Case report

Severe lactic acidosis after re-exposure to linezolid in a person living with HIV and multidrug resistant tuberculosis: a case report

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Abstract:
Linezolid-induced lactic acidosis is rare and portends a poor prognosis. The mechanism of toxicity may be related to inhibition of mitochondrial ribosomes. We present the first case in the literature of a patient with HIV and multidrug resistant tuberculosis with fatal lactic acidosis secondary to linezolid re-exposure.

The index case relates to a 37-year-old lady with a background medical history of HIV, on fixed combination antiretroviral therapy. In addition, she had multidrug resistant pulmonary tuberculosis and was being treated on a salvage antituberculosis regimen containing linezolid. She presented with a 1-day history of back pain, nausea and vomiting. Clinically she was severely acidotic with a lactate of 12 mmol/L, which peaked at 19 mmol/L. A presumptive diagnosis of lactic acidosis was made based on the history and exclusion of other causes. The patient demised despite management in the intensive care unit with continuous veno-venous haemodialysis (CVVH) and mechanical ventilation.

The diagnosis of linezolid-induced lactic acidosis requires a high index of suspicion and exclusion of other causes. In the absence of definitive treatment, early diagnosis, drug discontinuation and prompt supportive management including continuous veno-venous haemodiafiltration are key in helping to reduce the high mortality associated with this toxicity.

Keywords: Linezolid, lactic acidosis, Human Immunodeficiency Virus, multidrug resistant tuberculosis

INTRODUCTION

Linezolid is indicated for infections caused by vancomycin-resistant enterococci, methicillin resistant Staphylococcus aureus and multidrug resistant tuberculosis.(1,2) Serious adverse effects include optic neuritis, myelosuppression, and lactic acidosis.(2) The latter having a case fatality rate of 26%, based on a literature review of 35 articles and 47 cases.(3)

Linezolid induced lactic acidosis is due to inhibition of mitochondrial ribosomes which leads to reduced protein synthesis and a reduction in the enzymes required for aerobic metabolism and oxidative phosphorylation. This limits aerobic energy production, with increase in anaerobic glycolysis and increased lactate production. The end result is the accumulation of lactate to facilitate anaerobic metabolism for the generation of ATP.(4,5) Mitochondrial DNA A2706G and G3010A mitochondrial 16S rRNA polymorphisms are linked with linezolid induced lactic acidosis.(2,5) Mammalian mitochondrial ribosomes contain more proteins and less rRNA than bacterial ribosomes.(5) However, mammalian mitochondrial ribosomes have similarities with bacterial ribosomes especially in the
linezolid-binding site. This is aligned with the endosymbiotic theory, stating that mitochondria and bacteria originated from a common ancestor, which explains why mitochondrial ribosomes are unintended off-targets of drugs acting on the bacterial ribosomes.

CASE STUDY

The index case was a 37-year-old female with a background of HIV, on a fixed drug combination antiretroviral treatment consisting of tenofovir, lamivudine and dolasetrigravir for an unknown duration. She was virologically suppressed, with a CD4 count of 619 cells/mm³. Her retroviral disease was complicated with multidrug resistant pulmonary tuberculosis (MDR-TB) diagnosed in June 2020. Around the time of initial diagnosis of MDR-TB, she was started on a short bedaquiline regimen containing bedaquiline, linezolid, isoniazid, levofloxacin, clofazimine, pyrazinamide, and ethambutol. The initial dose of linezolid was 600 mg daily and it was prescribed for 2 months. There were no adverse events noted during the initial exposure to linezolid. Approximately 1 year later, on 27 May 2021 she was failing the short bedaquiline regimen and was switched to a rescue regimen containing bedaquiline, linezolid, terizidone, para-aminosalicylic acid, ethionamide, delaminid, imipenem, co-amoxicillin/clavulanic acid and clofazimine. She presented 5 weeks later with a 1-day history of back pain, nausea and vomiting. She was normotensive and alert despite a lactate of 12 mmol/L. Her creatinine level was 68 μmol/l with an eGFR of > 60 ml/min/1.73 m², before initiation of linezolid. A provisional diagnosis of linezolid-induced lactic acidosis was made. Her APACHE II score was 9.

MANAGEMENT AND OUTCOME

All medicines were stopped, and an 8.5% sodium bicarbonate infusion was initiated at 100 ml/hour. In addition, a dextrose infusion supplemented with potassium was administered for correction of hypoglycaemia and hypokalaemia. Slow low efficiency dialysis was commenced, however 15 minutes later she developed hypotension. Haemodialysis was discontinued, and normal saline bolus infusions and quadruple strength adrenaline infusions was required to maintain her blood pressure. Despite four hours of continuous veno-venous haemodialysis she had cardiorespiratory arrest and demised.

DISCUSSION

Linezolid induced lactic acidosis is a diagnosis of exclusion requiring a high index of suspicion. The patient had no significant renal or liver disease and was not septic and was well perfused. We therefore attributed the hyperlactataemia to linezolid. Management included cessation of all drugs and institution of supportive therapy. Linezolid-induced lactic acidosis has been reported in patients with MDR-TB. However, there are no published reports of a fatal episode occurring during second exposure to linezolid.

Her lactate peaked at 19 mmol/l. The highest published linezolid induced hyperlactataemia is 38.1 mmol/l in a 6-month-old female with protein losing enteropathy, liver impairment and glycosylation disorder. In a case series of 47 patients with linezolid induced hyperlactataemia, more than half the patients had lactate levels between 3 and 10 mmol/L. In our opinion, her lactate of 19 mmol/l in the setting of MDR TB, retroviral disease and resource limited public health care sector, portends a poor prognosis.

The incidence of linezolid induced lactic acidosis in our setting is unknown. The Food and Drug Administration's adverse event reporting system found 275/6218 (4.42%) cases of linezolid induced lactic acidosis.

There is a paucity of data on risk factors for linezolid induced lactic acidosis. Genetic susceptibility and increased duration of therapy (>6 weeks) may be associated with a higher incidence of lactic acidosis.

Our patient had a total linezolid exposure of 13 weeks (8 weeks during the first exposure and another 5 weeks during the second exposure) with mild renal impairment, and this may have increased her risk of lactic acidosis. We are uncertain whether linezolid used in the first course, predisposed her to development of lactic acidosis during the second exposure. The literature varies substantially with respect to duration of linezolid therapy at time of diagnosis of lactic acidosis, from a minimum of 1 day to a maximum of 109 days of continued therapy.

Our case differs in that our patient developed lactic acidosis during a second exposure to linezolid. Reasons for this are unknown, but possible reasons may be that the patient was non-adherent to the first regimen, was asymptomatic during the first exposure or had normal renal function when linezolid was first used.

At our hospital, CVVHD can only be performed in the intensive care unit (ICU). There are limited ICU beds, and we reserve CVVHD for haemodynamically unstable patients. The patient was initially haemodynamically stable and thus CVVHD was not initiated. However, in retrospect, perhaps we should have initiated continuous renal replacement therapy as the patient was at high risk of haemodynamic instability given the severe lactic acidosis that may impair cardiac contractility and regulation of blood pressure.

In resource limited settings, peritoneal dialysis may be a therapeutic option in patients with linezolid induced lactic acidosis. There are no published cases of the use of peritoneal dialysis for linezolid induced lactic acidosis.

Given the patients severe lactic acidosis and haemodynamic instability, it was improbable that she would have responded to high concentration of adrenaline infusion. Adrenaline may also contribute to vasoconstriction and production of lactic acid in under perfused tissues.
Severe lactic acidosis after re-exposure to linezolid in a person living with HIV

In the absence of definitive therapy for a condition with a high mortality, prevention or at least early detection may allow for timely discontinuation of the offending agent and institution of corrective measures. High risk individuals, example those on longer duration of linezolid use (>6 weeks), renal and liver impairment, should be identified and alerted to the symptoms of lactic acidosis and serial venous blood gasses performed to monitor lactate levels. For rapid results, perhaps point of care “lactometers” may be used.

CONCLUSION
Linezolid induced lactic acidosis requires clinicians to have a high index of suspicion and is a diagnosis based on exclusion of other causes. Given the high fatality rate of this condition, management includes cessation of linezolid and best supportive care in a critical care unit.

Table 1. Blood gasses

<table>
<thead>
<tr>
<th>VBG* 10:00 04/07/2021</th>
<th>ABG* 17:32 04/07/2021</th>
<th>VBG* 18:16 04/07/2021</th>
<th>VBG* 19:45 04/07/2021</th>
<th>VBG* 20:42 04/07/2021</th>
<th>ABG* 2:38 05/07/2021</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>6.785</td>
<td>6.792</td>
<td>7.02</td>
<td>7.24</td>
<td>7.23</td>
</tr>
<tr>
<td>PCO₂ (mmHg)</td>
<td>12.5</td>
<td>38</td>
<td>27</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>PO₂ (mmHg)</td>
<td>26</td>
<td>279</td>
<td>23</td>
<td>41</td>
<td>34</td>
</tr>
<tr>
<td>BE (mmol/l)</td>
<td>–30</td>
<td>–25.6</td>
<td>–22.7</td>
<td>–21.8</td>
<td>–20</td>
</tr>
<tr>
<td>HCO₃⁻ standard (mmol/l)</td>
<td>1.83</td>
<td>5.5</td>
<td>5.1</td>
<td>9.0</td>
<td>9.9</td>
</tr>
<tr>
<td>SpO₂ (%)</td>
<td>98</td>
<td>96%</td>
<td>17%</td>
<td>65%</td>
<td>52</td>
</tr>
<tr>
<td>Na (mmol/l)</td>
<td>141</td>
<td>149</td>
<td>139</td>
<td>140</td>
<td>140</td>
</tr>
<tr>
<td>K (mmol/l)</td>
<td>4.6</td>
<td>4.7</td>
<td>3.9</td>
<td>2.9</td>
<td>3.8</td>
</tr>
<tr>
<td>Ca (ionised) (mmol/l)</td>
<td>1.15</td>
<td>1.17</td>
<td>1.01</td>
<td>0.60</td>
<td>0.74</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>11.4</td>
<td>9.0</td>
<td>5.5</td>
<td>3.4</td>
<td>2.9</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>12.0</td>
<td>19.0</td>
<td>&gt;15.0</td>
<td>&gt;15.0</td>
<td>&gt;15.0</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>0.35</td>
<td>Not recorded</td>
<td>0.42</td>
<td>0.29</td>
<td>0.32</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>11.9</td>
<td>10.1</td>
<td>13.0</td>
<td>9.0</td>
<td>9.9</td>
</tr>
</tbody>
</table>

Key: VBG* - Venous blood gas; ABG* - Arterial blood gas

REFERENCES