CASE REPORT

Fatal Metformin-associated Lactic Acidosis

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Abstract

Introduction: Metformin-associated lactic acidosis is a rare, yet fatal condition, especially in the presence of risk factors. Therapeutic use of metformin may induce lactic acidosis. Gastrointestinal bleeding, dehydration, acute renal failure, and drugs are major risk factors that increase the mortality risk associated with metformin-associated lactic acidosis. In this regard, this case study aimed to present a patient, who died due to metformin-associated lactic acidosis despite treatment.
Method: This case study featured a 45-year-old diabetic patient with metformin use, who presented to the emergency department with the complaint of low back pain. He had acute renal failure, severe lactic acidosis, and shock findings.
Discussion: The primary purpose of metformin-associated lactic acidosis treatment is to restore acid-base balance and provide hemodynamic support. Hemodialysis reduces the mortality due to metformin-associated lactic acidosis by decreasing lactate clearance. Supportive therapies should be used. Nevertheless, mortality still occurs in approximately 50% of the cases.
Conclusion: Metformin overdose or even therapeutic levels of metformin use can cause MALA in the presence of various risk factors. MALA, a rare clinical condition, is associated with mortality rates of up to 50%. The most crucial step in treating MALA is hemodialysis/venous hemofiltration. Given that metformin is a frequently used medication, care should be taken in the follow-up of patients using metformin, considering MALA.

Keywords: Metformin, Lactic Acidosis, Death

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INTRODUCTION

Metformin is a biguanide-derived drug, which has been used since the 1950s and is still considered the first-line treatment for type 2 diabetes treatment. Other biguanides are no longer used due to the lactic acidosis side effect [1].

Metformin is safe in patients with normal kidney function or mild kidney damage. Metformin-associated lactic acidosis is a rare, but fatal condition with mortality rates of 50% [2].

Metformin is the best-known biguanide. 40-60% of metformin is absorbed in the small intestine. The metformin concentration in the plasma reaches its peak level in an average of 6 hours. The metformin in the plasma is rapidly distributed to cells, where it binds little to proteins. 90% of the metformin is eliminated via the renal route. The half-life of metformin in the plasma is 4-8.7 hours, which is prolonged in case of renal failure [3].

Metformin is recommended as the first-line pharmacotherapy in patients with type 2 diabetes mellitus without contraindications, including stage 4-5 chronic renal failure, advanced heart failure, and lactic acidosis history [4].

In addition, the U.S. Food and Drug Administration (FDA) recommends that metformin be used only in patients with a glomerular filtration rate of > 30 mL/min/1.73m^2.[5] Adverse reactions of metformin are observed at concentrations above 5 mg/L [6].

The therapeutic use of metformin reportedly gives rise to gastrointestinal symptoms, including nausea, vomiting, abdominal pain, and diarrhea. Metformin has been associated with malabsorption syndromes resulting in electrolyte abnormalities and vitamin B12 deficiency. The incidence of metformin-associated lactic acidosis was reported as 5 per 100,000 at the therapeutic dose, compared to the incidence of hypoglycemia, which was reported as 60 per 100,000 [3].

In view of the foregoing, the objective of this study is to present a patient, who died due to severe lactic acidosis-related intoxication caused by the therapeutic use of metformin, a rare yet fatal condition, in comparison with the literature data.

CASE REPORT

A 45-year-old female patient presented to the emergency department with the complaint of severe low back pain. She was diagnosed with diabetes mellitus and hypertension. She was using oral antidiabetics irregularly. She was not receiving antihypertensive treatment.

Her vital signs were as follows; arterial blood pressure: 131/ 81 mmHg, heart rate: 63 beats/min, respiratory rate: 17/min, and body temperature: 36.6 °C. In addition, her laboratory test results were; blood glucose: 401 mg/dl, white blood cell (WBC)count: 64.90 10^9/L, hemoglobin: 9.3 g/dL, platelet: 369 10^3 u/L (156-373), blood urea nitrogen (BUN):

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20 mg/dL (15 - 40), creatinine: 1.92 mg/dL (<0.9) aspartate aminotransferase (AST): 58 U/L (0 - 31), and alanine aminotransferase (ALT):32 U/L (0 - 33). The blood gas analysis revealed pH: 6.8, pCO2:23.8 mmHg (35 - 48), HCO_3^-: 4.9 mmol/L (24 - 28), and lactate: 25 mmol/L (0.9 - 1.7). Cerebral computed tomography (CT) and thoracoabdominal CT angiography did not reveal any abnormal findings. Her arterial blood pressure decreased to 60/23 mm/Hg, and her heart rate dropped to 40/min on the third hour of admission. Her electrocardiogram (ECG) indicated sinus bradycardia. She was given hydration fluids, three times 1 mg intravenous (i.v.) atropine, 1meq/hr $NaHCO_3$ infusion, and empirical meropenem. She developed cardiopulmonary arrest at the fifth hour of her admission. Cardiopulmonary resuscitation (CPR) was started. After 2 minutes of CPR, spontaneous circulation was achieved. The patient was started on inotropic support as hypotension persisted despite fluid resuscitation.

It was learned from the patient's relatives that she has been taking her diabetes medication irregularly, frequently, and in large numbers and that there were 55 empty metformin capsules at her home. The patient was taken to hemodialysis (HD) during observation. Cardiac arrest developed again after HD. After 6 minutes of CPR, the rhythm was achieved. She was given a dextrose infusion due to resistant hypoglycemia and 30% dextrose at 50 cc/h and 1 mg Iv glucagon. Subsequently, she was started on pulse steroids and terlipressin. $NaHCO_3$ infusion dose was increased to 2 meq/hr, and a 10 amp iv push was performed. The patient, who developed cardiac arrest again during observation, did not respond to the CPR for 30 minutes and was deemed exitus at the 16th hour of admission.

DISCUSSION

The symptoms and findings of metformin-associated toxicity include gastrointestinal side effects (nausea, vomiting, and epigastric pain), bradycardia/tachycardia, hyper/hypotension, hypoglycemia, hypothermia, and neurological changes (convulsion, somnolence, and coma) [7]. Hyperlactatemia and lactic acidosis are the most pronounced and distinguishing characteristics of metformin-associated toxicity [3].The term lactic acidosis is used when the pH is <7.35 and the lactate level is more than 5 mmol/l [8].

Lactic acidosis is divided into two types: type A and type B. **Type A lactic acidosis commonly develops due to** systemic hypoperfusion (hypovolemic, septic, cardiogenic shock), local hypoperfusion (Torsion/volvulus, arterial/venous embolism), and decreased oxygen in the artery (Anemia, carbon monoxide poisoning), whereas t**ype B lactic acidosis commonly develops due to** underlying diseases (Severe liver disease, renal failure, malignancy, thiamine deficiency), drug use(biguanides, alcohol, cyanide, acetaminophen, ethylene glycol, salicylate, isoniazid), and congenital mitochondrial disorders.

Metformin-induced lactic acidosis does not imply any disease except significant metformin accumulation. Metformin inhibits gluconeogenesis by blocking pyruvate carboxylase, giving rise to lactate accumulation. Though it is recycled back to glucose with the Cori cycle under normal conditions, hyperlactatemia occurs when increased uptake/reduced elimination occurs.

Metformin-associated lactic acidosis (MALA) implies comorbid diseases with metformin accumulation featuring: (i) Increased lactate production by peripheral tissues due to hypoxia (heart failure, respiratory failure, sepsis, severe dehydration), (ii) Deterioration of lactate production mechanism in the gluconeogenesis pathway (liver failure), and (iii) Significant increase in metformin levels (renal failure) [9]. The frequency of metformin-associated lactic acidosis is 3-9 in 100,000 [6].

The MALA-related mortality rate has been reported to be between 30-50% [10]. The lactic acidosis-related mortality rate can be as high as 83% in critically ill patients [11]. A systematic review did not report any death in patients with a serum pH of >6.9 and lactate <25 mmol [12]. In contrast, another study reported pH and lactate as poor predictors of MALA-related mortality [13].

Additionally, it has been stated that the lactic acidosis level and the severity of metabolic acidosis increase the MALA-related mortality risk.[14-16] Given its poor clinical outcomes, rapid diagnosis and management of lactic acidosis are critical to reducing mortality. While the administration of supratherapeutic doses may cause lactic acidosis in patients taking metformin, the administration of therapeutic doses may also cause MALA resulting in mortality in the presence of risk factors. Acute gastrointestinal disease, dehydration, and renal failure are the most critical risk factors for developing MALA [6].

Medications such as angiotensin-converting enzyme (ACE) inhibitors, non-steroid anti-inflammatory drugs (NSAIDs), and conditions that can cause acute renal failure should also be considered [17]. In addition, attention should be paid to using drugs that interact with metformin. Contrast agents can interact with drugs such as H_2receptor blockers (ranitidine, famotidine, cimetidine), proton pump inhibitors, antimicrobials (trimethoprim, rifampin, cephalexin), beta-adrenergic blockers (atenolol, metoprolol), and anticancer drugs which can result in increased plasma concentrations of metformin, posing a risk for MALA [18].

Given that there is no antidote for metformin intoxication, basic and supportive treatments, including management of fluid-electrolyte, acid-base, respiratory, metabolic, renal, and hemodynamic disorders, are resorted the most in its treatment. Gastrointestinal decontamination (gastric lavage and activated charcoal) is also recommended. In cases where metformin intoxication can be hemodynamically tolerated, and acid-base and lactate levels can be restored, HD can also be considered; if not, venovenous hemofiltration should be continued [3]. It has been reported that early HD and continuous venovenous hemofiltration reduced mortality in MALA [19-21].

Due to the low binding of metformin to proteins, hemodialysis, and continuous venovenous hemofiltration play an essential role in lactate clearance. However, care should be taken to apply hemodialysis and continuous venovenous hemofiltration for a sufficient time until acidosis is corrected [22]. HD was used in the patient presented herein since she hemodynamically tolerated metformin intoxication.

Nevertheless, contrary to reports on avoiding mortality with HD, the patient presented in this case report died due to MALA.

Although sodium bicarbonate is commonly used under pH<7.2 to restore the acid-base balance, it is ineffective in correcting intracellular acidosis in patients subject to MALA since the primary problem is intracellular lactate increase, and it decomposes, resulting in hydrogen ions in the cell [3]. As a matter of fact, sodium bicarbonate infusion was started in the patient presented herein due to severe acidosis, yet it was not very effective. Tris-hydroxymethyl aminomethane (THAM) is an alternative treatment to sodium bicarbonate in achieving alkalization. However, it is less effective than sodium bicarbonate in the event of renal dysfunction. In the presence of hypoglycemia, MALA should be treated with aggressive dextrose. Insulin/dextrose treatment may also be considered to increase the usability of dextrose, maintain glycolysis, and reduce lipolysis [3]. Glucagon is not the first-line treatment in the presence of hypoglycemia, yet it helps release glucose into the blood endogenously by stimulating hepatic glycogenolysis and gluconeogenesis. Glucocorticoids affect glucose metabolism by reducing insulin sensitivity and decreasing glucose uptake in the liver and muscle tissue [23]. In comparison, glucagon was started in the patient featured in this case report due to persistent hypoglycemia despite dextrose infusion, and hypoglycemia was not observed again in the follow-up until cardiac arrest.

Vasopressin and terlipressin are recommended taking into consideration the vasodilator shock that provides hemodynamic support in cases unresponsive to norepinephrine and epinephrine, reducing the mortality risk. [24] In addition, it has been reported that, albeit not conclusively, metformin increased NO synthesis, and methylene blue inhibited guanyl cellulose in the NO pathway, providing hemodynamic support in cases with peripheral vasodilation-associated lactic acidosis [25]. In comparison, terlipressin infusion was started in the case presented herein after norepinephrine treatment, yet shock findings continued, and severe hypotension persisted.

CONCLUSION

Metformin overdose or even therapeutic levels of metformin use can cause MALA in the presence of various risk factors. MALA, a rare clinical condition, is associated with mortality rates of up to 50%. The most crucial step in treating MALA is hemodialysis/venovenous hemofiltration. Given that metformin is a frequently used medication, care should be taken in the follow-up of patients using metformin, considering MALA.

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