

## Cerebrospinal Fluid Linezolid Concentrations in Postneurosurgical Central Nervous System Infections

Gram-positive (GP) cocci, mainly methicillin-resistant staphylococci, are the most frequent pathogens involved in central nervous system (CNS) postneurosurgical infections (4). Linezolid (PNU-100766), a synthetic oxazolidinone, has shown good in vitro and in vivo activities against drug-susceptible and drug-resistant staphylococci, streptococci, and enterococci, with MICs for 90% of the isolates generally ranging from 0.5 to 4 µg/ml (6). Linezolid has shown good CNS penetration and thus seems a promising candidate for treatment of CNS infections (1, 2); however, at present, only a few anecdotal data, dealing with vancomycin-resistant-enterococcus meningitis, have been reported about efficacy and safety in this setting (3, 7, 8).

As part of an expanded-access program for patients with nosocomial infections, we assayed the plasma and cerebrospinal fluid (CSF) linezolid levels in five patients treated for postneurosurgical CNS infections due to GP pathogens and with a history of either failure to respond to or untoward events with vancomycin-based regimens (Table 1). Linezolid was administered intravenously (1-h infusion) at the dosage of 600 mg twice a day (mean treatment time, 20 days). Patients received no other antimicrobials. Plasma and CSF specimens were collected simultaneously after multiple doses and assayed for linezolid concentrations by a specific high-performance liquid chromatography technique (5). Clinical features and outcome will be detailed elsewhere. Briefly, during linezolid treatment, clinical signs improved dramatically, with both complete clinical resolution and normalization of CSF findings in all patients.

Plasma linezolid trough concentrations ranged from 0.54 to 5.3 µg/ml, CSF linezolid trough levels ranged from 1.46 to 7.0 µg/ml, and the ratio between CSF and plasma linezolid trough concentrations always exceeded 1 (mean, 1.6; range, 1.2 to 2.3) (Table 1). Importantly, CSF linezolid trough concentrations largely exceeded the MICs for the four isolates in our patients. Also, these findings were recorded after at least 6 days of treatment, when the blood-brain barrier permeability could have had a trend towards normalization.

These findings parallel those of Shaikh et al. (7), who observed CSF/plasma ratios of trough drug concentrations of 17 (2.39/0.14 µg/ml) and 1.9 (2.98/1.53 µg/ml) after 2 and 19 days, respectively, in one patient affected with vancomycin-resistant-enterococcus meningitis, successfully treated with 600 mg of intravenous linezolid.

Also, the relatively constant CSF linezolid concentration observed at the end of 1-h drug infusion confirms a slow flow of linezolid across the blood-brain barrier, as suggested by Shaikh (7).

As a matter of fact, CSF linezolid peak concentrations are relatively delayed, and the CSF/plasma trough ratios obtained in our study and in Shaikh et al.'s are higher than those in patients without meningitis (6). Such findings, which are in agreement with linezolid's amphiphilic properties (log partition coefficient between *n*-octanol and water, 0.55), indicate that the severity of meningeal inflammation could influence penetration of linezolid into the brain and the CSF.

Even though a complete pharmacokinetic profile of linezolid in CSF could not be obtained, our results show that the daily dose of 600 mg produces plasma and CFS linezolid concentrations greater than those predicted to be effective against a variety of clinically important multidrug-resistant cocci (6).

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TABLE 1. Concentrations of linezolid in plasma and CSF and other clinical data for five patients with CNS infections

Patient	Infection	Pathogen <sup>a</sup>	Day of treatment	CSF protein (mg/dl)	CSF glucose (mg/dl)	CSF WBC <sup>b</sup> (no./µl)	Linezolid <sup>c</sup>		
							CSF (µg/ml)	Plasma (µg/ml)	CSF/plasma ratio
1	Ventriculitis	MRSE	7	114	39	24	2.35	2.0	1.2
2	Meningitis	MRSE	6	132	44	52	2.3	1.83	1.25
			12	87	58	4	3.23	2.47	1.3
3	Meningitis	PSSP	6	217	33	122	1.46	0.54	2.7
			20	87	48	4	3.76	3.23	1.2
4	Meningitis	GP cocci <sup>d</sup>	6	121	54	8	7.0 (6.9)	5.3 (12.4)	1.32 (0.55)
5	Meningitis	MRSA	8	63	43	200	3.9 (5.5)	1.71 (11.5)	2.3 (0.5)

<sup>a</sup> MRSE, methicillin-resistant *Staphylococcus epidermidis*; MRSA, methicillin-resistant *Staphylococcus aureus*; PSSP, penicillin-susceptible *Streptococcus pneumoniae*.

<sup>b</sup> WBC, leukocytes.

<sup>c</sup> At 0 h postdose. Values obtained at 1 h postdose are given in parentheses.

<sup>d</sup> Gram stain.

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