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INTRODUCTION

Metformin is a first line oral medication for diabetes mellitus shown to decrease cardiovascular morbidity and mortality. Though the prevalence of metformin-associated lactic acidosis (MALA) is low, mortality is high, ranging from 25-50%. Therefore, it presents a diagnostic challenge that is critical to identify, particularly in patients with renal impairment at baseline. Traditionally patients with creatinine greater than 1.5 mg/dL have been excluded from using metformin; however, metformin might be acceptable in some patients with chronic kidney disease (CKD).

CASE PRESENTATION:

A 69 year old female with a past medical history of diabetes mellitus, hypertension, breast cancer, and no chronic kidney disease was sent to the hospital by her rehabilitation facility secondary to her being found unresponsive. This was in the presence of decreased appetite and impaired mobility limiting her ability to feed herself in the 2 weeks prior to hospital admission. Her medications included metformin, insulin glargine, anastrozole, and hydrochlorothiazide. She had nausea and vomiting the night prior to admission. Despite her decreased oral intake, she continued taking her full dose of metformin and insulin throughout that two week period.

On arrival to the emergency room, her vitals were rectal temperature 90.6° F, heart rate 66 beats per minute, blood pressure 60/40 mmHg, respiratory rate 25 breaths per minute, and oxygen saturation 88% on room air. Her Glasgow Coma Scale was 2 with physical exam findings significant for limited withdrawal to noxious stimuli. Her initial labs were significant for bicarbonate of 2 mEq/L (normal range 24-32 mEq/L), potassium of 6.7 mEq/L (normal range 3.5-5.0 mEq/L), blood urea nitrogen of 110 mg/dL (normal range 7-26 mg/dL), creatinine of 9.7 mg/dL (normal range 0.7-1.4mg/dL) with a baseline of 0.7 mg/dL 2 months ago, and lactate of 26 mmol/L (normal range 0.5-2.2 mmol/L). A venous blood gas was significant for a pH of 6.65. Plasma metformin level was not available.

DIFFERENTIAL DIAGNOSIS

The differential was broad including septic shock, toxin ingestion, cardiogenic shock, and intracranial abnormality. Drug toxicity was ruled out as her urine drug screen and alcohol level were negative. Severe sepsis was ruled out when cultures (urine, blood, bronchoalveolar lavage) were negative. CT chest, abdomen, and pelvis did not show any source of infection. CT head was within normal limits. A transthoracic echocardiogram did not show significant abnormalities. Given her elevated anion gap metabolic acidosis with concomitant osmolar gap, a diagnosis of MALA was made.

OUTCOME AND FOLLOW UP

Patient was intubated and admitted to the medical intensive care unit. She was empirically started on broad-spectrum antibiotics, stress dose steroids, intravenous fluids, and vasopressors for presumed septic shock. Given her low bicarbonate level, a bicarbonate drip was started, and nephrology was consulted for acute renal failure and metabolic acidosis management. The nephrology team initiated her on continuous veno-venous hemofiltration (CVVH) therapy. She had 3 days of CVVH, after which she was transitioned to intermittent hemodialysis. Patient's urine output gradually improved throughout her hospital stay. Upon discharge, she was alert, oriented, and conversing appropriately.

DISCUSSION

Metformin is renally cleared and therefore accumulates in states of decreased creatinine clearance. It also inhibits mitochondrial electron transport, thereby increasing anaerobic metabolism and lactate production.¹ It has been proposed that in acute kidney injury, metformin levels accumulate, contributing to worsening lactic acidosis, which further compounds nausea and vomiting, and thereby reducing renal perfusion.² The incidence of MALA is thought to be 1-5 cases per 100,000 patient years but can be as high as 30 cases per 100,000 patient years.³ Mortality ranges from 25-50%.⁴

The 5 characteristics highly suggestive of MALA are: severe acidemia (pH < 7.1) with an anion gap greater than 20 mEq/L (normal anion gap ≤ 12 mEq/L), very low serum

bicarbonate (7 +/- 4 mEq/L), markedly elevated lactic acid (12.4 +/- 8 mmol/L), history of metformin ingestion, and history of renal insufficiency.^{1,5} With infectious and other drug toxicities ruled out in this patient, MALA was the most likely cause of her lactic acidosis as the patient met all 5 aforementioned points. We propose that this patient, in the presence of decreased oral intake in the weeks prior to her presentation, developed acute kidney injury, which decreased her ability to clear metformin. Consequently, she started developing lactic acidosis, which likely worsened any nausea or vomiting, further exacerbating her acute renal failure leading to anuria.

Given the lack of randomized control trials in the study of MALA, much of the existing literature on MALA are case series, retrospective studies, and observations. The goal in the acute management of MALA is to provide airway, breathing, and circulatory support and to correct the underlying acidosis with possible intravenous bicarbonate and/or renal replacement therapy.⁶

A retrospective analysis study compared cases of severe acidosis with pH < 7.0 secondary to MALA and lactic acidoses of other origins. Despite the pH being lower in the former group, the mortality was 100% in the latter group as compared to 50% in the former. This shows that despite a greater degree of acidosis and renal failure in MALA patients, early recognition and aggressive medical therapy including renal replacement therapy improves the survival.⁷

A recently published retrospective study looked at the incidence of MALA in those with and without impaired renal function. The 77,601 identified patients were divided into different groups based on glomerular filtration rate (GFR): normal, mildly reduced, moderately reduced, or severely reduced. They found an incidence of 10.37 per 100,000 patient years. What is more significant is that they did not find a significant difference in the development of MALA among the 4 groups.⁸ This calls for more awareness amongst general internists such that impending signs of MALA should be recognized earlier. A recent review article suggests that given the mild association between metformin and lactic acidosis, metformin can be used in those with impaired renal function but should be dosed by GFR secondary to metformin's varied benefits.⁹

Prognosis of MALA is more favorable than other etiologies of lactic acidosis.¹⁰ This may be secondary to the absence of a critical underlying condition causing lactic acidosis such as severe ischemia. Rather the lactic acidosis is a result of toxic drug accumulation, which can be successfully

removed by renal replacement therapy.¹⁰ Furthermore, though our patient did not have any CKD at baseline, she should have been counseled on stopping her metformin during periods of poor appetite or dehydration. Physicians need to be comfortable and knowledgeable with using metformin alongside medications that interfere with renal hemodynamic regulation such as angiotensin-converting-enzyme inhibitors, aldosterone receptor blockers, and nonsteroidal anti-inflammatory drugs.³

KEY POINTS

Metformin is currently a first-line agent in the management of diabetes. Though it can cause metformin-associated lactic acidosis, the prevalence is relatively low. High clinical suspicion is, however, important. In those taking metformin and presenting with lactate greater than 15 mmol/L and pH less than 7, MALA must be strongly considered. To prevent MALA, patients on metformin should be counseled on its use in states of potential kidney injury such as volume depletion as was the case in our patient. Overall, patients who have MALA should receive aggressive resuscitation methods including fluid repletion, airway protection, vasopressors, intravenous bicarbonate, and/or renal replacement therapy depending on the severity of the acidosis.

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