Serum and Cerebrospinal Fluid Concentrations of Linezolid in Neurosurgical Patients

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Linezolid is a new antimicrobial agent effective against drug-resistant gram-positive pathogens commonly
responsible for central nervous system (CNS) infections in neurosurgical patients hospitalized in intensive
care units. In order to study the penetration of this antimicrobial into the cerebrospinal fluid (CSF) of such
patients, the disposition of linezolid in serum and CSF was studied in 14 neurosurgical patients given linezolid
at 600 mg twice daily (1-h intravenous infusion) for the treatment of CNS infections caused by gram-positive
pathogens or for prophylactic chemotherapy. Serum and CSF linezolid steady-state concentrations were
analyzed by high-pressure liquid chromatography, and the concentration-time profiles obtained were analyzed
to estimate pharmacokinetic parameters. The mean ± standard deviation (SD) linezolid maximum and
minimum measured concentrations were 18.6 ± 9.6 µg/ml and 5.6 ± 5.0 µg/ml, respectively, in serum and
10.8 ± 5.7 µg/ml and 6.1 ± 4.2 µg/ml, respectively, in CSF. The mean ± SD areas under the concentration-time
curves (AUCs) were 128.7 ± 83.9 µg · h/ml for serum and 101.6 ± 59.6 µg · h/ml for CSF, with a mean
penetration ratio for the AUC for CSF to the AUC for serum of 0.66. The mean elimination half-life of linezolid
in CSF was longer than that in serum (19.1 ± 19.0 h and 6.5 ± 3.6 h, respectively). The serum and CSF
linezolid concentrations exceeded the pharmacodynamic breakpoint of 4 µg/ml for susceptible target pathogens
for the entire dosing interval in the majority of patients. These findings suggest that linezolid may achieve
adequate concentrations in the CSF of patients requiring antibiotics for the management or prophylaxis of
CNS infections caused by gram-positive pathogens.

Linezolid is the first member of a new synthetic class of antimicrobials, the oxazolidinones, to be used in clinical practice. It acts by selectively inhibiting the initiation of bacterial protein synthesis with a unique mechanism that precludes cross-resistance to currently available agents (10). In vitro and in vivo studies have demonstrated that linezolid has significant bacteriostatic activity against multiresistant gram-positive pathogens, such as coagulase-negative Staphylococcus species, Staphylococcus aureus, vancomycin-resistant enterococci, and Streptococcus pneumoniae, with MIC50s generally ranging from 0.5 to 4 µg/ml (5, 26).

Gram-positive cocci, mainly staphylococci, are the most frequent pathogens involved in central nervous system (CNS) postneurosurgical infections (26). Severe CNS infections caused by gram-positive pathogens may also be related to head trauma with skull fracture in neurosurgical patients, especially in the presence of an external drainage or ventriculoperitoneal shunt. Thus, these patients require antibiotics either for the management of infections or for prophylaxis against such infections. The frequency of CNS infections subsequent to neurosurgical procedures is estimated to be ~4% (25). As the epidemiology of CNS infection in neurosurgical patients evolves and the prevalence of multidrug-resistant strains among gram-positive organisms in intensive care units (ICUs) has become increasingly common (15), the management of nosocomial CNS infections presents a challenge (25).

Unfortunately, data directly supporting the use of linezolid for the treatment of human CNS infections remain largely anecdotal (13). To date, experience with linezolid for the treatment of CNS infections is limited to single case reports, dealing with vancomycin-resistant enterococcal meningitis (14, 21, 28), methicillin-resistant staphylococcal meningitis (13, 16), and some other CNS postneurosurgical infections caused by gram-positive pathogens (25). Moreover, although the pharmacokinetics (PKs) of linezolid in serum and the good rate of penetration of the drug into the CNS have been studied by the use of experimental animal models, healthy volunteers, and children (25), no pharmacokinetic data on linezolid concentrations in the serum and CSF of critically ill neurosurgical patients are available.

The purpose of the study was to determine the steady-state serum and CSF pharmacokinetic profile of intravenous (i.v.) linezolid administered at 600 mg twice daily to critically ill neurosurgical patients and also to assess the penetration of
linezolid into the CSF of patients with meningial inflammation.

**MATERIALS AND METHODS**

This was a prospective, open-labeled, uncontrolled study that took place at the ICU of KAT Hospital (Athens, Greece), after the study protocol was approved by the Hospital Ethics and Research Committee. The study was performed in accordance with good clinical practice guidelines. Informed consent was waived because CSF samples were obtained during hydrocephalus drainage for acute hydrocephalus or lumbar puncture for suspected CNS infection, as medically indicated.

**Patients.** Fourteen white adult neurosurgical patients were administered linezolid for the management of a CNS infection caused by gram-positive pathogens or as prophylactic chemotherapy against gram-positive pathogens. All patients enrolled in the study required CSF drainage for acute hydrocephalus or lumbar puncture for suspected CNS infection, as medically indicated. Patients were eligible for enrollment in the study if they met the following criteria: age ≥ 18 years; renal function defined by a calculated creatinine clearance (Clcr), as determined by the formula of Cockcroft and Gault (6), ≥ 80 ml/min; normal hepatic function (an alanine aminotransferase, aspartate aminotransferase, or bilirubin level lower than twice the upper limit of normal); cranio-cerebral injury; skull fracture; neurosurgical interventions; subarachnoidal hemorrhage of traumatic or pathological etiology; a documented CNS infection caused by a gram-positive pathogen; or a documented infection caused by a gram-positive pathogen anywhere in the body plus one of the five first criteria.

The exclusion criteria were a history of allergy to oxazolidinone antibiotics, uncontrolled infections (except for linezolid, known residual activity against the infecting gram-positive bacteria to linezolid, concomitant use of a drug known to show adverse effects in combination with linezolid (for example, monoaminooxidase inhibitors), and technical or other reasons that did not permit the collection of CSF samples. The patients enrolled in the study were subsequently divided into two groups, according to the presence or the absence of CSF drainage. For all the patients the following data were collected and recorded in an electronic database: age, sex, weight, height, Clcr, and degree of illness severity on the basis of their APACHE II and SAPS II score.

**Drug administration and sample collection.** All patients received 1-h intravenous infusions of linezolid (Zyvoxid; Pfizer) at 600 mg twice daily through an external drainage catheter just before the initiation of infusion and at 1.5, 2.5, and 3.5 h after the start of the infusion. Prior to the collection of CSF from those patients with an external drainage catheter, small volumes of the serum and CSF samples were sent for microbiological assay, using the method developed by Tobin et al. (24). Chromatography was performed on a Hypersil SODS column with a mobile phase of methanol-water-phosphoric acid (30:69:1) and with the addition of 2 g/liter heptane sulfonic acid, and the pH was adjusted to 5 by the addition of 10 M sodium hydroxide. The method used UV detection, with UV set at a wavelength of 254 nm. The serum and CSF samples were diluted with an equal volume of acetone-tert and centrifuged at 5,000 × g, and 20 μl of the supernatant was injected into the chromatograph. For the serum and CSF samples, different standard curves were constructed with blank serum and CSF. The assay response was linear over the concentration range of 0.5 to 30 μg/ml for linezolid in serum and CSF. The validation results indicated good precision and accuracy (relative standard deviations [SDs] of <1.48% and 5.31% and accuracies of 96.34 to 100.34% and 98.71 to 100.67% for the intra- and interday coefficients of variation, respectively). The lower limits of detection were 0.07 μg/ml for serum and 0.03 μg/ml for CSF.

**Statistical analysis.** All data are expressed as means ± SDs. For each patient, the age, weight, height, sampling time, concentrations of linezolid in serum and CSF, SAPS II score, APACHE II score, Glasgow coma scale, Clcr, and all pharmacokinetic parameters were defined as quantitative continuous variables, while sex and the kind of biological sample (serum or CSF) were considered nominal variables.

All data sets were tested for normality by the Wilk-Shapiro test, and quantitative variables were compared by use of the Mann-Whitney test. Spearman’s correlation test was used to evaluate the relation between the linezolid concentrations in serum and CSF as well as the relation between serum or CSF linezolid concentrations and other demographic or pharmacokinetic parameters. A P value of <0.05 was considered statistically significant. Statistical processing and data analysis were performed with GraphPad Prism 4 software (GraphPad Software Inc.).

**Pharmacokinetic evaluations.** The pharmacokinetic parameters for linezolid in serum and CSF were estimated from the concentration-time data of individual patients by noncompartmental, steady-state analysis with the WinNonlin pharmacokinetic software package (Pharsight Corporation, Mountain View, Calif.) and included the elimination half-life in serum and CSF (tl/2,serum and tl/2,CSF, respectively) and the area under the curve from the time of dosing to the time of the last observation for serum and CSF (AUC0–24,serum and AUC0–24,CSF, respectively). AUCs were calculated by the linear trapezoidal method. The elimination rate constants for linezolid in serum and CSF (kl,serum and kl,CSF, respectively) were estimated by log-linear regression of the terminal portion of the concentration-versus-time curve (on the basis of the last three datum points), while the elimination half-lives for serum and CSF (tl/2,serum and tl/2,CSF, respectively) were calculated as ln2/AUC0–24,serum and ln2/AUC0–24,CSF, respectively.

Approximate estimations for Cl and V, based on the terminal phase from serum concentration-time data, were computed as follows: Cl = dose/AUC0–24 and V = dose/(kl,serum + AUC0–24,serum), where AUC0–24,serum is equal to AUC0–24,serum + Cmin <min,serum × tmin,serum and Cmin <min is the minimum linezolid concentration in serum measured at time 12 h.

The pattern penetration of linezolid into CSF was calculated by determination of the AUC CSF/AUCserum ratio for each patient (17).

**Pharmacodynamic breakpoints.** In animal models of infection, the duration that the serum linezolid concentration exceeds the MIC (T > MIC) determines the outcome. For a T > MIC of >40%, a bacteriostatic effect for both staphylococci and pneumococci is predicted. In human studies, T > MIC and the AUC from time zero to 24 h (AUC0–24,serum/MIC have been related to bacteriological and clinical outcomes. Efficacy has been shown to be optimal with a T > MIC of >85% or an AUC/MIC of >100 (7, 18).

**RESULTS**

Fourteen adult neurosurgical patients (nine men and five women) hospitalized in the ICU of the KAT Hospital (Athens, Greece) between May 2004 and May 2005 were included in the study. Linezolid administration and the CSF collection procedures were well tolerated, and no adverse effects were observed. Nine patients underwent CSF drainage (first group), whereas for the remaining five patients, CSF samples were collected by lumbar puncture (second group). In three patients in the second group, only a single CSF sample was obtained at 1.5 h after the initiation of infusion. Three of the 14 patients were older than 65 years, and consequently, their renal function was reduced, i.e., they had a calculated Clcr of 40.3 ± 0.5
The patients' demographics and characteristics are summarized in Table 1.

Two patients received linezolid for the management of a CNS infection caused by *Staphylococcus* sp., as confirmed by positive CSF cultures. Their outcomes were favorable after 14 days of therapy. Twelve patients were administered the antibiotic as prophylactic chemotherapy; one of these patients had a blood culture positive for methicillin-resistant *Staphylococcus epidermidis* as a causative pathogen. After a week of linezolid treatment, two consecutive blood cultures for this patient became negative. He died after 2 weeks of treatment, but his death was unrelated to either the infection or the treatment. The pathogens isolated from cultures were susceptible to linezolid, as confirmed by laboratory sensitivity tests. The cellular status and the chemical status of the CSF samples were indicative of the presence of meningeal inflammation in all the patients enrolled. The ranges of laboratory values for CSF were as follows: CSF glucose, 10 to 96 mg/dl; total protein, 41 to 299 mg/dl; lactate, 2.7 to 5 mmol/liter; and white blood cell count, 500 to 4,000/mm³.

The mean ± SD maximum measured linezolid concentrations were 18.6 ± 9.6 µg/ml in serum (n = 14) at 1.5 h and 10.8 ± 5.7 µg/ml in CSF (n = 9) at 2.6 h after the start of the 1-h intravenous infusion. The mean ± SD linezolid trough concentrations in serum (n = 14) were 5.4 ± 4.7 µg/ml at zero time and 5.8 ± 5.2 µg/ml at 12 h after the start of the infusion, indicating that steady state was reached. The corresponding trough values at time zero and 12 h in the CSF (n = 9) were 5.8 ± 3.9 µg/ml and 6.5 ± 4.4 µg/ml, respectively. Mean ± SD steady-state serum and CSF linezolid concentration-versus-time profiles are shown in Fig. 1. For the second group of patients, from whom CSF samples were obtained by lumbar puncture, the linezolid concentrations in CSF at 1.5 h after the start of the infusion were found to be 4.4, 6.3, 3.4, 5.3, and 3.6 µg/ml for patients 1, 6, 2, 12, and 13, respectively.

The mean CSF concentration-to-serum concentration ratios progressively increased with time, from 0.44 almost immediately after dosing to 1.11 at the end of the dosing interval. The mean ± SD linezolid exposures (AUC values) were 128.7 ± 83.9 µg · h/ml for serum (n = 14) and 101.6 ± 59.6 µg · h/ml for CSF (n = 9), with a mean penetration ratio of 0.66, i.e., 66%. The pharmacokinetic parameters for linezolid in serum and CSF are reported in Tables 2 and 3, respectively.

The linezolid concentrations achieved in the study patients were significantly higher in serum than in CSF (P = 0.001). No

![Mean ± SD concentration-time profiles of linezolid in serum (●; n = 14) and CSF (□; n = 9) after a study dose. The maximum inhibitory concentration (dotted line; 4 µg/ml) and the MIC (dashed line; 0.5 µg/ml) of linezolid for common pathogens are also shown (26).](image-url)
TABLE 3. Mean ± SD steady-state linezolid pharmacokinetic variables following intravenous administration of 600 mg twice daily to critically ill neurosurgical patientsa

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>$C_{\text{max}}$ (µg/ml)</th>
<th>$C_{\text{min}}$ (µg/ml)</th>
<th>$T_{\text{max}}$ (h)</th>
<th>$t_{1/2}\text{CSF}^b$ (h)</th>
<th>AUCCSF (µg · h/ml)</th>
<th>Ratio of AUCCSF to AUCCSera</th>
<th>$C_{\text{max}}$ (µg/ml)</th>
<th>$C_{\text{min}}$ (µg/ml)</th>
<th>$T_{\text{max}}$ (h)</th>
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<tbody>
<tr>
<td>3</td>
<td>5.9</td>
<td>1.2</td>
<td>1.5</td>
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<td>4</td>
<td>6.2</td>
<td>1.9</td>
<td>1.5</td>
<td>6.2</td>
<td>46.2</td>
<td>0.7</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>5</td>
<td>5.7</td>
<td>1.9</td>
<td>4</td>
<td>5.2</td>
<td>46.8</td>
<td>0.6</td>
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<tr>
<td>7</td>
<td>9.3</td>
<td>5.1</td>
<td>4</td>
<td>9.6</td>
<td>88.7</td>
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<td></td>
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<tr>
<td>8</td>
<td>20.4</td>
<td>12.7</td>
<td>2.5</td>
<td>24.8</td>
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<tr>
<td>9</td>
<td>16.8</td>
<td>10.8</td>
<td>2.5</td>
<td>13.0</td>
<td>171.5</td>
<td>0.6</td>
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<tr>
<td>10</td>
<td>7.8</td>
<td>6.3</td>
<td>2.5</td>
<td>33.3</td>
<td>86.8</td>
<td>0.6</td>
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<tr>
<td>11</td>
<td>8.0</td>
<td>5.7</td>
<td>2.5</td>
<td>62.9</td>
<td>77.8</td>
<td>0.5</td>
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<tr>
<td>14</td>
<td>17.5</td>
<td>9.6</td>
<td>2.5</td>
<td>12.4</td>
<td>165.9</td>
<td>0.7</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean</td>
<td>10.8</td>
<td>6.1</td>
<td>2.6</td>
<td>19.1</td>
<td>101.6</td>
<td>0.7</td>
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<tr>
<td>SD</td>
<td>5.7</td>
<td>4.2</td>
<td>0.9</td>
<td>19.0</td>
<td>59.6</td>
<td>0.1</td>
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</tr>
</tbody>
</table>

a Data are for nine patients.

b The half-lives calculated from CSF data may be considered only estimates, as the 12-h dosing interval could not be considered adequate for the calculations of such long $t_{1/2}$.

The half-lives calculated from CSF data may be considered only estimates, as the 12-h dosing interval could not be considered adequate for the calculations of such long $t_{1/2}$.

statistically significant difference in the observed AUCs between male and female patients was noted ($P > 0.05$).

A strong positive correlation between the maximum linezolid concentrations in serum and CSF ($r = 0.8; P = 0.001$) was demonstrated. Furthermore, statistically significant correlations were found between the maximum serum linezolid concentrations and $\text{CL}_{\text{CR}}$ ($r = -0.8; P = 0.002$) and body weight ($r = -0.8; P = 0.001$). Statistically significant correlations were also found between the maximum CSF linezolid concentrations and $\text{CL}_{\text{CR}}$ ($r = -0.9; P < 0.0001$) and body weight ($r = -0.8; P = 0.002$).

Nonparametric data analysis also revealed a strong positive correlation between $\text{CL}$ and $\text{CL}_{\text{CR}}$ ($r = 0.8; P = 0.0007$) and a quite strong negative correlation between body weight and $V$ ($r = -0.5; P = 0.05$).

The $\text{MIC}_{90}$ of linezolid for antibiotic-susceptible and -resistant gram-positive organisms is $\leq 4$ µg/ml (7). Using this value, we calculated AUCCSF/MIC$_{90}$ ratios (where AUCCSF = $2 \times$ AUCCSera) for serum and CSF and found them to be 64.3 (range, 13 to 132) and 50.8 (range, 19 to 96), respectively. Serum linezolid concentrations exceeded the breakpoint of 4 µg/ml for 9 ± 3.3 h, while CSF linezolid concentrations were above this threshold value for 10.4 ± 2.5 h. For pathogens with MICs of 2 µg/ml, e.g., Streptococcus spp., S. epidermidis, and Enterococcus (7), these ratios and the percentage of time that the drug remained above the MIC$_{90}$ were considerably greater.

**DISCUSSION**

Our study investigated the CSF disposition of linezolid administered in critically ill neurosurgical patients for the management of CNS infection due to gram-positive pathogens or as prophylactic chemotherapy.

The PK/pharmacodynamic (PD) profile of linezolid in serum has been extensively studied by the use of various in vitro and human models (3, 10, 12, 18, 23). However, those studies were generally carried out with healthy volunteers, and few pharmacokinetic data for patients with infections caused by gram-positive pathogens (2, 19, 22, 27) are available, so much remains to be learned about pathophysiologic conditions that may influence the pharmacokinetic profile of linezolid.

The mean values for the volume of distribution of linezolid (52.8 liters) and the clearance of linezolid (7.3 liters/h) estimated from our study data were consistent with those reported in previous studies following twice-daily i.v. administration of linezolid to healthy volunteers and patients with infections, i.e., 45.5 to 57.0 liters and 7.4 to 9.2 liters/h, respectively (2, 18, 23). Also, in a previous study with critically ill patients in an ICU (27), a comparable mean volume of distribution was found, i.e., 0.63 liter/kg, whereas the value in our study was 0.77 liter/kg. In contrast, the mean $t_{1/2}$ (6.5 h), steady-state $C_{\text{max}}$ (18.6 µg/ml), and AUCCSF (128.7 µg · h/ml) were found to be higher in our critically ill neurosurgical patients than in healthy volunteers and patients with ventilator-associated pneumonia, i.e., 4.4 to 4.8 h, 15.1 to 17.7 µg/ml, and 77.3 to 93.4 µg · h/ml, respectively, with a SAPS II score of 40 ± 13. However, in a study with patients with multiple underlying disease states and comorbid conditions (19), mean AUCCSF values similar to our values were found, but with greater variability, i.e., the range in the previous study was 56.8 to 871 µg · h/ml, whereas the range in our study was 49.6 to 528.6 µg · h/ml.

The high variability in the values of the linezolid serum and CSF concentrations/pharmacokinetic parameters (mainly AUC and CL values) noted in this study is consistent with that reported in previous studies with critically ill patients (19, 22, 27) and healthy volunteers (18) and may be partly explained by interindividual variability in age and sex (11), body weight (27), and renal clearance (4). More specifically, significant correlations were found between maximum serum linezolid concentrations/CSF linezolid concentrations and body weight and, consequently, creatinine clearance in our study patients. Nonrenal clearance due to the nonenzymatic metabolism of linezolid (23) may also contribute to the variability in clearance between patients. In a study conducted by Meagher et al. (19), liver function, location of care, $\text{CL}_{\text{CR}}$, and body weight were found to be significant covariates and accounted for 19% of the variance in the average total clearance.

When the dispositions of linezolid in CSF and serum were compared, all the findings (the longer $T_{\text{max}}$ CSF, the longer $t_{1/2}$ CSF, and the AUCCSF/AUCSerum of ~66%) were consistent with the fact that linezolid moves in and out of the blood-brain barrier slowly (21) due to its amphiphilic properties (log partition coefficient between n-octanol and water, 0.55) (26) and its relatively low level of plasma protein binding (31%) (10).

The substantial penetration of linezolid into CSF is in agreement with the findings of other investigators in studies with both animals and humans, although a complete pharmacokinetic profile of the drug in the CSF of critically ill patients with meningeal inflammation has not been obtained. In a study with a rabbit meningitis model, the authors noted that linezolid showed good penetration into the cerebrospinal fluid of rabbits (mean ± SD, 38% ± 4%) (8). In a limited study of CSF penetration in patients with ventricular-peritoneal shunts and noninfamed meninges, the CSF concentration/plasma concentration ratio was 0.7:1.0 after multiple linezolid doses (18). Likewise, in case reports of diagnostic lumbar puncture procedures carried out with patients with meningitis, reported CSF concentration/plasma concentration ratios were 0.74, 7 h
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after dose administration and after 1 week of therapy (28). 0.8, 5 h and 12 h after infusion on day 5 of therapy (14), and 0.92 on day 9 of treatment (16). The ratio of the CSF trough concentrations to the plasma trough concentrations exceeded 1.0 on day 5 of treatment in all patients treated for postneurosurgical CNS infections due to gram-positive pathogens (26). Finally, Shaikh et al. (21) found CSF concentration/plasma concentration ratios of 17 (2.39/0.14 μg/ml) and 1.9 (2.98/1.53 μg/ml) on days 2 and 19 of therapy, respectively, in one patient affected with vancomycin-resistant-enterococcus meningitis and successfully treated with 600 mg i.v. linezolid.

Maintenance of antibiotic concentrations within a therapeutic range is of particular importance in critically ill patients. Considering the high incidence of microorganisms with MIC90 close to 4 μg/ml in ICU settings and based upon a pharmacodynamic goal of a 24-h serum AUC/MIC ratio of 50 to 100 (1), it appears from our study that a dosage regimen of 600 mg given intravenously twice daily would probably be efficacious against organisms with MICs as high as 2 to 4 μg/ml (1, 9, 20). Moreover, the 9-h time period in which serum concentrations remained above the MIC90, combined with the 2-h postantibiotic effect of linezolid (23), support the approved twice-daily intravenous dosing schedule of linezolid. However, the wide interindividual pharmacokinetic variability encountered in our critically ill neurosurgical patients suggests that linezolid dosages should be further investigated to ensure an optimal individual PK/PD profile.

When the target site for therapy is the CSF, the principal determinant of antibiotic effectiveness is the relation between the drug concentrations in CSF and the MIC90 for the infecting microorganism (17). Notably, in this study, the CMIN at steady state (6.1 μg/ml) was found to mostly exceed the MIC90 (4 μg/ml) for the target pathogens with the highest MIC90 (S. aureus, enterococci) and CSF linezolid concentrations remained above the MIC90 for 100% of the dosing interval in the majority of patients. Furthermore, the positive clinical outcomes for the two patients with documented CNS infections caused by gram-positive pathogens illustrate that linezolid is effective in eradicating the causative organisms isolated.

Conclusions. Our study showed that the intravenous administration of linezolid at 600 mg twice daily in critically ill neurosurgical patients with meningeval inflammation provided a satisfactory linezolid penetration in CSF of 66% and serum and CSF concentrations exceeding the MIC of the targeted pathogens throughout the dosing interval. Eradication of the causative pathogens was achieved in two patients with documented CNS infections and in one patient with bacteremia due to a Staphylococcus sp. However, considerable variabilities in linezolid serum and CSF concentrations and pharmacokinetic parameters were observed in our critically ill neurosurgical patients. Therefore, the dosages of linezolid used should be aimed at optimizing individual PK/PD profiles.

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