

Linezolid in Children: Recent Patents and Advances

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Abstract: Linezolid is the first approved member of a new generation of antibiotics, the synthetic oxazolidinones, to become available, with a broad spectrum of *in vitro* activity against Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecalis* and vancomycin-resistant *Enterococcus faecium*.

It has an excellent bioavailability both intravenously and orally and a very good safety profile both in adults and in children.

With regards to its antimicrobial action, linezolid has a predominantly bacteriostatic action, rather than a bacteriocidal effect and is active against Gram-positive bacteria that are resistant to other antibiotics.

Linezolid is currently showing great promise for the treatment of multi-resistant Gram-positive infections, both in the community and in a hospital setting. Clinical indications so far include skin and soft tissue infections, community-acquired or nosocomial pneumonia due to MRSA, VRE bacteremia and community-acquired pneumonia due to penicillin-resistant *Streptococcus pneumoniae*.

We anticipate that this new generation of antimicrobial agents will provide adequate cover in the future for infections that cause significant treatment failures so far, such as VRE-associated endocarditis, bone and joint multi-drug resistant infections and possibly central nervous system infections, both in adult and children populations. Some patents on linezolid are also discussed in this review.

Keywords: Linezolid, children, pharmacokinetics, indications, safety, tolerability.

INTRODUCTION

Linezolid is the first member of a new generation of antibiotics, the synthetic oxazolidinones, to become available. These compounds enhance protein synthesis by ligation to the 50S subunit of ribosomes [1,2]. It has a broad spectrum of *in vitro* activity against Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecalis* and vancomycin-resistant *Enterococcus faecium* [1,2]. New oxazolidinone and/or isoxazoline derivatives in the form of solution and non-aromatic alcohol act as antibacterial agents against Gram positive pathogens e.g. methicillin resistant *Staphylococcus aureus*, vancomycin and methicillin resistant strains, aminoglycoside and beta-lactam resistant *E. faecium* [3-5].

In May 2000, linezolid has been approved by the Food and Drug Administration (FDA) in the United States as therapy for patients with Gram-positive infections, including MRSA nosocomial pneumonia and complicated skin and skin structure infections [6] and ocular infections [7,8]. It is an antibiotic that is currently investigated by various research groups and is rapidly gaining approval for use in many clinical circumstances, both in adults and children. The indications for administration of linezolid include infections

from vancomycin-resistant enterococci (VRE), methicillin-resistant *S. aureus* and penicillin-resistant strains of *Streptococcus pneumoniae* [9-11]. In 2003, the FDA approved the use of linezolid for the treatment of diabetic foot ulcers. Oxazolidinone derivatives possess antibiotic activity which are used against Gram positive and Gram negative pathogens [12].

ANTIMICROBIAL ACTION AND RESISTANCE EMERGENCE

The chemical structure of linezolid is unique, it does not resemble any other antimicrobial agent and it is a synthetic compound. Its mechanism of action is also unique Fig. 1. It blocks the synthesis of protein at an earlier stage when compared with other antibiotics with a similar mode of action, such as aminoglycosides, macrolides, clindamycin and streptogramins. Linezolid binds with the 50S subunit of ribosomes, enhancing the formation of the initiation compound of protein synthesis. Specific ribosome-binding properties as well as ligands that may act as protein synthesis inhibitors are used specifically to kill or inhibit the growth of any target organism [13,14]. For this reason, it does not result in cross-resistance with the above mentioned antimicrobial agents [9,10]. More methods for the synthesis of linezolid has been patented [15-17].

Linezolid is active against Gram-positive bacteria that are resistant to other antibiotics. *in vitro* Studies have demonstrated that the minimal inhibitory concentration (MIC) of linezolid against coagulase-negative staphylococci, *S. aureus*

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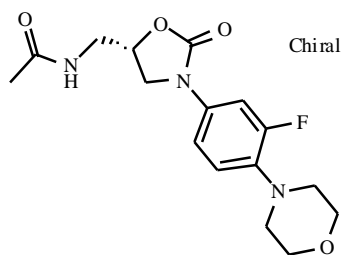


Fig. (1). Structure of linezolid.

(including the methicillin-resistant strains), *S. pneumoniae* (including the penicillin-resistant strains) and enterococci (including the VRE strains) is 0.5-4 $\mu\text{g/ml}$. In the United States of America, staphylococci are considered sensitive when MIC is $<2 \mu\text{g/ml}$. Sensitive strains of enterococci and pneumococci are those with MIC $<4 \mu\text{g/ml}$. Linezolid is active against *S. aureus* strains with partial or complete resistance to vancomycin, as well as against Gram-positive anaerobic microorganisms [11,18-20].

Linezolid has also been effective against rapidly growing atypical mycobacteria, such as *Mycobacterium fortuitum* and *Mycobacterium chelonae* [21]. This antibiotic has proven active against *Nocardia* species, as well [22].

Linezolid has a predominantly bacteriostatic action, rather than a bacteriocidal effect. Studies on animal models, however, as well as clinical studies have demonstrated that it is an effective alternative in the management of endocarditis from a vancomycin-resistant *Enterococcus* [9,23,24].

This antibiotic's resistance has been attributed to certain mutations in the region V of subunit 23S of rRNA. To the present day, there have been reports of linezolid resistance during therapy to VRE and MRSA strains, as well as coagulase-negative *Staphylococci*. Most of these strains are originated from adult populations that received prolonged courses of linezolid or had central vein catheters. A small number of resistant strains, however, originate from children who were never administered linezolid [24,25].

PHARMACOKINETICS

A remarkable feature of linezolid is that it has 100% oral bioavailability: nearly identical peak serum concentrations and elimination profiles are achieved when the drug is administered by either the oral or the parenteral route [26]. This allows treatment to be initiated orally or intravenously with the option to switch to the oral formulation. With oral therapy the adverse reactions associated with vascular lines are avoided and hospital discharge may occur sooner, reducing the risk of nosocomial infections. Novel crystalline forms are also used to treat gram positive bacterial infections designed in Form TIII, Form V, Form VI, Form IX, Form X, Form XII, Form XIV, Form XVII, and Form XVIII [27]. Powdered linezolid in combination has been used in drug resistance preventing treatment [28].

This antibiotic has a time-dependent action, which means that its effectiveness is maximal at the time when its concentration on the infection site is greater than the minimal inhibitory concentration (MIC) of the microorganism.

Linezolid is capable of achieving adequate concentrations in various tissues, such as the skin, bones, muscles, adipose tissue, extracellular lung fluid and cerebrospinal fluid, both in adults and in children. This significant tissue penetration ability is attributed mainly to linezolid's low binding capacity with albumin [29,30].

Linezolid is widely distributed and is eliminated by both renal and non-renal mechanisms. The metabolic breakdown of linezolid has not been fully elucidated, but its two major oxidative metabolites do not appear to have significant antimicrobial activity or toxicity. Under steady-state conditions, plasma concentrations of metabolites account for only 25-35% of the linezolid area under the concentration-time curve. Approximately 30% of a linezolid dose is excreted in the urine as the parent drug, 55% in urine as metabolites, and 10% in feces as metabolites [31]. The half-life in adults and older children is 4 to 6 hours, which suggests that it can be administered twice daily [30]. No dose adjustments are required in patients with renal impairment or mild to moderate liver disease, although in renal failure, inactive metabolites tend to pile up, a finding with no known clinical significance so far [32,33].

The pharmacokinetic of linezolid in pediatric patients has been evaluated in 4 clinical trials, including more than 180 patients ranging in age from preterm newborn infants up to 18 years of age and was found to be age-dependent. Children younger than 12 years of age have a smaller area under the drug concentration-time curve, a faster clearance and a shorter elimination half-life than adults. Although clearance rates in newborn infants are similar to those in adults, clearance increases rapidly during the first week of life, becoming 2- to 3- fold higher than in adults by the seventh day of life. The clearance of linezolid decreases gradually among young children, becoming similar to adult values by adolescence. The pharmacokinetics of linezolid in children age 12 years and older is not significantly different from that of adults. Because of the higher clearance and lower area under the drug concentration-time curve, a shorter dosing interval for linezolid is required for children younger than 12 years of age to produce adequate drug exposure against target Gram-positive pathogens [34].

It would seem, therefore, that the age differences in linezolid's pharmacokinetics are important with regards to dosage formulation. This drug needs to be administered in shorter time intervals in infants and small children since its effectiveness depends on the duration of time during which the serum concentration is above MIC [35,36].

The US trade name of linezolid is Zyvox and it is formulated as an oral suspension, tablet or intravenous infusion. Linezolid is administered in children younger than 12 years of age at a dose of 10 mg/kg three times per day for most infections (Table 1). The only exception is uncomplicated skin infection, in which case the antibiotic could be given at a dose of 10 mg/kg twice daily in children 5 to 11 years old. In preterm infants (<34 weeks gestation), the recommended dose would be 10 mg/kg twice daily until one week of age, and 10 mg/kg three times per day thereafter. All other newborns are given 10 mg/kg three times per day. Teenagers (> 12 years old) and adults are given 600 mg twice daily [37,38].

Table 1. Recommended Dosage of Linezolid in Children and Adults

Indications	Children (> 7 days to 11 years old) 1	Teenagers and adults (> 12 years old)
- Complicated skin and soft tissue infections - Pneumonia - Bacteremia	10 mg/kg intravenously or orally every 8 hours	600 mg intravenously or orally every 12 hours
- Simple skin and soft tissue infections	< 5 years: 10 mg/kg intravenously or orally every 8 hours 5-11 years: 10 mg/kg intravenously or orally every 12 hours	600 mg intravenously or orally every 12 hours 2

1. The dosage in newborns <7 days old is 10 mg/kg intravenously every 12 hours

2. Adults with mild skin infections can receive 400 mg every 12 hours

CLINICAL INDICATIONS OF LINEZOLID

Linezolid is currently showing great promise for the treatment of multi-resistant Gram-positive infections, both in the community and in a hospital setting [39] (Table 2). As the incidence of these infections increases, it is estimated that linezolid's indications of administration will increase, as well. Clinical indications so far include skin and soft tissue infections, community-acquired or nosocomial pneumonia due to MRSA, VRE bacteremia and community-acquired pneumonia due to penicillin-resistant *S. pneumoniae* [9,39,40].

Table 2. Indications for Use of Linezolid

Approved indications	- MRSA skin and soft tissue infections - MRSA pneumonia - MRSA or VRE bacteremia - Pneumonia due to penicillin-resistant <i>S. pneumoniae</i>
Limited case series documentation of successful use of linezolid	- VRE endocarditis - MRSA bone and joint infections - Meningitis

The most significant clinical trial so far was performed in adults and linezolid was provided for treatment of multidrug-resistant, Gram-positive infections through a compassionate-use program. Patients (n = 796) received 600 mg of linezolid intravenously or orally every twelve hours (828 treatment courses). Bacteremia was present in 46% of infections, endocarditis was present in 10.6%, and line-related infections were present in 31.1%. Other infections included intra-abdominal infections (15.1%), complicated skin and skin-structure infections (13.3%), and osteomyelitis (10.7%). Causative pathogens included vancomycin-resistant *Enterococci* (66.3%) and methicillin-resistant *Staphylococci* (22.1%). Clinical intent-to-treat (ITT) outcomes in the evaluable population were as follows: cure 73.3%, failure 6.8% and indeterminate 19.9%. Microbiological ITT outcomes in evaluable population were as follows: cure 82.4%, failure 14.1% and indeterminate 3.5%. At the test of cure assessment, the clinical cure and microbiological success rates were 91.5% and 85.8%, respectively. Linezolid, therefore,

provided high rates of clinical cure and microbiological success in this complicated patient population [9].

Randomized studies that compare linezolid versus vancomycin have been conducted in adults and in children. Some concluded that both antibiotics are equally effective [41], although others that linezolid may be a preferable choice [20, 42, 43]. Probably the most comprehensive study so far was conducted in adults and had the objective to assess the effect of baseline variables, including treatment, on outcome in patients with nosocomial pneumonia due to methicillin-resistant *Staphylococcus aureus*. It was a multinational study with 134 sites that provided a retrospective analysis of data from two prospective, randomized, double-blind studies. A total of 1,019 patients with suspected Gram-positive nosocomial pneumonia, including 339 patients with documented *S. aureus* pneumonia (*S. aureus* subset) and 160 patients with documented MRSA pneumonia (MRSA subset) were treated with linezolid 600 mg, or vancomycin 1 gr, every twelve hours for 7 to 21 days, each with aztreonam. Outcome was measured by survival and clinical cure rates (assessed 12 to 28 days after the end of therapy). Logistic regression analysis was used to determine the effect of treatment and other baseline variables on outcome. Kaplan-Meier survival rates for linezolid versus vancomycin were 80.0% (60 of 75 patients) versus 63.5% (54 of 85 patients) for the MRSA subset (p = 0.03). Logistic regression analysis confirmed that the survival difference favoring linezolid remained significant after adjusting for baseline variables. Other baseline variables associated with significantly higher survival rates in MRSA pneumonia were serum creatinine levels less than or equal to two times the upper limit of normal and absence of cardiac comorbidities. Clinical cure rates for linezolid versus vancomycin (excluding indeterminate or missing outcomes) were 59.0% (36 of 61 patients) versus 35.5% (22 of 62 patients) for the MRSA subset (p<0.01). Logistic regression analysis confirmed that the difference favoring linezolid remained significant after adjusting for baseline variables. Other baseline variables associated with significantly higher clinical cure rates in MRSA pneumonia were single-lobe pneumonia, absence of ventilator-associated pneumonia, and absence of oncologic and renal comorbidities. The study concluded that initial therapy with linezolid was associated with significantly better survival and clinical cure rates than was vancomycin in patients with nosocomial pneumonia due to MRSA [43].

Linezolid was also compared to vancomycin in the management of skin and soft tissue infections, as well as surgical infections due to MRSA in adult population. The study concluded that the clinical and bacteriological effectiveness of linezolid was greater, while the mean hospital stay was significantly shorter [44]. Another research in children demonstrated a better outcome with linezolid in the treatment of complicated skin and skin structure infections [45].

A relatively small number of patients with central nervous system infections due to MRSA, VRE and methicillin-resistant *Staphylococcus epidermidis* were effectively managed with linezolid. This includes neurosurgical patients with post-traumatic or post-surgical infections, as well as patients with ventriculo-peritoneal shunts or other implanted devices. Although these are mere case-studies, they point out that linezolid is adequate in this setting, producing high concentrations in the cerebrospinal fluid [46].

Although linezolid has not been formally approved for use in patients with endocarditis, there are nevertheless certain case-studies documenting successful management of VRE associated endocarditis with this compound [24].

Linezolid penetrates adequately bone and joint tissues, maintaining relatively high concentrations. It could, therefore be used in the management of bone and joint infections due to Gram-positive microorganisms. Although it has not been systematically evaluated so far in this context, linezolid has already been efficiently administered in a number of similar cases [47, 48].

SAFETY AND TOLERABILITY OF LINEZOLID

Clinical trials have shown that linezolid (600 mg twice daily in adults) is safe and generally well tolerated for up to 28 days. Drug-related adverse events, which are typically mild to moderate in intensity and of limited duration, include diarrhea, nausea and headache in adults [49], and diarrhea, loose stools and vomiting in children [50]. *Clostridium difficile*-related complications with linezolid are uncommon. Linezolid is a weak, reversible monoamine oxidase inhibitor: foods containing high concentrations of tyramine should be avoided, and linezolid should be used with caution in patients taking adrenergic or serotonergic agents or in those with uncontrolled hypertension. In the majority of patients, linezolid has minimal adverse effects on blood chemistry or hematology. There have been case reports of reversible thrombocytopenia, anemia and neutropenia associated with linezolid therapy for >2 weeks, in adults [49] and in children [51], which are not however significant especially in children. Nevertheless, complete blood counts should be monitored weekly in patients receiving linezolid for more than 14 days and treatment should be discontinued if there is evidence of myelosuppression. Finally, a rare neuropathy observed in adults is associated with prolonged use of linezolid (more than 6 months), with concomitant use of selective serotonin re-uptake inhibitor drugs [52].

CURRENT & FUTURE DEVELOPMENTS

Linezolid is a relatively new antibiotic that is rapidly gaining approval for use in many clinical situations both in adults and in children. Linezolid is currently showing great

promise for the treatment of multi-resistant Gram-positive infections, both in the community and in a hospital setting since it has an excellent bioavailability both intravenously and orally with a very good safety profile.

We anticipate that this new generation of antimicrobial agents will provide adequate cover in the near future for infections that cause significant treatment failures so far, such as VRE-associated endocarditis, bone and joint multi-drug resistant infections and possibly central nervous system infections, both in adult and children populations.

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