



Metformin associated lactic acidosis in the setting of acute kidney injury: a case report

Bryce N. Taylor, Sangeeta Mutnuri, Helena Kurian, Mahendra Agraharkar

Department of Internal Medicine and Nephrology, Bayshore Medical Center, 4000 Spencer Highway, Pasadena, TX, USA

Correspondence to: Bryce N. Taylor, MS. Department of Internal Medicine and Nephrology, Bayshore Medical Center, 4000 Spencer Hwy, Pasadena, TX 77504, USA. Email: bryce.taylor@lmunet.edu.

Abstract: Metformin is often a first choice medication for patients with type 2 diabetes mellitus. It is considered to have a high efficacy as well as a mild adverse drug effect profile, and can be used in both monotherapy and polytherapy regimens. The drug is not altered at the molecular level during metabolism, and is cleared almost entirely through the renal system, so the major comorbidity that practitioners consider when starting Metformin is renal disease. As a patient's renal function declines, there can be a build-up of unaltered and active Metformin that can lead to toxic events. Metformin toxicity leads to a build-up of lactic acid, primarily through its inhibition of gluconeogenesis. The FDA has guidelines for Metformin use in patients with chronic kidney disease, but at this time, no guidelines exist for patients with acute kidney injury. We present a report on a 64-year-old female with a long-standing history of diabetes type 2 on Metformin therapy who experienced an acute kidney injury secondary to dehydration as a sequelae of acute gastrointestinal upset. This case illustrates the toxic effects that Metformin can have at supratherapeutic levels, as well as the importance of the discontinuation of Metformin in circumstances that may lead to acute kidney injury.

Keywords: Toxicology; shock; Metformin; acute kidney injury; encephalopathy; lactic acidosis

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Introduction

Metformin is considered a first line therapy for patients with type 2 diabetes mellitus. It is frequently chosen as both monotherapy and as a component of larger treatment regimens due to its mild side effect profile and inability to independently induce hypoglycemia (1). The drug is also particularly efficacious, and is credited with decreasing peripheral insulin resistance and decreasing hepatic gluconeogenesis (1). While the drug has several proposed mechanisms of action, it is generally accepted that it exerts its main effect on complex I of the electron transport chain, which leads to a decrease in gluconeogenesis (1). This effect on the mitochondria is also proposed to secondarily activate the AMP kinase pathway through the change in energy status exerted onto the cell. The anti-hyperglycemic effects are a result of the decrease in gluconeogenesis, and

the decrease in peripheral insulin resistance is a result of the induction of the AMP kinase pathway (1).

Metformin is not metabolized at the molecular level, and is excreted entirely through the renal system through transporters in the proximal collecting tubule (2). It is generally regarded as safe in patients without renal comorbidity, however it is used more cautiously as renal pathology increases in severity (3). The point at which a patient's renal function makes the use of metformin unsafe is still being debated (3,4). Recently, the FDA has released new guidelines that lowered the threshold of contraindication in patients with renal disease and support its use as long as the eGFR remains above 30 mL/min (5). Prescribing physicians generally maintain a very close following on their patients that have lowered baseline renal function, which allows for the discontinuation of Metformin as function declines in a chronic and step-wise fashion beyond the level of comfort

for their prescriber. This does not account for transient and rapid declines in eGFR. Unfortunately, to our knowledge, the risk of MALA in patients with acute kidney injury is not well described in the literature, even though the theoretical risk and mechanism for it exist.

The major effect of Metformin toxicity is lactic acidosis, primarily through its inhibition of gluconeogenesis, as this decreases the conversion of lactic acid to pyruvate (2,6). Metformin has also been found to promote conversion of glucose to lactic acid in the gastrointestinal tract vasculature as well (7). While Metformin does increase lactic acid levels, in the absence of overdose or significant comorbidities leading to increased production of lactic acid or decreased clearance of lactic acid or the drug, lactic acidosis has not been found to be a significant risk (3).

Case presentation

A sixty-four-year-old Caucasian female with a reported history of type 2 diabetes mellitus, obesity, ulcerative colitis, asthma, depression, hypertension, hypothyroidism, and previous episode of Metformin associated lactic acidosis (MALA) presented to the emergency department for evaluation of an altered mental status as reported by neighbors. Patient's only complaint at time of evaluation was a global weakness and she was noted to be confused by neighbors and EMS. Patient's home medications included Tylenol/Codeine 3,300/30 mg as needed, Zoloft 100 mg daily, Levothyroxine 100 mcg daily, Metformin 500 mg daily, Atorvastatin 20 mg daily, Albuterol 90 mcg as needed, Amitriptyline 50 mg daily, and Lisinopril 20 mg daily. Initial exam showed a morbidly obese female with dry mucus membranes and tachycardia. Patient was obtunded and hypotensive with a blood pressure of 84/55 and a pulse of 86 beats per minute. Initial labs revealed a lactate level at 2.2 mmol/L, a BUN of 49 mg/dL, and a creatinine of 4.3 mg/dL. The patient also had a leukocytosis, with a white blood cell count at 12.9 k/mm³.

At this point, sepsis protocol was immediately initiated including empiric antibiotic coverage with intravenous Levofloxacin and aggressive fluid resuscitation. The workup at this point was geared towards uncovering a site of infectious invasion, which could be triggering a systemic inflammatory response, while simultaneously stabilizing the patient. Chest radiographs, urinalysis, and blood cultures, were continuously negative for infectious processes, however.

Shortly after arriving to the floor, the patient experienced a period of severely decreased responsiveness and hypoventilation,

requiring a rapid response. The rapid response team initiated bilevel positive airway pressure treatment, after which the patient experienced an improvement in her condition. At this time, arterial blood gases indicated a hypercarbic respiratory failure with pH 7.18, CO₂ 62.6, O₂ 83, and HCO₃ 21. A second lactic acid level drawn four and a half hours later showed improvement, with a normalizing value at 1.6 mmol/L. Computer tomography of the head was negative for acute processes. Urinary drug screen was positive for opioids, however the state's prescription monitoring program indicated that patient has morphine tablets for use at home. Orders were given for Naloxone, which did not lead to improvement, and nephrology was consulted. Patient now suspected to have obstructive sleep apnea, encephalopathy, and lactic acidosis without sepsis.

With a negative infectious workup and the values from the comprehensive metabolic panels, the differentials came to include acute kidney injury, and MALA with was considered. Metformin was held at this time. Anti-hypertensive medications were also temporarily discontinued at this time due to hypotension.

Fluid resuscitation was continued with concurrent correction of electrolyte abnormalities. The patient's mentation was restored, electrolytes were restored to be within normal limits, and GFR increased to be greater than 60 mL/min. At this time, the patient had a BUN of 29 mg/dL and creatinine of 0.70 mg/d. Patient was discharged home with instructions to continue oral hydration and follow up. Metformin was discontinued.

At outpatient nephrology follow up several days after discharge, the patient had returned completely to her baseline mentation. It was at this point that she endorsed several days of nausea, with minimal vomiting and diarrhea, immediately prior to arrival at the ED. She stated that she was predominantly bothered by the nausea, and that she had a complete intolerance to oral intake including fluids. Since discharge, the patient had been tolerating oral fluids well. Renal function values were all within accepted normal limits, and the patient was determined to not be in a state of chronic kidney disease.

Discussion

Metformin is a widely used anti-diabetic drug due to its generally well-tolerated side effect profile and high level of efficacy (1). While the side effects for metformin for a population with solely clinical manifestations secondary to insulin resistance are sparse and mild, the risk for major

adverse events increase with the patient's comorbidity profile (3,6). It is a well-accepted fact that renal disease has a high prevalence among the population of people with type 2 diabetes, with recent studies indicating that greater than 40% of this population could be experiencing chronic kidney disease (8). Metformin is a drug that is not altered at the molecular level during metabolism, and it is cleared through the renal system, requiring an adequate GFR to filter enough of the drug to avoid a toxic accumulation (2). When dosed in a manner only accounting for the clearance of the drug in a patient without renal pathology, a patient with renal pathology could continue to gradually have an increase in serum levels of the drug with the culmination of toxicity (2).

Fortunately, practitioners prescribing Metformin are well aware of the risk of MALA in patients with renal disease, and they generally use caution and follow these patients closely. This does not take into account acute or transient loss of renal function, which every single person in the general population is susceptible to. Currently, guidelines only exist restricting Metformin use in patients with severe chronic kidney disease stage 4, with GFR values lower than 30 mL/min (3). There are no guidelines pertaining to the discontinuation of Metformin in the setting of acute kidney injury, although many practitioners that prescribe it do discontinue the drug in instances of dehydration and with diagnostic procedures that may decrease the GFR. Empiric application of the pharmacokinetics of Metformin would indicate that MALA is a risk in acute kidney injury due to the significantly decreased clearance, but it is not yet well defined in the literature.

The patient presented had no history of renal disease prior to admission, and her renal function returned to normal limits after discharge. The etiology of this patient's lactic acidosis is complex, and likely involves several factors exerting synergistic effects on each other. Over the several days prior to presentation, the patient became dehydrated, which likely led to an acute kidney injury due to volume depletion, as well as some degree of hypoperfusion with lactic acid production (9). It is likely that the Metformin contributed greatly to this by increasing lactic acid production through the mechanisms described above. With the acute kidney injury, there was a lowered clearance of both the Metformin and lactic acid, leading to an imbalance involving an increased lactic acid production in the setting of inadequate lactic acid clearance. Metformin toxicity is suspected to be a major cause in this patient's clinical manifestation due to the severity of shock and lactic acidosis

upon admission. The patient's dehydration was secondary to a relatively simple gastrointestinal upset with predominant nausea and minimal vomiting and diarrhea spanning less than a week. While she was not taking in fluids, she also was not losing excessive fluid volume either. We believe that this state of dehydration is enough to insight an acute kidney injury, but alone is not enough to cause the magnitude of shock with lactic acidosis that she initially presented with. Even though we cannot be sure which factor initiated this patient's lactic acidosis, there is little question that both held major synergistic roles. The patient is also taking an ACE inhibitor, which further contributed to decrease the GFR, and possibly played a small role in contributing to the increased levels of the drug (10).

The patient's altered mentation and hyporesponsiveness were likely the results of a toxic encephalopathy secondary to the increased lactic acid. There are many mechanisms proposed behind this, but when an environment of a neuron decreases in pH, that neuron's excitability also decreases (11). This leads to a neuroinhibitory effect, and thus a hyporesponsiveness, leading to an encephalopathic manifestation (11). Toxic encephalopathy is further supported in this patient by the drastic improvement in mentation with corrections of her metabolic profile. The patient's obstructive sleep apnea likely existed prior to this event, especially given her morbid obesity, and was likely an ailment unrelated to this patient's pathogenesis.

Conclusions

This case highlights the importance of the consideration of Metformin toxicity in patients with acute kidney injury. Under normal physiologic circumstances and at therapeutic levels, Metformin is a relatively innocuous medication with a high efficacy, but at toxic levels it can lead to significant disease and mortality. Patients that are taking Metformin regularly should be warned of the signs, symptoms, and precipitating factors of acute kidney injury, and should be instructed to use caution and seek medical guidance in such situations. Medical providers should also be aware of the possibility of an association between acute kidney injury and MALA. Early recognition and resuscitation in MALA are vital to improved outcomes.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Plans to write a case reports on this hospital course were discussed with the patient during her follow up appointment with nephrology, and at that time, verbal consent was given. All information in this report has been adequately de-identified and is compliant with institutional policy.

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