Annals of Clinical Case Reports

Case Report
Published: 09 Mar, 2021

A Case of Lactic Acidosis after Resumption of Metformin and SGLT2 Inhibitors

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Abstract

Despite being uncommon among patients with diabetes mellitus, lactic acidosis may occasionally develop among metformin-treated patients. Alternatively, although SGLT2 inhibitors are known to cause ketosis, their association with lactic acidosis has been rarely reported. Accordingly, both metformin and SGLT2 inhibitors have been prioritized for use in diabetes treatment guidelines and are often concurrently administered. We herein report a case involving lactic acidosis after resumption of metformin and SGLT2 inhibitors. Thus, lactic acidosis and euglycemic ketoacidosis or their overlap should be carefully considered among ill patients receiving these agents.

Keywords: Diabetes mellitus; Lactic acidosis; Metformin; SGLT2 inhibitors

Introduction

Lactic acidosis is characterized by the accumulation of excess lactic acid in the blood. With the discontinuation of phenformin therapy in the United States, lactic acidosis has become uncommon in patients with diabetes mellitus. However, it may occasionally occur in metformin-treated patients and must still be considered among acidotic patients, particularly in those who are seriously ill [1]. Most of the cases of metformin-associated lactic acidosis have occurred in patients having contraindications for metformin use, particularly renal failure [2,3]. Recent medical treatment guidelines for diabetes have recommended the combined use of metformin and SGLT2 inhibitors. We herein report a case involving lactic acidosis after resumption of metformin and SGLT2 inhibitors.

Case Presentation

A 50-year-old man was diagnosed with diabetes at X-30 years, and insulin injection therapy was initiated at X-20 years. An SGLT2 inhibitor was then added to the treatment regimen at X-1 year; however, the patient stopped visiting owing to financial reasons at X-10 months. He was referred to a nearby doctor for vomiting and diarrhea at X-4 years and was diagnosed with gastroenteritis and dehydration. Serum creatinine was 1.78 mg/dL, but metformin, SGLT2 inhibitors, and insulin, which he had stopped, taking, were resumed. However, considering that both vomiting and diarrhea persisted, the patient consulted a nearby doctor again. Blood tests revealed a remarkable increase in serum creatinine level, for which he was referred to our hospital. His medical history included hypertension, dyslipidemia, and preproliferative diabetic retinopathy. He had been taking vildagliptin 100 mg/day, metformin 1000 mg/day, pioglitazone 15 mg/day, amlodipine 5 mg/day, luseogliflozin 2.5 mg/day, pitavastatin 2.5 mg/day, insulin lispro 6 units/day, and insulin glargine 4 units/day. Physical examination revealed a height of 168 cm, body weight of 57 kg, body mass index of 20.2 kg/m^2, blood pressure of 180/95 mmHg, pulse rate of 100 beats/min, a clear consciousness, and Kussmaul breathing. Laboratory test data are presented in Table 1. Based on the aforementioned findings, the patient was diagnosed with acute renal failure and lactic acidosis. Previously prescribed oral hypoglycemic drugs were then discontinued, and emergency dialysis was initiated, which subsequently relieved his symptoms. Thereafter, urine volume stabilized, and intravenous infusion and subcutaneous insulin injection treatment was continued. Lactic acid levels improved to 2.74 mmol/L on the third day of hospitalization along with gradual improvement in renal function. The patient was discharged at 18 days of hospitalization, with his serum creatinine level improving to 2.41 mg/dL (Figure 1). Even after discharge, the patient continued to receive multiple insulin injections and a DPP4 inhibitor.

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Received Date: *10 Feb 2021*
Accepted Date: *03 Mar 2021*
Published Date: *09 Mar 2021*

Citation:
Tominaga T, Ozaki M, Kanda M, Maeda R, Otuka H, Otake K, et al. A Case of Lactic Acidosis after Resumption of Metformin and SGLT2 Inhibitors. Ann Clin Case Rep. 2021; 6: 1924.

ISSN: 2474-1655

Table 1: The Laboratory Results of the Patient.

Complete blood count		Biochemistry		Diabetes-related examination	
WBC	17300/μL	TP	7.0 g/dL	Glu	397 mg/dL
RBC	440 × 10⁴/μL	Alb	4.0 g/dL	HbA1c	9.70%
Hb	12.7 g/dL	T-bil	0.4 mg/dL	S-CPR	0.3 ng/ml
Ht	39.10%	BUN	81.6 mg/dL	Anti-GAD Ab	negative
PLT	20.4 × 10⁴/μL	Cr	12.15 mg/dL		
Urinalysis		AST	17 IU/L	Venous blood gas analysis	
Specific Gravity	1.01	ALT	11 IU/L	pH	7.162
pH	6	CPK	156 IU/L	pCO2	27.2 mmHg
UP	4.59 g/gCr	LDH	323 IU/L	pO2	52.8 mmHg
Glu	3+	Na	131 mEq/L	BE	-17.6 mmol/L
uOB	3+	K	5.2 mEq/L	Bicarbonate	9.5 mmol/L
Ketone	1+	Cl	81 mEq/L	Lactate	15.40 mmol/L
WBC Elastase	-	Ca	8.8 mg/dL	An-GAP	40.9 mmol/L
Nitrate	-	CRP	0.20 mg/dL		

WBC: White Blood Cells; RBC: Red Blood Cells; Hb: Hemoglobin; Ht: Hematocrit; PLT: Platelet; TP: Total Protein; Alb: Albumin; T-bil: Total bilirubin; Cr: Creatinine; AST: Aspartic Aminotransferase; ALT: Alanin Aminotransferase; CPK: Creatine Phosphokinase; LDH: Lactate Dehydrogenase; CRP: C-Reactive Protein; Glu: Glucose; HbA1c: Hemoglobin A1c; S-CPR: Serum C Peptide; GAD: Glutamic Acid Decarboxylase; BE: Base Excess; UP: Urine Protein; uOB: urine Occult Blood; IU: International Units

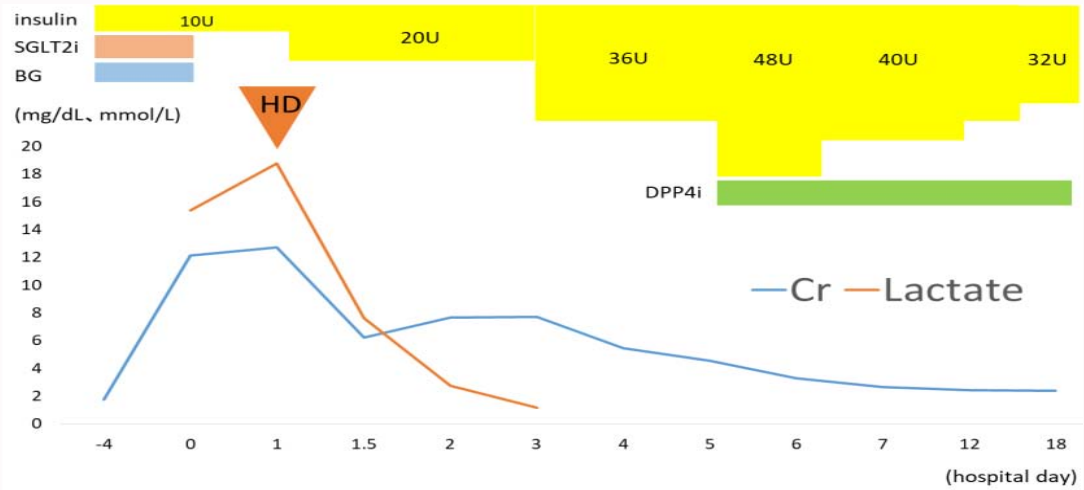

Figure 1: The clinical course of intravenous infusion and subcutaneous insulin injection treatment.

Discussion

Despite its relatively low reported incidence of 3/100,000 person-years, metformin-associated lactic acidosis is a complication with a poor prognosis and 25% mortality rate [4]. Alternatively, although SGLT2 inhibitors have been known to cause ketosis, their association with lactic acidosis has been rarely reported [5-7]. One report showed that metformin use promotes ketone body production in rats, whereas another indicated the possibility of overlap between metformin-related lactate acidosis and euglycemic ketoacidosis due to simultaneous administration of metformin and SGLT2 inhibitors [8,9]. In the present case, vomiting and diarrhea were observed before the resumption of metformin. Therefore, we speculated an overlap between hyperglycemia and SGLT2 inhibitor-induced intravascular dehydration in the presence of acute gastroenteritis, resulting in prerenal renal failure and metformin-associated lactic acidosis. Unfortunately, although quantitative examination of ketone bodies had not been conducted, we suspect that lactic acidosis and euglycemic ketoacidosis coexisted owing to starvation and lack of insulin action. Although alkaline agent administration and hemodialysis can be considered for lactic acidosis, their use has been considered controversial considering the lack of conclusive evidence for either [10]. Alternatively, correction of dehydration and insulin administration are important for improving the pathological condition in patients with both euglycemic ketoacidosis and lactic acidosis and should be actively performed [11].

Both metformin and SGLT2 inhibitors have been prioritized by diabetes treatment guidelines and are often concurrently administered. In Japan, recommendations on appropriate use of metformin and SGLT2 inhibitors have been put forth by the Diabetes Society, and compliance with such recommendations is desirable. In conclusion, lactic acidosis and euglycemic ketoacidosis or their overlap should be carefully considered among ill patients receiving metformin and SGLT2 inhibitors.

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