

Linezolid Contributed to *Clostridium difficile* Colitis with Fatal Outcome

L.T. Zabel, S. Worm

Abstract

Linezolid, the first of a new class of antibacterial drugs, the oxazolidinones, has inhibitory activity against a broad range of gram-positive aerobic cocci and also against certain anaerobes. Although diarrhea is one of the most frequently encountered adverse effects of linezolid, *Clostridium difficile*-related complications are very uncommon. One case of fatal *C. difficile* colitis in a patient with spondylodiscitis, who had received a long-term course of linezolid therapy, is presented. Colitis was able to be exclusively assigned to linezolid. Factors contributing to the colitis are discussed.

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Introduction

Linezolid is the first of a new class of antibacterial drugs, the oxazolidinones. It has inhibitory activity against a broad range of gram-positive aerobic cocci, including methicillin-resistant *Staphylococcus aureus* (MRSA), glycopeptide-intermediate *S. aureus*, vancomycin-resistant enterococci, and penicillin-resistant *Streptococcus pneumoniae*. The drug also shows activity against certain anaerobes like *Clostridium difficile*. Infections caused by MRSA, like sepsis and osteomyelitis, have been successfully treated with linezolid. Apart from surgical intervention, treatment of osteomyelitis and spondylodiscitis often requires a prolonged antimicrobial treatment with the potential hazard of adverse reactions. Adverse effects of linezolid comprise diarrhea, nausea and headache [1] but also effects on blood chemistry or hematology, such as reversible thrombocytopenia, anemia, and neutropenia [2] are known.

A recent study focussed on the use of linezolid in the treatment of osteomyelitis [3]. Although 18 events with gastrointestinal disturbances occurred out of 89 patient courses, none was classified as serious. Although diarrhea is a frequent adverse effect of linezolid therapy, *C. difficile*-related complications are expected to be uncommon [4]. Here we present a case of fatal *C. difficile* colitis in a patient with spondylodiscitis, who had received a long-term course of linezolid therapy. The colitis could be exclusively assigned to this therapy.

Case Report

The patient, a 60-year-old man, suffered from a spondylodiscitis of T5/6, which he probably acquired from a fistulating osteomyelitis in the left medial clavicle after bypass surgery. Further severe diseases comprised coronary heart disease, chronic renal insufficiency, and non-insulin-dependent diabetes mellitus. During previous hospitalizations, microbiological examinations of several intraoperatively taken swabs from the clavicle and from blood cultures revealed growth of a MRSA. Antimicrobial testing showed sensitivity to vancomycin, linezolid, and rifampin. Apart from repeated surgical debridements of the clavicle, antibiotic therapy with vancomycin was administered at a dose of 1 g twice daily during these previous hospitalizations. Because of his reduced general condition the spondylodiscitis was supposed to be treated conservatively. During the last hospitalization in December 2002 he developed acute renal failure under vancomycin therapy and the treatment regimen had to be changed to linezolid (2 × 600 mg/d, intravenously), which was stopped upon his discharge in January 2003.

In February 2003, he was admitted to the hospital again, because the clavicle wound had to be revised. The revision was performed on February 4, 2003. Complementary to the surgical debridement the antimicrobial therapy with linezolid 600 mg intravenously twice daily was recommenced. During his hospitalization, he suffered acute paraplegia and collapsed. The indication was then given to stabilize the spine operatively and this operation was performed on February 13, 2003. Again MRSA was isolated from intraoperatively taken wound swabs. At day 15 of linezolid treatment, the patient developed profuse bloody diarrhea. He had signs of an acute abdomen and severe sepsis with hypotension < 90 mmHg, tachycardia > 90/min, leukocytosis (15.51/nl), and anuria. *C. difficile* toxin A and B were repeatedly demonstrated in the feces of the patient using an ELISA (RIDASCREEN®, R-Biopharm, Germany). *C. difficile* toxin A and B were subsequently also detected in a *C. difficile* strain isolated from his stool culture.

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Due to the clinical signs of the patient, the laboratory findings, which are summarized in table 1, and the *C. difficile* toxin detection in stools, a pseudomembranous colitis was diagnosed and intravenous treatment with metronidazole (500 mg twice daily, intravenously) was started. The patient responded rapidly to this therapy. At that time the patient received no other drugs which could be assigned to *C. difficile* colitis. Metronidazole administration was continued for 4 weeks. A relapse occurred soon after discontinuation of the metronidazole treatment and was controlled by restarting the metronidazole regimen again. Unfortunately, the patient's condition deteriorated due to his underlying diseases and he developed a second relapse with sepsis. In agreement with the family no life-prolonging measures were taken and he died of multiorgan failure in April 2003.

Discussion

C. difficile-related complications with linezolid are expected to be very uncommon [4]. Recently, in a world-wide assessment of linezolid clinical safety and tolerability [5], *C. difficile* was reported in 0.2% of the linezolid-treated patients and in 0.4% of the comparative drug-treated patients. Whereas *C. difficile* diarrhea or colitis was reported in six comparative drug-treated patients, none was diagnosed in the linezolid-treated patients. Pseudomembranous colitis developed in one (0.05%) patient, in each of the linezolid and comparative groups [5]. Therefore, the occurrence of a pseudomembranous colitis during linezolid therapy seemed to be extremely rare.

Two factors were assumed to contribute to the emergence of the pseudomembranous colitis in our patient: The prior hospitalizations with prolonged antimicrobial therapy may have caused the risk of *C. difficile* infections [6] and as a consequence of the intravenous application regimen, no effective concentrations of linezolid could be achieved in the enteric lumen.

A review of the literature using various databases (MEDLINE, BIOSIS Previews, Current Contents, Derwent Drug File) and "*Clostridium difficile*" and "linezolid"

as key words revealed no report about linezolid directly contributing to pseudomembranous colitis and only one case report by Lazzarini and De Lalla [7], who reported the failure of linezolid to cure a *C. difficile* colitis. Their patient also received linezolid intravenously and it was suggested that the critical factor for the efficacy of eradicating *C. difficile* was the fecal concentration of the antibiotic.

Indeed, most studies concerning the effects of linezolid on the enteric lumen focussed on oral administration: Lode et al. [8] examined the effects of linezolid versus amoxicillin/clavulanic acid on the normal intestinal microflora. During the oral administration of linezolid, the numbers of bifidobacteria, lactobacilli, clostridia and Bacteroides spp. decreased markedly.

Although the amount of active substance recovered in the feces ranged from 5.3 to 16.9% of the orally administered doses [9], this antimicrobial agent was supposed to be promising in studies on the efficacy for the treatment of *C. difficile*-associated diarrhea [10]. Paelaez et al. [10] investigated the *in vitro* activity of linezolid against 115 toxigenic *C. difficile* isolates. The susceptibility breakpoint for linezolid was suggested to be greater or equal to 4 mg/l, as recommended by the European Committee on Antimicrobial Diseases [11] and all of these strains were susceptible to linezolid. The *C. difficile* strain from our patient was tested by E-test against linezolid and showed a MIC of 2 mg/l. According to the breakpoints mentioned above, it was also subsequently classified as susceptible to linezolid. However, serum breakpoints may not be relevant for intraluminal infections and therefore these MIC results may reflect false susceptible strains for this compartment.

Linezolid is mainly metabolized by non-renal clearance to two metabolites without antibacterial activity and renal clearance of the parent compound. Approximately 50% of an administered dose appears in the urine as the two major metabolites, and approximately 30% appears as the parent drug [12].

Parameter (reference)	Day 15 ^a	Day 22 ^b	Day 50 (first relapse) ^c	Final (second relapse) ^d
C-reactive protein (< 0.8 mg/dl)	22.92	5.80	24.48	27.09
White blood cell count (4.00–9.00/nl)	15.51	11.16	14.77	16.83
Creatinine (0.6–1.2 mg/dl)	3.2	1.6	1.7	1.5
Thromboplastin time (70–100%)	64	72	75	61
PTT (28.0–40.0 s)	70.1	50.6	63.8	57.5

^a February 24, 2003; ^b March 1, 2003; ^c March 25, 2003; ^d April 22, 2003; PTT: partial thromboplastin time

Data on the fecal concentration of linezolid following intravenous administration are sparse. One report [12] outlined that no parent drug is found in the feces, while the metabolites could be detected at between 3 and 6% of the administered dose. It may therefore be assumed that the fecal concentration of intravenously given linezolid is not sufficient to suppress enteric growth of *C. difficile* and this may select strains, even when these strains are *in vitro* susceptible to linezolid.

We conclude that the rate of *C. difficile* colitis under linezolid treatment may be underestimated, especially when the drug is given intravenously in long-term courses as in patients with osteomyelitis. Patients with underlying diseases and prior hospitalizations, who develop diarrhea under antimicrobial therapy with linezolid, should be routinely tested for *C. difficile* toxin.

References

- Moise PA, Forrest A, Birmingham MC, Schentag JJ: The efficacy and safety of linezolid as treatment for *Staphylococcus aureus* infections in compassionate use patients who are intolerant of, or who have failed to respond to, vancomycin. *J Antimicrob Chemother* 2002; 50: 1017–1026.
- Birmingham MC, Rayner CR, Meagher AK, Flavin SM, Batts DH, Schentag JJ: Linezolid for the treatment of multidrug-resistant, gram-positive infections: experience from a compassionate-use program. *Clin Infect Dis* 2003; 36: 159–168.
- Rayner CR, Baddour LM, Birmingham MC, Norden C, Meagher AK, Schentag JJ: Linezolid in the treatment of osteomyelitis: results of compassionate use experience. *Infection* 2004; 32: 8–14.
- French G: Safety and tolerability of linezolid. *J Antimicrob Chemother* 2003; 51 (Suppl. 2): 1145–1153.
- Rubinstein E, Isturiz R, Standiford HC, Smith LG, Oliphant TH, Cammarata S, Hafkin B, Le V, Remington J: Worldwide assessment of linezolid's clinical safety and tolerability: comparator-controlled phase III studies. *Antimicrob Agents Chemother* 2003; 47: 1824–1831.
- Wistrom J, Norrby SR, Myhre EB, Eriksson S, Granstrom G, Lagergren L, Englund G, Nord CE, Svenungsson B: Frequency of antibiotic-associated diarrhoea in 2462 antibiotic-treated hospitalized patients: a prospective study. *J Antimicrob Chemother* 2001; 47: 43–50.
- Lazzarini L, De Lalla F: Failure of intravenous linezolid to treat *Clostridium difficile* associated diarrhea. *J Chemother* 2003; 15: 299–300.
- Lode H, Von der Hoh N, Ziege S, Borner K, Nord CE: Ecological effects of linezolid versus amoxicillin/clavulanic acid on the normal intestinal microflora. *Scand J Infect Dis* 2001; 33: 899–903.
- Slatter JC, Stalker DJ, Feenstra KL, Welshman IR, Bruss JB, Sams JP, Johnson MG, Sanders PE, Hauer MJ, Fagerness PE, Stryd RP, Peng GW, Shobe EM: Pharmacokinetics, metabolism, and excretion of linezolid following an oral dose of drug. *Metab Dispos* 2001; 29: 1136–1145.
- Peláez T, Alonso R, Pérez C, Alcalá L, Cuevas O, Bouza E: In vitro activity of linezolid against *Clostridium difficile*. *Antimicrob Agents Chemother* 2002; 46: 1617–1618.
- Philips I, Baquero F, Bryskier A, Goldstein F, Mouton J, Schito G, Sidorenko S, Wiedeman B and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID): Linezolid breakpoints. *Clin Microbiol Infect* 2000; 7: 283–284.
- MacGowan AC: Pharmacokinetic and pharmacodynamic profile of linezolid in healthy volunteers and patients with gram-positive infections. *J Antimicrob Chemother* 2003; 51 (Suppl. 2): 117–125.