Review Article

Linezolid: A Hope Against Gram Positive Bacteria

***Saha S[1], Rizwan ASM[2], Islam MM[3], Islam S[4] , Uddin SAM[5]**

Abstract :

Linezolid is an oxazolidinone antimicrobial agent which inhibit protein synthesis by blocking the formation of the 70S ribosomal initiation complex. Linezolid has almost 100% bioavailability after oral administration and the safety and tolerability of this drug are excellent.It has been approved for the treatment of infections caused by vancomycin-resistant Enterococcusfaecium(VRE), methicillin-resistant Staphylococcus(MRSA), hospital-acquired pneumonia caused by Staphylococcus aureus, complicated skin and skin structure infections and communityacquired pneumonia caused by Streptococcus pneumoniae. linezolid resistance among these pathogens remains low, commonly < 1% although the prevalence of resistance is reported in many countries. Considering the potentiality of linezolid in the treatment of infections caused by Gram-positive bacteria, this review was undertaken.

Key words: Antibiotic, Bacteria, Gram positive,Linezolid, MRSA, VRE.

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Introduction:

Linezolid is the first member of oxazolidinone group which was introduced in 1978 for its effectiveness in controlling plant diseases. Six years later, their antibacterial characteristics, with significantly improved antibacterial properties relative to their progenitor compounds, were documented.[1] Vancomycin and teicoplanin are traditionally considered the drugs of choice for treating complicated gram-positive infections but development of resistance against these drugs was create an impulse among the scientists to find out a new antibiotic. In addition, vancomycin cannot be given orally for its poor intestinal absorption. The emergence of VRE was initially recognized by CDC in the 1980s and they published a report after studying nosocomial infections due to VRE in ICU patients.[2,3] On the contrast teicoplanin is a good option against gram positives but its toxicity requires continued observation of levels in parenteral administration.[4,5] The increasing prevalence of MRSA has become a major therapeutic problem for the hospital infection which causes extra treatment costs and longer hospital staying.[6] In the last 40 years, oxazolidinones have been considered as new class of antibiotics which are currently used in clinics specially linezolid[7] and showing a new hope against gram positive organisms.

1. Dr. Sanjoy Saha, Associate Professor, Department of Pharmacology, Ad-din Sakina Women's Medical College, Jashore, Bangladesh.

2. Dr. ASM Rizwan, Assistant Professor, Department of Medicine, Ad-din Sakina Women's Medical College, Jashore, Bangladesh.

3. Dr. Mir Moyeedul Islam, Associate Professor, Department of Pharmacology, Ad-din Sakina Women's Medical College, Jashore, Bangladesh.

4. Dr. Serajul Islam, Associate Professor, Department of Community Medicine, Ad-din Sakina Women's Medical College, Jashore, Bangladesh.

5.Dr. Sk. Amin Mohi uddin, Assistant Professor, Department of Anatomy, Ad-din Sakina Women's Medical College, Jashore, Bangladesh.

***Correspondence:** dr.sanjoysahammc@gmail.com

Mechanism of action of linezolid

Linezolid is a synthetic antibiotic which prevents the synthesis of bacterial protein via binding to rRNA on both the 30S and 50S ribosomal subunits.[8] It inhibits the formation of initiation complex which can reduce the length of the developed peptide chains and decrease the rate of translation reaction.[8] Linezolidhas a unique binding site of inhibition so development of cross-resistance to other protein synthesis inhibitors has not yet been decumented.[9] Linezolid may also prevent the expression of virulence elements which cause minimum toxin production by the gram-positive pathogens.[10]

Pharmacokinetics

Linezolid is well absorbed orally with a bioavailability of almost 100%.[1,11]The presence of food does not affect its absorption;[5] therefore, the administration route of antibiotic can be changed from intravenous (IV) to oral in clinically stable patients.[6] Co-administration with antacids like magnesium hydroxide and aluminum hydroxide have no effect on the oral absorption.[12] Plasma protein-binding level of the molecule is approximately 31%. The volume of distribution approximates 40–50 L, and the plasma half-life ranges from 3.4 to 7.4 h. The compound is metabolized to inactive forms including hydroxyethylglycine and aminoethoxy-acetic acid.[12] The clearance rate is 80±29 mL/min and renal tubular reabsorption may occur. A fraction of the dose may be excreted urine in active form.[13]

Mechanism of Resistance

Structures of linezolid showed that it binds to a deep cleft of 50S ribosomal subunit that is surrounded by 23S rRNA nucleotides.[14,15] Mutation of 23S rRNA has been established as one of the linezolid resistance mechanisms. Moreover, mutations in particular regions of ribosomal proteins uL3 and uL4 are increasingly being associated with linezolid resistance, although these proteins are placed further away from the bound drug.

Clinical Uses and Spectrum of Linezolid

Linezolid has been approved for the treatment of the following conditions: 1. Hospital-acquired pneumonia caused by Staphylococcus aureus, including methicillin-susceptible (MSSA) and methicillin-resistant S. aureus (MRSA) strains or Streptococcuspneumoniae including multidrug-resistant strains; 2. Vancomycinresistant Enterococcus faecium infections; 3. Complicated skin and skin structure infections (SSIs) including diabetic foot infections without concomitant osteomyelitis, caused by S. aureus (MSSA and MRSA), Streptococcus pyogenes, or Streptococcus agalactiae; 4. Uncomplicated SSSIs caused by MSSA or S. pyogenes; 5. Community-acquired pneumonia caused by S. pneumoniae, including cases with simultaneous bacteremia, or MSSA[9] and;6. Pneumococcal meningitis caused by penicillin-resistant S. pneumoniae. [10]

Adverse Effects

Adverse effects of linezolid are peripheral[16] and ocular[17] neuropathy, anemia that occurs by direct effect of linezolid on red cell population of bone marrow[18], diarrhoea, thrombocytopenia[19], hyperlactatemia[18], nausea, headache[20,21] hypoglycemia[22] and reticulocytopenia.[23]

Drug Interactions

Linezolid can be safely co-administered with aztreonam; however, there is no enough evidence about the interaction between linezolid and rifampin.[17] Co-administration with ceftazidime, ciprofloxacin, meropenem, and gentamicin-have no adverse effect. Using linezolid with amphotericin B and azoles;aminoglycosides, antivirals, fluoroquinolones, or β-lactams do not affect their sufficiency. It therefore seems that linezolid can be used with other antimicrobials with no interaction.Linezolid can cause life-threatening serotonin toxicity when combined with serotonin reuptake inhibitors.[24, 25]

Conclusion

Linezolid is an excellent and promising new antibiotic for the treatment of resistant gram-positive pathogens having number of favourable characteristics which includes a spectrum of activity against MDR agents, good tissue penetration into

skin, bone, muscle, fat, alveolar cells, lung extracellular lining fluid, blister fluids and cerebrospinal fluid.It has near 100% bioavailability when administered by oral route and a unique mechanism of action involving inhibition of protein synthesis at a very early stagewhich avoids cross-resistance with existing antimicrobials.So pharmacovigilance should be implemented to detect adverse effects in a broad scale as well as prescribers should be more couscous regarding its rationality and development of resistance as a public health practice.

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