Case Report

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TANAFFOS

Methylprednisolone-Induced Hyperlactatemia: A Case Report

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Lactic acidosis is commonly encountered in critical care and can be a harbinger of life-threatening conditions and end-organ ischemia. Importantly, however, other etiologies of lactic acidosis exist. We review the first case of methylprednisolone-induced lactic acidosis in a previously healthy patient who suffered from traumatic spinal cord injury (SCI). A 19-year-old female presented to a level 1 trauma center after a fall resulted in lower extremity paralysis. After imaging revealed a chance fracture dislocation of T7-8 along with spinal cord compromise and swelling, the patient underwent emergent T5-T11 instrumented fusion. Postoperatively, she was given high-dose methylprednisolone in hopes of improving neurologic outcome; soon after administration, she developed lactic acidosis. After workup ruled out hypoperfusion and type A lactic acidosis, we determined that methylprednisolone likely induced non-ischemic, type B, lactic acidosis. The lactate quickly returned to baseline after steroid discontinuation. It is important for clinicians to consider type B lactic acidosis in the ICU in patients with persistent lactic acidosis after tissue hypoperfusion has been ruled out.

Keywords: Resuscitation; Lactic acidosis; Steroids; Spinal cord injury

INTRODUCTION

Lactic acidosis is commonly seen in the intensive care unit (ICU) and is often related to poor oxygen delivery with shock, hypoperfusion, and resultant anaerobic metabolism, termed "type-A" lactic acidosis (1). Accordingly, lactate is frequently assessed in those with shock or at risk of hypoperfusion, and lactate-guided resuscitation, where clinicians titrate fluid resuscitation to lactate normalization, is commonly employed. Importantly, however, hyperlactatemia can be due to other, non-perfusion-related causes. These, grouped as "type B" etiologies of lactic acidosis, can be related to hepatic or renal dysfunction (type B1), drugs or toxins (type B2), or inborn/acquired derangements in lactate metabolism (type B3). Type B2 is most common in intensive care, where beta-agonists are commonly administered (Table 1) (2). While type-A lactic acidosis may be a harbinger of life-threatening shock or tissue compromise, type-B lactic acidosis, particularly when medication-induced, is often benign. Differentiating type-A from type-B lactic acidosis can be crucial to patient management.

Methylprednisolone is a corticosteroid that may improve neurologic outcomes in acute traumatic spinal cord injury (SCI), though this is debated. When utilized, early initiation is strongly preferred, and high doses are typical. Changes in glucose and protein metabolism are expected, and adverse effects can occur, including significant hyperglycemia and immune or adrenal suppression (3,4).

Table 1. Etiologies of Type A versus Type B Lactic Acidosis. Type A lactic acidosis is characterized by inadequate tissue perfusion and a shift to anaerobic metabolism. Type B lactic acidosis occurs with normal tissue perfusion

Type A Lactic Acidosis: *Inadequate Perfusion*	**Type B Lactic Acidosis:** *Adequate Tissue Perfusion*
Increased Oxygen Demand e.g. Extreme exercise, seizures ***Inadequate Oxygen Delivery*** Generalized hypoperfusion including shock of all types. Regional hypo perfusion including mesenteric ischemia, compartment syndrome, tourniquet placement and more.	***Type B1: Related to Disease States*** Asthma, liver failure, malignancy, thiamine deficiency, and more ***Type B2: Drug-Induced*** Via Beta-adrenergic receptor agonism: Albuterol, epinephrine and more Via mitochondrial-uncoupling: metformin, alcohols, cyanide, propofol and more ***Type B3: Errors of Metabolism*** Pyruvate dehydrogenase deficiency, Glucose-6-phosphatase deficiency, fatty acid oxidation defects and more.

While high-dose methylprednisolone can result in elevated lactate and lactic acidosis in healthy dogs and horses (5,6), limited reports of steroid-induced lactic acidosis in humans exist. No cases have been described in previously healthy patients or those with trauma. We present the first reported case of methylprednisolone-induced lactic acidosis in a previously healthy patient with acute spinal cord injury (SCI).

CASE SUMMARIES

Informed, written consent and HIPAA authorization were obtained from the patient to discuss this case.

A previously healthy 19-year-old female presented to a level 1 trauma center after a 12-foot fall onto concrete. She complained of severe back pain, loss of sensation below her umbilicus, and bilateral lower extremity paralysis. Initial laboratory assessments were benign. Imaging revealed a Chance fracture dislocation of T7 and T8 with spinal canal compromise and local spinal cord swelling (Figure 1). Other imaging included contrast-enhanced computerized tomography of the abdomen and pelvis, which was negative for pneumatosis, pneumoperitoneum, gastrointestinal tract wall thickening, or other abnormalities.

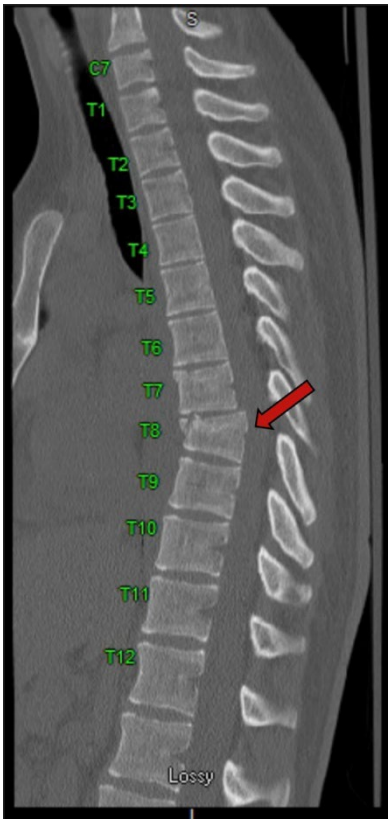

Figure 1. Initial Computerized Tomography Imaging of the Thoracic Spine. A Chance fracture is demonstrated at T7-8 (arrow)

To manage her acute SCI, an emergent T5-T11 instrumented fusion with T7-T8 laminectomy was performed without complication. Postoperative management included typical care for acute SCI, including respiratory clearance and bowel & bladder regimens. A mean arterial blood pressure target of >85 mmHg was achieved with a phenylephrine infusion (dose range of 0.08-1.5 mcg/kg/min). In addition, intravenous fluid resuscitation with lactated ringers totaling 80 mL/kg in the first 24 hours was administered. With these, no hypotensive events were noted. In addition, a bolus of 30 mg/kg methylprednisolone was given, followed by an infusion of 5.4 mg/kg over the following 23 hours.

While initial labs did not show lactic acidosis, serial labs showed a lactate elevation to 6.4 mmol/L (normal <2 mmol/L) five hours after the methylprednisolone initiation. This peaked at 8.2 mmol/L seven hours later (Figure 2), then slowly recovered, even in the face of an

ongoing methylprednisolone infusion. Serial physical examinations showed adequate extremity perfusion with normal warmth, pulses, and capillary refill and a benign abdomen with bowel sounds and without pain, discomfort, or distension. Her neurologic examination remained unchanged. Given persistent lactatemia, contrast-enhanced computed tomography of the abdomen and pelvis was repeated and was unrevealing. Lactic acidosis resolved seven hours before steroid discontinuation (Figure 2).

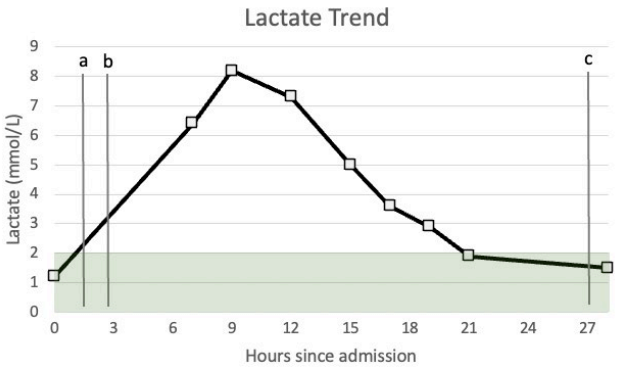

Figure 2. Temporal Lactate Trends.

Lactate was normal on admission (1.2 mmol/L) but was found to be elevated five hours after initiation of a methylprednisolone bolus (a) This bolus was followed by a methylprednisolone infusion starting (initiated at "b"), delivered over 23-hours (ending at "c"). Lactate peaked approximately seven hours after the bolus, then resolved approximately 19-hours later, despite an ongoing methylprednisolone infusion.

DISCUSSION

Lactate levels are often used as a surrogate marker for tissue perfusion, and elevations can be indicative of global ischemia and shock, or regional hypoperfusion like mesenteric ischemia. When the etiology of lactic acidosis is unclear, it is incumbent to distinguish between type-A lactic acidosis, which may be a harbinger for a life-threatening disease process, and type-B lactic acidosis, which may be benign. First, hypoperfusion with type-A lactic acidosis must be ruled out via comprehensive physical examination, dedicated imaging, and a broad laboratory assessment. Type-B lactic acidosis, meanwhile, remains a diagnosis of exclusion (1).

When unclear, the lactate-to-pyruvate ratio (LPR) can help to differentiate type-A and type-B lactic acidosis. Typically, pyruvate is metabolized into lactate via the reaction:

$$Pyruvate + NADH + H^+ \leftrightarrow Lactate + NAD^+$$

Under normal, aerobic physiologic conditions, pyruvate is produced and then used by mitochondria to produce energy via the Krebs cycle and via oxidative phosphorylation in the electron transport chain, and this reaction occurs at a 1:10 ratio (or, conversely, a LPR of ~10). When oxygen is not available due to hypoxia or hypoperfusion, or when mitochondrial energy production is blocked (e.g., with mitochondrial disease or cyanide), pyruvate accumulates, cellular acidosis develops (↑H+), and the ratio of NADH-to-NAD increases. Accordingly, the LPR increases greatly (LPR>>10; Figure 3) (2).

The mechanism for steroid-induced lactic acidosis is likely via steroid-induced hepatic gluconeogenesis, insulin resistance, and aerobic glycolysis. Steroids also increase catecholamine production and tissue catecholamine responsiveness. Catecholaminergic beta-2 agonism then further increases hyperglycemia and aerobic glycolysis. As a result, both steroids and beta-2 agonists like albuterol and epinephrine can cause elevations in pyruvate (2). If this elevation is significant, hyperlactatemia can result as a consequence of pyruvate metabolism (Figure 3) (2).

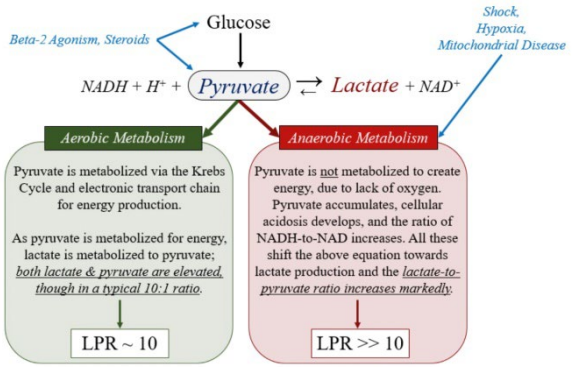

Figure 3. Differentiating type-A and type-B lactic acidosis with the Lactate-to-Pyruvate ratio (LPR). The LPR can help differentiate lactate elevations related to shock and/or hypoxia from drug-induced and other etiologies

Steroid-induced elevations in lactate have been reported after perioperative use of very high-dose dexamethasone (1 mg/kg) for patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) (7). Two

additional reports exist. First, hyperlactatemia to 6.7 mmol/L was noted after methylprednisolone 1 g/day administration in a patient with chronic obstructive pulmonary disease, pneumonia, and granulomatosis with polyangiitis (8). Second, a patient admitted for severe septic shock was initiated on stress-dose hydrocortisone, which resulted in tumor lysis syndrome related to an undiagnosed diffuse large B-cell lymphoma, where lactate was also found to be elevated. The etiology of their lactic elevation was unclear and likely multifactorial (9). Interestingly, lactic acidosis can also occur with endogenous glucocorticoid elevation due to Cushing's Syndrome. This can be resolved with partial adrenalectomy (10).

CONCLUSION

We report the first case of a previously healthy trauma patient with methylprednisolone-induced type-B lactic acidosis. Clinicians should be aware of this unusual complication and consider early assessment of the LPR to prevent unnecessary fluid resuscitation and imaging.

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