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CASE REPORT

Hyperlactatemia Due to Linezolid Use: A Case Report

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Abstract

Lactate is a by-product of anaerobic respiration, and is cleared from blood by the liver and kidneys. Lactate levels greater than 2 mmol/L is defined as hyperlactatemia, and higher than 4 mmol/l with acidosis is defined as lactic acidosis. It is the most common cause of metabolic acidosis in hospitalized patients. Linezolid is an antibiotic in the oxazolidinone class that directly inhibits protein synthesis in the mitochondria of bacteria and may cause lactic acidosis, which may have a high mortality. In our article, we aimed to present a case who used linezolid for pneumonia and developed hyperlactatemia on the 12th day of treatment.

Keywords: Hyperlactatemia; lactic acidosis; linezolid

Lactate is a product of anaerobic glycolysis and is cleared from blood by the liver and kidneys. The daily lactate production in a normal adult is 15-20 mmol/kg and it is the product of pyruvate, which is formed by anaerobic respiration from all tissues. The liver is the primary organ responsible for lactate clearance. Under normal conditions, it metabolizes 100 mmol lactic acid per hour and keeps its plasma level below 1 mmol/L. The kidneys are responsible for the removal of 20-40% of the formed lactate. In hypoxia periods, lactate is converted to glucose by the Cori cycle to provide energy. A lactate level higher than 2 mmol/l is defined as hyperlactatemia, and lactic acidosis (LA) is defined as a pH level of <7.35 with a lactate level higher than 4 mmol/l. It is the most common cause of metabolic acidosis in hospitalized patients. It is usually associated with an increased anion gap, but can also be observed with a moderately normal anion gap (especially if hypoalbuminemia is present). There are two groups of LA: Type A and Type B. Type A is more common and may occur in patients with impaired tissue perfusion, with or without hypoxia. Type B is caused by genetic disorders that can cause accumulation of certain drugs, chemicals, toxic components or lactate. Unlike Type A LA, there is no systemic hypoperfusion in Type B LA. This type is seen due to a disorder at the cellular metabolism level. The most important problem in LA is the decrease in blood pH and myocardial depression, resulting in fatal cardiac arrhythmias. Below pH 7.2, this effect is even more evident. Decreased intracellular pH impairs myocardial contractility. Linezolid is an oxazolidinone antibiotic that targets bacterial protein synthesis by inhibiting the bacterial ribosomal subunit. The use of linezolid leads to Type B LA by directly inhibiting mitochondrial protein synthesis. The aim of treatment is to eliminate the underlying cause and to provide tissue perfusion [1–2].

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Case Report

A 74-year-old female patient, a housewife, applied to the emergency department with coughing and shortness of breath. She had a history of rheumatoid arthritis (for 30 years) and thyroid cancer (diagnosed with anaplastic thyroid cancer 1 year ago). The patient refused treatment (she's without follow-up). Her family history was unremarkable. There was no alcohol use or smoking. There was no history of medicine use. Vital signs of the patient in the emergency department were as follows: Fever: 36.4°C, pulse: 77/min and rhythmic, arterial blood pressure: 132/78mmHg, respiratory rate: 25/min and SpO2: 97%. On physical examination, the general status of the patient was moderate, with normal level of cooperation and orientation. There was a mass of 15*20 cm in the patient's neck, to the right of the midline, which was also explored by neck ultrasound. She had was stridor lung sounds and had tachypnea. In the chest computed tomography (CT), the chest anteroposterior (AP) diameter increased, the ascending aortic diameter was 39 mm, and the cardiothoracic ratio was increased, at the upper limit of normal. There were peribronchial cuffing and pleural thickening at the level of the basal segments of both lungs, and there were several fibronodular densities in the basal segments of both lungs, the largest of which was approximately 7 mm in diameter in the subpleural area at the level of the left lung lower lobe laterobasal segment. Electrocardiography featured sinus rhythm, and heart rate was 95/min. Ejection fraction on echocardiography was 60%, with a mild aortic regurgitation present. The laboratory test results of the patient were as follows: leukocytes: 31,000, neutrophils: 29,000, Hb: 10.3 g/dL, HCT: 33.5, MCV: 75.2, Plt: 395,000, Glucose: 113 mg/dL, AST: 12 IU /L, ALT:<6 IU/L, BUN:19 mg/dL, Creatinine: 0.63 mg/dL, Albumin:4.01 g/dL, Na:136 mEq/L, K:4.4 mEq/L; in arterial blood gas (ABG) measurement, pH: 7.36, pO_2: 94 mmHg, pCO_2: 42 mmHg, sO_2: 97%, HCO3: 23 mmol/L, Lactate: 2.6mmol/L, Anion gap: 10, C-reactive protein (CRP): 6.1 mg/dL , procalcitonin: 0.19 ng/dL; in the complete urinalysis, density: 1013, pH: 5, ketone: trace, protein: ++, glucose: trace, erythrocyte: 2, leukocyte: 57. The patient was interned for operation by the otorhinolaryngology (ENT) diseases department. Meropenem 2*1 gr, Colistin 2*110 mg, Linezolid 2*600 mg treatment was started by Infectious Diseases Department for the treatment of pneumonia during hospitalization in the ENT diseases service. Meropenem-susceptible Klebsiella pneumoniae was isolated from the deep tracheal aspirate culture. During the follow-ups, creatinine levels increased (2.11mg/dL) and colistin was discontinued due to its nephrotoxic effect. The patient was transferred to the Internal Medicine Department with the diagnosis of acute renal failure and pneumonia on the 5th day of linezolid and meropenem treatment. On the 12th day of the antibiotic treatment, the patient's general condition worsened and her blood gas measurements were as follows: pH: 7.42, pO_2: 88 mmHg, pCo_2: 20 mmHg, HCO_3: 16.9 and hyperlactatemia (lactate: 7.1 mmol/L). The patient who had no growth in the control cultures, with continued leukocytosis and elevated CRP levels, and negative procalcitonin level (0.77 ng/dL), was consulted to the Hematology Department with peripheral smear. Leukocytosis was thought to be secondary to malignancy. In consultation with Infectious Diseases Department, hyperlactatemia was thought to be due to linezolid, and the antibiotic treatment of the patient whose active infection disappeared was terminated. In subsequent arterial blood gas follow-ups, serum lactate levels decreased and the general condition of the patient improved (Fig. 1). On the 16th day of treatment, the patient's lactate value was 3.2 mmol/L, creatinine was 1.49 mg/dL, and BUN was 28 mg/dL. The patient, whose general condition improved and pneumonia treatment was completed, was discharged for oncological treatment and follow-up.

Discussion

The prognosis of lactic acidosis is quite poor. Mortality is 75% in those with a serum lactate level of 5 mmol/L, and survival rate is very poor when the lactate level reaches 10 mmol/L [2]. In a 2015 study involving 72 patients, the incidence of LA was found to be 6.8% in patients using linezolid [3]. In a meta-analysis of 47 patients in which 35 articles were reviewed, 25% of patients who developed LA due to linezolid resulted in death [4]. In our case, lactate levels regressed after discontinuation of linezolid, and the clinical status of the patient improved. Although the first

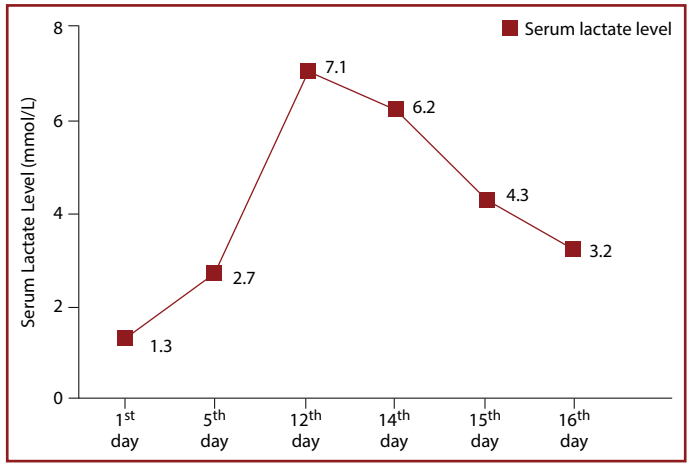

Figure 1. Serum lactate level change.

reported case of LA due to linezolid was due to prolonged antibiotic use, other cases occurred soon after initiation of the drug. In our case, hyperlactatemia developed after prolonged antibiotic use and our case did not have acidosis in blood gas measurements. In LA, blood pH may be normal or increased secondary to other underlying conditions. In our patient, hyperlactatemia was accompanied by respiratory alkalosis. Therefore, no acidosis was detected in blood gas. The fact that the lactate level was at the upper limit (1.3 mmol/L) even before antibiotic use can be explained by the rather large neck tumor mass (15*20 cm) which produces lactate by anaerobic glycolysis. The aim of the treatment of hyperlactatemia and lactic acidosis is to eliminate the underlying cause and to provide tissue perfusion. For this purpose, vasopressors, fluid therapy, bicarbonate therapy, renal replacement therapy (RRT) and alternative buffer treatments (Tromethamine (THAM), carbicarb, dichloroacetate) can be used. Bicarbonate therapy is recommended in severe acidemia (pH<7.1 and serum bicarbonate level below 6 mEq/L). Rapid infusion of bicarbonate may increase the partial pressure of CO2 and lactate production in the blood, decrease the level of ionized calcium, and cause hypernatremia. The potential side effects of bicarbonate therapy in patients with lactic acidosis have prompted the emergence of alternative tamponade therapies. The first of these, THAM, is an amino alcohol. Its advantage over bicarbonate is that it reduces CO_2. The second alternative buffer is carbicarb. Carbicarb is a mixture of equimolar sodium carbonate (Na_2CO_3) and sodium bicarbonate ($NaHCO_3$) and creates less CO_2. Dichloroacetate, on the other hand, is a molecule that accelerates the metabolism of lactate by increasing the activity of the pyruvate dehydrogenase enzyme [5]. RRT options are, bicarbonate hemofiltration, peritoneal dialysis, and continuous veno-venous hemofiltration. Bicarbonate hemofiltration binds lactate to remove it from the blood and improves the acidosis state. Bicarbonate hemofiltration was found to be superior to other options in correcting acidosis [6]. Our patient did not have severe acidosis, and her blood pressure was within normal limits. Therefore, no bicarbonate therapy or vasopressor therapy was required. Lactate levels regressed after discontinuation of linezolid.

As a result, an increase in lactate level affects many systems, especially the cardiovascular system, and deepening acidosis can cause mortality. It should be kept in mind that hyperlactatemia and lactic acidosis develop at a serious rate of 6.8% in patients who are started on linezolid, and a strict blood gas, serum lactate level and vital signs follow up should be performed.

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

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