Metformin-Associated Lactic Acidosis in a Patient With Normal Renal Function

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Presentation

S.S. was a 53-year-old woman with a history of type 2 diabetes and asthma who presented to the emergency department with coughing and shortness of breath. Five days before this visit, she developed wheezing and a cough productive of yellow sputum. Her primary care physician started her on amoxicillin for possible bacterial bronchitis, but her symptoms persisted. Three days later, she became acutely short of breath and presented to the emergency department. At that time, a chest X-ray was obtained, revealing a linear opacity questionable for pneumonia. She was treated with a nebulizer in the emergency department, started on prednisone 60 mg for 5 days, and switched from amoxicillin to levofloxacin. However, despite these interventions, she continued to cough and experience dyspnea, prompting her return to the emergency department.

At this visit, S.S. denied any fever, chills, anorexia, chest pain, nausea, vomiting, or diarrhea. Her presenting vital signs included a temperature of 97.7°F, pulse of 118 bpm, blood pressure of 149/91 mmHg, respiratory rate of 24 breaths per minute, and O_2 saturation of 100% on room air. On physical examination, she had end-expiratory wheezes in the lower posterior lung fields. Her heart was tachycardic without any murmurs, rubs, or gallops. Otherwise, the physical examination was unremarkable. Initial chemistry values included sodium of 129 mEq/L, potassium of 4.9 mEq/L, chloride of 93 mmol/L, bicarbonate of 18 mmol/L, glucose of 207 mg/dL, blood urea nitrogen of 32 mg/dL, and creatinine of 1 mg/dL. The serum anion gap was 18. Initial complete blood count included a white count of 12.0, a hematocrit of 40.0, and a platelet count of 358,000.

S.S.'s diabetes medication consisted only of metformin, which had been increased 6 weeks earlier to 1,000 mg twice daily. In addition to type 2 diabetes, she had a history of hypothyroidism, hypertension, asthma, and hyperlipidemia, for which she took levothyroxine, spironolactone, montelukast, and pravastatin, respectively. She had no history of acute or chronic renal disease.

In the emergency department, S.S. was given 200 mg of benzonatate orally for her cough and 1 hour of continuous nebulizer treatment containing albuterol and ipratropium bromide. However, because her spasmodic coughing did not improve and she denied feeling better, she was given 125 mg of methylprednisolone and was admitted for observation and nebulizer treatments. Her antibiotic coverage was also switched to ceftriaxone 2 g intravenously daily and azithromycin 500 mg intravenously daily.

On day 1 of admission, the hospitalist took a detailed medical history and noted that the patient's voice was hoarse. S.S. reported that hoarseness had been her most worrisome and awkward symptom for the past few days and that most of her doc-

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umented "wheezes" could be better described as voice hoarseness. On physical examination, her lungs were clear in all fields, with no prolonged expiration. However, a laryngeal wheeze was noted. On review of her blood work, the hospitalist reasoned that her low bicarbonate and normal oxygenation contradicted the diagnosis of asthma exacerbation with pneumonia. S.S., hoping to find an answer to her persistent unexplainable symptom, agreed to an arterial blood gas, which revealed metabolic acidosis with secondary respiratory alkalosis, with a pH of 7.44, $PaCO_2$ of 22 mmHg, PaO_2 of 118 mmHg, bicarbonate of 14.9 mEq/L, and oxygen saturation of 99%. The acetone level came back negative, but the lactate level was found to be increased, at 7.3 mmol/L.

Lactic acidosis secondary to metformin use was suspected, so metformin was discontinued. Over the next 48 hours, S.S.'s lactate level gradually decreased from 7.3 to 6.5, 5.4, and finally to 3.0 mmol/L, concomitant with an increase in her bicarbonate level from 16 to 21, and finally to 23 mmol/L. She showed gradual clinical improvement and remained hemodynamically stable. Her diabetes treatment was changed to detemir 5 units daily during her hospital stay, but she was switched to glargine on discharge for better 24-hour coverage. She was not re-challenged on metformin because of the dramatic response of her lactate level correlating with her improved condition after metformin was stopped.

Questions

1. For which patients with diabetes is metformin currently recommended?
2. Is it possible for a patient with normal renal function to develop metformin-associated lactic acidosis?
3. How can health care providers recognize lactic acidosis as a potential complication of metformin?

Commentary

Metformin is a biguanide that works by increasing insulin-mediated glucose utilization. In the absence of any contraindications, metformin is considered to be the first-line pharmacological treatment for type 2 diabetes and should be initiated at the time of diagnosis, along with lifestyle interventions (1). Some of the advantages of metformin over other oral antidiabetic medications include a decreased likelihood of hypoglycemia, favorable effects on lipids, and a decreased likelihood of cardiovascular events and mortality (2,3). Of all the contraindications to metformin use, impaired renal function is the most concerning because of the increased risk of lactic acidosis.

Although lactic acidosis is a widely recognized side effect of metformin, its occurrence is actually quite rare, with an incidence rate of 9 cases per 100,000 person-years of metformin exposure (4). Most cases of metformin-associated lactic acidosis are from patients who either had abnormal kidney function or overdosed on metformin. This case shows a rare instance of metformin-associated lactic acidosis in a patient with normal renal function taking a normal dose of metformin. A similar case was published in 2011 by van Stolen et al. (5). In their case, the patient's serum lactate levels corresponded to metformin levels at baseline, withdrawal, re-challenge, and subsequent withdrawal.

It is unclear how frequently these types of responses occur. However, because metformin is so widely prescribed, it is likely that some other patients taking metformin may also have increased lactate levels. For this reason, it is important that clinicians be able to recognize and diagnose metformin-associated lactic acidosis.

Signs and symptoms of lactic acidosis are nonspecific and may include nausea, vomiting, abdominal pain, anorexia, hyperventilation, or hypotension. Therefore, it is important to maintain a high index of suspicion for lactic acidosis in patients treated with metformin. If lactic acidosis is suspected, a basic chemistry workup, an arterial blood gas, and a lactate level should be ordered. In this case, we suspect that concomitant acute illness such as pneumonia may have played a role in the development of lactic acidosis in this patient with diabetes and normal kidney function.

Clinical Pearls

- Metformin-associated lactic acidosis remains a rare complication of a common medication.
- Metformin-associated lactic acidosis should not be automatically excluded in patients with normal renal function, particularly in the presence of a concomitant acute illness.
- Health care providers should consider ordering a serum lactate level for acutely ill patients taking metformin, especially in the presence of acidosis on blood chemistry results.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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