Case Report

Metformin-Related Acute Lactic Acidosis in a Woman with Normal Renal Function

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Abstract

Metformin is a first-line oral anti-hyperglycemic agent. It decreases insulin resistance, decreases hepatic glucose output, and enhances peripheral glucose uptake. Metformin is used as monotherapy or in combination with other oral hypoglycemic agents. A major toxicity of metformin is lactic acidosis. In the absence of acute overdose, metformin-associated lactic acidosis rarely develops in patients without comorbidities, such as renal or hepatic insufficiency or acute infection. Here we report a case of metformin-related lactic acidosis happening in a woman previously with a normal renal function. She was found to have acute renal injury and profound lactic acidosis after diarrhea for days. The conditions of lactic acidosis were corrected after two sessions of hemodialysis.

KEY WORDS: metformin intoxication, lactic acidosis, hemodialysis

Introduction

Metformin is a biguanide anti-diabetic medication, and an active extract from the plant Galega officinalis (also called goat’s rue, French lilac, Italian fitch, or professor-weed), which was used in medieval Europe to treat diabetes. Metformin mainly acts on the liver. It reduces the release of glucose from liver, enhances insulin effect on peripheral tissues, and decreases blood glucose. Among drugs used for blood sugar control, metformin is a first-line drug. The most serious side effect of metformin is lactic acidosis, the major underlying mechanisms include conversion of glucose to lactic acid in the plexuses near the small intestines (1) and inhibition of hepatic gluconeogenesis (2). Conversion of lactic acid, pyruvic acid, or alanine to glucose reduced. Lactic acid and other substances that can be used for the synthesis of lactic acid increase significantly. The yearly incidence rates of lactic acidosis in previous reports were less than 5 episodes in every 100 thousand people (3). It was first reported in 1988. A 55-year-old diabetic woman treated with chlorpropamide and metformin for three years presented with acute oliguric renal failure and lactic acidosis from which she died. The plasma metformin level was very high suggesting that the lactic acidosis was caused by the drug (4). Currently there is no effective antidote for metformin-induced lactic acidosis, and its treatment mainly focuses on the correction of acidemia. Considerable efficacy has been observed in the use of hemodialysis to treat acute or chronic metformin-induced lactic acidosis. Hemodialysis application is currently recommended in patients with severe metabolic acidosis (pH < 7.1) and renal failure. Use of sodium bicarbonate in metformin-induced lactic acidosis is still controversial. Current studies suggest its use only in more severe cases of acute metabolic acidemia (arterial pH < 7.10-7.15). The following is a report on a typical case of metformin-related lactic acidosis. The 56-year-old woman had suffered from endometrial cancer and heart failure caused by chemotherapy toxicity. She took amoxicillin for skin infection but experienced a series of diarrhea episodes complicated with acute renal failure and severe lactic acidosis.
Ms. Chang, 56-year-old, came to the hospital’s emergency room in early January 2012. Her main complaint was shortness of breath that had persisted for two days. She was accompanied by her mother to the emergency room and appeared to be gasping for air while walking. She even had difficulty breathing sitting still. Physical examination showed mild cyanosis of the lips; no obvious rales, wheezing, or rhonchi in the lungs; no visible edema of the extremities; shortness of breath (respiratory rate: 40/min); body temperature of 35.0°C; heart rate of 87/min; and blood pressure of 86/44 mmHg. Blood oxygen level was only 77% under normal ambient oxygen levels. She was asked to put on a non-rebreathing mask immediately (15 L/min) which then managed to keep blood oxygen level at around 90%. Chest X-ray revealed cardiomegaly (See Fig. 1) but the lung markings were not obvious. Emergency blood gas analysis indicated metabolic acidemia (pH of 7.142, PCO₂ of 21.8 mmHg, PO₂ of 22 mmHg, and HCO₃ of 9.6 mmol/L). The biochemistry blood test report showed worsened renal function (blood urea nitrogen [BUN] of 83 mg/dL, creatinine [Cr] of 3.5 mg/dL). The patient’s previous blood test report of two months ago indicated BUN of 33 mg/dL and Cr of 0.9 mg/dL. Other data at this time included brain natriuretic peptide of 3,680 pg/mL, lactate of 127.3 mg/dL, glucose of 542 mg/dL, and central venous pressure level of 15 cmH₂O. As the patient suffered from both metabolic acidemia and respiratory failure, an endotracheal tube was inserted to maintain breathing after consent from the patient was obtained.

The medical history of the patient showed endometrial cancer discovered in 2007 and chemotherapy that began after debulking surgery in 2008. The patient underwent a total of 18 courses of doxorubicin- and cisplatin-based chemotherapy between 2008 and 2011. In July 2011, since the systemic dose of doxorubicin had already reached its ceiling, only cisplatin was used in the subsequent three chemotherapy courses. The patient started to experience symptoms such as chest tightness, chest pain, and gasping for air while climbing stairs or walking in September 2011. The cardiologist diagnosed and determined that it was doxorubicin-induced heart failure. The patient underwent cardiac catheterization in October 2011 and the possibility of coronary artery disease was ruled out. Her heart failure at the time was categorized as NYHA F1. The LVEF (Left Ventricular Ejection Fraction) measured by echocardiography was only 39%. In addition, the patient was diagnosed with diabetes in August 2008 and started to take one tablet of novonorm 1 mg three times a day. The dose was increased because of uncontrolled blood sugar and the HbAc₁ ranging from 8% to 9%. Before the onset of heart failure in December 2011, the patient was treated with Levasir 16U qd, Metformin (500 mg) 1*tid and Novonorm 1*tid to keep blood sugar under control.

The patient described that around three weeks before the onset of heart failure, she saw a dermatologist for a furuncle in her hip and had been taking amoxicillin for about a week. Then she suffered from gastrointestinal discomfort and experienced continuous diarrhea for a period of around two weeks. The symptoms were not serious in the beginning and involved only more frequent bowel movements, and loose, watery stools. The patient did not think that it was serious so she did not seek medical advice. Subsequently, her urination volume gradually reduced and she became thirsty much more easily. Her appetite decreased. She became weak physically and prone to gasping while walking and climbing stairs. She was even gasping for air when sitting still in the two days prior to the current visit to the doctor. Finally, she went to the emergency room for help.

An endotracheal tube was inserted and a ventilator was set up to help her breathe in the emergency room. Later, she was admitted to the intensive care unit for close monitoring and treatment. On the night of hospital admission, emergency hemodialysis-
sis was arranged. After a total of two hemodialysis sessions, she did not suffer dehydration. Her lactic acid level dropped to 14.4 mg/dL. She was discharged from the hospital upon achieving a stable condition. Her renal function also recovered gradually during follow-up with normal urination that eventually returned to Cr: 1.4 mg/dL.

**Discussion**

Lactic acidosis is the most serious drug toxicity of metformin. The mortality rate is around 45% to 48%. Its fatality predictive factors are not related to lactic acid or drug levels in the blood but to underlying diseases. Abnormal liver function, in particular, is the most accurate indicator (5).

In clinical practice, acidosis from lactic acid buildup usually occurs among patients with the following predisposing conditions: [1] renal insufficiency (Cr > 1.5 mg/dL for men and Cr > 1.4 mg/dL for women) or low creatinine clearance; [2] underlying liver disease or history of alcohol abuse; [3] heart failure; [4] history of lactic acidosis; [5] insufficient tissue perfusion or unstable hemodynamic status; and [6] hypoxemia (6). The patient in this report, for example, developed chronic heart failure due to multiple chemotherapy toxicities (the last echocardiography EF = 39% before onset of heart failure). Acute renal failure was inferred to be the result of consecutive days of incessant diarrhea, reduced appetite and water intake, dehydration, and those trigger factors reduced tissue perfusion. Serum creatinine increased from 0.9 mg/dL to 3.5 mg/dL (Table 1). Renal failure led to metabolic acidemia (the first arterial blood oxygen analysis in the emergency room showed pH = 7.142, PCO\(_2\) = 21.8 mmHg, PO\(_2\) = 22 mmHg, and HCO\(_3^-\) = 9.6 mmol/L). Further analysis of the metabolic acidemia indicated Na = 131 mmol/L, HCO\(_3^-\) = 7.5 mmol/L, and Cl = 91 mmol/L at the time of blood collection. The anion gap was 32.5, suggesting high-anion gap acidosis. Tests for common anion sources, such as blood ketone, appeared negative. The level of lactate, on the other hand, was 127.3 mg/dL. Considering that the patient had no history of drinking alcohol, taking of salicylic acid-containing drugs, nor serious sepsis, it was then determined to be acidemia resulting from lactic acidosis. Along with the patient’s medical history of incessant recent diarrhea, acute renal failure, and the use of metformin, it was inferred to be a side effect of lactic acid buildup and acidosis as a result of accumulated drug concentration after acute renal failure. Metabolic acidemia, in turn, further affected cardiac contraction and exacerbated heart failure (the post-admission echocardiography showed poor LV contractility, global hypokinesis, and LVEF = 34%) so that tissue perfusion was even more insufficient and renal failure became worse. It was a vicious circle (See Fig. 2).

There are currently no effective antidotes for the said metformin-induced lactic acidosis and its treatment focuses mainly on the correction of acidemia (6, 7). Most patients, unless experiencing respiratory failure, do not need to be supported by an endotracheal tube. The increase in respiration rates or heart rates among intoxicated patients is usually a form of compensation for metabolic acidemia and does not necessarily lead to respiratory failure. If the patient has reached respiratory failure and requires intubation, care should be taken to keep the ventilator settings at a level where the ventilation is sufficient to compensate for acidemia, and to regularly monitor the patient through arterial blood gas analyses until the patient’s condition stabilizes. Data of a series of blood gas analyses done in the emergency room for the patient in this report are shown in Table 2. Gradual improvements were observed after use of the ventilator following intubation.

On the first two nights of hospital admission, emergency hemodialysis was performed due to severe lactic acidosis. Lactic acidosis is a rare but potentially fatal adverse effect of metformin, particularly in patients with predisposing conditions.
seems to contribute significantly to the management of this life-threatening condition and the improvement in outcome. The patient’s serum lactic acid values dropped significantly after hemodialysis. See Table 3.

A review of literature shows that considerable efficacy has been observed in the use of hemodialysis to treat acute or chronic metformin-induced lactic acidosis. Metformin dialysance by dialysis appears satisfactory (68 mL/min) even in the case of relatively low blood flow; this value reached 170 mL/min under good hemodynamic conditions. Hemodialysis efficiently removes metformin and corrects metabolic acidosis in patients with metformin-induced lactic acidosis (8). Currently, use of hemodialysis is recommended for critically ill patients and patients with severe metabolic acidemia (pH < 7.1), failed supportive treatment, and renal failure. Treatment may have to be repeated until metabolic derangements are corrected. This applies to our case. A bicarbonate buffer must be used in hemodialysis. Its main efficacy is to correct metabolic acidemia, instead of removing metformin from the blood (9). As for continuous venovenous hemofiltration (CVVH), since it is inferior to conventional hemodialysis in terms of efficacy in removing drugs from the blood (10), its application is only recommended for patients with unstable hemodynamic status and to whom conventional hemodialysis does not apply.

The role of sodium bicarbonate in metformin-induced lactic acidosis: The use of sodium bicarbonate in the treatment of metformin-induced lactic acidosis is still controversial at the moment. It is only suggested to be used in more severe cases of acute metabolic acidemia (arterial pH < 7.10-7.15) due to the following rationale. Severe metabolic acidemia reduces cardiac contractility, which leads to insufficient tissue perfusion. Intravenous injection of sodium bicarbonate in such cases helps increase the pH value in the blood directly and enhance the efficiency of oxygen being brought to tissues. However, excess lactic acid is eventually converted to bicarbonate ions, which are likely to cause metabolic alkalosis as a rebound, and increase the total amount of sodium ions in the body (11, 12). Research has shown that bicarbonate ions can only stay at a concentration temporarily in the blood because it will then react with excess hydrogen ions to form water and carbon dioxide.

Table 2. Blood gas analysis shows improvement in acidemia after intubation and the use of ventilator

<table>
<thead>
<tr>
<th>Date/Time</th>
<th>Day 1</th>
<th>Day 1</th>
<th>Day 1</th>
<th>Day 1</th>
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<tbody>
<tr>
<td>pH</td>
<td>7.142</td>
<td>7.083</td>
<td>7.243</td>
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<tr>
<td>PCO₂ (mmHg)</td>
<td>28.1</td>
<td>25.1</td>
<td>29</td>
<td>19.7</td>
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<tr>
<td>PO₂ (mmHg)</td>
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<td>45</td>
<td>60.8</td>
<td>284.8</td>
</tr>
<tr>
<td>HCO₃ (mmol/L)</td>
<td>9.6</td>
<td>7.5</td>
<td>12.7</td>
<td>14</td>
</tr>
</tbody>
</table>

Fig. 2. The vicious circle of heart failure and lactic acidosis.
form carbon dioxide. When a patient suffers from respiratory and circulatory failure, the excess carbon dioxide cannot be completely eliminated from the lungs and will accumulate in the venous system to further worsen acidemia (13, 14). The patient in this report did not receive sodium bicarbonate as part of emergency management. Instead, an endotracheal tube was inserted to keep her breathing and hemodialysis was utilized to correct acidemia. Hemodialysis is ready for use at any time in a hospital setting and the condition of metabolic acidosis will be greatly improved after hemodialysis. (Table 4)

In 2011, the Department of Health in Taiwan took the use of metformin in patients with Cr of 1.5 mg/dL and above as a contraindication and excluded patients who are 80 years and older from treatment with metformin. For those younger than 80 years old, special caution is recommended. For any patient with possible lactic acidosis, medical history collected should include the dose, frequency, and concurrent use of other antihyperglycemic agents, if any. Patients are likely to develop symptoms such as nausea and abdominal pain. It is possible that physical examination will show a rapid heart rate, reduced blood pressure, and accelerated respiration. Laboratory tests must include biochemistry tests, such as those for blood glucose, renal function, arterial blood oxygen analysis, bicarbonate and serum lactic acid levels, and electrocardiogram. For women of childbearing potential, a pregnancy test must also be performed. The results of all the above combined are the bases for the determination and exclusion of other possible causes. The measurement of serum metformin levels has not been accepted as a routine so far mainly because few hospitals are capable of providing real-time measurement methods and data, and the correlation between drug level and clinical severity is not high. When serum metformin appears negative, the possibility of drug-induced lactic acidosis can then be excluded. For patients receiving metformin, it is still necessary to consider if there are other possible causes, such as sepsis or intestinal ischemia, that are inducing lactic acidosis.

Dosage reports on patients with metformin-induced lactic acidosis in the past tended to be unreliable. There is also no specific literature at the moment to indicate the approximate minimum dose required for causing acidosis. Clinicians, particularly primary care physicians, who often use metformin as their first-line drug of choice for diabetic patients, should pay close attention to the possibility of intoxication in patients with abnormal liver function, renal insufficiency or heart failure, or those who may have overdosed. Prevalence of heart failure among the elderly is quite considerable. Therefore, attention should be paid to the possible occurrence of lactic acidosis, even if renal function test results appear normal.

References


### Table 3. Lactic acid level dropped after hemodialysis

<table>
<thead>
<tr>
<th>Day 1 (Before)</th>
<th>Day 1 (After 1st Hemodialysis)</th>
<th>Day 2 (After 2nd Hemodialysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate (mg/dL)</td>
<td>15:54</td>
<td>20:00</td>
</tr>
<tr>
<td>127.3</td>
<td>96.6</td>
<td>47.3</td>
</tr>
</tbody>
</table>

### Table 4. Treatment

1. Secure airway, breathing, and circulation
2. For acute ingestions, give activated charcoal
3. For patients with profound acidosis (pH < 7.10), consider sodium bicarbonate infusion
4. For patients with profound acidosis, renal disease, or critical illness, hemodialysis will correct metformin-induced acid-base disturbance


