

REVIEW OF LINEZOLID

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ABSTRACT

Linezolid may have been the first antibiotic in the class of oxazolidinone antibiotics. This substance is a synthetic antibiotic that binds to rRNA to prevent bacteria from synthesising proteins. Additionally, it suppresses the initiation complex's formation during protein synthesis, which can shorten formed peptide chains and slow down the rate at which translation elongation occurs. Linezolid has been shown to bind a deep cleft of the 50S ribosomal subunit that is surrounded by 23S rRNA nucleotides through analysis of high-resolution structures of the drug. It has been demonstrated that 23S rRNA mutations cause linezolid resistance. More recent antibiotics that target resistant Gram-positive bacteria include linezolid, a synthetic oxazolidinone. Since 2000, linezolid has been widely accessible for the treatment of Gram-positive infections and is effective against a variety of Gram-positive bacteria.

Key words: Linezolid, Mode of action, Pharmacokinetic, Drug interactions, Microbiological activity, Administration

1. INTRODUCTION

Among the oxazolidinone antibiotic class, linezolid is regarded as the pioneer member. Because of their efficacy in managing plant diseases, oxazolidinones were initially introduced in 1978. It was discovered six years later that these compounds have antibacterial qualities that were noticeably better than those of their parent compounds.¹ Known as the first genuine lead compounds in the oxazolidinone family, these oxazolidinone compounds.

A chemical that exhibits pharmacological characteristics that suggest the compound's potential as a foundational material for therapeutic development is known as a lead compound.² According to research by Barbachyn et al., additional structural debate resulted in the creation of piperazine derivatives utilising lead compounds.² Due to their exceptional antibacterial activity and acceptable safety profile, these compounds were chosen for additional modification. Linezolid was first made available in 1996 after thorough testing at Pharmacia³, where it was later shown to be a lead compound. In 2000, the US Food and Drug Administration authorised linezolid. Over the past forty years, oxazolidinones—which are being utilised in clinics—have gained attention as a genuinely novel class of antibiotics.⁴

Structure–activity relationship of Linezolid

Studies on the link between structure and activity in oxazolidinones showed that the 5-S configuration and N-aryl group are critical to the activity. The action is due to the 5-acylaminomethyl group. It has been demonstrated that the aryl ring's electron-withdrawing group increases activity. While additional substituents on the proximal aromatic ring can alter solubility and pharmacokinetics, they have no effect on antibacterial efficacy.⁵

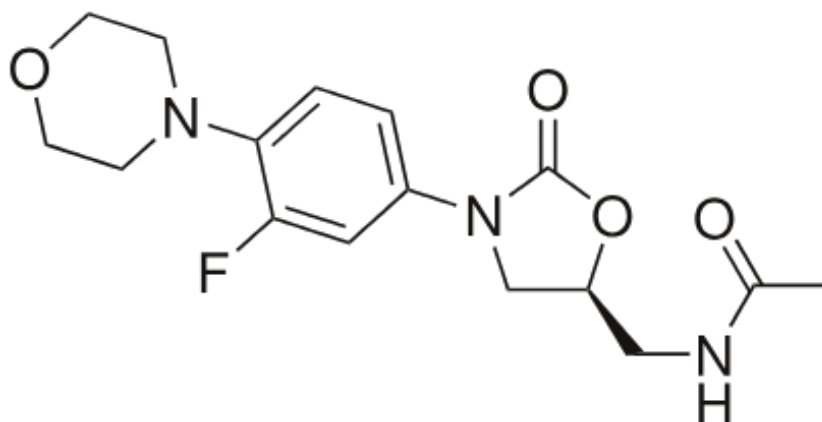


Fig 1: Structure of Linezolid

Mode of action

According to Figure 2, oxazolidinones attach to the bacterial ribosome's 50S subunit and stop it from complexing with mRNA, initiation factors, 30S subunit, and formylmethionyl-tRNA.^{6,7} As a result, translation of the mRNA is inhibited by blocking the assembly of a functional initiation complex for protein synthesis. The current class of protein synthesis inhibitors, which include macrolides, lincosamides, tetracyclines, and chloramphenicol, permits mRNA translation to start but inhibits peptide elongation, has a different mechanism of action than this one. Although this difference might

appear intellectual, it could be important in two ways. Because of this mode of action, clotting factors, hemolysins, and protein A are examples of staphylococcal and streptococcal virulence factors that appear to be particularly effective in blocking the production of linezolid.⁸ Second, the target of linezolid does not overlap with that of the currently available inhibitors of protein synthesis; as a result, the rRNA methylases that alter 23S rRNA to prevent the binding of macrolides, clindamycin, and group B streptogramins do not influence linezolid's efficacy.

Preventing peptide elongation is not intrinsically more deadly than preventing the start of protein synthesis. As a result, linezolid shares many bacteriostatic properties with clindamycin, macrolides, tetracyclines, and chloramphenicol. The aminoglycosides are the only protein synthesis inhibitors that exhibit potent bactericidal activity. They work by misreading mRNA, which results in the creation of faulty proteins that, among other things, destabilise the membrane structure and allow cell contents to seep out. While the ribosomes of Gram-positive cocci are equally sensitive to linezolid, Gram-negative bacteria exhibit resistance to oxazolidinones, with a few minor exceptions listed below. This resistance is likely due to the recognition and excretion of oxazolidinones by endogenous efflux pumps.⁶

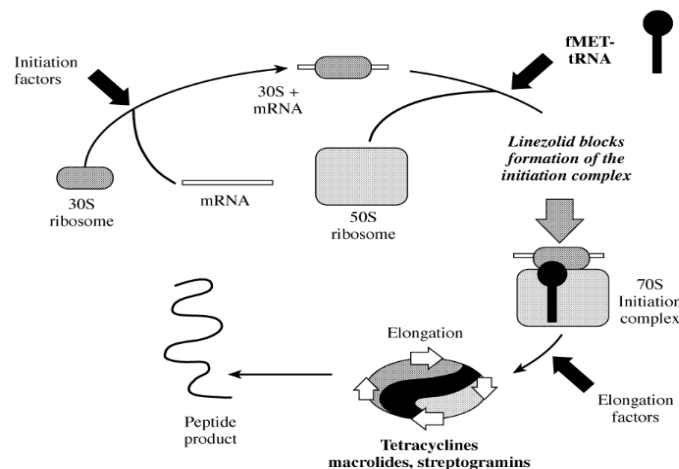


Fig.2: Mode of action of the oxazolidinones

Pharmacokinetics

Absorption: With an absolute bioavailability of almost 100%, linezolid is well absorbed when taken orally. Food delays the rate but not the extent of oral absorption, therefore the medication can be given orally or intravenously without requiring a change in dosage.⁷

Distribution: With a roughly 31% plasma protein binding, linezolid spreads easily to well-perfused tissues. In healthy adults, the volume of distribution (Vd) at steady-state is roughly 40 to 50 litres. Because it may penetrate the blood-brain barrier, linezolid is a great treatment for MRSA-caused CNS infections.⁸ The research discovered that in nearly all patients with drug-resistant tuberculosis, linezolid concentrations in the lung remained above the minimum inhibitory concentration (MIC) and mutation prevention concentration (MPC) values, even if these concentrations were lower in the lung than in the serum.⁹

Metabolism: The morpholine ring of linezolid is oxidised, producing two inactive carboxylic acid metabolites (A and B). Metabolite B is created via a non-enzymatic chemical oxidation process, whereas metabolite A is synthesised enzymatically.

Excretion: About 40 mL/min of renal clearance indicates tubular reabsorption. About 30% of the dose is excreted in the urine as linezolid under steady-state circumstances, and the remaining 40% and 10% are removed as metabolites A and B, respectively. Patients with renal impairment may have an accumulation of linezolid metabolites.¹⁰

Drug interactions

The body may respond differently to a medication when it is given in combination with another medication. Such an interaction could have negative effects or delay, reduce, or raise the absorption of one or both medications.¹¹⁻¹³

It is safe to combine linezolid with aztreonam; however, there is insufficient data to determine how linezolid and rifampin interact.¹⁴ There were no harmful effects from co-administration of ceftazidime, ciprofloxacin, meropenem, and gentamicin with Gram-negative antibiotics. Furthermore, the sufficiency of antifungal medications such as aminoglycosides, β -lactams, amphotericin B and azoles, fluoroquinolones, and aminoglycosides was not affected by the use of linezolid in combination with them. Thus, it appears that there will be no interactions when using linezolid with other antimicrobials.¹⁴

Due to its nonspecific inhibition of monoamine oxidase, linezolid when coupled with serotonin reuptake inhibitors might result in potentially fatal serotonin poisoning.^{15,16} Findings suggest that linezolid is not contraindicated in this condition,

however clinicians should be aware of this potentially serious interaction and closely monitor patients who are given linezolid in combination with serotonergic therapies.¹⁷

Microbiological activity

A variety of Gram-positive aerobic bacteria¹⁸ and certain Gram-positive anaerobes, such as *Actinomyces* spp., are susceptible to the action of linezolid. Additionally, it has the ability to combat several Mycobacterial species, some Gram-negative anaerobic bacteria, and *Nocardia* spp.

Gram-positive aerobic bacteria

Penicillin-resistant pneumococci (PRP), vancomycin-resistant enterococci (VRE), and other resistant strains of many types of Gram-positive anaerobic bacteria are among the many bacteria that linezolid effectively combats. Compared to *S. aureus* species, the minimum inhibitory concentrations (MICs) of coagulase-negative staphylococci (CoNS) to linezolid are often lower. Whether a strain of *S. aureus* or CoNS is resistant or sensitive to methicillin has no effect on its¹⁹ MICs to linezolid:20 There is no correlation between staphylococcal species' reduced susceptibility to linezolid and vancomycin.²¹

Many streptococci, such as enterococci, viridians streptococci, and group A, B, C, F, and G β -hemolytic streptococci, are active against linezolid.²²⁻²⁴ The majority of streptococci have MICs of up to 2 mcg/mL, while some strains of viridians and group A streptococci have been reported to have MICs of up to 4 mcg/mL²⁵ PRP are still vulnerable to linezolid.²⁶ VRE and enterococci susceptible to vancomycin share MICs with linezolid. Linezolid is effective against^{19,20} *Corynebacterium* species, *Listeria monocytogenes*, *Bacillus* species, *Rhodococcus equi*, *Nocardia* species, and many *Lactobacillus* species.^{23, 27-30}

Anaerobic bacteria

Linezolid is effective against a number of Gram-positive and Gram-negative anaerobic bacteria, such as numerous strains of *Clostridium difficile*,^{31,32} *Fusobacterium* spp.,³³ *Prevotella* spp.,³⁴ and *Bacteroides* spp. 35 Some *Actinomyces* spp. strains are susceptible to the effects of linezolid.³⁶

Mycobacteria

Linezolid exhibits efficacy against many atypical mycobacteria and *Mycobacterium tuberculosis*. Linezolid can often be used to treat slow-growing mycobacteria, while some, including *M. avium* Complex (MAC), are typically resistant.³⁷ Atypical mycobacteria that grow quickly are less vulnerable, and MICs must be ascertained.³⁸

Applications of linezolid

The Food and Drug Administration has authorised the use of linezolid in the following conditions: Hospital-acquired pneumonia

- (a): caused by *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 concurrent osteomyelitis, caused by *Streptococcus aureus* (MSSA and MRSA);
- (d): caused by MSSA or *S. pyogenes*;
- (e): community-acquired pneumoniae, including cases with simultaneous bacteremia, or MSSA; and
- (f): pneumococcal meningitis caused by penicillin-resistant *Streptococcus aureus*

Administration

Available Dosage Forms and Strengths

Linezolid is available in tablets, suspension, and injection. The dosage of intravenous (IV) and tablet formulations are interchangeable. Renal dosing is not required. Invert gently to mix before administration, and do not vigorously shake the oral suspension. Linezolid is available as an injectable solution at a concentration of 2 mg/mL, an oral suspension of 100 mg/5 mL, and tablets containing 600 mg. Administer linezolid IV infusion over 30 to 120 minutes. Do not mix or infuse with other medications.

When using the same IV line for sequential infusion, flush the line with D5W, normal saline, or lactated Ringer's solution before and after infusing linezolid.

The yellow color of the injection may intensify with time without affecting potency. Linezolid use may result in a suboptimal clinical response when treating organisms with a MIC (minimum inhibitory concentration) of 4 mcg/ml or greater and warrants a complete infectious disease re-assessment and change in drug therapy.

Adult Dosage**Nosocomial pneumonia**

- Dose: The recommended dose for nosocomial pneumonia is 600 mg, administered IV or orally every 12 hours.
- Duration: Treatment is typically continued for 10 to 14 days.

Community-acquired pneumonia with concurrent bacteremia

- Dose: The recommended dose of community-acquired pneumonia with concurrent bacteremia is 600 mg administered IV or orally every 12 hours.
- Duration: Treatment usually continues for 10 to 14 days.

Complicated skin and skin structure infections

- Dose: In complicated skin and soft tissue infections (cSSTIs), the recommended linezolid dosage is 600 mg IV or orally every 12 hours.
- Duration: Treatment typically is for 10 to 14 days.

Uncomplicated skin and skin structure infections

- Dose: Adults should take a dose of 400 mg orally every 12 hours.
- Duration: Treatment typically is for 10 to 14 days.

Vancomycin-resistant *Enterococcus faecium* infections, including concurrent bacteremia

- Dose: The recommended dose for vancomycin-resistant *Enterococcus faecium* infections, including concurrent bacteremia, is 600 mg administered IV or orally every 12 hours.
- Duration: Treatment is extended for a period of 14 to 28 days.

Specific Patient Populations

Hepatic impairment: Linezolid pharmacokinetics remain unchanged in mild-to-moderate hepatic impairment (Child-Pugh class A or B), and no dosage adjustment is recommended. The risk of hematological toxicity increases in patients with cirrhosis.

Renal impairment: Use linezolid with caution in renal impairment due to the risk of thrombocytopenia.

Breastfeeding considerations: Linezolid is excreted into breast milk at concentrations likely to be effective against staphylococcal strains commonly found in mastitis. Limited clinical data suggest that infants would receive 6% to 9% of the standard infant dose through breast milk; thus, monitoring the infant for potential gastrointestinal effects, such as diarrhea and vomiting, is advisable. Due to limited published experience with linezolid during breastfeeding, an alternative drug may be preferred, especially when nursing a newborn or preterm infant.

Pregnancy considerations: A lack of pharmacokinetic and controlled studies of linezolid are available in pregnant women. A case report demonstrated positive maternal outcomes without fetal teratogenesis during a 4-week course of linezolid initiated at the 14th week of pregnancy. Linezolid could be used during pregnancy when the potential benefits outweigh the risks. Linezolid has also been used in pregnancy for multidrug resistant tuberculosis (MDR-TB); however, clinicians should monitor for adverse effects.

Animal studies indicate that higher doses in mice resulted in maternal toxicity, increased embryo death, and decreased fetal body weights, with costal cartilage fusion. Reduced fetal body weights and decreased ossification of sternebrae at the higher dose were seen in rats.

Pediatric patients**Nosocomial pneumonia:**

- Dose: The recommended dose for nosocomial pneumonia is 10 mg/kg IV or orally every 8 hours.
- Duration: Treatment is typically continued for 10 to 14 days.

Community-acquired pneumonia with concurrent bacteremia:

- Dose: The recommended dose for community-acquired pneumonia with concurrent bacteremia is 10 mg/kg IV or orally every 8 hours.
- Duration: Treatment usually continues for 10 to 14 days.

Complicated skin and skin structure infections:

- Dose: In complicated skin and soft tissue infections (cSSTIs), the linezolid dosage is 10 mg/kg IV or orally every 8 hours.
- Duration: Treatment typically is for 10 to 14 days.

Uncomplicated skin and skin structure infections:

- Dose: For uncomplicated skin and skin structure infections, children aged less than 5 should be prescribed 10 mg/kg orally every 8 hours. Children aged 5 to 11 should be prescribed 10 mg/kg orally every 12 hours.
- Duration: Treatment typically is for 10 to 14 days.

Vancomycin-resistant *Enterococcus faecium* infections, including concurrent bacteremia:

- Dose: The recommended dose for vancomycin-resistant *Enterococcus faecium* infections, including concurrent bacteremia, is 10 mg/kg IV or orally every 8 hours
- Duration: Treatment is extended for a period of 14 to 28 days.

Older patients: Clinical studies did not reveal significant disparities in the safety or effectiveness of linezolid between older and younger patients. However, increased sensitivity to linezolid in older patients is possible.

Adverse Effects

The most common adverse effects experienced with linezolid use include decreased platelets, hemoglobin, white blood cell counts, headache, nausea, diarrhea, elevated pancreatic enzymes, elevated liver function tests, and neuropathy. Warnings associated with linezolid include duration-related myelosuppression (thrombocytopenia, anemia, leukopenia), serotonin syndrome, hypoglycemia; caution in patients on insulin or hypoglycemic drugs, seizures, lactic acidosis, hypertension when used with adrenergic drugs, and irreversible peripheral and optic neuropathy when used for 28 days or greater. Reports exist of blurred vision in patients receiving shorter courses of linezolid. Prolonged use may result in fungal or bacterial infection, including *Clostridioides difficile*-associated diarrhea (CDAD) and pseudomembranous colitis. CDAD can occur greater than 2 months after postantibiotic treatment. Lactic acidosis may also occur with use; evaluate patients who develop recurrent nausea and vomiting, unexplained acidosis, or low bicarbonate concentrations.

Drug-Drug Interactions

Adrenergic drugs: Avoid using linezolid with adrenergic drugs such as pseudoephedrine, epinephrine, norepinephrine, dopamine, or dobutamine due to the risk of hypertensive crisis.

Serotonergic drugs: Serotonin syndrome can occur when linezolid is co-administered with serotonergic agents such as SSRI. Therefore, linezolid should not be used with patients taking serotonergic antidepressants or other medications like tricyclic antidepressants, bupropion, buspirone, triptans, or meperidine unless clinically necessary and closely monitored for signs of serotonin syndrome or neuroleptic malignant syndrome. If urgent linezolid treatment is required for patients already taking serotonergic drugs, discontinue the antidepressant and administer linezolid. Monitor for 2 weeks and up to 5 weeks with fluvoxamine.

Myelosuppressive agents: Linezolid should be cautiously used with drugs that can cause bone marrow suppression. Concurrent administration of linezolid with drugs such as clozapine and cladribine should be avoided.

2. CONCLUSION

Linezolid is an antibiotic that has proven effective against serious infections caused by Gram-positive bacteria, including resistant strains such as MRSA and VRE. Its mechanism of action involves inhibiting protein synthesis, making it valuable in treating infections when other antibiotics fail. However, it is important to use linezolid judiciously due to the potential for adverse effects, such as bone marrow suppression and peripheral neuropathy. Monitoring and appropriate dosing are crucial to minimize these risks. Overall, linezolid remains a vital option in the antibiotic arsenal against drug-resistant infections, but careful consideration of its benefits and risks is essential in clinical practice.

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