

Linezolid: a review of its properties, function, and use in critical care

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Abstract: Linezolid can be considered as the first member of the class of oxazolidinone antibiotics. The compound is a synthetic antibiotic that inhibits bacterial protein synthesis through binding to rRNA. It also inhibits the creation of the initiation complex during protein synthesis which can reduce the length of the developed peptide chains, and decrease the rate of reaction of translation elongation. Linezolid has been approved for the treatment of infections caused by vancomycin-resistant *Enterococcus faecium*, hospital-acquired pneumonia caused by *Staphylococcus aureus*, complicated skin and skin structure infections (SSSIs), uncomplicated SSSIs caused by methicillin-susceptible *S. aureus* or *Streptococcus pyogenes*, and community-acquired pneumonia caused by *Streptococcus pneumoniae*. Analysis of high-resolution structures of linezolid has demonstrated that it binds a deep cleft of the 50S ribosomal subunit that is surrounded by 23S rRNA nucleotides. Mutation of 23S rRNA was shown to be a linezolid resistance mechanism. Besides, mutations in specific regions of ribosomal proteins uL3 and uL4 are increasingly associated with linezolid resistance. However, these proteins are located further away from the bound drug. The methicillin-resistant *S. aureus* and vancomycin-resistant enterococci are considered the most common Gram-positive bacteria found in intensive care units (ICUs), and linezolid, as an antimicrobial drug, is commonly utilized to treat infected ICU patients. The drug has favorable in vitro and in vivo activity against the mentioned organisms and is considered as a useful antibiotic to treat infections in the ICU.

Keywords: linezolid, intensive care unit, MRSA, VRE, antibacterial drugs

Introduction

Linezolid can be considered as the first member of the class of oxazolidinone antibiotics. Oxazolidinones were first introduced in 1978 for their effectiveness in the control of plant diseases. Six years later, their antibacterial characteristics, with significantly improved antibacterial properties relative to their progenitor compounds, were documented.¹ These oxazolidinone compounds are referred to as the first real lead compounds in the oxazolidinone family.

A lead compound can be defined as a compound that displays pharmacological parameters proposing the compound's value as a starting point for therapeutics development.² Further structural discussion led to the development of piperazine derivatives using lead compounds, as shown in studies by Barbachyn et al.² Such compounds were selected for further modification as they possessed outstanding antibacterial activity with a suitable safety profile. Linezolid was introduced in 1996 following intensive examinations at Pharmacia³ and has since been identified as a lead compound. Linezolid was approved by the US Food and Drug Administration in 2000. During the last 40 years, oxazolidinones have been considered a truly new class of antibiotics which are currently used in clinics.⁴

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Mechanism of action of linezolid

Linezolid is a synthetic antibiotic which prevents the synthesis of bacterial protein via binding to rRNA on both the 30S and 50S ribosomal subunits.⁵ It inhibits the formation of initiation complex which can reduce the length of the developed peptide chains and decrease the rate of translation reaction.⁵ However, the initiation process at the site of inhibition takes place prior to that of other protein synthesis inhibitors that prevent the elongation procedure. Because of the unique site of inhibition, cross-resistance to other protein synthesis inhibitors has not yet been demonstrated.⁶ Linezolid may also prevent the expression of virulence elements leading to decreased toxins produced by Gram-positive pathogens.⁷ The chemical structure of linezolid is shown in Figure 1. The activity of the compound is increased by the morpholino group in the first ring (from the left) and the fluoride atom in the second ring.⁴

Structure–activity relationship of linezolid

The structure–activity relationship studies on oxazolidinones revealed that the N-aryl group and 5-S configuration are essential for the activity.⁸ The 5-acylaminomethyl group is responsible for the activity. The electron-withdrawing group in the aryl ring has been shown to increase the activity. Extra substituents on the proximal aromatic ring do not affect the antibacterial activity but can change the solubility and pharmacokinetics.⁸

Applications of linezolid

Summary of antibacterial activity

Linezolid has been approved by the Food and Drug Administration for the treatment of the following: (a) hospital-acquired pneumonia caused by *Staphylococcus aureus*, including

methicillin-susceptible (MSSA) and methicillin-resistant *S. aureus* (MRSA) strains, or *Streptococcus pneumoniae* including multidrug-resistant strains; (b) vancomycin-resistant *Enterococcus faecium* (VREF) infections, including cases with concurrent bacteremia; (c) complicated skin and skin structure infections (SSSIs), including diabetic foot infections (DFIs) without concomitant osteomyelitis, caused by *S. aureus* (MSSA and MRSA), *Streptococcus pyogenes*, or *Streptococcus agalactiae*; (d) uncomplicated SSSIs caused by MSSA or *S. pyogenes*; (e) community-acquired pneumonia caused by *S. pneumoniae*, including cases with simultaneous bacteremia, or MSSA;⁹ and (f) pneumococcal meningitis caused by penicillin-resistant *S. pneumoniae*.¹⁰

Recent advances in the use of linezolid

Linezolid-containing regimens have been suggested as promising potential alternatives to treat patients with multidrug-resistant tuberculosis (MDR-TB) or extensively drug-resistant TB (XDR-TB). Therefore, linezolid could be considered as an effective choice for treating MDR-TB/XDR-TB.¹¹

In the recent published guidelines for the treatment of MRSA pneumonia, linezolid has been considered as a first-line antibiotic.¹² Moreover, several studies including the recent ZEPHYR trial¹³ have reported higher treatment effectiveness for linezolid compared to vancomycin. However, it remains debatable whether linezolid is better than vancomycin for its approved indications such as SSSIs and nosocomial pneumonia or not. Several recent studies have supported the clinical use of linezolid in complicated MRSA-SSSIs, including DFIs without osteomyelitis.¹⁴ Figure 2 shows the pictorial representation of linezolid applications.

Examples of treatment effects

In a case report, linezolid was used in addition to penicillin and clindamycin for suppression of toxic shock syndrome (TSS). In the study, the patient had right upper extremity necrotizing fasciitis and group A streptococcus TSS that were treated by adding linezolid as the patient showed no improvement on penicillin and clindamycin.¹⁵

Studies have suggested that linezolid can be efficient in treating MDR-TB and XTR-TB.^{16–27}

In a case report, a patient with subarachnoid hemorrhage, who underwent ventriculostomy and embolization of cerebral aneurysms, was affected by multiple infections after her operation. The patient was successfully treated with linezolid.²⁸

In another study, ten patients with central nervous system infections (infections in three cases were caused by mycobacteria) were treated by linezolid because of its good cerebrospinal fluid penetration.²⁹

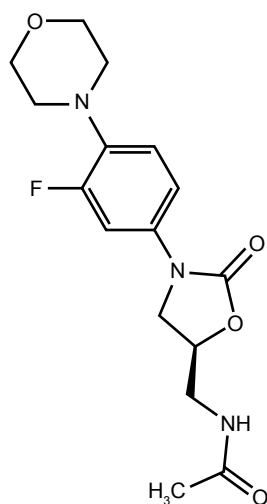


Figure 1 Chemical structure of linezolid. The empirical formula of the compound is $C_{16}H_{20}FN_3O_4$ (molecular weight: 337.35 g/mol).



Figure 2 Pictorial representation of the linezolid applications.

Abbreviations: MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *S. aureus*.

In a study on 80 patients with MRSA and vancomycin-intermediate *S. aureus* endocarditis, linezolid alone was administered to 66.7% of patients, while the rest received a combination therapy.³⁰

Linezolid has been reported to be very effective in the treatment of ventilator-associated pneumonia and catheter-related bacteremia, and hence, it is reasonable to use linezolid in the intensive care unit (ICU).³¹

Pharmacokinetics

Linezolid is very well absorbed orally with a bioavailability of 100%.^{1,32} The presence of food does not affect its absorption.⁵ Therefore, the administration route of antibiotic can be changed from intravenous (IV) to oral (per os [PO]) in clinically stable patients.⁶ Moreover, co-administration with antacids like magnesium hydroxide and aluminum hydroxide had no effect on the oral absorption.³³

Plasma protein-binding level of the molecule is approximately 31%. The volume of distribution approximates to the whole-body water content of 40–50 L, and the plasma half-life ranges from 3.4 to 7.4 h. The compound is

metabolized to inactive metabolites including hydroxyethyl glycine and aminoethoxy-acetic acid.³³ The clearance rate is 80 ± 29 mL/min through both nonrenal and renal mechanisms, and renal tubular reabsorption may take place. A fraction of the dose is excreted in unaltered form in urine.³⁴ The pharmacokinetics of linezolid in different groups of patients with dissimilar doses has been studied in detail.³³ A low degree of nonlinearity has been found, with a 30% reduction in clearance, after a fivefold increase in the dose. The nonlinearity is not related to the therapeutic dosage range. Plasma concentrations of linezolid in elderly patients, and patients with mild-to-moderate hepatic damage or mild-to-chronic renal failure were similar to those obtained in healthy or young volunteers. It has been reported that a dose adjustment is not necessary when females have a higher concentration compared to males. Patients with severe renal impairment with the requirement for hemodialysis are reported to have seven- to eightfold higher exposures to the drug metabolites than patients with normal renal function. Hence, recommendation should be carefully evaluated. Clearance of linezolid is shown to be higher in children compared to adults. This can

lead to higher requirement of daily doses of drug per kilogram of body weight in children.³³

Adverse effects

Some of the adverse effects associated with linezolid are as follows: (a) peripheral³⁵ and ocular^{36–39} neuropathy; (b) anemia that occurs by direct effect of linezolid on red cell population of bone marrow;⁴⁰ (c) thrombocytopenia;^{41–43} (d) hyperlactatemia (lactic acidosis with plasma lactate level >2 mmol/L);^{40,44–46} (e) diarrhea, nausea, and headache;^{47,48} (f) hypoglycemia;⁴⁹ and (g) reticulocytopenia.⁵⁰

Drug interactions

When a drug is administered along with a second drug, a change in the drug's effectiveness on the body may occur. Such interaction may delay, diminish, or increase the absorption of either or both the drugs or cause adverse effects.^{51–53} Linezolid can be safely co-administered with aztreonam; however, there is no enough evidence about the interaction between linezolid and rifampin.⁴⁰ Co-administration with Gram-negative antibiotics, ceftazidime, ciprofloxacin, meropenem, and gentamicin had no adverse effect. Besides, using linezolid with antifungal drugs such as amphotericin B and azoles, aminoglycosides, antivirals, fluoroquinolones, or β -lactams did not affect their sufficiency. It therefore seems that linezolid can be used with other antimicrobials with no interaction.⁴⁰

Linezolid can cause life-threatening serotonin toxicity when combined with serotonin reuptake inhibitors since it is a nonspecific inhibitor of monoamine oxidase.^{54,55} While clinicians must be aware of this potentially severe interaction and carefully monitor patients who are given linezolid in combination with serotonergic therapeutics, findings indicate that linezolid is not contraindicated in this condition.⁵⁶

Patents of linezolid

There are a number of patents as inventions to provide better forms of the linezolid in oral dosage forms. Some examples are discussed here. An invention (publication number: US6451345B1) provided taste-masked microcapsules of linezolid, as oral dosage forms in which the bitter taste of linezolid included therein is covered by a mixture of microencapsulation. These oral dosage forms are suitable for the oral administration.⁵⁷ Another invention (publication number: US9492459B2) aims to provide a novel pharmaceutical composition comprising linezolid form III along with pharmaceutically satisfactory excipients and a procedure to make

such composition.⁵⁸ An invention (publication number: US20170066728A1) relates to a process of preparation of enantiomeric pure linezolid form I. The process comprised converting an enantiomerically pure linezolid hydroxide compound of formula II to linezolid form I compound of formula I.⁵⁹

Comparison with other antibiotics

Vancomycin has been considered the “gold standard” drug against serious MRSA infections. Although, the weak clinical effects, appearance of less susceptible strains, and enhanced nephrotoxicity with high-dose treatment are challenging its current role as a first-line treatment. Linezolid is suggested for PO or IV treatment of SSSIs and pneumonia caused by MRSA. Daptomycin (IV) should be used in complicated SSSIs and in patients with right-sided endocarditis as well as MRSA bacteremia but should not be used to treat MRSA pneumonia. Both telavancin and tigecycline can be used as alternative (IV) treatments for SSSIs caused by MRSA; however, safety concerns have restricted the usage of these drugs. Ceftaroline is the latest approved parenteral drug for the treatment of SSSIs caused by MRSA. A number of investigational factors for the treatment of infections caused by drug-resistant Gram-positive bacteria are being developed originally to treat MRSA infections. These factors include tedizolid, dalbavancin, and oritavancin.¹⁴ The linezolid vs daptomycin and vancomycin comparison is discussed below with some examples.

Linezolid vs daptomycin

A report of the treatment of vancomycin-resistant enterococcal (VRE) bacteremia showed that 30-day mortality of daptomycin was higher than that of linezolid. Moreover, the infection-related mortality and the in-hospital mortality were higher in the daptomycin group compared to the linezolid group. A study showed that treatment with daptomycin led to abnormal liver function test results, although adverse effects had no significant difference.^{60–63}

In another study, among 212 patients with VRE, 141 received daptomycin and 71 received linezolid. All-cause 14-day mortality was higher in the daptomycin group (36.9% vs 21.1%; $p=0.03$), and higher-dose daptomycin led to enhanced survival than lower-dose daptomycin. Compared to lower-dose daptomycin, higher-dose daptomycin and linezolid independently predicted lower mortality. However, in terms of mortality, linezolid was not superior to higher-dose daptomycin and higher-dose daptomycin had more survival benefits than linezolid, and the findings revealed

that the recommended daptomycin dose is suboptimal for treating VRE bacteremia.⁶⁴

Linezolid vs vancomycin

The results of a systematic review and meta-analysis indicated that there is no difference between linezolid and vancomycin in the treatment of nosocomial pneumonia. Besides, the results showed that there were no statistically significant differences between linezolid and comparator vancomycin or teicoplanin in analysis of microbiological eradication.⁶⁵ Similar results were obtained when the analysis was stratified according to the comparator vancomycin or teicoplanin. In the main analysis, there were statistically significant higher rate of gastrointestinal events with linezolid compared to glycopeptides. In addition, compared to vancomycin, there was a significantly higher rate of thrombocytopenia with linezolid. In the incidence of renal failure, there was no statistically significant variance between the treatments.⁶⁵

Some studies demonstrated that administration of linezolid is more cost-effective than vancomycin in the treatment of MRSA infection because of earlier discharge from the hospital.^{66,67} Generally, linezolid may reduce mortality of patients compared to vancomycin.^{68,69}

In a report, linezolid was compared with vancomycin for the treatment of patients with suspected or confirmed skin and soft tissue infections caused by MRSA. Skin and soft tissue infections are common causes of mortality in both hospital and community settings. The study included patients with MRSA infections involving substantial areas of skin or deeper soft tissues, such as abscesses, cellulitis, infected ulcers, or burns. In the intent-to-treat population, 92.2% and 88.5% of patients were treated with linezolid and vancomycin, respectively. Linezolid outcomes were superior to those of vancomycin, and drug-related adverse effects were similar in both linezolid and vancomycin group. The results of this study showed that linezolid therapy is superior to vancomycin for the treatment of skin and soft tissue infections due to MRSA.^{70–72}

Mechanism of resistance

Analysis of high-resolution structures of linezolid showed that it binds to a deep cleft of 50S ribosomal subunit that is surrounded by 23S rRNA nucleotides.⁷³ Accordingly, mutation of 23S rRNA has been established as one of the linezolid resistance mechanisms. Moreover, mutations in particular regions of ribosomal proteins uL3 and uL4 are increasingly being associated with linezolid resistance, although these proteins are placed further away from the

bound drug. Furthermore, based on new findings on the Cfr methyltransferase, the transferable modification of 23S rRNA can cause high resistance to linezolid. Such precise information of the linezolid-binding site has enabled the design of a novel generation of oxazolidinones that display enhanced characteristics against the identified resistance mechanisms.⁷⁴

Recently, a novel oxazolidinone resistance gene, *optrA*, has been identified, and the extent to which this gene is expressed in *E. faecalis* and *E. faecium* has been investigated.⁷⁵ *Optra* is an adenosine triphosphate-binding cassette (ABC) transporter. A common mechanism by which bacteria develop antibiotic resistance is by using the ABC transporters to strongly pump the drugs from the cell. The ABC-F family contains proteins conferring resistance to a diversity of clinically significant ribosome-targeting antibiotics. It has been reported that these proteins use ribosome protection mechanisms by interacting with the ribosome and shifting the drug from its binding site.⁷⁶

Use of linezolid in critical care

Severe infections in critically ill patients exhibit high rates of morbidity and mortality, and approximately half of the bloodstream infections in such patients are caused by Gram-positive bacteria.⁷⁷ A major part of the Gram-positive infections are caused by multidrug-resistant strains including MRSA and VRE that are extremely common in the ICUs.⁷⁸ Linezolid is an antimicrobial drug that is commonly utilized by the ICU patients. The drug has favorable in vitro and in vivo activity against the mentioned organisms and is considered a useful antibiotic to treat infections in the ICU.^{79,80,91} Some recent clinical trial findings on the use of linezolid in ICU are summarized in Table 1.

Conclusion

The present treatment options for infections caused by common pathogens in the ICU are limited. Inclusion of linezolid in multiple clinical practice guidelines demonstrates that the drug can be a beneficial addition to the antibiotic armamentarium against MRSA and VRE.⁴ Outcomes from the current clinical trials on linezolid for MRSA pneumonia and VRE infections are worthwhile for clinicians and give certainty that the drug is efficient. Although linezolid is efficient against multidrug-resistant strains, researchers must strive and optimize infection-control measures to inhibit their spread. While most patients tolerate linezolid well, the ongoing surveillance is important to find potential and serious adverse reactions including thrombocytopenia

Table I Summary of some trials of linezolid for pneumonia caused by MRSA and VRE infections

| Study | Type of study | Results |
|-------------------------------|--|---|
| Peyrani et al ⁸¹ | Prospective observational trial for VAP due to MRSA | Clinical success occurred in 85% of linezolid-treated patients compared with 69% of vancomycin-treated patients ($p=0.009$) |
| Jiang et al ⁸² | Meta-analysis of nosocomial pneumonia | Evaluation of 12 RCTs showed that although linezolid was more effective in microbiological eradication than glycopeptide antibiotics for nosocomial pneumonia patients, it did not represent superiority in clinical cure |
| Awad et al ⁸³ | RCT for nosocomial pneumonia including VAP | Cure rates in nosocomial pneumonia (excluding VAP) patients for ceftibiprole vs ceftazidime and linezolid were 59.6% vs 58.8% and 77.8% vs 76.2%. Cure rates in VAP patients were 23.1% vs 36.8% and 37.7% vs 55.9% |
| Wang et al ⁸⁴ | Systematic review employing meta-analysis on suspected MRSA nosocomial pneumonia | Evaluation of nine RCTs found linezolid was not superior to vancomycin for clinical cure |
| Whang et al ⁸⁵ | Systematic review and meta-analysis on VRE-BSIs | There were limited data to inform clinicians on optimal antibiotic selection (linezolid vs daptomycin) for VRE-BSIs. Available studies were limited by small sample size, lack of patient-level data, and inconsistent outcome definitions |
| Balli et al ⁸⁶ | Systematic review and meta-analysis on VRE bacteremia | Ten retrospective studies comparing daptomycin to linezolid treatment for VRE bacteremia were identified. Patients treated with daptomycin had significantly higher 30-day all-cause mortality (OR, 1.61; 95% CI, 1.08–2.40) and infection-related mortality (OR, 3.61; 95% CI, 1.42–9.20) rates than patients treated with linezolid |
| Chuang et al ⁸⁷ | Systematic review and meta-analysis on VRE bacteremia | Although limited data were available, the meta-analysis showed that linezolid treatment for VRE bacteremia was associated with a lower mortality than daptomycin treatment |
| Britt et al ⁸⁸ | Retrospective cohort on VRE-BSIs | Treatment with linezolid for VRE-BSIs resulted in significantly higher treatment failure in comparison to daptomycin. Linezolid treatment was also associated with greater 30-day all-cause mortality and microbiological failure in this cohort |
| Crank et al ⁸⁹ | Retrospective cohort on VRE-BSIs | There were no significant differences in mortality of VRE-BSIs between patients receiving daptomycin or linezolid |
| Erlandson et al ⁹⁰ | Retrospective review on VRE-BSIs | Univariate analysis indicated significantly more deaths in the quinupristin-dalfopristin group (OR, 5.45; 95% CI, 1.89–15.9) and in the other-agents group (OR, 2.94; 95% CI, 1.09–7.94) than in the linezolid group |

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci; VAP, ventilator-associated pneumonia; RCT, randomized controlled trial; BSI, blood stream infection; OR, odds ratio.

and anemia as well as permanent adverse effects such as optic neuritis and peripheral neuropathy. Further clinical investigations are required to clarify the role of linezolid in various patient populations and treating particular conditions. Cost-control issues affect antimicrobial stewardship plans; therefore, more investigation is required to evaluate the cost-effectiveness of linezolid, and the resulting measurements are essential to help reduce health care costs in resource-restricted settings.

Disclosure

The authors report no conflicts of interest in this work.

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