

Severe Acidemia in a Patient With Waldenström Macroglobulinemia



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INTRODUCTION

Lactate is produced through the metabolism of glucose and subsequently eliminated by both the liver and the kidneys. Lactic acidosis develops when the rate of production of lactate overwhelms the body's ability to clear it.¹ There are 2 main types of L-lactic acidosis: A (ischemic) and B (nonischemic). Etiologies for type B lactic acidosis² include: liver dysfunction, thiamine deficiency, malignancy, several drug associations, ketoacidosis, and mitochondrial disease (Table 1).³

Waldenström macroglobulinemia is a lymphoplasmacytic lymphoma with an IgM monoclonal gammopathy. A single case of Waldenström macroglobulinemia has been reported as cause of type B lactic acidosis.⁴ The proposed etiology of lactic acidosis in lymphoma is multifactorial, with contributions from anaerobic metabolism, liver dysfunction, and thiamine deficiency.⁵

CASE PRESENTATION

A 59-year-old man with a history of progressive IgM Waldenström macroglobulinemia despite chemotherapy (diagnosed 6 years before presentation), hypertension, and recent necrotizing pneumonia presented with neutropenic fever. A computed tomography scan of the chest on admission showed improving necrotizing pneumonia as well as bulky bilateral axillary lymphadenopathy. On day 9 of admission, blood cultures grew vancomycin-resistant *Enterococcus faecium*. At that time, venous L-lactate was 2.3 mmol/l, lactate dehydrogenase 657 U/L, bicarbonate 20 mg/dl, anion gap 13 meq/l, and creatinine 2.5 mg/dl. He was initiated on antibiotics with oral linezolid 600 mg every 12 hours for 2 days, and then received 5 days of intravenous linezolid 600 mg every

12 hours. On day 15, his blood pressure was 121/84 mm Hg, his heart rate was 86 beats/min, his temperature was 36.8 °C, and his respiratory rate was 18 breaths/min. The physical examination was unremarkable, including normal cardiovascular and pulmonary examination. The venous lactate was 17 mmol/l and venous pH 7.26, venous PCO₂ 25 mm Hg, serum bicarbonate 10 meq/l, and anion gap 28 meq/l. The trend of laboratory values is shown in Table 1. Creatinine was 1.6 mg/l, aspartate aminotransferase was 74 U/l, alanine aminotransferase was 83 U/l, albumin was 1.5 g/dl, total protein was 8.3 g/dl, and total bilirubin was 2.8 mg/dl. The patient's white blood cell count was 20,400/μl with an absolute neutrophil count of 0/μl and a platelet count of 30,000/μl. Lactate dehydrogenase rose to 1253 U/l. He had not received acetaminophen, metformin, salicylates, isoniazid, or propofol.

Upon recognition of lactic acidosis, linezolid was discontinued. The patient was subsequently started on isotonic, intravenous bicarbonate therapy (150 meq/l sodium bicarbonate in 5% dextrose at 150 ml/hr) in addition to empiric thiamine administration. Intravenous calcium was given as needed. The pH, lactate, and bicarbonate measurements improved over the next several days (Figure 1).

DISCUSSION

The patient's laboratory values are consistent with an elevated anion gap metabolic acidosis with respiratory compensation (expected PCO₂, 23 mm Hg ± 2). Thus, a broad differential diagnosis includes the components of GOLDMARK⁶: glycols, oxoproline, L-lactate, D-lactate, methanol, aspirin, renal failure, and ketoacidosis.

In this case, we have a markedly elevated L-lactate level in the absence of ischemia or hypoperfusion. The

Table 1. Etiologies of L-lactic acidosis

Type A lactic acidosis	Type B lactic acidosis
Hypoperfusion	Drug-induced (e.g., linezolid, metformin, isoniazid, antiretrovirals, propofol, β -adrenergic agonists, or cyanide)
	Alcoholism
	Malignancy
	Thiamine/riboflavin deficiency
	Congenital or acquired mitochondrial defect
	Liver dysfunction

etiology of lactic acidosis was temporally associated with linezolid administration with a possible contribution of hematologic malignancy. Other etiologies of L-lactic acidosis are summarized in Table 2.

Lactate is effectively metabolized and excreted by both the liver and kidneys, with the liver clearing $\leq 70\%$ of whole-body lactate.⁷ While data are sparse, lactate (molecular weight, 89.1 g/mol) clearance during intermittent or continuous hemodialysis is approximately 20% of endogenous clearance.^{7,8} Kidney replacement therapy should be considered in patients with significantly impaired kidney function, respiratory acidosis, profound acidemia (sustained pH < 7.1), or liver failure. Linezolid (molecular weight, 337 g/mol) has a half-life of 3–7 hours; 50% is excreted by the kidneys and 31% is protein bound. Kidney replacement therapy removal of linezolid may be considered in patients with significant kidney impairment, as drug levels can be reduced $\leq 30\%$ by hemodialysis.⁹

In our case, the patient was started on intravenous isotonic bicarbonate therapy (150 meq/l sodium bicarbonate in 5% dextrose at 150 ml/h). His pH remained above 7.1 and he maintained adequate respiratory compensation, thus we did not resort to kidney replacement therapy.

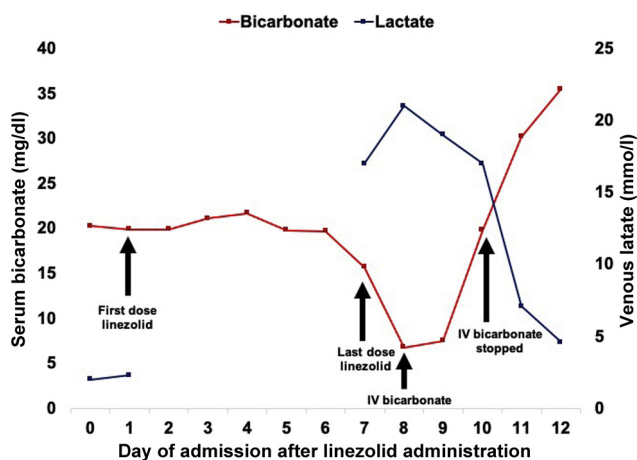


Figure 1. Trend of venous pH, carbon dioxide partial pressure, L-lactate, and bicarbonate. Day 6 refers to the day after initiation of linezolid treatment. The last dose of linezolid was given on day 7. Treatment with intravenous bicarbonate therapy was started on day 8 and stopped on day 10.

Linezolid is a bacteriostatic antimicrobial that targets the A-site of the peptidyl transferase center in bacterial ribosomes, blocking aminoacyl-transfer RNA from binding to the 23S portion of the 50S subunit and preventing bacterial protein synthesis. Linezolid can also bind human mitochondrial ribosomes and disrupt protein synthesis (Figure 2).^{S1} Mitochondrial DNA encodes proteins involved in the respiratory chain complex. Interference with synthesis of these proteins can limit aerobic respiration, leading to anaerobic glycolysis and increased lactic acid generation.^{S1}

While linezolid-induced lactic acidosis is uncommon, the incidence has been reported near 7% with mortality reported to be $>40\%$.^{S1,S2} Interestingly, duration of linezolid use has not been consistently described as a clear risk factor.^{S2} In a 2017 systematic review, linezolid-induced lactic acidosis was reported in 48 adults with a mean age of 63 years and an average linezolid treatment duration of 35 days. Blood lactate levels averaged 13 mmol/l among these patients.^{S1} Of note, 27% of these patients had acute kidney injury or chronic kidney disease at the time of linezolid therapy initiation. Though linezolid trough levels are not routinely measured in clinical practice, abnormally high levels were found in all 5 patients in whom levels were measured. In addition to severe metabolic acidosis, these patients may also present with nonspecific signs and symptoms, including tachycardia, nausea, vomiting, abdominal discomfort, dyspnea, anemia, thrombocytopenia, liver dysfunction, pancreatitis, hypoglycemia, or cardiovascular collapse.^{S1}

Risk factors of linezolid-induced lactic acid are long term administration (>6 weeks), advanced age, impaired kidney function, and cotreatment with drugs that inhibit P-glycoprotein expression and thus linezolid clearance (e.g., omeprazole, amiodarone, amlodipine, or rifampin).^{9,S1,S3} Therapeutic drug monitoring may be prudent in those patients who receive cotreatment with medications that act as P-glycoprotein inhibitors.^{S3} Severe lactic acidosis associated with linezolid use has been reported in patients with mitochondrial DNA polymorphisms in the 16S portion of the 39S mitochondrial ribosome subunit.^{S4,S5} Pathophysiologically, these polymorphisms present a compelling risk factor for linezolid-induced lactic acidosis. However, the high

Table 2. Trend of venous pH, carbon dioxide partial pressure, L-lactate, and bicarbonate

	Day 6	Day 7	Day 8	Day 10	Day 11	Day 12
pH	—	7.26	7.06	7.38	7.44	7.46
PCO ₂ , mm Hg	—	25	22	37	48	54
HCO ₃ ⁻ , mg/dl	19.7	11	6.8	19.8	30.2	35.5
L-lactate, mmol/l	—	17	21	17	7.1	4.6

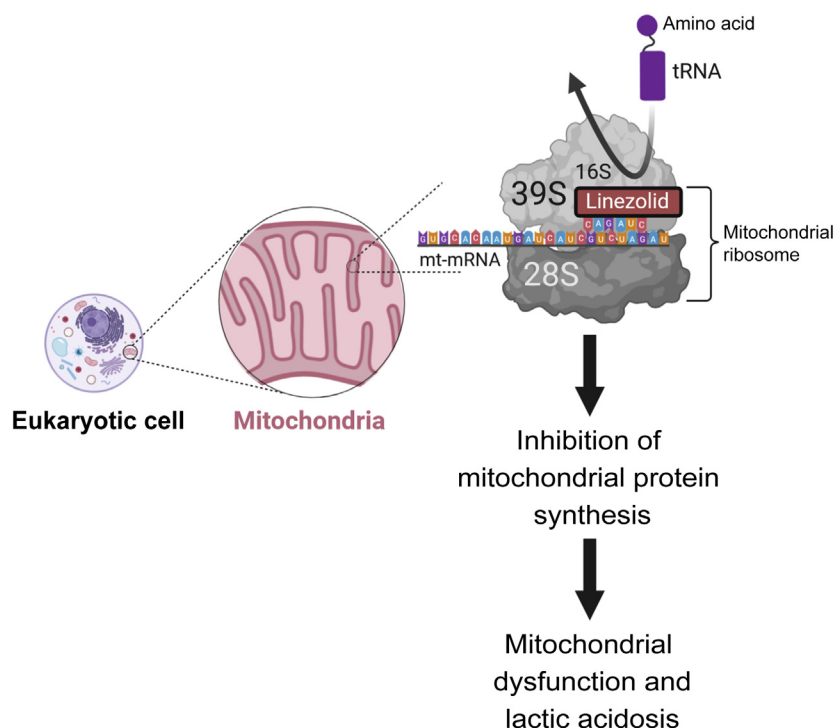


Figure 2. Linezolid prevents bacterial protein synthesis by blocking aminoacyl-transfer ribonucleic acid (tRNA) from binding to the ribosome at the A-site of the peptidyl transferase center where peptide-bond formation occurs. It can similarly bind to the 16S portion of the 39S subunit of eukaryotic mitochondrial ribosomes and disrupt translation of mitochondrial (mt)- messenger (m)RNA to prevent synthesis of proteins involved in the respiratory chain complex - thus limiting aerobic respiration and increasing lactic acid generation. Figure created with [BioRender.com](#).

frequency of mitochondrial DNA polymorphisms and rarity of this disease process suggest that additional risk factors are likely at play.

Potential mechanisms for development of lactic acidosis caused by hematologic malignancy include impaired lactate clearance from liver and kidney dysfunction, high rate of anaerobic glycolysis in neoplastic cells, tumor necrosis factor- α (can impair pyruvate dehydrogenase), local tissue hypoperfusion from mass effect or leukemic microemboli, thiamine deficiency/availability, and tumor lysis syndrome. In this case, it is possible that the presence of high tumor burden caused by Waldenström macroglobulinemia played a role in development of lactic acidosis as the patient's lactate dehydrogenase nearly doubled as the lactate rose. In patients with type B lactic acidosis, oxygen delivery is generally preserved. High venous oxygen saturation levels have been reported in patients with linezolid-induced lactic acidosis, thus supporting a state of preserved oxygen delivery with diminished

mitochondrial function.^{S1} Increasing oxygen delivery has not been shown to be effective in these cases.

In conclusion, this case shows that severe lactic acidosis in the setting of linezolid may present without obvious symptoms and can be successfully managed with intravenous buffer solutions and withdrawal of the medication. Teaching points from this case are summarized in [Table 3](#). Here, venous lactate and serum bicarbonate returned to normal 5 days after stopping linezolid. Health care providers should maintain a high index of suspicion for lactic acidosis in patients who are taking linezolid, particularly in those with risk factors including malignancy, reduced kidney function, liver dysfunction, acquired or inherited mitochondrial defects, and poor nutritional status.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

[Supplemental References.](#)

Table 3. Teaching points

Linezolid administration can precipitate type B lactic acidosis via mitochondrial protein synthesis disruption

Causes of type B lactic acidosis include congenital or acquired mitochondrial defects, malignancy, and liver dysfunction

Severe lactic acidosis in the setting of linezolid can be successfully managed with intravenous bicarbonate

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