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BEYOND ANTIMICROBIAL THERAPY : A CASE SERIES OF LINEZOLID ASSOCIATED ADVERSE DRUG REACTIONS IN A TERTIARY TEACHING HOSPITAL

[1*] Rini Sara John, [2] Dr. Parvathy P.R,[3]Dr.Harikrishnan S ,[4]Dr. Akhil Joseph Issac

[1*] Department of Clinical Pharmacy, Nazareth College of Pharmacy, Othera, Thiruvalla, Kerala, India

[2] Assistant Professor, Department of Pharmacology , Believers Church Medical College Hospital , Thiruvalla, Kerala, India

[3, 4] Department of Clinical Pharmacy, Believers Church Medical College Hospital , Thiruvalla, Kerala, India

Abstract:

Linezolid is the first clinically approved oxazolidinone antibiotic, which is vitally used to treat multi drug-resistant gram-positive infections due to its excellent oral bioavailability, effective tissue distribution and favourable pharmacokinetics. Extended or inappropriate use has increasingly been linked to significant adverse drug reactions such as hematological related toxicity, metabolic, neurological and immune system complications. This retrospective case series describes ten patients who developed linezolid-associated adverse drug reactions during treatment. Cases were identified through adverse drug reaction monitoring centre and evaluated using medical records, medication history, laboratory findings, temporal association, management and other follow up outcomes. The adverse reactions included hypoglycaemia, anemia, leukopenia, thrombocytopenia, DRESS syndrome, peripheral neuropathy, hypotension and neuropsychiatric toxicity. Most reactions occurs in patients with potential risk factors such as advanced age, diabetes mellitus, renal dysfunction, malignancy or prolonged therapy. Causality assessment using the WHO-UMC and Naranjo scale classified most reactions as probable. Linezolid was discontinued in all cases, with supportive and specific management provided. All patients showed clinical improvement after discontinuation .These findings emphasize the need for early recognition, regular laboratory monitoring, and individualized risk assessment during linezolid therapy, particularly in vulnerable patients receiving prolonged treatment or significant comorbidities.

Keywords: *Linezolid, adverse drug reactions, myelosuppression, hypoglycemia, thrombocytopenia, leukopenia, peripheral neuropathy, DRESS syndrome, pharmacovigilance*

Corresponding author:
Rini Sara John,
Department of Clinical Pharmacy,
Nazareth College of Pharmacy, Othera,
Thiruvalla, Kerala, India

QR CODE

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INTRODUCTION:

Linezolid is the first clinically available oxazolidinone, antimicrobial agent and plays an important role in the management of multi drug-resistant gram-positive infections such as Methicillin resistant staphylococcus aureus (MRSA), vancomycin – resistant enterococcus (VRE), and resistant streptococcus pneumonia. Its high oral bioavailability, good tissue penetration, and availability in both intravenous and oral formulation make it a preferred choice for treating skin and soft tissue infections, pneumonia, bone infections, diabetic foot ulcers, and drug-resistant tuberculosis.

Linezolid act by binding to the 23 s rRNA of the bacterial 50 s ribosomal subunit ,thereby blocking the formation of the 70s initiation complex required for protein synthesis . Increasing clinical use has led to greater recognition of adverse drug reactions. This disruption affects energy production through oxidative phosphorylation, particularly in the bone marrow increasing risk of hematological toxicities such as anemia, leukopenia and thrombocytopenia.

In addition to bone marrow suppression, linezolid has been associated with less common but serious adverse drug reaction including hypoglycemia, peripheral neuropathy, lactic acidosis, serotonin syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), cardiovascular complications and neuropsychiatric disturbances. Factors such as older age, diabetes mellitus, kidney dysfunction, long duration, concurrent chemotherapy, and pre-existing hematological disorders have been identified as risk factors for these toxicities. These reactions may be resolved with early recognition, discontinuation of linezolid and appropriate supportive care.

This case series describe 10 patients who developed adverse drug reactions during linezolid therapy, emphasizing the importance for prompt identification, causality assessment, and appropriate management to improve outcomes.[1] [2] [3]

AIM

This study aims to describe the adverse drug reactions associated to linezolid in routine clinical practice, promote early recognition through active pharmacovigilance and highlight the importance of regular clinical and laboratory monitoring to enhance patient safety and treatment outcomes.

MATERIAL AND METHODS

We describe a series of 10 patients who developed diverse adverse drug reactions during treatment with linezolid. The reported adverse drug reactions include hypoglycemia (n=1), anemia (n= 2), leukopenia (n= 2), thrombocytopenia (n= 1), dress syndrome (n= 1), peripheral neuropathy (n= 1), hypotension (n= 1) and neuropsychiatric symptoms (n= 1).

Patient involved in this study aged between 29 to 80 years old and they were treated for conditions such as cellulitis, pneumonia, infective colitis, tuberculosis and other complex gram-positive infections.

A clear temporal association was observed between initiation of linezolid therapy and reactions. Discontinue the drug and provide supportive care led to full or partial recovery in every patient. Causality assessments using the WHO–Uppsala monitoring centre (WHO- UMC) system and the Naranjo scale classified most reactions as probable, with neuropsychiatric cases related as possible.

This retrospective case series included patients who developed suspected linezolid- related adverse drug reactions at a tertiary teaching hospital. Cases were identified via the adverse drug reaction monitoring centre following thorough review of medical records, medication history, laboratory results and follow up data. Only patients with well documented clinical information and plausible temporal connection between linezolid exposure and onset of suspected adverse drug reactions were included, supportive measures – were tailored to each patient's clinical condition, and outcomes were monitored during follow up.

Written- informed consent was obtained from all participants and confidentiality was strictly maintained throughout the study.

CASE SERIES:

CASE NO 1- LINEZOLID ASSOCIATED HYPOGLYCEMIA

A 61-year-old woman with poorly controlled type 2 diabetes, diabetic nephropathy, peripheral neuropathy, retinopathy, hypertension, hypothyroidism, acute kidney injury, vascular disease, a non –healing leg ulcer, and two weeks of fever presented to outpatient clinic. She was admitted with suspected right lower limb cellulitis and started on IV antibiotics, including linezolid 600 mg twice daily, while continuing her usual diabetes medications.

After taking linezolid, she experienced repeated episodes of dizziness, sweating, weakness, and altered mental status. After testing blood glucose testing

showed 68 mg/ dl, to confirms symptomatic hypoglycaemia. Further evaluation ruled out worsening kidney function, sepsis progression, adrenal insufficiency, liver problems, medication errors or poor food intake. After taking linezolid hypoglycaemic episodes occurs a drug induced causes were suspected. Linezolid was stopped and her glucose levels stabilized.

CASE NO 2- LINEZOLID ASSOCIATED ANAEMIA

A 76-year-old woman with rheumatoid arthritis, type 2 diabetes and hypertension presented with severe fatigue, weakness, shortness of breath, and palpitations. She had recently undergone surgery for infected bursitis and was prescribed linezolid postoperatively for a gram positive infectious. During prior hospitalization she developed thrombocytopenia which required linezolid discontinuation.

On admission she showed marked pallor but no active bleeding. Lab tests revealed moderate anaemia. A blood smear showed a mix of normocytic and microcytic red cells with increased reticulocytes. Iron studies indicated deficiency, while coombs test, LDH, and haemolysis markers were negative. She received two units of packed red blood cells and improved clinically. After stopping the drug, the Hb levels remain stable.

CASE NO 3- LINEZOLID ASSOCIATED LEUKOPENIA

A 63-year-old woman with triple negative breast cancer undergoing chemotherapy was admitted for left lower limb cellulitis. Initial treatment with ceftriaxone was escalated to piperacillin - tazobactam and then to IV linezolid 600 mg twice daily due to inadequate response. During her stay, serial blood counts showed a progressive drop in white blood cells to 3200 / mm3. Chemotherapy –related suppression was considered but no infection, viral illness or blood disorder explained the leukopenia. After stopping linezolid, white cell counts gradually recovered without needing growth factor support.

CASE NO 4- LINEZOLID ASSOCIATED DRESS SYNDROME

A 74-year-old man with diabetes, hypertension, chronic kidney disease, coronary artery disease, stroke history, and hyperparathyroidism presented with fever, chills and worsening redness in his left leg. He was started with linezolid due to cellulitis and about a week later he developed high fever, intense itching and a widespread maculopapular rash affecting trunk and arms. On examination he had facial swelling and difficulty swallowing. Lab showed eosinophilia, elevated inflammatory markers and increased liver enzymes .Other testing ruled out infections, autoimmune conditions and other drug causes. Based on clinical features a diagnosis of linezolid induced dress syndrome was made. Then the drug was stopped immediately and then the condition improved progressively .

CASE NO 5- LINEZOLID ASSOCIATED CHRONIC IRON DEFICIENCY ANAEMIA

A 35-year-old female nurse with a history of heavy menstrual bleeding presented with fatigue, weakness , palpitations , breathlessness and leg pain. One month earlier she had completed a course of oral linezolid 600 mg twice daily for community acquired pneumonia. Lab tests revealed iron deficiency anaemia (haemoglobin initially 8.5 g/dl , dropping to 7.5 g/dl in hospital) .Platelet count and blood smear were normal , iron studies confirmed deficiency . Imaging showered resolving pneumonia, with no signs of active bleeding, haemolysis or other causes. Chronic blood loss from menorrhagia possibly worsened by transient myelosuppression from linezolid, was considered the most likely explanation .She received iron supplements, nutritional advice and referrals to haematology and gynaecology .Blood counts improved gradually after stopping linezolid and she was discharged in good condition.

CASE NO 6- LINEZOLID ASSOCIATED THROMBOCYTOPENIA

An 80-year-old man with type 2 diabetes mellitus , hypertension and newly diagnosed pneumonia presented with abdominal pain , bloating and diarrhoea lasting three days . He was diagnosed with infective colitis and managed supportively. Due to suspected gram-positive involvement, oral linezolid 600 mg once daily was added.

His initial platelet count was normal , but serial tests showed a gradual decline to 136×10^9/l . He remained asymptomatic – no bruising, petechiae , or mucosal bleeding . Workup excluded disseminated intravascular coagulation , sepsis , viral infections , hypersplenism and other blood disorders . Given the temporal association and absence of other causes , linezolid induced thrombocytopenia was suspected . The drugs were stopped , and he was monitored conservatively . Platelets count improved without transfusing and gastrointestinal symptoms resolved .he was discharged stable with advice to avoid linezolid . The reaction classified as probable.

CASE NO 7- LINEZOLID ASSOCIATED PERIPHERAL NEUROPATHY

A 29-year-old woman with tuberculous meningitis and hydrocephalus was receiving oral linezolid 600 mg daily as part of her antitubercular regimen , along with clofazimine and other drugs . She had been on linezolid for about ten months (January to November 2023) . After prolonged use , she gradually developed numbness and tingling in both legs which began to affect walking and daily activities . Neurological exam showed reduced sensation around the ankles and knees though muscle strength was s preserved . Test for vitamin B12 , thyroids function , glucose , kidney and electrolyte were normal . She had no history of diabetes , alcohol use or exposure to other neurotoxic drugs. Given the long duration of therapy and lack of alternative explanations, linezolid induced peripheral neuropathy was suspected, the drug was discontinued and she began physiotherapy , vitamin supplementation and follow up . Symptoms improved gradually m thigh mild tingling persisted .The reaction was classified as probable.

CASE NO 8 – LINEZOLID ASSOCIATED HYPOTENSION

A 74-year-old female with a history of type 2 diabetes mellitus , hypertension , and hypothyroidism was admitted to the hospital with symptoms of sepsis. After initial assessment , the patient was placed on intravenous fluid resuscitation and received oral linezolid (600 mg twice a day) as an empiric antibiotic for gram positive sepsis . Nearly a week later , the patient developed sudden hypotension with accompanying dizziness and weakness . Her blood pressure was around 100 mm Hg and was not responsive to intravenous fluids. After extensive cardio monitoring , no arrhythmia or myocardial ischemia was detected . No active bleeding , adrenal insufficiency or septic shock was detected on examination . Routine laboratory tests and ECG were unremarkable . The likely causes of hypotension was linezolid induced vasodilation because of the temporal relationship between linezolid administration and hypotension development . Symptomatic treatment was given , and linezolid was discontinued .Her blood pressure gradually improved over the following days with no recurrence of hypotension .The patient was discharged in good clinical condition .

CASE NO 9 – LINEZOLID ASSOCIATED LEUKOPENIA

A 63-year-old female with history of type 2 diabetes mellitus and vulvar carcinoma presented with painful unilateral; leg swelling, erythema and tenderness .The patient had no history of haematological diseases ,and her routine blood tests were withing normal limits before treatment initiation .Oral linezolid (300 mg twice daily) was prescribed for suspected gram-positive cellulitis .During the course of treatment , the patient received linezolid for 2 days with no signs of improvement . Serial blood tests revealed a gradual decrease in total WBC from about 3200 to 2700 cell/mm3 .Throughout her hospitalization , the patient remained afebrile with gradually resolving cellulitis symptoms . An extensive work up was done , ruling out bacterial sepsis , viral infections , nutritional deficiencies , autoimmune disease and other medication side effects that could contribute to leukopenia .Based on the temporal link between linezolid and leukopenia along with absence of other factors linezolid induced leukopenia was considered . The patient condition gradually improved without any supportive therapy after linezolid discontinuation and was discharged in good clinical condition.

CASE NO 10 - LINEZOLID ASSOCIATED NEUROPSYCHIATRIC TOXICITY

A 55-year-old male with history of coronary artery disease was admitted to the hospital for treatment -t of an acute infectious disease .Oral linezolid (600 mg twice daily) was initiated after diagnosis with a gram-positive infection .Before admission ,the patient was alert and oriented with no reported of mental illness or psychiatric disorders .

A few days after linezolid initiation , the patient developed sudden neuropsychiatric symptoms. He became increasingly agitated , confused and was reported to have been showing signs of restlessness , irritability and occasional delirium .His close relatives stated that he appeared to be acting strange after receiving antibiotic treatment . Following extensive assessment , hypoglycaemia , electrolyte imbalance, hepatic encephalopathy , acute cerebrovascular accident , meningitis , encephalitis and another infectious etiologist was rules out . Neuroimaging did not reveal acute findings . Then linezolid was discontinued and patient received supportive care with follow up .

Table no 1 – Clinical characteristics , adverse drug reactions, causality assessment , management and outcomes of patients with linezolid induced adverse drug reactions

Case	Age/sex	Primary diagnosis	Linezolid regimen	Adverse drug reaction	WHO - UMC	Naranjo	Intervention	Outcome
1	61/F	Right lower limb cellulitis	600 mg IV twice daily	Hypoglycemia	Probable	Probable	Linezolid discontinued , IV glucose , glucose monitoring adjustment done	Recovered
2	76/F	Post surgical infected bursitis	600 mg orally once daily	Anemia	Probable	Probable	Linezolid discontinued and RBC transfusion done	Recovered
3	63/F	Left lower limb cellulitis	600 mg IV twice daily	Leukopenia	Probable	Probable	Linezolid discontinued and monitoring done	Recovered
4	74/M	Cellulitis	600 mg IV every 12 H	DRESS syndrome	Probable	Probable	Linezolid discontinued , systemic corticosteroids , antihistamines given	Recovered
5	35/F	Community acquired pneumonia	600 mg orally twice daily for 14 days	Iron deficiency anemia	Probable	Probable	Linezolid discontinued and iron replacement therapy done	Recovered
6	80/M	Infective colitis	600 mg orally once daily	Thrombocytopenia	Probable	Probable	Linezolid discontinued , platelet monitoring done	Recovered
7	29/F	Tuberculous meningitis	600 mg orally once daily	Peripheral neuropathy	Probable	Probable	Linezolid discontinued , physiotherapy and vitamin supplementation given	Recovered
8	74/F	Suspected gram positive sepsis	600 mg orally twice daily	Hypotension	Probable	Probable	Linezolid discontinued and supportive care provided	Recovered
9	63/F	Cellulitis	300 mg orally twice daily	Leukopenia	Probable	Probable	Linezolid discontinued , serial CBC monitoring done	Recovered
10	55/M	Gram positive infection	600 mg orally twice daily	Neuropsychiatric toxicity	Probable	Probable	Linezolid discontinued and supportive care provided.	Recovered

DISCUSSION:

This case series highlights the broad range of adverse drug reactions associated with linezolid in routine clinical practice. Haematological toxicity including anemia , leukopenia and thrombocytopenia were the most frequently observed followed by metabolic , neurological , cardiovascular and immunological complications. Most patients had one or more recognised risk factors such as advanced age, diabetes , renal dysfunction , malignancy, prolonged duration , or concomitant cytotoxic therapy .

Haematological toxicity was the most frequent issues in this case series. Previous studies has demonstrated that linezolid induces reversible mitochondrial dysfunction in bone marrow precursors, leading to suppressed blood cell production . Inhibition of mitochondrial protein synthesis impairs energy generation , resulting in temporary bone marrow suppression . All hematological abnormalities in these patients improved following discontinuation of linezolid , supporting the reversible nature of these toxicities a finding consistent with previous pharmacovigilance reports.

One patient develops hypoglycemia , despite having ,multiple comorbidities including diabetes and acute kidney injury .Although uncommon, such cases are increasingly reported , especially in diabetic patients on insulin or oral hypoglycemic agent. The proposed mechanism involve reversible inhibition of monoamine oxidase , which may increase insulin release and sensitivity. Prompt discontinuation of linezolid together with glucose supplementation resulted in complete clinical recovery of patient.
One patient developed Drug Reaction with eosinophilia and systemic symptoms (DRESS syndrome) , approximately one week later after initiation of Linezolid therapy. Although DRESS syndrome is most frequently associated with anticonvulsants , allopurinol and antimicrobial agents. Linezolid has being increasingly recognized as a rare but clinically significant causative agent. Prompt recognition, immediate discontinuation of Linezolid and initiation of systemic corticosteroids therapy, resulted in progressive clinical improvement which highlights the importance of early diagnosis and timely intervention.

Peripheral neuropathy occurred in a young patient after ten months of linezolid therapy for multi drug resistant tuberculosis .Long term exposure is known to causes cumulative mitochondrial damage in peripheral nerves. Although symptoms improved after discontinuation of Linezolid and initiation of rehabilitation, residual paraesthesia remained which indicate neurological recovery may be incomplete even with early action.

Hypotension and neuropsychiatric toxicity were rare adverse events in these patients. In both cases, thorough clinical assessments ruled out other potential causes , with symptoms emerging shortly after starting linezolid .The clinical improvement following discontinuation of Linezolid supported a likely causal association.

A key strength of this case series lies in its documentation of both common and uncommon manifestation of linezolid toxicity encountered in everyday clinical practice. In contrast to individual case reports these findings provide a more comprehensive overview picture of the spectrum of adverse effects linked to the drug. From a clinical pharmacy standpoint , these observations highlight the importance of baseline assessments and regular monitoring of complete blood counts, platelet levels , renal and liver function , blood glucose and neurological status during treatment . Consistent pharmacovigilance and multidisciplinary collaboration are crucial for timely identification and proper management of adverse drug events. [1] [2]

CONCLUSION:

This case series shows that linezolid even though it plays a part in treating infections that are resistant to many drugs can cause a wide range of serious side effects. These side effects are more likely when the drug is used for a time or in people with other health issues . In this group of patients with haematological issues like anemia, low white blood cell count and low platelet count were common. Other side effects like hypoglycemia, peripheral neuropathy ,a severe skin reaction called DRESS , hypotension and changes in mental state were less common but still very serious.
Most of the side effects happened when patients were taking linezolid and got better after stopping the medicine and getting care. This shows how important it is to spot these issues and act quickly. Older people , those with renal dysfunction, malignancy, diabetes mellitus , existing haematological toxicities and those getting strong treatments or those for a long time need extra attention. So when using linezolid it is important to do a check-up before starting and keep checking blood counts, platelet levels, kidney and liver function, blood sugar and nervous system health .Active tracking of side effects thinking about the risks and

benefits and working with a team of experts can help find and handle problems early.

Ethical approval: Institutional Review Board approval is not required.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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