

CASE REPORT

Linezolid induced refractory lactic acidosis causing atrial fibrillation A case report of serious adverse event

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ABSTRACT

Linezolid has been approved for the treatment of MDR and XDR TB by the WHO. It is one of the most effective drugs for treating drug-resistant tuberculosis (DR-TB), but it carries a considerable risk of toxicity and is poorly tolerated because of its side effects of peripheral neuropathy, anemia/thrombocytopenia and optic neuritis, etc. Linezolid may also induce lactic acidosis. The incidence of lactic acidosis is relatively low but it is a serious adverse drug reaction that can result in multi-organ failure and death. We report a case of linezolid-induced refractory lactic acidosis causing atrial fibrillation in a 20-year-old female receiving an "all-oral longer MDR-TB regimen" for MDR tuberculosis.

Key Words: Linezolid, MDR-TB, XDR-TB, Lactic acidosis, Atrial fibrillation
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CASE REPORT

A 20-year-old female was admitted to the emergency department of J. N. Medical College and Hospital, AMU with complaints of difficulty in breathing and dyspnea, extreme weakness, muscle cramps and pain, and mental confusion. She has a medical history of receiving treatment for multidrug-resistant extra-pulmonary tuberculosis and psoas abscess. She was taking bedaquiline, levofloxacin, linezolid, cycloserine, and clofazimine for the last 2 months. The dose of linezolid was 600 mg once daily.

On admission, blood pressure was 90/60 mmHg, the body temperature was 36.6°C, respiratory rate was 29 breaths/min, heart rate was 119 beats/min, and SpO₂ 92%. Results of laboratory tests included the following values: WBC $13 \times 10^3/\text{mm}^3$, with 84.7% neutrophils, hemoglobin 6.4 g/dL, urea nitrogen 20 mg/dL, creatinine 0.74 mg/dL, uric acid 6.7 mg/dL serum bilirubin 1.3 mg/dL, ALT 181 U/L, AST 320 U/L. Arterial blood gas analysis (ABG) revealed: pH 6.98, PaCO₂ 15 mmHg, PaO₂ 153 mmHg, sodium 141 mmol/L, potassium 4.5 mmol/L, glucose 69 mg/dL lactic acid >15 mmol/L, HCO₃⁻ 3.5 mmol/L and

base excess -26.4 mmol/L. Her x-ray chest was normal.

Following admission, the patient was treated with the antibiotic ceftriaxone and sodium bicarbonate (150 mEq diluted in 1L of DSW infused during the first hour and then 50 mEq every six hours) to correct acid-base balance. Injectable pantoprazole was given to reduce the production of stomach acid. Two units of blood were also transfused. Anti-tubercular treatment was stopped.

Repeat investigations after 12 hours revealed the following: ABG -pH 7.10, PaCO₂ 13 mmHg, PaO₂ 119 mmHg, lactate above the level of detection (> 15 mmol/L), and the base excess was -23.5 mmol/L. Haemoglobin was 8.3 g/dL.

The patient was diagnosed with lactic acidosis. The concentration of serum linezolid could not be assessed and similarly, the patient was not tested for mitochondrial DNA A2706G gene polymorphism as the facilities were not available in our hospital.

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The patient was transferred to the intensive care unit (ICU) for continued treatment. The patient's condition deteriorated as she developed atrial fibrillation. She died despite every effort to revert the atrial fibrillation.

DISCUSSION

Linezolid has been classified as a Group A drug by the World Health Organization (WHO) for the treatment of multi-drug resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB). It has been included in the regimen for MDR-TB and XDR-TB patients in National Tuberculosis Elimination Program (NTEP), India¹. It is one of the most effective drugs for treating drug-resistant tuberculosis (DR-TB), but it carries a considerable risk of toxicity and is poorly tolerated because of its side effects.

Some of the side effects associated with the use of linezolid are anemia², thrombocytopenia³, peripheral neuropathy⁴, ocular neuropathy⁵, and lactic acidosis^{2,6}. Lactic acidosis is a rare serious adverse drug reaction that usually occurs after prolonged use (≥ 28 days)⁷. It can cause multi-organ failure and death⁸. Linezolid-induced lactic acidosis is due to the untoward interaction between the drug and mitochondrial ribosomes. Linezolid prevents the formation of a 70S initiation complex by binding to the 50S ribosomal subunit near its interface with the 30S unit and thus inhibits bacterial growth by interfering with bacterial protein synthesis⁹⁻¹². It is speculated that linezolid inhibits mitochondrial protein translation by a similar mechanism of action¹³. The respiratory chain enzyme content is diminished due to the inhibition of mitochondrial protein synthesis and thus limits aerobic energy production. As a result, anaerobic glycolysis and lactate generation accelerate independently from tissue hypoxia⁷.

Linezolid-induced lactic acidosis should be suspected only after the exclusion of other, more common causes of lactic acidosis such as hypoxemia, anemia, or low cardiac output. A primary defect in oxygen use at the mitochondrial level is suspected when there are normal-to-high whole-body oxygen delivery, high venous oxygen saturation, and lack of response to interventions that increase tissue oxygen⁹. Our patient was not in shock and had no evidence of acute renal or liver failure. There was no history of diabetes mellitus. She was not taking any other medication which may cause lactic acidosis. Normal acid-base balance before the start of

linezolid, temporal association of linezolid use with the development of lactic acidosis, and no other explanation for a rise in lactate levels make linezolid the most likely cause of lactic acidosis in our case.

The mortality of linezolid-induced lactic acidosis is considered to be relatively high. Yiyang Mao et.al in their meta-analysis reported the mortality of linezolid-induced lactic acidosis to be 25.5%.⁶ This high mortality may be because the onset of lactic acidosis was usually abrupt and the majority of patients developed serious respiratory failure. In our case, the patient developed atrial fibrillation which is a very rare complication of lactic acidosis. Many workers have reported the mechanism of the development of atrial fibrillation in lactic acidosis. Allesie et al¹⁴ reported a strong association between ischemia and accompanying acidosis and the development of atrial fibrillation. Intracellular acidification may lead to Na⁺ influx and further cause Ca²⁺ overload with arrhythmogenesis through activation of the Na⁺/Ca²⁺ exchanger in cells^{14, 15}. In addition, lactic acidosis may induce cellular uncoupling thereby electrically isolating the ischemic area. These characteristics have pro-arrhythmic effects on cardiac tissue and thus may cause atrial fibrillation¹⁶.

CONCLUSION

Linezolid-induced lactic acidosis is relatively low but has a serious adverse effect and the mortality due to this is relatively high. During therapy with linezolid, blood drug, and lactate levels should be regularly monitored. The current standard-of-care treatment of linezolid-induced lactic acidosis consists of drug withdrawal to reverse mitochondrial intoxication and inter-current life support.

Conflict of interest: None

Written informed Consent: Taken

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