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Kinetics of Ofloxacin and Its Metabolites in Cerebrospinal Fluid after a Single Intravenous Infusion of 400 Milligrams of Ofloxacin

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Ofloxacin has been reported to diffuse readily into the cerebrospinal fluid (CSF) in subjects with both inflamed and uninflamed meninges. However, with moderately susceptible bacteria, ofloxacin concentrations in CSF may be subtherapeutic after administration of an intravenous (i.v.) dose of 200 mg. For this reason, the kinetics of a higher dose of ofloxacin in CSF was studied with humans. Six patients with occlusive hydrocephalus caused by cerebrovascular diseases who had undergone external ventriculostomy received 400 mg of ofloxacin i.v. over 30 min. Serum and CSF samples were drawn repeatedly. Serum from 12 healthy volunteers was sampled repeatedly after they had received 400 mg of ofloxacin i.v. over 60 min. Ofloxacin, ofloxacin-*N*-oxide, and *N*-desmethyl-ofloxacin concentrations were determined by high-pressure liquid chromatography with fluorescence detection. The maximum ofloxacin concentrations in the serum of the patients ranged from 7.36 to 11.6 mg/liter (mean, 9.55 mg/liter), the apparent volume of distribution/body weight was 0.96 to 1.19 liters/kg (mean, 1.11 liters/kg), and the total body clearance was 115 to 280 ml/min (mean, 192 ml/min). In healthy volunteers, the volume of distribution/body weight and the total body clearance were higher and amounted to 1.27 ± 0.18 liters/kg and 217 ± 43 ml/min (means ± standard deviations), respectively. These differences were attributed to the older ages of the patients than the volunteers. In the CSF of patients, maximum concentrations of 1.00 to 2.85 mg/liter (mean, 2.04 mg/liter) were observed 0.5 to 4 h following the completion of the ofloxacin infusion. Ofloxacin elimination from CSF was slightly slower than that from serum (half-lives, 4.33 to 10.02 versus 4.27 to 9.14 h). The overall penetration of ofloxacin into CSF, as expressed by the ratios of the areas under the concentration-time curves, amounted to 0.59 to 0.81 (mean, 0.65). The more hydrophilic metabolites ofloxacin-*N*-oxide and *N*-desmethyl-ofloxacin passed less readily than ofloxacin into the CSF. In conclusion, the concentrations in CSF attained after a single i.v. infusion of 400 mg of ofloxacin in the absence of meningeal inflammation appear to be high enough to inhibit the growth of most staphylococci and members of the family *Enterobacteriaceae*, which are often involved in CSF shunt infections. Yet, in view of pharmacodynamic studies suggesting a peak concentration in CSF of at least 10-fold the MIC, the use of ofloxacin for central nervous system infections is optimal only with highly susceptible pathogens (MIC, ≤0.12 mg/liter).

Ofloxacin is a moderately lipophilic quinolone with an octanol-water partition coefficient of 0.41 at pH 7.0, 0.33 at pH 7.2, and 0.28 at pH 7.3 (1, 7, 22) and a molecular mass of 361.4 Da. It is active against gram-positive and gram-negative bacteria. Its antibacterial spectrum may allow ofloxacin to be used for the therapy of ventricular shunt infections. In subjects with inflamed and uninflamed meninges, ready passage of ofloxacin into the cerebrospinal fluid (CSF) has been observed after administration of an oral or intravenous (i.v.) dose of 200 mg (2, 15, 20, 21). The concentrations in CSF were, however, not high enough to be relied upon for use in treating central nervous system (CNS) infections caused by the staphylococci predominantly involved in ventriculitis (2, 15, 20, 21).

The aim of the present study was to evaluate whether (i) the transport of ofloxacin into CSF is approximately linear and (ii) adequate concentrations can be obtained in CSF by doubling the dose. Since ventricular shunt infections are often accompanied by minor disturbances of the blood-CSF barrier, the study was performed with patients with noninflammatory CNS diseases. Furthermore, the pharmacokinetic parameters of ofloxacin calculated from the concentrations in the sera of these critically ill patients were compared with those for healthy volunteers.

MATERIALS AND METHODS

Six patients who had undergone external ventriculostomy for occlusive hydrocephalus caused by cerebrovascular diseases received ofloxacin for the treatment of respiratory or urinary tract infections (for further details on the patients studied, see Table 1). Patients with CNS infections or impaired renal function (creatinine level in serum, ≥1.2 mg/dl) were not included. The permeability of the blood-CSF barrier was characterized by the protein content in CSF and the ratio of the albumin content in CSF to that in serum (Q_{Alb}) (16). The disturbance of the blood-CSF barrier ranged from not detectable to moderate. Comedications included benzodiazepines, opioids, antibiotics, catecholamines, diuretics, antihypertensives, osmotherapeutics, corticosteroids, H_2-receptor blockers, and heparin according to clinical necessities. The study protocol was approved by the Ethics Committee of the Medical Faculty of the University of Göttingen. Informed consent for participation in the study was obtained from the patients' nearest relatives. A total of 400 mg of ofloxacin (Tarivid;

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TABLE 1. Characterization of the patients investigated by descending peak ofloxacin concentrations in CSF[a]

Patient no.	Body wt (kg)	Age, sex	Disease	Serum creatinine concn (mg/dl)	CSF analysis			
					Protein (mg/liter)	Q_{Alb} (10^3)	WBC (per mm^3)	RBC (per mm^3)
1	75	67, m	Subarachnoid hemorrhage	0.5	1,314	14.3	39	25,259
2	75	71, m	Subarachnoid hemorrhage	0.8	617	5.2	28	17,920
3	80	54, f	Subarachnoid hemorrhage	0.4	102	1.8	3	1,536
4	70	62, f	Infratentorial infarction	0.6	442	5.2	10	7,595
5	65	76, f	Subarachnoid hemorrhage	0.7	1,749	10.0	272	85,333
6	80	65, m	Intracerebral hemorrhage	0.9	1,795	2.0	5	2,986

[a] m, male; f, female; Q_{Alb}, ratio of albumin concentration in CSF to that in serum; WBC, leukocyte count; RBC, erythrocyte count.

Hoechst AG, Frankfurt am Main, Germany) was infused i.v. over 30 min once daily. Simultaneous blood and CSF samples were drawn before; at the end; and at 10 and 30 min and 1, 2, 4, 7, 10, 13, 16, 20, and 24 h after the end of the first infusion.

Twelve healthy volunteers (six females and six males; age, 28 ± 8 years, body weight, 67 ± 14 kg; values are means ± standard deviations [SDs]) with no comedication received 400 mg of ofloxacin over 60 min. Blood was sampled before; at 15, 30, and 45 min during the ofloxacin infusion; at the end of the infusion; and at 5, 10, 20, 30, and 45 min and 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 30, 36, 48, 60, and 72 h after the end of the infusion. Healthy volunteers gave written informed consent.

The samples were centrifuged at 3,000 × g for 5 min, and the supernatant was stored at −70°C for less than 3 months. Storage for up to 6 months did not affect the assay results.

The concentrations of ofloxacin, ofloxacin-*N*-oxide, and *N*-desmethyl-ofloxacin in serum and CSF were measured by high-pressure liquid chromatography in an isocratic system (column, Spherisorb ODS II 5 μm; mobile phase, acetonitrile, 0.1 M citric acid, ion pairing reagents) by fluorescence detection (excitation wavelength, 293 nm; emission wavelength, 490 nm). Peaks were quantitated by comparing their areas with those obtained with CSF and serum spiked with standard solutions of ofloxacin, ofloxacin-*N*-oxide, and *N*-desmethyl-ofloxacin. The quantification limits of ofloxacin were 0.0049 mg/liter in serum and 0.0046 mg/liter in CSF, those of ofloxacin-*N*-oxide were 0.0020 mg/liter in serum and 0.00096 mg/liter in CSF, and those of *N*-desmethyl-ofloxacin were 0.0010 mg/liter in serum and 0.00096 mg/liter in CSF. The assay of ofloxacin and its metabolites in serum and CSF was linear between 0.0049 and 10 mg/liter (ofloxacin), 0.001 and 10 mg/liter (*N*-desmethyl-ofloxacin), and 0.002 and 10 mg/liter (ofloxacin-*N*-oxide). A full standard curve of the concentrations of ofloxacin and its metabolites in serum and CSF was constructed with each batch of samples. With ofloxacin, the interday coefficient of variation for replicate determinations was 2.0% at a concentration of 9.64 mg/liter and 1.8% at 0.01 mg/liter in serum, and 1.6% at 8.89 mg/liter and 1.3% at 0.09 mg/liter in CSF. The interday coefficients of variation of *N*-desmethyl-ofloxacin were 1.8% (1.01 mg/liter in serum), 6.7% (0.01 mg/liter in serum), 2.9% (1.00 mg/liter in CSF), and 3.7% (0.01 mg/liter in CSF); those of ofloxacin-*N*-oxide were 2.4% (1.03 mg/liter in serum), 6.7% (0.01 mg/liter in serum), 1.7% (0.97 mg/liter in CSF), and 3.4% (0.01 mg/liter in CSF) (n = 4 to 6).

Maximum concentrations in serum and CSF (C_{maxS} and C_{maxCSF}, respectively) and the time from the end of infusion to reach C_{maxCSF} (t_{maxCSF}) were taken from the concentration-time curves. Pharmacokinetic calculations were performed by the programs Excel 2.2 (Microsoft Co., Redmond, Wash.) and Topfit 1.1 (Gödecke-Schering-Thomae, Freiburg-Berlin-Biberach, Germany). After using the weighting function $g(y_i) = 1/y_i$ (where g is the data set weighting function and y_i is the individual observed datum point), the elimination rate constants (k_β) were estimated by log-linear regression analysis, and elimination half-lives ($t_{1/2\beta}$) were calculated as ln $2/k_\beta$. The areas under the concentration-time curve from the beginning of the infusion to the last concentration measured in serum ($AUC_{S\ 0-t}$) and CSF ($AUC_{CSF\ 0-t}$) were estimated by the linear trapezoidal rule. AUC_{0-t} was extrapolated to infinity (AUC_S and AUC_{CSF}, respectively) by adding the last concentration measured divided by k_β. Total body clearance (CL) was calculated as dose/AUC_S, and the apparent volume of distribution (V_β) was calculated as dose/$AUC_S \cdot k_\beta$.

The ratios $AUC_{CSF\ 0-t}/AUC_{S\ 0-t}$ of ofloxacin, *N*-desmethyl-ofloxacin, and ofloxacin-N-oxide were compared by the U test

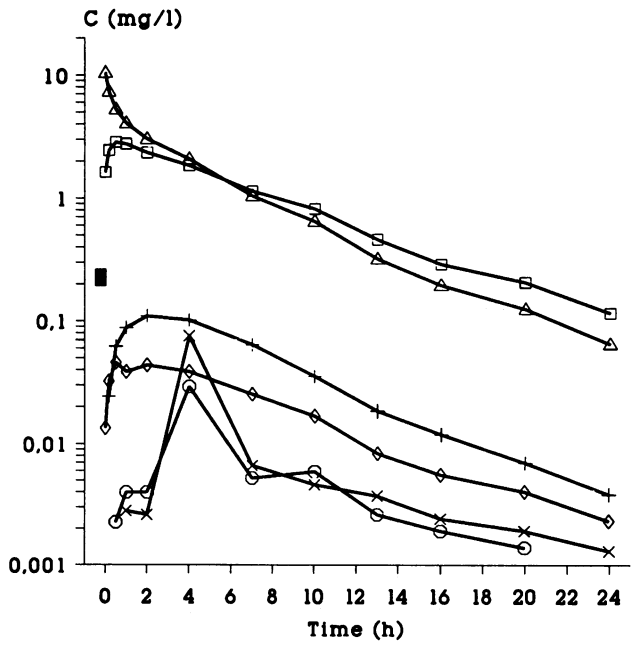

FIG. 1. Semilogarithmic plot of the concentration-time curves of ofloxacin, ofloxacin-*N*-oxide, and *N*-desmethyl-ofloxacin in patient 1 after i.v. administration of 400 mg over 30 min. Note that ofloxacin passed the blood-CSF barrier readily, whereas passage of the two metabolites into CSF was lower. The ofloxacin concentration in serum (△) and CSF (□), the ofloxacin-*N*-oxide concentration in serum (+) and CSF (×), and the *N*-desmethyl-ofloxacin in serum (◇) and CSF (○) were measured.

TABLE 2. Pharmacokinetics of ofloxacin in serum after administration of the first i.v. infusion of 400 mg over 30 min

Patient no.	C_{max} (mg/liter)	$t_{1/2\beta}$ (h)	CL (ml/min)	V_β (liter)	V_β/body weight (liters/kg)	AUC (mg · h/liter)
1	10.4	4.27	239	88.5	1.06	27.9
2	11.6	9.14	115	90.8	1.14	58.1
3	7.36	4.33	280	105	1.19	23.8
4	9.23	4.64	193	77.4	1.00	34.6
5	9.74	5.33	142	65.5	0.96	47.0
6	8.97	6.54	184	104	1.29	36.3
Mean ± SD	9.55 ± 1.43	5.71 ± 1.88	192 ± 61	88.5 ± 15.3	1.11 ± 0.12	38.0 ± 12.7

of Mann and Whitney for statistical differences. AUC_S, CL, V_β/body weight, and $t_{1/2\beta}$ in serum for the patients and the healthy volunteers were compared by the unpaired t test.

To relate the penetration of ofloxacin and its metabolites to their physicochemical properties, the partition coefficients (P_{app}s) of *N*-desmethyl-ofloxacin and ofloxacin-*N*-oxide between octanol and phosphate buffer were determined at pH 7.4: $\log_{10} P_{app} = (A_0 - A_1) \cdot A_0^{-1} \cdot V_a \cdot V_o^{-1}$, where A_0 and A_1 are the absorbances of the aqueous phase before and after partitioning, respectively, and $V_a \cdot V_o^{-1}$ is the ratio of the volumes of the aqueous and the lipid phases.

RESULTS

In patients the maximum concentrations of ofloxacin were 7.36 to 11.6 mg/liter in serum and 1.00 to 2.85 mg/liter in CSF. Maximum concentrations in CSF were observed 0.5 to 4 h after the end of the infusion. The elimination of ofloxacin from serum and CSF was log-linear, with the $t_{1/2\beta}$ being slightly slower in CSF ($t_{1/2\beta CSF}$) than in serum ($t_{1/2\beta S}$) ($t_{1/2\beta CSF}$, 4.33 to 10.02 h; $t_{1/2\beta S}$, 4.27 to 9.14 h). On the basis of the ratio AUC_{CSF}/AUC_S, the overall penetration of ofloxacin into CSF was 0.59 to 0.81. The two more hydrophilic metabolites ofloxacin-*N*-oxide and *N*-desmethyl-ofloxacin passed less readily than the parent compound into the CSF; the $AUC_{CSF\ 0-t}/AUC_{S\ 0-t}$ of ofloxacin was significantly greater than those of *N*-desmethyl-ofloxacin ($P = 0.03$) and ofloxacin-*N*-oxide ($P = 0.002$), and *N*-desmethyl-ofloxacin penetrated more readily than ofloxacin-*N*-oxide into CSF ($P = 0.04$). The pharmacokinetic data are summarized in Tables 2 to 5. Representative concentration-time curves of ofloxacin and its metabolites are shown in Fig. 1.

The AUC_{CSF}/AUC_S and $AUC_{CSF\ 0-t}/AUC_{S\ 0-t}$ of ofloxacin did not positively correlate with the protein content in CSF (Spearman's rank correlation coefficient [r_S] = −0.09 and −0.5, respectively) and correlated only on a low level with Q_{Alb} (r_S = 0.39 and 0.30, respectively). In contrast, strong correlations were present between the values of $AUC_{CSF\ 0-t}/AUC_{S\ 0-t}$ for ofloxacin-*N*-oxide and *N*-desmethyl-ofloxacin and the protein content in CSF (r_S = 0.67 and 1.00, respectively). The values of $AUC_{CSF\ 0-t}/AUC_{S\ 0-t}$ for ofloxacin-*N*-oxide and *N*-desmethyl-ofloxacin and Q_{Alb} were also correlated (r_S = 0.76 and 0.36, respectively). In healthy volunteers, C_{maxS} was 6.64 ± 1.48 mg/liter, $t_{1/2\beta S}$ was 4.59 ± 0.89 h, CL was 217 ± 43 ml/min, and V_β/body weight amounted to 1.27 ± 0.18 liters/kg (means ± SDs). Although $t_{1/2\beta S}$ was shorter, and CL and V_β/body weight were greater in the healthy volunteers than in the patients, these differences were not statistically significant ($P > 0.05$).

The octanol/phosphate buffer partition coefficient of *N*-desmethyl-ofloxacin at pH 7.4 was 0.0085; that of ofloxacin-*N*-oxide was 0.0098.

DISCUSSION

The linearities of the pharmacokinetic parameters of fluoroquinolones have not been unequivocally accepted. A nonlinear plasma-CSF transit dependent on the concentration of drug in plasma has been observed with ciprofloxacin in rats, which may have been caused by a carrier-mediated transport from CSF to blood (8). In contrast, the CSF ofloxacin concentrations measured in the present study were approximately twofold greater than those found after administration of the first dose of 200 mg to subjects with uninflamed meninges (2, 20); i.e., at doses of 200 and 400 mg, passage from serum to CSF was approximately linear in humans.

In the presence of meningeal inflammation, after administration of the third dose of 200 mg of ofloxacin administered at 12-h intervals, the maximum concentrations in CSF were comparable to those that we observed after administration of the first dose (15).

On the basis of the ratios AUC_{CSF}/AUC_S and $AUC_{CSF\ 0-t}/$

TABLE 3. Pharmacokinetics of ofloxacin in CSF after administration of the first i.v. infusion of 400 mg over 30 min

Patient no.	C_{max} (mg/liter)	T_{max} (h)	$t_{1/2\beta}$ (h)	AUC (mg · h/liter)	AUC_{CSF}/AUC_S	$AUC_{CSF\ 0-t}/AUC_{S\ 0-t}$	C_{max}/MIC^a	AUC_{CSF}/MIC (h)^a
1	2.85	0.5	5.13	22.5	0.81	0.79	5.7	45.0
2	2.36	1	10.02	37.7	0.65	0.62	4.7	75.4
3	2.03	1	4.33	15.5	0.65	0.65	4.1	31.0
4	2.01	2	4.73	20.4	0.59	0.58	4.0	40.8
5	1.97	2	7.11	29.8	0.63	0.58	3.9	59.6
6	1.00	4	8.60	21.5	0.59	0.53	2.0	43.0
Mean ± SD	2.04 ± 0.61	1.75 ± 1.25	6.65 ± 2.31	24.6 ± 7.9	0.65 ± 0.08	0.62 ± 0.09	4.1 ± 1.2	49.1 ± 15.8

[a] C_{maxCSF}/MIC and AUC_{CSF}/MIC were calculated by assuming a MIC of 0.5 mg/liter.

TABLE 4. *Kinetic* data for the metabolites ofloxacin-*N*-oxide and *N*-desmethyl-ofloxacin in serum after i.v. infusion of 400 mg of ofloxacin over 30 min

Patient no.	Ofloxacin-*N*-oxide				*N*-Desmethyl-ofloxacin			
	C_{max} (mg/liter)	T_{max} (h)	$t_{1/2\beta}$ (h)	AUC_{0-t} (mg · h/liter)	C_{max} (mg/liter)	T_{max} (h)	$t_{1/2\beta}$ (h)	AUC_{0-t} (mg · h/liter)
1	0.109	4	4.47	0.95	0.046	0.5	5.25	0.41
2	0.033	4	8.36	0.47	0.042	2	13.6	0.66
3	0.037	4	3.89	0.35	0.052	2	5.64	0.55
4	0.027	2	4.56	0.22	0.023	1	5.37	0.22
5	0.059	7	7.92	0.79	0.052	4	9.56	0.95
6	0.029	2	7.76	0.32	0.035	0.5	10.0	0.48
Mean ± SD	0.049 ± 0.032	3.8 ± 1.8	6.16 ± 2.05	0.51 ± 0.29	0.042 ± 0.011	1.7 ± 1.3	8.24 ± 3.39	0.54 ± 0.25

$AUC_{S\ 0-t}$, there was a high level of penetration of ofloxacin into CSF (0.59 to 0.81 and 0.53 to 0.79, respectively). It exceeded the level of penetration of the more hydrophilic drug ciprofloxacin into CSF (partition coefficient, 0.078 at pH 7.4) (22) after i.v. infusion of 200 mg, as estimated by us by using the same protocol (10), by more than twofold. The degree of transit of the lipophilic quinolone pefloxacin (partition coefficient at pH 7.4, 1.51) (22) into CSF after administration of an i.v. dose of 400 mg was almost as high as that of ofloxacin; mean ratios of drug concentrations in CSF/plasma were 0.59 and 0.65 at 6 and 24 h after dosing (3), and mean AUC_{CSF}/AUC_S, as estimated by the linear trapezoidal rule from Figures 1 and 2 of reference 3, approximated 0.43. Similarly, the $AUC_{CSF\ 0-t}/AUC_{S\ 0-t}$ of ofloxacin was significantly higher than those of the more hydrophilic metabolites *N*-desmethyl-ofloxacin and ofloxacin-*N*-oxide. N-methylation of the 4′ nitrogen position of the piperazine ring has been identified to increase lipophilicity and diffusion through membranes. The N-oxide metabolite, which lacks the betaine structure of the parent compound, which leads to a strong decrease in lipophilicity, penetrated the least readily into the CSF. The difference between the parent compound and the metabolites is well explained by their octanol/water partition coefficients at pH 7.4.

The AUC_{CSF}/AUC_S of ofloxacin (present study), pefloxacin (as estimated previously [3]), and ciprofloxacin (10) compared well with the tears/plasma AUC ratios of ofloxacin in humans (17). There was a high degree of penetration of the lipophilic drugs pefloxacin, fleroxacin, and ofloxacin into tears (tears/plasma AUC ratio, >0.5), but the degree of penetration was considerably lower with the more hydrophilic substances norfloxacin, enoxacin, and ciprofloxacin (tears/plasma AUC ratio, <0.3) (17). Our study also demonstrated not only that CL but also that V_β are lower in patients than in healthy volunteers. This is most likely caused by a reduced total body water content because of the older ages of the subjects in the patient group. Recently, we showed that V_β and CL of ciprofloxacin are also reduced in elderly patients (9).

Fluoroquinolones are antibacterial agents with higher degrees of lipophilicity than β-lactams or aminoglycosides. They have been shown to penetrate into many compartments of the body more readily than β-lactam or aminoglycoside antibiotics (6). Until now, 10 fluoroquinolones have been used in humans. Their extracerebral pharmacokinetics have been shown to be governed by their pH-dependent lipophilicities (17–19). Our data for ofloxacin and its two metabolites and the results obtained from simultaneous concentration-time curves for ciprofloxacin and pefloxacin in the CSF and serum of humans (3, 10) indicate that the entry of quinolones into CSF in the absence of meningeal inflammation in humans also is predominantly determined by lipophilicity.

In the present study, the AUC_{CSF}/AUC_S and $AUC_{CSF\ 0-t}/AUC_{S\ 0-t}$ of ofloxacin were not clearly correlated with the protein content in CSF and Q_{Alb}, suggesting a minor effect of the blood-CSF barrier function on the penetration of ofloxacin into CSF. The $AUC_{CSF\ 0-t}/AUC_{S\ 0-t}$ of the two hydrophilic metabolites, however, did correlate with the protein content in CSF and, less strongly, with Q_{Alb}; these parameters characterize the permeability of the blood-CSF barrier. Similarly, the AUC_{CSF}/AUC_S of the two hydrophilic β-lactams cefotaxime and ceftriaxone correlated with the protein content in CSF, while the passage of rifampin (octanol/water partition coefficient, 15.6) into CSF was independent of the protein content in CSF and Q_{Alb} (11, 12). This suggests that the transit of

TABLE 5. Kinetic data for the metabolites ofloxacin-*N*-oxide and *N*-desmethyl-ofloxacin in CSF after i.v. infusion of 400 mg of ofloxacin over 30 min

Patient no.	Ofloxacin-*N*-oxide				*N*-Desmethyl-ofloxacin			
	C_{max} (mg/liter)	T_{max} (h)	AUC_{0-t} (mg · h/liter)	$AUC_{CSF\ 0-t}/AUC_{S\ 0-t}$	C_{max} (mg/liter)	T_{max} (h)	AUC_{0-t} (mg · h/liter)	$AUC_{CSF\ 0-t}/AUC_{S\ 0-t}$
1	0.075	4	0.26	0.27	0.029	4	0.14	0.34
2	<0.001				0.011	4	0.13	0.19
3	<0.001				0.004	7	0.041	0.07
4	0.002	7	0.007	0.03	0.002	7	0.021	0.10
5	0.006	16	0.11	0.14	0.038	4	0.38	0.50
6	0.002	4	0.037	0.12	0.034	7	0.48	0.99
Mean ± SD					0.020 ± 0.016	5.5 ± 1.6	0.20 ± 0.19	0.37 ± 0.35

lipophilic antibiotics into CSF—because of their ability to cross lipid layers—depends less on the state of the blood-CSF barrier than does the transit of hydrophilic drugs. It provides the rationale for the use of lipophilic antimicrobial agents for the treatment of CNS infections with minimal impairment of the blood-CSF and blood-brain barrier.

With *Staphylococcus aureus*, MICs for 90% of isolates tested (MIC_{90}s) of 0.5 mg/liter (14) and 2 mg/liter (5) have been reported. The MIC_{90}s for methicillin-susceptible and -resistant coagulase-negative staphylococci were 0.5 mg/liter (14) and 16 mg/liter (5), respectively; the MIC_{50} in the latter study was 0.5 mg/liter. Thus, the maximum concentrations in CSF in the present study exceeded the MICs for the majority of *S. aureus* and *Staphylococcus epidermidis* strains by a factor of 2 to 6. The maximum concentrations in CSF were 4- to 12-fold greater than the MICs for susceptible members of the family *Enterobacteriaceae* (MIC_{90}, 0.25 mg/liter [14]; range, 0.12 to 0.5 mg/liter [5]). The CSF concentrations that we found in CSF, however, were less than or close to the MIC_{90} for *Pseudomonas aeruginosa* (4 mg/liter [14] and 8 mg/liter [5]) and *Streptococcus pneumoniae* (2 mg/liter [5, 14]).

In humans with extracerebral infections, a peak concentration/MIC ratio of >10 (4) was related to a favorable outcome. Similarly, in the rabbit model of pneumococcal meningitis, CSF quinolone concentrations at least fivefold greater than the MBC (the MBC was usually one titer above the MIC) were necessary for moderate bactericidal activity, and C_{maxCSF}/MBC ratios of at least 10 were required for a rapid bactericidal effect (13). A similar relation has been established with β-lactam antibiotics (23). For these reasons, a therapeutic regimen leading to maximum CSF quinolone concentrations of less than 10 times the MIC is probably suboptimal. Assuming a MIC of 0.5 mg/liter, in all patients in the present study the C_{maxCSF}/MIC ratio was less than 10. The lowest maximum concentration observed in CSF was 1.0 mg/liter. For this reason, ofloxacin should not be used to treat CNS infections caused by bacteria for which the MIC is greater than 0.125 mg/liter. The use of ofloxacin in CNS infections is further limited by the fact that it, like other quinolones, is relatively contraindicated in children.

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REFERENCES

1. **Ashby, J., L. J. V. Piddock, and R. Wise.** 1985. An investigation of the hydrophobicity of the quinolones. J. Antimicrob. Chemother. **16**:805–808.
2. **Bitar, N., R. Claes, and P. van der Auwera.** 1989. Concentrations of ofloxacin in serum and cerebrospinal fluid of patients without meningitis receiving the drug intravenously and orally. Antimicrob. Agents Chemother. **33**:1686–1690.
3. **Dow, J., J. Chazal, M. Frydman, P. Janny, R. Woehrle, F. Djebbar, and J. Gaillot.** 1986. Transfer kinetics of pefloxacin into cerebrospinal fluid after one hour IV infusion of 400mg in man. J. Antimicrob. Chemother. **17**(Suppl. B):81–87.
4. **Drusano, G. L., D. E. Johnson, M. Rosen, and H. C. Standiford.** 1993. Pharmacodynamics of a fluoroquinolone antimicrobial agent in a neutropenic rat model of *Pseudomonas* sepsis. Antimicrob. Agents Chemother. **37**:483–490.
5. **Fu, K. P., S. C. Lafredo, B. Foleno, D. M. Isaacson, J. F. Barrett, A. J. Tobia, and M. E. Rosenthale.** 1992. In vitro and in vivo antibacterial activities of levofloxacin (*l*-ofloxacin), an optically active ofloxacin. Antimicrob. Agents Chemother. **36**:860–866.
6. **Gerding, D. N., and J. A. Hitt.** 1989. Tissue penetration of the new quinolones in humans. Rev. Infect. Dis. **11**(Suppl. 5):105–116.
7. **Hirai, K., H. Aoyama, S. Suzue, T. Irikura, S. Iyobe, and S. Mitsuhashi.** 1986. Isolation and characterization of norfloxacin-resistant mutants of Escherichia coli K-12. Antimicrob. Agents Chemother. **30**:248–253.
8. **Jaehde, U., M. W. E. Langemeijer, A. G. de Boer, and D. D. Breimer.** 1992. Cerebrospinal fluid transport and disposition of the quinolones ciprofloxacin and pefloxacin in rats. J. Pharmacol. Exp. Ther. **263**:1140–1146.
9. **Naber, K. G., F. Sörgel, F. Kees, and H. Schumacher.** 1989. Pharmacokinetics of ciprofloxacin in young (healthy volunteers) and elderly patients, and concentrations in prostatic fluid, seminal fluid, and prostatic adenoma tissue following intravenous administration. Am. J. Med. **87**(Suppl. 5A):57S–59S.
10. **Nau, R., H. W. Prange, J. Martell, S. Sharifi, H. Kolenda, and J. Bircher.** 1990. Penetration of ciprofloxacin into the cerebrospinal fluid of patients with uninflamed meninges. J. Antimicrob. Chemother. **25**:965–973.
11. **Nau, R., H. W. Prange, S. Menck, H. Kolenda, K. Visser, and J. K. Seydel.** 1992. Passage of rifampicin into the cerebrospinal fluid of adults with uninflamed meninges. J. Antimicrob. Chemother. **29**:719–724.
12. **Nau, R., H. W. Prange, P. Muth, G. Mahr, S. Menck, H. Kolenda, and F. Sörgel.** 1993. Passage of cefotaxime and ceftriaxone into cerebrospinal fluid of patients with uninflamed meninges. Antimicrob. Agents Chemother. **37**:1518–1524.
13. **Nau, R., T. Schmidt, K. Kaye, J. L. Froula, E. Sande, and M. G. Täuber.** 1994. Therapie der Pneumokokken-Meningitis mit Antibiotika, die nicht der Gruppe der β-Laktame angehören, abstr. 11. Arbeitstagung der Arbeitsgemeinschaft für Neurologische Intensivmedizin, Heidelberg, Germany, 13 to 15 January 1994.
14. **Phillips, I., A. King, and K. Shannon.** 1988. In vitro properties of the quinolones. *In* V. T. Andriole (ed.), The quinolones. Academic Press, London.
15. **Pioget, J. C., M. Wolff, E. Singlas, M. J. Laisne, B. Clair, B. Regnier, and F. Vachon.** 1989. Diffusion of ofloxacin into cerebrospinal fluid of patients with purulent meningitis or ventriculitis. Antimicrob. Agents Chemother. **33**:933–936.
16. **Reiber, H., and K. Felgenhauer.** 1987. Protein transfer at the blood-cerebrospinal fluid barrier and the quantitation of the humoral immune response within the central nervous system. Clin. Chim. Acta **163**:319–328.
17. **Sörgel, F., U. Jaehde, K. Naber, and U. Stephan.** 1989. Pharmacokinetic disposition of quinolones in human body fluids and tissues. Clin. Pharmacokinet. **16**(Suppl. 1):5–24.
18. **Sörgel, F., and M. Kinzig.** 1993. Pharmacokinetics of gyrase inhibitors, part 1: basic chemistry and gastrointestinal disposition. Am. J. Med. **94**(Suppl. 3A):44–55.
19. **Sörgel, F., and M. Kinzig.** 1993. Pharmacokinetics of gyrase inhibitors, part 2: renal and hepatic elimination pathways and drug interactions. Am. J. Med. **94**(Suppl. 3A):56–69.
20. **Staffensky, R.-H., D. Stolke, and R. Malottke.** 1990. Die Liquorgängigkeit von Ofloxacin (Tarivid) bei nicht entzündeten Meningen. Neurochirurgia **33**:110–112.
21. **Stübner, G., W. Weinrich, and U. Brands.** 1986. Study of the cerebrospinal fluid penetrability of ofloxacin. Infection **14**(Suppl. 4):250–253.
22. **Takacs-Novak, K., M. Jozan, I. Hermecz, and G. Szasz.** 1992. Lipophilicity of antibacterial fluoroquinolones. Int. J. Pharmaceut. **79**:89–96.
23. **Täuber, M. G., and M. A. Sande.** 1990. General principles of therapy of pyogenic meningitis. Infect. Dis. Clin. N. Am. **4**:661–676.