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CASE REPORT

Case of ketoacidosis by a sodium-glucose cotransporter 2 inhibitor in a diabetic patient with a low-carbohydrate diet

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ABSTRACT

We present a case of a 32-year-old diabetic woman with Prader–Willi syndrome who developed severe ketoacidosis caused by a sodium-glucose cotransporter 2 (SGLT2) inhibitor, a novel class of antihyperglycemic agents, during a strict low-carbohydrate diet. At admission, a serum glucose level of 191 mg/dL was relatively low, though laboratory evaluations showed severe ketoacidosis. This is the first report of ketoacidosis caused by a SGLT2 inhibitor. It is necessary to not only pay attention when using a SGLT2 inhibitor in patients following a low-carbohydrate diet, but also to start a low-carbohydrate diet in patients treated with a SGLT2 inhibitor because of a high risk for developing ketoacidosis.

INTRODUCTION

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a novel class of antihyperglycemic agents that inhibit glucose reuptake in the kidney[1]. A low-carbohydrate diet is believed to be effective in weight loss when producing ketosis[2]. However, a few cases of ketoacidosis without having diabetes mellitus were reported during a low-carbohydrate diet[3,4].

We recently encountered a case of severe ketoacidosis caused by a SGLT2 inhibitor during a low-carbohydrate diet. Here we present this case, because, to our knowledge, there have been no prior reports on the disease conditions shown in this case.

CASE REPORT

A 32-year-old woman with Prader–Willi syndrome was diagnosed with diabetes at the age of 10 years, and was recommended to start a strict low-carbohydrate diet by her family because of poorly-controlled glycemia at the age of 21 years. Before starting a strict low-carbohydrate diet, her bodyweight was 54 kg, but gradually increased as a result of an excessive intake of protein and lipid. It recently increased up to 67 kg. She received glimepiride (2 mg/day), metformin (2,250 mg/day) and linagliptin (5 mg/day), but these oral medicines were switched to a SGLT2 inhibitor, ipragliflozin (50 mg/day) alone 13 days before admission. Immediately after taking a SGLT2 inhibitor, polyuria developed and the patient's bodyweight decreased by approximately 3 kg for 10 days. Epigastralgia developed 2 days before admission, and water and dietary intake decreased. Tachypnea developed 1 day before admission. As her symptoms became worse, she visited the emergency room of Aichi Medical University Hospital, Nagakute, Aichi, Japan. Laboratory evaluation showed severe acidosis, ketonuria, ketonemia and a normal level of lactate (Table 1). Chest X-ray, electrocardiogram, abdominal computed tomography and urinary sediments showed no abnormalities, indicating the unlikelihood of infectious diseases. We diagnosed the patient with ketoacidosis. Immediately after admission, continuous intravenous insulin, Ringer's solution and glucose infusion was initiated in an intensive care unit. Ketoacidosis was improved, and the patient's bodyweight increased by approximately 2 kg on the second day after admission (Figure 1). Antiglutamic acid

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Table 1 | Physical examination and laboratory data at admission

Physical examination

BH 150 cm, BW 63.9 kg, BMI 28.4 kg/m^2, RR 32 times/min, HR 112 times/min, BP 139/77 mmHg, level of consciousness: alert

Peripheral blood				Urinalysis	
WBC	13700/μL	Plt	25.7 × 10^4/μL	pH	5.0
RBC	501 × 10^4/μL			Glucose	(4 +)
Hb	15.2 g/dL			Ketone body	(3 +)
Ht	45.9%			Occult blood	(–)
				Sediments	none

Blood chemistry				Blood gas analysis	
Na	135 mmol/L	T-chol	202 mg/dL	pH	7.055
K	3.4 mmol/L	HDL-chol	28 mg/dL	$PaCO_2$	10.9 mmHg
Cl	104 mmol/L	LDL-chol	151 mg/dL	PaO_2	125.0 mmHg
TP	7.8 g/dL	TG	116 mg/dL	HCO_3	3.0 mmol/L
Alb	3.9 g/dL	Glucose	191 mg/dL	Base excess	–25.3 mmol/L
BUN	17.5 mg/dL	HbA1c	9.3%	Lactate	8.7 mg/dL
Cre	0.4 mg/dL	GA	19.6%		
UA	6.5 mg/dL	C-peptide	0.4 ng/mL		
Amy	51 IU/L	Anti-GAD Ab	<0.3 U/mL		
T-Bil	0.4 mg/dL	Anti-IA-2 Ab	<0.4 U/mL		
AST	15 IU/L	Insulin Ab	<0.4 U/mL		
ALT	11 IU/L	Total ketone body*	7473 μmol/L		
γ-GTP	24 IU/L	Acetoacetate*	1915 μmol/L		
ALP	264 IU/L	3-Hydroxybutyrate*	5558 μmol/L		

*These were determined 15 h after the initiation of treatment with insulin. Ab, antibody; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine transferase; Amy, amylase; AST, aspartate aminotransferase; BH, body height; BMI, body mass index; BP, blood pressure; BW, body weight; BUN, blood urea nitrogen; Cl, chloride; Cre, creatinine; GA, glycated albumin; GAD, glutamic acid decarboxylase; γ-GTP, gamma-glutamyl transpeptidase; Hb, hemoglobin; Hct, hematocrit; HDL-chol, high-density lipoprotein cholesterol; HR, heart rate; IA-2, insulin autoimmune-2; K, potassium; LDL-chol, low-density lipoprotein cholesterol; Na, sodium; Plt, platelet; RBC, red blood cells; RR, respiratory rate; T-Bil, total bilirubin; T-chol, total cholesterol; TG, triglyceride; TP, total protein; UA, uric acid; WBC, white blood cells.

decarboxylase antibody, islet antigen-2 antibody and insulin autoantibody were negative. The serum C-peptide was 0.4 ng/mL and the urinary C-peptide was undetectable at admission, but increased up to 40.2 μg/day on the sixth day after admission. At admission, the plasma glucose, glycated hemoglobin (HbA1c) and glycated albumin levels were 191 mg/dL, 9.3% and 19.6%, respectively. After ketoacidosis was improved, basal–bolus insulin therapy was continued for a while. At discharge, the patient was treated with insulin glargine (24 units/day), lixisenatide (20 μg/day) and metformin (2,250 mg/day). A nutritionist instructed the patient to follow a 1,500-kcal diet, containing 65 g of protein, 45 g of fat and 210 g of carbohydrate. One month later, HbA1c and glycated albumin levels were remarkably improved to 6.8% and 13.7%, respectively.

DISCUSSION

In the present report, we have described a case of severe ketoacidosis caused by a SGLT2 inhibitor during a low-carbohydrate diet. The most widely used diagnostic criteria for diabetic ketoacidosis include blood glucose >250 mg/dL, arterial pH <7.3, serum bicarbonate <15 mEq/L and a moderate degree of ketonemia and/or ketonuria[5]. The conditions of this patient are consistent with the diagnostic criteria, except for the blood glucose level. The fact that the lactate level was normal and that the patient did not consume alcohol indicated that her conditions were neither lactic acidosis nor alcoholic ketoacidosis. Through the fact that she did not consume excessive soft drinks, soft drink ketosis was unlikely. There seems to be a discrepancy between the values of glycated albumin and HbA1c. The glycated albumin level of 19.6% at admission was relatively low compared with the HbA1c level of 9.3%, showing that the blood glucose level declined with the administration of a SGLT2 inhibitor for approximately 2 weeks before severe ketoacidosis developed. The characteristic feature of this patient was that the blood glucose level of 191 mg/dL at admission was relatively low despite severe ketoacidosis.

The urinary C-peptide that was undetectable at admission increased up to 40.2 μg/day after the start of a diet containing 210 g carbohydrate/day. It has been suggested that endogenous insulin secretion is suppressed during ketosis or ketoacidosis and improves after treatment in patients with non-insulin-dependent diabetes[6]. Therefore, the insulin secretory capacity of

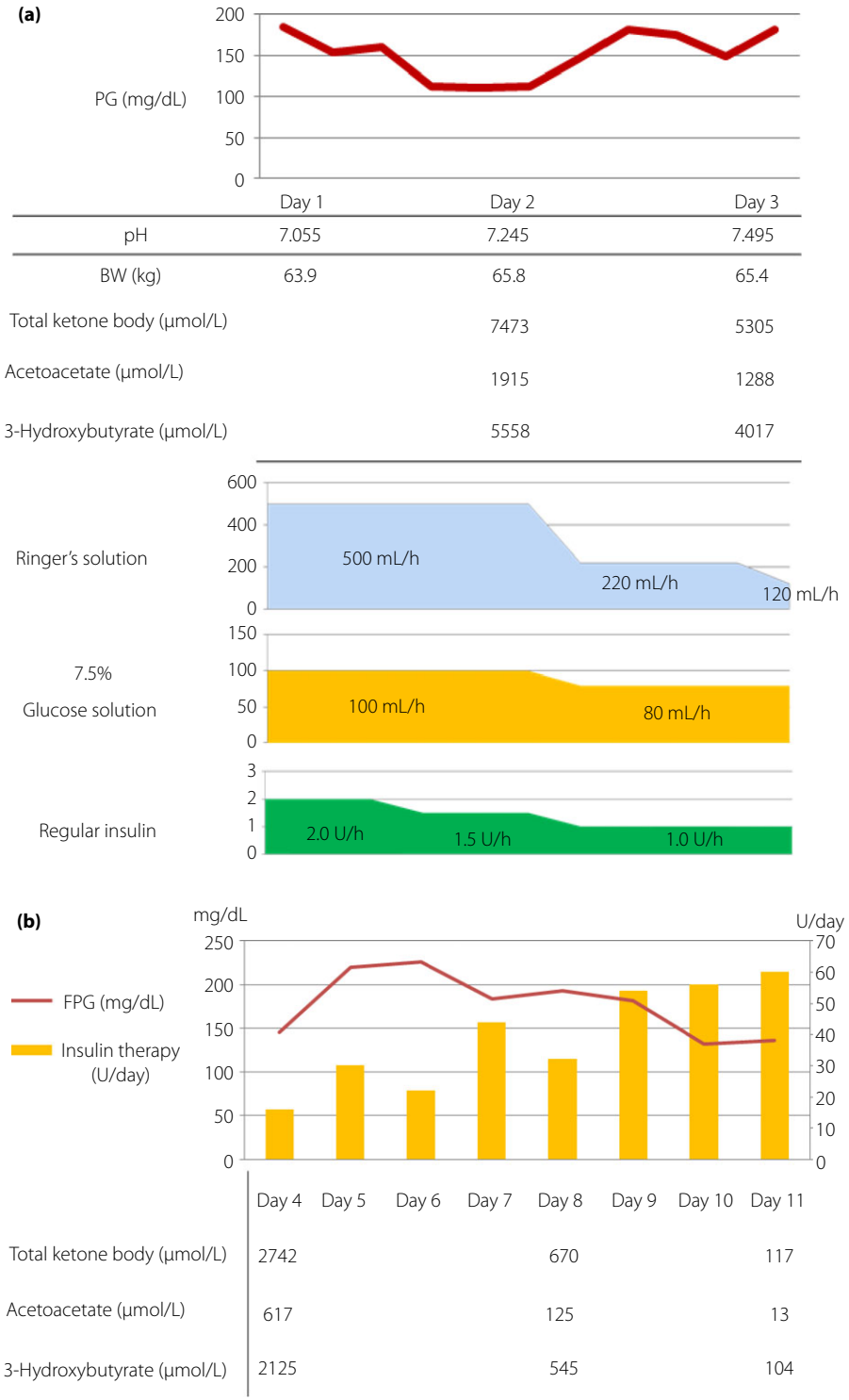

Figure 1 | Clinical course. (a) Clinical course in days 1–3. (b) Clinical course in days 4–11. BW, bodyweight; FPG, fasting plasma glucose; PG, plasma glucose.

this patient would be preserved enough to prevent ketoacidosis under the former treatment.

Investigation of the patient's eating habits showed that the total calories of her daily meals was 1,860 kcal, consisting of 27.4% protein, 55.1% fat and 14.3% carbohydrate. Her estimated carbohydrate intake was just 66 g/day. Therefore, the patient would have been chronically prone to ketosis on a strict low-carbohydrate diet. It was recently shown that a SGLT2 inhibitor

increased endogenous glucose production, serum glucagon level and serum ketone bodies[7–9]. Acceleration of urinary glucose excretion by a SGLT2 inhibitor, and discontinuation of the former treatment with a sulfonylurea, metformin and dipeptidyl peptidase-4 inhibitor that managed to maintain the insulin action enough not to cause ketoacidosis would lead to the "no carbohydrate available" state and the completely insulin deficient condition, resulting in exacerbating ketosis and finally in ketoacidosis. In addition, dehydration would contribute to the development of ketoacidosis. Even in patients with enough insulin secretory capacity, therefore, a combination of a strict low-carbohydrate diet and a SGLT2 inhibitor might cause ketoacidosis.

In conclusion, we for the first time described a case of severe ketoacidosis caused by the administration of a SGLT2 inhibitor during a low-carbohydrate diet. It is necessary to not only pay attention to the use of a SGLT2 inhibitor in patients following a low-carbohydrate diet, but also to start a low-carbohydrate diet in patients treated with a SGLT2 inhibitor because of a high risk for developing ketoacidosis.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Fujita Y, Inagaki N. Renal sodium glucose cotransporter 2 inhibitors as a novel therapeutic approach to treatment of type 2 diabetes: clinical data and mechanism of action. *J Diabetes Investig* 2014; 5: 265–275.
2. Bravata DM, Sanders L, Huang J, *et al.* Efficacy and safety of low-carbohydrate diets: a systematic review. *JAMA* 2003; 289: 1837–1850.
3. Chen TY, Smith W, Rosenstock JL, *et al.* A life-threatening complication of Atkins diet. *Lancet* 2006; 367: 958.
4. Shah P, Isley WL. Ketoacidosis during a low-carbohydrate diet. *N Engl J Med* 2006; 354: 97–98.
5. Kitabchi AE, Umpierrez GE, Murphy MB, *et al.* Management of hyperglycemic crises in patients with diabetes. *Diabetes Care* 2001; 24: 131–153.
6. Tanaka K, Moriya T, Kanamori A, *et al.* Analysis and a long-term follow up of ketosis-onset Japanese NIDDM patients. *Diabetes Res Clin Pract* 1999; 44: 137–146.
7. Merovci A, Solis-Herrera C, Daniele G, *et al.* Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. *J Clin Invest* 2014; 124: 509–514.
8. Seino Y. Luseogliflozin for the treatment of type 2 diabetes. *Expert Opin Pharmacother* 2014; 15: 2741–2749.
9. Mudaliar S, Henry RR, Boden G, *et al.* Changes in insulin sensitivity and insulin secretion with the sodium glucose cotransporter 2 inhibitor dapagliflozin. *Diabetes Technol Ther* 2014; 16: 137–144.