Case Report

Metformin-Associated Lactic Acidosis: A Case Report

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Abstract

Introduction
Metformin is considered a first-line therapy for patients with diabetes secondary to its cost efficiency, minimal side effects, and marked improvement in one's hemoglobin A1c; however, metformin is avoided in patients with renal insufficiency out of concern for drug accumulation and lactic acidosis. In fact, there is a black box warning for metformin, identifying lactic acidosis as the inciting trigger for fatal arrhythmias and death.

Case Presentation
A 62-year-old male presented with multiple episodes of nausea, vomiting, abdominal pain, and decreased urine output for 3 days after working on a roof, all day in the summer heat. He did not drink more than a bottle of water throughout that day and noted that afterward, he seemed to have little to no urine output. At presentation, he was in moderate distress due to abdominal pain and was diaphoretic, tachypneic, and hypertensive. The patient was given dextrose and started on a sodium bicarbonate drip. He was also given calcium gluconate. His mentation and respiratory status continued to decline throughout that day, and he required intubation and mechanical ventilation. The patient ultimately recovered quite rapidly upon receiving hemodialysis.

Conclusion
This case report shows the critical nature of identifying and quickly treating metformin toxicity.

Keywords
metformin; metformin/adverse effects; type 2 diabetes mellitus; lactic acidosis; renal failure; toxicity; metabolic acidosis

Introduction
Metformin-associated lactic acidosis (MALA) is a rare but serious condition that can cause severe organ dysfunction, arrhythmias, and death.[1] Metformin is considered a first-line therapy for patients with diabetes due to its low cost and favorable side effect profile[2]; however, metformin is avoided in patients with renal insufficiency out of concern for drug accumulation and lactic acidosis.[3] The black box warning for metformin includes lactic acidosis with the risk of causing "death, hypothermia, hypotension and resistant bradyarrhythmias."[4] The etiology of MALA is uncertain. It is believed that the cause of the acidosis is due to type-B lactic acidosis, which is an over-production or lack of ability to metabolize the lactic acid in the liver. Metformin inhibits mitochondrial respiration, predominantly in the liver.[5] The drug is contraindicated in those with moderate to severe renal impairment due to the possibility of increased concentrations of lactic acid in the blood.[6]

MALA is exceedingly rare, with less than 10 cases per 100 000 patient-years.[5] The mortality rate for MALA can reach 50% and is difficult to diagnose, as the symptoms are nonspecific and the course can be indolent until the patient becomes acutely ill.[5] To diagnose metformin-induced-lactic acidosis, a serum metformin level must be obtained; therefore, most cases of

metformin poisoning remain MALA, as defining MALA does not require definitive testing and is made based on the clinical picture.[6] Patients with higher than normal lactic acid levels can increase the suspicion for MALA, and in 1 retrospective study the combined parameters of lactate greater than 8.4 mmol/L, creatinine greater than 2.9 mg/dL, and a history of metformin use had 99% specificity for MALA in suspected sepsis-induced lactic acidosis.[7]

There are multiple strategies that can be used to treat MALA, once suspicion has arisen, but definitive treatment requires extracorporeal removal, or hemodialysis, and is recommended for lactic acid concentration of greater than 20 mmol/L, severe acidosis with a pH under 7.0, or a failure to improve within 2-4 hours with bicarbonate therapy. Dialysis is also suggested in the following scenarios: lactic acid levels between 15-20 mmol/L; pH between 7.0-7.1; shock-requiring vasopressor therapy; acute kidney injury with creatinine of greater than 2 mg/dL in adults; chronic kidney disease stage 3b or higher; liver failure defined by INR over 1.5 without other cause; or encephalopathy.[8]

Case Presentation

A 62-year-old male with a medical history of type 2 diabetes, coronary artery disease status post placement of 6 stents in 2019, and essential hypertension presented with multiple episodes of nausea, vomiting, abdominal pain, and decreased urine output for 3 days. His symptoms began after working outside on a roof, all day in the summer heat. He had noted that while working, he did not drink more than a bottle of water throughout that day and that it was quite hot outside. He noted that after work he seemed to have little to no urine output, at most 1 episode of urination a day for the following 3 days. He had no hematuria or dysuria. He denied any history of renal or liver failure or history of drug or alcohol use. His reported home medications included amlodipine 5 mg daily, aspirin 81 mg daily, atorvastatin 40 mg daily, clopidogrel 75 mg daily, and metformin 1000 mg twice daily. He noted that he was taking all of his medications as prescribed throughout this time.

At the time of examination, he was in moderate distress due to abdominal pain and was diaphoretic, tachypneic, and hypertensive. He had voluntary guarding of the abdomen, but otherwise, the rest of the exam showed no abnormalities. His vital signs showed a temperature of 36.4° C, pulse oximetry of 99% on room air, blood pressure of 171/114 mmHg, a respiratory rate of 20 breaths/minute, and a pulse rate of 68 beats per minute. An electrocardiogram showed peaked T-waves, but no ST or T-wave changes. Labs showed potassium of 6.4 mmol/L, blood glucose of 20 mg/dL, blood urea nitrogen (BUN) of 98 mg/dL, and creatinine of 13.3 mg/dL. His anion gap was 17. Lactic acid levels were not ordered at this time. His troponins were negative for elevation. The patient's white blood cell count was 12.6 x 10^3/µL with neutrophil predominance. Urinalysis showed traces of blood with 0-5/lpf red blood cells, 0-5/lpf hyaline casts, 100 mg/dL protein, and no other findings. His urine drug screen was positive only for cannabinoids. Acetaminophen and salicylate levels were negative. An arterial blood gas test (ABG) showed a pH of 6.9, PCO_2 of 25 mmHg, and HCO_3 of 5 mmol/L. This result indicated metabolic acidosis with insufficient respiratory compensation and therefore, respiratory alkalosis. Computed tomography of the abdomen and pelvis without oral or intravenous contrast was negative for any acute findings.

Based on the lab results, the patient was immediately given 2 ampules of dextrose 50% (25 g of dextrose in 50 mL water), 2 ampules of bicarbonate (8.4% sodium bicarbonate, 50 mEq per ampule), and started on a sodium bicarbonate 150 mEq in 1L drip at 100 mL/hr. He was also given 1 g of calcium gluconate. The patient was then admitted to the intensive care unit for further workup. Additional labs showed negative c-anti-neutrophil cytoplasmic antibodies (ANCA), p-ANCA, rheumatoid factor, and anti-nuclear antibodies. Thyroid-stimulating hormone was 0.53 uIU/mL, lipase was negative, triglycerides were 250 mg/dL, and creatine kinase was 568 units/L. Magnesium was normal and phosphate was 5.5 mg/dL. His lactic acid level was 11.7 mmol/L.

His mentation and respiratory status continued to decline throughout the day of presentation, and he required intubation and mechanical ventilation soon after arrival at the intensive care unit. Fluid resuscitation was also started, and

more bicarbonate therapy was given several times. Even after intervention, his ABG had worsened, now with a pH of 6.78, PCO_2 of 22 mmHg, and HCO_3 of 3 mmol/L. The anion gap was 37 as the sodium was 140 mg/dL, the chloride was 96 mg/dL, and the bicarbonate was 7 mg/dL on the metabolic panel. The lactic acid was redrawn and was 20.7 mmol/L. The patient required pressor support with a norepinephrine intravenous drip and more bicarbonate was given. A hemodialysis catheter was placed, and the patient received emergent dialysis. The patient ultimately recovered quite rapidly upon receiving this intervention. The following day he was awake and alert and able to pass a spontaneous breathing trial. Blood cultures remained negative throughout the visit. Echocardiogram showed 70-75% ejection fraction without any valvular or wall-motion abnormalities. His urine output improved to up to 2 liters on the day of discharge; his final BUN was 34 mg/dL and his creatinine was 2.9 mg/dL. He was discharged from the hospital 3 days after admission. Medications were reconciled, and metformin was discontinued upon discharge.

Discussion

Rapid recognition of metformin toxicity is the key to success in treating this potentially fatal illness. A thorough history and physical exam will show classic signs and symptoms consistent with MALA, and recognizing it as part of the differential is important for providers.[9] These symptoms include severe abdominal pain and nausea out of proportion to imaging findings, acidosis, and a history consistent with severe renal failure and concomitant metformin continuation. Part of diagnosing MALA is ruling out other causes, and in our case, the patient was found to have no acetaminophen and salicylate levels, auto-immune markers were non-reactive, and no drugs found in his system were consistent with this presentation. Cardiac shock, septic shock, rhabdomyolysis, severe electrolyte derangements, or other causes that could lead to this level of lactic acidosis were not found. He also presented with the recognized criteria consistent with MALA, which include renal failure, extremely high lactate levels, and a history of metformin use. Realizing how critical patients can become is paramount in ensuring that the proper treatment and level of care are given rapidly. In our case, swift treatment was given following the appropriate standards of care during his hospitalization. The tenants of proper care include ABCs (airway, breathing, circulation) and prompt removal of the agent.[10] Our patient was promptly intubated and ventilated in the intensive unit and started on pressors. The patient received hemodialysis, which corrected his acidosis and removed the metformin, which is dialyzable.

Conclusion

This case provides an example of swift and effective treatment of MALA. It also serves as an important reminder to readers to consider MALA as part of the differential diagnosis when treating patients that are acutely ill, so that proper decision-making can be made to potentially save a life.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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