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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 MIC_{90}s 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).

For an antibiotic to be effective against CNS infections, therapeutic concentrations should be achieved at the site of infection. The presence of the blood-brain barrier restricts the entry of drugs into cerebrospinal fluid (CSF) (17). However, linezolid has shown good penetration into CNS, achieving levels in CSF 30 to 70% of those present in serum (13), and thus, it seems to be a promising tool for the treatment of CNS infections (26).

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 enterococcus meningitis (14, 21, 28), methicillin-resistant staphylococcus 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

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linezolid into the CSF of patients with meningeal 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 CSF examination and cultures for suspected CSF infection.

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 (CL_{CR}), as determined by the formula of Cockroft and Gault (6), ≥40 ml/min; normal hepatic function (an alanine aminotransferase, aspartate aminotransferase, or bilirubin level lower than twice the upper limit of normal); craniocerebral 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, untoward effects from linezolid, known resistance of 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, CL_{CR}, and degree of illness severity on the basis of their APACHE II and SAPS II scores.

Protein, glucose, lactate, red blood cell, and white blood cell concentrations in CSF were determined to estimate the degree of impairment of the blood-CSF barrier on the study day.

Drug administration and sample collection. All patients received 1-h intravenous infusions of linezolid (Zyvoxid; Pfizer) at 600 mg twice daily through a central venous catheter. Blood samples were collected when the steady-state concentrations of linezolid had been achieved, i.e., after at least 2 days of administration of the dosage regimen. Blood samples (5 ml) were collected through an arterial catheter just before the initiation of infusion and at 1.5, 2.5, 4, 6, 9, and 12 h thereafter. After centrifugation at 3,000 rpm for 5 min, the serum samples were stored at −70°C until they were assayed.

CSF samples of 0.5 ml each were collected simultaneously with each blood sample through an external drainage catheter from all patients except the group of patients without a CSF drain, from whom CSF samples were obtained by lumbar puncture, performed twice within a 12-h period, at 1.5 and 12 h after the start of the infusion. Prior to the collection of CSF from those patients with an external drainage catheter, 1 to 2 ml of CSF was discarded to allow correct sampling. The CSF samples were immediately centrifuged and stored at −70°C until they were analyzed.

The maximum linezolid concentration measured in serum (C_{max}) reflects the drug concentration 30 min after the end of the infusion, while C_{MAX} is the maximum concentration measured in CSF at the time of C_{max} (T_{max}).

The minimum linezolid concentrations in serum and CSF (C_{min} and C_{MIN}, respectively) correspond to the mean drug concentrations measured at zero time and 12 h after the start of the infusion. Strict adherence to sampling times was maintained in order to ensure reliable calculations of the linezolid pharmacokinetic variables, i.e., the area under the concentration-time curve (AUC), clearance at steady state (CL), volume of distribution (V), elimination rate constant (k_{el}), and elimination half-life ($t_{1/2}$), for each patient.

The construction of a complete pharmacokinetic curve was feasible only for those patients with a CSF drain.

A lumbar puncture was performed only if it was neurosurgically indicated. Small volumes of the serum and CSF samples were sent for microbiological examination.

Sample analysis. Quantification of linezolid in human serum and CSF specimens was performed by an isocratic high-performance liquid chromatography assay, using the method developed by Tobin et al. (24). Chromatography was performed on a Hypersil 5ODS 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 acetonitrile 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, CL_{CR}, 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 ($t_{1/2\ serum}$ and $t_{1/2\ CSF}$, respectively) and the area under the curve from the time of dosing to the time of the last observation for serum and CSF (AUC_{serum} and AUC_{CSF}, respectively). AUCs were calculated by the linear trapezoidal method. The elimination rate constants for linezolid in serum and CSF ($\lambda_{z\ serum}$ and $\lambda_{z\ CSF}$, 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 ($t_{1/2\ serum}$ and $t_{1/2\ CSF}$, respectively) were calculated as $\ln 2/\lambda_{z\ serum}$ and $\ln 2/\lambda_{z\ CSF}$, respectively.

Approximate estimations for CL and V, based on the terminal phase from serum concentration-time data, were computed as follows: $CL = dose/AUC_{serum}$ and $V = dose/(\lambda_{z\ serum} \cdot AUC_{INF})$, where AUC_{INF} is equal to $AUC_{serum} + C_{min\ 12\ h}/\lambda_{z\ serum}$ ($C_{min\ 12\ h}$ is the minimum linezolid concentration in serum measured at 12 h).

The percent penetration of linezolid into CSF was calculated by determination of the AUC_{CSF}/AUC_{serum} 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 (AUC_{0-24})/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 CL_{CR} of 40.3 ± 0.5

TABLE 1. Patients' demographics and characteristics at enrollment

Characteristic	Value
Age (yr)	58.7 ± 17.3[a]
Sex (no. of M/no. of F[b])	9/5
Wt (kg)	67.6 ± 11.8[a]
Ht (cm)	168.8 ± 8.5[a]
Creatinine clearance (ml/min)	81.3 ± 39.6[a]
Degree of illness severity	
SAPS II score	50.7 ± 3.6[a]
APACHE II score	18.7 ± 1.2[a]
Glasgow coma scale	5.9 ± 1.1[a]
Underlying CNS disease (no. [%] of patients)	
Acute hydrocephalus (intracerebral hemorrhage, subarachnoid hemorrhage)	9 (64.3)
Suspicion of CNS infection (head trauma, intracerebral hemorrhage)	5 (35.7)

[a] Data are expressed as means ± SDs for 14 patients.
[b] M, male; F, female.

TABLE 2. Mean ± SD steady-state serum linezolid pharmacokinetic variables following intravenous administration of 600 mg twice daily to critically ill neurosurgical patients[a]

Patient no.	C_{max} (μg/ml)	C_{min} (μg/ml)	$t_{1/2\ serum}$ (h)	CL (liters/h)	V (liters)	AUC_{serum} (μg · h/ml)
1	9.2	2.1	5.9	10.7	90.9	56.1
2	5.5	1.1	3.6	21.9	114.2	24.8
3	9.4	1.0	3.3	11.9	57.1	50.4
4	12.1	1.3	3.4	8.2	39.8	72.8
5	19.4	1.4	3.4	7.7	38.3	77.7
6	12.8	3.2	6.3	8.1	72.6	74.5
7	21.0	2.8	3.6	5.0	25.7	119.5
8	30.0	13.9	11.4	2.3	38.0	259.3
9	32.4	13.4	9.1	2.3	29.9	264.3
10	19.1	8.2	12.1	4.2	73.8	141.7
11	19.1	7.3	8.3	3.8	45.7	156.6
12	21.4	11.8	12.7	3.0	55.9	197.4
13	10.8	0.9	2.6	10.4	38.7	57.7
14	38.3	9.5	5.2	2.4	18.2	248.5
Mean	18.6	5.6	6.5	7.3	52.8	128.7
SD	9.6	5.0	3.6	5.4	26.9	83.9

[a] Data are for 14 patients.

ml/min. Also, renal impairment, indicated by CL_{CR} values of 41.5 ± 1.8 ml/min, was observed in two patients (each of whom was aged 58 years). No patients had established liver disease. The patients' demographics and characteristics are summarized in Table 1.

Two patients received linezolid for the management of a CNS infection caused by a *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/mm^3.

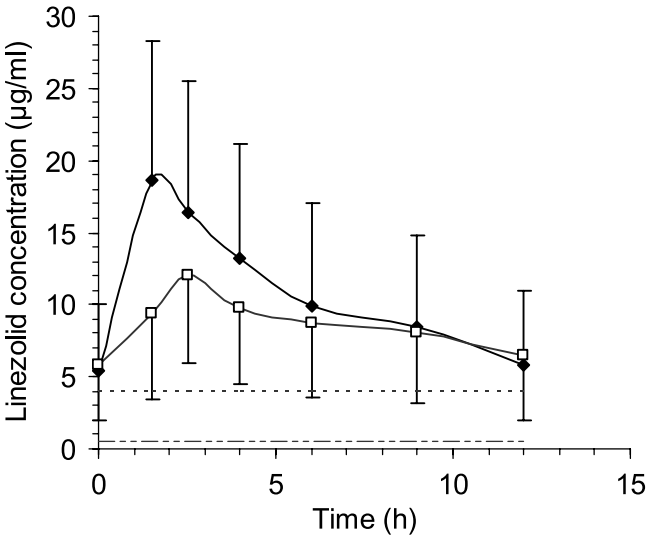

FIG. 1. Mean ± SD concentration-time profiles of linezolid in serum (◆; $n = 14$) and CSF (□; $n = 9$) after a study dose. The maximum inhibitory concentration (dotted line; 4 μg/ml) and the MIC (dashed line; 0.5 μg/ml) of linezolid for common pathogens are also shown (26).

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

TABLE 3. Mean ± SD steady-state CSF linezolid pharmacokinetic variables following intravenous administration of 600 mg twice daily to critically ill neurosurgical patients[a]

Patient no.	C_{max} (μg/ml)	C_{min} (μg/ml)	T_{max} (h)	$t_{1/2}$ CSF[b] (h)	AUC_{CSF} (μg · h/ml)	Ratio of AUC_{CSF} to AUC_{serum}
3	5.9	1.2	1.5	4.9	37.7	0.7
4	6.2	1.9	1.5	6.2	46.2	0.7
5	5.7	1.9	4	5.2	46.8	0.6
7	9.3	5.1	4	9.6	88.7	0.7
8	20.4	12.7	2.5	24.8	192.6	0.7
9	16.8	10.8	2.5	13.0	171.5	0.6
10	7.8	6.3	2.5	33.3	86.8	0.6
11	8.0	5.7	2.5	62.9	77.8	0.5
14	17.5	9.6	2.5	12.4	165.9	0.7
Mean	10.8	6.1	2.6	19.1	101.6	0.7
SD	5.7	4.2	0.9	19.0	59.6	0.1

[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 $t_{1/2}$s.

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 CL_{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 CL_{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 CL and CL_{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 MIC_{90} of linezolid for antibiotic-susceptible and -resistant gram-positive organisms is ≤4 μg/ml (7). Using this value, we calculated AUC_{0-24}/MIC_{90} ratios (where $AUC_{0-24} = 2 \times AUC_{0-12}$) 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 $t_{1/2\ serum}$ (6.5 h), steady-state C_{max} (18.6 μg/ml), and AUC_{serum} (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 AUC_{0-24} 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, CL_{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 $T_{max\ CSF}$, the longer $t_{1/2\ CSF}$, and the AUC_{CSF}:AUC_{serum} 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 noninflamed 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

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 MIC_{90}s 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 MIC_{90}, 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 MIC_{90} for the infecting microorganism (17). Notably, in this study, the C_{MIN} at steady state (6.1 μg/ml) was found to mostly exceed the MIC_{90} (4 μg/ml) for the target pathogens with the highest MIC_{90} (*S. aureus*, enterococci) and CSF linezolid concentrations remained above the MIC_{90} 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 meningeal 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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