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Case report

Successful treatment of linezolid-induced severe lactic acidosis with continuous venovenous hemodiafiltration: A case report

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ABSTRACT

Linezolid is an oxazolidinone antibiotic. Linezolid-associated lactic acidosis has been reported in 6.8% of linezolid-treated patients. Lactic acidosis is associated with poor clinical outcomes, with high blood lactate levels resulting in organ dysfunction and mortality. This case report describes the development of lactic acidosis in a 64-year-old Chinese woman who had received 33 days of treatment with antituberculosis drugs and 28 days of treatment with oral linezolid for tuberculous meningitis. Severe lactic acidosis was reversed by withdrawing antituberculosis drugs and using continuous venovenous hemodiafiltration (CVVH). When the patient's condition was stable, she was transferred to the infectious disease department, and antituberculosis drugs, with the exception of linezolid, were reintroduced. This did not result in recurrence of lactic acidosis. The causal relationship between lactic acidosis and linezolid was categorized as 'probable' on the Adverse Drug Reaction Probability Scale. This case demonstrates that CVVH has potential as an alternative to discontinuation of linezolid alone for rapid reversal of linezolid-associated severe lactic acidosis.

1. Introduction

Linezolid is an oxazolidinone antibiotic used to treat a variety of gram-positive coccal infections, including pneumonia or skin and soft tissue infections produced by vancomycin-resistant Enterococcus, penicillin-resistant Streptococcus, and methicillin-resistant Staphylococcus aureus (Colca et al., 2003). Linezolid can also be used to treat nocardia, multidrug-resistant tuberculosis, and other mycobacterium infections (French, 2003; Fortún et al., 2005). Linezolid inhibits bacterial growth by binding to the 50S ribosomal subunit and preventing formation of the 70S ribosomal subunit, thereby inhibiting protein synthesis (Thibault et al., 2019).

Lactic acidosis is associated with poor clinical outcomes, with higher blood lactate levels resulting in increased organ dysfunction and mortality (Kraut and Madias, 2014; Santini et al., 2017; Christopher and Robert, 2018). There remains an unmet clinical need to raise awareness about lactic acidosis among physicians. In particular, physicians may not know that linezolid can induce lactic acidosis, even though the incidence rate of linezolid-associated lactic acidosis in linezolid-treated patients is estimated at 6.8% (Im et al., 2015). Linezolid-associated lactic acidosis leads to inhibition of mitochondrial oxidative phosphorylation in the absence of obvious tissue hypoxia (Liu et al., 2021). Human mitochondrial DNA polymorphisms (A2706G) have been associated with linezolid-associated lactic acidosis (Del Pozo et al., 2014).

Here, we report a rare serious case of coma caused by linezolid-associated lactic acidosis in a patient with multiple risk factors,

Abbreviations: CVVH, continuous venovenous hemodiafiltration; PaO_2, arterial partial pressure of oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; FIB, fibrinogen; ICU, intensive care unit; CRRT, continuous renal replacement therapy; ADR, Adverse Drug Reaction; ESRD, end-stage renal disease.

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including older age (>60 years), extended linezolid therapy (28 days), kidney dysfunction (left kidney atrophy), and prior use of a combination of antituberculosis drugs that can cause liver damage. Severe lactic acidosis was rapidly reversed after the antituberculosis drugs were withdrawn and with the use of continuous venovenous hemodiafiltration (CVVH). Informed consent was obtained from the patient for publication of this case report.

2. Case report

A 64-year-old Chinese woman was taken to the emergency department of our hospital as she was weak, unable to walk, listless and lethargic and had decreased consciousness, a drooping left eyelid, labored breathing and dyspnea. She had received 33 days of antituberculosis therapy for tuberculous meningitis. 28 days prior to admission, oral linezolid was added to the antituberculosis regimen because MRI showed multiple abnormal signals in the brain and spinal cord, and the patient was diagnosed with suspected tuberculous meningoencephalitis/ encephalomyelomeningitis. 23 days prior to admission, laboratory tests revealed liver damage, and rifampicin was replaced with rifapentine. Thus, the antituberculosis regimen consisted of isoniazid (600 mg intravenously once a day), rifapentine (0.45 g orally twice a week), ethambutol (750 mg orally once a day), pyrazinamide (0.5 g orally three times a day), levofloxacin (0.5 g intravenously once a day) and linezolid (600 mg intravenously every 12 h). The patient's medical history included significant left kidney atrophy and a 10-year history of hypertension that was well controlled with oral antihypertensive drugs, and no history of type 2 diabetes mellitus or drug or food allergies.

On admission, the patient's temperature was 37.6 °C (high; normal range: 36–37 °C), oxygen saturation (%) was 94% (normal; normal range: 91.9–99%), blood pressure was 84/60 mmHg (low; normal range:140–90/90–60 mmHg), heart rate was 130 beats/min (high; normal range: 60–100 beats/min), and respiratory rate was 29 breaths/min (high; normal range: 12–20 breaths/min). Results of laboratory tests were: white blood cells 17.3 $\times$ 10^9/L (high; normal range: 3.5–9.5 $\times$ 10^9/L), neutrophil ratio 91% (high; normal range: 40–70%), serum potassium 6.47 mmol/L (high; normal range: 3.5–5.5 mmol/L), serum creatinine 177.2 μmol/L (high; normal range: 58–110 μmol/L), blood gas pH 6.944 (low; normal range:7.35–7.45), lactate 16.5 mmol/L (high; normal range:0.7–2.5 mmol/L), arterial partial pressure of oxygen (PaO_2) 177.1 mmHg (high; normal range: 80–100 mmHg), arterial partial pressure of carbon dioxide ($PaCO_2$) 11.9 mmHg (low; normal range: 35–45 mmHg), and base excess −27.3 mmol/L (low; normal range: −3–3). Coagulation tests showed prothrombin time (PT) was 23.4 s (high; normal range: 10–15 s), activated partial thromboplastin time (APTT) was 106.6 s (high; normal range: 20–40 s), thrombin time (TT) was 27.8 s (high; normal range: 13–21 s), fibrinogen (FIB) was 0.7 g/L (low; normal range: 2–4 g/L), and D-dimer was 1.96 mg/L (high; normal range: < 0.5 mg/L). Following admission, the patient was treated with ceftriaxone for infection, calcium gluconate and high glucose and insulin to reduce potassium, and sodium bicarbonate to correct acid-base balance.

Nine hours later, blood gas analysis showed pH 7.184, lactate was above the level of detection (max. 20 mmol/L), and the base excess was −21.1 mmol/L. The patient was diagnosed with lactic acidosis, acute renal injury and hyperkalaemia, and was critically ill. Relevant testing was not available in our hospital, therefore, the patient was not tested for mitochondrial DNA A2706G gene polymorphism or serum linezolid concentration.

Ten hours later, the patient was transferred to the intensive care unit (ICU) for continued treatment. The patient's condition continued to worsen and she required hemodynamic support with vasoactive drugs, 250 mL 5% sodium bicarbonate was used to correct lactic acidosis, ulinastatin was administered as an anti-inflammatory, and omeprazole was used to reduce the production of stomach acid. Antituberculosis drugs are a potential cause of lactic acidosis; therefore, treatment with antituberculosis drugs was withdrawn. Hemodynamic instability and worsening acidosis prompted the decision to initiate CVVH to clear antituberculosis drugs (which had been administered 12 h prior) and correct the lactic acidosis and acute renal injury.

CVVH was initiated with a fresenius multifiltrate polysulfone membrane AV600s filter for 75 h. As the patient had abnormal coagulation function, she was not administered anticoagulant. The pipeline was prefilled with normal heparin solution and the right femoral vein provided access for continuous renal replacement therapy (CRRT). Parameters were: blood flow rate 180 mL/min, replacement fluid 4L/h, predilution 90% postdilution 10%, 5% calcium chloride 5 mL/h, and management of body fluid balance. Thirty minutes of CVVH therapy alleviated the patient's acidosis. CVVH therapy also improved the patient's hemodynamics, and intravenous vasopressor dosages were titrated down and eventually discontinued. At the conclusion of CVVH (75 h later), arterial blood gas analysis showed pH 7.495, $PaCO_2$ 25.7 mmHg, PaO_2 175 mmHg, K^+ 2.59 mmol/L, base excess −2.4 mmol/L, hemoglobin 7.6 g/dL, and serum lactic acid 2.3 mmol/L. The patient could blink and control her eye movements. Six days after admission to the ICU, blood gas analysis showed normal lactate levels (1.5 mmol/L) (Fig. 1). The patient's symptoms (fatigue, confusion, hypotension, tachycardia, and dyspnea) resolved within the same period. On Day 9 after admission to the ICU, the patient was transferred to the infectious disease department. Antituberculosis drugs, with the exception of linezolid, were reintroduced, with no increase in blood lactate level.

The patient provided this perspective: "*Because of tuberculous meningitis, my nervous system is damaged, my lower limbs are stiff and numb, and walking is difficult, so I need to walk with the help of crutches. However, memory, digestion and defecation are normal. Tuberculous meningitis has been cured. Thank you for the timely diagnosis, timely use of hemofiltration and cessation of linezolid, otherwise I would have been died.*"

Informed consent was obtained from the patient for publication of this case report details.

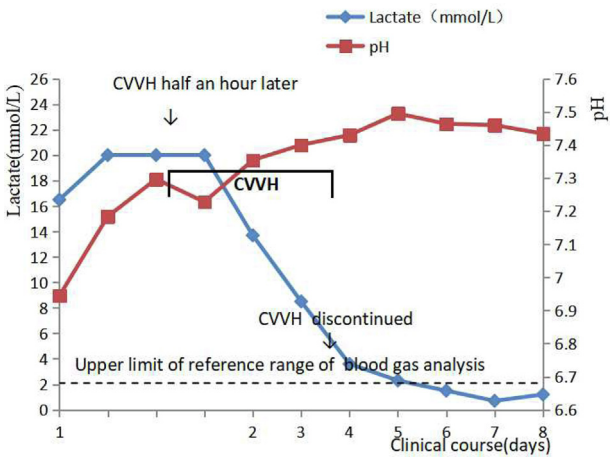

Fig. 1. Patients clinical course, showing days before and after the patient was transferred to the ICU. On admission to the ICU, blood lactate was above the level of detection (max. 20 mmol/L). CVVH was performed on admission to the ICU at 18:00 to ICU Day 4 at 21:00.

3. Discussion

In this case report, we describe a 64-year-old Chinese woman with a diagnosis of tuberculous meningitis who was admitted to our hospital with lactic acidosis. The patient was being treated with an oral antituberculosis regimen that included isoniazid, ethambutol, pyrazinamide, levofloxacin, rifapentine, and linezolid.

Three weeks before admission to our hospital the patient had abnormal liver function, which was restored after stopping rifampicin. Electrocardiogram and color ultrasound excluded lactic acidosis caused by other pathology. Isoniazid overdose has been associated with lactic acidosis; however, the patient was taking the prescribed dose. Severe lactic acidosis was reversed by withdrawing antituberculosis drugs and using CVVH. When the patient's condition was stable, she was transferred to the infectious disease department and antituberculosis drugs, with the exception of linezolid, were reintroduced. This did not result in recurrence of lactic acidosis. The causal relationship between lactic acidosis and linezolid was categorized as 'probable' on the Adverse Drug Reaction (ADR) Probability Scale (Naranjo et al., 1981). This case demonstrates that CVVH has potential as an alternative to discontinuation of linezolid alone for rapid reversal of linezolid-associated severe lactic acidosis.

Linezolid-associated lactic acidosis results in a defect in oxygen utilization at the mitochondrial level. Patients have normal-to-high oxygen delivery, high venous oxygen saturation, but do not respond to interventions that effectively increase whole-body oxygen delivery (Im et al., 2015). Mitochondrial ribosomes are closely related to bacterial ribososmes, such that linezolid-associated lactic acidosis is caused by an interaction between linezolid and mitochondrial ribosomes (Santini et al., 2017). Linezolid inhibits mitochondrial protein synthesis, decreases mitochondrial respiratory chain enzyme activity, limits aerobic respiration, and accelerates anaerobic glycolysis and lactate generation independently from tissue hypoxia (Santini et al., 2017). Lactic acidosis is characterized by a build-up of lactate in the body and excessively low pH in the tissues and blood.

Risk factors for linezolid-associated lactic acidosis include older age, extended linezolid therapy (Apodaca and Rakita, 2003; De Vriese et al., 2006; Velez and Janech, 2010; Cheng et al., 2018), liver (Sasaki et al., 2011; Ager and Gould, 2012; Filho et al., 2016) and/or kidney dysfunction (Dellinger et al., 2013), mitochondrial DNA A2706G polymorphism (Del Pozo et al., 2014), and polypharmacy (Pea et al., 2006; Kraut and Madias, 2014; Song et al., 2015; Cattaneo et al., 2016; Morata et al., 2016; Santini et al., 2017; Christopher and Robert, 2018), which can impact mitochondrial function. In the present case, the patient was diagnosed with tuberculous meningitis. The patient (age > 60 years) had a history of left kidney atrophy and was treated with linezolid for 28 days and a combination of antituberculosis drugs that can cause liver damage, all of which increased her risk for linezolid-associated lactic acidosis.

Screening, risk stratification, and prognosis of lactic acidosis is determined by blood lactate level (Kraut and Madias, 2014). While transient hyperlactatemia may not be predictive of poor prognosis (Velez and Janech, 2010), sustained hyperlactatemia has been associated with adverse outcomes, including increased risk of in-hospital mortality (Kraut and Madias, 2014). There is a dose-response relationship between blood lactate levels and mortality (Filho et al., 2016). Late recognition of severe lactic acidosis tends to result in worse outcomes (Kraut and Madias, 2014). Patients experiencing linezolid-associated lactic acidosis may suffer dyspnea, nausea, vomiting, mental status changes, tachycardia, and hypotension (Asadi et al., 2017). In our patient, maximum blood lactate level was above the level of detection, and she experienced acute kidney dysfunction, tachypnea, lethargy, fatigue, muscle weakness, diarrhea, hypotension, and tachycardia.

The effectiveness of linezolid can be optimized by therapeutic drug monitoring. Adequate dose exposure (2–10 mg/L) will ensure sufficient therapeutic activity and minimize the incidence of adverse events (Pea et al., 2012; Cattaneo et al., 2013; Nukui et al., 2013; Matsumoto et al., 2014; Richards and Brink, 2014). Select patients, such as those with impaired liver and renal function, may be more susceptible to linezolid-associated lactic acidosis. Accordingly, patients with Child's class C liver cirrhosis and end-stage renal disease (ESRD) should receive decreased doses of linezolid and be monitored after 48 h (steady state) until therapeutic trough concentration has been achieved (Pea et al., 2017).

The initial dose of linezolid is usually 1200 mg/d. To ensure long-term efficacy and tolerability, after 4 to 6 weeks, the dose of linezolid should be reduced to 600 mg/d, or 300 mg/d if patients experience adverse reactions (Koh et al., 2009; Lee et al., 2012; Chang et al., 2013; Tang et al., 2015; Srivastava et al., 2017). A systematic review and meta-analysis investigating the efficacy and tolerability of linezolid in the treatment of patients with multidrug-resistant or extensively-drug-resistant tuberculosis revealed treatment success was 89.47% for linezolid daily doses > 600 mg and 76.14% for linezolid daily doses $\leq$ 600 mg/d, with no significant difference between groups (P = 0.069) (Agyeman and Ofori-Asenso, 2016).

Similar to the management of metformin-associated lactic acidosis, patients with lactic acidosis and hyperlactemia (>15 mmol/L) and acidemia (pH < 7.2) should be suggested for renal replacement therapy (Calello et al., 2015),which should be ceased at a lactate concentration < 3 mmol/L and pH of > 7.35. Hemodialysis and CVVH are the most common renal replacement therapy (Pannu and Gibney, 2005). CVVH has been used for the treatment of severe acidosis (Leonaviciute et al., 2018), and is an option for linezolid-associated severe lactic acidosis. In our case, severe lactic acidosis was rapidly reversed by withdrawing antituberculosis drugs and using CVVH.

4. Conclusion

Linezolid-induced lactic acidosis is a life-threatening disease that requires close monitoring of blood gases, blood lactate level, and serum linezolid trough concentration during treatment, especially in elderly patients with prolonged linezolid exposure, liver and kidney dysfunction, and a prior history of combination therapy that affects mitochondrial function. Treatment of critically ill patients with linezolid-induced severe lactic acidosis should couple drug discontinuation with renal replacement therapy rather than being limited to drug discontinuation alone.

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Author contributions

All authors meet the ICMJE authorship criteria. NZ was responsible for data collection and drafting the manuscript. FZ and ZC participated in the critical care of the patient. RH participated in study design. JL and JX participated in drafting the manuscript, critically revising it for important intellectual content, and approved the final version for submission.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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