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Case Report

Metformin Associated Lactic Acidosis without Organ Dysfunction and Effective Treatment

Abstract

Lactic acidosis generally occurs in those who have kidney, liver, lung or heart dysfunction. Herein, a 73-year-old woman diagnosed as type B lactic acidosis due to metformin without any organ dysfunction was presented. Even if kidney functions are normal in metformin-associated lactic acidosis, early hemodialysis may provide rapid clinical improvement.

Introduction

Metformin is an oral antidiabetic from biguanide class and is the first-line treatment option for type 2 diabetes mellitus (DM) [1]. Most common side effects of metformin include gastrointestinal system side effects such as abdominal cramp, diarrhea, nausea and vomiting [2]. Lactic acidosis is a rare but fatal serious side effect of metformin and its incidence is found 9 in every 100.000 patient years [3]. Nevertheless, this side effect generally occurs in those who have organ dysfunction (kidney, liver, lung or heart dysfunction etc.) [3,4]. In general, it is not expected in those who have no organ dysfunction. In this article, a case of severe lactic acidosis due to metformin in a patient with type 2 DM without any organ dysfunction was presented.

Case Presentation

A 73-year-old woman was brought to emergency department due to sudden weakness, nausea and vomiting, and impaired consciousness. In her past medical history; she had been followed-up for type 2 DM and hypertension for 10 years. Her symptoms started 2 days ago, and she was brought to emergency department due to impaired consciousness that occurred within last a few hours. It was also learnt that she previously used gliclazide and acarbose, but stopped those medicines without any doctor recommendation and had started to use metformin 2000 mg/day for a week. She was also taking lisinopril/hydrochlorothiazide 20/12.5 mg/

day for hypertension. In her physical examination, she was conscious, but, cooperation and orientation revealed limited. Her blood pressure was 120/70 mmHg and cardiovascular system examination was normal. No defensive or rebound were determined in abdominal examination except the tenderness at right upper quadrant. There was no other finding except tachypnea (respiratory rate was 18 per minute). The laboratory results were as follow; glucose 516 mg/dL, urea 26 mg/dL, creatinine 0.63 mg/dL, sodium 139 mg/dL, potassium 4.2 mg/dL, and chloride 101 mg/dL. Her estimated glomerular filtration rate was 98.45 mL/min/1.73 m². In blood gas analysis; pH 7.08, HCO₃ 10.1 mEq/L, PCO₂ 41 mmHg, PO₂ 87 mmHg, lactate 9.9 mmol/L and anion gap was 27.9. Delta (Δ) anion gap and Δ bicarbonate ratio (calculated to determine whether vomiting had any contribution to current metabolic state) was 1.28. In urinalysis, protein, ketone and nitrite were all negative and 12 of leukocytes and 2 of erythrocytes were determined in every field. Because of high blood glucose, ketone was studied in serum to rule out diabetic ketoacidosis and determined negatively. Metformin and lisinopril/hydrochlorothiazide were stopped. Insulin infusion was started to control blood glucose and 0.9 % saline infusion was also started intravenously. Based on laboratory parameters, she was diagnosed as type B lactic acidosis due to metformin. She was treated with emergent hemodialysis for 4 hours for both correcting acidosis and providing lactate and metformin clearance. Echocardiography and contrast enhanced abdominal computerized tomography (CT) were performed in terms of excluding type A lactic acidosis due to congestive heart failure or mesenteric ischemia. Ejection fraction was 60 % and she had no heart failure sign. No pathological findings were determined except stone in right upper ureter in abdominal CT. She was dialyzed for 4 hours on the next day because of sustained lactic acidosis. The course

of laboratory results was given in Table 1. After supportive therapy, acidosis and her conscious improved gradually. In clinic follow-up, her general condition was excellent and she was advised not to use metformin again, and insulin therapy was continued for treatment of DM and discharged from the hospital on the 12th day of admission.

Discussion

Lactic acidosis, the most severe side effect of metformin therapy, is a very rare complication and it may especially occur in those who have organ dysfunction such as kidney failure, heart failure, lung or liver disease or whose organ dysfunction develops during metformin use [4,5]. The possibility of lactic acidosis is quite low without organ dysfunction.

Three types of lactic acidosis have been identified [6]. The first is called type A lactic acidosis that occurs due to anaerobic respiration secondary to tissue perfusion abnormalities at respiratory or circulatory failure. The second is called type B lactic acidosis that occurs depending on metformin use or in some types of cancer with accumulation of lactate at cellular level. The third is D-lactic acidosis which occurs by absorption of D-lactate formed due to fermentation of excess glucose by bacteria in short bowel syndrome or any other malabsorption syndrome. There were not any symptoms or signs of respiratory or circulatory failure in our patient. In addition, mesenteric ischemia, which might cause local circulatory failure, was also ruled out. Moreover, there was not short bowel syndrome or malabsorption in our patient.

In a previous case, it was emphasized that hyperlactemia may develop depending on metformin use without renal failure [7]. But, our case was different from that case in some aspects. Firstly, our patient was younger. Secondly, her creatinine clearance was higher. Thirdly, there was not only hyperlactatemia but also lactic acidosis in our patient and she was treated by HD. Best of our knowledge, this was the first case developed lactic acidosis without organ dysfunction.

In metformin-associated lactic acidosis, different formation mechanisms were accused. The first one of those mechanisms is that metformin convert of glucose to lactate at splenic bed [8]. The second mechanism is that metformin inhibits mitochondrial respiratory chain complex 1 and

suppresses hepatic gluconeogenesis from different substrate [9]. The third mechanism is accumulating metformin in body because of renal failure. The fourth mechanism is respiratory or circulatory failure that causes tissue perfusion defect. Our patient had no organ dysfunction such as heart, respiratory or renal failure. Therefore, possible mechanisms of lactic acidosis in our patient could be the first and second mechanisms above.

The Society of Endocrinology and Metabolism of Turkey recommend to begin metformin at the dose of 500 mg per day especially in patients with gastrointestinal sensitivity, to increase the dose of 500 mg every 1 or 2 weeks and to reach the effective doses (usually 2x1000 mg per day, maximum of 3000 mg per day) within 1 or 2 months [10]. Also patients should be controlled after 15 days of metformin prescription. In the case presented here, she was taking a dose of 2000 mg per day and there was no talk of control (self-prescribed). Perhaps she was taking more than dose of 2000 mg per day and she might not have been told us.

In conclusion, in patients with lactic acidosis, metformin use should necessarily be considered and differential diagnosis of type A or type B lactic acidosis should be made. Even if kidney functions are normal in metformin-associated type B lactic acidosis, early HD treatment may provide a rapid clinical improvement by increasing metformin and lactate clearance.

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Table 1: The Course of Laboratory Results of Patient.

	pH	PO ₂ *	PCO ₂ *	HCO ₃ **	Lactate**	Hemodialysis
Admission Day	7.08	87	41	10.1	9.9	Yes
Admission Day***	7.27	90	31	14.2	8.2	
1 st Day	7.35	85	34	18.8	7.3	Yes
2 nd Day	7.45	90	36	25	2.0	No
3 rd Day	7.37	92	43	24.9	1.7	No
Discharge Day	7.46	98	37	26.3	0.9	No

*mmHg; **mmol/L; ***After Hemodialysis

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