The oxazolidinones as a new family of antimicrobial agent

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The oxazolidinones are a new chemical class of synthetic antimicrobials characterized by a unique mechanism of protein synthesis inhibition. Linezolid is the first compound of this class and has recently received approval for the treatment of community- and hospital-acquired pneumonia and skin and skin structure infections. In vitro tests demonstrate that linezolid possesses a significant activity against Gram-positive pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), vancomycin-intermediate strains (VISA) and penicillin-resistant pneumococci (PRPN). Combined with other drugs linezolid interacts favourably against many important pathogens and it is able to affect some bacterial virulence factors as well as produce a postantibiotic effect.

Results from experimental models of infection reveal linezolid to be highly active in vivo against infections due to Gram-positive pathogens.

Linezolid may be administered either intravenously or orally with oral bioavailability of approximately 100% and limited adverse effects. The clinical efficacy of linezolid has been investigated in several phase II and III trials. Linezolid has been proved to be useful in severe infections sustained by multiresistant Gram-positive micro-organisms. Synthesis of the second-generation oxazolidinones with improved potency against Gram-positive and negative bacteria is currently under way.

Keywords oxazolidanone, linezolid, in vitro activity, in vivo activity

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CHEMICAL STRUCTURE

The oxazolidinones are a new synthetic class of antimicrobials, structurally unrelated to any agent presently available to the clinician.

Discovered by E.I. du Pont de Nemours and colleagues in 1987, oxazolidinones are heterocyclic molecules with nitrogen and oxygen in a five-membered ring and bridged with a carbonyl group [1]. The two positional forms are the 4- and 5-isomers. The 5-substituted oxazolidinones are especially endowed with antibacterial activity.

Linezolid (PNU-100766), the first compound of this class approved by the US FDA in 2000, is a 3-(fluorophenil)-2-oxazolidinone that has a morpholin-1yl group substitution (Figure 1) [2].

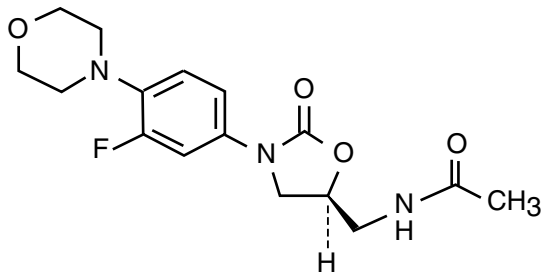

Figure 1 Chemical structure of linezolid.

SPECTRUM OF ACTIVITY

The oxazolidinone appear to have significant activity against Gram-positive bacterial pathogens such as *S. aureus*, *S. epidermidis*, *Streptococcus pneumoniae*, *Enterococcus faecalis* and *E. faecium*. Importantly, these molecules also have activity against several pathogens that are resistant to one or more antibiotics, namely methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant

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enterococci (VRE), vancomycin-intermediate strains (VISA) and penicillin-resistant pneumococci (PRPN) [3].

INDICATIONS

According to its spectrum of activity linezolid received approval for the treatment of community- and hospital-acquired pneumonia, skin and skin structure infections (uncomplicated and complicated), including cases caused by drug-resistant Gram-positive pathogens (MRSA, VRE) [4].

MECHANISM OF ACTION

Studies on the mechanism of action of oxazolidinones concluded that they function by inhibiting a very early step in bacterial protein synthesis [5,6]. Oxazolidinone binding to the 50S subunit distorts the site for formyl-methionyl RNA ($tRNA^{fMet}$), inhibiting ternary initiation complex formation and thus preventing initiation of translation. The linezolid binding site has been found to be located in the ribosomal peptidyl transferase centre (domain V of 23S rRNA) [7,8]. Following uncoupling of the transcription-translation reaction, linezolid demonstrates a modest effect on elongation and termination of translation.

This unique mechanism of action of oxazolidinones avoids cross-resistance with other inhibitors of protein synthesis (such as chloramphenicol, macrolides, lincosamides, streptogramins, aminoglycosides and tetracyclines) [9].

DEVELOPMENT OF RESISTANCE

Laboratory testing to select for resistant mutants has met with only limited success [10,11]. Spontaneous mutation frequencies ranged from $< 8 \times 10^{-11}$ to $< 1 \times 10^{-9}$ for several strains of methicillin-susceptible and -resistant *S. aureus* and *S. epidermidis* [10,11]. After exposure to linezolid at 2×, 4×, 8× minimal inhibitory concentrations (MICs) no mutants were found in the strains tested [10,11]. Step pressure selection did not produce rapid development of resistance in staphylococci and enterococci [10].

In vivo development of resistance to linezolid has been described for *E. faecium* in two patients after 4 or 6 weeks of treatment. Linezolid MICs increased from 2 mg/L to 16–32 mg/L and in addition the strains were resistant to almost every agent tested [12].

In Gram-negative micro-organisms other studies have demonstrated that linezolid penetrates the *E. coli* outer membrane but this is rapidly excreted from the cell by efflux pumps. The susceptibility of Gram-positive organisms to the oxazolidinones can be attributed to a lack of transmembrane pumps with an oxazolidinone specificity [13].

TENTATIVE BREAKPOINT

Two tentative breakpoints for linezolid have been proposed. Supported by preliminary pharmacokinetic data [14,15] some authors have suggested the following values: MICs $\leqslant 4$ mg/L for susceptibility and $\geqslant 16$ mg/L for resistance [16]. More recently Wise *et al* proposed a breakpoint of 2 mg/L after analysis of distribution of susceptibilities [17], but the first breakpoint seems more likely to be accepted.

IN VITRO ACTIVITY

Oxazolidinones display bacteriostatic activity against many important pathogens including MRSA, coagulase-negative staphylococci and VRE. Bactericidal activity was demonstrated against *S. pneumoniae*, *B. fragilis* and *C. perfringens* [10,18–20].

Human serum did not affect linezolid efficacy [21], while incubation in CO_2 was found to depress the activity of linezolid only against pneumococci [22].

Gram-positive micro-organisms

Linezolid possesses good activity against staphylococci, comparable with that of vancomycin. All isolates of *S. aureus* tested had MIC values $\leqslant 4$ mg/L [10,18,23–34]. The same holds true for *S. epidermidis* and *S. haemolyticus* (MIC range from 1 to 2 mg/L) [10,25,28,32] (Table 1). MICs of linezolid were not affected by resistance to β-lactams or fluoroquinolones in staphylococci [35]. In fact, MIC_{90} ranges for MRSA and methicillin-resistant coagulase-negative staphylococci were superimposable (Table 1). Against VISA and glycopetide-resistant coagulase-negative staphylococci linezolid maintains complete activity [36–38].

Against *S. pneumoniae* linezolid was highly effective irrespective of the level of penicillin-susceptibility (Table 1). Linezolid was also active against pneumococci resistant to ceftriaxone [39], erythromycin, clindamycin, chloramphenicol and tetracycline [40]. MICs required to inhibit 90% of strains ranged from 1 to 2 mg/L according to different studies [10,27,28,30–33]. The same range of MIC_{90} has also been found for *S. pyogenes* [31,39]. Erythromycin-resistant *S. pyogenes* were susceptible to linezolid [31] (Table 1).

Linezolid MIC_{90} range for *S. agalactiae* was 0.5–2 mg/L.

Linezolid demonstrated excellent activity against *E. faecalis* and *E. faecium* (MIC_{90} for these two pathogens ranged from 1 to 4 mg/L and from 2 to 4 mg/L, respectively), and significantly, as already highlighted for staphylococci, linezolid was also active against glycopeptide-resistant enterococci (both Van A and Van B phenotypes). For these last micro-organisms MIC_{90} values ranged from 1 to 4 mg/L [38,41]. Similarly 90% of non-*faecalis* and *faecium* enterococci were inhibited by 1–4 mg/L of linezolid (Table 1).

Table 1 MIC_{90} ranges of linezolid against Gram-positive aerobic cocci

Micro-organism	MIC_{90} range (mg/L)	Reference
S. aureus	1–4	18, 23, 24, 25
S. aureus MS	2–4	10, 23, 26, 27, 29, 33, 34
S. aureus MR	2–4	10, 23, 24, 26, 27, 29, 33, 34
S. epidermidis MS	2–4	10, 26, 27, 29, 33
S. epidermidis MR	2–4	10, 26, 27, 29, 33
S. haemolyticus MS	1	29
S. haemolyticus MR	1	29
Coagulase-negative staphylococci	1–2	29, 18, 23, 25, 33, 34
S. pneumoniae	1–2	26, 29, 31
S. pneumoniae pen-S	1–2	10, 23, 32, 34
S. pneumoniae pen-I/R	1–2	10, 23, 32, 33, 34
S. pneumoniae ery-R	1–2	31, 40
S. pyogenes	1–2	10, 29, 31, 34
S. pyogenes ery-R	2	31
S. agalactiae	0.5–2	26, 31, 34
Streptococcus spp.	1–2	29, 34
E. faecalis	2–4	23, 24, 26, 27
E. faecalis vanco-S	1–4	10, 29, 30, 34
E. faecalis vanco-R	1–4	10, 29, 30, 34
E. faecium	2–4	23, 24, 26, 27, 33
E. faecium vanco-S	2	10, 29, 34
E. faecium vanco-R	2–4	10, 29, 30, 34
E. avium	4	30
E. raffinosus	4	30
E. casselliflavus	4	30
Enterococcus spp.	1	29

MS, methicillin-susceptible; MR, methicillin-resistant; pen-S, penicillin-susceptible; pen-I/R, penicillin-intermediate + penicillin-resistant; ery-R, erythromycin-resistant; vanco-S, vancomycin-susceptible; vanco-R, vancomycin-resistant.

Linezolid showed potent activity against other Gram-positive organisms, including *Nocardia* spp. (MIC_{50} 2–4 mg/L and MIC_{90} 2–8 mg/L), *Bacillus* spp. (MIC range: 0.5–1 mg/L), *Corynebacterium* spp. (MIC range: 0.25–0.5 mg/L), *Listeria monocytogenes*, *Mycobacterium tubercolosis* (MIC range: 0.5–2 mg/L) and *Rhodococcus* spp. [10,41–43].

Against the anaerobes *Clostridium difficile* and *C. perfringens* linezolid displayed MIC_{90} of 1–2 mg/L and 1–4, respectively (Table 2) [10,44,45].

Gram-negative micro-organisms

Although linezolid does not encompass in its spectrum Gram-negative bacteria, it demonstrates modest activity against *M. catarrhalis*, *B. pertussis* and *Legionella* spp. (MIC_{90} 4 mg/L), *H. influenzae* (MIC_{50} 4 mg/L) and *Neisseria gonorrhoeae* (MIC_{90} 16 mg/L) [10,29,43,46–48]. Enterobacteriaceae and *Pseudomonas aeruginosa* were not inhibited by linezolid [10,29]. Gram-negative anaerobes including *Bacteroides* spp., *Fusobacterium nucleatum* and *Prevotella* spp. were generally inhibited by linezolid concentrations ranging from 0.5 to 4 mg/L (Table 2) [10,44,45,49]. Linezolid was also tested against *Helicobacter pylori* and for this pathogen MICs ranged from 8 to 64 mg/L [50].

Effects on virulence factors

In vitro experiments showed that linezolid at sub-MICs inhibits the expression of some virulence factors of *S. aureus* and *S. pyogenes*. Growth in 0.5–0.125 × MIC (0.8–0.2 mg/L) of linezolid inhibited synthesis of α-hemolysin, δ-hemolysin and coagulase in *S. aureus*. Susceptibility to phagocytosis was also increased after treatment with linezolid at 0.5 × MIC. When *S. pyogens* was grown in 0.5 and 0.25 × MIC linezolid, streptolysin O and DNAase production was diminished. Susceptibility to phagocytosis of *S. pyogenes* exposed to linezolid was also enhanced: 52.8% of bacteria ingested vs. 37.5% [51].

Association with other drugs

The in vitro activity of linezolid combined with other drugs against staphylococci (including β-lactamase-producers strains), penicillin-susceptible and -resistant pneumococci, vancomycin-

Table 2 MIC ranges of linezolid against Gram-positive anaerobes

Micro-organism	MIC range (mg/L)	Reference
B. fragilis	2–4	10, 44, 45, 49
Clostridium spp.	⩽2	49
C. difficile	1–2	10, 44, 45, 49
C. perfringens	1–4	10, 44, 45, 49
Fusobacterium spp.	0.5–8	45, 49
F. nucleatum	0.5	10, 44
Peptostreptococcus spp.	0.25–2	10, 44, 45
P. acnes	0.25–1	10, 44, 45
Prevotella spp.	2–4	10, 44, 45, 49

susceptible and -resistant enterococci and enteric bacteria has been extensively investigated by Sweeny *et al* [52,53] by the checkerboard broth microdilution method. Linezolid was associated with ampicillin, amoxicillin, oxacillin, penicillin, cefoxitin, cephalothin, cefotaxime, ceftazidime, cefpodoxime, cefdinir, aztreonam, imipenem, clindamycin, erythromycin, gentamicin, neomycin, tetracycline, rifampin, vancomycin, teicoplanin, fusidic acid, bacitracin, metronidazole and chloramphenicol. Out of 938 organism–drug combinations, 924 produced an additive/indifferent response (98.5%), eight were synegistic (0.9%), and six were antagonistic (0.6%). Against *H. pylori* (70 strains) the combination of linezolid with amoxicillin, clarithromycin or metronidazole showed either partial synergy or indifference for the majority of strains [50].

Post-antibiotic effect (PAE)

At 1 × MIC and 4 × MIC, linezolid showed in vitro PAEs of 0.5 ± 0.2, 0.3 ± 0.5, 0.8 ± 0.5 h and 0.6 ± 0.0, 1.1 ± 0.9, 1.4 ± 0.3 h, respectively, for methicillin-resistant *S. aureus*, methicillin-susceptible *S. aureus* and vancomycin-resistant *E. faecium* [3,31].

In a mouse thigh infection model linezolid doses of 20 and 80 mg/kg produced similar PAEs of 3.6 and 3.8 h with penicillin-susceptible *S. pneumoniae* and 3.9 and 3.7 h with methicillin-susceptible *S. aureus* respectively [54].

IN VIVO ACTIVITY

Systemic infections

Effective dose (ED_{50}) values obtained with oral linezolid against experimental bacteremia in a mouse intraperitoneal model ranged from 2 to 7 mg/kg/day for MRSA and MSSA. Against the same strains vancomycin ED_{50} ranged from 1.8 to 13.2 mg/kg/day [2]. Linezolid was more active than amoxicillin and penicilllin against penicillin-resistant *S. pneumoniae* (ED_{50} 2.5–3.8 vs. 3.4 to >20 mg/kg/day and was more active than clindamycin against *S. pyogenes* (ED_{50} 5 vs. 8.6 mg/kg/day) [2]. Against vancomycin-resistant *E. faecium* (ED_{50} > 100 mg/kg/day), linezolid showed an ED_{50} of 24. Linezolid was less effective (ED_{50} 10 mg/kg/day) than vancomycin (ED_{50} 0.5 mg/kg/day) against vancomycin-susceptible *E. faecalis* [2]. As expected by in vitro results, linezolid was ineffective against bacteremia sustained by Gram-negative pathogens.

Endocarditis

The activity of linezolid was compared with that of vancomycin in two rat models of experimental methicillin-resistant *S. aureus* endocarditis and vancomycin-resistant *E. faecium* endocarditis. In the first model linezolid at 40 mg/kg reduced by 2.9 $\log_{10}$ CFU/g bacterial vegetation counts. Bacterial loads remained unchanged in animals treated with vancomycin 60 mg/kg [55,56]. In a study of experimental endocarditis in rabbits sustained by methicillin-susceptible *S. aureus* both linezolid and vancomycin reduced bacterial vegetation counts significantly [57]. Linezolid treatment (25 mg/kg) was more active than vancomycin treatment (25 mg/kg) in *Enterococcus* experimental endocarditis [58].

Meningitis

Linezolid showed good penetration (38 ± 4%) into the meninges of rabbits with levels in the cerebrospinal fluid ranging from 9.5 to 1.8 mg/L after two intravenous injections (20 mg/kg). Linezolid reduced both penicillin-susceptible and -resistant cerebrospinal fluid pneumococcal counts. However, at the above-mentioned dose regimen it was less active than ceftriaxone (125 mg/kg) against a penicillin-susceptible *S. pneumoniae*. Against a penicillin-resistant strain, linezolid had slightly inferior killing rates than the standard regimen (ceftriaxone plus vancomycin) [59].

Osteomyelitis

The efficacy of linezolid was evaluated in a rat model of MSSA experimental osteomyelitis, but the linezolid effect was not significantly different from that observed in the control untreated animals [60].

Soft-tissue infections

In a subcutaneous *S. aureus* abscess model, after 5 days of oral treatment, linezolid cured 50% of infections at 39 mg/kg, vancomycin at 4.7 mg/kg and subcutaneous clindamycin at 75 mg/kg [2]. Linezolid also compared favorably with vancomycin in the treatment of experimental soft-tissue infections

caused by *E. faecalis* and *E. faecium* [58]. Against these microorganisms, linezolid provided 50% of microbiological cure at 11 and 12.5 mg/kg, respectively; for vancomycin the ED_{50} was 16.2 and 41.8 mg/kg, respectively. Linezolid combined with aztreonam cured polymicrobic soft-tissue infections sustained by gentamicin-susceptible *E. coli* plus gentamicin-resistant *S. aureus* (ED_{50} 5.6 mg/kg/day).

Otitis media

A chinchilla model was utilized by Pelton and colleagues [61] to evaluate the efficacy of linezolid against experimental otitis media due to *S. pneumoniae* or *Haemophilus influenzae*.

After 5 days of treatment all animals in the linezolid group (25 mg/kg twice a day) had sterile middle ear cultures and eradication of *S. pneumoniae* from the nasopharynx. In the amoxicillin group, all animals remained middle ear and nasopharynx positive.

Experimental infection and nasopharyngeal colonization due to nontypable *H. influenzae* persisted despite the achievement of concentrations in the middle ear that were above the MIC.

Other experimental infections

Oral linezolid (25, 50 and 100 mg/kg) reduced spleen and lung bacterial counts in a mouse model of *M. tuberculosis* infection. However, isoniazid (25 mg/kg) was more active than linezolid at the highest dose [62].

Linezolid cured animals in a neutropenic murine model against vancomycin-resitant *E. faecium* and aminoglycoside-resistant *E. faecalis*. The in vivo effectiveness of linezolid against one strain each of *E. faecalis* and vancomycin-resistant *E. faecium* was examined in a rat model of intrabdominal abscess. At a dosage of 100 mg/kg/day linezolid treatment led to an approximately 100-fold reduction in viable *E. faecalis* cells/gram of abscess. Against *E. faecium* infection linezolid reduced bacterial densities approximately $2 \log_{10}$ CFU/g [63].

PHARMACOKINETIC

(See also article by Bouza and Muñoz [64].)
Linezolid is rapidly and completely absorbed after oral administration, reaching the maximum plasma concentration (C_{max}) within 1–2 h and having an average bioavailability of 103% [3,13,54]. Plasma protein binding has been estimated to be 32%. Pharmacockinetic data indicate that linezolid may be administered without regard to meals [65,66].

Intrapulmonary pharmacokinetic results indicate that linezolid is likely to be an effective agent for the treatment of pulmonary diseases [67]. Total and renal clearances of linezolid were 120 and 50 mL/min. The elimination half-life ($t1/2_z$) was 4.5–5.5 h under single dose and steady-state conditions [13,14]. Metabolism studies indicated that linezolid undergoes slow non-enzymatic oxidation [68]. Drug interaction studies have been conducted for linezolid administered with aztreonam and with gentamicin. There was no change in the plasma concentration profiles of linezolid or aztreonam when given separately or together. The same was true for linezolid plus gentamicin [69,70]. In adult volunteers the pharmacokinetic parameters of linezolid were not very influenced by age or gender [71], while total body clearance was greater in children than in adults [72,73].

Dosage adjustment is not necessary in patients with mild to moderate impaired renal function and liver disease, while in patients on hemodyalisis additional or post-dyalisis linezolid doses are recommended [74,75].

CLINICAL EFFICACY

(See also article by Bouza and Muñoz [64].)
Oral and intravenous linezolid has been proved to be effective in treating several infections, including community-acquired pneumonia in both adults and children [76,77], nosocomial pnemonia [78], skin/soft-tissue infections [79], bacteremia [80–83], intra-abdominal infections [84], endocarditis [85] and infections due to VRE and MRSA in patients with severe conditions (renal failure, liver transplantation, malignancies, vertebral osteomyelitis, human immunodeficiency virus infection) [86,87].

ADVERSE EFFECTS

(See also article by Bouza and Muñoz [64].)
Linezolid is generally well tolerated [3]. The most common adverse effects involve the gastrointestinal tract [13,14,67,88,89] and are nausea, diarrhea, tongue discoloration and oral candidosis. Enzyme kinetic parameters indicate a mild reversible and competitive inhibition of human monoamino oxidase (MAO), but no adverse effects due to MAO inhibition have been reported during linezolid treatment [65,66].

MICROBIOLOGICAL ADVERSE EFFECTS

Gastrointestinal complications related to *C. difficile* overgrowth and toxin production associated with the use of linezolid have been investigated. Data were reviewed for 4047 patients included in seven comparator-controlled trials. The drugs included for comparison were vancomycin, clarithromycin, ceftriaxone, cefpodoxime, oxacillin and dicloxacillin. Overall, *C. difficile*-related adverse events of 0.2% and 0.4% for linezolid and comparators, respectively, were reported [90].

NEW OXAZOLIDINONES

The oxazolidinone template provides ample structural latitute for diverse synthetic modifications and development of extensive structure–activity relationships. New generations of analogs have been synthesized in an effort to enhance the potency and spectrum of the class [91]. New oxazolidinones of interest are: 3′-Fluoro-4′Thioether Phenyloxazolidinones, 4′amido-3′Fluoropheniloxazolidinones, 4′-Acylamino-3′Fluoro phenyloxazolidinones and tetrahidro-4(2H)-thiopyranPhenyloxazolidinones Sulfoxides and Sulfones and 2-aminomethyl thiadizole oxazolidinones [92–96]. Some molecules (PNU-182347, VRC-3406, VRC 3125, VRC 3599, VRC3881) belonging to these structural subclasses show improved Gram-positive potency and improved potency for the fastidious Gram-negative pathogen *H. influenzae* [92–96].

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