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CASE REPORT

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A rare case report of linezolid induced thrombocytopenia

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ABSTRACT

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Introduction: Oxazolidinone like linezolid are widely used antibiotics because of the growing prevalence of resistant gram-positive infections. Because of its unique mode of action by inhibiting protein synthesis, it is widely effective against various resistant strains like penicillin-resistant and vancomycin-resistant strains of various gram-positive bacteria. It is widely used in the treatment of skin and soft tissue infection including MRSA and MSSA, also used in community-acquired pneumonia, and the combination is used in extensively drug-resistant tuberculosis. The most common side effect of linezolid includes gastrointestinal disturbances like nausea and vomiting. Serious adverse effects include Myelosuppression including thrombocytopenia, anemia, pancytopenia, and leukopenia. Peripheral neuropathy, optic neuritis, and lactic acidosis are also reported.

Case Presentation: Here we report a case of progressive but reversible thrombocytopenia in 75 years old male patient after receiving linezolid therapy for severe sepsis with multi-organ dysfunction with AKI on CKD with hepatic encephalopathy, severe hyponatremia with aspiration pneumonia. On the 9th day of linezolid, therapy thrombocytopenia was noted and immediately linezolid was stopped. After the 12th day, his platelet count went up which might be suggestive of linezolid induced thrombocytopenia.

Conclusion: Physicians should be more vigilant in monitoring complete blood count, especially in elderly patients who are receiving linezolid for more than two weeks. They should also make a risk assessment based on creatinine clearance, baseline platelet count, immunosuppression therapy, baseline hemoglobin, and prior/present antibiotics therapy so that adverse reactions can be prevented.

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Introduction

The growing prevalence of resistant gram-positive infection in the world leads to recognition of Oxazolidinone-like linezolid. It also gains popularity because of its distinguish pharmacokinetic profile. It works by inhibiting protein synthesis by binding to the P site of 23S ribosomal RNA of the 50S subunit and further preventing the formation of the larger ribosomal-fMet-tRNA complex which is useful in initiating the protein synthesis. It is widely effective against gram-positive bacteria like staphylococcus, streptococcus, enterococcus,

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etc. It is poorly active against most gram-negative bacteria. Because of their distinctive mode of action, they are very effective against various resistant strains like penicillin-resistant and vancomycin-resistant strains of various gram-positive bacteria (Tsuji *et al*., 2017).

It is well tolerated orally with 100% bioavailability and can be taken irrespective of food. Generally, the dosing regimen is the same for both oral and intravenous administration. It is usually 30 % protein-bound and widely distributed to well-perfused tissues (Manfredi *et al*., 2006). No dose adjustment is required in renal insufficiency. It is widely used in the treatment of skin and soft tissue infection including MRSA and MSSA, also used in community-acquired pneumonia, and in combination used also used in extensively drug-resistant tuberculosis (French *et al*., 2003).

The most common side effect of linezolid includes gastrointestinal disturbances like nausea and vomiting. Serious adverse effects include Myelosuppression including thrombocytopenia, anemia, pancytopenia, and leukopenia. Peripheral neuropathy, optic neuritis, and lactic acidosis are also reported. Here we report a case of progressive but reversible thrombocytopenia in an elderly patient after receiving linezolid therapy for severe sepsis with multi-organ dysfunction with AKI on CKD with hepatitis encephalopathy, severe hyponatremia with aspiration pneumonia (French *et al*., 2003).

Case report

A 75-year-old male patient came with complaints of altered sensorium for 2 days, loss of appetite, and decreased urine output for 3 days along with headache in the parietal region, dull aching, and continuous not associated with photophobia and phonophobia. He also had a diabetic foot ulcer. He was known for cases of type 2 Diabetes Mellitus and hypertension for 10 years and was irregular on medication. His CT scan brain revealed extradural hemorrhage along with right parietal convexity with the maximum thickness (11 mm). There is mild prominence of sulci and gyri with mild dilation of bilateral ventricle suggestive of cerebral cortical atrophy. It also revealed chronic small vessel ischemic changes. He was diagnosed with severe sepsis with multi-organ dysfunction with AKI on CKD with hepatitic encephalopathy, severe hyponatremia with aspiration pneumonia. He was prescribed with Inj. Meropenem (500 mg) IV 12 hourly, Inj. Levofloxacin (250mg) IV 24 hourly, Tab Linezolid (600 mg) BD. On the ninth day, his platelet count decreased to 60,000. After which Tab. Linezolid (600 mg) was kept on hold after three days of discontinuation i.e. on the twelfth day his platelet count went up to 1.5 lakh, which might be suggestive of linezolid induced thrombocytopenia. After that linezolid was stopped completely. No re-challenge was done. Laboratory data and Medication charts are mentioned in **Table 1** and **Table 2** respectively.

Medication chart

Table 1: Drugs therapy prescribed

Drug (Brand Name)	Generic Name	Dose	Frequency
Inj. Syscan	Fluconazole	200 mg	24 hourly
Inj. Meropenem	Meropenem	1 g	8 hourly
Inj.Levoflox	levofloxacin	500 mg	12 hourly
Tab. linezolid	Linezolid	600 mg	BID**
Inj Emset	Ondansetron	4 mg	SOS****
Inj Pan	Pantoprazole	40 mg	BID
Tab Sobsis	Sodium bicarbonate	500 mg	TID***
IVF NS	Normal saline	0.9% (60 cc/h)	2pint/day
Syp. Potklor	Potassium chloride	15mL with ½ glass water	TID
Tab. Moxonidine	Moxonidine	0.3 mg	BID
Tab. Telma	Telmisartan	40 mg	OD*
Tab Amlo	Amlodipine	10 mg	OD
Inj. HAI	Human Actrapid insulin	2U-2U-4U	TID

*OD- once daily, **BID- twice daily, ***TID- thrice daily, ****SOS- as and when required

Laboratory data:

Table 2: laboratory data

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12
Hb(g/dL)	10.1	10.2	10.5	10.9	11.3	10.7	10.6	10.7	10.8	10.9	10.9	11.1
Tc(10^3cells/mm^3)	48000	50000	38000	35500	30500	36000	3500	3300	3325	3125	3100	4000
Dc(%)(Neutrophil/Monocyte)	93/2	88/3	90/2	92/2	90/3	91/2	90/2	91/2	90/2	91/2	92/3	92/3
Eosinophils/ Basophils (%)	2/3	5/4	4/4	3/3	3/3	3/4	3/4	3/4	2/3	2/3	2/3	2/3
ESR(mm/h)	114				112							
Platelets($10^{3/}$ mm^3)	1.57	1.59	1.52	1.4	1.4	1.2	1.19	1	60000	50000	50000	1.5
Na (mEq/L)	112	106	109	117	124	127	130	131	132	130	132	132
K(mEq/L)	4.0	3.6	3.8	3.5	3.7	3.3	3.1	3.0	3.1	3.1	3.1	3.2
C(mEq/L)	81	78	79	89	92	96	97	98	98	99	99	99
Urea(mg/dL)	75		84	80	67	50		45	44	40	36	38
Creatinine (mg/dL)	4.2		3.9	3.0	1.8	1.4		1.3	1.2	1.2	1.2	1.2
Billirubin(mg/dL)	0.8				0.5							
SGOT (units/L)	125				57							
SGPT(units/L)	55				27							
CRP(mg/L)	103.59				48.03							
D-Dimer(ng/mL)						2990						
PCV(%)	28.9	28.6	31.2	29.4	30.3	29.7	30.1	30.2	31.2	31.4	31.4	31.5
MCV (µm3)	29.4	29.8	29.8	29.4	29.6	29.9	30	29.9	29.9	30.1	30.2	30
MCH(pg)	35.7	35.8	34.8	35.2	35.4	35.6	35.7	35.6	35.5	35.8	35.6	35.9
MCHC(g/dL)	35.7	35.8	34.8	36.2	36.1	35.8	36.7	36.8	36.2	37.3	36.8	36.4
RBC(10^6/mm^3)	3.41	3.43	3.76	3.56	3.78	3.78	3.70	3.79	3.76	3.78	3.77	3.70
RDW(%)	13.2	13.2	13.6	13.1	13.5	13.6	13.5	13.7	13.9	13.5	13.6	13.7

His HbA1C was 8.8 %, Urine osmolality was 165.2 mOsm/kg, Urine sodium, potassium, and chloride was 16

mEq/mL, 17 mEq/mL and 40 mEq/mL respectively. His creatinine clearance was 17 mL/min and BUN/Cr. ratio was 8.9 mg/dL.

Peripheral smear:

RBC: Normocytic Normochromic

WBC: leukocytosis with shift to right

Toxic changes in neutrophil in form of vacuoles and granules

Causality assessment

Causality and severity assessment has been done with the help of five different scales and results as mentioned in **Table 3**.

Table 3: Causality assessment

Scale's name	Result
Naranjo's algorithm	Probable
Hartwig and siegel	Moderate (Level 4)
Karch and lasagna	Probable
Who-Umc Scale	Probable

Discussion

Our case report is consistent with previously documented linezolid induced thrombocytopenia which is a serious adverse drug reaction (Waldrep *et al*., 2002; Sakka *et al*., 2009; Halpem *et al*., 2002; Cossu *et al*., 2014). On the 9th day of linezolid treatment, progressive thrombocytopenia was observed and linezolid was kept on hold. Even after discontinuation of linezolid therapy platelet count continued to decrease. Only after the 12th day (3rd day of holding linezolid therapy) its platelet count goes up. Meropenem and levofloxacin are also known to cause thrombocytopenia, but the adverse event resolved after discontinuation of linezolid therapy suggestive of linezolid induced thrombocytopenia. Naranjo's scale was used for causality assessment and categorized as possible adverse drug reaction (Naranjo *et al*., 1981).

The mechanism behind linezolid-induced thrombocytopenia is still unclear. It has been documented that drug-induced myelosuppression can occur by two major mechanisms: immune-mediated and direct toxic effects to hematopoietic cells. It is believed that linezolid-induced thrombocytopenia is immune-mediated rather than bone marrow suppression (Brenstein *et al*., 2003).

Risk factor for linezolid induced thrombocytopenia includes: Creatinine clearance < 30 mL/min , baseline Hb < 10.5 g/dl, baseline platelet count < 200*10^3 /mm^3 , prior /present treatment with antibiotics, immunosuppression therapy (Choi *et al*., 2019; Han *et al*., 2021). In our case baseline platelet count was < 200*10^3 /mm^3, Creatinine clearance < 30 mLmin, baseline Hb < 10.5 g/dLand antibiotics therapy of meropenem and levofloxacin was given which may be the risk factor for thrombocytopenia.

Conclusion

Linezolid-induced thrombocytopenia is reversible after discontinuation of the drug. The physician should be more vigilant in monitoring complete blood count, especially in elderly patients who are receiving linezolid for more than two weeks. They should also make a risk assessment based on creatinine clearance, baseline platelet count, immunosuppression therapy, baseline hemoglobin, and prior/present antibiotics therapy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. 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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Conflicts of interest

There are no conflicts of interest

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