Levofloxacín Disposition in Cerebrospinal Fluid in Patients with External Ventriculostomy

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In vitro levofloxacín exhibits both potent or intermediate activity against most of the pathogens frequently responsible for acute bacterial meningitis and synergistic activity with some beta-lactams. Since levofloxacín was shown to penetrate the cerebrospinal fluid (CSF) during meningeal inflammation both in animals and in humans, the disposition of levofloxacín in CSF was studied in 10 inpatients with external ventriculostomy because of communicating hydrocephalus related to subarachnoid occlusion due to cerebral accidents who were treated with 500 mg of levofloxacín intravenously twice a day because of extracerebral infections. Plasma and CSF levofloxacín concentrations were analyzed by high-pressure liquid chromatography. The peak concentration of levofloxacín at steady state (Cmax ss) was 10.45 mg/liter in plasma and 4.06 mg/liter in CSF, respectively, with the ratio of the Cmax ss in CSF to the Cmax ss in plasma being 0.47. The areas under the concentration-time curves during the 12-h dosing interval (AUC0–12 h for CSF to the AUC0–12 h for plasma) were 47.69 mg·h/liter for plasma and 33.42 mg·h/liter for CSF, with the ratio of the AUC0–12 h for CSF to the AUC0–12 h for plasma being 0.71. The terminal-phase half-life of levofloxacín in CSF was longer than that in plasma (7.02 ± 1.57 and 5.51 ± 1.36 h, respectively; P = 0.034). The ratio of the levofloxacín concentration in CSF to the concentration in plasma progressively increased with time, from 0.30 immediately after dosing to 0.99 at the end of the dosing interval. In the ventricular CSF of patients with uninflamed meninges, levofloxacín was shown to provide optimal exposure, which approximately corresponded to the level of exposure of the unbound drug in plasma. The findings provide support for trials of levofloxacín with twice-daily dosing in combination with a reference beta-lactam for the treatment of bacterial meningitis in adults. This cotreatment could be useful both for overcoming Streptococcus pneumoniae resistance and for enabling optimal exposure of the CSF to at least one antibacterial agent for the overall treatment period.

Levofloxacín is a fluoroquinolone antibiotic characterized by a broad antimicrobial spectrum that covers, among other organisms, the pathogens most frequently responsible for acute bacterial meningitis (Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, and Escherichia coli) and also other sporadic agents of central nervous system (CNS) infections, such as Streptococcus agalactiae (13).

In in vitro studies based on the time-kill curve method, levofloxacín was recently shown to exhibit synergistic (or at least additive) activity with some beta-lactam antibiotics against both gram-positive and gram-negative microorganisms (11, 27, 33, 35). The degree of this synergy was sometimes of the same extent as that which occurs between beta-lactams and aminoglycosides (4).

Previous pharmacokinetic studies documented that levofloxacín could adequately penetrate the cerebrospinal fluid (CSF) in the presence of meningeal inflammation both in animals and in humans (8, 32). However, ratios of the concentration in CSF to the concentration in plasma (CSF to plasma concentration ratios) may vary substantially according both to different sampling times and to the status of the blood-CSF barrier. For example, Ohi et al. (23) found that 3 h after the administration of a single 200-mg dose of levofloxacín to healthy volunteers with uninflamed meninges, the CSF to plasma ratio ranged between 0.08 and 0.24. Although assessment of the level of antibiotic exposure in CSF on the basis of a single sampling time might provide incomplete information (19), an evaluation of exposure based on multiple sampling times covering the whole dosing interval should be more meaningful (19).

Moreover, although most fluoroquinolones are lipophilic agents whose penetration into CSF should be only minimally affected by the degree of meningeal inflammation, assessment of the penetration of levofloxacín into the CSF in the presence of an uninflamed blood-CSF barrier would be more informative. Finally, considering that antibiotic concentrations may be severalfold higher at the lumbar CSF level than at the ventricular CSF level (21), it might be more appropriate to assess the level of exposure in the latter compartment. The purpose of this study was to assess levofloxacín ventricular CSF concentrations during the whole dosing interval in patients with minimal alteration of the blood-brain barrier, namely, hydrocephalic patients with external ventriculostomies.

MATERIALS AND METHODS

Study entry criteria. This study was performed with a cohort of 10 inpatients (four males and six females) who received external ventriculostomies during...
The pharmacokinetic parameters of levofoxacin in plasma and CSF were obtained from the nearest relative of each patient. Criteria for inclusion in the pharmacokinetic study were as follows: age, >18 years; estimated creatinine clearance (CLcr) determined by the formula of Cockcroft and Gault (6), > 50 ml/min; stable renal function (daily serum creatinine level ≤ 2.0 mg/dl); and levofoxacin treatment for extracerebral infections.

Levofoxacin disposition. The disposition of levofoxacin was assessed under steady-state conditions, that is, after at least 3 days of unmodified treatment. Blood samples were collected through an indwelling catheter before and after peak concentrations (Cmax) and 12 h after the morning 12-h iv. infusion of 500 mg of levofoxacin. After centrifugation, the plasma samples were stored at −80°C until they were assayed.

CSF samples were collected simultaneously with each blood sample through an indwelling external drainage ventricular catheter (Codman, Rome, Italy). This system was set as a sterile closed circuit consisting of a single tap in order to avoid bacterial contamination as much as possible. Before collection, 1 to 2 ml of CSF was aspirated to avoid bacterial contamination.

High-pressure liquid chromatography analysis. Plasma and CSF levofoxacin concentrations were analyzed by a high-pressure liquid chromatography method validated in our laboratory, as described previously (28, 32). The analytical method chosen was not stereospecific, since levofoxacin has been shown to be stereochemically stable in body fluids without any metabolic inversion to desoxofoxacin (10, 34). The inter- and intraday coefficients of variation of the assay were less than 10%. The low limit of detection was 0.1 mg/liter.

Pharmacokinetic evaluations. According to the Akaike information criterion (37), plasma concentration-versus-time data for individual patients were estimated by a two-compartment open model with first-order elimination by using the WinNonlin pharmacokinetic software package (Pharsight Corporation, Mountain View, Calif.). The pharmacokinetic parameters for levofoxacin in plasma explored in this study included the maximum concentration in plasma at steady state (Cmax,ss), the volume of distribution at steady state (Vss,ss), elimination half-life (t1/2z), total body clearance (CL), and the area under the plasma concentration-time curve (AUC) during the 12-h observational period (AUC0–12).

The pharmacokinetic parameters of levofoxacin in CSF included Cmax,ss in CSF (Cmax,ss CSF), time to reach Cmax,ss in CSF (tmax,ss CSF), t1/2z in CSF, and total exposure of CSF during the 12-h observational period (AUC0–12 CSF). The elimination rate constant for levofoxacin in CSF (k0 CSF) was obtained by log-linear regression of the terminal portion of the CSF concentration-versus-time curve (on the basis of at least three datum points), while t1/2z CSF was calculated as ln 2/k0 CSF. The AUCmax CSF for levofoxacin in CSF was calculated by the linear trapezoidal method.

Since patients received standard levofoxacin dosages, to avoid bias due to interindividually different body weight, the dose-related pharmacokinetic parameters (Cmax,ss CSF, AUC0–12) were expressed as the ratio of the mean values to the geometric mean of the body weight (kg) of each patient. The AUCmax,ss CSF was calculated as the ratio of the AUC0–12 CSF to the total body weight (kg) of each patient.

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Theoretical pharmacodynamic breakpoints in CSF. It is well known that the two most relevant pharmacodynamic parameters for the concentration-dependent bactericidal activity of levofoxacin are the ratio of the peak concentration in plasma to the MIC (Cmax/MIC) and the ratio of the daily AUC (AUC0–24/MIC) (1). According to previous studies, a Cmax/MIC ratio of 12.2 and an AUC0–24/MIC ratio of 125 h were shown to be valid thresholds for optimal drug exposure with the intent of preventing the selection of resistant strains and/or obtaining a clinical and microbiological cure with levofoxacin (3, 12, 29). On this basis, the theoretical pharmacodynamic breakpoints of levofoxacin in CSF (PD BP CSF) were defined as the theoretical highest MIC which might have enabled optimal drug exposure against a potential pathogen in CSF according to both of these thresholds (12.2 for the Cmax/MIC ratio and 125 h for the AUC0–24/MIC ratio) and the patients’ observed Cmax,ss CSF and AUC0–12 CSF were calculated by the following formulas: PD BP CSF = Cmax,ss CSF/12.2, and PD BP CSF = AUC0–24 CSF/125.

Statistical analysis. According to the normal or the nonnormal distribution, as estimated by the Kolmogorov-Smirnov test, the findings were expressed as means ± standard deviations (SDs) or medians and ranges, respectively. Statistical analysis was performed by the t test and/or the Mann-Whitney rank sum test, as appropriate, by using SigmaStat software (Jandel Scientific, GmbH, Erkrath, Germany). A statistically significant difference was defined as a P value <0.05.

### Table 1. Patient demographics on study day

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>56 (26–74)</td>
</tr>
<tr>
<td>Sex (no. of males/no. of females)</td>
<td>4/6</td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>72.3 (60–102)</td>
</tr>
<tr>
<td>Level of bilirubinemia (mg/dl)</td>
<td>0.6 (0.3–1.4)</td>
</tr>
<tr>
<td>Level of albuminemia (mg/dl)</td>
<td>3.2 (2.5–3.8)</td>
</tr>
<tr>
<td>CLcr (ml/min/kg)</td>
<td>1.76 (1.11–3.36)</td>
</tr>
</tbody>
</table>

### Table 2. Patients’ admission diagnosis, underlying infectious diseases, etiological agents of infection, and CSF chemical status

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Underlying CNS disease</th>
<th>Time from event (days)</th>
<th>Etiological agent(s)</th>
<th>Antibiotic cotreatment</th>
<th>HAD(s)</th>
<th>Protein conc in CSF (mg/liter)</th>
<th>WBC count in CSF (no. of cells/μl)</th>
<th>Glucose conc in CSF (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Extradural hematoma</td>
<td>12</td>
<td>P. aeruginosa, MS S. aureus</td>
<td>Dopamine, mannitol</td>
<td>150</td>
<td>1</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Subarachnoid hemorrhage</td>
<td>11</td>
<td>Enterobacter spp., MS S. aureus</td>
<td>Dopamine, mannitol</td>
<td>270</td>
<td>1</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Subarachnoid hemorrhage</td>
<td>9</td>
<td>H. influenzae, Enterobacter spp.</td>
<td>Vancomycin, Dopamine, mannitol</td>
<td>220</td>
<td>3</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Intracerebral hemorrhage</td>
<td>10</td>
<td>Klebsiella oxytoca, E. coli</td>
<td>Dopamine, mannitol</td>
<td>201</td>
<td>3</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Intracerebral hemorrhage</td>
<td>11</td>
<td>Proteus mirabilis</td>
<td>Dopamine, mannitol</td>
<td>141</td>
<td>86</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Subarachnoid hemorrhage</td>
<td>9</td>
<td>E. coli</td>
<td>Dopamine, mannitol</td>
<td>383</td>
<td>3</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Intracerebral hemorrhage</td>
<td>10</td>
<td>Proteus mirabilis</td>
<td>Furosemide, Mannitol</td>
<td>413</td>
<td>3</td>
<td>114</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Subdural hemorrhage</td>
<td>9</td>
<td>MS S. aureus</td>
<td>Oxacillin, Mannitol</td>
<td>220</td>
<td>1</td>
<td>181</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Frontal meningeoma</td>
<td>8</td>
<td>P. aeruginosa, Methicillin-resistant</td>
<td>Piperacillin-</td>
<td>63</td>
<td>109</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Thalamic hemorrhage</td>
<td>10</td>
<td>MS S. aureus</td>
<td>Teicoplanin, Mannitol</td>
<td>188</td>
<td>218</td>
<td>79</td>
<td></td>
</tr>
</tbody>
</table>

Total 9.9 ± 1.2

224.9 ± 107.1

3 (0–218)

98.8 ± 33.19

### Notes

1. All patients had ventilator-associated pneumonia. Abbreviations: HAD(s), hemodynamically active drug(s); MS, methicillin sensitive.
2. Data are expressed as means ± SDs.
3. Data are expressed as medians (ranges).
RESULTS

Patient characteristics and microbiology. The patients’ diagnoses on admission, the etiological agents for the extracerebral infections, and the chemical and cellular status of the CSF are shown in Table 2. Among the 10 patients included in the study, the diagnoses on admission to the ICU was cerebrovascular accident in nine patients and surgical ablation of frontal meningoia in one patient. All of the patients were treated with levofoxacin because of ventilator-associated pneumonia. Three of the 10 patients had normal ventricular CSF protein concentrations (50 to 150 mg/liter), whereas 7 patients had moderate elevations of CSF protein concentrations (>150 mg/liter); but the albumin concentration was <100 mg/liter in all patients. A moderate hyperglycorrhachia was observed in about half of the patients, whereas three patients (patients 5, 9, and 10) had CSF pleocytosis (presence of WBCs at about half of the patients, whereas three patients (patients 5, 9, and 10) had CSF pleocytosis (presence of WBCs at <5 cells/µl), probably due to the underlying cerebrovascular disease and/or to a sterile inflammatory response, as confirmed by negative CSF cultures for all patients. RBCs were detectable in only small amounts in lysate form.

Pharmacokinetic analysis. Mean ± SD plasma and CSF levofoxacin concentration-versus-time profiles are shown in Fig. 1. The average levofoxacin Cmax ss was 10.45 mg/liter in plasma and 4.06 mg/liter in CSF immediately and at 1.7 h after the end of the 1-h intravenous infusion, respectively, with an average ratio of the Cmax ss in CSF to the Cmax ss in plasma (CSF to plasma Cmax ss ratio) of 0.47.

The pharmacokinetic parameters for levofoxacin in plasma and CSF are summarized in Tables 3 and 4, respectively. The average levofoxacin exposures (AUC0–ss) were 47.69 mg·h/liter for plasma and 33.42 mg·h/liter for CSF, with a mean ratio of the AUC0–ss for CSF to the AUC0–ss for plasma (CSF to plasma AUC0–ss ratio) of 0.71. The elimination of levofoxacin from CSF showed a log-linear decay, with a mean terminal half-life of 7.02 h.

The average CSF-to-plasma-concentration ratios progressively increased with time, from 0.30 immediately after dosing to 0.99 at the end of the dosing interval.

Dose-normalized data showed that for each 1 mg of levofoxacin per kg/12 h, the mean ± SD dose-normalized Cmax ss were 1.47 ± 0.44 mg/liter in plasma and 0.59 ± 0.26 mg/liter in CSF, whereas the mean fractional AUC0–ss were 6.80 ± 2.44 mg·h/liter for plasma and 4.84 ± 1.90 mg·h/liter for CSF.

No correlation between AUC0–ss CSF or Cmax ss CSF and the protein concentration in CSF was found.

The mean theoretical PD BPCSF values for the optimal bactericidal efficacy of levofoxacin in CSF were 0.53 and 0.33 mg/liter for an AUC0–ss/MIC ratio threshold of 125 h and a Cmax/MIC ratio threshold of 12.2, respectively (Table 4).

DISCUSSION

Our study investigated the ventricular CSF disposition of levofoxacin in patients with external ventriculostomies treated because of documented or suspected extracerebral infections.

The pharmacokinetics of levofoxacin in plasma confirmed our previous findings for patients with early-onset ventilator-associated pneumonia (28), suggesting that high b.i.d. dosages (500 mg b.i.d.) are needed to ensure optimal drug exposure in ICU patients, mainly because the renal clearance of levofoxacin, which is the most predictive parameter of its interindividual pharmacokinetic variability (28, 30), may be increased due either to the frequent hyperdynamic conditions or to co-treatment with hemodynamically active drugs.

When the dispositions of levofoxacin in CSF and plasma were compared, all the findings (the AUC corresponded to about 70% of the total exposure in plasma, the rapid achievement of a peak level in CSF corresponded to about one-half of that in plasma, and the terminal half-life was only slightly significantly longer than that in plasma) were consistent with the fact that levofoxacin freely crosses the blood-CSF barrier by passive diffusion (19, 21, 24), according to its physicochemical properties (namely, small size, moderate level of lipophilia, and negligible plasma protein binding [20 to 30%]).

This substantial penetration of levofoxacin into CSF is in agreement with the findings of other investigators both in animals and in humans. In an experimental meningitis model, Destache and coworkers (8) found that the average level of CSF exposure to levofoxacin ranged between 53 and 76% of the corresponding level of plasma exposure in rabbits chal-

### TABLE 3. Steady-state levofoxacin pharmacokinetic parameters in plasma during i.v. administration of 500 mg b.i.d. in 10 ICU patients with external ventriculostomies

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dose (mg/kg/12 h)</th>
<th>Cmax ss (mg/liter)</th>
<th>Vss (liters/kg)</th>
<th>t1/2 (h)</th>
<th>CL (ml/min/kg)</th>
<th>AUC0–ss (mg·h/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>7.17 ± 1.30</td>
<td>10.45 ± 3.54</td>
<td>1.13 ± 0.30</td>
<td>5.51 ± 1.36</td>
<td>2.75 ± 1.18</td>
<td>47.69 ± 17.24</td>
</tr>
<tr>
<td>CV (%)</td>
<td>18</td>
<td>34</td>
<td>27</td>
<td>25</td>
<td>43</td>
<td>36</td>
</tr>
</tbody>
</table>

*a CV, coefficient of variation.*
lenged with *S. pneumoniae*. Likewise, in a previous study (32), based on a single sampling time during a diagnostic lumbar puncture in patients with acute bacterial meningitis treated with a combination of a beta-lactam plus levofloxacin at 500 mg b.i.d. i.v., the CSF to plasma \(C_{\text{max, CSF}}/C_{\text{max, ser}}\) ratio 2 h after dosing averaged 35%, ranging between 23 and 42%. Finally, in six patients with external ventriculostomy, Nau and coworkers (20) demonstrated that after administration of a single 400-mg dose, the level of CSF penetration of ofloxacin, namely, the racemate of \(l\)- and \(d\)-ofloxacin, enabled an average CSF-to-serum-AUC ratio of 0.65 (range, 0.59 to 0.81) and a mean peak level in CSF of 2.04 mg/liter to be achieved 1.75 h after dosing.

The persistence in the ventricular CSF of effective concentrations that lasted for the entire dosing interval suggested that optimal exposure to levofloxacin may be achieved in all parts of the CSF system, considering that, in general, antibiotic concentrations were found to be severalfold lower at the ventricular CSF level than at the lumbar CSF level (21).

It is noteworthy that the free penetration of levofloxacin into CSF, irrespective of the barrier status, may have important consequences for the treatment of bacterial meningitis. In fact, although the penetration of the reference agents for the therapy of bacterial meningitis, namely, hydrophilic agents such as cefotaxime, ceftriaxone, and ampicillin, is expected to decrease day by day because of the progressive healing of the barrier promoted by the antimicrobial therapy and/or by corticosteroid-associated action (26), the unimpeded access of levofloxacin to the CNS might ensure a highly effective exposure lasting not only for the first days of therapy but also for the overall treatment period.

With the intent of preventing both clinical failure and the spread of resistance (9), according to the theoretical pharmacodynamic breakpoints for levofloxacin in CSF, a levofloxacin regimen of 500 mg b.i.d. i.v. may provide optimal exposure in CSF against microorganisms for which MICs are <0.5 mg/liter. This value is lower than the MIC at which 90% of strains are inhibited for most but not all of the etiological agents of spontaneous bacterial meningitis. For *S. pneumoniae*, the most frequent causative agent of meningitis, the levofloxacin MIC at which 90% of strains are inhibited is 1 mg/liter. Therefore, although AUC/MIC ratios as low as 30 to 50 h were recently postulated to be enough, both in vitro and in vivo, for the eradication of *S. pneumoniae* with fluoroquinolones (1, 16–18, 22), these data support the potential utility of levofloxacin in the treatment of spontaneous bacterial meningitis in combination with a reference beta-lactam. Other antipseudomococcal fluoroquinolones that are more potent in vitro, namely, moxifloxacin and gatifloxacin, could also be useful for these purposes. The coadministration of an antipseudomococcal fluoroquinolone for the treatment of meningitis might be especially helpful whenever *S. pneumoniae* strains intermediately susceptible or resistant to cefotaxime and/or ceftriaxone may be involved, as the low degree of susceptibility of this pathogen is a factor negatively associated with the outcome of pneumococcal-related meningitis (25, 36). This hypothesis is supported by the recent finding of synergism between ceftriaxone and levofloxacin in the treatment of experimental meningitis in rabbits challenged with penicillin-resistant *S. pneumoniae* strains (L. Flatz, M. Cottagnoud, J. M. Entenza, P. Moreillon, M. G. Tauber, and P. Cottagnoud, Abstr. 42nd Intersci. Conf. Antimicrob. Agents Chemother., abstr. B-1429, p. 56, 2002).

Although pharmacokinetic-pharmacodynamic relationships provide evidence for the potential utility of levofloxacin in the treatment of bacterial meningitis, the facts that fluoroquinolones are not licensed for pediatric use and are not devoid of side effects in the CNS should not be overlooked. However, the proconvulsant activities of fluoroquinolones were shown to be dependent on both chemical structure and dosages (7, 31), and among the various compounds, levofloxacin was shown to be one of the least epileptogenic, having excitatory activity even less than that of the ofloxacin racemate, probably due to its weaker binding affinity to the \(\gamma\)-aminobutyric acid receptor in the CNS (14). Accordingly, the low potential for neurotoxicity is confirmed by the very low incidence of convulsions during treatment in humans (2, 5, 15).

In conclusion, both the favorable pharmacokinetics and the theoretical pharmacokinetic-pharmacodynamic analysis of levofloxacin in the ventricular CSF of patients with uninfamed meninges provide support for trials of levofloxacin with b.i.d. dosing in combination with a reference beta-lactam for the treatment of bacterial meningitis in adults. This cotreatment could be especially helpful both in overcoming *S. pneumoniae* resistance and in enabling optimal CSF exposure to at least one antibacterial agent for the overall treatment period.
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REFERENCES


