In vitro activity of linezolid against Clostridium difficile

Grit Ackermann*, Daniela Adler and Arne C. Rodloff

Institute for Medical Microbiology and Epidemiology of Infectious Diseases, University of Leipzig, Liebigstrasse 24, 04103 Leipzig, Germany

*Corresponding author. Tel: +49-341-971-5200; Fax: +49-341-971-5209; E-mail: ackermg@medizin.uni-leipzig.de

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Sir,

The increasing rates of infections due to multiresistant Gram-positive bacteria have intensified the search for treatment alternatives. Streptogramin combinations, ketolides, new glycopeptides and the oxazolidinones were developed to overcome problems with multidrug-resistant Gram-positive bacteria. Linezolid is the first compound of a novel class of synthetic antimicrobial agents, the oxazolidinones. The compound reached the market in the USA in 2000 and in Europe in 2001. The major binding sites of oxazolidinones are the large (50S) ribosomal units. The effect on a variety of clinically important human pathogens is predominantly bacteriostatic.1,2

Linezolid has inhibitory activity against a broad range of Gram-positive aerobic cocci, including methicillin-resistant Staphylococcus aureus, glycopeptide-resistant enterococci (GRE) and penicillin-resistant Streptococcus pneumoniae. Linezolid is much less active against Gram-negative aerobes. In vitro activity of linezolid against common anaerobic bacteria shows MICs in the range 1–8 mg/L, with some studies reporting bactericidal effect against Bacteroides fragilis and Clostridium perfringens.1,3 Resistance against linezolid can be induced in vitro by spiral plating against S. aureus and vancomycin-resistant Enterococcus faecalis. Genomic characterization of these strains revealed specific mutations in the peptidyl transferase centre of the 23S rRNA region (G2447→U for S. aureus and G2576→U for E. faecalis).3,4 The activity of linezolid is unaffected by mutations or mechanisms responsible for resistance against macrolide–lincosamide–streptogramin B (MLSB) antibiotics, aminoglycosides, chloramphenicol or tetracycline. Resistance to linezolid in clinical isolates was rarely observed and occurred only during prolonged therapy (i.e. of an undrained focus of infection).1

Clostridium difficile is the major cause of nosocomial diarrhea and antimicrobial-associated colitis. Patients often (15–20%) suffer from relapsing infections after treatment with vancomycin or metronidazole. In addition, the search for alternative treatments is driven by reports of decreased susceptibility of C. difficile against vancomycin and metronidazole and the known potency for the selection of GRE due to a prolonged therapy with vancomycin.5–7

Several studies have investigated the activity of linezolid against C. difficile.5,8,9 The MICs of the tested isolates were less than or equal to the suggested susceptibility breakpoint for linezolid of ≤4 mg/L.3 One study reported an impact of linezolid on the aerobic and anaerobic intestinal microflora with reduced numbers of enterococci, bifidobacteria, lactobacilli, Clostridia and Bacteroides spp.10 However, further studies are needed to prove the activity of linezolid against C. difficile and to evaluate clinical efficacy. It has been shown that antimicrobial resistance in C. difficile is growing and is associated with different classes of antibiotics.11 These investigations were extended to determine whether resistance in C. difficile against new compounds is already emerging.

One hundred and ninety-two clinical isolates of C. difficile were tested, recovered from patients of two university hospitals in Germany. MICs of linezolid were evaluated using Etest, as described previously.11 Plates were cultured anaerobically at 37°C for 48 h. Genotypes were determined using PCR and DNA sequencing.11 MICs and genotypes are shown in Table 1.

Linezolid was highly active against the C. difficile strains tested. MIC50/90 values were 0.75 and 3 mg/L (range 0.125–6 mg/L). All but 11 C. difficile strains were susceptible to linezolid. These strains exhibited low-level resistance (MIC 6 mg/L) against linezolid. Elevated MICs of linezolid (MIC between 3 and 6 mg/L) were found for 23 strains showing high-level resistance to erythromycin and clindamycin (MIC ≥ 256 mg/L) (Table 1). Elevated MICs were not found for other strains. In all but three isolates, erm(B) gene sequences were found. Interestingly, 12 of the 23 strains also showed high-level resistance to moxifloxacin. Nine strains harboured a mutation at codon 83 (Escherichia coli coordinates) in the gyrA gene resulting in an amino acid exchange (ACT→ATT, resulting in threonine→isoleucine).

To treat C. difficile infections effectively, sufficient levels of linezolid are required in the colon. The drug is absorbed efficiently in the gastrointestinal tract and 12–23% of line-
zolid is excreted unchanged in the stool after oral dosing.\textsuperscript{8,10} Thus, linezolid may offer an alternative for the treatment of \textit{C. difficile}-associated diarrhoea (CDAD). However, serum breakpoints may not be relevant for intraluminal infections. Currently no clinical data are available on the efficacy of linezolid in \textit{C. difficile} infection.

This is the first report of an association between elevated linezolid MICs and high-level resistance to MLS\textsubscript{B} antimicrobials and fluoroquinolones. Concerning growing resistance against MLS\textsubscript{B} antimicrobials in \textit{C. difficile}, the use of linezolid to treat CDAD must be considered cautiously.

### References


