



Metformin-Associated Lactic Acidosis Detected Days after Acute Gastroenteritis

Akut Gastroenteritten Günler Sonra Tespit Edilen Metforminle İlişkili Laktik Asidoz

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Abstract

Metformin-associated lactic acidosis in a diabetic patient is a rare and severe complication. The severity of the condition is associated with the underlying disease. The diagnosis may be delayed due to its rarity and the fact that its symptoms and signs are frequently confused with other pathologies. In such cases, generally, the underlying renal disease helps to establish the diagnosis. In this paper, we present the case of lactic acidosis in a patient without a serious underlying disease who was using metformin, ramipril and spironolactone for diabetes and hypertension. The level of blood creatinine was found to be 1.4 mg/dL. It should be kept in mind that metformin can cause life-threatening lactic acidosis, especially in patients using renin-angiotensin-aldosterone system blockers, even without a serious deterioration in renal functions.

Keywords: Metformin, lactic acidosis, acute gastroenteritis

Öz

Diyabetik hastalarda metformin ilişkili laktik asidoz nadir ve ciddi bir komplikasyondur. Ciddiyet düzeyi altta yatan hastalık ile ilişkilidir. Nadir görülmesi ve belirtileri ve bulgularının diğer patolojiler ile karıştırılması nedeni ile, tanı geç konulabilir. Bu gibi durumlarda, genellikle, altta yatan böbrek hastalığı teşhis konmasına yardımcı olmaktadır. Sunduğumuz bu olgu; altta yatan ciddi bir hastalığı olmayan, diyabet ve hipertansiyon nedeni ile metformin, ramipril ve spironolacton kullanan bir hasta, 1,4 mg/dL kan kreatinin düzeyi ve laktik asidoz ile acil polikliniğimize getiriliyor. Metforminin, özellikle renin-angiotensin-aldosteron sistemi blokeri kullanan olgularda, renal fonksiyonlarda ciddi bir bozulma olmadan laktik asidoza yol açabileceği akılda tutulmalıdır.

Anahtar kelimeler: Metformin, laktik asidoz, akut gastroenterit

Introduction

Since metformin is a cheap, safe and efficient agent and does not associate with hypoglycemia and weight gain, it is recommended as a first-line oral antidiabetic after lifestyle modification in patients with type 2 diabetes mellitus (T2DM). Lactic acidosis, which is a fatal situation, is the most important side effect of metformin (1). The risk of metformin-associated lactic acidosis increases with deterioration of renal function and advanced age (2). In addition, usually, there is an underlying factor such as renal dysfunction, congestive heart failure, dehydration, hepatic and respiratory failure, nonsteroidal anti-inflammatory agents and angiotensin converting enzyme use affecting clearance or energy metabolism. The incidence of lactic acidosis is reported as 9 cases per 100000 patient-years (3). The diagnosis of lactic acidosis is established when blood pH is under 7.35 and the level of serum lactic acid is above 5 mmol/L. A high index of clinical suspicion is required for

timely diagnosis and treatment. Infusion of sodium bicarbonate and renal replacement modalities are applied in the fight against acidosis and hyperkalemia.

Case Report

A sixty-one-year-old female patient with a history of T2DM and hypertension (HT) for ten years, who was using metformin 1000 mg 2x1, nifedipine 60 mg 1x1, spironolactone 25 mg 1x1, ramipril 10 mg 1x1, was admitted to the emergency department for the complaints of anorexia, numbness in the hands and feet, and weakness affecting activities of daily living, that started 10 days ago after watery diarrhea 3 to 4 times per day and continued for three days. She reported no history of medications, supplements or herbal compounds use during diarrhea. There were no significant illnesses other than T2DM and HT in the patient's and her parents' history. At the admission, the patient was conscious,

oriented and cooperative. Her blood pressure was 160/80 mmHg and heart beat was 60 in per minutes. Her respiration rate was normal with 20 breaths/min. Her body temperature was 36 degrees Celsius. The patient's skin turgor was observed to be mildly decreased. The laboratory findings were as follows: pH: 7.21, PO₂: 98 mmHg, PaCO₂: 23 mmHg, HCO₃: 15.7 mmol/L, base deficit 25 meq/L, glucose: 178 mg/dL, blood urea nitrogen: 60 mg/dL, creatinine: 1.4 mg/dL, glomerular filtration rate: 69 mL/minute (with Cockcroft-Gault formula), Na: 130 mmol/L, K: 8.1 mmol/L, and chlor: 98 mmol/L. There were no ketones in the urine. Peaked T waves and prolonged QRS intervals were observed in the electrocardiogram. HbA1c was reported as 7%. The patient was transferred to our clinic with an initial diagnosis of adrenal insufficiency. Metformin, ramipril and spironolactone were discontinued. Calcium gluconate and glucose-insulin were administered intravenously for hyperkalemia. After adrenocorticotrophic hormone stimulation test, 100 mg of prednisolone was administered intravenously. Intravenous fluids and NAHCO₃ replacement were started with urine output. Her baseline cortisol level was 12.8 µg and stimulated levels at 30 and 60 minutes were 27 and 31 µg, respectively. Because of high levels of stimulated cortisol levels, diagnosis of adrenal insufficiency was ruled out. Due to calculated increased anion gap (25 mmol/L), the causes of metabolic acidosis with increased anion gap were investigated. After excluding other reasons and the patient's lactate level was found to be 5.3 mmol/L, the diagnosis of metformin-associated lactic acidosis was confirmed.

Hemodialysis and hemofiltration treatments recommended to the patient were not accepted. Glucose-insulin was administered intravenously for several times daily with potassium-binding resins, rehydration therapy and β-2 mimetic agents for three days. After the third day, blood gases, lactate, potassium and creatinine levels were improved to normal levels and remained within normal limits.

Discussion

Metformin is a biguanide that has been widely used to treat T2DM since 1957, and today, it is the only used member of that group. Metformin has positive effects on insulin resistance, lipid profile and chronic complications, and unlike sulfonylureas, is not associated with hypoglycemia and weight gain (4). Despite being rare, lactic acidosis is a fatal condition and is the most serious side effect of the drug. Mortality rate is 13-45% (1). In contrast with the reported meta-analysis by the Cochrane collaboration that pooled data and concluded that there was no evidence for metformin-associated risk of life-threatening lactic acidemia, patients with normal creatinine levels have been reported to have metformin-associated lactic acidosis (5,6,7), however, most of the reported cases had acute kidney injury (8,9,10). The pathogenesis of metformin-associated lactic acidosis is likely due to blockage of pyruvate carboxylase and, as a result, inhibition of gluconeogenesis (11). Inhibition of the first step of gluconeogenesis leads to accumulation of lactic acid (11). Additionally, biguanides decrease hepatic metabolism of lactate (11).

The current therapeutic approach to metformin-associated lactic acidosis includes normalization of the acid-base and electrolyte imbalance, extracorporeal removal of metformin, and treatment of the underlying cause. In the treatment of lactic acidosis, sodium bicarbonate could be administered to raise pH, but sodium bicarbonate treatment may worsen intracellular acidosis and, elevation in lactate levels may be seen (5,12). Therefore, long-term sodium bicarbonate treatment is not recommended. Hemodialysis and continuous veno-venous hemofiltration are recommended to correct metabolic acidosis in severe metformin-associated lactic acidosis. These modalities have the advantages of both removing metformin and treating metabolic acidosis without an associated risk of intravenous sodium bicarbonate infusion (12).

Our patient was a female, was not at an advanced age, had no known history of kidney disease, however, had acute gastroenteritis few days before hospital admission. At the admission, the creatinine level was 1.4 mg/dl and she was mildly dehydrated. Her general condition was not bad and there was no typically Kussmaul's breathing. For patients who do not accept invasive treatment modalities, as in this case, supportive care should be well planned. Besides rehydration therapy, short-term treatment of sodium bicarbonate with close follow-up may be required. For serious hyperkalemia, treatment modalities such as β2 mimetic, oral potassium binding resins and glucose-insulin infusions can be utilized.

Although creatinine levels in our patient prior to the admission was not known, the authors believe that, renal injury with detected level of creatinine (1.4 mg/dL) alone could not be responsible for lactic acidosis. As dehydration leads to mild creatinine elevation, the use of ramipril and spironolactone might aggravate acidosis and lead to resistant hyperkalemia.

Conclusion

Metformin, without a serious deterioration of renal function, can cause life-threatening lactic acidosis. Health care professionals should be careful even in cases of mild dehydration, especially in patients using renin-angiotensin-aldosterone system blockers.

Authorship Contributions

Informed Consent: Consent form was filled out by all participants, Concept: Emin Murat Akbaş, Adem Güngör, Volkan Arslan, Design: Emin Murat Akbaş, Adem Güngör, Volkan Arslan, Data Collection or Processing: Emin Murat Akbaş, Adem Güngör, Volkan Arslan, Analysis or Interpretation: Emin Murat Akbaş, Adem Güngör, Volkan Arslan, Literature Search: Emin Murat Akbaş, Adem Güngör, Volkan Arslan, Writing: Emin Murat Akbaş, Adem Güngör, Volkan Arslan, Peer-review: External and Internal peer-reviewed, Conflict of Interest: No conflict of interest was declared by the authors, Financial Disclosure: The authors declared that this study has received no financial support.

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