Pharmacokinetics of Intravenous Linezolid in Cerebrospinal Fluid and Plasma in Neurointensive Care Patients with Staphylococcal Ventriculitis Associated with External Ventricular Drains

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The pharmacokinetic profile of linezolid in cerebrospinal fluid (CSF) in five neurointensive care patients with staphylococcal ventriculitis was studied. The mean area under concentration-time curve (± standard deviation) was 63 ± 18.9 mg · h/liter, with a CSF-to-plasma ratio of 0.8 ± 0.3. Times above MIC in CSF were 99.8% and 57.2% for pathogens with MICs of 2 mg/liter and 4 mg/liter, respectively.

External ventricular drain (EVD) catheters are of importance in the treatment of various acute neurological disorders such as subarachnoid hemorrhage, traumatic brain injury, and intracerebral hemorrhage, with elevated intracranial pressure secondary to acute hydrocephalus. However, EVDs are not without complications, the most significant of which is infection resulting in ventriculitis or ventriculomeningitis (2, 4, 14) caused predominantly by gram-positive bacteria, especially multiresistant coagulase-negative staphylococci (CoNS) and methicillin-resistant Staphylococcus aureus (MRSA) (7). Standard antimicrobial therapy with vancomycin has major limitations: the penetration of vancomycin in the cerebral spinal fluid (CSF), even through inflamed meninges and ventricular ependyma, is poor (1, 19). Adverse effects, mainly its nephrotoxicity, often represent contraindications for vancomycin therapy in critically ill patients. Furthermore, strains with decreased susceptibility (11) and outright resistance (10) to vancomycin have emerged. The oxazolidinone antibiotic linezolid represents an alternative to this agent with a similar spectrum (15). Linezolid is predominantly bacteriostatic and has a broad spectrum of activity against gram-positive pathogens (3, 6, 18). The efficacy of linezolid for the treatment of gram-positive central nervous system (CNS) infections has been demonstrated recently (17, 21, 22, 23). Importantly, however, limited data are available on CSF pharmacokinetics of linezolid in patients with acute neurological illnesses requiring mechanical ventilation and hemodynamic support. Therefore, the present study determined the pharmacokinetic profile of intravenous linezolid after single and multiple doses in plasma and CSF in critically ill patients with EVD-associated ventriculitis.

Five consecutive critically ill patients (three women and two men) with obstructive hydrocephalus resulting from acute subarachnoid hemorrhage (n = 4) or severe traumatic brain injury (n = 1) requiring external ventricular drainage...
with microbiologically proven gram-positive ventriculitis (MRSA, n = 3; CoNS, n = 2) were enrolled in the study. All patients required mechanical ventilation. Concomitant drug therapy consisted of intravenous catecholamines (dobutamine, norepinephrine, and/or phenylephrine), sedation with midazolam and/or propofol, and analgesia with sufentanil. During the study period, patients received no other antimicrobial therapy with the exception of linezolid. According to our study protocol, no removal and reinsertion of EVD despite catheter-related infection was performed. Approval was obtained from the Ethics Committee of Innsbruck Medical University (protocol number UN19305). All patients received a dose of 600 mg linezolid (Zyvoxid, 2-mg/ml Infusionslösung; Pfizer Corporation, Vienna, Austria) every 12 h over a period of 30 min by a programmable infusion pump into a central venous line separate from that used for other drugs. Paired serial blood and CSF samples were collected at 1, 4, 8, and 12 h after every start of the infusion during the multiple-dose study period of 7 days. Total linezolid levels in plasma and CSF were determined by a previously published but modified high-performance liquid chromatography method (5). The lower limit of quantification was calculated to be 0.01 mg/liter. Intraday and interday coefficients of variation were <7%. Pharmacokinetic analysis was performed using the computer software TopFit V.2.0 (8), and statistical calculations were done with Testimate V.6.2 software (IDV Data Analysis, Munich, Germany). The pharmacokinetic and pharmacodynamic analysis methods used have been described previously (16).

All five patients completed the study and were included in the safety analysis. Mean age and body weight were 49.2 ± 19.5 years and 64.8 ± 23.1 kg, respectively. The mean simplified acute physiology score II (13) at enrollment was 59 ± 4. Demographic and laboratory data are presented in Table 1. CSF cultures were sterile from day 2 after initiation of therapy. Treatment was continued for 7 days following microbiologically confirmed CSF clearance. Study drug administration was well tolerated by all patients. No clinically evident study drug-related adverse events were observed during the study period. The patients received neurological, electrophysiological, and neuroimaging follow-up within 3 to 6 month of discharge, with no findings indicating toxicity to the central and/or peripheral nervous system.

After a single intravenous dose of 600 mg linezolid, $C_{\text{max}}$ and $C_{\text{min}}$ values (mean ± standard deviation [SD]) were 12.4 ± 4.2 mg/liter and 0.5 ± 0.3 mg/liter for plasma compared to 6.6 ± 1.7 mg/liter and 1.3 ± 0.5 mg/liter for CSF, respectively. Steady-state conditions of linezolid were reached in plasma and CSF after administration of the fifth intravenous dose, with $C_{\text{max}}$ and $C_{\text{min}}$ values (mean ± SD) of 19.5 ± 5.1 mg/liter and 2.0 ± 1.7 mg/liter for plasma versus 7.1 ± 2.2 and 3.1 ± 1.8 mg/liter for CSF, respectively. Ratios (mean ± SD) of the area under the concentration-time curve (AUC) from 0 to 12 h (AUC$_{0-12}$) and AUC at steady state (AUC$_{\text{SS}}$) for CSF to the AUC$_{0-12}$ and AUC$_{\text{SS}}$ for plasma were 1.0 ± 0.3 and 0.8 ± 0.3, respectively. At steady state, the ratios (mean ± SD) of peak and trough linezolid concentrations in CSF to those in plasma were 0.4 ± 0.1 and 1.7 ± 0.5, respectively. Pharmacokinetic parameters are shown in Tables 2 and 3. Plasma and CSF

<table>
<thead>
<tr>
<th>Patient</th>
<th>Parameter</th>
<th>Plasma*</th>
<th>Ventricular CSF*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$C_{\text{max}}$ (mg/liter)</td>
<td>$C_{\text{min}}$ (mg/liter)</td>
<td>$AUC_{0-12}$ (mg · h/liter)</td>
</tr>
<tr>
<td>1</td>
<td>17.4</td>
<td>0.3</td>
<td>60.4</td>
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<tr>
<td>2</td>
<td>8.1</td>
<td>0.7</td>
<td>31.2</td>
</tr>
<tr>
<td>3</td>
<td>10.2</td>
<td>0.4</td>
<td>18.5</td>
</tr>
<tr>
<td>4</td>
<td>11.0</td>
<td>0.3</td>
<td>26.0</td>
</tr>
<tr>
<td>5</td>
<td>9.2</td>
<td>0.4</td>
<td>21.4</td>
</tr>
</tbody>
</table>

Mean ± SD: $C_{\text{max}}$ = 12.4 ± 4.2 mg/liter; $C_{\text{min}}$ = 0.5 ± 0.3 mg/liter; $AUC_{0-12}$ = 60.4 ± 7.8 mg · h/liter; $AUC_{\text{SS}}$ = 55.6 ± 7.5 mg · h/liter; $V_{d}$ = 3.2 ± 0.2 liters; $k_{el}$ = 0.3 ± 0.1 liters/h; $t_{1/2}$ = 157 ± 8.6 h; $F$ = 0.21 ± 0.083; $f_{CSF}$ = 45.1 ± 4.9% for all patients.

TABLE 2. Pharmacokinetic parameters of linezolid for plasma and ventricular CSF following the first single intravenous dose of 600 mg
concentrations of linezolid following the first infusion and the peak and trough levels of linezolid during the multiple-dose administration are presented in Fig. 1. Times above MIC in CSF were 99.8% and 57.2% for pathogens with MICs of 2 mg/liter and 4 mg/liter, respectively.

Regarding CSF, the main pharmacokinetic parameters are in agreement with previously published results from patients with gram-positive community-acquired and nosocomial CNS infections (13, 17, 23). Our study also confirms the relative delay in CSF linezolid peak concentrations (240 min versus 60 min for plasma after bolus infusion), which is in agreement with the amphiphilic properties of the substance (6). In addition, recent studies demonstrated that tissue penetration of antimicrobial agents is markedly determined by the presence of local or systemic inflammation (12, 19). Therefore, the severity of inflammation of the ventricular ependyma could influence the penetration of linezolid into the CSF.

Linezolid is a time-dependent bacteriostatic agent and has significant post-treatment antibacterial effects against most target pathogens (24). Our study also confirms the relative delay in CSF linezolid peak concentrations (240 min versus 60 min for plasma after bolus infusion), which is in agreement with previously published results from patients with MICs of 2 mg/liter and 4 mg/liter, respectively.

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Table 3. Pharmacokinetic parameters of linezolid for plasma and ventricular CSF after multiple intravenous doses of 600 mg linezolid intravenously twice daily (steady-state kinetics of the fifth interval).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Plasma</th>
<th>Ventricular CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\text{\text{max}} (mg/liter)</td>
<td>0.83</td>
<td>0.83</td>
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<tr>
<td>C\text{\text{min}} (mg/liter)</td>
<td>0.09</td>
<td>0.09</td>
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<tr>
<td>t\text{\text{1/2}} (h)</td>
<td>3.4</td>
<td>3.4</td>
</tr>
<tr>
<td>AUC\text{\text{SS}} (mg · h/liter)</td>
<td>3.7</td>
<td>3.7</td>
</tr>
<tr>
<td>V\text{\text{z}} (liters)</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>k\text{\text{el}} (liters/h)</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>CL\text{\text{tot}} (ml/min)</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Mean \( ± \) SD

1.8 \( ± \) 0.2

0.9 \( ± \) 0.1

3.4 \( ± \) 0.8

2.4 \( ± \) 0.6

1.6 \( ± \) 0.2

0.6 \( ± \) 0.1

0.5 \( ± \) 0.1

FIG. 1. Time-concentration curves (means \( ± \) SDs) of linezolid in plasma and CSF: (a) Profile after administration of a single intravenous dose of 600 mg linezolid (T\text{\text{max}} = 1 h for all patients). (b) Profile after multiple intravenous administrations of 600 mg linezolid twice daily (T\text{\text{max}} = 4 h for all patients). The dotted horizontal lines represent MICs (2 and 4 mg/liter) for susceptible pathogens.
for pathogens with an MIC of 2 mg/liter. The corresponding calculated AUC\textsubscript{0-24}/MIC ratio (mean ± SD) was 75.3 ± 20.6 and exceeded the generally accepted breakpoint of >50 h (3). However, considering the least susceptible strains with MICs close to 4 mg/liter, T > MIC and the mean AUC\textsubscript{0-24}/MIC ratio were considerably shorter (57% and 37.7 ± 10.1, respectively). Therefore, dose escalation might be warranted in certain cases to achieve maximal antibacterial activity and to ensure an adequate clinical response. In addition, it should be kept in mind that the relatively small number of patients does not permit extrapolation to all critically ill patients with nosocomial CNS infections. Another key finding of our study is the prompt response of staphylococcal ventriculitis to linezolid with the eradication of the pathogen in CSF during the study period of 7 days; the CSF of each patient remained sterile in subsequent cultures, and no recurrence of ventriculitis was observed for the length of time that the EVD remained in place.

For optimizing cerebral perfusion pressure to improve neurological outcome (20), our patients received extensive fluid resuscitation and medium- to high-dose intravenous catecholamines. Linezolid is a reversible nonseductive inhibitor of monoamino oxidase (9) and therefore has the potential to interact with adrenergic substances, enhancing the pressor response. The magnitude of the blood pressure changes in our five patients did not differ significantly during the period of linezolid therapy compared with those at the times prior to and after study drug administration. However, due to the relatively small number of patients in our study, this important issue in the critical care setting requires further investigation, and continuous monitoring of blood pressure is mandatory for the coadministration of potent vaso-presseors and linezolid.

In conclusion, our study demonstrates that the intravenous administration of 600 mg linezolid twice daily provides satisfactory pharmacokinetic results in neurocritical care patients, with a percentage of penetration of linezolid of approximately 80% at steady state and concentrations exceeding the MIC of the targeted pathogens in CSF.

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REFERENCES