CASE REPORT
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Metformin-associated lactic acidosis and acute kidney injury

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Abstract

Diabetes mellitus is a common disease worldwide. Metformin is included in the first-line treatment of type 2 diabetes mellitus. Metformin-associated lactic acidosis (MALA) is rare but can be life-threatening. In this case report, MALA and acute kidney injury (AKI) were detected in a 74-year-old female patient who presented with impaired consciousness. The patient was treated with hydration and hemodialysis (HD). MALA diagnosis was based on metformin levels > 5 mg/L, decreased pH, low bicarbonate levels, lactate levels > 5 mmol/L, and increased anion gap.

Keywords: Diabetes mellitus, metformin, lactic acidosis, acute kidney injury

INTRODUCTION

Diabetes Mellitus is one of the non-communicable diseases with an increasing global prevalence. Over the past few decades, the incidence of diabetes mellitus has risen sharply worldwide. It currently affects an estimated 537 million adults aged between 20 and 79 globally. It is estimated that by 2030, 643 million people will have diabetes mellitus, and this number is expected to rise to 783 million by 2045. Patients with diabetes mellitus may experience symptoms ranging from unexpected weight loss to increased urination, thirst, and hunger (1). The diagnosis of type 2 diabetes mellitus is made when one of the following criteria is present: fasting blood glucose ≥ 126 mg/dL, glycated hemoglobin A1c ≥ 6.5%, or postprandial glucose ≥ 200 mg/dL. Metformin is an antidiabetic drug that, in addition to its potential efficacy in lowering blood sugar levels, has beneficial effects on body weight, plasma lipids, and the risk of microvascular and macrovascular complications (2).

Metformin controls blood glucose levels by reducing gluconeogenesis and inhibiting glycogen breakdown. Additionally, it prevents hyperglycemia by decreasing glucose absorption from the gastrointestinal system and enhancing insulin signaling and glucose utilization. Metformin is generally considered safe and well-tolerated. However, gastrointestinal side effects such as diarrhea, nausea, and vomiting are relatively common and can affect up to 30% of patients using metformin. Less commonly, some patients may experience chest discomfort, headaches, sweating, hypoglycemia, weakness, and rhinitis while on metformin. Metformin may cause vitamin B12 deficiency in the long term. Metformin overdose has been linked to hypoglycemia and lactic acidosis (3-4).

This article presents a case report discussing metformin intoxication in a patient followed up with a diagnosis of diabetes mellitus.

CASE

A 74-year-old female patient was admitted to the emergency department with impaired consciousness. Her medical history included diabetes mellitus and hypertension, for which she was taking gliclazide, metformin, olmesartan, and hydrochlorothiazide. On physical examination, her general condition was poor, she was confused, uncooperative, drowsy, and her blood pressure was 100/60 mmHg with a heart rate of 107 bpm. Other physical examinations were normal. Laboratory investigations revealed glucose of 46 mg/dL, blood urea nitrogen (BUN) of 70 mg/dL, serum creatinine of 6.8 mg/dL, sodium of 148 mmol/L, potassium of 6.4 mmol/L, and hemoglobin of 10.4 g/dL. Due to anuria, a urine test could not be performed. Arterial blood gas analysis demonstrated

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a pH of 7.15, PCO2 of 34 mmHg, HCO3 of 12 mEq/L, lactate level of 7.3 mmol/L, and an anion gap of 17 mEq/L.

The patient was suspected of having MALA and acute kidney injury (AKI). She was treated in the emergency department with 20% dextrose for hypoglycemia and hydration for lactic acidosis. Active charcoal was administered for MALA. Additionally, sodium bicarbonate replacement was initiated due to a pH <7.2 and the presence of AKI. The patient was admitted to the intensive care unit (ICU). In the ICU, repeat blood gas analysis revealed a pH of 7.11, PCO2 of 25 mmHg, HCO3 of 8.1 mEq/L, and a lactate level of 9.8 mmol/L. Despite normalization of glucose levels, the patient's altered mental status persisted, and she remained drowsy.

The patient underwent hemodialysis (HD) for MALA and AKI, and hydration therapy was continued. After HD, her mental status improved. On the first day, blood gas analysis demonstrated a pH of 7.2, PCO2 of 24 mmHg, HCO3 of 11 mEq/L, and a lactate level of 2.4 mmol/L. Due to persistent AKI, blood gas abnormalities, and oliguria, she underwent a second HD session. A total of two HD sessions were performed. On the second day, urine output was adequate, and blood gas analysis normalized, so further HD was not required. The patient's serum creatinine level decreased to 1.3 mg/dl on the 5th day. At a follow-up clinic visit one week later, her renal function had returned to normal.

DISCUSSION

Metformin is a commonly used antidiabetic medication for patients with type 2 diabetes mellitus. The therapeutic plasma concentration of metformin is known to be <2mg/L (the maximum therapeutic concentration of metformin is between 1.5 and 3 mg/L), with peak levels reached 4 to 8 hours after absorption and an elimination half-life of 18 hours. MALA is a serious complication defined by blood lactate levels >5 mmol/L, blood metformin levels >5 mg/L, decreased pH, decreased bicarbonate, and increased anion gap. The incidence of MALA is estimated to range between 1 and 9 per 100,000 individuals. Lactate levels increase due to either overproduction or reduced clearance. MALA occurs due to decreased metformin clearance, renal dysfunction, decreased lactate clearance in liver disorders, and/or increased lactate production (e.g., in sepsis, congestive heart failure, respiratory failure, acute myocardial infarction, decreased tissue perfusion, or anoxia). Although metformin is not contraindicated in dehydration, shock, alcohol consumption, or hypoxic states, these conditions increase the risk of lactic acidosis. MALA can also develop in patients with even mild renal dysfunction (5-9).

Severe toxicity, such as MALA, can occur during critical illness due to metformin accumulation. It causes mitochondrial dysfunction through the inhibition of oxidative phosphorylation by metformin. Therefore, it causes lactic acidosis even in the presence of oxygen. This dysfunction affects multiple tissues, including the liver, skeletal muscles, heart, kidneys, and platelets. Metformin is absorbed primarily in the small intestine, binds negligibly to proteins in the blood, undergoes minimal metabolism, and is excreted unchanged by the kidneys (9). The most serious side effect of metfomin is lactic acidosis. MALA and metformin-induced lactic acidosis (MILA) remain controversial topics, as they are two distinct conditions with different origins and prognoses. Measuring plasma metformin concentration can aid in diagnosing MILA or MALA. In one study, 173 patients (109 MILA, 64 MALA) were included. MALA patients more frequently experienced shock, and mortality was associated with underlying conditions, with metformin accumulation exacerbating lactic acidosis. The mortality rate was 26% for MALA and 7% for MILA. HD patients had a higher mortality rate and a higher prevalence of sepsis (10).

Kim and colleagues evaluated metformin levels in 107 patients, 19 (17.8%) of whom met MALA diagnostic criteria. Among these MALA patients, 15 (78.9%) had AKI, and 4 (21.1%) had end-stage renal disease (ESRD). Sixteen patients received renal replacement therapy, with 9 undergoing intermittent HD, 4 receiving continuous renal replacement therapy, and 3 receiving both treatments sequentially. The mortality rate was 36.8% (11).

AKI associated with MALA is rare but well-documented. In one study, all patients with MALA also had AKI. In this study, it was suggested that AKI was triggered by dehydration resulting from vomiting and diarrhea due to metformin toxicity. In addition, plasma lactate levels increase with AKI and the risk of lactic acidosis increases. (12). In a case study of a 70-year-old female patient with type 2 diabetes mellitus, MALA was diagnosed, and AKI and hyperkalemia prompted treatment with renal replacement therapy. This patient was also found to be COVID-19 positive (13). Ariga and colleagues reported a case of a 60-year-old male patient diagnosed with MALA and AKI who was taking a normal dose of metformin. The patient presented with complaints of dizziness, malaise, and oliguria. In addition, metformin levels were found to be high in this patient (14).

In the treatment of the patient, metformin therapy was discontinued, 20% dextrose was administered for hypoglycemia, and hydration was initiated. The patient underwent HD due to anuric AKI and lactic acidosis. After two sessions of HD, the patient was not subjected to further sessions due to the presence of urine output and a downward

trend in serum creatinine levels. The management of MALA is controversial and is largely supportive. Treatment options include hydration, activated charcoal, sodium bicarbonate, HD, or continuous venovenous hemofiltration. Early administration of activated charcoal may be considered. Contraindications to activated charcoal include bowel obstruction, perforation, hypotension, or reduced bowel motility. Severe acidosis is treated with sodium bicarbonate infusion, although the use of sodium bicarbonate replacement remains debated. However, sodium bicarbonate replacement should be considered in patients with a pH <7.15. Bicarbonate replacement is recommended for pH < 7.20 in cases of cardiovascular disease and/or hemodynamic instability in the patient. Hypotension and shock should be managed with intravenous crystalloids and vasopressors as needed. Intermittent HD and continuous renal replacement therapy are effective in treating MALA, although documentation is limited to a few case series and reports worldwide. The Extracorporeal Treatment in Poisoning (EXTRIP) workgroup recommends initiating HD in cases with pH ≤7.0, lactate >20 mmol/L, and/or the presence of shock, acute or chronic renal or liver failure, or altered mental status. HD can be discontinued once lactate levels drop below 3 mmol/L and pH reaches 7.35 (5,6,15-17). The mortality rate associated with MALA ranges from 30% to 50% (18).

CONCLUSION

Patients with type 2 diabetes mellitus who are using metformin should be closely monitored for the risk of MALA and AKI. If risk factors for MALA are present, metformin use should be discontinued or paused. Although MALA is rare, it carries a high mortality rate.

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