A Case Report Of Linezolid (Lzd) Induced Complete Myelosuppression

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Abstract: Linezolid (Lzd) is an oxazolidinone group of antibiotic used for the treatment of serious infections caused by Gram-positive bacteria that cause disease, including streptococci, vancomycin-resistant enterococci (VRE), and methicillin-resistant Staphylococcus aureus (MRSA). Lzd is associated with adverse haematological effects particularly thrombocytopenia. But pancytopenia and complete myelosuppression is a rare adverse reaction. This is a case report of a 50-year male patient diagnosed as Lower limb cellulitis with septicaemia and was started on Tab. Lzd 600mg BD along with other drugs and supportive treatments. He developed pancytopenia after 4 days of treatment. Lzd was stopped. Patient's blood count improved significantly after 7 days of drug withdrawal. Hence physicians need to be aware of this rare but serious side effect of Lzd and the importance of routine haematological monitoring to decrease the morbidity and mortality. [Vedang T NJIRM 2017; 8(1):126-128]

Key Words: Linezolid (Lzd), Myelosuppression, Septicaemia

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Introduction: Linezolid (Lzd) is an antibiotic used for the treatment of serious infections caused by Gram-positive bacteria that are resistant to other antibiotics. It is a bacteriostatic antibiotic belonging to oxazolidinone group of antimicrobials that inhibits bacterial ribosomes by binding to the 23S ribosome and preventing the 30S-50S fusion [1]. Lzd is active against most Gram-positive bacteria that cause disease, including streptococci, vancomycin-resistant enterococci (VRE), and methicillin-resistant Staphylococcus aureus (MRSA) [2, 3].

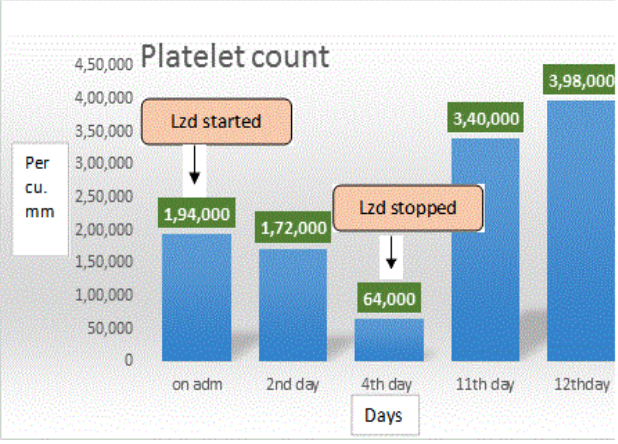
The principal toxicity of Lzd is haematological. Thrombocytopenia is the most common manifestation with prevalence rates of 15-50% but anaemia and neutropenia may also occur. Other side effects attributed to Lzd are optic neuropathies & lactic acidosis. All this Adverse drug reactions (ADRs) are particularly observed with prolonged courses of Lzd [4]. Our case report is unique since it reports complete myelosuppression with Lzd which is a rare adverse reaction and has been less documented in literature. In our case, it occurred shortly after initiation of Lzd therapyand not after prolonged therapy.

Case Report: This is a case report of a 50-year male patient who presented at emergency department with complains of fever with chills & right lower limb pain & swelling with one episode of loss of consciousness. In the hospital, patient was diagnosed as Right Lower limb cellulitis with septicaemia with septic shock & acute kidney injury with hypoglycaemia with no other significant past history. The patient had no known drug allergies and was prescribed Inj. Dopamine 2ampoule IV at 2ml/hr. in 50c.c. NS, Inj. Noradrenaline 2ampoule IV at 2ml/hr., Tab. Linox (Lzd) 600mg BD, Inj. Cefoperazone 1.5 gm IV BD, Inj. Metronidazole 100ml IV BD, Inj. Pantoprazole 40mg IV BD, Inj. Ondansetron 4mg IV BD. After 4 days of this treatment patient's blood investigations showed Pancytopenia (an abnormal deficiency of all blood cells). (Table 1, Figure. 1) Physician diagnosed it as a case of Lzd induced complete myelosuppression and stopped the suspected Tab. Linox(Lzd), Inj. Cefoperazone, Inj. Metronidazole were all discontinued and changed to Inj. Piperacillin & Tazobactam 4.5gm IV BD, Inj. Clindamycin 600mg IV OD and other supportive treatment. Since then the patient's blood count gradually increased and returned to normal after one-week cessation of Lzd therapy. With the initiation of intravenous hydration and blood transfusion and the discontinuation of Lzd, the patient's condition and blood counts improved in next 4 days of treatment. Patient's blood count report came normal after 1 week of this treatment started. Patient had an uneventful discharge thereafter. This case was reported to the nearest Pharmacovigilance centre with report ID: 2016-09618.

Table:1 Haematological parameters corresponding to day from the start and stopped of Lzd therapy.

Days	Haemoglobin Level (Hb Level) gm%	Total Leucocyte Count (TLC) cells/cumm
Baseline	12.0	17,000
2nd day	10.3	11,600
4th day	8.44	4,400
11th day	10.2	11,000
12th day	10.9	9,700

Figure. 1: Lzd induced Thrombocytopenia as depicted.



Discussion: Reversible myelosuppression including anaemia, leucopenia, pancytopenia and, in particular, thrombocytopenia has been reported and blood counts should be monitored weekly in patients receiving Lzd. Patients particularly at riskare those who have received Lzd for more than10 to14 days, who are receiving other bone marrow suppressant drugs, orwho have pre-existing myelosuppression or severe renal impairment [5].

In this case report Lzd induced myelosuppression was complete. There was not only thrombocytopenia but also fall in Haemoglobin and WBC count indicating serious Adverse Drug Reaction (Table 1). The myelosuppression could be more serious in this case because of patient's concomitant disease.

Prolonged treatment duration, renal insufficiency, chronic liver disease, malignancy, previous vancomycin use, baseline platelet count has been reported as possible risk factors for LZD-associated Myelosuppression [6].

On long term use, Bone marrow suppression, characterized particularly by thrombocytopenia (low platelet count), may occur during Lzd treatment; it appears to be the only adverse effect that occurs significantly more frequently with Lzd than with glycopeptides or beta-lactams [7,8]. Hence the authors have implicated linezolid as the suspected drug for the above ADR. However current label for Lzd carries 'Black Box' warning related to clinical myelosuppression. Lzd affects mitochondrial protein synthesis in mammalian cell as similar to chloramphenicol as they share common chemical structure [9]. An immune mediate phenomenon may be associated with this type of adverse reaction. Our case report differed from previous reports because myelosuppression occurred within 4 days of initiation of Lzd therapy. Our patient was receiving other antimicrobials like Cefoperozone and Metronidazole for which adverse haematological effects have been documented. Cefoperazone has been known cause platelet dysfunction primarily and cause hypoprothrombinaemia. Metronidazole is also known to cause temporary leucopenia and thrombocytopenia [5]. In our case report Lzd was identified as suspected drug because this has been documented in the literature in the past and patient's condition improved dramatically after withdrawal. Cefoperozone and Metronidazole are not associated with serious Myelosuppression. According to WHO-UMC Causality Assessment this Adverse Drug Reaction will fall under "Probable" category.

Although Lzd has a favourable pharmacokinetic profile and reported to be safe in patients with impaired renal function. The finding in our case may suggest Lzd accumulation leading to exaggerated Myelosuppression. This could also be explained by the patient's acute renal dysfunction [Acute Kidney Injury] which may lead to accumulation of Lzd[10]. In our patient the reaction had started within four days, and normal erythropoiesis was restored after the cessation of Lzd therapy.

Reversible myelosuppression with red-cell hypoplasia after therapy with Lzd has already been reported in Phase 3 clinical trials of Lzd (2.4%) and in other recent studies. Thus, Monson and co-workers reported a case of reversible pure red blood cell aplasia that developed in a patient who had been on Lzd therapy for 8 weeks, and Green and co-workers reported reversible Lzd-associated hypoproliferative anaemia in three patients who were receiving 600 mg Lzd twice daily for 6–12 weeks [8].

Hence physicians need to be aware of this rare but serious side effect of Lzd and the importance of routine haematological monitoring to decrease the morbidity and mortality.

Acknowledgment: We arethankful to the Dean of Smt. NHL MMC & Professor & Head of Emergency Medicine.

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Conflict of interest: None
Funding: None
Cite this Article as: Vedang T, Devang R, Sapna G, Supriya Ma.Linezolid (Lzd) Induced Complete Myelosuppression. Natl J Integr Res Med 2017; 8(1): 126-128