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Pharmacokinetics and Sputum Penetration of Ciprofloxacin in Patients with Cystic Fibrosis

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Levels of ciprofloxacin in serum and sputum were studied for eight patients with cystic fibrosis who were infected with *Pseudomonas aeruginosa*. Patients were studied in a steady state on a dosage of 500 mg every 8 h. Peak levels in serum ranged from 1.27 to 5.6 mg/liter (mean, 3.16 ± 1.27), and absorption was rapid, the time to peak concentration ranging from 0.5 to 3.0 h (mean, 1.5 ± 0.9). The antibiotic penetrated sputum well, achieving areas under the curve of approximately 46% of those obtained in serum.

Ciprofloxacin has a high in vitro activity against a broad spectrum of organisms and appears to be considerably more active against *Pseudomonas aeruginosa* than currently available penicillins, cephalosporins, or aminoglycosides (6, 7). A further major advantage is that the drug is well absorbed when administered orally (1). The major pathogen present in the sputum of adult patients with cystic fibrosis (CF) is *P. aeruginosa*. At present, acute infective exacerbations are treated with parenterally administered antibiotics, usually a combination of either an antipseudomonal penicillin or a cephalosporin with an aminoglycoside. Some patients also require long-term treatment with aerosol antibiotics. An oral preparation active against *P. aeruginosa* would be of great advantage to these patients.

Almost all patients with CF have abnormal pancreatic function with malabsorption, and absorption of some antibiotics was shown to be slower in CF patients than in controls (3). Furthermore, the elimination of some antibiotics appears to be accelerated in CF patients (3). The purpose of this study was, therefore, to investigate the pharmacokinetic properties of ciprofloxacin after oral administration in young adults with CF and to determine the penetration of the antibiotic into sputum.

Eight adults with CF who were chronically infected with *P. aeruginosa* and who required hospital admission for intensive therapy were studied. There were four males and four females, with a mean age of 24.3 years (range, 18 to 30 years). Their mean body weight was 55.2 kg (range, 40 to 73 kg). On day 1 of the study, before administration of the drug, each patient underwent a detailed clinical examination and routine hematological and biochemical screening. They were then given oral dosages of 500 mg of ciprofloxacin every 8 h for a total of 10 days. Pharmacokinetic studies were performed on day 3 of therapy. Blood samples were taken from an indwelling intravenous cannula at 0, 15, 30, and 60 min and at 2, 3, 4, 5, 6, 7, and 8 h after the administration of the first morning dose. Serum was separated from all samples within 1 h of collection and stored at −20°C until assayed. Sputum was obtained at the same sampling times and similarly stored at −20°C.

Ciprofloxacin concentrations in serum and sputum were assayed by high-performance liquid chromatography by using a slightly modified version of the method described by Gau et al. (2). The limit of sensitivity was 0.05 mg/liter, and in our laboratory, the coefficients of variation were less than 3%. Peak concentrations (C_{max}) in serum and sputum and the time taken to reach the peak (T_{max}) were measured. Individual concentrations of ciprofloxacin in serum were plotted semilogarithmically against time, and values were obtained for the terminal elimination half-life ($t_{1/2\beta}$). Reliable estimates of the $t_{1/2\beta}$ of ciprofloxacin from sputum could not be

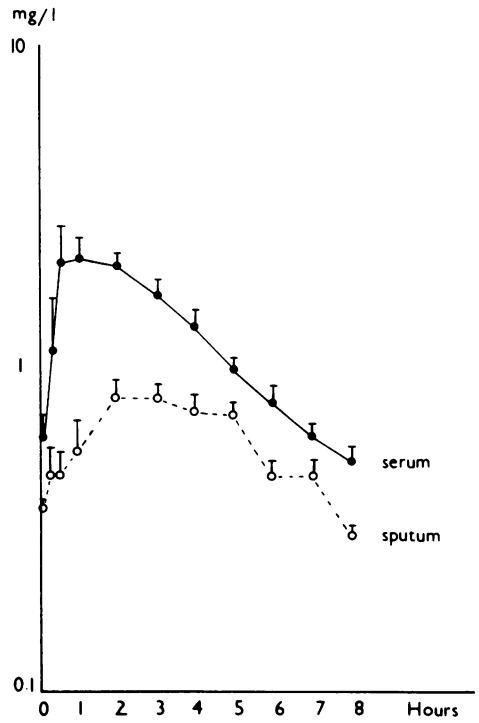

FIG. 1. Mean concentrations of ciprofloxacin in serum and sputum (n = 8). Vertical bars represent the standard error of the mean.

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TABLE 1. Pharmacokinetic parameters of ciprofloxacin obtained from serum and sputum of CF patients (n = 8)

Patient	Pharmacokinetics of ciprofloxacin in:						
	Serum				Sputum		
	T_{max} (h)	C_{max} (mg/liter)	AUC_{0-8} (mg·h/liter)[a]	$t_{1/2\beta}$ (h)	T_{max} (h)	C_{max} (mg/liter)	AUC_{0-8} (mg·h/liter)[a]
1	2.0	1.93	7.77	3.7	0.25	0.98	3.60
2	2.0	3.13	11.31	4.8	2.0	1.00	5.37
3	1.0	1.49	8.21	4.2	3.0	0.92	5.24
4	2.0	2.46	9.49	2.8	2.0	1.18	5.05
5	0.5	5.60	17.80	3.5	3.0	1.43	7.43
6	1.0	3.74	11.23	4.4	2.0	0.57	3.08
7	3.0	3.26	13.01	2.1	3.0	1.07	4.85
8	0.5	3.65	8.40	3.2	1.0	0.92	4.28
Mean (SD)	1.5 (0.9)	3.16 (1.27)	10.90 (3.33)	3.6 (0.9)	2.0 (1.0)	1.01 (0.24)	4.86 (1.32)

[a] AUC from 0 to 8 h.

obtained. Areas under the curve (AUCs) were calculated from 0 to 8 h by the trapezoidal rule and corrected for body weight in each individual. Correlations between levels in serum and sputum were determined by linear regression analysis.

The mean concentrations of ciprofloxacin in the serum and sputum of the CF patients are shown in Fig. 1. The pharmacokinetic data are summarized in Table 1. The mean C_{max} of ciprofloxacin in serum ± the standard deviation was 3.16 ± 1.27 mg/liter (range, 1.49 to 8.04 mg/liter), and the mean T_{max} was 1.5 ± 0.9 h. The mean trough level at time 0 (on day 3 of therapy) was 0.64 ± 0.35 mg/liter. Peak concentrations in sputum occurred at a mean of 2.0 ± 1.0 h after the dose was administered and were approximately 30% of those obtained in serum (mean 1.01 mg/liter compared with 3.16 mg/liter in serum), and the mean ratio of the sputum-serum AUC was 0.46 ± 0.11. There was a significant correlation between ciprofloxacin levels in serum and sputum (r = 0.621, $P < 0.05$). The mean $t_{1/2\beta}$ of ciprofloxacin in serum was 3.6 ± 0.9 h. AUCs in serum (mean, 10.90 ± 3.33 mg · h/liter) were reasonably consistent. AUCs in sputum ranged from 3.08 to 7.43 mg · h/liter.

A previous study of ciprofloxacin pharmacokinetics for normal subjects demonstrated that the drug was rapidly absorbed after oral administration and that levels in serum well above the MICs for *Enterobacteriaceae*, *Haemophilus influenzae*, *P. aeruginosa*, and *Staphylococcus aureus* could be achieved after a single dose of 500 mg (1).

The results of the present study confirm that ciprofloxacin is also well absorbed in CF patients, and the mean C_{max} in serum of 3.2 mg/liter is very similar to that reported by Le Bel et al. (M. Le Bel, F. Vallee, and M. G. Bergeron, Proc. 14th Int. Congr. Chemother., p. 176, 1985) of 3.5 mg/liter for normal controls taking 500 mg every 8 h. Lower AUCs were obtained for the CF patients (mean, 10.90 ± 2.98 mg · h/liter) than for normal subjects studied in a steady state (mean, 19.34 ± 8.41 mg · h/liter [Le Bel et al., 14th ICC). However, this may in part be due to a greater variation in AUCs in the normal subjects. T_{max} for the CF patients was slightly later than that found for normal subjects (1.5 ± 0.9 and 1.04 ± 0.42 h, respectively [Le Bel et al., 14th ICC]). Furthermore, the mean serum $t_{1/2\beta}$ of 3.6 ± 0.9 h for the CF patients was very similar to that found for normal subjects (3.9 ± 0.8) (1).

The MIC for 90% of the *P. aeruginosa* strains (MIC_{90}) of ciprofloxacin was shown in several studies to be around 0.25 mg/liter. (6, 7; A. Dalhoff, G. Döring, and W. Goldstein, Proc. 9th Int. Cystic Fibrosis Congr., p. 289, 1984). Concentrations in serum well above this level were achieved for all patients during the 8-h study period. The results of the sputum studies show that ciprofloxacin penetrates sputum well and concentrations above the MIC_{90} for *P. aeruginosa* were achieved for all patients. This is in striking contrast to many other antibiotics used in the treatment of *P. aeruginosa* infection in CF patients. For instance, studies of levels of gentamicin, carbenicillin, azlocillin, and ticarcillin in sputum after intravenous administration show relatively poor penetration into sputum, with levels well below the MIC for *P. aeruginosa* (4, 5). For four of the eight patients, levels of ciprofloxacin in sputum fell below 0.25 mg/liter after 7 h. In view of this, it may be that larger or more frequent doses should be considered in pulmonary infections if levels in sputum consistently above the MIC_{90} are desired.

As already stated, *P. aeruginosa* is by far the most common pathogen encountered in the sputum of adult patients with CF. Two other organisms, *S. aureus* and *H. influenzae*, are also encountered very frequently. Ciprofloxacin was shown to have high in vitro bactericidal activity against both of these organisms, with reported MIC_{90}s of 0.5 mg/liter and <0.25 mg/liter, respectively.

There are a number of reasons, therefore, why ciprofloxacin may theoretically be a very useful antibiotic in the treatment of pulmonary infections in CF patients. The results of this study show that the drug is well absorbed in CF patients and has good penetration into the sputum. There is a need for further clinical trials to establish whether ciprofloxacin is a possible alternative to conventional parenteral or aerosol antipseudomonal therapy.

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