When History Repeats Itself: Metformin Associated Lactic Acidosis in a Patient with a Prior Episode of the Same Diagnosis

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ABSTRACT

Metformin associated lactic acidosis (MALA) has risk factors that include acute and chronic kidney disease. When a patient has an episode of acute kidney injury (AKI) and lactic acidosis requiring dialysis, the risk of recurrent acute kidney injury and development of chronic kidney disease (CKD) is increased, and re-evaluation of medication dosages and monitoring of renal function becomes paramount. If outpatient or inpatient providers do not monitor patients with this clinical history, the patient is at risk of a more severe presentation of acute kidney injury and lactic acidosis. We present a patient that had a previous episode of MALA that required dialysis, who was admitted with a recurrence of AKI and lactic acidosis, that was so severe the patient became encephalopathic and required mechanical ventilation. Our case underscores not just the long-term consequences of AKI, but also the necessity for clinicians to re-evaluate medications dosages and monitor renal function more frequently when cases of MALA occur.

Key words: Metformin. Lactic Acidosis; Acute Kidney Injury; Chronic Kidney Disease, Dialysis; Hemodialysis; Continuous Renal Replacement Therapy

INTRODUCTION

Metformin is a popular treatment agent for patients with type 2 diabetes mellitus. It is a biguanide that reduces blood glucose levels through decreasing gluconeogenesis, decreases insulin resistance, and decreasing intestinal absorption of glucose. [1] It is generally well tolerated, and was FDA approved in 1994 as a replacement for an older biguanide, phenformin, that was removed from the market the decade prior due to high incidence of lactic acidosis [1,2]

While much less common than its predecessor, cases of metformin associated lactic acidosis (MALA) have been reported and carry a mortality of up to 50 percent [3]. The rare incidence of the disease also contributes to clinicians
overlooking this diagnosis in their differential as studies estimate MALA to have an incidence of 1 to 9 cases per 100,000 people [3]. Predisposing acute and chronic comorbidities such as chronic kidney disease (CKD) can make the patient more vulnerable to MALA, especially if the metformin dose is not appropriately adjusted for the decrease in estimated glomerular filtration rate (eGFR) [3]. We present a patient on the highest maintenance dose of extended-release metformin per manufacturer’s recommendations, with a diagnosis of chronic kidney disease CKD stage IIIa after a previous episode of AKI and MALA four years prior, who presented with recurrent severe MALA and acute kidney injury leading to shock and acute metabolic encephalopathy requiring mechanical ventilation. Since the prior episode, the patient’s estimated glomerular filtration rate eGFR declined on several outpatient labs to the 50-60 ml/min range, but she wasn’t monitored every three to six months per recommendations with her new baseline and was kept on the same dose of metformin [1]. In the setting of severe metabolic abnormalities leading to clinical decline, physicians should have a lower threshold for adjusting metformin dose, or possibly not resuming this agent and switching to other alternatives, to prevent a second and more severe episode of MALA.

CASE REPORT

A 70-year-old female with a medical history significant for type 2 diabetes mellitus, neuropathy, hypertension, and hyperlipidemia presented with a chief complaint of nausea, vomiting, fatigue and confusion. The patient’s husband stated that the patient complained of dizziness and lightheadedness the night before and woke up with nausea and vomiting which prompted them to come to the emergency department. Home medications included extended-release metformin 1000 mg twice daily and Lantus 20 Units at night. Her electronic medical chart review shows that she has had a prior hospitalization four years ago that was complicated by AKI and lactic acidosis and since then eGFR ranged from 50 to 60 ml/min on a couple of outpatient follow up visits, with creatinine ranging around 1.1 mg/dL. The patient required hemodialysis during that admission, and MALA was attributed as the cause of her metabolic derangements.

The vitals on admission were 113/55 mmHg, heart rate of 111 beats per minute, respiratory rate of 28, and temperature of 36 degrees Celsius. Physical exam was notable for an elderly woman in mild acute distress but alert and oriented with tachycardia. Labs were notable for serum creatinine of 6.2 mg/dl, blood urea nitrogen of 40, lactic acid of 18 mmol/L, beta-hydroxybutyrate of 1.8 mmol/L, bicarbonate of 6 mmol/L, anion gap of 37 mmol/L, and initial pH of 6.63.

The patient was initiated on maintenance intravenous fluids and sodium bicarbonate infusion as well given her severely low pH, but she continued to deteriorate in mentation and hemodynamics, with her lactic acid peaking at 40 mmol/L. She was intubated and transferred to the ICU. The patient’s hospitalization was further complicated by shock requiring pressors and stress dose steroids. The patient was started on continuous renal replacement therapy (CRRT) and within 24 hours her lactic acidosis resolved, her mentation improved, and she was liberated from the mechanical ventilator. CRRT continued for a total of three days.
DISCUSSION

Our patient had profound acidosis, with her pH of 6.63 below the acceptable range of 7.35 to 7.45 \(^4\). There are only a few cases of patients in this pH range surviving \(^4\). Her lactate level of above 5 mmol/L and serum bicarbonate of less than 18 mmol/L established a diagnosis of lactic acidosis \(^5\). Lactic acidosis is associated with poor clinical outcomes, and when accompanied by sepsis or shock, mortality is increased nearly by a factor of 3 \(^6\). MALA is a Type B form of lactic acidosis given that its process is not hypoxic in nature \(^7\). The pathophysiological basis of MALA is postulated to be due to inhibition of oxidative phosphorylation in mitochondria \(^6\). The risk increases when renal function is impaired, whether abruptly from an acute pathology, or if the patient is on other medications that decrease the eGFR, such as medications that block the renin-angiotensin-aldosterone system or nonsteroidal anti-inflammatory drugs \(^8\). Forms of hemodialysis therapy can effectively remove metformin due to its low molecular weight, but length of dialysis is often prolonged due to its high volume of distribution and two-compartment elimination kinetics \(^8\). Therefore, CRRT or continuous hemodialysis is the preferred mode of renal replacement therapy.

Metformin is already contraindicated in male patients with serum creatinine greater than 1.5 mg/dL and female patients with serum creatinine of 1.4 mg/dL \(^9\). Our patient had a baseline of 1.1 after her first hospitalization for MALA, and her eGFR went down to the 50 to 60 ml/min range on a handful of outpatient labs in the span of the four years between the two hospitalizations, giving her a diagnosis of CKD IIIa. CKD is defined as the presence of kidney damage or an eGFR of less than 60 ml/min, persisting for 3 months or more \(^10\). Metformin is absolutely contraindicated for eGFR less than 30 ml/min, and the manufacturer label lists an eGFR between 30 to 45 ml/min as recommending against initiation of metformin. When the eGFR is between 45 to 60 ml/min, as is the case in our patient, the eGFR is to be monitored every 3 to 6 months, which this patient did not have despite outpatient labs consistent with a declined renal function, while remaining on the highest maintenance dose of extended-release metformin, without any alternative agents for her type 2 diabetes mellitus being considered \(^1\). The patient’s baseline GFR had her on the maximum extended-release dose per most international recommendations, with guidelines in Canada recommending reducing the dose in this range \(^11\). The American Diabetes Association and European Association for the Study of Diabetes recommends a dose reduction at 45 ml/min, which the patient was approaching \(^11\). Even more alarming, it is recommended that metformin be avoided completely if kidney function is expected to become unstable, as is the case in our patient who had MALA that was so severe, she required hemodialysis and her eGFR declined as a direct result\(^11\).

The decline in eGFR following AKI and severe subsequent clinical presentation years after is an unfortunately common course, as patients who survive AKI have a higher rate of long-term mortality, and several studies have shown an association with developing recurrent AKI as well as CKD \(^12,13,14\). Regarding her baseline creatinine, it should be noted that 2012 KDIGO guidelines suggest cystatin C-based equations be used in patients in this eGFR range.
range, and given her gender and age, adjusting for her reduced muscle mass is warranted \cite{15}. Metformin has also been demonstrated with higher lactate concentration regardless of baseline renal function, and it is suggested by many that metformin be held even in illnesses that may predispose someone to develop AKI \cite{5}.

Metformin is a commonly used medication among patients with type 2 diabetes mellitus, due to its weight neutral profile and low risk of hypoglycemia \cite{1}. However, dosage should be re-evaluated after illnesses that predispose patients to AKI, such as prior history of AKI and suspected history of CKD. Instituting this practice will prevent severe recurrent AKI in the future and severe manifestations such as life-threatening lactic acidosis, metabolic encephalopathy, and shock, leading to better outcomes in this patient population.

REFERENCES

