

Pharmacotherapy Perspectives

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Linezolid

(Zyvox® - Pharmacia & Upjohn)

Indications: Linezolid is approved for the treatment of severe infections caused by vancomycin-resistant *Enterococcus faecium*, nosocomial pneumonia caused by *Staphylococcus aureus* and *Streptococcus pneumoniae*, complicated skin and skin structure infections caused by *S. aureus*, *S. pyogenes*, and *S. agalactiae*, uncomplicated skin and skin structure infections, and community acquired pneumonia caused by *S. aureus* and *S. pneumoniae*. At the UWHC, linezolid use is restricted to infections caused by VRE, methicillin-resistant *S. aureus*, and other gram-positive infections in patients who are unable to tolerate conventional agents. Approval of an Infectious Disease attending or fellow is required.

Contraindication: Linezolid is contraindicated for use in patients who have a known hypersensitivity to the parent compound or any of the product components.

Monitoring parameters: Patients should be monitored for the clinical signs and symptoms of infection including, fever, white blood cell count, and pain. Thrombocytopenia has been associated with linezolid use, particularly with prolonged therapy.

Dose: The dose and duration of treatment with linezolid depends upon the type of infection. All doses are given q12h. For vancomycin-resistant *Enterococcus faecium* the recommended dose is 600 mg intravenous infusion (IV) or by mouth (PO) for 14 to 28 days. For pneumonia or complicated skin and skin structure infections, the approved dose is 600 mg IV or PO for 10 to 14 consecutive days. The recommended dose of linezolid for uncomplicated skin and skin structure infections is 400 mg IV or PO for 10 to 14 days.

Pediatrics: The safety and efficacy of linezolid have not been established in this population. Pharmacokinetic information indicates that pediatric patients dosed with 10 mg/kg IV have a similar peak concentration but a higher average clearance and shorter elimination half life when compared to adults receiving 625 mg of linezolid.

Geriatrics: No overall differences in safety or effectiveness of linezolid were seen in this population compared to younger patients and dose modifications are not needed.

Breast feeding: Linezolid and its metabolites are excreted into the milk of lactating rats. The concentration in the milk

was similar to that of the plasma. The excretion of linezolid to human milk is not known so caution should be used when administered to nursing women.

Pregnancy category: C. Linezolid was not teratogenic in mice or rats at exposure levels 4-fold or equivalent to the human dose, based on area under concentration-time curve (AUC). However, fetal toxicities were seen in doses that caused maternal toxicity. The data correlated with increased postimplantation embryo death, including total litter loss, decreased fetal body weights, and in increase incidence of costal cartilage fusion. Pups that matured to reproductive age, when mated, showed increase in preimplantation loss, with a corresponding decrease in fertility.

Cost: Linezolid is available as 100, 400, and 600 mg ready-to-use bags for intravenous administration, 400 and 600 mg oral tablets, and a powder for oral suspension which when constituted contains 150 mL of linezolid 100 mg per 5 mL. The UWHC cost for a single dose of intravenous linezolid 600 mg is \$56.64; the average wholesale price is \$71.87. The UWHC cost for a 20-count bottle of the 600 mg tablets is \$837.33; the average wholesale price is \$1062.50. The cost for a 14-day course of therapy of linezolid 600 mg orally twice daily is \$1172; the cost for a comparable course of IV therapy is \$1586. In comparison, the cost for a 14-day course of therapy with quinupristin/dalfopristin (Synecid®) 500 mg three times daily is \$1760.

Introduction

Due to the increase of multiple-drug-resistant strains of gram-positive bacteria, the development of new and novel acting antimicrobial agents is at the forefront of pharmaceutical research. Currently, the prevalence of methicillin-resistant staphylococci (MRSA) and vancomycin-resistant enterococci (VRE) is a major clinical problem.¹ Linezolid (Zyvox®-Pharmacia & Upjohn) is a new antimicrobial agent of the oxazolidinone class which possesses a wide spectrum of activity against gram-positive organisms, including MRSA and VRE. Because of linezolid's novel mechanism of action, cross-resistance with other antimicrobial agents is thought unlikely. Linezolid is therefore a viable therapeutic option for certain types of infectious disease.

Pharmacology / Pharmacokinetics

Linezolid appears to target an early event in translation

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involving the binding of the N-formylmethionyl-tRNA (fMet-tRNA) to the ribosome.^{2,3} Binding of linezolid primarily involves interaction with the 50S subunit, and to a lesser extent, the 30S subunit. Binding to the 50S subunit prevents the formation of the necessary 70S complex and ultimately protein synthesis of the organism.^{3,4} This mechanism has so far precluded cross-resistance with other antimicrobial agents. In time-kill studies, linezolid was shown to be bacteriostatic against enterococci and staphylococci and bacteriocidal against streptococci.⁵

Following oral administration, linezolid is completely absorbed, reaching peak plasma concentrations (C_{max}) within 1-2 hours (t_{max}), and exhibiting a mean absolute bioavailability of 103%.⁶ A single 600 mg oral dose of linezolid reached a C_{max} of 12.70 mcg/mL (SD 3.96) and an area under concentration-time curve (AUC) of 91.40 mcg h/mL (SD 39.30). The elimination half-life ($t_{1/2}$) was 4.26h (SD 1.65) and total clearance (CL) was 127 mL/min (SD 48). Following a 600 mg IV dose, a C_{max} of 12.90 mcg/mL (SD 1.60) was reached in 0.5 hours (SD .10) with an AUC of 80.20 mcg h/mL (SD 33.30). The elimination half-life was 4.40 hr (SD 2.40) and a CL of 138 mL/min. Linezolid is metabolized by oxidation yielding 2 inactive metabolites.⁷ Animal and human pharmacokinetic studies have shown that linezolid distributes readily into well-perfused tissues. The fluid to plasma ratio of linezolid in the cerebrospinal fluid (non-inflamed meninges) is 0.7:1. Approximately 31% of linezolid is bound to plasma proteins and the steady-state volume of distribution averaged between 40 to 50 L in healthy adult volunteers.⁶ Nonrenal clearance accounts for 65% of the total clearance. Renal clearance is relatively low (avg 40 mL/min) suggesting net tubular reabsorption. Mild-to-moderate hepatic insufficiency does not influence the pharmacokinetics of linezolid. No dose adjustments are necessary although linezolid has not been evaluated in patients with severe hepatic insufficiency. The pharmacokinetics of linezolid are not altered by any degree of renal dysfunction, however the accumulation of the metabolites will increase with increasing renal dysfunction. No dose adjustment is needed for patients with renal insufficiency. Linezolid is not an inducer of cytochrome P450 in rats, and does not inhibit the activities of clinically significant human cytochrome P450 isoforms.⁶

Drug Interactions

Antibiotics

The pharmacokinetics of linezolid are not altered with concurrent administration of gentamicin or aztreonam.⁶

Monoamine Oxidase Inhibition

Linezolid is a weak, reversible, nonselective inhibitor of monoamine oxidase type A. The clinical significance of this effect is not known. Patients should avoid excessive quantities of food with high tyramine concentration (>100 mg) such as

aged cheese, sauerkraut, and tap beers. Physicians should exercise caution with patients taking MAO inhibitors such as phenelzine (Nardil®), tranylecypromine (Parnate®), and isocarboxazid (Marplan®), or serotonergic agents such as fluoxetine (Prozac®), sertraline (Zoloft®), and paroxetine (Paxil®). Pseudoephedrine and phenylpropanolamine can lead to a mild, reversible enhancement of pressor response.

Microbiology

Table 1 lists the relative microbiology data for linezolid and comparator agents for the pertinent organisms. In general, linezolid has MIC₅₀ values of 2 mcg/mL increasing to 4 mcg/mL for MIC₉₀.^{6,8} Linezolid has demonstrated *in vitro* activity against *Staphylococcus aureus*, and *Staphylococcus epidermidis*, including methicillin-resistant strains and ciprofloxacin-resistant strains. *In vitro* activity was seen in *Streptococcus pneumoniae*, including penicillin-intermediate and penicillin-resistant *S pneumoniae*. Linezolid has shown *in vitro* activity (MIC₉₀ < 4 mcg/mL) against the following organisms: *S. pyogenes*, *Corynebacterium* spp., *Moraxella catarrhalis*, *Listeria monocytogenes*, *Pasteurella multocida*, and *Bacteroides fragilis*.

Linezolid is not active against gram-negative bacilli.

Pharmacodynamics / Resistance

The results of time-kill studies have shown that linezolid is bacteriostatic against enterococci and staphylococci.⁶ Linezolid was shown to be bactericidal for the majority of strains of streptococci. In clinical trials, resistance to linezolid was seen in six patients with *E. faecium*, four of the six were treated with a dose of 200 mg every 12 hours and the remaining two received 600 mg every 12 hours. Resistance to linezolid developed in eight patients with *E. faecium* and one patient with *E. faecalis* in a compassionate use program. All patients had abscesses that were not drained or prosthetic devices that were not removed. *In vitro* studies have shown that point mutations in the 23S rRNA resulting in linezolid resistance develop at a frequency of 1×10^{-9} to 1×10^{-11} . Resistance to linezolid has not been seen in patients with *Staphylococcus* spp or *Streptococcus* spp, including *Streptococcus pneumoniae*.

Clinical Trials

Community acquired Pneumonia (CAP)

A randomized, multicenter (international), open label trial of 747 patients with demonstrated or presumptive *S. pneumoniae* pneumonia requiring hospital admission compared linezolid 600 mg intravenous infusion (IV) every 12 hours followed by linezolid 600 mg by mouth (PO) every 12 hours with ceftriaxone 1 g IV every 12 hours followed by cefpodoxime 200 mg PO every 12 hours.¹⁸ Both test groups were treated for 7 to 14 days. Eligible patients had to provide a blood, pleural, or respiratory fluid specimen that on micro-

Table 1: MIC₉₀ Values of Linezolid and Comparators:

Organism	# of isolates	L	V	Q/D	E	Ref.
<i>S. pneumoniae</i>	79	1	1			9
	50	2	0.5	0.5		8
	300	1	0.5	0.5		17
<i>S. pneumoniae</i> penicillin-sensitive	75	1	0.25			15
<i>S. pneumoniae</i> penicillin-intermediate	55	1	0.5			15
	162	1	0.5			16
<i>S. pneumoniae</i> penicillin-resistant	73	1	0.5			15
	68	1	0.5			16
	8,5	2	2			
<i>S. aureus</i> oxacillin-sensitive	1,020	4	2			9
<i>S. aureus</i> methicillin-sensitive	34	2	1	0.5		10
	27	2	1	0.5		13
	59	1	0.5	0.5		14
	50	1	1	0.25		8
<i>S. aureus</i> oxacillin-resistant	451	4	2			9
<i>S. aureus</i> methicillin-resistant	62	2	1	1		10
	60	2	1	1		13
	118	1	1	0.5		14
	50	1	0.5	0.5		8
<i>S. aureus</i> methicillin- & ciprofloxacin-resistant	189	2	2	1		10
<i>S. epidermidis</i> oxacillin-sensitive	365	4	2		>4	9
<i>S. epidermidis</i> oxacillin-resistant	441	4	2		>4	13
<i>S. epidermidis</i> methicillin-sensitive	20	1	1	0.25		13
<i>S. epidermidis</i> methicillin-resistant	29	2	2	0.5		13
	63	1	2	1		14
<i>E. faecalis</i>	1137	4	8			9
	213	1	2			17
	49	1	64	2		8
<i>E. faecalis</i> VRE	31	4	512			11
<i>E. faecium</i>	452	4	>64			9
	47	1	1	4		17
	50	1	128	1		8
<i>E. faecium</i> VanA	23	2	512			11
<i>E. faecium</i> VanB	22	4	512			11
<i>E. gallinarum</i>	7,5	4	16			18
Group A <i>streptococci</i>	30,43	2	0.5			18
Group B <i>streptococci</i>	14,12	2	1			18
Group C <i>streptococci</i>	9,9	2	0.5			18
Group G <i>streptococci</i>	17,17	2	0.5			18
<i>S. oralis</i>	2,1	2	2			18
<i>S. sanguis</i>	2,5	2	1			18

Key: L = linezolid; V = Vancomycin; Q/D = quinupristin/dalfopristin; E = erythromycin

biological evaluation proved consistent with *S. pneumoniae*. The clinical success rates were 86.3% for linezolid and 82.1% for ceftriaxone/cefepodoxime [Confidence interval (CI) -2.2, 10.6]. The microbiologic eradication rates were 87.0% and 81.1%, respectively (CI -6.2, 16.4). In the subpopulation of patients with bacteremia (approximately 2% of the study population) linezolid was more effective than ceftriaxone/cefepodoxime. The clinical and microbiologic cure rates for linezolid were 90.3% and 93.3% respectively, compared to 61.5% and 69.6% for ceftriaxone/cefepodoxime.

Oral linezolid was compared to oral cefepodoxime in 548 outpatients with community-acquired pneumonia.²⁰ Patients were randomized to treatment with linezolid 600 mg or cefepodoxime 200 mg every 12 hours for 10 to 14 days. The investigators were masked to the individual patient treatment regimen. Definitive identification of the pathogens was not made. The clinical success rates were 84.5% for linezolid compared to 89.9% for the cefepodoxime population, (CI -12.2, 1.4). The microbiologic cure rates were 88.0% and 81.3% for linezolid and cefepodoxime, respectively. In the subpopulation of patients with bacteremia (approximately 8%) clinical success rates were 100% for linezolid compared to 60.0% for cefepodoxime.

Nosocomial Pneumonia

A randomized, multi-centered (international) double-masked study in 396 patients with nosocomially-acquired pneumonia compared linezolid 600 mg IV every 12 hours with vancomycin 1g IV every 12 hours.²⁰ Patients in both groups could receive aztreonam 1 to 2 g IV every 8 hours if gram-negative organisms were detected. The duration of treatment was 7 to 21 days in both treatment groups. Patients were selected based on a clinical presentation consistent with pneumonia and a confirmed organism consistent with a respiratory pathogen isolated from respiratory, sputum, or blood cultures. The clinical success rate for linezolid was 41.9% compared to 37.8% for vancomycin. The rate of mortality due to the initial infection was lower in the linezolid group than in the vancomycin group, but this difference was not statistically significant (5.4% v. 8.8%, $p=0.24$). According to the authors of the trial, the cure rates and microbiological eradication rates for linezolid and vancomycin were comparable for the treatment of primary organisms, *S. aureus* and *S. pneumoniae*.

Uncomplicated Skin and Skin Structure Infections

Oral linezolid was compared to oral clarithromycin in a double-masked, multicenter (North America) trial involving 753 patients with an uncomplicated skin or skin structure infection.²⁰ Treatment was randomized to linezolid 400 mg by mouth twice daily or clarithromycin 250 mg by mouth twice daily. The duration of treatment was 7 to 14 consecutive days for both treatment populations. Those enrolled had a suspected gram-positive (eg. *S. aureus*, *S. epidermidis*, *S. pyogenes*, *S.*

agalactiae, *E. faecalis*, or *E. faecium*) uncomplicated skin and superficial skin structure infection, such as simple abscesses, impetiginous lesions, that was accessible for gram stain culture. The clinical success rates were 95.4% for the linezolid-treated group vs 93.8% for the clarithromycin-treated patients. The microbiologic eradication rates were 90.9% and 84.1% for the linezolid and clarithromycin patients, respectively.

A randomized, double-masked, multicenter (multinational—excluding North America), comparator-controlled trial enrolled 341 patients with a suspected gram-positive uncomplicated skin and superficial skin structure infection.²⁰ Eligibility was contingent upon an accessible infection site for gram stain and culture. The patients were treated with either linezolid 400 mg or clarithromycin 250 mg PO twice daily. Patients were treated for 7 to 14 consecutive days. The clinical success rates were 91.1% and 92.7% for the linezolid-treated and clarithromycin-treated groups, respectively. In the microbiologically evaluable patients, the linezolid success rate of 98.1% vs 97.1% for the clarithromycin treated patients. Linezolid was as effective as clarithromycin in eradication of *E. faecalis*, *S. aureus*, *S. epidermis*, *S. agalactiae*, and *S. pyogenes*. In general, the effectiveness of the two treatments was similar among subgroups and comparable in the overall analysis.

Complicated Skin and Skin Structures

Oral or IV linezolid was compared to IV oxacillin or oral dicloxacillin in 826 patients with a suspected gram-positive skin or soft tissue infection that involved deeper soft tissue that may have required surgical intervention.²⁰ The multicenter (international) trial randomized patients to treatment with linezolid 600 mg PO or IV every 12 hour or oxacillin 2 g IV every 6 hours or dicloxacillin 500 mg PO four times a day for 10 to 21 days. Eligible patients had to have a suspected gram-positive complicated skin infection at a site accessible for gram staining. The clinical success rate for the linezolid patient population was 90.7% compared to 86.3% in the oxacillin/dicloxacillin-treated patient population. The microbiological success rate was 88.7% for the linezolid group and 85.4% for the oxacillin/dicloxacillin group. Linezolid was as effective as oxacillin/dicloxacillin in eradicating *S. aureus*, *S. epidermis*, *S. agalactiae*, and *S. pyogenes*. For patients with bacteremia (approximately 3% of the total population), the cure rates were 85.7% for linezolid and 77.8% for oxacillin/dicloxacillin.

Infections Due To Methicillin-Resistant Staphylococcal Species

A randomized, multicenter (international), open-label was conducted with 460 patients comparing the use of linezolid 600 mg IV every 12 hours (or switched to linezolid 600 mg PO every 12 hours) with vancomycin 1 g IV every 12 hours.²⁰ A third arm enrolled patients who received vancomycin 1 g IV every 12 hours followed by linezolid 600 mg PO every 12 hours; the arm was discontinued after 51 patients had been enrolled and was not included in the analysis. Treatment was

Table 2. Cost Comparison of Linezolid and Quinupristin/dalfopristin

	<u>Dose</u>	<u>Cost/Day</u>	<u>Cost/14 Days</u>	<u>Annual Cost*</u>	<u>Savings Compared to Quinupristin/Dalfopristin</u>
Linezolid	600 mg IV Q12h	113.29	1586.06	237,900	290,103
Linezolid	600 mg PO Q12h	83.73	1172.22	175,833	352,170
Linezolid	600 mg IV Q12h x 7 days + 600 mg PO Q12h x 7 days	98.51	1379.14	206,871	321,132
Quinupristin/ dalfopristin	500 mg IV Q8h	251.43	3520.02	528,003	—————
Vancomycin	1 g IV Q12h	4.09	57.26	8589	491,806

administered for 7 to 28 days. Patients had to have a known or suspected *Staphylococcus* infection as determined by a Gram stain or culture. The clinical success rate of the linezolid group was 46.3% compared to 45.9% for the vancomycin group. The cure rate for the linezolid-treated patients was 94.2% vs 87.3% in the vancomycin group. The microbiologic success rates were 59.4% and 64.2% for linezolid and vancomycin-treated patients respectively. Linezolid was as effective as vancomycin in eradicating *S aureus*, and coagulase negative *Staphylococcus*.

Infections Due To Vancomycin-Resistant Enterococci

A multicenter (North America) trial compared two doses of linezolid in 145 patients with known VRE infections. Patients were randomized to treatment with linezolid 600 mg every 12 hours or linezolid 200 mg q12h (IV or PO) for 7 to 28 days.²⁰ The investigators and patients were masked to the treatment regimen. The clinical success rates were 67.2% and 52.2% for the 600 mg and 200 mg doses, respectively. The bacteremic subpopulation had a clinical success rate of 55.6% for the 600 mg group compared to 25.0% for the 200 mg group. The high dose regimen was statistically superior in both clinical and microbiological success rates.

Linezolid in Experimental Otitis Media

The potential efficacy of linezolid vs amoxicillin was assessed in a chinchilla model of experimental otitis media due to multi-drug resistant *S. pneumoniae* and nontypeable *H influenzae*.¹² By day 5 of treatment all animals in the linezolid group (n=18) had complete eradication of *S. pneumoniae*, while all those treated with amoxicillin (n=9) continued to demonstrate infection with *S. pneumoniae*. Amoxicillin, but not linezolid, sterilized middle ear infections due to nontypeable *H. influenzae*. This study suggests that linezolid has the potential for effective use in otitis media. However, no data on human patients are available at this time.

Adverse Effects:

The frequency of adverse reactions associated with linezolid were similar to comparators.⁶ The most common adverse

reactions occurring in at least 2% of patients were diarrhea (8.3% vs 6.3%), headache (6.5% vs 5.5%), nausea (6.2% vs 4.6%), vomiting (3.7% vs 2.0%), insomnia (2.5% vs 1.7%), constipation (2.2%, 2.1%), rash (2.0% vs 2.2%), dizziness (2.0% vs 1.9%), and fever (1.6% vs 2.1%).⁶ In 85% of the cases these side effects were mild to moderate in intensity. Other, side effects occurring in less than 1% of the patients included oral moniliasis, vaginal moniliasis, hypertension, dyspepsia, localized abdominal pain, pruritus, and tongue discoloration. The overall adverse effect rate was 36.3%.

Cost, Dose, and How Supplied

The dose and duration of treatment with linezolid depends upon the type of infection. All doses are given every 12 hours. The recommended dose for vancomycin-resistant enterococci is 600 mg IV or PO for 14 to 28 days. For pneumonia or complicated skin and skin structure infections, the approved dose is 600 mg IV or PO for 10 to 14 consecutive days. The recommended dose of linezolid for uncomplicated skin and skin structure infections is 400 mg IV or PO for 10 to 14 days.

Linezolid is available as 200, 400, and 600 mg ready-to-use bags for intravenous administration, 400 and 600 mg oral tablets, and a powder for oral suspension which when constituted contains 150 mL of linezolid 100 mg per 5 mL. The average wholesale price for a single dose of intravenous linezolid 600 mg is \$71.87. Linezolid is available as 400 mg and 600 mg tablets. The average wholesale price for a 20-count bottle of the 600 mg tablets is \$1062.50.

Conclusion

The prevalence of multidrug-resistant gram-positive organisms has increased dramatically over the years.^{22,23} The percentage of nosocomial enterococci resistant to vancomycin increased from 0.3% in 1989 to 21.2% in 1998 ($p < 0.0001$).²³ In intensive care units, the percentage of enterococcal isolates resistant to vancomycin in patients with nosocomial infections increased from 0.4% in 1989 to 22.6% in 1998 ($p < 0.0001$). The percent of nosocomial MRSA isolates increased from 2% in 1974 to approximately 50% in 1997.²² Approximately 50% of

MRSA isolates identified at National Nosocomial Infection Surveillance (NNIS) system hospitals are susceptible only to vancomycin. The increased prevalence of multiple-drug-resistant strains of common gram-positive bacteria has led to the development of two new agents, quinupristin/dalfopristin and linezolid. Both drugs are effective against a variety of multidrug resistant gram positive organisms, but quinupristin/dalfopristin has several disadvantages which limit its use. Quinupristin/dalfopristin is only available as an intravenous formulation, no oral version is available; phlebitis and significant myalgias have been associated with its use; and it is incompatible with normal saline solutions. Like quinupristin/dalfopristin, linezolid is effective against vancomycin-resistant *Enterococcus faecium* and methicillin-resistant *S. aureus*, but unlike quinupristin/dalfopristin, linezolid is available as both an IV and an oral formulation, oral bioavailability is 100% allowing for step-down therapy, side effects are minimal and there are no known compatibility issues. Further research is needed to determine the respective roles of these two agents in treating infections from resistant gram-positive organisms.

It is recommended that linezolid be added to the UWMC medication formulary for treating vancomycin-resistant *Enterococcus faecium* infections, methicillin-resistant *S. aureus* infections in patients unable to tolerate vancomycin therapy, and the rare case of a patient with a gram-positive infection who is unable to tolerate other conventional antibiotics. The use of linezolid should be tightly controlled to reduce the development of resistant organisms. To protect against unnecessary use, prior authorization by an Infectious Disease attending or fellow will be required. Guidelines for use and a preprinted order form have been created to help guide prescribing. Quinupristin/dalfopristin will be retained on the formulary for 6 months to allow the Infectious Disease section an opportunity to evaluate the relative roles of the two agents.

References

Available on request. ■