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Lactic Acidosis and Thrombocytopenia Associated with Linezolid Therapy: A Case Report

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest:

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None declared

Patient: Female, 50
Final Diagnosis: Lactic acidosis and thrombocytopenia
Symptoms: Abdominal and/or epigastric pain
Medication: —
Clinical Procedure: —
Specialty: Cardiology

Objective: Diagnostic/therapeutic accidents

Background: Linezolid (LZD) has been reported to combat several intractable infectious diseases, including multidrug-resistant infections and tuberculosis. Although quite a number of adverse effects of LZD therapy have been abundantly described so far, LZD associated lactic acidosis and thrombocytopenia have rarely been studied. We described a patient dying of lactic acidosis and thrombocytopenia associated with LZD therapy complications. To the best of our knowledge, this is the first report focusing on LZD therapy complications in treating patients with deadly abnormalities in hemogram.

Case Report: A 50-year-old Chinese female was diagnosed with endocarditis and thus received LZD therapy for 25 days, then complained about 6 days' abdominal pain and vomiting before being admitted to the Emergency Department. Upon admission, lactic acidosis and thrombocytopenia were immediately observed.

Conclusions: Physicians should be aware of typical clinical manifestations of lactic acidosis related to LZD exposure, since this complication might be a life-threatening metabolic emergency.

MeSH Keywords: Acidosis, Lactic • Adverse Drug Reaction Reporting Systems • Pancytopenia

Abbreviations: LZD – linezolid; CRRT – continuous renal replacement therapy

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Background

Linezolid (LZD) is standardly used in treating multidrug-resistant (MDR) Gram-positive bacteria such as vancomycin-resistant *Staphylococcus aureus* (VRSA) and vancomycin-resistant *Enterococcus* (VRE). Recently, several adverse effects of LZD have been described, including metabolic acidosis, peripheral neuropathy, and hyperlactatemia. These known complications have rarely contributed to life-threatening conditions, while LZD associated lactic acidosis and thrombocytopenia could be a lethal process, which has seldom been reported worldwide. In this report, we described the therapeutic process of a patient developing lactic acidosis and thrombocytopenia after LZD therapy on endocarditis.

Case Report

A 50-year-old Chinese female was admitted to the Emergency Department (ED) of West China Hospital in May 2015, with complaint of 6 days' continuous abdominal pain and vomiting, whose hemogram indicated lactic acidosis and thrombocytopenia. She had a past history of aortic valve and mitral valve replacement for rheumatic heart disease in June 2010 and anemia due to chronic renal failure in July 2013.

One month before ED admission, she was admitted to the Department of Cardiology in West China Hospital due to palpitation and fever for 2 weeks. She was then diagnosed with endocarditis based on echocardiography and blood culture results. Specifically, methicillin-resistant *Staphylococcus intermedius* was found in her blood culture and her echocardiography

showed a neoplasm around the mechanical aortic valve. Meanwhile, the laboratory tests results manifested the following values: serum creatinine 331 $\mu\text{mol/L}$; estimated glomerular filtration rate of 23 mL/min/1.73 m^2 ; hemoglobin 78 g/L (normal range 115–150 g/L); leukocytes $8.7 \times 10^9/\text{L}$ (normal range $4\text{--}10 \times 10^9/\text{L}$) with $7.57 \times 10^9/\text{L}$ polymorphonuclear neutrophils (normal range $1.8\text{--}6.3 \times 10^9/\text{L}$); platelets $216 \times 10^9/\text{L}$ (normal range $100\text{--}300 \times 10^9/\text{L}$). Considering that most LZD consumed is not cleared through the kidney, the initial inpatient treatment regimen consisted of LZD (600 mg intravenously every 12 hours) for endocarditis and warfarin (1.25 mg orally every 12 hours) for mitral valve replacement. After a 13-day LZD treatment, the patient's condition improved, and her major symptoms gradually disappeared. Her body temperature also returned to normal and her multiple blood culture results were negative. Consequently, she was discharged from West China Hospital in April 30th and received LZD treatment in a local hospital for another 12 days.

Soon thereafter, she started to suffer from continuous abdominal pain and vomiting for 6 days prior to being re-admitted to the ED. Upon admission (May 13), she received LZD therapy for a continuous 25 days, after which time, she became drowsy, dyspneic, and unfortunately developed nausea, vomiting, and persistent periumbilical pain. To our relief, she didn't manifest with fever, chill, cough, diarrhea, expectoration, or rash. Physical examination indicated tachypneic (respiratory rate, 28 breaths/min), atrial fibrillation (heart rate, 83 beats/min), normotensive (blood pressure, 112/50 mmHg), and afebrile (temperature, 36.5°C). Table 1 showed the results of laboratory tests. Microbiological investigations (blood, urinary) were negative, no sputum specimen was collected. She was ultimately

Table 1. Time course of laboratory test results (reference range).

	D-2	D0 Start of LZD	D+5	D+10	D+25 admission	D+26	D+27	D+28
PH					6.94	6.86	7.09	7.08
PCO ₂ (mmHg)					<10	14	16.8	24.5
PO ₂ (mmHg)					178	118	449.6	100.3
Serum lactate (<2 mmol/L)					19	>20	>20	>20
Tot Bili (5.0–28.0 $\mu\text{mol/L}$)	4.6	5.4	7.2	7.1	8.1	7.6	9.9	10.5
Serum creatinine (37.0–110.0 $\mu\text{mol/L}$)	331	333	300	316	496	467	322	291
Platelet count ($100\text{--}300 \times 10^9/\text{L}$)	216	271	197	143	12	15	59	40
Leukocyte count ($3.5\text{--}9.5 \times 10^9/\text{L}$)	8.7	8.45	7.65	5.50	4.15	3.36	3.06	2.41
Red blood cell count ($3.8\text{--}5.1 \times 10^{12}/\text{L}$)	2.8	3.04	2.50	2.71	2.02	2.46	2.04	2.76

PaCO₂ – partial pressure of arterial carbon dioxide; PaO₂ – partial pressure of arterial oxygen; D – day, D0 refers to the day on which LZD therapy was initiated, D +5 refers to the day of admission to the ICU.

diagnosed with severe lactic acidosis and thrombocytopenia and was thus transferred to the Emergency Intensive Care Unit on May 14. The patient's condition continued to worsen despite uttermost supportive measures (heart rate 115 beats/min; atrial fibrillation; blood pressure 70/35 mmHg; respiratory rate 30 breaths/min) and the patient required hemodynamic support with continuous intravenous infusion of norepinephrine. Mechanical ventilation, continuous renal replacement therapy, 2U erythrocytes, 1U platelets were subsequently given. Unfortunately, the patient rapidly developed shock followed by multiple organ failure, and died on May 27.

Discussions

In our case report, the patient finally died of lactic acidosis and thrombocytopenia after a 25-day LZD exposure, which was extremely rare, according to our knowledge. Since other drugs in the regimen to treat endocarditis are commonly acknowledged to be unrelated to lactic acidosis and subsequent severe complications such as septic shock or liver failure confirmed by complete microbiological investigation and laboratory test results, the LZD exposure might have had a direct relationship with deadly lactic acidosis in this patient.

The patient in this report presented with signs of chronic renal failure 2 years ago. Although her urine volume increased to a normal range and her serum creatinine remained relatively stable after standard continuous renal replacement therapy (CRRT) therapy, the patient was vulnerable to LZD adverse effects since renal abnormalities could not possibly be eliminated. Previous studies recommended no adjustment of LZD dosage in patients with renal dysfunction (creatinine clearance, <40 mL/min) or patients with end-stage renal diseases depending on hemodialysis. However, from our experience, the patients tend to become increasingly susceptible to the adverse effects of LZD due to higher concentrations of metabolites of LZD in blood resulting from chronic renal failure. Therefore, physicians should pay more attention to LZD dosage [1].

The incidence of lactic acidosis induced by LZD exposure is unknown, since few cases have been published. Studies in rabbits and rats have demonstrated that LZD can interfere host mitochondrial protein synthesis process due to their similarities to bacterial mitochondrial ribosomes, which might result from LZD's binding to mitochondrial 16S ribosomal RNA [2]. De Vriese et al. [3] reported decreased mitochondrial enzymatic activity in the affected tissues of a patient treated with LZD. In addition, decreasing respiratory chain complex enzyme activity of the mitochondria was also observed in a number of researches [3–6]. In previous studies, manifestations of lactic acidosis were also documented 1 to 16 weeks after initiation

of LZD therapy, with a median onset of 6 weeks [2]. Meanwhile, a longer duration of LZD treatment (>6 weeks) was a risk factor for metabolic acidosis, while renal impairment, age, and DM were not obvious risk factors [7].

Our patient was diagnosed with lactic acidosis accompanied by thrombocytopenia. Earlier studies suggested that LZD was associated with reversible myelosuppression. In a study recruiting 796 patients who totally received 828 courses of LZD, thrombocytopenia was observed in only 2 patients (0.24%) [8]. Another study suggested that LZD-induced anemia was secondary to a chloramphenicol-like suppression of erythropoiesis after a combination of chloramphenicol with mitochondrial ribosomes [9]. Therefore, mechanisms inducing lactic acidosis and thrombocytopenia associated with LZD might be similar. The hematologic events reported were mild to moderate in severity, transient in nature, which was related to treatment duration. Moreover, hematologic events reversed when therapy was halted [10].

Preventing LZD-induced lactic acidosis requires careful evaluation of arterial blood gases. Decisively halting LZD therapy immediately and continuously monitoring laboratory values is the most important procedure when these symptoms appear. However, discontinuation of LZD therapy is inadequate to cure critically symptomatic patients. Moreover, as some scholars have suggested, a treatment plan that couples drug discontinuation with renal replacement therapy could be an efficient alternative. However, no large randomized studies on survival have been reported [11–15].

Conclusions

In this case report, we focused on the adverse effect of LZD therapy which might be triggered by continuous use within a short period of time. In the future, we have to be aware of the possible adverse effects when extensive use of LZD is mandatory and thus be prepared to administer specific drugs and techniques to combat adverse effects.

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Conflict of interests

None.

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