CLINICAL VIGNETTE

Metformin Associated Lactic Acidosis with Normal Renal Function

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A 60-year-old male presented to the ED with nausea and syncope. Medical history includes prediabetes and atherosclerotic cardiovascular disease with history of NSTEMI and drug-eluting stent placement. He was in his usual state of health until one day prior to presentation when he developed slow onset of nausea over several hours after lunch. Nausea was followed by lightheadedness, dizziness, and a syncopal event while sitting on his couch after which he vomited. The syncopal event was witnessed by his daughter who did not observe any unusual movements. There was no tongue-biting or incontinence.

EMS was called. He was afebrile but hypotensive with an initial blood pressure of 89/51 mmHg. SpO2 was 97% on room air. Labs in the ED were notable for a mild leukocytosis with a WBC of 11.7 and a metabolic anion gap acidosis with an anion gap of 20 and a bicarbonate of 20 mmol/L. Glucose was 110 mg/dl. Lactic acid was elevated at 8.5 mmol/L. Procalcitonin and troponins were undetectable. Urinalysis showed trace ketones but was otherwise unremarkable. Chest X-ray was unremarkable and EKG showed sinus tachycardia. Blood cultures were drawn and empiric antibiotics and IV fluids were started.

Over the next 24 hours, lactic acid levels decreased to 2.4 mmol/L at 8 hours and 1.6 mmol/L. Blood cultures remained negative and empiric antibiotics were stopped. He had no further episodes of nausea, vomiting, or syncope and was discharged after 48 hours of observation.

The patient's history of prediabetes was known for several years. A1c rose to 6.3% three months prior to admission and metformin 1000 mg twice daily was started by his primary care physician. He was taking metformin consistently without adverse effects.

Due to the lack of any other reasonable etiologies, the patient's lactic acidosis was attributed to metformin associated lactic acidosis. Metformin was held on admission and discontinued at discharge with a plan to switch to alternate medications to control blood sugars.

Discussion

Metformin is an anti-hyperglycemic oral medication that is FDA approved as first-line therapy for the treatment of non-insulin dependent diabetes mellitus (NIDDM).[1,2] Other common uses for metformin include the treatment of prediabetes, gestational diabetes, weight gain from antipsychotics, and polycystic ovarian syndrome (PCOS).[3] A biguanide compound, metformin is derived from guanidine, the active ingredient in *Galega officianlis*, also known as French lilac, a common herbal remedy in Europe.[4] Biguanide compounds are associated with an increased risk of lactic acidosis.[5] Phenformin and buformin, related compounds to metformin, were withdrawn from the market due to this reason.[5-7] Contraindications to the use of metformin include renal insufficiency, hepatic insufficiency, elderly age, and severe circulatory dysfunction such as heart failure.[8]

Although large trials have not shown a statistically significant increased incidence of lactic acidosis with use of metformin,[6] metformin is known to increase plasma lactic acid levels by around 2 mmol/L[9] and, in extremely rare cases, lead to metformin associated lactic acidosis (MALA) with an estimated risk of ≤10 events per 100,000 patient-years of exposure.[7] Most cases occur when there is a pre-disposing or concurrent event that predispose to lactic acidosis.[7,10] MALA can occur with normal levels of metformin and in the absence of diabetes mellitus.[11]

Lactic acidosis is a life-threatening condition characterized by low blood pH < 7.35 and elevated lactate levels > 5 mmol/L.[11] Lactate is produced during glycolysis primarily by the gut, liver and peripheral tissues. It is cleared mainly by the liver (60%) and kidney (30%).[12,13] As the normal hepatic clearance of lactate exceeds 320 mmol/hour, increased peripheral production of lactate is rarely the cause of lactic acidosis.[12] Rather, it is the combination of increased lactate production in the setting of decreased hepatic metabolism such as in cirrhosis, sepsis, or hypoperfusion that can lead to accumulation of plasma lactate and clinically significant lactic acidosis.[7,12]

The mechanism by which metformin and other biguanides cause lactic acidosis is attributed primarily to inhibition of mitochondrial complex 1 leading to impairment of oxidative phosphorylation.[14] Other mechanisms include inhibition of pyruvate carboxylase leading to increased generation of lactate[5] and inhibition of glucose-6-phosphatase leading to impairment of glycogenolysis.[15] If the resulting metabolic acidosis is severe, it can lead to a shock state with reduced hemodynamics, decreased myocardial contractility, decreased sympathetic tone, and multiorgan dysfunction.[16] As the shock state progresses,

renal and hepatic failure can further exacerbate the lactic acidosis by decreasing metformin and lactate clearance.[7]

MALA often presents with non-specific gastrointestinal symptoms including nausea, vomiting, abdominal pain and diarrhea as well as symptoms of acidosis including dyspnea, lightheadedness, fatigue, or malaise.[17] Severe cases can present with altered mental status or coma. Signs of MALA are similar to other acidemias and include tachypnea, tachycardia and in severe cases, shock and hypothermia.[18] Because MALA is a diagnosis of exclusion, a broad evaluation for the causes of anion gap metabolic acidosis and lactic acidosis should be performed. Metformin levels can be obtained if there is suspicion of toxicity or overdose based on history but because metformin levels are rarely locally performed, they have limited utility in immediate management.[11]

Mortality of MALA is variable but can be as high as 30-50%.[7] Mortality is associated with an initial pH < 7.1 and lactate > 25 mmol/L.[7] Prognosis correlates with the presence of sepsis, multi-drug intoxication, and organ failure (kidney, heart, liver).[7]

Management of MALA is supportive with the goal of restoring physiologic acid-base balance, treatment concomitant disease and if necessary, elimination of metformin.[19] This includes use of activated charcoal, intubation for airway protection, treatment of shock with intravenous crystalloids and vasopressors, sodium bicarbonate infusion, hemodialysis, and ECMO.[5,19-22]

Metformin can be used if the glomerular filtration rate (GFR) is above 30 ml/min/1.72 m^2. Due to the potential high mortality of MALA, monitoring of renal function every 3-6 months is advised.[23] To reduce the risk of MALA, metformin should be stopped in conditions of hypoxia and hypoperfusion.[24] It is recommended that metformin should also be stopped two days before general anesthesia and for three days after iodinated contrast.

The success of metformin as a first line treatment for non-insulin diabetes mellitus in comparison to previous biguanide treatments carries with it the risk of a rare but potentially fatal complication of lactic acidosis. Metformin should be prescribed after consideration of medical comorbidities, age, nutrition status, and concurrent medications. Prompt recognition of metformin as a cause of lactic acidosis can guide treatment and reduce morbidity and mortality.

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