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INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/11789
DOI URL: http://dx.doi.org/10.21474/IJAR01/11789

RESEARCH ARTICLE

LINEZOLID AND ITS ROLE IN DRUG RESISTANT ENDODONTIC INFECTIONS: A REVIEW

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Manuscript Info

Manuscript History
Received: 25 July 2020
Final Accepted: 28 August 2020
Published: September 2020

Key words: -
Linezolid, Drug Resistant Infection, Structure, Mechanism of Action, Antimicrobial Activity, Adverse Effects, Role in Endodontics

Abstract

With fast emerging multiple drug resistant infections in dentistry, every dentist should be aware of drugs available to treat such infections.Linezolid is an oxazolidinone antibacterial agent that acts by inhibiting the initiation of bacterial protein synthesis. It 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. The drug is well tolerated in both adults and children with a relatively good safety profile. It can also be used as an intracanal medicament to sterilize root canals in failed endodontic treatment. This article spotlights the salient features of this relatively safe drug with very few drug interactions.

Introduction:-

Use of broad-spectrum antibiotics in dental settings for therapeutic and prophylactic purpose has increased in an alarming fashion. This leads to development of drug resistance and treatment failure. These antibiotic resistant strains pose a major threat in patients especially those who are immunocompromised. Dentists should be well aware of the antibiotics that can be used for resistant infections. Linezolid is an antibiotic that can be used for resistant infections. Linezolid is the first member of the class oxazolidinone antibiotic. In 1978, oxazolidinone was introduced to treat plant diseases. It can be used systemically and as an intracanal medicament.

Drug resistance in dentistry:

The Infection Research Group of Glasgow Dental Hospital and School studied among 155 viridans group streptococci for their "Minimum Inhibitory Concentrations (MICs) to penicillin, amoxicillin, ceftriaxone, erythromycin, clindamycin, rifampicin, vancomycin, and teicoplanin" and revealed that 27% of S. oralis were resistant to penicillin, 51% resistant to erythromycin, and 6% resistant to clindamycin. Further, 11% of S. mitis were resistant to penicillin, 40% resistant to erythromycin and 3% resistant to clindamycin. Penicillin-resistant pathogens were also shown to be less sensitive towards other antimicrobials. [1]

Researchers of the Barkatullah University, India, studied sensitivity on gram-positive cocci (e.g., Streptococcus mutans, S. sobrinus, S. oralis, and S. sanguinis) and bacilli (Lactobacillus acidophilus, L. rhamnosus, L. fermentum). These pathogens show resistance for each antibiotic in this research as follows: "penicillin V: 72/150 (48%),

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tetracycline: 99/150 (66%), amoxicillin: 135/150 (90%), cloxacillin: 117/150 (78%), and erythromycin: 90/150 (60%). [2]

Another study from Nepal identified that 91% of invading pathogens were gram-positive and 9% were gram negative. Streptococcus mutans were resistant to penicillin (66.15%), tetracycline (60.76%), and cotrimoxazole (20%). S. aureus was found to be resistant towards penicillin (91.48%), tetracycline (86.17%) and ampicillin (61.70%). S. mitis was resistant to tetracycline (78.12%) and ciprofloxacin (65.62%). Pseudomonas spp. were 100% resistant to tetracycline and cotrimoxazole was 90.90%. [3]

Janaki medical school researchers documented gram-positive microorganisms were sensitive towards ciprofloxacin, gentamicin, and erythromycin 94.27%, 51.85%, and 49.49% respectively. The gram-negative organisms were sensitive to ciprofloxacin, imipenem and gentamicin, and ceftriaxone 100%, 89.28%, and 50% respectively. [4]

Another study from Brazil revealed that oral pathogens were highly resistant to ampicillin, amoxicillin+clavulanic acid, cefoxitin, cephalothin, amikacin, chloramphenicol, and nalidixic acid. This study also reported that carbapenems (meropenem and imipenem) were the most active antimicrobial agents and 1.6–2.3% pathogens showed resistance toward these medicines. Low resistance profile was also observed with ciprofloxacin and rifampicin. [5]

A Mexican study conducted among 60 children with active infections in the primary dentition revealed that Clindamycin in 8 lg/mL and 16 lg/mL exhibited the maximum (85.9%) microbial resistance followed by amoxicillin (43.7%) and amoxicillin-clavulanic acid (12.0%). [6]

The prevalence of antibiotic resistant strains of organisms in dentistry stress the need for reserve drug like linezolid to treat severe and resistant cases. With the emergence of Methicillin Resistant Staphylococcus aureus (MRSA) and Vancomycin Resistant Staphylococcus aureus (VRSA) in the community, resistant infections are becoming more common especially in patients with AIDS, diabetes, kidney transplant and dialysis and chemotherapy patients. In dentistry, MRSA is known to colonize the saliva. [7]

Structure of linezolid (FIG: 1):
The chemical structure of linezolid is $C_{16}H_{20}FN_3$ O4 and its molecular weight is 337.35g/mol. The N-aryl group and 5-S configuration are essential for its activity. Morpholino oligomer enhances pharmacokinetics and water solubility.

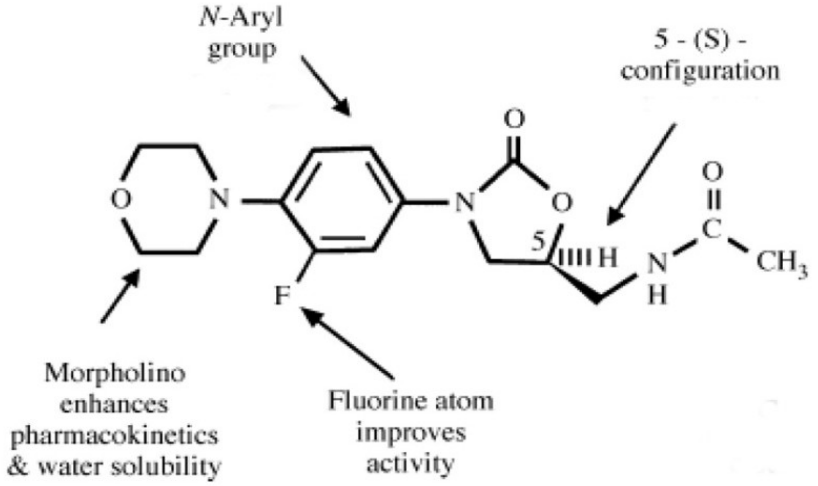

Fig 1:- Structure of linezolid.

Mechanism of action:
Linezolid 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 developing peptide chains and decrease the rate of translation reaction. The initiation process at the site of inhibition, however takes

place prior to that of other protein synthesis inhibitors that prevent the elongation procedure. Because of the unique site of inhibition, cross-resistance to other protein synthesis inhibitors has not yet been demonstrated. [9] Linezolid also prevent the expression of virulence elements leading to decreased toxins produced by gram-positive pathogens. [10]

Antimicrobial activity

Gram positive bacteria: Linezolid shows good activity against S. aureus, S. epidermidis, S. haemolyticus, penicillin resistant streptococcus pneumonia, 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 has in vitro activity against Moraxella catarrhalis, Haemophilus influenzae, Legionella spp., Neisseria gonorrhoaeand Bordetellapertussis. Pseudomonas aeroginosa, 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. perfringens. Additionally, linezolid has good activity against gram negative anaerobes including Bacteriodesspp., Fusobacterium nucleatumand Prevotellaspp.

Pharmacokinetics:

Linezolid is very well absorbed orally with a bioavailability of 100%. [11][12] The presence of food does not affect its absorption. [8]Plasma protein-binding level of the molecule is approximately 31%. The plasma half-life ranges from 3.4 to 7.4 h. The compound is metabolized to inactive metabolites -hydroxyethyl glycine and aminoethoxy-acetic acid. [13]The clearance rate is 80±29 mL/min, through both nonrenal and renal mechanisms. Renal tubular reabsorption may take place. A fraction of the dose is excreted in unaltered form in urine. [14]Plasma concentrations of linezolid in elderly patients, and patients with mild-to-moderate hepatic damage or mild-to-chronic renal failure were similar to those obtained in healthy or young volunteers. Patients with severe renal impairment with the requirement for hemodialysis, have seven to eightfold higher exposures to the drug metabolites than patients with normal renal function. Clearance of linezolid is shown to be higher in children compared to adults. This can lead to higher requirement of daily doses of drug per kilogram of body weight in children. [13]

Forms & strengths:

1. Injectable solution: 2mg/mL (100mL, 300mL infusion bags)
2. Oral suspension: 100mg/5mL
3. Tablet: 600mg

Dosage:

Oral and parenteral dosage: Doses of linezolid are administered every 12 hours

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

Vancomycin-resistant Enterococcus faecium infections, including concurrent bacteremia: 600 mg IV or by mouth every 12 hours for 14 to 28 consecutive days. Shorter courses of therapy (i.e., 10-14 days) may be suitable for other types of infections.

Linezolid injection should be administered over a period of 30 to 120 minutes. Do not use the intravenous infusion bag in series connections. Concomitant drugs should be administered separately. Adequate human studies have not been done in pregnant and lactating females so risk and benefits of using this drug should be considered individually.

Drug interactions:

Co-administration with Gram-negative antibiotics, ceftazidime, ciprofloxacin, meropenem, and gentamicin had no adverse effect. Besides, using linezolid with antifungal drugs such as amphotericin B and azoles, aminoglycosides, antivirals, fluoroquinolones and β-lactams did not affect their sufficiency. Linezolid can be safely co-administered with aztreonam; however, there is no enough evidence about the interaction between linezolid and rifampin. [15]

Linezolid can cause life-threatening serotonin toxicity when combined with serotonin reuptake inhibitors since it is a nonspecific inhibitor of monoamine oxidase.[16][17]Drugs that increase serotonin levels and interact with linezolid are selective serotonin reuptake inhibitor antidepressants [fluoxetine, sertraline, fluvoxamine], serotinin and norepinephrine reuptake inhibitor antidepressants[venlafaxine, duloxetine, mirtazapine], tricyclic antidepressants [amitriptyline], analgesics [tramadol, metadone, dextromethorphan, meperidine], antituberculosis drug[isoniazid]and anxiolytics[buspirone]. Features of serotonin toxicity are restlessness, confusion, dilated pupils, tachycardia and elevated blood pressure, twitching of muscles, loss of muscle coordination, heavy sweating and diarrhea.

Adverse side effects:

Linezolid is a relatively safe drug with an overall side effect of 1%. Gastrointestinal side effects associated with linezolid include diarrhoea (7.8%), nausea (3.7%), constipation (2%) and vomiting (2.9%). Recurrent nausea and vomiting may indicate that the patient is developing lactic acidosis. Other common side effects are headache (6.5%), insomnia, rashes, fever and dizziness. Less common side effects are oral moniliasis (0.5%), vaginal moniliasis, hypertension, dyspepsia, localised abdominal pain (1.3%) and pruritis (0.8%). Linezolid has been associated with anemia (0.9%), thrombocytopenia (0.7%) and neutropenia (0.2%) when given in the dose of 600mg for 28 days. Thrombocytopenia induced by linezolid occurs via a mechanism similar to that of quinine/ quinidine-induced immune mediated platelet destruction. The drug or metabolite binds to the platelet membrane glycoprotein IIb/IIIa, which then acts as an antigen to the immune system. Linezolid induced anemia and neutropenia is secondary to chloramphenicol like suppression of erythropoiesis. [18] As linezolid is a reversible inhibitor of human monoamine oxidase, it should be avoided along with tyramine rich foods [19] and caffeine. Foods containing considerable amount of tyramine include herring, meat that are pickled, smoked or fermented, yogurts, cheese, fermented plant foods such as alcoholic beverages, chocolate, bananas, dates, pineapple, red plumps and coconuts. Linezolid has been associated with reports of peripheral neuropathy [20] and optic neuropathy that has occasionally resulted in permanent loss of vision. Most of these side effects have occurred in patients who have been treated for more than 28 days. [21] Lactic acidosis has been associated with prolonged use (6.8%) [more than 28 days] of linezolid. [22]

Tooth discolouration has been reported after long duration of linezolid treatment (more than 28 days) and they are mostly reported in children. This tooth discolouration is of extrinsic type and is reversible (they can be removed by extensive cleaning). [23][24] Linezolid is rarely associated with lingua villosa nigra(1.3%) (Black hairy tongue). It's a benign and reversible condition and it can prevented by maintaining a good oral hygiene. [25]

Linezolid in endodontics:

During root canal therapy, biomechanical preparation and root canal shaping effectively reduce microbiota in the canals, but does not completely eliminate bacteria in lateral and accessory canals, isthmic and apical delta. Intracanal medication between appointments reduce bacteria from the complexities of root canal systems. Calcium hydroxide has been the most widely used intracanal medicament. Various studies have shown that E. faecalis resists the highly alkaline environment produced by calcium hydroxide dressing. [26] Hence alternate medicaments has been tried for eradicatingE. faecalisfrom complex root canals.

Linezolid has shown promising results in studies conducted against E. faecalis biofilm. In a study done by Sonali Taneja et.al., they compared the efficacy of linezolid, Nisin and calcium hydroxide in sterilising the root canal. In their study, linezolid gave the widest zone of inhibition followed by nisin and then calcium hydroxide. Also, the antimicrobial efficacy against E faecalis biofilm remained unchanged for linezolid and nisin group even after 7 days, whereas in calcium hydroxide group, the zone of inhibition decreased after 7 days. [27]

In another study by Rajdeep Pavaskar et al., in 2012, the intracanal effectiveness of calcium hydroxide and linezolid-based medicaments against Enterococcus faecalis was studied. It was found that linezolid was more effective against E. faecalis when compared to calcium hydroxide. [28]Rajdeep Pavaskar et al., again in the year 2014, compared the effectiveness of Chlorhexidine, Calcium hydroxide, Vitapex and Linezolid based intracanal medicaments against E. faecalis. In this study also linezolid was found to be more effective than 2% chlorhexidine, Vitapex and calcium hydroxide. [29]

Cytokines has been implicated in the development, maintenance and healing of periapical lesions. [30]The cytokines are low molecular weight proteins produced by immune cells and thereby function as signal substance between the host cells. In the presence of bacteria, monocytes/ macrophages produce proinflammatory cytokines such as

Interleukin (IL)- α, IL -β, Tumor necrosis factor – α and IL-6. John Danin et.al., studied the effect of systemic administration of linezolid on the levels of IL-1RA (receptor antagonist) in inflammatory periapical lesions (granulomas or cysts) associated with failed endodontic treatment. IL-1RA is a sensitive indicator of the effects of bacterial treatment on the severity of inflammation in periapical tissue. In their study, linezolid group exhibited a statistically significant decrease in the IL-1RA per millilitre of tissue compared with the control groups. This implies that linezolid help in healing process through cytokine activity in inflammatory periapical pathology. [31]

Conclusion:-

Linezolid is an effective antibiotic for treatment of resistant gram-positive infection with a good safety profile. It was found to be most effective against E. Fecalis. It can also be used as an intracanal medicament for sterilizing the root canal in resistant endodontic infections. Combined systemic and intracanal medication can be tried in large periapical lesions. Randomized clinical trials with longer follow up periods are needed to document the efficacy of this combination.

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