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Linezolid Therapy – A Cause of Bone Marrow Suppression in a Child

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Authors' contributions

This work was carried out in collaboration between all authors. Authors VA and AA diagnosed initially. All authors were involved in case management, drafting manuscript and literature review. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aim: To highlight the importance of monitoring rare side effects of commonly used drugs. Linezolid induced bone marrow (BM) suppression is rare side effect of therapy and rarely reported in the pediatrics age group.
Case Description: A seven year old patient, with persistent discharge from skull suture site following surgery, developed bone marrow suppression 28 days following the start of treatment with Linezolid. BM suppression was fully reversible following discontinuation of Linezolid and all cell lines returned to near baseline 2 weeks after the discontinuation of the drug.
Discussion: The potent activity of Linezolid against Gram-positive bacteria, and its excellent bioavailability after oral dosing, have made it an important addition to the antibiotic armamentarium. Linezolid is relatively a safer drug and BM suppression is a rarely reported side effect, which is particularly observed when the drug is administered for more than 14 days.
Conclusion: Case highlights the importance of weekly monitoring of complete blood counts in patients who receive Linezolid for more than 14 days.

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Keywords: Linezolid; bone marrow suppression; pediatric population.

1. INTRODUCTION

Linezolid is an antibiotic from the oxazolidinone group, particularly effective against gram positive microorganisms including vancomycin-resistant *Enterococcus faecium* and *Enterococcus faecalis*, methicillin-resistant staphylococcus and penicillin-resistant pneumococcus (PRP) [1,2]. In the absence of meningeal involvement, the level of linezolid in the cerebrospinal fluid (CSF) is 70% of that of the plasma [2]. Linezolid has been associated with adverse hematological effects, primarily thrombocytopenia [3,4]. A case of pancytopenia high likely associated with linezolid therapy is here reported.

2. CASE REPORT

A seven year old child a follow up case of head injury with foreign body (glass piece) impaction on right side of skull, underwent multiple surgeries for removal of the foreign body, and bone flap closure. The surgery was complicated by cerebrospinal fluid (CSF) leakage, and infectious complication at the suture site, manifested with a purulent discharge. Therefore, the patient was started on treatment with oral linezolid in dose of 10 mg/kg/dose 8 hourly (dose, route, interval of administration), which was continued for 4 weeks as per sensitivity pattern. Initially ameliorated by the anti-microbial treatment, however the patient re-presented to clinical attention due to the onset of fatigue, inappetence, and, fever.

Physical examination revealed child pallor, soft cystic swelling over the right parietal area of scalp with granulation tissue and no active discharge Remainder of the examination was unremarkable, Complete blood count on presentation revealed hemoglobin of (would guide the reader with minimal interpretation on what is low, what is high, what is normal) As per WHO guidelines Range of hemoglobin in children between 5-11 years of age is mild anemia 11-11.4 g/dL, moderate anemia 8-10.9 g/dl, severe anemia <8 g/dl). 6.2 g/dL, with an hematocrit of 18 and a red cell count of $2.16*10^{12}$/L. The mean corpuscular volume was 84fl, the mean corpuscular hemoglobin was 28.7 pg, and the mean corpuscular hemoglobin concentration was 34.3 g/dl platelet count was $24*10^9$ /dl, total leucocyte count was $1.8*10^9$/L with the following differential: N_{12} L_{36} M_0 E_2 with an absolute neutrophil count of 432/mm^3. Hepatitis panel (Hbs Ag & HCV DNA) and HIV serology serology/PCR? were negative.

Repeat peripheral blood complete blood counts revealed a declining trend (Table 1).

(Sounds like this is the sequence of events leading to R/O other causes?) This was the sequence of events, patient presented to us with pancytopenia we started the work up required to find out the underlying cause. In the meanwhile patient blood parameters declined further requiring transfusion. Our diagnosis was a diagnosis of exclusion. We discharged the patient after discontinuing lineolid and plan was to get other investigation done in case blood parameters doesnot come to normal. But luckily in our case they came to normal. Peripheral blood smear examination revealed mild anisocytosis, and normocytic normochromic to microcytic hypochromic RBCs, few macrocytes and ovalocytes, and occasional tear drop cells. A direct coombs test was negative. Coagulation studies showed a prothrombin time of17, a partial thromboplastin time of 21.8 Chest X-ray normal and abdominal ultrasonography did not show pathological finding. Iron studies showed a serum iron of 133.36 microgram/dl, a total iron binding capacity of 138.93, a transferring saturation of 95.99%, and a serum ferritin of 225.10 ng/ml. Serum folic acid levels were more than 20 ng/ml. A, fetal hemoglobulin -6.8%, with an hemoglobin $A_2$of 3.3%. A complete metabolic panel was unremarkable. A bone marrow biopsy was performed, revealing a marrow hypocellular for age. Myelopoesis was normal with normoblastic erythroid cells, and a myeloid: erythroid ratio of 2.6:1. Megakaryocytes were adequate in number. Lymphocytes represented 19% of all marrow cells, with occasional. Myelocytes were 18%, metamyelocytes 2%, neutrophils 31%, eosinophils 8%, lymphocytes 19%, and erythrocytes 22%.

In the absence of any other apparent secondary cause, the ongoing treatment with linezolid was thought to be associated with the declining blood counts.

Consequently treatment with Linezolid was interrupted, and the patient received parenteral antibiotics (ceftraixone and Amikacin) which one?, and RCC(spell out)as a part of treatment. Hemogram repeated after one month of interruption of linezolid showed significant improvement in blood counts, (Table1).

Table 1. Hematological parameters corresponding to day from the start of linezolid therapy

Parameter	Baseline day(Before start of drug)	On day of admission	Day 5 of admission	After 1 month of stopping Linezolid
Erythrocytes ($\times10^{12}$/L)	3.5	2.16	1.19	2.4
Hemoglobin (g/L)	10.2	6.2	3.6	9.6
Leukocytes ($\times10^{9}$/L)	6.7	1.8	2.4	5.2
Platelets ($\times10^{9}$/L)	1.6	.27	.24	1.1

3. DISCUSSION

The potent activity of linezolid against Gram-positive bacteria and its excellent bioavailability after oral dosing have made it an important addition to the antibiotic armamentarium [5]. In a study conducted in 950 children, frequently reported side effects included nausea, vomiting, diarrhea, headache, increased liver enzymes and skin rash (6.5-10.8% of the patients). Reversible bone marrow suppression, serotonin syndrome, hypertension, elevated liver enzymes, lactic acidosis and optic neuropathy were also reported, albeit at a lower frequency [6].

Thrombocytopenia is the most commonly reported hematological side effect of linezolid in the adult population, however, it has also been observed in children, albeit at a lower rate [2]. Bone marrow suppression, especially in the form of thrombocytopenia, has been reported in the second week of treatment with linezolid in many studies [6] (Ref each study, if feasible).

In study reported by Kuter and Tillotson [4], 11 of 13 cases of pancytopenia were reported to occurr after at least three weeks of therapy. In our case patient thrombocytopenia occurred after 28 days of treatment, instead. Myelosuppression with linezolid is time and dose-dependent, and itis reversible as observed in preclinical studies [7]. In the first six months of approved linezolid use in the United States, 72 cases of hematological abnormalities were recorded among 55,000 patients, and pancytopenia accounted for 13 of these cases [4]. A search requested from the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) database (from the date of linezolid marketing to April 30, 2003) revealed no reports of pancytopenia, while a World Health Organization database search with the keyword ‘pancytopenia and linezolid’ yielded 37 reports.

Most of aforementioned studies involved the adult patient population, and the data might not be directly applicable to the pediatric population, because the pharmacokinetic of linezolid is different between the two population, as for example a higher clearance of the drug has been observed in newborns and in children below 12 years of age. Thrombocytopenia was also observed in 3% of the patients who received linezolid during clinical trials [8].In the study conducted by Attassi et al. thrombocytopenia was observed in 32% patients who received linezolid for more than 10 days [9].

Hematological parameters improved seven to 14 days after the discontinuation of linezolid in the presented patient, as was observed in previously published descriptions [7].

4. CONCLUSIONS

It is important for clinicians to be aware of the potential hematological adverse effects of linezolid, including pancytopenia. We recommend that complete blood counts be monitored weekly in patients receiving linezolid for more than 14 days.

CONSENT

As per international standard or university standard written patient consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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