0.26	0.20/0.17	0.11/0.12
4	2.26/ND	1.56/ND	1.00/ND	0.58/0.44	0.45/0.48	0.26/0.37	0.20/0.26	0.14/0.21
5	ND	1.21/ND	0.57/1.33	0.45/0.92	0.36/0.83	0.25/0.56	0.18/0.40	0.11/0.35
Mean ± SEM	2.59 ± 0.22/ND	1.33 ± 0.08/ND	0.81 ± 0.09/ND	0.55 ± 0.05/ 0.49 ± 0.11	0.39 ± 0.04/ 0.52 ± 0.09	0.25 ± 0.03/ 0.36 ± 0.06	0.19 ± 0.03/ 0.24 ± 0.05	0.12 ± 0.02/ 0.19 ± 0.05

[a] One dose equalled 1.5 mg of ciprofloxacin per kg of body weight.
[b] Concentrations were 0 mg/liter at 0 h (predose).
[c] ND, Not done.

h if the amount of pleural fluid was sufficient), 1 to 2, 3 to 4, 5 to 6, and 7 to 8 h after the i.v. injection. From the patients receiving three doses, blood and pleural fluid were collected after the third dose according to the same schedule. Serum and pleural fluid samples were stored at −18°C until assay.

In the serum and the pleural fluid, ciprofloxacin was assayed by high-performance liquid chromatography by the method developed by Gau et al. (3). The assay was carried out by Bayer AG. The limit of sensitivity of the method was 0.05 mg/liter, and the coefficient of variation was between 1 and 6%. Two determinations each were done for concentrations in pleural fluid and in serum.

The mean concentrations of ciprofloxacin in the serum and pleural fluid are shown in Tables 2 and 3. After one and three injections, the mean concentrations in serum (mean ± standard error of the mean) were 0.55 ±0.05 and 0.86 ± 0.16 mg/liter, respectively, at 1 h and 0.12 ± 0.02 and 0.34 ± 0.09 mg/liter, respectively, at 8 h. The mean peak concentration in pleural fluid was reached at between 1 and 2 h, reaching concentrations of 0.52 ± 0.09 and 0.77 ± 0.15 mg/liter after one and three doses, respectively. The drug then disappeared slowly to reach concentrations of 0.19 ± 0.05 and 0.39 ± 0.10 mg/liter 7 to 8 h after injection. At 1 and 8 h, the ratios of mean concentrations in pleural fluid and serum were 112 and 158% after one injection and 77 and 122% after three injections, respectively.

The concentrations of ciprofloxacin in serum after i.v. administration that were observed in this study correlate well with those reported by others. Similar mean peak and trough concentrations after the i.v. injection of 100 mg of the drug were obtained elsewhere (1). Ciprofloxacin penetrates well and rapidly into body fluids; concentrations in many tissues are usually similar to or higher than those in serum (1).

In the present study, the mean concentration of ciprofloxacin in pleural fluid was similar to the corresponding concentration in serum. It must be noted that in our patients, the continuous drainage of the pleural fluid did not allow the drug to accumulate in the pleural space after multiple doses. However, this model represents the clinical situation in which pleural empyema is treated by antimicrobial therapy combined with continuous pleural drainage.

Pleural diffusion of ciprofloxacin has been poorly studied. In one study, five patients with postpneumonic pleural empyemas were given 500 to 750 mg of ciprofloxacin orally twice daily (2). A mean peak concentration in pleural fluid of around 1 mg/liter was obtained 1 h after administration and remained constant during the next 7 h. The ratio of concentration in pleural fluid to concentration in serum was 0.41, substantially less than that noted in the present work. In another study, concentrations in pleural fluid were studied in 16 patients 12 h after the i.v. injection of 200 mg of ciprofloxacin (4). Twelve hours after one and two doses of ciprofloxacin, the ratios of concentrations in pleural exudate to concentrations in serum were 1.1 and 1.8, respectively.

In conclusion, this study suggests that penetration of ciprofloxacin into pleural fluid is satisfactory. The concentrations achieved after i.v. injection of 1.5 mg of the drug per kg exceeded the MICs for *Haemophilus* spp. and most of the *Enterobacteriaceae* and are in the range of those for *P.*

TABLE 3. Concentrations of ciprofloxacin in serum and in pleural fluid after three doses[a]

Patient no.	Concn (mg/liter) in serum/concn in pleural fluid at following time (h) after dose:								
	0	0.08	0.25	0.5	1	2	4	6	8
6	ND[b]	2.16/ND	1.03/ND	0.77/ND	0.46/0.37	0.36/0.49	ND/0.32	0.17/0.22	0.08/0.10
7	0.41/ND	3.52/ND	2.14/ND	1.64/ND	1.24/0.77	0.98/1.08	0.75/0.86	0.63/0.74	0.54/0.62
8	0.23/0.26	3.54/ND	2.21/ND	1.37/0.70	1.00/0.99	0.89/0.91	0.64/0.63	0.49/0.39	0.41/0.30
9	0.11/0.24	ND	1.51/ND	0.70/0.12	0.49/0.39	0.43/0.36	0.30/0.37	0.25/0.38	0.22/0.33
10	0.22/0.44	2.91/ND	ND	1.70/0.73	1.43/1.03	0.91/1.02	0.61/0.87	0.42/0.70	0.36/0.59
Mean ± SEM	0.24 ± 0.06/ 0.31 ± 0.06	3.03 ± 0.29/ND	1.72 ± 0.28/ND	1.24 ± 0.21/ 0.52 ± 0.20	0.92 ± 0.19/ 0.71 ± 0.14	0.71 ± 0.13/ 0.77 ± 0.15	0.57 ± 0.10/ 0.61 ± 0.12	0.39 ± 0.08/ 0.48 ± 0.10	0.32 ± 0.08/ 0.39 ± 0.10

[a] One dose equalled 1.5 mg of ciprofloxacin per kg of body weight.
[b] ND, Not done.

aeruginosa and *Staphylococcus aureus*. The broad antibacterial spectrum and the encouraging kinetic properties of ciprofloxacin make it a promising agent for the treatment of nosocomial empyemas.

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