INTERNAL MEDICINE

□ CASE REPORT □

Atypical Ketoacidosis and Protracted Hyperglycosuria after Treatment with Ipragliflozin, an SGLT2 Inhibitor

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Abstract

We herein present the case of a 21-year-old diabetic obese woman who developed ketoacidosis following the administration of ipragliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor. At the time of admission, although her serum glucose level was only 175 mg/dL, laboratory tests showed ketoacidosis. Interestingly, hyperglycosuria persisted, even after the discontinuation of ipragliflozin. This is the first report of non-hyperglycemic ketoacidosis that might have been caused by protracted hyperglycosuria after the discontinuation of ipragliflozin. The development of non-hyperglycemic ketoacidosis should be monitored following the discontinuation of SGLT2 inhibitors, especially in patients who start to feel unwell and exhibit protracted hyperglycosuria after the discontinuation of treatment.

Key words: SGLT2 inhibitor, ipragliflozin, ketoacidosis, protracted hyperglycosuria

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Introduction

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a new class of oral glucose-lowering drugs that exert their action through the novel mechanism of inhibiting the SGLT2 receptors in the proximal tubules; thus promoting the excretion of glucose in urine (1). Since they not only lower blood glucose levels, but also cause weight loss (2-4), they hold great promise in the treatment of patients with type 2 diabetes for whom a high body mass index (BMI) is a matter of concern (5). However, the side effects of SGLT2 inhibitors include hypoglycemia as well as other issues such as dehydration and urinary tract infection as a result of osmotic diuresis, and warnings have been issued in this regard (6-8). In fact, case reports of elderly patients with dehydration and cerebral infarction have already been published (9). Thus, the current opinion is that these agents are only suitable for comparatively young obese patients with preserved insulin secretion. However, recent reports have described ketoacidosis in young obese patients treated with SGLT2 inhibitors, and the clinical management of such patients requires an extremely low-carbohydrate diet (10). Thus, it seems that diet is another factor that should be considered, in addition to age and obesity, before the administration of SGLT2 inhibitors.

Ipragliflozin, a SGLT2 inhibitor, was used for the treatment of an obese patient with early-onset type 2 diabetes and preserved endogenous insulin secretion. However, she developed non-hyperglycemic ketoacidosis during the treatment, despite not being on a low-carbohydrate diet, and persistent hyperglycosuria even after the discontinuation of ipragliflozin. We believe that the persistence hyperglycosuria after the discontinuation of ipragliflozin is an important finding and that it may be a mechanism underlying the development of non-hyperglycemic ketoacidosis.

Case Report

Patient: 21-year-old woman, Principal complaint: Nausea, Family history: Paternal grandfather with diabetes, Medical history: Developed type 2 diabetes at age 16. No other specific history. Lifestyle: Social drinker, non-smoker, Occupation: Student

Medications: Metformin (2,250 mg/day), pioglitazone (7.5 mg/day), furosemide (20 mg/day), ipragliflozin (50 mg/day).

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History of current condition: At a school health checkup at 16 years of age, the patient's height was 163 cm, her body weight was 85 kg, and her BMI was 31.9 kg/m^2. At a local clinic, she was diagnosed with obesity and diabetes according to the World Health Organization (WHO) Class I criteria. Laboratory tests revealed that her HbA1c level was 9.0% and that her casual blood glucose level was 283 mg/dL. She was referred to our hospital for further management. Endocrine tests showed no specific abnormalities, and because tests for anti-GAD antibodies and other autoantibodies were also negative, she was diagnosed with early-onset type 2 diabetes. Accordingly, she was started on a 1,400 kcal/day diet and metformin (750 mg/day). Following treatment, her body weight and HbA1c level improved to 77 kg and 5.2%, respectively, and she was subsequently monitored without medication.

After graduation from high school in 2011, the body weight increased to 86 kg over 2 years and her HbA1c level increased to HbA1c 7.9%; she was therefore restarted on metformin. Her HbA1c level showed a temporary improvement; however, by 2013, it had increased to 8.5% and pioglitazone (7.5 mg) was added, together with furosemide (20 mg; for the treatment of peripheral edema).

The patient could not adhere to the diet therapy, and in June 2014 she was started on ipragliflozin (50 mg/day). Before the initiation of ipragliflozin, her daily glucose excretion in 24-h urine was 10.2 g/day; this markedly increased to 85.2 g/day at 1 month after the start of ipragliflozin. After 3 months of ipragliflozin, her body weight decreased by 4 kg and her HbA1c level improved from 8.4% to 8.0%.

In October 2014, however (after approximately 4 months of administration), the patient reported feeling lethargic and nauseous on several occasions. She concluded she was sick and stopped taking all medications. On the following days, she still had no appetite and drank approximately 1 L of water or tea per day to prevent dehydration. At a regular clinical examination 3 days later, her gastrointestinal symptoms had still not improved and postural hypotension and weight loss were apparent. Her postprandial blood glucose level was only 175 mg/dL; however, despite the absence of hyperglycemia, a urinalysis was positive for ketone bodies and a blood gas analysis showed metabolic acidosis. She was diagnosed with ketoacidosis and was immediately admitted to hospital.

The physical examination on admission

The patient was lucid, her body height was 163 cm, her body weight was 79 kg, her BMI was 29.7 kg/m^2, her blood pressure was 100/73 mmHg, her heart rate was 100 bpm, her oral mucosa was dry. No abnormal cardiopulmonary or abdominal signs, edema of the lower limbs, neurological disorders, or fundal abnormalities were observed.

The test results on admission

An arterial blood gas analysis showed metabolic acidosis with a high anion gap; the patient was positive for urinary ketones, and her levels of blood ketone bodies, predominantly β-hydroxybutyric acid, were high. Her serum lactic acid level was within the normal range, ruling out lactic acidosis. The patient was therefore diagnosed with ketoacidosis (Table). However, her postprandial blood glucose was only 175 mg/dL, below the casual blood glucose values of 250-300 mg/dL regarded as typical of diabetic ketoacidosis.

The post-admission course

Because severe dehydration was evident on both physical examination and from the laboratory test results, a high-volume intravenous saline infusion was initiated. As the patient was prohibited from eating, an infusion of 4.3% glucose solution was also started (calorie content, 172 kcal/day; glucose 43 g/day). A treatment plan was established to administer insulin injections should the patient's blood glucose level increase past 200 mg/dL. However, the value hovered around the 110-180 mg/dL range until the patient started eating on admission day 3 (6 days after the discontinuation of ipragliflozin) (Figure).

The patient's nausea started to improve on the day after admission, and the laboratory test results on admission day 2 showed the resolution of metabolic acidosis. The intravenous infusion was discontinued on admission day 3, when the patient was able to eat 1,400 kcal/day. The patient's urinary glucose excretion was monitored over this period by 24-h urine collection, and the results showed an abnormally high level of up to 66.9 g/day until 6 days after the discontinuation of ipragliflozin, despite the fact that her blood glucose level was <180 mg/dL. This possibly suggested a protracted effect of the SGLT2 inhibitor. The patient's 24-h urinary glucose excretion showed a gradual decrease and was 1.8 g/day on admission day 6 (9 days after the discontinuation of ipragliflozin). The patient's general condition showed a marked improvement and she was discharged from the hospital without medications.

Discussion

We treated an obese patient with early-onset type 2 diabetes and preserved endogenous insulin secretion, who developed non-hyperglycemic ketoacidosis while being treated with ipragliflozin, with persistent hyperglycosuria - even after the discontinuation of ipragliflozin. The development of ketoacidosis while the patient was treated with ipragliflozin, despite her almost normal blood glucose levels - suggests the possibility that ipragliflozin may itself play a role in ketoacidosis.

Cases of diabetic ketoacidosis (DKA) have been reported in patients receiving SGLT2 inhibitors, mainly in Europe and North America (11-13), and the United States Food and Drug Administration (FDA) has therefore issued a warning regarding the possible development of DKA during the use of SGLT2 inhibitors (14).

One of the most readily understandable mechanisms of DKA is the absolute lack of a necessary amount of insulin

Table. Laboratory Data on Admission.

Peripheral blood		Urinalysis	
Leukocytes	10,850 /μL	Protein	(-)
Hemoglobin	15.4 g/dL	Glucose	(3+)
Hematocrit	45.6 %	Ketone body	(3+)
Platelets	35.9×10^4 /μL	Occult blood	(-)
Blood chemistry		Others	
Sodium	132 mmol/L	Glucose	175 mg/dL
Potassium	4.4 mmol/L	HbA1c	7.9 %
Chloride	100 mmol/L	C-peptide	1.85 ng/mL
BUN	13 mg/dL	Anti-GAD antibody	<0.3 U/mL
Creatinine	0.67 mg/dL	Anti-IA-2 antibody	<0.4 U/mL
Uric acid	11.8 mg/dL	Total-ketone bodies	4,882 μmol/L
Total protein	7.7 g/dL	Acetoacetate	1,011 μmol/L
Albumin	4.4 g/dL	3-Hydroxybutyrate	3,871 μmol/L
AST	20 IU/L	Lactate	12.0 mg/dL
ALT	37 IU/L		
γ-GTP	31 IU/L		
Amylase	35 IU/L		
LDL-C	157 mg/dL		
HDL-C	45 mg/dL		
Triglyceride	217 mg/dL		
Blood gas analysis			
pH	7.268		
HCO_3^-	14.3 mmol/L	Anion gap	17.7 mmol/L
PCO_2	31.6 mmHg	Base excess	−11.3 mmol/L

BUN: blood urea nitrogen, AST: aspartate aminotransferase, ALT: alanine transferase, γGTP: gamma-glutamyl transpeptidase, LDL-C: LDL-cholesterol, HDL-C: HDL-cholesterol, GAD: glutamic acid decarboxylase, IA-2: insulin autoimmune-2

in insulin-treated type 1 diabetics who use SGLT2 inhibitors to reduce the insulin dose in order to avoid hypoglycemia (11, 12). Cases of DKA among patients undergoing pancreatectomy and chronic pancreatitis have been reported after switching from an insulin-based treatment to an SGLT2 inhibitor (15). A common characteristic feature is the development of DKA following a dose reduction or the discontinuation of insulin in patients with insufficient insulin secretion. However, our case differs from previously reported cases in that insulin secretion was maintained and there was no change in insulin treatment. The likely mechanism underlying the development of DKA in our patient is the small amount of food consumed by the patient in association with a loss of appetite and nausea during her illness. A post-marketing report by a Japanese drug manufacturer mentioned a case of DKA that might have been induced by starvation (16). Thus, we suspect that the combined effects of undereating and the SGLT2 inhibitor could have caused elevation of ketone bodies.

There have been a few reports of patients who developed DKA despite having only very mild hyperglycemia; with blood glucose level close to normal values, and this condition, known as SGLT2 inhibitor-induced euglycemic diabetic ketoacidosis (euDKA), is currently the subject of a thorough investigation (13). It is likely that the elevation in the blood glucose level was also relatively mild in our case.

According to Rosenstock et al. (17), the mechanisms underlying SGLT2 inhibitor-induced euDKA include the fact that insulin deficiency and resistance are both milder in comparison to DKA, causing less glucose overproduction and underutilization - resulting in blood glucose levels that are comparatively low. More importantly the renal glucose clearance in euDKA is twice as high that in DKA (18, 19); this also results in a milder increase in the blood glucose level.

Data from the Japanese Phase 2 and 3 clinical trials of SGLT2 inhibitors have also warned against the potential for an increase in ketone bodies (20). Many studies have discussed other potential mechanisms of SGLT2 inhibitor-related increases in ketone bodies, including the enhanced resorption of ketone bodies in renal tubules (21), the enhanced glucagon secretion (22-24), and the inhibition of insulin secretion (25).

Interestingly, another difference is that the urinary glucose excretion in our patient persisted after a drug holiday, despite the absence of hyperglycemia. This is a particularly noteworthy case because this may have caused a further increase in the level of ketone bodies and because it presumably had a major effect on the onset and progression of ketoacidosis.

There are no reports of protracted persistent hyperglycosuria, similar to that seen in the present case. This impor-

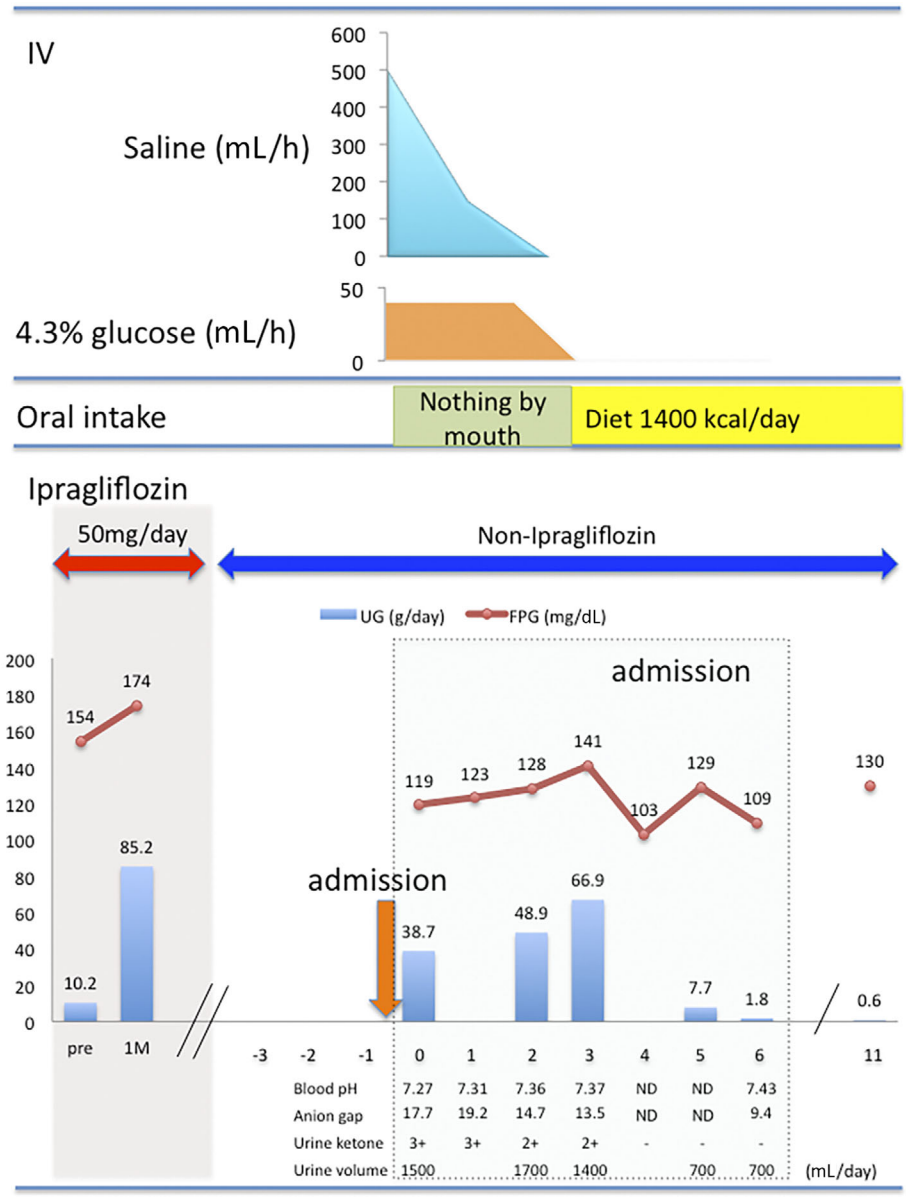

Figure. **Changes in the daily urinary glucose excretion before and after the use of ipragliflozin, an SGLT2 inhibitor, and the post-admission course. IV: intravenous fluid, UG: daily urinary glucose excretion, FPG: fasting plasma glucose, ND: no data**

tant, both when considering the mechanism underlying the onset of DKA and for confirming whether other similar cases have been encountered but not reported - in order to ensure the safety of SGLT2 inhibitor use.

It is also important to discuss the mechanism underlying the protracted persistent hyperglycosuria that was observed in our patient from the viewpoints of the drug half-life and tissue penetration. Tahara et al. (26) classified ipragliflozin, the drug used in the present case, in addition to dapagliflozin, as long-acting based on experiments in euglycemic and diabetic mice following their finding of 18-h-long hyperglycosuria. They also showed that ipragliflozin has the highest renal $T_{1/2}$/blood $T_{1/2}$ ratio, indicating its rate of distribution in the kidneys (26). With regard to this point, the advantage of an adequate pharmacological effect must be weighed against the possibility that this may be a mechanism underlying the persistence of this effect, even after discontinuation, resulting in protracted hyperglycosuria.

The administration of luseogliflozin to insulin-resistant rats with metabolic syndrome resulted in the downregulation of the SGLT2 expression in the renal tubules, suggesting the down-regulation of the downstream expression of SGLT 1 (27). Although this phenomenon may be difficult to observe in human renal tissues, it is totally conceivable that the downregulation of the SGLT2 expression by SGLT2 inhibition could lead to the persistence of protracted hyperglycosuria - even after discontinuation of the SGLT2 inhibitor, and such scenarios must be investigated. It is possible that this phenomenon could occur following the use of any SGTL2 inhibitor and that there may be individual differences in the expression of SGLT2. Further studies are needed to compare the effects of different SGLT2 inhibitors

and to determine the expression of SGLT2 at the genetic level.

One clear difference between our case and previously reported cases of SGLT2 inhibitor-related euDKA is the latency between the initiation of SGLT2 inhibitor therapy and the development of euDKA. In previously reported cases, euDKA manifested after only 1-14 days (10, 15); in contrast, our patient developed euDKA several months after the start of oral therapy. Thus, the length of the treatment period could be related to the development of euDKA (e.g., drug accumulation in the tissues). It is also known that most drugs show pH-dependent binding to plasma proteins (28). Although the binding capacity of SGLT2 inhibitors to albumin is unknown at present, it is possible that in our case - under conditions of severe acidosis - the SGLT2 inhibitor bound to albumin, and dissociated from albumin upon the correction of acidosis by treatment. The released SGLT2 inhibitors may have then transferred to the urinary tubules and remained active, despite the fact that the drug was no longer being administered.

Other factors could also explain the protracted urinary glucose excretion. It is noteworthy that the AUC of ipragliflozin is higher than the AUC values of other SGLT2 inhibitors, according to the PK/PD data of SGLT2 inhibitors reported by Tahara et al. (26), which may also influence its protracted efficacy.

The present case report is associated with some limitations, including, the inclusion of a single patient, which meant that we could not investigate issues such as the increase in ketone bodies, the mechanism of the onset of DKA, and the mechanism underlying the patient's persistent hyperglycosuria. This was due to the fact that we were unable to determine the drug concentrations in blood, urine, and renal tissue. We were also unable to investigate the effects of metformin and diuretics, which were discontinued at the same time. It is likely that the protracted effect of the drug on urinary glucose excretion after its discontinuation made a significant contribution to the progression or severity of the DKA in our case. However, it remains possible that DKA had already developed before the discontinuation of ipragliflozin. In addition, although free fatty acids (FFAs) contribute to the development and progression of DKA, we did not measure the levels of FFAs in our case. Since the patient did not wear a continuous glucose monitor, we do not know if she ever developed extreme hyperglycemia during the 24-hour period. The fact that non-hyperglycemic ketoacidosis was diagnosed based on regular blood glucose measurements while the patient was prohibited from eating is a further limitation.

At present, we encourage patients to discontinue treatment with SGLT2 inhibitors on sick days. Furthermore, we encourage them to visit the hospital if they complain of a poor physical status after the discontinuation of SGLT2 inhibitors.

In conclusion, we presented the case of a young, obese diabetic woman with preserved endogenous insulin secretion who developed non-hyperglycemic ketoacidosis while on treatment with ipragliflozin, and who showed persistent hyperglycosuria even after the discontinuation of ipragliflozin. Large-scale studies will be needed to determine the actual mechanism involved in order to ensure the safety of this new drug before it is widely used.

The authors state that they have no Conflict of Interest (COI).

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