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CASE REPORT

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Adverse reactions caused by high serum concentration of linezolid: Two case reports and literature review

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Key Clinical Message

Linezolid is a potent oxazolidinone for the treatment of various gram-positive bacterial infections. However, the drug can cause potential adverse reactions such as thrombocytopenia, hyperlactacidemia and serotonin syndrome, which warrant consideration by the medical team when planning treatment. The existing literature has reported some adverse reactions caused by linezolid, but most of these are based on clinical characteristics and simple treatment measures. Two cases of linezolid overdose resulting in thrombocytopenia, hyperlactacidemia and serotonin syndrome are presented, which were successfully managed with therapeutic drug monitoring. A dose adjustment strategy was adopted to safely and effectively mitigate linezolid-related adverse events.

KEYWORDS

hyperlactatemia, linezolid, serotonin syndrome, therapeutic drug monitoring, thrombocytopenia

1 | INTRODUCTION

In 2000, linezolid (LZD) was introduced as the first completely synthetic oxazolidinone antibacterial therapy. This drug aids in tackling diverse gram-positive bacterial infections, such as those caused by methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), penicillin-resistant *Streptococcus pneumoniae* (PRSP), and vancomycin-resistant enterococci (VRE), thus becoming a commonly utilized antibacterial agent in medical settings.[1] However, the clinical use of linezolid is prone to adverse reactions, including optic neuritis, thrombocytopenia, hyperlactacidemia, and serotonin syndrome (SS),[2] which may compromise the integrity of the treatment.

Linezolid treatment benefits from therapeutic drug monitoring (TDM). To achieve a balance between efficacy and safety, a steady-state plasma drug concentration range of 2–7 mg/L should be maintained.[3] The plasma concentration of linezolid is closely associated with the incidence of adverse reactions (ADR). When the steady-state trough concentration exceeds 7.5 mg/L, the incidence of thrombocytopenia is significantly increased.[4] Moreover, the incidence of other adverse reactions, such as neuropathy and lactic acidosis, increases considerably as the exposure to and treatment duration of linezolid increases.[5] In this report, two cases of SS, thrombocytopenia, and lactic acidosis caused by increased serum concentrations of linezolid are presented. Based on the dose adjustment of linezolid under the guidance of serum concentration monitoring,

a dose adjustment strategy for preventing ADR in clinical practice was proposed to ensure safety and efficacy.

2 | CASE HISTORY

2.1 | Case 1

A 72-year-old man with a history of Stage 5 chronic kidney disease, hemodialysis status, lung infection, and Grade 3 hypertension, currently receiving regular hemodialysis on Tuesday and Saturday each week, oral levoamlodipine tablets to control blood pressure in good condition. One month prior to presentation, he had a productive cough and fever of up to 39°C. His symptoms began to worsen and he had dyspnoea on exertion, even with minimal activity. The patient presented to the hospital with these symptoms. The initial workup showed an elevated white count and procalcitonin, and the imaging revealed pneumonia. Our patient was initiated on broad-spectrum antibiotics piperacillin-tazobactam combined with levofloxacin.

2.2 | Case 2

A 85-year-old female with history of diabetes on insulin noticed an ulcer on the left foot initially about 1 year ago, he also with history of Grade 3 hypertension, a high-risk group for hypertensive heart disease. This was followed closely as an outpatient. Recently, the patient noticed redness, swelling, and pain in this foot, with no discharge. A workup, including a CT scan, showed soft tissue swelling in the left foot. He was admitted to our hospital for further management. The initial workup showed an elevated white count and procalcitonin, and the imaging revealed hyperosteogeny. The laboratory examination results of the case 2 during their hospital stay are listed in Table 1.

3 | INVESTIGATIONS AND TREATMENT

3.1 | Case 1

The microbiology workup revealed *S. aureus* and *Pseudomonas aeruginosa*. The patient was initiated on meropenem 1 g iv q8h with linezolid 0.6 g iv q12h on Day 1. By Day 4, we started noticing a worsening of lactic acid and platelets. As linezolid could cause side effects, we started monitoring cholinezolid serum levels. By the fifth day, the patient was clinically much improved. The serum linezolid and blood lactic acid levels kept increasing (Table 2). As we were concerned about the possibility of linezolid toxicity causing lactic acid syndrome and low platelets, we held linezolid. Vitamin B1 5 mg po bid was initiated, and the lactic acid and platelet monitoring was done. On Day 9, as the infection index escalated, linezolid was reintroduced at 0.3 g q12h. On Day 12, a progressive decline in the platelet count was witnessed, and the serum linezolid level was lower than before. Fearing the potential for linezolid-induced thrombocytopenia, the drug was once again discontinued. Platelets gradually returned to normal after stopping linezolid.

3.2 | Case 2

Our patient was initiated on broad-spectrum antibiotics. However, the lower limb pain continued, and the healing of the ulcer was slow after the fifth day. Hence, linezolid was introduced, initially at 0.6 g ivgtt q12h.On the Day 6, the patient developed discomfort from nasal bleeding. After intravenous injection of linezolid, he experienced dizziness, slurred speech and limb tremor. The blood concentration of linezolid was 13.05 mg/L. Considering the 5-hydroxytryptamine syndrome caused by linezolid, the dose of linezolid was increased to 0.3 g po q12h on the Day 7.

TABLE 1 The laboratory examination of case 2 during the hospital.

Investigations	Day 1	Day 3	Day 6	Day 7	Day 10	Reference range
CRP (mg/L)	5.79	NA	4.81	NA	NA	0.00–3.00
ESR (mm/h)	40	NA	NA	NA	NA	0–15
CREA (μmol/L)	147	NA	147	NA	160	53.0–115.0
UREA (μmol/L)	12.8	NA	9.5	NA	10.2	2.90–8.20
LZD (mg/L)	NA	NA	NA	13.05	5.08	2–7
Fasting blood glucose (mmol/L)	NA	7.4	7.9	6.2	6	4.4–6.1
Blood glucose 2 h after lunch (mmol/L)	14.1	10.3	10.4	9.5	9.1	≤7.8
Blood glucose 2 h after dinner (mmol/L)	7.8	7.6	8.7	8.6	8.4	≤7.8

Abbreviations: CREA, creatinine; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; LZD, linezolid; UREA, urea.

TABLE 2 The laboratory examination of case 1 during the hospital.

Investigations	Day 1	Day 3	Day 5	Day 9	Day 12	Day 14	Reference range
WBC ($\times 10^9$/L)	8.63	6.15	7.54	5.9	9.71	9.35	3.97–9.15
PLT ($\times 10^9$/L)	271	243	293	55	46	168	85.0–303.0
NEU ($\times 10^9$ /L)	7.39	5.56	6.16	5.3	9.38	8.74	2.0–7.0
NE%	85.7	90.3	81.7	90.5	96.6	93.4	50.0–70.0
ESR (mm/h)	108	NA	NA	NA	NA	NA	0–15
CREA (μmol/L)	569	588	622	794	641	689	53.0–115.0
PCT (μg/L)	1.15	1.42	0.98	1.01	1.39	0.46	0.00–0.50
CRP (mg/L)	114.28	95.51	47.69	47.59	58.36	66.8	0.00–3.00
LAC (mg/L)	2.37	3.51	4.09	NA	NA	3.69	0.5–2.37
LZD (mg/L)	NA	NA	19.44	NA	10.44	6.1	2–7

Abbreviations: CREA, creatinine; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; LAC, lactic acid; LZD, linezolid; NE%, neutrophil ratio; NEU, neutrophils; PCT, procalcitonin; PLT, platelet; WBC, white blood cell.

4 | OUTCOME AND FOLLOW-UP

4.1 | Case 1

On the Day 14, the serum linezolid concentration was normal range, and the platelet count returned to normal, and the changes in linezolid serum concentration, platelet count, and blood lactate concentration of this case are depicted in Figure 1. The patient had no obvious fever, improved infection index and was discharged in good health.

4.2 | Case 2

On the Day 9, the patient regained normal skin color on the legs without any sign of infection. On the Day 10, the blood concentration of linezolid was 5.08 mg/L, and no other special discomfort was discharged.

5 | DISCUSSION

5.1 | Case 1

Linezolid is a synthetic oxazolidinone antibiotic that inhibits bacterial protein synthesis by binding to the 30S and 50S subunits of rRNA.[6] Linezolid selectively inhibits its mitochondrial protein synthesis and mitochondrial respiratory chain and causes secondary nuclide imbalance by inducing adverse drug interactions with mitochondrial ribosomes. Aerobic metabolism is thereby limited, which leads to anaerobic glycolysis and lactic acid production, accelerating tissue hypoxia and ultimately resulting in hyperlactacidemia.[7,8] The patient's infection index decreased and the inflammation was relieved after 5 days of linezolid administration, but the blood lactic acid level increased gradually. The serum drug concentration of linezolid was increased significantly, and the blood lactic acid level decreased after

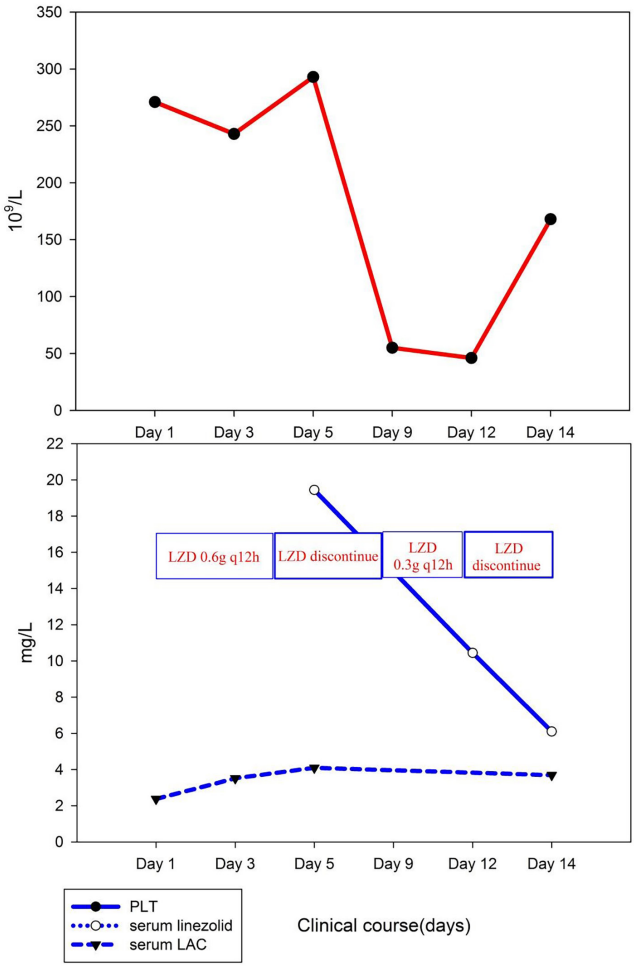

FIGURE 1 The changes in linezolid serum concentration, platelet count, and blood lactate concentration of case 1. LAC, lactic; PLT, platelet.

drug withdrawal. According to the criteria for the evaluation of ADRs, the increase in lactic acid level in Case 1 could be attributed to linezolid therapy.

Hematological adverse reactions are one of the most common and serious adverse effects of linezolid and are mainly related to reversible bone marrow suppression, immune-mediated erythropoiesis inhibition, and platelet destruction. According to the adverse drug event reporting system of the US FDA, the incidence of thrombocytopenia caused by linezolid since its introduction was 3.74% (876/23449).[9] In Case 1, the patient's serum linezolid concentration increased significantly 5 days after receiving the drug at a dose of 0.6 g q12h. Owing to the progression of the infection, anti-infective therapy with linezolid was resumed at 0.3 g q12h 4 days after discontinuing it, and the platelet counts were found to be significantly lower than the previous levels. No special treatment was given, and the platelet counts were checked. After the reintroduction of linezolid for 3 days, the serum concentration of linezolid remained high and the platelet counts decreased progressively. However, the platelet count returned to normal after treatment with linezolid for 3 days.Factors that can cause thrombocytopenia include leukemia, related autoimmune diseases, drug- and vaccine-induced thrombocytopenia, and patients without associated diseases.[10] According to the criteria for assessing adverse drug reactions, the thrombocytopenia concentration in this case might have been caused by linezolid. It has been reported in the literature that linezolid-induced thrombocytopenia usually occurs within 10–14 days after the initiation of treatment. Linezolid-induced thrombocytopenia might be the possible mechanism, and it could be ascribed to myelosuppression and immune-mediated platelet destruction. Platelet counts and linezolid plasma concentrations should therefore be monitored regularly in all patients receiving linezolid therapy for more than 7 days.[11]

5.2 | Case 2

Serotonin syndrome is a recognized adverse reaction of linezolid interactions with serotonin inhibitors, serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and opioids.[12] This syndrome is a disease of the central nervous system, and its clinical manifestations include altered mental status, ataxia, restlessness, lower extremity hyperreflexia, and sweating, which can progress to severe symptoms such as confusion, seizures, shock, coma, and death.[13] Linezolid has been reported to cause serotonin syndrome in combination with antipsychotic drugs such as venlafaxine, citalopram, paroxetine, sertraline, and fluoxetine, and opioids such as fentanyl, pethidine, and methadone.[14] The diagnostic criteria for serotonin syndrome comprise the use of serotonin medications and the following: spontaneous clonus, induced clonus plus restlessness or sweating, ocular clonus plus restlessness or sweating, tremor plus hyperreflexia, and hypertension plus a temperature of <38°C combined with ocular clonus or induced clonus.[15] The patient developed dizziness, slurred speech, and limb tremor after 5 days of linezolid use. Psychiatrists assess the patient's symptoms, along with the necessary physical examination and comprehensive assessment of the medication treatment plan. The plasma concentration of linezolid was significantly high. The neurological symptoms disappeared after reducing the dose of linezolid. According to the diagnostic criteria for serotonin syndrome and the assessment criteria for adverse drug reactions, the condition may be diagnosed as serotonin syndrome caused by linezolid.

The serum drug concentration of linezolid is closely associated with the incidence of adverse reactions. Studies have demonstrated that excessive exposure to linezolid can lead to a >50% possibility of developing thrombocytopenia. This threshold for linezolid is set at a trough concentration of <7–10 mg/L.[16] In addition, excessive exposure to linezolid can lead to lactic acidosis and serotonin syndrome.[17,18] Therefore, therapeutic drug monitoring is used to guide the initial dosing regimen and dose adjustment of linezolid in clinical practice, especially in critically ill patients, children, patients with renal insufficiency, the elderly, those with obesity, and those taking other drugs that interact with linezolid.

6 | CONCLUSION

Therapeutic drug monitoring-guided dose adjustment of linezolid, especially early therapeutic drug monitoring after the initiation of a linezolid-based therapeutic regimen, may reduce interindividual differences in drug exposure and improve the tolerability of linezolid. In the overexposed linezolid treatment regimen, the use of therapeutic drug monitoring as a tool may not alleviate the occurrence of adverse reactions under the premise of ensuring the effectiveness of drug treatment.

AUTHOR CONTRIBUTIONS

Renzhu Liu: Data curation; funding acquisition; writing – original draft. **Lu Xiao:** Data curation; formal analysis; writing – review and editing. **Can Xiao:** Data curation; visualization; writing – review and editing. **Wencan Li:** Formal analysis; writing – review and editing. **Xiang Liu:**

Project administration; resources; visualization; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The original data presented in the study are included in the article, and further queries can be directed to the corresponding authors.

ETHICS STATEMENT

The study was reviewed and approved by the Ethics Committee of Xiangtan Central Hospital (approval number: 2023-07-006).

CONSENT

Written informed consent has been obtained from the patient to publish this paper. Participants agreed to the same terms as outlined in Wiley's standard informed consent form. All authors agree to peer review and publication of this manuscript by Clinical Case Reports. Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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