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Emergency Medicine

A RARE CAUSE OF REFRACTORY LACTIC ACIDOSIS

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ABSTRACT Lactate, or lactic acid, is an end-product of anaerobic metabolism. Type A lactic acidosis, caused by the body's inability to meet oxygen delivery demands, is a common reason for the accumulation of lactate. If lactic acidosis continues, other potential causes should be investigated. Here, we describe the case of a 53-year-old male who initially presented with abdominal distension and was found to have significant lactic acidosis. His blood sugar levels improved with dextrose supplementation; however, lactic acidosis persisted despite fluid hydration and empiric antibiotics. After excluding other causes of lactic acidosis, he was started on intravenous thiamine due to suspicion of thiamine deficiency. Thiamine supplementation led to a significant improvement in lactic acid levels. Thiamine, a water-soluble vitamin, acts as a necessary cofactor in various biochemical reactions.

KEYWORDS :

INTRODUCTION

Lactic acidosis is a potentially life-threatening event that may occur in primary and acquired diseases. In critical care, lactate serves as a prognostic indicator, where high mortality and adverse outcomes are often linked with lactic acidosis. Lactic acidosis type A is the most common type, characterized by hypoxemia that is typically a result of septic shock. However, it can also be caused by hypovolemic shock, cardiogenic shock, and other diseases that result in tissue hypoperfusion. Treatment for lactic acidosis suspected to be caused by septic shock involves swift fluid resuscitation and IV antibiotic administration to address a possible underlying infection. Type B lactic acidosis is suspected in patients with consistently high blood lactate levels but no signs of oxygen deficiency. There are several potential causes of type B lactic acidosis, including multiorgan failure, drugs/toxins (e.g., metformin), vitamin deficiencies (e.g., thiamine), and metabolic abnormalities.[1]

Severe thiamine deficiency, a rare cause of type B lactic acidosis, is often linked to chronic alcoholism, GI malabsorption, and poor nutrition in underdeveloped countries.

Case Presentation

A 53-year-old man was admitted to the ICU after experiencing abdominal distension for 3 days following a binge drinking episode where he had 14 standard drinks. At the time of evaluation, his vital signs demonstrated tachycardia at 128 bpm and hypotension at 100/60 mmHg. Lethargy was a notable observation during his physical examination. The preliminary blood work displayed mild leukocytosis, normocytic anemia, hyponatremia, and elevated liver function tests (Table 1). Apart from disclosing usual alcohol use, family members observed developing fatigue and a 5-kilogram decrease in weight. ABG findings on admission revealed an elevated anion gap metabolic acidosis, with values such as severe hyperlactatemia exceeding the measurement capabilities of our hospital's ABG machine. The patient was treated with isotonic bicarbonate fluids. Over the next few hours, lactate levels stayed elevated above 15 mmol/l as pH showed slow improvement. The urine analysis hinted at the presence of a urinary tract infection. Thiamine deficiency and alcoholic hepatitis were considered clinically following the exclusion of other causes of hyperlactatemia like hypoxia and drug-induced lactic acidosis. Thiamine therapy at a high dosage of about 900 mg per day was initiated for the patient for three days. Lactate levels dropped below 15mmol/l after 28 hours of ICU admission and returned to normal after 48 hours, with significant improvement in the patient's sensorium.

DISCUSSION

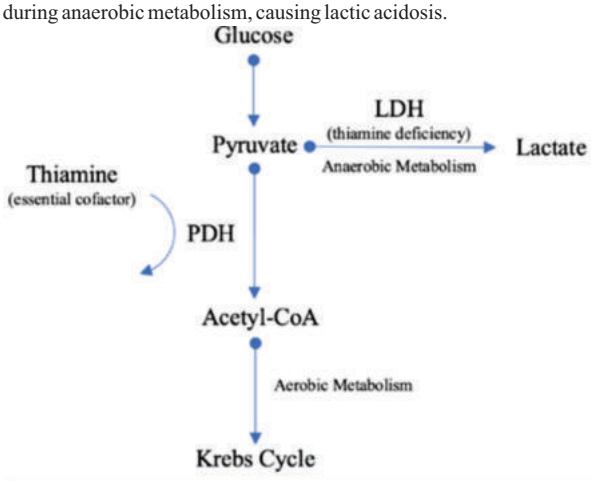
Lactate, a byproduct of anaerobic metabolism, is produced by the majority of body tissues and serves as a clinical prognostic indicator. Lactic acidosis can result from various factors, including sepsis, hypovolemia, medications, hypoxia, and systemic hypoperfusion. There are three types of lactic acidosis: type A, B, and D.

Type A lactic acidosis occurs due to severe hypoxia leading to reduced blood flow in conditions like septic shock, cardiac arrest, or low blood volume.

Severe thiamine deficiency can be a rare and often overlooked reason for type B lactic acidosis, commonly observed in chronic alcoholism, GI malabsorption, and in undernourished populations in developing nations.[2]

Typically, during aerobic metabolism, pyruvate goes into the mitochondria and gets converted to acetyl-CoA by the pyruvate dehydrogenase (PDH) complex. Acetyl-CoA is utilized in the Krebs cycle to produce adenosine triphosphate (ATP).

The absence of thiamine results in lactic acidosis as thiamine plays a crucial role in the PDH complex converting pyruvate to acetyl-CoA. When there is a thiamine deficiency and pyruvate cannot enter the Krebs cycle, it is transformed into lactate by lactate dehydrogenase during anaerobic metabolism, causing lactic acidosis.



LDH. lactate dehydrogenase; PDH. pyruvate dehydrogenase.

Reported causes of thiamine deficiency–associated lactic acidosis in literature encompass insufficient vitamin intake, prolonged alcohol abuse, and functional deficiency. Thiamine deficiency can be observed in various conditions related to malnourishment, including Crohn disease and hyperemesis gravidarum. Primary thiamine deficiency is caused by genetic factors and defective transport. Thiamine deficiency can also result from extended use of IV dextrose solutions/TPN lacking thiamine support or in children with thiamine-deficient diets. Methotrexate in hematological malignancies can interfere with

thiamine transport systems, potentially leading to lactic acidosis due to reduced thiamine availability, similar to thiamine deficiency.

In case studies involving pediatric patients, enteral or parenteral malnutrition are the main reported causes of thiamine deficiency-related lactic acidosis.[3]

Thiamine deficiency disorders are classified into 5 categories according to the typical symptoms observed in specific age groups.

The first group describes the acute cardiological manifestation commonly found in infants who are only breastfed. It starts with general symptoms such as colic and restlessness, then progresses to cyanosis and signs of heart failure.

The aphonic form, the second type of thiamine deficiency disorders, typically occurs between the ages of 4 to 6 months. It shows signs such as a hoarse cry, restlessness, and breathlessness.

Third, the pseudomeningitis form typically presents in infants aged 7 to 9 months. This form is characterized by nystagmus, muscle twitches, a bulging fontanelle, seizures, and may result in loss of consciousness.

Encephalopathy, the fourth category, is more commonly seen in older children or adults but can also manifest in infants. Patients might show apathy, nystagmus, ophthalmoplegia, ataxia, and, eventually, impaired consciousness/coma.

Peripheral neuropathies, often observed in both children and adults, are defined by symptoms like pain, tingling in extremities, muscle atrophy, reduced reflexes, and potential cranial nerve issues. Importantly, most symptoms are nonspecific, which makes the diagnosis challenging as patients are unlikely to present with all signs within a category.[4]

Potential Complications

Failure to consider various factors could harm thiamine-deficient patients, such as using extracorporeal therapies in critical illness and the dangers of giving IV glucose products before thiamine.

If untreated, lactic acidosis from thiamine deficiency can worsen into a critical condition requiring life-saving extracorporeal treatments. Additionally, pharmacokinetic changes have been documented for several micronutrients while on extracorporeal therapies.[5–7]

It is important to consider the impact of ECMO and CRRT on thiamine's pharmacokinetics, such as increased volume of distribution and exacerbated losses. It is crucial to identify and treat thiamine deficiency in these patients for their recovery.

In a state of thiamine deficiency, the body reverts to anaerobic metabolism, converting pyruvate to lactate. Providing glucose before addressing the thiamine deficiency will trigger glycolysis, resulting in increased pyruvate production without generating ATP. Pyruvate accumulates and continues to produce more lactate, worsening the lactic acidosisCells in an ATP-deficient state struggle to carry out essential functions, leaving them susceptible to external stressors like reactive oxygen species, resulting in cellular damage and eventual programmed cell death.[8]

Serum thiamine concentrations in several institutions need to be sent to a different lab for processing, leading to a wait of a week or more for results. Due to the delay and the seriousness of the illness, it may not be possible to wait for the serum thiamine concentration results before starting therapy. It is advisable to consider giving thiamine supplements to patients with persistent lactic acidosis despite conventional therapies, and to observe for any signs of improvement in their acidic state.

Furthermore, critical illness and the resulting organ dysfunction may necessitate the use of intricate extracorporeal therapies like CRRT and/or ECMO for many patients. Considering the potential impact on thiamine treatment is essential when evaluating these treatment modalities. ESPEN guidance states that CRRT contributes to a loss of water-soluble micronutrients, varying between the equivalent of 1 to 2 extra adult doses of selenium, zinc, and thiamine each day[9]. Hence, we suggest doubling or tripling the therapeutic IV thiamine dose during CRRT therapy.

An ECMO circuit can alter the pharmacokinetics of multiple medications, especially micronutrients.[10] Water-soluble vitamins, such as thiamine, are likely to be affected. There may be significant losses from hydrophilic medications getting stuck in the hydrophilic circuit. Furthermore, the use of priming solutions in the ECMO circuit can cause dilutional effects leading to an increase in volume of distribution. Ultimately, this causes a reduction in the amount of hydrophilic compounds in the plasma.

Lastly, it is important to consider preventing Wernicke encephalopathy and Korsakoff syndrome in patients deficient in thiamine. It is advisable to consider giving thiamine before administering IV glucose products to patients suspected of thiamine deficiency to prevent a severe outcome.

CONCLUSION

Even though there are no definite recommendations for the dosing and timeframe of IV thiamine in treating lactic acidosis resulting from thiamine deficiency, case studies indicate doses between 25 to 1000 mg IV as a single dose or multiple doses daily for several days. Considering the safety and affordability of IV thiamine, it could be justifiable to contemplate these dosing plans and monitor closely for any signs of improvement. Furthermore, if conventional treatments for lactic acidosis are ineffective, giving thiamine early to patients suspected of being deficient may prevent worsening of critical illness. Recommendations for critically ill adults suggest a dosage range from thiamine 100 mg IV once daily to 400 mg IV twice daily.

Although there is no specific data to support increasing thiamine supplementation in patients requiring extracorporeal therapies like CRRT and/or ECMO, we recommend raising the therapeutic dose. We suggest doubling or tripling the therapeutic dose during CRRT treatment. The recommended increase in dosage for ECMO is by at least 100% to 200%, with a maximum of 500 mg IV, 3 times a day throughout ECMO therapy. Lastly, it is advisable to provide thiamine to patients before giving IV glucose to prevent potential permanent neurological damage in lactic acidosis patients.

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