CASE REPORT

Peritoneal Dialysis Fluid Concentrations of Linezolid in the Treatment of Vancomycin-Resistant *Enterococcus faecium* Peritonitis

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Objective. To determine linezolid concentrations in peritoneal dialysis fluid after multiple oral doses of the drug in a 46-year-old man with vancomycin-resistant *Enterococcus faecium* peritonitis who was undergoing peritoneal dialysis.

Methods. After administration of oral linezolid 600 mg twice/day was started, peritoneal dialysis fluid was collected at the end of several 4- and 8-hour dwell times and submitted for analysis of linezolid concentration. Before linezolid therapy was begun, and immediately after several peritoneal dialysis exchanges, 30 ml of expended peritoneal dialysis fluid was collected in a sterile container and immediately frozen at -70°C until analysis by high-performance liquid chromatography.

Results. Peritoneal dialysis concentrations of linezolid greater than 4 µg/ml were achieved after the first dose of linezolid and maintained after repeated doses. During the course of therapy, mean linezolid concentrations in peritoneal dialysis fluid tended to increase (mean 7.60 µg/ml, range 3.54–16.2 µg/ml). All assayed peritoneal dialysis samples demonstrated linezolid concentrations greater than 4 µg/ml at the end of 4- or 8-hour dwell times, except for one level after a missed dose on linezolid treatment day 3. Duration of dwell times did not appear to correlate with linezolid concentrations.

Conclusion. In this patient, linezolid 600 mg twice/day penetrated into peritoneal dialysis fluid at or above the concentrations necessary to treat common gram-positive bacteria. Linezolid therapy is likely to have a role in peritoneal dialysis–associated peritonitis based on its antimicrobial activity, pharmacokinetic properties, ease of administration, and tolerability.

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Linezolid, the first commercially available oxazolidinone antibacterial, demonstrates in vitro activity against a variety of gram-positive organisms, such as methicillin-resistant staphylococci, penicillin-resistant pneumococci, and vancomycin-resistant *Enterococcus faecalis* and *E. faecium* (VREF). Recently, linezolid has demonstrated in vitro activity against glycopeptide-intermediate[1] and vancomycin-resistant *Staphylococcus aureus*.[2, 3] With the emergence of resistant gram-positive pathogens, linezolid becomes an increasingly important therapeutic option.

In the past year, our institution experienced an increased number of infections caused by

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vancomycin-resistant *Enterococcus* and *Staphylococcus* species, requiring treatment with linezolid. Several patients developed infections while receiving peritoneal dialysis. Linezolid is a viable treatment option for infections associated with peritoneal dialysis because the most important complication of this treatment is infection of the peritoneal cavity or the catheter exit site. This infection usually is caused by gram-positive organisms.[4]

Although dosing recommendations for linezolid in patients undergoing peritoneal dialysis have not been published, some pharmacokinetic data for patients with impaired renal function are available.[5] The pharmacokinetics of the parent drug are not altered in patients with any degree of renal insufficiency.[6] Similar plasma concentrations of linezolid are achieved regardless of renal function; thus, no dosage adjustment is recommended for patients with renal insufficiency.[6] During intermittent hemodialysis, linezolid clearance is increased by approximately 80%.[6] Because about 30% of a 600-mg dose of linezolid is removed during a 3-hour hemodialysis session, current recommendations suggest that linezolid be administered after hemodialysis is completed.[6] However, few data are available regarding the effect of peritoneal dialysis on the pharmacokinetics of linezolid or penetration of linezolid into peritoneal dialysis fluid. Inappropriate dosing could result in subtherapeutic drug concentrations and therapeutic failure.

To our knowledge, this is the first report of linezolid concentrations measured in several samples of peritoneal dialysis fluid obtained after oral administration of the drug in a patient with VREF peritonitis who was undergoing peritoneal dialysis. Quinupristin-dalfopristin was a treatment option for our patient, since a few published case reports indicated its success in patients with gram-positive peritonitis[7, 8]; however, we chose linezolid based on its antimicrobial activity, pharmacokinetic properties, ease of administration, and tolerability.

Case Report

A 46-year-old man was admitted to the University of Michigan Health System with a chief complaint of chest pain. He had a history of coronary artery disease, cerebral vascular accident, bilateral lower extremity ulcers, and end-stage renal disease, secondary to diabetes, that required peritoneal dialysis. On admission, his blood urea nitrogen and creatinine levels were 100 and 10 mg/dl, respectively. He had been noncompliant with his peritoneal dialysis therapy and subsequently was transferred to the nephrology service for peritoneal dialysis and monitoring.

On day 2 of his hospital stay, the patient experienced fever up to 101.2°F and acute changes in mental status. Chest radiography was performed, and blood, urine, and peritoneal dialysis fluid were obtained for culture. Empiric therapy with intravenous vancomycin and piperacillin-tazobactam was begun. The chest radiograph was inconsistent with pneumonia, and all cultures were negative except for blood cultures drawn from the patient's indwelling central catheter, which grew methicillin-resistant *Staphylococcus epidermidis*. After removal of the catheter, culture of the tip also revealed methicillin-resistant *S. epidermis*. The piperacillin-tazobactam was discontinued; the patient continued receiving only the intravenous vancomycin.

The patient's mental status improved initially, but his fever continued as high as 102.5ºF over the next few days despite two sets of negative blood cultures. On hospital day 9, intravenous gentamicin was added to his treatment regimen for gram-negative coverage. A transesophageal echocardiogram revealed a large superior vena cava thrombus at the site of the removed catheter. The patient's fever continued as high as 102.7ºF over the next week despite therapy with intravenous vancomycin and gentamicin. Repeated blood and urine cultures and a chest radiograph were negative. On day 21, a culture of peritoneal dialysis fluid grew *Pseudomonas stutzeri*, and the patient's antibiotic therapy was changed to intravenous piperacillin and vancomycin, and intraperitoneal gentamicin.

On hospital day 32, after a peritoneal dialysis fluid culture revealed the presence of VREF, antimicrobial therapy was changed to oral linezolid 600 mg every 12 hours (in addition to the intraperitoneal gentamicin). The patient responded clinically and remained afebrile for the duration of antibiotic therapy. Four subsequent peritoneal dialysis fluid cultures and three sets of blood cultures were negative. The patient had no other clinical signs or symptoms of infection and was discharged to a nursing home on day 46, after completing a 2-week course of therapy with intraperitoneal gentamicin and oral linezolid. Linezolid therapy was well tolerated, with no clinical evidence of adverse events.

Throughout the patient's linezolid treatment, peritoneal dialysis was continued, with five daily cycles consisting of four 4-hour dwell times and an overnight 8-hour dwell time of standard peritoneal dialysate of 1.5% dextrose with 2-L bag exchanges.

Methods

Just before linezolid therapy was begun and immediately after several peritoneal dialysis exchanges, 30 ml of expended peritoneal dialysis fluid from the patient was collected in a sterile container and immediately frozen at -70ºC until analysis by high-performance liquid chromatography (HPLC) assay.[9] The system consisted of an HPLC pump (Model 515, Waters, Milford, MA) with a gradient controller (Model 680, Waters) and a solvent select valve, a fixed-volume autosampler (Model 8875, Spectra Physics, San Jose, CA), an ultraviolet detector (Model 486, Waters), a computer (Macintosh 7100, Apple Computers Inc., Cupertino, CA), and an HPLC data management system (Dynamax, Rainin, Woburn, MA).

The standard curve for linezolid ranged from 0.5–30 µg/ml. Absolute recovery of linezolid was 95%. The within-sample precision (percent coefficient of variation) of validation for a single standard concentration was 0.69%; overall validation precision across all standards was 1.04–4.39%.

Collection and analysis of the peritoneal dialysis fluid were conducted in accordance with human subject research guidelines and policies set forth by the University of Michigan Health System institutional review board.

Results

After administration of oral linezolid 600 mg twice/day was started, peritoneal dialysis fluid was collected at the end of several 4- and 8-hour dwell times and submitted for analysis of linezolid concentration (Figure 1). Peritoneal dialysis fluid concentrations of linezolid above 4 µg/ml were achieved after the first dose of linezolid and were maintained after multiple doses. Of note, the patient did not receive the scheduled fourth dose of linezolid due to an unintentional administration error, which is reflected by the transient decrease in linezolid concentrations in the peritoneal dialysis fluid on linezolid treatment day 3.

Despite the missed dose, the linezolid concentration in the patient's peritoneal dialysis fluid was 3.54 µg/ml 19 hours after administration of the third dose. During the course of therapy, mean linezolid concentrations in peritoneal dialysis fluid tended to increase (mean 7.60 µg/ml, range 3.54–16.2 µg/ml). Duration of dwell times did not appear to correlate with linezolid concentrations in peritoneal dialysis fluid. Plasma samples were not obtained for linezolid analysis.

Discussion

Linezolid is bacteriostatic against most susceptible organisms but displays bactericidal activity against some strains of pneumococci.[10] The breakpoint concentration for linezolid-susceptible enterococci and streptococci is a minimum inhibitory concentration (MIC) of 2 µg/ml or below, and for susceptible staphylococci 4 µg/ml or below. Breakpoints for other gram-positive pathogens have not been established.[5]

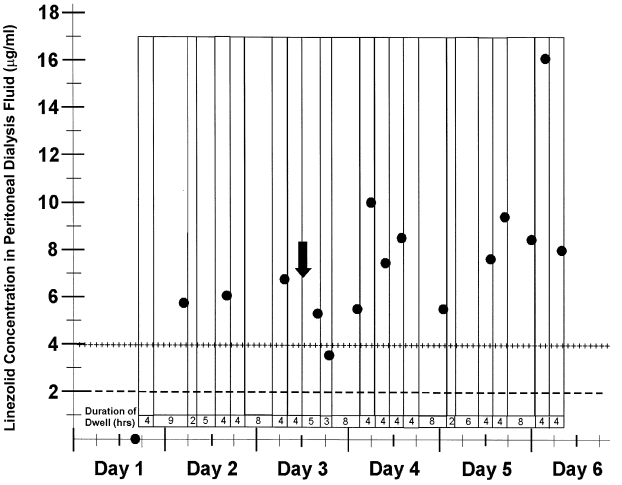

Figure 1. Peritoneal dialysis fluid concentrations of linezolid in a patient receiving multiple oral doses of oral linezolid 600 mg every 12 hours for treatment of peritonitis. Peritoneal dialysis fluid cultures yielded vancomycin-resistant *Enterococcus faecium*. Linezolid administration times were 12 P.M. and 12 A.M.. The patient was scheduled to receive dialysis in cycles of four 4-hour and one 8-hour dwell times/day. However, each dwell time actually differed slightly due to interruptions throughout the day (e.g., patient out of his room for a procedure). In addition, the patient did not receive the scheduled fourth dose of linezolid (arrow), which is reflected by the transient decrease in linezolid concentrations in his peritoneal dialysis fluid on treatment day 3. ++++ indicates the breakpoint concentrations for susceptible staphylococci to linezolid (minimum inhibitory concentration [MIC] ≤ 4 µg/ml); – – – indicates breakpoint concentrations for susceptible enterococci and streptococci to linezolid (MIC ≤ 2 µg/ml).

Linezolid exhibits rapid and complete absorption after oral administration to healthy subjects; peak plasma concentrations are achieved within 1–2 hours, and mean oral bioavailability is approximately 100%, whether or not the drug is administered with meals.[5] Therefore, administration of linezolid may be oral or intravenous. In healthy subjects, steady-state peak and trough serum concentrations of 21.20 ± 5.78 and 6.15 ± 2.94 µg/ml, respectively, are achieved after oral linezolid 600 mg twice/day, with an elimination half-life is 4.5–5.5 hours.[5] Linezolid has a steady-state volume of distribution of 40–50 L and is 31% bound to plasma protein.[5]

Linezolid undergoes hepatic oxidation to metabolites with minimal or no antimicrobial activity. Its metabolism does not involve cytochrome P450 (CYP) and does not inhibit or induce any clinically significant CYP isoforms, such as 1A2, 2C9, 2C19, 2D6, 2E1, or 3A4. The parent drug and its metabolites are primarily cleared by renal excretion; approximately 30% of the dose excreted is unchanged in urine.[5] The recommended linezolid dosage for adult patients with infection caused by susceptible gram-positive pathogens is 600 mg every 12 hours.

The main reason we obtained these linezolid concentrations in peritoneal dialysis fluid was to ensure that our patient had therapeutic linezolid concentrations at the site of infection. Animal data suggest that the major pharmacodynamic parameter determining efficacy for linezolid is the amount of time the drug concentration remains above the MIC of the pathogen.[11] Therefore, drug concentrations at the site of infection should be maintained at or above the MIC for most of the dosing interval. In our patient, administration of oral linezolid 600 mg twice/day produced peritoneal dialysis fluid concentrations consistently above 4 µg/ml at the end of 4- and 8-hour dwell times, except for one instance after inadvertent omission of the patient's fourth dose.

Animal and human pharmacokinetic data have demonstrated that linezolid readily distributes into well-perfused tissues.[5] The pharmacokinetic properties of linezolid, such as a large volume of distribution and low protein binding, suggest that the drug should distribute well into tissues and aqueous fluid, such as peritoneal dialysis fluid. Data from a few healthy volunteers have suggested sufficient penetration of drug into a variety of sites, such as skin blister and pancreatic abscess fluids as well as pulmonary and osteoarticular tissues.[12–15] Linezolid appears to penetrate into these tissues at or above the concentrations necessary to treat common gram-positive bacteria (MIC ≥ 4 µg/ml).

One study investigated the penetration of linezolid into peritoneal dialysis fluid in seven patients who exhibited no evidence of peritonitis and were undergoing continuous ambulatory or continuous cycling peritoneal dialysis.[16] Patients were given a single dose of linezolid 600 mg immediately after an exchange of 2 L of 2.5% dextrose solution. Linezolid concentrations in serum and peritoneal dialysis fluid were measured hourly for 6 hours and at 24 hours after the dose. The combined data for both types of dialysis provided a peritoneal dialysate:plasma ratio of 0.69 for the area under the curve. Concentrations of linezolid in peritoneal dialysis fluid were maintained at above 2 µg/ml for an average of 22 hours after the single dose.

Another study reported the first case of peritoneal dialysis–associated VREF peritonitis treated with linezolid.[17] A loading dose of 1200 mg administered by nasogastric tube was followed by a maintenance dosage of intravenous linezolid 600 mg every 12 hours. In a single sample of peritoneal dialysis fluid obtained 20.5 hours after the loading dose, linezolid concentration was 7.14 µg/ml. Concomitant plasma samples were not obtained.

Conclusion

To our knowledge, this is the first report of linezolid concentrations measured in peritoneal dialysis fluid after multiple doses of oral linezolid 600 mg twice/day in a patient with VREF peritonitis who was undergoing peritoneal dialysis. Several samples of peritoneal dialysis fluid were obtained during therapy and analyzed to determine linezolid concentrations. Our data suggest that linezolid 600 mg twice/day penetrates into peritoneal dialysis fluid at or above the concentrations necessary to treat common gram-positive bacteria. Linezolid therapy is likely to have a role in peritoneal dialysis–associated peritonitis based on its antimicrobial activity, pharmacokinetic properties, ease of administration, and tolerability. No data have yet been published regarding treatment of peritonitis by intraperitoneal administration of linezolid. Further clinical studies are needed to adequately assess the use of linezolid for treatment of gram-positive peritonitis.

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References

1. **Rybak MJ, Hershberger E, Moldovan T, Grucz RG**. In vitro activities of daptomycin, vancomycin, linezolid, and quinupristin-dalfopristin against staphylococci and enterococci, including vancomycin-intermediate and -resistant strains. Antimicrob Agents Chemother 2000;44:1062–6.
2. **Centers for Disease Control and Prevention**. *Staphylococcus aureus* resistance to vancomycin: United States, 2002. MMWR Morb Mortal Wkly Rep 2002;51:565–7.
3. **Centers for Disease Control and Prevention**. Vancomycin-resistant *Staphylococcus aureus*: Pennsylvania, 2002. MMWR Morb Mortal Wkly Rep 2002;51:902.
4. **Bowker KE, Wootton M, Holt HA, MacGowan AP**. In vitro activity of linezolid against gram-positive isolates causing infection in continuous ambulatory peritoneal dialysis patients. J Antimicrob Chemother 2002;49:578–80.
5. **Pharmacia & Upjohn**. Zyvox (linezolid) package insert. Kalamazoo, MI; 2001.
6. **Brier ME, Stalker DJ, Aronoff GR, et al**. Pharmacokinetics of linezolid in subjects with varying degrees of renal function and on dialysis. Presented at the 38th interscience conference on antimicrobial agents and chemotherapy, San Diego, CA, September 24–27, 1998.
7. **Troidle L, Kliger AS, Gorban-Brennan N, Fikrig M, Golden M, Finkelstein FO**. Nine episodes of CPD-associated peritonitis with vancomycin-resistant enterococci. Kidney Int 1996;50:1368–72.
8. **Lynn WA, Clutterbuck E, Want S, et al**. Treatment of CAPD-peritonitis due to glycopeptide-resistant *Enterococcus faecium* with quinupristin/dalfopristin. Lancet 1994;344:1025–6.
9. **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.
10. **Clemett D, Markham A**. Linezolid. Drugs 2000; 59:815–27.
11. **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.
12. **Conte JE Jr, Golden JA, Kipps J, Zurlinden E**. Intrapulmonary pharmacokinetics of linezolid. Antimicrob Agents Chemother 2002;46:1475–80.
13. **Gee T, Ellis R, Marshall G, Andrews J, Ashby J, Wise R**. Pharmacokinetics and tissue penetration of linezolid following multiple oral doses. Antimicrob Agents Chemother 2001;45:1843–6.
14. **Rana B, Butcher I, Seaton RA, Murnaghan, C, Tobin C, Grigoris P**. Linezolid penetration into osteoarticular tissues [abstr]. In: Program and abstracts of the annual meeting of the Infectious Diseases Society of America, Chicago, IL, October 24–27, 2002:56.
15. **Gopal Rao G, Steger A, Tobin CM**. Linezolid levels in pancreatic secretions. J Antimicrob Chemother 2001;48:931–2.
16. **Gendjar SR, Moriyama B, Bailey EM, et al**. Pharmacokinetics of oral linezolid in patients on peritoneal dialysis [abstr]. In: Proceedings of the American Society of Nephrology/ International Society of Nephrology World Congress of Nephrology, San Francisco, CA, October 13–17, 2001:A2205.
17. **Bailey M, Faber MD, Nafziger DA**. Linezolid for the treatment of vancomycin-resistant enterococcal peritonitis. Am J Kidney Dis 2001; 38:1–3.