Case Report

Metformin-associated Lactic Acidosis and Acute Renal Failure in a Type 2 Diabetic Patient

Metformin belongs to a class of drugs known as the biguanides that are widely used in the treatment of type 2 diabetes mellitus. Its association with lactic acidosis is well established, although rare. Metformin-associated lactic acidosis is recognized as a potentially lethal condition that can occur in patients with contraindications to the drug, such as renal dysfunction, liver diseases, alcoholism, and cardiopulmonary diseases. In these cases, the plasma concentration of metformin is not necessarily abnormally high. We describe a 75-year-old diabetic woman with acute renal failure and lactic acidosis due to metformin intoxication. Clinical manifestations included vomiting, diarrhea, hypothermia, hypotension and transient blindness. Her initial renal function was recovered after hemodialysis and she was discharged 3 months after admission.

CASE REPORT

A 75-year-old woman suffered from nausea, vomiting, diarrhea, and weakness for 2 days before arrival to our hospital. On the day of admission, she experienced sudden blindness. The patient had a history of type 2 diabetes mellitus for more than 10 years, complicated with diabetic foot 2 years previously. She had received metformin 1000 mg twice daily for the past year due to poor glycemic control. The drug was prescribed to patients who do not have impaired hepatic, renal or cardiopulmonary function.

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Correspondence to: Wei-Hsiung Hu, MD, Department of Emergency Medicine, Taichung Veterans General Hospital, 160, Sec. 3, Taichung-Kang Road, Taichung 407, Taiwan.
Fax: +886-4-2359-4065; E-mail: hwh1213@vghtc.gov.tw
and magnesium oxide for diabetes and hypertension. The patient had been compliant in taking all medicines. The base-line level of creatinine (Cr) was 1.2 mg/dL 7 months before this admission.

Physical examination revealed acute respiratory distress. Her Glasgow coma scale was 13/15. Temperature was 32 °C, pulse rate was 125 beats per minute, blood pressure was 67/42 mm Hg, and respiratory rate was 20 breaths per min ute. The lung fields were clear and there were no signs of heart failure. The abdomen was normal. Neurological examination revealed absence of pupillary reflex and loss of visual acuity. Arterial blood gases while on 3 L/min oxygen were pH 6.648, PaCO₂ 16.9 mm Hg, PaO₂ 130 mm Hg, HCO₃⁻ 1.9 mEq/L, base excess -34.7 mEq/L. Laboratory tests revealed the following serum values: glucose 179 mg/dL, sodium 142 mEq/L, potassium 5.2 mEq/L, chloride 91 mEq/L, blood urea nitrogen 63 mg/dL, Cr 7.7 mg/dL, creatinine phosphokinase 161 IU/L, and C-reactive protein 5.9 mg/dL. Serum ketone showed weakly positive (+). Her total white blood cell count was 27,600/mm³ with 70% segments, 2% bands, and 18% lymphocytes. Urinalysis was protein 75 mg/dL, weakly positive for ketone. Chest roentgenogram showed mild cardiomegaly. Electrocardiogram showed atrial fibrillation with rapid ventricular response. Abdominal sonography showed no significant abnormalities. An ophthalmology consultation was requested and revealed no light perception and no retinopathy. Posterior ischemic optic neuropathy was suspected, and surgery for the magnetic resonance imaging of brain showed slight dilatation of ventricular system and no significant abnormalities over bilateral occipital lobes.

The acidemia was treated with 366.7 mEq of sodium bicarbonate (NaHCO₃), administered intravenously at the emergency department. Dopamine and norepinephrine were initiated for persistent hypotension. Trimethoprim-sulfamethazole was administered due to presumed infectious enterocolitis after blood and stool cultures were done, but was discontinued 1 day later due to lack of evidence of infectious source. Respiratory failure developed and the patient was intubated with ventilatory support. A second arterial blood gases analysis showed pH 6.947, PaCO₂ 27.0 mm Hg, PaO₂ 190 mm Hg, HCO₃⁻ 5.9 mEq/L, base excess -24.6 mEq/L. She was then transferred to the intensive care unit (ICU). The first hemodynamic readings in the ICU revealed a central venous pressure 24 mm Hg, pulmonary artery wedge pressure 31 mm Hg, cardiac index 2.63 L/min/m², cardiac output 4.16 L/min and systemic vascular resistance 538 dynes/sec/cm⁵. Serum lactate level (113.6 mg/dL) was determined due to severe metabolic acidosis. Toxicological screen was negative for methanol and ethanol. Salicylates level was 6.3 mg/dL. There was no confirmed history of ethylene glycol ingestion. A list of the patient’s medications...
was provided by her family and metformin was identified, establishing the diagnosis of metformin intoxication. Due to hypotension, emergent continuous venovenous hemodialysis (CVVHD) with bicarbonate-base fluid was instituted to re move the metformin and correct LA. The patient’s mental status and visual acuity improved and her hemodynamic status became stable after CVVHD for 20 hours. The curve levels of lactate in serial samples are shown in Fig. 1. Cr decreased to 1.8 mg/dL after CVVHD and creatinine clearance rate (Ce) was 48.9 ml/min. Blood cultures were negative and stool cultures showed normal flora. However, the patient could not be weaned from ventilator and ventilator-associated pneumonia developed a few days later. She received tracheostomy during hospitalization due to complications of long-term intubation. The serum Cr was 1.3 mg/dL when she was discharged 3 months later.

**DISCUSSION**

In a case with increased anion gap acidosis, the causes of acidosis, such as LA (type A and B), ketoadidas (diabetic, alcoholic, starvation), toxins (ethylene glycol, methanol, salicylates) and renal failure (acute and chronic), should be determined. No evidence of infection was found in this patient (i.e., blood and stool cultures were negative). The causes of metabolic acidosis other than LA were ruled out, so aci diosis in this patient was likely the result of the metformin toxicity. Although the patient had concomitant ketoadidas at the time of initial presentation, this was most likely secondary to the metformin toxicity rather than primary diabetic ketoacidosis.

LA is defined as a state of increased serum lactate concentrations (> 45 mg/dL or > 5 mmol/L), decreased blood pH (< 7.25), and disturbances of electrolytes with an increased anion gap. Lactate is principally removed by hepatic metabolism, but significant renal excretion occurs at high blood levels. Disorders of lactate metabolism have been divided into either an aerobic (type A) or anaerobic (type B). The character of type A LA is tissue hypoxia resulting in anaerobic production of lactate. The most common causes of type A LA are cirrhotic in sufficiency (shock and heart failure), sepsis, anemia, reduced tissue perfusion and arterial hypoxemia. Type B LA is less common and tissue hypoxia is not an obvious feature. It is associated with systemic disorders such as liver disease, malignancies, drugs and toxins that impair the metabolism of lactate.

The signs and symptoms of MALA are non-specific and include anorexia, nausea, vomiting, diarrhea, epigastric pain, thirst, somnolence, lethargy, and hyperpnea. Hypothermia is common in patients who develop depression of central nervous system as associated with MALA. Hypotension, hypoglycemia and LA have been seen in people with metformin presenting in toxic concentrations. Abnormal reflexes including loss of corneal reflexes and pupillary response to light have been reported in patients with biguanide toxicity. Transitory blindness in such patients may be a rare presentation associated with LA. The condition is considered in patients with a presumed inhibition of oxidative metabolism in the retina.

Biguanides are primarily absorbed by the small intestine and have a high affinity for protein-binding in cells of the gastrointestinal tract. They also undergo enterohepatic recirculation. Biguanides act to lower serum glucose levels by inducing anorexia, decreasing gastrointestinal absorption of carbohydrates, inhibiting hepatic gluconeogenesis from alanine, pyruvate and lactate, increasing cellular uptake of glucose and increasing the binding of insulin to its receptor. In toxic concentrations, impairing oxidative phosphorylation and gluconeogenesis and also enhancing glycolysis may result in increased lactate levels.

Treatments of MALA includes volume expansion, NaHCO₃ administration, so dium dichloroacetate, bicarbonate-based buffering hemodialysis and mechanical ventilatory support if respiratory failure develops. Correction of metformin acidosis is crucial to treatment. The use of a large amount of intravenous NaHCO₃ in the managent of LA seems necessary as the aci diosis becomes severe, but there are well-known precautions as so ciated with its use, including leftward shift of the oxyhemoglobin dissociation curve, rebound metabolic alkalosis, reflex vasodilatation after bolus injection, sodium overload, electrolyte disturbances and decreased myocardial contractility due to production of carbon dioxide.
Dichloroacetate has been used to reverse LA experimentally by transiently improving acidemia, but it fails to alter either hemodynamics or survival rates. Although our patient’s arterial pH at the time of initial presentation suggested a poor prognosis, hemodialysis appeared to facilitate her rapid recovery. Hemodialysis with bicarbonate-base fluid has been used successfully in the treatment of MALA. It corrects the acidosis and removes metformin from plasma efficiently, preventing further overproduction of lactate without the associated risks of intravenous administration of NaHCO₃. Additionally, CVVHD is a better choice for the patient with unstable hemodynamic status.

REFERENCES