ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 1987, p. 899–902
0066-4804/87/060899-04$02.00/0

Vol. 31, No. 6

Penetration of Ciprofloxacin into Cerebrospinal Fluid of Patients with Bacterial Meningitis

M. WOLFF,[1]* L. BOUTRON,[2] E. SINGLAS,[2] B. CLAIR,[1] J. M. DECAZES,[3] AND B. REGNIER[1]

Intensive Care Unit, Claude Bernard Hospital, 75019 Paris,[1] Department of Clinical Pharmacy, Bicêtre Hospital, 94270 Kremlin-Bicêtre,[2] and Department of Infectious Disease, Saint Louis Hospital, 75475 Paris Cedex 10,[3] France

Received 12 January 1987/Accepted 25 March 1987

We evaluated the diffusion of ciprofloxacin into the cerebrospinal fluid (CSF) in 23 patients with bacterial meningitis or ventriculitis undergoing treatment with other antibiotics. Three successive ciprofloxacin doses of 200 mg were administered intravenously at 12-h intervals, first between days 2 and 4 and again between days 10 and 20 after the admission. Concentrations of ciprofloxacin in plasma and CSF obtained at 60, 120, 240, and 480 min after the third infusion were determined by high-performance liquid chromatography. In addition, serial samples were obtained from ventricular fluid in four patients. The concentrations of ciprofloxacin in CSF ranged from 0.35 to 0.56 μg/ml. These concentrations were equal to or higher than the MICs for most of the enterobacteria.

Ciprofloxacin has an extremely broad range of antibacterial activity, including most organisms responsible for purulent meningitis, except *Streptococcus pneumoniae* (1). In a recent study it has been demonstrated that ciprofloxacin diffuses into the cerebrospinal fluid (CSF) of rabbits with experimental ampicillin-resistant *Haemophilus influenzae* meningitis. Moreover, it was rapidly bactericidal in this model (M. W. Sobiesky and W. M. Scheld, Program Abstr. 25th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 216, 1985). These in vitro and in vivo studies led to the current evaluation of the penetration of ciprofloxacin into the CSF of patients with bacterial meningitis who were undergoing concurrent treatment with conventional antibiotics.

(This work was presented in part at the 26th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, La., October 1986.)

MATERIALS AND METHODS

A total of 23 hospitalized patients, 20 with purulent meningitis and 3 with associated ventriculitis, were included in the study. There were 16 males and 7 females, whose ages ranged from 19 to 79 years (mean, 47). The mean Glasgow coma score was 8 ± 3. Leukocyte count ranged from 63 to 23,300/mm^3 of CSF with a predominance of polymorphonuclear leukocytes (60 to 100%) in all but three patients (no. 4, 8, and 14). CSF protein concentration ranged from 80 to 8.00 mg/dl. The ratio of glucose in CSF to blood was less than 0.30 in all but two cases (no. 4 and 8). One patient (no. 7) had severe renal failure.

All 23 patients were under treatment with other antibiotics (Table 1).

Three successive ciprofloxacin doses of 200 mg were infused over 30 min at 12-h intervals during the acute stage of meningitis, between days 2 and 4 after admission. After 10 to 14 days of treatment with the other antibiotics, when the meninges were considered to be healed, 14 patients received three additional doses of ciprofloxacin. The mean dose was 3 ± 0.50 mg/kg.

CSF samples were obtained 60 (patients 1 to 7), 120 (patients 8 to 12), 240 (patients 13 to 17), and 480 (patients 18 to 23) min after the end of the third infusion of ciprofloxacin. Blood was sampled before the third dose (trough level), at the end of the infusion (peak level), and at the time of CSF drawing. In addition, serial samples were drawn from ventricular fluid in the three patients with ventriculitis, either via a Rickam catheter (no. 6) or by ventricular drainage (no. 14 and 15). A 24th patient with *Listeria monocytogenes* meningitis and acute hydrocephalus was included in the study.

Informed consent was obtained from each patient or from his family. All patients were monitored for adverse reactions.

The concentrations of ciprofloxacin in plasma and CSF were determined by high-performance liquid chromatography with a spectrofluorometric detector. The chromatographic system consisted of a pump (Lirec A801), an automatic sample injector (Wisp 710 B, Waters), and a Lichrosorb RP18 column (5 μm to 125 mm, Merck). The

TABLE 1. Antibiotic treatment

Patient no.	Etiological agent	Antibiotic(s)	Daily dose (mg/kg)
1–3, 5, 7–10, 16, 17, 19–23	*Streptococcus pneumoniae*	Ampicillin	200
4, 13	*Listeria monocytogenes*	Ampicillin	200
		Gentamicin	3
14	*Enterococcus faecalis*	Ampicillin	150
		Gentamicin	3
6	*Streptococcus milleri*	Ampicillin	150
		Chloramphenicol	50
18	*Haemophilus influenzae*	Cefotaxime	100
11	*Pseudomonas aeruginosa*	Ceftazidime	100
		Tobramycin	3
15	*Staphylococcus aureus*	Vancomycin	30
		Amikacin	15

* Corresponding author.

TABLE 2. Ciprofloxacin concentrations in CSF and plasma

Sampling time (min)	Patient no. (age [yr], sex)	Etiological agent	Ciprofloxacin concn (μg/ml) at time: Days 2 to 4 CSF	Plasma	CSF/plasma (%)	Days 10 to 14 CSF	Plasma	CSF/plasma (%)
60	1 (28, M)	*Streptococcus pneumoniae*	0.22	0.85	25.8	0.19	2.12	8.9
	2 (19, M)	Aseptic	0.11	0.99	11.1	0.11	1.42	7.7
	3 (19, F)	*Neisseria meningitidis*	0.38	0.85	44.7	0.12	1.06	11.3
	4 (64, M)	*Listeria monocytogenes*	0.35	2.47	14.1	ND[a]	ND	ND
	5 (66, F)	*Neisseria meningitidis*	0.68	2.15	31.6	ND	ND	ND
	6 (49, M)	*Streptococcus milleri*	0.30[b]	0.86	34.8	0.18[b]	0.60	30
	7 (48, F)	*Neisseria meningitidis*	0.68	2.95	23	ND	ND	ND
	Mean		0.39	1.59	26.4	0.15	1.30	14.4
	SD		0.22	0.91	11.7	0.04	0.64	10.4
120	8 (60, M)	*Streptococcus agalactiae*	0.63	1.37	45.9	0.31	1.29	24
	9 (43, M)	*Streptococcus pneumoniae*	0.46	1.10	41.8	0.14	0.78	17.9
	10 (59, M)	*Streptococcus pneumoniae*	0.23	1.31	17.5	ND	ND	ND
	11 (28, M)	*Pseudomonas aeruginosa*	0.29	0.83	34.9	0.28	ND	ND
	12 (16, M)	*Streptococcus pneumoniae*	1.20	2.60	46.1	0.33	1.28	25.7
	Mean		0.56	1.44	37.2	0.27	1.12	22.5
	SD		0.39	0.68	11.9	0.09	0.29	4.1
240	13 (63, F)	*Listeria monocytogenes*	0.80	2.49	32.1	0.50	1.37	36.5
	14 (36, M)	*Enterococcus faecalis*	0.39[b]	0.70	55.7	0.25[b]	0.83	30.1
	15 (60, M)	*Staphylococcus aureus*	0.26[b]	0.69	37.6	ND	ND	
	16 (79, F)	*Streptococcus pneumoniae*	0.53	0.73	72.6	0.15	0.74	20.2
	17 (49, M)	*Streptococcus pneumoniae*	0.49	0.57	86	0.16	0.42	38
	Mean		0.49	1.04	56.8	0.27	0.84	31.2
	SD		0.20	0.82	22.8	0.16	0.39	8.1
480	18 (63, M)	*Haemophilus influenzae*	0.61	0.40	153	0.14	0.17	82.3
	19 (35, M)	*Neisseria meningitidis*	0.45	0.33	136	0.16	0.22	72.7
	20 (45, M)	*Neisseria meningitidis*	0.24	0.09	266	ND	ND	ND
	21 (35, F)	*Neisseria meningitidis*	0.07	0.18	38.8	ND	ND	ND
	22 (53, F)	*Streptococcus pneumoniae*	0.53	0.33	160	ND	ND	ND
	23 (37, M)	*Streptococcus pneumoniae*	0.22	0.11	200	ND	ND	ND
	Mean		0.35	0.24	159	0.15	0.20	77.5
	SD		0.21	0.13	75	0.01	0.04	6.8

[a] ND, Not determined.
[b] Ventricular concentrations of ciprofloxacin.

spectrofluorometric detector (Shimadzu RF 530) was used to measure the ciprofloxacin at an excitation/emission wavelength pair of 276/441 nm. The peak areas were measured on a Delsi Icap 50 recorder. The degassed mobile phase consisted of a mixture of methanol (RP Normapur; Prolabo) and Pic A (tetrabutyl-ammonium phosphate; Waters) acidified to pH 3.00 with orthophosphoric acid, monitored by a pH meter. The proportions of the methanol-Pic A mixture were, respectively, 20 and 80% for the plasma levels and 18 and 82% for the CSF levels. The flow rate was 1.5 ml/min for the plasma and 1.3 ml/min for the CSF.

The samples were frozen at −80°C and stored until analyzed. They were centrifuged for 5 min at 3,000 rpm. Samples with an internal standard [synthetic quinolone: 1-allyl-6-fluoro-1,4-dihydro-4-oxo-7(4-methyl-1-piperazinyl) quinoline 3-carboxylic acid] were precipitated by an equal volume of acetone. The mixture was vortexed for 1 min after centrifugation at 3,000 rpm for 5 min; 20 μl of the clear upper phase was then injected into the column.

The lower limit of sensitivity was 0.02 μg/ml, and the coefficient of variation on replicate determinations at 2.5 μg of ciprofloxacin per ml was 2.5%. There was no interference with the ciprofloxacin assay when samples of plasma containing ampicillin, gentamicin, cefotaxime, and vancomycin at therapeutic concentrations were extracted and 20 μl was injected into the chromatographic column.

RESULTS

The mean peak levels in plasma were 5.5 ± 3.53 μg/ml during the acute stage of the disease and 4.42 ± 2.93 μg/ml during the late stage. The mean trough levels were 0.27 ± 0.37 and 0.13 ± 0.09 μg/ml, respectively. However, trough levels were undetectable in seven cases. The concentrations of ciprofloxacin in CSF and in plasma obtained at the time of CSF drawing are shown in Table 2. While mean plasma levels decreased from 1.59 ± 0.91 to 0.24 ± 0.13 μg/ml between hours 1 and 8, there were no significant differences in mean CSF levels, which were 0.39 ± 0.22, 0.56 ± 0.39, 0.49 ± 0.20, and 0.35 ± 0.21 μg/ml, respectively, when the meninges were most inflamed. When the meningitis was considered to be cured, ciprofloxacin levels in CSF were 0.15 ± 0.04, 0.27 ± 0.09, 0.27 ± 0.16, and 0.15 ± 0.01 μg/ml at 60, 120, 240, and 480 min, respectively, after completion of the third infusion. The percentages of penetration, ex-

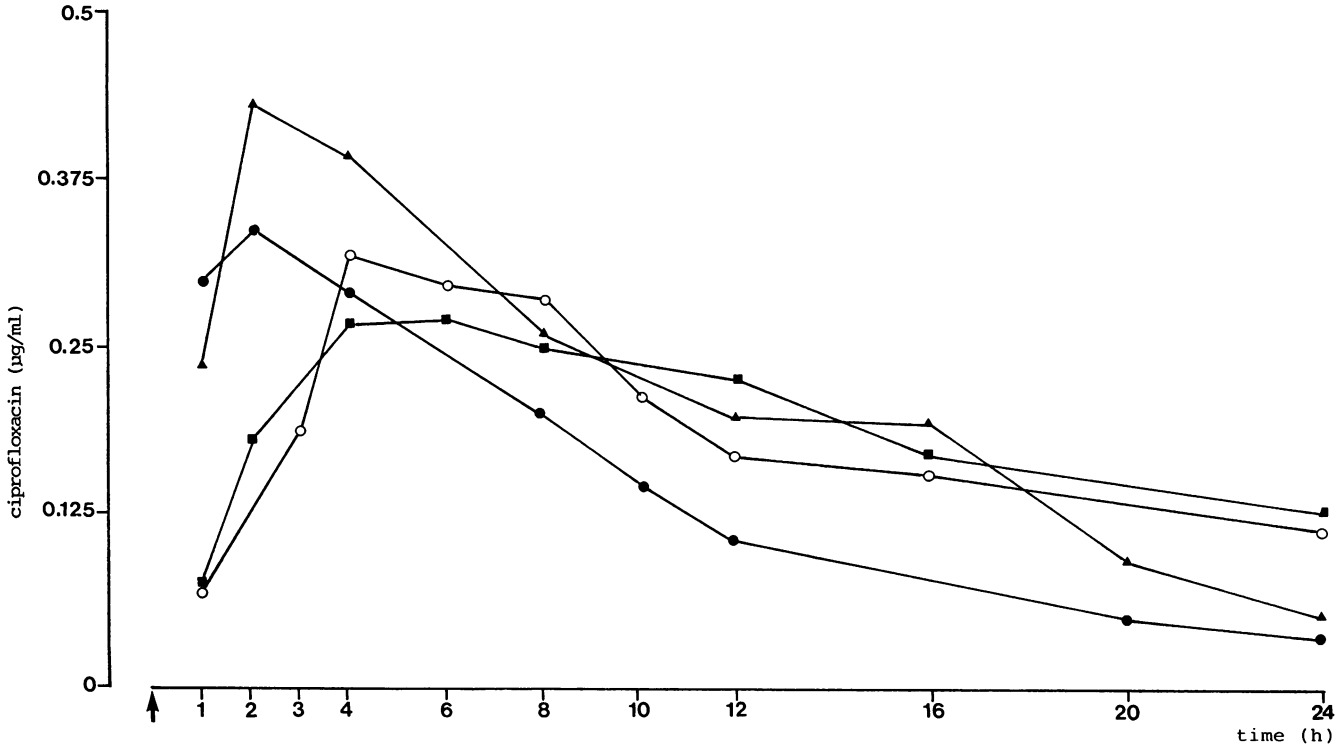

FIG. 1. Ventricular concentrations of ciprofloxacin in patients 4 (●), 14 (▲), 15 (■), and 24 (○). Arrow indicates the end of the ciprofloxacin infusion.

pressed as the ratio of CSF concentration to simultaneous plasma level, are indicated in Table 2. The percentages in CSF of the peak plasma concentrations were 6.5 ± 3.1, 9.0 ± 6.2, 16.2 ± 15.3, and 10.2 ± 5.5% during the acute stage and 4.5 ± 1.4, 5.5 ± 2.1, 9.9 ± 7.7, and 4% during the late stage of the disease.

Ciprofloxacin levels obtained in ventricular fluid are shown in Fig. 1. Peak concentrations occurred between 2 and 4 h after the third dose. No significant relationship was observed between amount of drug in CSF and the protein or glucose concentrations. Ciprofloxacin was still detectable at hour 24.

No adverse reaction was noted.

DISCUSSION

In this study ciprofloxacin appeared to penetrate into the CSF of patients with bacterial meningitis. The concentrations of ciprofloxacin in CSF were equal to or higher than the reported MICs or MBCs against most enterobacteria. During the first 2 h after the infusion, the percentages of penetration were 26 and 37% in the early stage of the disease. These values are very similar to those found by Sobiesky and Scheld (25th ICAAC) in an experimentally induced *H. influenzae* meningitis. In their model a single 50-mg/kg dose of ciprofloxacin, administered intramuscularly, resulted in a mean peak level in the CSF of 0.61 µg/ml. The mean percentage of penetration into the CSF was 21.7%. At dosages ranging from 1 to 30 mg/kg per h the percentage of penetration was 18% in rabbits with *Pseudomonas aeruginosa* meningitis. At 5 mg/kg per h, ciprofloxacin was in this model as effective as the combination of ceftazidime and tobramycin in reducing bacterial titers (2).

As the ciprofloxacin plasma half-life is about 4 h, the percentage of penetration into the CSF appeared to be inversely proportional to the plasma concentrations. Therefore the values of 56 and 159% observed at 4 and 8 h are not reliable. Since the concentrations of ciprofloxacin in CSF remained approximately the same during the 8-h period, the percentages in CSF of the peak plasma concentrations were more constant, ranging from 6.5 to 16%. In the late stage of meningitis the percentages of penetration were 14.5 and 22.5% during the first 2 h. In the 14 patients who were studied during both periods of the disease, the mean ratio of plasma concentrations in the acute to late stage was very near 1. In contrast, the mean ratio was 2.4 in CSF, suggesting that the diffusion of ciprofloxacin was 2.5 times higher during the acute stage. Ciprofloxacin diffuses in ventricular fluid, and detectable levels are found even 24 h after the last dose. An infant with *P. aeruginosa* ventriculitis was recently successfully treated with intravenous ciprofloxacin at a daily dose of 4 mg/kg. CSF ventricular concentrations ranged from 0.10 to 0.37 µg/ml (3). Another patient with *P. aeruginosa* meningitis was cured by ciprofloxacin associated with tobramycin, but the CSF concentrations of ciprofloxacin were not measured (4).

From these data we suggest that (i) ciprofloxacin diffuses well into the CSF of patients with bacterial meningitis, (ii) this diffusion appears to persist (but to a lesser extent) beyond the point at which the meningitis is cured, and (iii) CSF concentrations exceed the MICS for most strains responsible for purulent meningitis. However, (iv) these levels may be close to the MICs for *P. aeruginosa* and staphylococci, and (v) further studies are needed to evaluate CSF bactericidal titers in patients treated with this agent.

LITERATURE CITED

1. **Chin, N. X., and H. C. Neu.** 1984. Ciprofloxacin, a quinolone carboxylic acid compound active against aerobic and anaerobic bacteria. Antimicrob. Agents Chemother. **25**:319–326.
2. **Hackbarth, C. J., H. F. Chambers, F. Stella, A. M. Shibl, and M. A. Sande.** 1986. Ciprofloxacin in experimental *Pseudomonas aeruginosa* meningitis in rabbits. J. Antimicrob. Chemother. **18**(Suppl. D):65–69.
3. **Issacs, D., M. P. E. Slack, A. R. Wilkinson, and A. W. Westwood.** 1986. Successful treatment of *Pseudomonas* ventriculitis with ciprofloxacin. J. Antibicrob. Chemother. **17**:535–538.
4. **Millar, M. R., M. A. Bransby-Zachary, D. S. Tompkins, P. M. Hawkey, and R. Gibson.** 1986. Ciprofloxacin for *Pseudomonas aeruginosa* meningitis. Lancet **i**:1325.