CASE REPORTS

Linezolid Clearance During Continuous Venovenous Hemodiafiltration: A Case Report

Michael D. Kraft, Pharm.D., Deborah A. Pasko, Pharm.D., Daryl D. DePestel, Pharm.D., Jessica J. Ellis, Pharm.D., Charles A. Peloquin, Pharm.D., and Bruce A. Mueller, Pharm.D., FCCP

Objective. To determine the linezolid clearance and serum concentrations in a critically ill man receiving continuous venovenous hemodiafiltration (CVVHDF).

Methods. Intravenous linezolid 600 mg every 12 hours was administered to a critically ill, 85-year-old man with anuria who was receiving CVVHDF at a dialysate flow rate of 2000 ml/hour and a mean ultrafiltrate production rate of 775 ml/hour. Samples of blood and spent dialysate and ultrafiltrate were obtained at the time of linezolid peaks and troughs, and linezolid concentrations were determined.

Results. The CVVHDF yielded a mean linezolid clearance of 36.5 ml/minute and an elimination half-life of 7.5 hours. The linezolid saturation coefficient ranged from 0.77–0.81. Administration of intravenous linezolid 600 mg every 12 hours yielded suitable serum trough concentrations.

Conclusion. Administration of intravenous linezolid 600 mg every 12 hours maintained therapeutic serum trough concentrations in this critically ill patient receiving CVVHDF.

(Pharmacotherapy 2003;23(8):1071–1075)

The number of infections caused by gram-positive bacteria continues to increase, with *Staphylococcus aureus*, coagulase-negative staphylococci, and *Enterococcus* sp among the most common causes of bacteremia.[1] Antimicrobial resistance among these pathogens continues to increase. From 1994–1998, infections caused by oxacillin-resistant *S. aureus* and vancomycin-resistance *Enterococcus* sp have increased 40%.[2] Linezolid, a novel oxazolidinone antimicrobial, is effective for the treatment of infections caused by gram-positive pathogens such as methicillin-resistant *S. aureus*[3–7] and vancomycin-resistant *Enterococcus* sp.[8] With the emergence of resistant gram-positive organisms such as these, and most recently vancomycin-resistant *S. aureus*,[9, 10] linezolid becomes an increasingly important antimicrobial agent.

In the last 12–24 months, our institution has experienced an increase in the number of infections caused by vancomycin-resistant *Enterococcus* and methicillin-resistant *Staphylococcus* sp that require treatment with linezolid. Many patients with these infections have been critically ill and required intensive care. Six also had kidney failure and required continuous renal replacement therapy (CRRT). Like many other institutions,[11] we have been providing CRRT as treatment of acute kidney failure in intensive care

From the Department of Clinical Sciences, College of Pharmacy, University of Michigan (Drs. Kraft, Pasko, DePestel, and Mueller) and the Department of Pharmacy Services, University of Michigan Health System (Drs. Kraft, Pasko, DePestel, Ellis, and Mueller), Ann Arbor, Michigan; and the Infectious Diseases Pharmacokinetics Laboratory, National Jewish Medical and Research Center, Denver, Colorado (Dr. Peloquin).

Supported by an unrestricted educational grant from Pharmacia & Upjohn Company, Kalamazoo, Michigan.

Address reprint requests to Michael D. Kraft, Pharm.D., Department of Pharmacy Services, UH/B2D301, University of Michigan Health System, 1500 East Medical Center Drive, Ann Arbor, MI 48109-0008; e-mail: mdkraft@umich.edu.

patients.

To our knowledge, dosing recommendations for linezolid in patients receiving CRRT have not been published; however, some pharmacokinetic properties of the drug have been elucidated. Under steady-state conditions in a healthy adult, approximately 30% of linezolid is eliminated by way of the kidneys as the parent drug and 50% as carboxylic acid metabolites.[12] Although linezolid clearance is reduced with decreased renal function, total clearance remains constant in patients with minimal renal function.[13] During intermittent hemodialysis, linezolid clearance is increased by approximately 80%.[12] Approximately 30% of a linezolid dose is removed in a 3-hour hemodialysis session.[12] One study reported a dialysis extraction ratio of 38% that remained constant throughout the dialysis session.[13] However, the elimination rate constant did not change, and the authors concluded that no linezolid dosing adjustment is necessary in patients receiving intermittent hemodialysis.[13]

Given that linezolid is removed by intermittent hemodialysis and has a small molecular weight (337 daltons), it is possible that a significant amount of linezolid is removed during CRRT, which provides renal replacement therapy 24 hours/day. Inappropriate dosing could result in subtherapeutic serum concentrations and therapeutic failure.

We describe a patient receiving linezolid and continuous venovenous hemodiafiltration (CVVHDF) who did not appear to be responding to linezolid therapy. Consequently, steady-state serum and dialysate linezolid concentrations were determined to assess whether adequate linezolid concentrations were being achieved and to determine CVVHDF linezolid clearance.

Case Report

An 85-year-old man with a history significant for hypertension, coronary artery disease, atrial fibrillation, chronic obstructive pulmonary disease, peripheral vascular disease, peptic ulcer disease, osteoarthritis, and a cerebrovascular accident was admitted to the hospital for repair of an abdominal aortic aneurysm and right renal artery reimplantation. The patient had a prolonged hospital course complicated by ischemic colitis, intraabdominal infection, sepsis, respiratory failure requiring prolonged mechanical ventilation, and acute renal failure. He also underwent several colonoscopies, exploratory laparotomies, and a total colectomy. In addition, he was receiving broad-spectrum antibiotic therapy with vancomycin, metronidazole, and levofloxacin throughout his hospital stay. Thirteen days after his surgery, a peritoneal fluid culture revealed vancomycin-resistant *E. faecium* sensitive to linezolid, as determined by the Kirby-Bauer disk diffusion method. Subsequently, vancomycin was replaced with intravenous linezolid 600 mg every 12 hours.

A second peritoneal fluid sample was obtained and sent for culture and sensitivities on postoperative day 24. This culture also grew vancomycin-resistant *Enterococcus* sp sensitive to linezolid. On postoperative day 27, CVVHDF was started for volume control. At this point, the patient's weight was 100.1 kg (dry weight approximately 80 kg), serum albumin 2.8 g/dl, and hematocrit 30.2%. His recovery continued to be slow, and he did not appear to be responding to therapy. Serum and combined dialysate-ultrafiltrate (effluent) samples were obtained and linezolid content assayed to ensure appropriate linezolid dosing during CVVHDF. The patient was receiving the following drugs on the day the samples were obtained: hydralazine 20 mg every 8 hours via nasogastric tube, isosorbide dinitrate 20 mg 3 times/day via nasogastric tube; intravenous digoxin 0.25 mg every 48 hours, intravenous linezolid 600 mg every 12 hours, intravenous levofloxacin 500 mg every 48 hours, intravenous metronidazole 500 mg every 8 hours, intravenous doxycycline 100 mg every 12 hours, continuous intravenous infusion of propofol titrated to effect; subcutaneous enoxaparin 40 mg/day; and total parenteral nutrition with 20% fat emulsion daily.

The patient received CVVHDF for 23 days, during which time he had anuria. Several days after linezolid samples were obtained, his clinical course continued to worsen, and he required high-dose vasopressor support. Eventually, the patient's family and physicians agreed to remove life-support therapy, and he died 50 days after his surgery.

Methods

Continuous Venovenous Hemodiafiltration

Continuous venovenous hemodiafiltration was accomplished using a CRRT machine (Diapact, B. Braun, Bethlehem, PA). A polysulfone hemodiafilter (F70 NR, Fresenius Medical Care North America, Lexington, MA) (ultrafiltration coefficient 49 ml/hr/mm Hg, surface area 1.6 m^2)

Table 1. Peak and Trough Linezolid Concentrations in a Critically Ill Patient Receiving Continuous Venovenous Hemodiafiltration

Parameter	Trough 1	Peak	Trough 2
Prefilter blood sample	7.2 µg/ml	16.4 µg/ml	6.2 µg/ml
Postfilter blood sample	7.2 µg/ml	ND	6.1 µg/ml
Effluent sample	5.6 µg/ml	13.6 µg/ml	5.0 µg/ml
Time since end of previous dose infusion	9.38 hrs	0.5 hrs	12.0 hrs
Calculated saturation coefficient	0.77	ND	0.81

ND = not done.

was used throughout the treatment. Descriptions and properties of various methods of CRRT, such as CVVHDF, have been described.[14] The blood flow rate was maintained at 200 ml/minute throughout the treatment period. The dialysate flow rate was maintained at 33.3 ml/minute; the ultrafiltrate production rate was varied from 11.2–14.5 ml/minute (mean 12.9 ml/min) to meet fluid removal goals and maintain the patient's blood pressure level.

The dialysate used was a custom-made solution containing sodium 135 mEq/L, potassium 3 mEq/L, chloride 107 mEq/L, bicarbonate 28 mEq/L, magnesium 1 mEq/L, and glucose 100 mg/dl. For anticoagulation, a citrate dextrose solution (ACD, Baxter-Fenwal, Deerfield, IL) was used. Anticoagulation was reversed using calcium chloride infused in a central venous catheter not connected to the CRRT circuit.

Blood samples were obtained from extracorporeal blood access sites prefilter (A) and postfilter (V). Effluent from the hemofilter containing a combination of spent dialysate (D) and ultrafiltrate (F) were obtained simultaneously from the dialysate side sampling port. All blood and effluent samples were obtained 15 minutes before the dose was administered (trough 1), and 30 minutes after the end of a 1-hour infusion (peak) and again at the end of the dosing interval, approximately 12 hours later (trough 2).

Calculations

Standard equations were used to calculate pharmacokinetic properties of half-life, elimination rate, and volume of distribution (V_d). The saturation coefficient was calculated using the standard formula:

$$SA = C_E/C_p,\ C_p = (C_A + C_V)/2$$

where SA is the saturation coefficient, C_E is the concentration in the effluent, C_p is the linezolid concentration in the plasma, C_A is the linezolid concentration in the plasma drawn from the prefilter sampling port, and C_V is the linezolid concentration in the plasma drawn from the postfilter sampling port.

Total body clearance was calculated as:

$$Dose/AUC_{0-\infty}$$

where $AUC_{0-\infty}$ is the area under the concentration versus the time curve.

The clearance from CRRT was calculated as:

$$Cl_{CRRT} = (Q_D + Q_F) \bullet SA$$

where Cl_{CRRT} is clearance from CRRT, Q_D is the dialysate flow rate, and Q_F is the ultrafiltrate production rate.

Assay Methodology

Serum concentrations of linezolid were determined using a validated high-performance liquid chromatography (HPLC) assay.[15] Samples were measured using a system consisting of a Waters 515 HPLC pump (Waters, Milford, MA) with a Waters model 680 gradient controller and a solvent select valve, a Spectra Physics model 8875 fixed-volume autosampler (Spectra Physics, San Jose, CA), a Waters model 486 ultraviolet detector, a Macintosh 7100 computer (Apple Computers Inc., Cupertino, CA), and the Rainin Dynamax HPLC data management system (Rainin, Woburn, MA). The plasma standard curve for linezolid ranged from 0.5–30 mg/ml; absolute recovery of linezolid from plasma was 95%. The within-sample precision (percent coefficient of variation) of validation of a single standard concentration was 0.69%, and the overall validation precision across all standards was 1.04–4.39%. The lower detection limit of the assay was 0.5 µg/ml.

Results

Blood and effluent samples were obtained as planned for the two trough values. However, for the peak values, only the ultrafiltrate and the A blood sample were obtained correctly. The V

sample was not obtained from the postfilter venous site. Instead, the nurse took a sample from a central venous site not connected to the CRRT circuit. Consequently, a saturation coefficient was not calculated for the linezolid peak. Blood and effluent concentrations are shown in Table 1.

While the patient was receiving CVVHDF, his calculated linezolid V_d was approximately 49 L, total body clearance 84.7 ml/minute, and half-life approximately 7.5 hours. The saturation coefficient ranged from 0.77–0.81 at the troughs. Using the mean of these two saturation coefficient values, Cl_{CRRT} was calculated to be 36.5 ml/minute; mean effluent flow rate was 46.2 ml/minute.

Discussion

Linezolid is bacteriostatic against most gram-positive aerobic bacteria, but it displays bactericidal activity against some strains of *Streptococcus pneumoniae*.[12, 16, 17] Breakpoint concentrations for linezolid against *Enterococcus* and *Streptococcus* sp indicate that susceptible organisms have a minimum inhibitory concentration (MIC) of 2 µg/ml or less, whereas susceptible *Staphylococcus* sp have an MIC of 4 µg/ml or less.[12] Breakpoints for other gram-positive pathogens are not established.

The reported linezolid elimination half-life is 4.5–5.5 hours in patients with normal renal function.[12] Linezolid has a steady-state V_d of about 40–50 L and is 31% bound to plasma protein.[12] The recommended dosage for these patients is either oral or intravenous linezolid 600 mg every 12 hours. Linezolid pharmacokinetics are not significantly altered, and dosage adjustments are unnecessary for patients with renal insufficiency[12]; however, it is recommended that linezolid be administered after hemodialysis.[12, 13] Reports of linezolid disposition in patients receiving CRRT have appeared, to our knowledge, in only one published abstract.[18]

We obtained these serum and effluent linezolid values in our patient to ensure that his serum trough concentrations were therapeutic and to determine the extent of linezolid clearance by CVVHDF. Animal data suggest that the major pharmacodynamic parameter that determines efficacy of linezolid is the time that the drug concentration remains above the MIC for the pathogen.[17] Therefore, serum linezolid concentration should be maintained at or above the MIC for most of the dosing interval. In our patient, trough serum concentrations achieved with intravenous linezolid 600 mg every 12 hours were 7.2 and 6.1 µg/ml, well above the previously reported MICs.[12] In our patient, the peak and trough serum concentrations achieved with this dosing regimen also are similar to previous reports with repeated 600-mg intravenous and oral doses.[12]

In patients receiving continuous hemofiltration, the sieving coefficient is used in calculating drug clearance. In our patient, continuous hemodiafiltration was administered, and effluent flowing from the dialysate out port contains both spent dialysate and ultrafiltrate. Consequently, measuring linezolid content in effluent cannot be used to distinguish how much drug appears in the effluent because of dialysis and how much because of hemofiltration. The C_E:C_p ratio yields the saturation coefficient, which is probably very close to the sieving coefficient at low dialysate flow rates.[19, 20] The saturation coefficient of linezolid we observed (0.77–0.81) is similar to that of the reported nonprotein bound fraction of linezolid.

In patients with normal renal function, linezolid plasma protein binding is approximately 31%.[12] In critically ill patients (or those with renal failure) the extent of protein binding is unknown. Some experts suggest that the unbound fraction of a drug can be used as a sieving coefficient when the sieving coefficient is unknown.[14, 19, 21] Regarding linezolid, it appears that this literature-derived estimate (~0.7) provides a reasonable estimate of the saturation coefficient, and consequently, the sieving coefficient. However, we did not assess actual linezolid plasma protein binding in our patient.

The outflow from the dialysate side of the hemofilter was 33.3 ml/minute dialysate flow plus a mean of 12.9 ml/minute of ultrafiltrate flow. This ultrafiltrate production was necessary to remove the 5-ml/minute citrate solution used as an anticoagulant, to provide adequate fluid removal for the obligate fluid intake due to nutrition and intravenous drugs, and to provide adequate volume removal in our patient, who was overloaded with fluids. The mean desired net hourly fluid loss was 3.3 ml/minute for this patient. His ultrafiltrate production rate resulted in more of a mixed hemodiafiltration rather than a strict diffusional CRRT like continuous hemodialysis. Consequently, the calculated clearance of 36.5 ml/minute derived from the saturation coefficient values results from both diffusive and convective drug clearance. In

patients with normal renal function, total drug clearance ranges from 80–146 ml/minute, with renal clearance accounting for 40 ml/minute, or about 35–40% of total clearance.[12] This is approximately what was achieved with our CRRT regimen, which yielded a mean effluent rate of 46.2 ml/minute. Total body clearance in our patient was 84.7 ml/minute, and Cl_{CRRT} was 36.5 ml/minute, meaning that CRRT yielded approximately 43% of all clearance.

Linezolid half-life in our patient was approximately 7.5 hours during CVVHDF, compared with the reported elimination half-life of about 5 hours in patients with normal renal function.[12] Linezolid half-life in patients with renal failure is not substantially different from that in patients with normal renal function,[12, 13] that is, about 7 hours.[12] The calculated linezolid V_d in our fluid-overloaded patient was approximately 49 L; normal V_d is 40–50 L.[12] Repeated samples were not obtained after the fluid was removed, so we were unable to determine what effect fluid overload had on linezolid V_d.

Conclusion

The manufacturer's dosing recommendation of intravenous linezolid 600 mg every 12 hours achieved appropriate serum trough concentrations in our patient, who was receiving CVVHDF at 2–3 L/hour of dialysate and ultrafiltrate production. Although CVVHDF contributed 36.5 ml/minute of linezolid clearance, it was insufficient to warrant increasing the dosage. These findings confirm those of a preliminary report[18] that CVVHDF does not significantly remove linezolid.

References

1. **Pfaller MA, Jones RN, Doern GV, and Kugler K**. Bacterial pathogens isolated from patients with bloodstream infection: frequencies of occurrence and antimicrobial susceptibility patterns from the SENTRY antimicrobial surveillance program. Antimicrob Agents Chemother 1998;42:1762–70.
2. **Fridkin SK, Gaynes RP**. Antimicrobial resistance in intensive care units. Clin Chest Med 1999;20:303–16.
3. **Antony SJ, Bitter KM, Moreland T, Raudales F, Diaz-Luna H**. Methicillin-resistant *Staphylococcus aureus* infection in a renal allograft recipient treated successfully with a novel new antimicrobial agent (linezolid): new treatment options for infections due to resistant organisms. Clin Infect Dis 1999;29:1341–2.
4. **Melzer M, Goldsmith D, Gransden W**. Successful treatment of vertebral osteomyelitis with linezolid in a patient receiving hemodialysis and with persistent methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* bacteremias. Clin Infect Dis 2000;31:208–9.
5. **Bassetti M, DiBiagio A, Cenderello G, et al**. Linezolid treatment of prosthetic hip infections due to methicillin-resistant *Staphylococcus aureus* (MRSA). J Infect 2001;43:148–9.
6. **Rubinstein E, Cammarata SK, Oliphant TH, Wunderink RG**. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. Clin Infect Dis 2001;32:402–12.
7. **Stevens DL, Herr D, Lampiris H, et al**. Linezolid versus vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* infections. Clin Infect Dis 2002;34: 1481–90.
8. **Till M, Wixson RL, Pertel PE**. Linezolid treatment for osteomyelitis due to vancomycin-resistant *Enterococcus faecium*. Clin Infect Dis 2002;34:1412–14.
9. **Centers for Disease Control and Prevention**. *Staphylococcus aureus* resistant to vancomycin: United States, 2002. MMWR Morb Mortal Wkly Rep 2002;51:565–7.
10. **Centers for Disease Control and Prevention**. Vancomycin-resistant *Staphylococcus aureus*: Pennsylvania, 2002. MMWR Morb Mortal Wkly Rep 2002;51:902.
11. **Mehta RL, Letteri JM**. Current status of renal replacement therapy for acute renal failure. Am J Nephrol 1999;19:377–82.
12. **Pharmacia & Upjohn Company**. Zyvox (linezolid) package insert. Kalamazoo, MI; 2000.
13. **Brier ME, Stalker DJ, Aronoff GR, et al**. Pharmacokinetics of linezolid in subjects with varying degrees of renal function and on dialysis [abstr]. J Investig Med 1998;46:276A.
14. **Joy MS, Matzke GR, Armstrong DK, Marx MA, Zarowitz BJ**. A primer on continuous renal replacement therapy for critically ill patients. Ann Pharmacother 1998;32:362–75.
15. **Shaikh ZH, Peloquin CA, Ericsson CD**. Successful treatment of vancomycin-resistant *Enterococcus faecium* meningitis with linezolid: case report and literature review. Scand J Infect Dis 2001;33:375–9.
16. **Clemett D, Markham A**. Linezolid. Drugs 2000;59:815–27.
17. **Zurenko GE, Gibson JK, Shinabarger DL, Aristoff PA, Ford CW, Tarpley WG**. Oxazolidinones: a new class of antibacterials. Curr Opin Pharmacol 2001;1:470–6.
18. **Mauro LS, Sharief I, Assaly R, Malhotra D**. Determination of linezolid clearance via continuous hemodiafiltration [abstr]. Pharmacotherapy 2001;21:1279.
19. **Reetze-Bonorden P, Bohler J, Keller E**. Drug dosage in patients during continuous renal replacement therapy: pharmacokinetic and therapeutic considerations. Clin Pharmacokinet 1993;24:362–79.
20. **Schetz M, Ferdinande P, Van den Berghe G, Verwaest C, Lauwers P**. Pharmacokinetics of continuous renal replacement therapy. Intensive Care Med 1995;21:612–20.
21. **Golper TA**. Drug removal during continuous hemofiltration or hemodialysis. Contrib Nephrol 1991;93:110–16.