JOURNAL OF CLINICAL MICROBIOLOGY, Feb. 2004, p. 929–932 Vol. 42, No. 2
0095-1137/04/$08.00+0 DOI: 10.1128/JCM.42.2.929–932.2004

Treatment of Meningitis Due to Methicillin-Resistant *Staphylococcus epidermidis* with Linezolid

Wolfgang A. Krueger,[1]* Bernd Kottler,[1] Bernd E. Will,[2] Alexandra Heininger,[1] Heinz Guggenberger,[1] and Klaus E. Unertl[1]

Department of Anesthesiology and Intensive Care Medicine[1] and Department of Neurosurgery,[2] Tübingen University Hospital, 72076 Tübingen, Germany

Received 20 June 2003/Returned for modification 18 September 2003/Accepted 4 November 2003

Methicillin-resistant *Staphylococcus epidermidis* (MRSE) can cause nosocomial meningitis in the presence of prosthetic devices. Vancomycin is the treatment of choice, but its penetration into the cerebrospinal fluid is poor, especially in cases without severe meningeal inflammation. We successfully used linezolid to treat a case of posttraumatic MRSE meningitis with a low-level inflammatory response. Therapeutic effectiveness was documented microbiologically and by the simultaneous measurement of linezolid levels in serum and cerebrospinal fluid.

CASE REPORT

An 18-year-old female sustained a severe cerebral trauma in a road accident. She was pinned in her car and could not be accessed until 45 min after the accident. Her initial Glasgow Coma Scale score was 5. She was intubated and then transferred by helicopter to our hospital. Computed tomography scans showed severe left frontal intracerebral bleeding, traumatic subarachnoid hemorrhage, and generalized swelling of the brain. An external ventricular drainage was placed to measure intracranial pressure, and a chest tube was inserted to drain a right-sided pneumothorax, which had developed as a result of serial rib fractures and lung contusions. She was then taken to the operating room for evacuation of a subcapsular hematoma of the liver. She had also sustained several pelvic fractures which did not require surgical intervention.

The following day, intracranial pressure rose to 40 mm of Hg despite antiedematous treatment, requiring immediate bifrontal decompressive craniectomy. The patient remained deeply sedated for several weeks due to excessive swelling of the brain, as documented by repeated computed tomography scans. On day 15, she developed a central venous catheter-associated bacteremia caused by methicillin-resistant *Staphylococcus epidermidis* (MRSE), which grew in two peripherally drawn blood cultures as well as on the tip of the central venous catheter. The patient received treatment with vancomycin and nonsteroidal anti-inflammatory drugs; two subsequent blood cultures drawn 1 and 2 days after removal of the central venous catheter gave negative results. After 5 days of treatment with vancomycin, leukocyte levels had dropped to 740/μl with 19% neutrophils. The leukocyte counts recovered only after treatment with granulocyte colony-stimulating factor (filgrastim). While the swelling of the brain gradually decreased, the patient progressively developed posttraumatic hydrocephalus leading to protrusion of brain tissue beyond the bifrontal craniectomy defects. Repeat lumbar punctures were performed, and after complete recovery from leukopenia, a lumbar cerebrospinal fluid (CSF) drainage was inserted. On day 46, the patient's temperature rose to 39°C accompanied by a leukocyte count of 18,500/μl and a C-reactive protein level of 2.0 mg/dl. Physical examination revealed suspected mild neck stiffness, and a complete workup for infectious focus (including chest X ray, abdominal ultrasound, blood cultures, change of intravascular catheters, and microbiological examinations of respiratory secretions, urine, and CSF) was started. Whereas the results for all other cultures remained negative, the CSF total cell count yielded 260/μl, a glucose level of 48 mg/dl with a corresponding serum level of 100 mg/dl, and mildly elevated protein and lactate levels (Table 1). Microscopic CSF examination after centrifugation revealed the presence of gram-positive cocci. A single dose of 15 mg of vancomycin was administered via the lumbar CSF drainage, which was then immediately removed. The lumbar drainage was not replaced, and the increased intracranial pressure was subsequently treated by repeated lumbar punctures. Since the patient had experienced a neutropenic episode for which vancomycin might have been one of the possible causes, intravenous treatment with 600 mg of linezolid twice daily was started and no further doses of vancomycin were given. MRSE sensitive to vancomycin and to linezolid grew from the initial CSF sample and on the following day, but all subsequent samples gave negative culture results. The antibiotic resistance pattern of the isolate was different from that of the MRSE strain that had been isolated from the tip of the central venous catheter 31 days before. The cell count and lactate level in CSF peaked on the second day of treatment with linezolid and then fell, while protein levels remained slightly elevated. All parameters finally returned to normal on day 16 and treatment with linezolid was stopped 1 day later (Table 1).

Linezolid levels in blood and CSF were measured during treatment and determined by high-performance liquid chromatography and UV detection using slightly modified methods previously described by others (23). The samples had been

* Corresponding author. Mailing address: Department of Anesthesiology and Intensive Care Medicine, Tübingen University Hospital, Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany. Phone: 49-7071-298-6622. Fax: 49-7071-29-5533. E-mail: wolfgang.krueger@uni-tuebingen.de.

stored at −20°C and were thawed at room temperature immediately before measurement. Aliquots of 200 μl were then diluted with 700 μl of deionized water, 100 μl of 0.1 N HCl, and 5 μg (50 μl) of *p*-nitroaniline, which served as an internal standard. After pH adjustment to 3.5 to 4.5, 10 μl of each sample was injected. The mobile phase consisted of 840 ml of deionized water, 170 ml of acetonitrile, 3 mmol of heptane sulfonic acid/liter, and 6 g of *ortho*-phosphoric acid (85%). The column was a Nova-Pak C_{18} with a pore size of 4 μm (150 by 3.9 mm inside diameter; Waters, Eschborn, Germany), and the temperature was set at 30°C. UV detection was at 253 nm (Dionex, Idstein, Germany). The limit of quantification was 0.2 μg/ml, and the response from calibration standards was linear from 0.2 to 20.0 μg/ml. On day 9 of treatment with linezolid, the trough level in serum was 4.14 μg/ml; a simultaneously drawn CSF sample yielded 3.79 μg/ml, thus giving a CSF-to-serum ratio of 0.92. Peak levels in serum on days 10 and 13 of treatment were 21.42 and 19.01 μg/ml, respectively, and a further serum trough level taken on day 13 measured 4.55 μg/ml.

The further clinical course of the patient was uneventful except for one episode of generalized seizures on day 57 after the trauma. A ventriculo-peritoneal shunt was implanted for treatment of hydrocephalus on day 62 and the patient was transferred to a special physical rehabilitation center on day 83. At that stage, she was able to sit up and eat with help and was breathing through a tracheostomy without supplemental oxygen. Her skull bones were reimplanted 2 months later. When she left the physical rehabilitation center 9 months after the accident she was able to talk and to look after herself without external help. Slight motor deficits prevented her from returning to her original job but she was ready to train for a different occupation.

TABLE 1. Time course of infectious parameters measured in CSF during treatment with linezolid

Day of treatment	Result				
	Culture grown	Cell count (cells/μl)	Protein (mg/dl)	Lactate (mmol/liter)	Glucose (mg/dl)
−6	NA[a]	0	29	1.5	54
1	MRSE	260	43	3.6	48
2	MRSE	2,320[b]	39	4.3	51
3	None	220	39	3.4	55
7	None	40[c]	53	2.9	56
9	None	40[c]	54	2.4	46
12	None	0	53	2.6	52
16	None	0	15	1.8	68

[a] NA, not applicable.
[b] Differential cell counts showed predominantly granulocytes, several monocytes, and few lymphocytes.
[c] Differential cell counts showed predominantly lymphocytes and few granulocytes and monocytes.

Community-acquired meningitis is most commonly caused by pneumococci and meningococci, although the spectrum of pathogens also includes streptococci, *Haemophilus influenzae*, and *Listeria* species (7). These characteristics are substantially different from those of nosocomially acquired intracranial infections, which may be caused by a wide array of microbes, including staphylococci, gram-negative bacilli, and yeasts. In the presence of prosthetic devices, coagulase-negative staphylococci are among the most common pathogens and—as in this case—they are frequently resistant to methicillin (6). In such cases, removal of the prosthetic device and intravenous administration of vancomycin are considered the treatment of choice (1, 16). However, some experimental and clinical data suggest that the penetration of vancomycin into CSF is weak and sometimes unpredictable in cases without severe meningeal inflammation or in combination with anti-inflammatory treatment with steroids (1). Some authors have reported that continuous intravenous administration of vancomycin may lead to higher penetration in patients with meningitis, as maximum CSF concentrations ranged from 5.7 to 19.0 mg/liter. In contrast, CSF concentrations usually remain below 4 mg/liter in patients without meningitis (2). This means that the breakpoint for susceptible organisms is not reached consistently in patients without severe meningeal inflammation even when high daily doses of up to 4 g are used. Therefore, some authors advocate intrathecal administration of vancomycin (17), although a comprehensive evaluation of the benefits has yet to be made and the associated risks (such as ototoxicity) remain unclear (1, 13). Furthermore, this treatment strategy has not been formally approved by the Food and Drug Administration (1).

For our patient, a single dose of vancomycin was administered intrathecally but (given the above-mentioned disadvantages) we elected not to continue this treatment after removal of the lumbar CSF drainage. Furthermore, our patient had already experienced a leukopenic episode during treatment with vancomycin. Although we cannot rule out the possibility that the episode was triggered by other drugs (such as the nonsteroidal anti-inflammatory drugs) that were sporadically administered to our patient, vancomycin has on rare occasions been implicated in such side effects (18, 19) and we tried to avoid any drug that might possibly have caused leukopenia in our patient. This prompted us to start intravenous treatment with linezolid, even though—to our knowledge—there are only two reports on the use of linezolid to treat CSF infections caused by *Staphylococcus epidermidis* (9, 24). There is, however, growing evidence from case series that linezolid is effective against meningitis caused by vancomycin-resistant enterococci (10, 12, 20, 21, 24, 26).

To lower the increased intracranial pressure, we repeatedly performed lumbar punctures for our patient. This enabled us to document successful eradication of MRSE, as the CSF cultures became sterile 2 days after we began intravenous treatment with 600 mg of linezolid twice a day. This finding is consistent with the reports of other authors, who found that enterococci disappeared from the CSF after 2 (10, 20) to 4 (26) days of intravenous linezolid. Even though microbiological documentation was not always possible (9, 21) and additional antibiotics were applied in most cases (12, 20, 26), these data are remarkable, especially since linezolid is only bacteriostatic against staphylococci and enterococci (8) and bactericidal antibiotics are usually recommended for the treatment of meningitis (15).

The peak and trough levels in serum in our patient were very

similar to those described in investigations conducted with healthy volunteers (14). Even though we documented penetration in only a single pair of measurements, our data confirm the posited high-level CSF concentrations of linezolid (12), which can even exceed serum levels in some cases of meningitis (25). The ratio of the area under the plasma concentration-time curve to the MIC has been found to be an outcome predictor for treatment of bacteremia with linezolid (B. Cirincione, T. Grasela, S. Sardella, E. Ludwig, D. J. Stalker, B. Hafkin, J. B. Bruss, and E. Antal, Abstr. 40th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 1389, 2000). Such pharmacokinetic-pharmacodynamic analyses are difficult to obtain for human CSF. However, the CSF trough level in our patient was only slightly below the linezolid MIC for susceptible bacteria (4 mg/liter) (14), which fits well with the clinical finding that MRSE was cleared from the CSF on the second day of treatment with linezolid. The effectiveness of linezolid in the treatment of such infections is further corroborated by the fact that the infectious episode in our patient was accompanied by only a low degree of meningeal inflammation and a moderate level of systemic inflammation. This is evidenced by the low CSF cell count and by protein, lactate, and glucose levels that were close to normal when penetration of linezolid into the CSF was measured. In contrast, the majority of beta-lactam antibiotics and vancomycin do not penetrate to the CSF in relevant amounts in the absence of meningeal inflammation (4).

Our case report has several limitations. Since our patient initially received one dose of vancomycin intrathecally, the sterilization of the CSF cannot be attributed exclusively to the presence of linezolid. On the other hand, data on the combined use of linezolid and vancomycin are conflicting, since additive (3), indifferent (22), and even antagonistic (11) effects have been found in studies in vitro; antagonistic effects have also been reported in an animal model of endocarditis (5). The pharmacokinetics and optimal dosage of intrathecally administered vancomycin are also unclear. In adults, doses between 5 and 20 mg are usually administered every 24 h; however, large variations in CSF concentrations and half-lives have been described (1, 15, 17). Furthermore, it has been suggested that drugs administered via lumbar access—as was the case in our patient—might not be distributed evenly within the intrathecal space (1, 15). We did not determine CSF levels of vancomycin in our patient, but since the culture obtained 24 h after the administration of 15 mg of vancomycin still grew MRSE and became sterile only after continued treatment with linezolid, it can be assumed that the single dose of intrathecal vancomycin did not result in any substantial benefit for our patient.

It is also difficult to assess the benefit of antibiotic treatment in the functional recovery of our patient, because the major neurological damage was due to severe trauma which was further complicated by increased intracranial pressure resulting from posttraumatic swelling of the brain and the development of hydrocephalus. Nevertheless, the overall neurological outcome after several months was very positive, showing that our patient sustained no severe sequelae from MRSE meningitis.

In conclusion, our case report provides further evidence that linezolid can be a valuable option for the treatment of meningitis caused by MRSE whenever the use of vancomycin is unfeasible or even contraindicated.

We thank Edgar Hoffmann, technician at the Center for Medical Research, Department of Anesthesiology and Intensive Care Medicine, Tübingen University Hospital, for the measurement of linezolid levels in serum and cerebrospinal fluid.

REFERENCES

1. **Ahmed, A.** 1997. A critical evaluation of vancomycin for treatment of bacterial meningitis. Pediatr. Infect. Dis. **16:**895–903.
2. **Albanèse, J., M. Léone, B. Bruguerolle, M.-L. Ayem, B. Lacarelle, and C. Martin.** 2000. Cerebrospinal fluid penetration and pharmacokinetics of vancomycin administered by continuous infusion to mechanically ventilated patients in an intensive care unit. Antimicrob. Agents Chemother. **44:**1356–1358.
3. **Allen, G. P., R. Cha, and M. J. Rybak.** 2002. In vitro activities of quinupristin-dalfopristin and cefepime, alone and in combination with various antimicrobials, against multidrug-resistant staphylococci and enterococci in an in vitro pharmacodynamic model. Antimicrob. Agents Chemother. **46:**2606–2612.
4. **Andes, D. R., and W. A. Craig.** 1999. Pharmacokinetics and pharmacodynamics of antibiotics in meningitis. Infect. Dis. Clin. N. Am. **13:**595–618.
5. **Chiang, F.-Y., and M. Climo.** 2003. Efficacy of linezolid alone or in combination with vancomycin for treatment of experimental endocarditis due to methicillin-resistant *Staphylococcus aureus*. Antimicrob. Agents Chemother. **47:**3002–3004.
6. **De Bels, D., A. M. Korinek, R. Bismuth, D. Trystram, P. Coriat, and L. Puybasset.** 2002. Empirical treatment of adult postsurgical nosocomial meningitis. Acta Neurochir. **144:**989–995.
7. **de Gans, J., D. van de Beek, and The European Dexamethasone in Adulthood Bacterial Meningitis Study Investigators.** 2002. Dexamethasone in adults with bacterial meningitis. N. Engl. J. Med. **347:**1549–1556.
8. **Diekema, D. J., and R. N. Jones.** 2000. Oxazolidinones. A review. Drugs **59:**7–16.
9. **Gill, C. J., M. A. Murphy, and D. H. Hamer.** 2002. Treatment of *Staphylococcus epidermidis* ventriculo-peritoneal shunt infection with linezolid. J. Infect. **45:**129–132.
10. **Graham, P. L., K. Ampofo, and L. Saiman.** 2002. Linezolid treatment of vancomycin-resistant *Enterococcus faecium* ventriculitis. Pediatr. Infect. Dis. **21:**798–800.
11. **Grohs, P., M.-D. Kitzis, and L. Gutmann.** 2003. In vitro bactericidal activities of linezolid in combination with vancomycin, gentamicin, ciprofloxacin, fusidic acid, and rifampin against *Staphylococcus aureus*. Antimicrob. Agents Chemother. **47:**418–420.
12. **Hachem, R., C. Afif, Z. Gokaslan, and I. Raad.** 2001. Successful treatment of vancomycin-resistant *Enterococcus* meningitis with linezolid. Eur. J. Clin. Microbiol. Infect. Dis. **20:**432–434.
13. **Klibanov, O. M., J. E. Filicko, J. A. DeSimone, and D. S. Tice.** 2003. Sensorineural hearing loss associated with intrathecal vancomycin. Ann. Pharmacother. **37:**61–65.
14. **Krueger, W. A., and K. E. Unertl.** 2002. New treatment option for Gram-positive infections in critically ill patients—overview over linezolid. Anästh. Intensivmed. Notfallmedmed. Schmerzther. **37:**199–204.
15. **Lutsar, I., G. H. McCracken, Jr., and I. R. Friedland.** 1998. Antibiotic pharmacodynamics in cerebrospinal fluid. Clin. Infect. Dis. **27:**1117–1129.
16. **Parsonnet, J., and R. L. Deresiewicz.** 2001. Staphylococcal infections, p. 889–900. *In* E. Braunwald, A. S. Fauci, D. L. Kasper, S. L. Hauser, D. L. Longo, and J. L. Jameson (ed.), Harrison's principles of internal medicine, 15th ed., vol. 1. McGraw-Hill, New York, N.Y.
17. **Pfausler, B., H. P. Haring, A. Kampfl, J. Wissel, M. Schober, and E. Schmutzhard.** 1997. Cerebrospinal fluid (CSF) pharmacokinetics of intraventricular vancomycin in patients with staphylococcal ventriculitis associated with external CSF drainage. Clin. Infect. Dis. **25:**733–735.
18. **Sanche, S. E., W. N. Dust, and Y. M. Shevchuk.** 2000. Vancomycin-induced neutropenia resolves after substitution with teicoplanin. Clin. Infect. Dis. **31:**824–825.
19. **Schwartz, M. D.** 2002. Vancomycin-induced neutropenia in a patient positive for an antineutrophil antibody. Pharmacotherapy **22:**783–788.
20. **Shaikh, Z. H. A., C. A. Peloquin, and C. D. Ericsson.** 2001. Successful treatment of vancomycin-resistant *Enterococcus faecium* meningitis with linezolid: case report and literature review. Scand. J. Infect. Dis. **33:**375–379.
21. **Steinmetz, M. P., M. A. Vogelbaum, M. A. De Georgia, J. C. Andrefsky, and C. Isada.** 2001. Successful treatment of vancomycin-resistant enterococcus meningitis with linezolid: case report and review of the literature. Crit. Care Med. **29:**2383–2385.
22. **Sweeney, M. T., and G. E. Zurenko.** 2003. In vitro activities of linezolid combined with other antimicrobial agents against staphylococci, enterococci, pneumococci, and selected gram-negative organisms. Antimicrob. Agents Chemother. **47:**1902–1906.
23. **Tobin, C. M., J. Sunderland, L. O. White, and A. P. MacGowan.** 2001. A

simple, isocratic high-performance liquid chromatography assay for linezolid in human serum. J. Antimicrob. Chemother. **48:**605–608.
24. **Viale, P., L. Pagani, F. Christini, R. Stefini, R. Bergomi, P. Colombini, and G. Carosi.** 2002. Linezolid for the treatment of central nervous system infections in neurosurgical patients. Scand. J. Infect. Dis. **34:**456–459.
25. **Villani, P., M. B. Regazzi, F. Marubbi, P. Viale, L. Pagani, F. Cristini, B. Cadeo, G. Carosi, and R. Bergomi.** 2002. Cerebrospinal fluid linezolid concentrations in postneurosurgical central nervous system infections. Antimicrob. Agents Chemother. **46:**936–937.
26. **Zeana, C., C. J. Kubin, P. Della-Latta, and S. M. Hammer.** 2001. Vancomycin-resistant *Enterococcus faecium* meningitis successfully managed with linezolid: case report and review of the literature. Clin. Infect. Dis. **33:**477–482.