Linezolid Use for Resistant Gram-positive Infections in Children
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The development of vancomycin-resistant Enterococcus species (VRE) has created the need for new antibiotics effective against Gram-positive organisms. Linezolid, the first agent in a new class of drugs called oxazolidinones, offers an effective alternative for infections caused by VRE, methicillin-resistant Staphylococcus aureus (MRSA), and other antibiotic-resistant Gram-positive bacteria. While these organisms are uncommon in the pediatric population, there are patients predisposed to infections with resistant pathogens, such as those with prolonged hospital admissions or in-dwelling intravenous catheters. Linezolid has been found to be effective in the treatment of these patients and was approved for pediatric use by the Food and Drug Administration in December 2002.

Mechanism of Action
Although the exact mechanism of activity for linezolid has not been determined, it is believed to act via inhibition of the initiation phase of bacterial protein synthesis by disrupting the interaction of fMet-tRNA with the 50S subunit during formation of the preinitiation complex.1-3

Antibacterial Spectrum
Linezolid is effective against most Gram-positive organisms, including staphylococcal strains resistant to methicillin and vancomycin and enterococcal strains resistant to vancomycin, including E. faecalis and E. faecium. Linezolid is also effective against most streptococcal strains, Bacillus and Cornebacterium species, Listeria monocytogenes, and Mycobacterium tuberculosis. Linezolid is bactericidal against streptococcal species and bacteriostatic against most Staphylococcus and Enterococcus species.

In addition to its Gram-positive coverage, linezolid has activity against some anaerobes, including Clostridium perfringens, C. difficile, Peptostreptococcus species, Bacteroides fragilis, and Fusobacterium species. Linezolid has only moderate activity against Haemophilus influenzae and Moraxella catarrhalis. It has no significant activity against Enterobacteriaceae or Pseudomonas species.

Although in vitro studies have failed to produce bacterial resistance to linezolid, linezolid-resistant strains of E. faecium, E. faecalis, Staphylococcus epidermidis and Streptococcus oralis have been reported in clinical use.1-5

Clinical Use in Children
A limited number of publications are available describing the use of linezolid in infants and children.6-14 In 2001, Kaplan and colleagues published the results of a multicenter trial of linezolid as empiric treatment for community-acquired pneumonia in children.7 Seventy-eight hospitalized children between the ages of 12 months and 17 years were treated in this Phase II open-label study. The children received a linezolid dose of 10 mg/kg every 12 hours (up to 600 mg) intravenously (IV), followed by oral dosing when appropriate. Data from 66 children were evaluated. At follow-up, 61 patients (92.4%) were considered cured. One patient failed therapy, and four patients’ results were considered indeterminate. The patient who failed therapy was a 1 year old child with MRSA isolated from pleural fluid and blood. She responded to a two week course of vancomycin.

The mean length of treatment was 12.2+6.2 days (range 6 to 41 days). Intravenous therapy was provided for an average of 4.8+4.3 days (range 2 to 27 days). The mean peak serum concentration was 9.5+4.8 mcg/ml, well above the 90% minimum inhibitory concentration (MIC90) for most Gram-positive pathogens. The mean trough concentration was 0.8+1.2 mcg/ml. The most common adverse effects were diarrhea (10.3% of patients), neutropenia (6.4%), and elevated liver function tests (6.4%). The authors concluded that linezolid was well tolerated and an effective alternative to vancomycin in children.
In a 2002 abstract, Bruss and colleagues (publishing for the Linezolid Pediatric Study Group) described the preliminary results of a Phase III randomized, blinded, multicenter trial comparing linezolid to cefadroxil for the treatment of uncomplicated skin and soft tissue infections in children. A total of 440 patients between the ages 5 and 17 years were randomized to receive either linezolid or cefadroxil. Patients 5 to 11 years of age received either linezolid 10 mg/kg (up to 600 mg) or cefadroxil 15 mg/kg (up to 500 mg) as an oral suspension every 12 hours. Patients 12 to 17 years of age received either linezolid 600 mg tablets or cefadroxil 500 mg capsules orally every 12 hours. The duration of therapy ranged from 10 to 21 days. Clinical cure rates were not significantly different between the groups at follow-up (91% for linezolid and 90% for cefadroxil). In patients with infections caused by S. aureus, there was a pathogen eradication rate of 89.6% and 88.8% in the linezolid and cefadroxil groups, respectively. Eradication rates for S. pyrogenes were 94.1% and 96.3%. Both drugs were well tolerated, with a comparable incidence of serious adverse effects (0.8% for linezolid and 1.6% for cefadroxil).

In a subset analysis from this study, the authors found that linezolid was effective in treating children with MRSA. In the 13 evaluable children with MRSA who received linezolid, the cure rate at follow-up was 92.9% versus 77.8% in the seven cefadroxil-treated MRSA patients.

Earlier this year at the 2003 Pediatric Academic Societies’ Annual Meeting, these researchers presented three additional clinical trials comparing linezolid to vancomycin. In one study, 120 children (newborn to 11 years) with Gram-positive complicated skin and soft tissue infections were enrolled. Eighty patients were treated with linezolid (10 mg/kg IV or PO every 8 hours), and 40 received vancomycin (10 to 15 mg/kg IV every 6 to 24 hours). Clinical cure rates were comparable (86% for linezolid versus 82% for the intention-to-treat analysis and 93% versus 90% in the clinically evaluable patients). Rates of bacterial eradication were also similar between the two groups.

In another study, the authors compared linezolid and vancomycin for the treatment of bacteremia with resistant Gram-positive organisms. A total of 113 children (newborn to 11 years of age) were randomized in the manner described with the previous study. Again, linezolid and vancomycin produced similar rates of clinical cure and bacterial eradication. In patients with bacteremia associated with in-dwelling catheters, the cure rate in the clinically evaluable patients was 85% with linezolid versus 80% with vancomycin. For patients with bacteremia who did not have a source of infection identified, the cure rates were 79% versus 69%. The frequency of adverse effects was similar between the groups.

In the third abstract, the authors compared linezolid and vancomycin for MRSA infections. Thirty-four children (newborn to 11 years) were randomized in the same manner as in the previous abstracts. The antibiotics produced similar clinical cure and bacterial eradication rates. In patients with evaluable cultures, the microbiologic success rate was 88% for linezolid and 90% for vancomycin.

There are also several case reports describing the successful use of linezolid in treating resistant infections in children. Prokop and colleagues reported two cases of MRSA following trauma surgery treated with linezolid, one a 73 year old man and the other a 14 year old girl. Both were treated with a dose of 600 mg/day IV over 3 weeks. Graham and colleagues reported the successful treatment of a 7 month old infant with ventriculitis associated with a VRE infection of a ventriculoperitoneal shunt. A dose of 10 mg/kg was given IV every 8 hours for 21 days. Follow-up cultures were negative, and no adverse effects were noted.

Pharmacokinetics
The pharmacokinetic profile of linezolid has been studied in children, adolescents, and adults. Linezolid is rapidly absorbed after oral administration, with a bioavailability of approximately 100%. Peak plasma concentrations are typically achieved 1 to 2 hours after an oral dose. The drug is only moderately protein bound (31%) and has an average volume of distribution in adults of 0.6 L/kg. Linezolid is metabolized via oxidation to two inactive compounds. Nonrenal clearance accounts for approximately two-thirds of the total clearance. The rate of clearance in adults has been estimated at 0.1 L/hr/kg, with an elimination half-life of 4.5 to 5.5 hours. Dosage adjustment is not required in patients with renal or hepatic dysfunction. Linezolid is partially removed by hemodialysis (30%), and it is recommended that doses be given after dialysis.

Compared to values for adults, the volume of distribution of linezolid in children is larger, the clearance more rapid and the elimination half-life shorter. Kearns and colleagues of the Pediatric Pharmacology Research Unit Network studied the pharmacokinetic profile of linezolid in 58
children ranging in age from 3 months to 16 years. Fourty-four children were given a single 1.5 mg/kg intravenous dose, and 14 received a 10 mg/kg dose. A significant correlation was found between age and total body clearance. The mean volume of distribution was 0.73±0.18 L/kg, with a mean total clearance of 0.34±0.15 L/hr/kg, and a mean elimination half-life of 3.0±1.1 hours. By 12 hours, plasma linezolid concentrations were below the MIC₉₀ for selected pathogens, suggesting that a shorter dosing interval may be needed for younger children.

Clearance appears to undergo the most dramatic changes during the first weeks of life. In 2002, Jungbluth and colleagues reported the results of their study of linezolid pharmacokinetics in neonates and young infants. Forty-two patients less than 12 weeks postnatal age were each given a single 10 mg/kg IV dose of linezolid for assessment. Patients ≤ 1 week postnatal age had significantly slower rates of clearance than did infants > 1 week postnatal age. In patients ≤ 1 week at the time of the study who had been born at less than 34 weeks gestational age, the mean clearance was 1.99±0.96 ml/min/kg, compared to 3.95±2.00 ml/min/kg in those born at greater than 34 weeks gestational age. In patients > 1 week of age, clearance values were similar between the two groups (5.17±1.21 ml/min/kg in the patients less than 34 weeks and 5.39±1.60 ml/min/kg in the greater than 34 weeks group).

**Adverse Effects**

Linezolid appears to be well tolerated by most patients. Data from studies in children are similar to that in adults. In clinical trials of adults, the most common adverse effects associated with linezolid were diarrhea (4 to 8% of patients from pooled data), headache (2 to 6%), nausea (3 to 6%), myelosuppression (1 to 10%), vomiting (1 to 3.7%), altered taste or tongue discoloration (1 to 2%), and transient elevation in liver function tests (1 to 2%). In a summary published earlier this year of results from a compassionate-use program, the most frequent adverse effects were gastrointestinal disturbances (9.8%), thrombocytopenia (7.4%), anemia (4.1%), and rash (4%).

Because of the myelosuppression associated with linezolid, it is recommended that a complete blood count be monitored weekly, especially in patients on long-term therapy or in those with preexisting bone marrow depression or receiving drugs that produce this effect. Other serious, but rare, adverse effects associated with linezolid include the development of pseudomembranous colitis, changes in blood pressure, atrial fibrillation, and neuropathy.

**Drug Interactions**

Linezolid is a reversible, non-selective inhibitor of monoamine oxidase and may increase the effects of adrenergic drugs such as dopamine and epinephrine. If these agents are required during linezolid therapy, the initial dose should be reduced and slowly titrated to achieve the desired response. Patients should also be instructed to avoid cold remedies and decongestant products containing pseudoephedrine.

Linezolid may also potentiate the effects of serotonergic drugs such as the selective serotonin reuptake inhibitors. If linezolid is used in patients receiving these agents, there should be close monitoring for signs of serotonin syndrome, such as fever or mental status changes. Patients should avoid a high tyramine diet including foods such as aged cheeses and meats, soy sauce, sauerkraut, and alcohol.

**Availability and Dosing Recommendations**

Linezolid (Zyvox; Pfizer) is available as a 2 mg/ml injection in 100, 200, and 300 ml premixed bags, 400 and 600 mg tablets, and a 100 mg/5 ml suspension. In adults, the recommended dose of linezolid for patients with VRE, MRSA, nosocomial or community-acquired pneumonia, or complicated skin and soft tissue infections is 600 mg given IV or orally every 12 hours. In patients with VRE infections, the recommended duration of therapy is 14 to 28 days. For the other indications, a treatment period of 10 to 14 days is recommended. In patients with uncomplicated skin and soft tissue infections, the recommended linezolid dose is 400 mg given orally every 12 hours for 10 to 14 days.

In infants and children up to 11 years of age, the recommended dose of linezolid is 10 mg/kg every 8 hours. Children older than 12 years of age may be treated using the guidelines for adults. Pre-term neonates less than 7 days of age should receive the pediatric dose of 10 mg/kg at an interval of every 12 hours, to account for the slower rate of elimination.

Intravenous doses of linezolid should be administered over 30 minutes to 2 hours. Oral doses of linezolid may be taken with or without food. The oral suspension should be stored at room temperature and may be used for up to 3 weeks after reconstitution. The suspension dosage formulation contains 20 mg phenylalanine per teaspoon.

**Cost**

The average wholesale price (AWP) of a single 600 mg linezolid tablet is $56.31. Based on this
pricing, a typical 10 day oral treatment regimen would cost over $1,000. The oral suspension price is $281.56 for 150 ml. The premixed IV solutions are $38.10 for the 100 ml (200mg) size and $76.19 for the 300 ml (600 mg) size. There is currently no AWP information on the 400 mg tablet strength.\textsuperscript{19}

**Summary**

Linezolid is the first of a new class of antibiotics, the oxazolidinones, that provide activity against most Gram-positive infections, including vancomycin-resistant strains. A limited number of studies suggest that linezolid is safe and effective for the treatment of resistant infections in infants and children, but additional research is needed to more clearly define its role.

**References**


**Pharmacology Literature Review**

**Famotidine Kinetics in Renal Insufficiency**

In this study of 18 pediatric patients (1-18 years of age), famotidine pharmacokinetics were evaluated after a single IV dose of 0.5 mg/kg (max 20 mg). As anticipated, there was a linear relationship between clearance and severity of renal insufficiency. The authors suggest that dosing in children with renal insufficiency be based on creatinine clearance (CrCL). In children with CrCL \(\geq 50\) ml/min/1.73m\(^2\), the dosing interval should be every 12 to 24 hours. In those with CrCL between 10 and 50 ml/min/1.73m\(^2\), the dosing interval should be every 36 to 48 hours, and in patients with CrCL < 10 ml/min/1.73m\(^2\), the interval should be 72 to 96 hours or the dose may be decreased by 50% and given every 36 to 48 hours. Maples HD, James LP, Stowe CD, et al. Famotidine disposition in children and adolescents with chronic renal insufficiency. J Clin Pharmacol 2003;43:7-14.

**Formulary Update**

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 5/30/03:

1. Teriparatide (Forteo\textsuperscript{\textregistered}), a recombinant form of parathyroid hormone was added to the Formulary for the treatment of osteoporosis, with restriction to Endocrinology.
2. Aripiprazole (Abilify\textsuperscript{\textregistered}) was added to the Formulary. Use of this agent is restricted to patients under the care of a psychiatrist.
3. Escitalopram (Lexapro\textsuperscript{\textregistered}), a selective serotonin reuptake inhibitor for depression, was also added. Citalopram was removed from the Formulary.

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