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 ($\pm$ standard deviation) was 63 ± 18.9 mg $\cdot$ 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 vanco-

mycin 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

TABLE 1. Patient characteristics and CSF parameters pre- and posttreatment^a

Patient	Gender	Age (yr)	BMI (kg/m ²)	Main diagnosis	Pathogen	CSF parameter							
						Protein (mg/dl)	Pretreatment				Posttreatment		
							GlucR	WBC/ μ l	RBC/ μ l	Protein (mg/dl)	GlucR	WBC/ μ l	RBC/ μ l
1	M	51	25.7	SAH	MRSA	82	0.39	1,875	675	45	0.67	3	25
2	M	72	23.5	SAH	MRSA	302	0.48	765	15,600	108	0.38	20	1,620
3	F	52	23.0	SAH	CoNS	134	0.77	190	2,390	86	0.66	4	240
4	F	53	21.6	SAH	CoNS	70	0.55	125	25	41	0.87	7	185
5	F	18	19.0	TBI	MRSA	64	0.47	35	100	59	0.58	1	55

^a BMI, body mass index; GlucR, glucose CSF/blood ratio; RBC, red blood cell count; SAH, aneurysmal subarachnoid hemorrhage; TBI, traumatic brain injury; WBC, white blood cell count.

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FIG. 1. Time-concentration curves (means $\pm$ SDs) of linezolid in plasma and CSF. (a) Profile after administration of a single intravenous dose of 600 mg ($n = 5$). (b) Profile after multiple intravenous doses (600 mg twice daily; $n = 5$). The dotted horizontal lines represent MICs (2 and 4 mg/liter) for susceptible pathogens.

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 posttherapeutic antibacterial effects against most target pathogens (24). Calculating the percent time above the MIC ($T > \text{MIC}$) in CSF in our patients, the recommended dosage regimen of 600 mg linezolid intravenously twice a day resulted in a percent $T > \text{MIC}$ of 99.8%

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

Patient	Parameter ^a												
	Plasma ^b						Ventricular CSF ^c						
	$C_{\max}$ (mg/liter)	$C_{\min}$ (mg/liter)	$t_{1/2}$ (h)	AUC _{SS} (mg · h/liter)	V_z (liters)	k_{el} (liters/h)	CL_{Tot} (ml/min)	$C_{\max}$ (mg/liter)	$C_{\min}$ (mg/liter)	$t_{1/2}$ (h)	AUC _{SS} (mg · h/liter)	V_z (liters)	k_{el} (liters/h)
1	26.9	4.5	3.6	166	18.9	0.19	60.4	10.5	5.3	17.2	85.7	173	0.04
2	19.3	0.6	3.5	59.2	51.0	0.20	169	4.5	1.1	4.0	34.9	99.2	0.17
3	21.6	0.6	2.6	70.0	31.8	0.27	143	6.5	4.4	7.3	70.5	90.2	0.09
4	13.8	1.3	3.6	63.4	49.7	0.19	158	6.6	2.8	3.3	68.0	42.2	0.21
5	16.0	2.6	5.4	74.6	62.7	0.13	134	7.5	1.9	2.5	56.0	38.5	0.28
Mean ± SD	19.5 ± 5.1	1.94 ± 1.69	3.7 ± 1.0	86.5 ± 44.5	42.8 ± 17.4	0.02 ± 0.1	133 ± 42.6	7.1 ± 2.2	3.1 ± 1.8	6.8 ± 6.0	63.0 ± 18.9	88.7 ± 54.7	0.16 ± 0.1

^a $t_{1/2}$: half-life; V_z : apparent volume of distribution; k_{el} : elimination constant; CL_{tot} : total body clearance; T_{max} : time to peak concentration.
^b $T_{\text{max}} = 1$ h for all patients.
^c $T_{\text{max}} = 4$ h for all patients.

for pathogens with an MIC of 2 mg/liter. The corresponding calculated AUC_{0-24}/MIC ratio (mean $\pm$ 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_{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 nonselective inhibitor of monoamine 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 vasopressors 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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