Drug Therapy

Linezolid

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Linezolid is an oxazolidinone antibacterial agent that acts by inhibiting the initiation of bacterial protein synthesis. Linezolid has a wide spectrum of activity against gram-positive organisms including methicillin resistant staphylococci, penicillin resistant pneumococci and vancomycin resistant enterococcus faecalis and E. faecium. Linezolid has a good bio-availability orally and could be switched from parenteral to oral therapy while treating serious infections. Linezolid is well tolerated in children.

Keywords: *Gram-positive infections, Linezolid .*

Linezolid is a synthetic antimicrobial agent of the oxazolidinone class(1). It is chemically unrelated to currently available agents and inhibits bacterial protein synthesis.

Pharmacokinetic profile

Linezolid is rapidly and completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours and having a mean absolute bioavailability of 100%(2). The half life is approximately 4 to 6 hours. Linezolid is 31% protein bound and distributes widely to well perfused tissues. It has a good CSF penetration also.

Linezolid is primarily metabolized by oxidation of the morpholine ring, which results in two inactive ring-opened carboxylic acid metabolites. These two metabolites increase in patients with renal insufficiency, so caution is required while using during severe renal insufficiency. Both linezolid and the two metabolites are eliminated by dialysis so linezolid should be given after hemodialysis but no information is available of the effect of peritoneal dialysis on the pharmacokinetics of linezolid. Linezolid does not involve cytochrome P450, a major enzyme inducing system.

Mechanism of action

Linezolid inhibits protein synthesis. Linezolid prevents formation of the 70S ribosome complex that initiates protein synthesis by binding to the 23S subunit of the 50S subunit. Because of its unique binding site and its action at the early ribosome assembly step of protein synthesis, there is no cross resistance with other drug classes. Resistance is due to mutation of the ribosomal binding site(3,4). Resistance has been reported clinically only for enterococci, although resistant mutants have been selected from strains of *S. aureus* by passage of Linezolid *in vitro*(5).

Organism profile

Gram positive bacteria

- Linezolid shows good activity against *S. aureus* which is generally equivalent to that of vancomycin. *S. epidermidis* and *S. haemolyticus* have similar susceptibilities to linezolid and vancomycin.
- Linezolid is highly effective against penicillin resistant *streptococcus pneumoniae*. Additionally, linezolid remains active

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against strains of pneumococci resistant to ceftriaxone, erythromycin, clinda-mycin and tetracycline.

- Linezolid has activity against all *enterococcal* isolates tested, regardless of vancomycin resistance pattern.
- Linezolid has potent activity against other gram-positive organisms including *S. pyogenes, Bacillus* spp., *Corynebacterium* spp., *Listeria monocytogenes*, *Mycobacterium tuberculosis* and *Rhodococcus* spp.

Gram negative bacteria

Linezolid lacks significant effects against most gram negative pathogens but have in vitro activity against *Moraxella catarrhalis, Haemophilus influenzae, Legionella* spp., *Neisseria gonorrhoae* and *Bordetella pertussis*. *Pseudomonas aeroginosa* and enterobacteriaceae including *E. coli, Klebsiella pneumoniae* and *Proteus* are not susceptible to Linezolid.

Anaerobes

Linezolid demonstrated similar activity as vancomycin against *Clostridium difficile* and *C. perfringes.* Additionally, linezolid has good activity against gram negative anaerobes including *Bacteriodes* spp., *Fusobacterium nucleatum* and *Prevotella* spp.

Therapeutic uses

US Food and Drug Administration (FDA) has approved linezolid for the treatment of gram positive infection in infants and children.

Linezolid is an excellent alternative to vancomycin for the treatment of nosocomial pneumonia caused by methicillin resistant *Staphylococcus aureus*, including ventilator associated pneumonia(6,7). Linezolid is also a cost effective alternative to vancomycin for the treatment of ventilator associated pneumonia (8). In 1 year to 17-year-old children with community acquired pneumonia, Linezolid was well tolerated and could be considered alternative to vancomycin for serious infection caused by antibiotic resistant gram positive cocci(9).

Clinical success rates exceeding 89% were observed in adult patients with complicated and uncomplicated skin/soft tissue infections(10). Linezolid also exhibited similar efficacy to oxacillin / dicloxacillin and vancomycin(11).

Linezolid has shown good CSF penetration and thus seems a promising candidate for treatment of CNS infections(12). Intravenous linezolid appears to be safe and effective therapy for vancomycin resistant enterococcus meningitis(13,14).

Linezolid should be reserved as an agent of last resort for treatment of infections caused by multiple drug resistant strains. It should not be used when alternative agents are likely to be effective. Indiscriminate use and overuse will hasten selection of resistant strains and the eventual loss of this valuable new agent.

Adverse effects

The drug seems to be well tolerated, with generally minor side effects. Drug related adverse events occurred in 32.7% of patients, were generally mild to moderate intensity, resolved during continuous linezolid treatment, and were not dose-related. The most commonly occurring drug related adverse events were nausea (5.4%), diarrhea (5.2%), tongue discoloration (2.5%), oral moniliasis (2.3%), taste perversion (2.3%) and headache (2.3%). Thrombocytopenia or a significant reduction in platelet count has been associated with linezolid. The reported incidence is 2.4% and its occurrence is related to duration of therapy.

Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving linezolid but when linezolid was discontinued, the affected hematologic parameters rise towards pretreatment levels. Weekly monitoring of complete blood count should be done in patients who receive linezolid, particularly in those who receive linezolid for longer than 2 weeks, those with preexisting myelosuppression, those receiving concomitant drugs that produce bone marrow suppression, or those with a chronic infection who have received previous or concomitant antibiotic therapy. Linezolid should be discontinued in patients who develop or have worsening myelosuppression. People who are at increased risk of bleeding disorders or have low platelets should get their platelet count monitoring during linezolid treatment. Recurrent nausea and vomiting due to lactic acidosis has been reported with the use of linezolid. In patients who present with diarrhea subsequent to administration of linezolid possibility of pseudomembranous colitis should be considered as with all antibacterial agents.

Linezolid is a reversible, nonselective inhibitor of monoamine oxidase (MAO), and a potential interaction with adrenergic or serotonergic agents is possible. Patients should avoid consuming food or beverages containing tyramine since pressor response was observed when administered with tyramine. Dopamine, epinephrine or decongestants containing pseudoephedrine may also produce an exaggerated pressor response. Careful dosing titration is recommended when initiating dopamine or epinephrine.

Several incompatibilities have been reported on coadministration with amphotericin B, ceftriaxone, chlorpromazine, diazepam, erythromycin, phenytoin, and trimethoprim-sulfamethoxazole(11).

Disease interactions

Caution is advised if one has a history of high blood pressure, hyperthyroidism, pheochromocytoma, carcinoid syndrome, thrombocytopenia or other bleeding disorders, diarrhea, or decreased kidney function.

Over dosage

In the event of over dosage, supportive care is advised with maintenance of glomerular filtration. Hemodialysis may facilitate more rapid elimination of Linezolid.

Dosage and administration

Oral and parentral dosage forms:

- Children - 10 mg/kg every 12 hours.
- Adults - 600 mg every 12 hours.

The duration of treatment for most of the infections like pneumonia including community acquired pneumonia and skin infections is 10-14 days. It is advised to give therapy for 14-28 days in Vancomycin resistant enterococcal infections.

Linezolid is available as tablets containing 600 mg (linospan, lizomed, linox, lizbid), as injections of 100 mL and 300 mL containing 2 mg/mL (linospan, linox IV) and oral suspension (20 mg/mL). Cost of a tablet is Rs. 75-100 and 100 ml injection is Rs. 150-200.

IV administration: IV administration of drug should be done over 30-120 min.

Pregnant and lactating mothers: Adequate human studies have not been done in pregnant and lactating females so risk and benefits of using this drug should be considered individually.

Unique features

- Outstanding activity against variety of gram positive organisms
- Novel mode of action makes cross resistance unlikely
- 100% bioavailability allows rapid switch over from i.v. to tablets
- No dosage adjustment required in patients with hepatic impairment and renal impairment
- Safe and well tolerated

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