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Case Reports

Case of hyperosmolar hyperglycemic state by a sodium-glucose cotransporter 2 inhibitor

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Inhibitors of sodium-glucose cotransporters type 2 (SGLT2) are proposed as a novel approach for the management of type 2 diabetes mellitus. SGLT2 cotransporters are responsible for reabsorption of 90 % of the glucose filtered by the kidney. The glucuretic effect resulting from SGLT2 inhibition contributes to reduce hyperglycaemia and also assists weight loss and blood pressure reduction.
In this study, we presented the case of a 59-year-old male who developed hyperosmolar hyperglycemic state (HHS), possibly caused by a sodium-glucose cotransporter 2 (SGLT2) inhibitor, a novel class of antihyperglycemic agents. This case highlights that HHS can develop in patients with diabetes treated with SGLT2 inhibitors

Key Words: Diabetes mellitus, Hyperosmolar hyperglycemic state, Sodium-glucose cotransporter 2 inhibitor

The kidneys are a vital body organ in charge of adjustment and discharge of sodium and all kinds of ions. The kidneys also play an important role in maintaining glucose homeostasis through new growth and re-absorption of glucose. It is known that 90% of glucose re-absorption in the kidneys is carried out by sodium glucose cotransporter (SGLT)2.[1] A SGLT2 inhibitor was developed in order to regulate blood glucose by selectively inhibiting SGLT2 and increasing glucose discharge through the urine.

The best advantage of SGLT2 is that it reduces blood glucose without being dependent on insulin and is not affected by beta cell dysfunction or insulin sensitivity. It is also has a low risk for hypoglycemia and may promote weight loss; and in combined use with insulin, weight increase resulting from insulin treatment may be decreased. Reduction in blood pressure is expected in relation to diuretic action.[2]

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However, SGLT2 inhibitors may trigger urinary tract infections, and in elderly patients, they may cause dehydration resulting from a decrease in body fluid volume and fractures from falls brought about by orthostatic hypotension; caution is necessary when using SGLT2 inhibitors.[3] Furthermore, according to the database of the Food and Drug Administration Adverse Event Reporting System, 20 patients who took SGLT2 inhibitors from March 2013 to June 2014 succumbed to acidemia such as diabetic ketoacidosis.[4] Nonetheless, the condition of hyperosmolar hyperglygemic syndrome (HHS) in patients who took SGlT2 inhibitors has not been reported yet.

Neverthless, the authors experienced a patient's HHS that occurred after taking a SGLT2 inhibitor. It is a side-effect not reported before and therefore we report this case because we experienced a patient needing a new examination.

CASE

Patient: Park ( )-su, male, 59 years old

Main complaint: hyposthenia

Current history: The patient visited our hospital with main complaints of hyposthenia, anorexia, and dizziness that had occurred from four days before. He was diagnosed with type 2 diabetes mellitus 10 years ago and had taken metformin but stopped taking it from three months ago and took dapagliflozin only. From two months ago, he experienced weight loss and felt frequent hunger and his appetite increased. In addition, he frequently drank sodas, coffee drinks high in calories, and fruit juice.

Past history: After he was diagnosed with diabetes mellitus 10 years ago, he took 2,000 mg of metformin until six months ago. Ordinarily his blood sugar was well controlled with HbA1C at 6.1~6.3%. He was obese with his body mass index at 35.2 kg/m^2 (height: 178.4 cm, weight: 111.4 kg). Six months ago, with the expectation of the additional effect of weight loss, metformin was reduced to 1000 mg/day, instead of which dapagliflozin at 10 mg/day was added. HbA1C measured as an outpatient three months ago was lower at 5.7%. Therefore, he stopped taking metformin and took dapagliflozin only. He had high blood pressure and hyperlipidemia; he was taking amldoipine, olmesartan, pitavastatin, fenofibrate, and aspirin.

Family history: There was no specific finding.

Findings from physical examination: His weight, blood pressure, pulse, respiration, and body temperature were 104.5 kg, 120/70 mmHg, 88 breaths/min, 20 beats/min, and 37.4℃, respectively. His mental state was clear but he had an acute ill-looking appearance. He had low skin tension. His mucous membrane of the oral cavity was severely dry, which was accompanied by dehydration. His breathing sound and bowel sound were good. There were no specific findings produced from an abdominal examination.

Findings by the laboratory: His level of hemoglobin, white blood cells, and platelet count was

15.3 g/dL, 12,210/mm^3 (segmented neutrophil: 95%, lymphocyte:3%), and 264,000/mm^3, respectively. His level of blood glucose, HbA1C, blood urea nitrogen, and creatinine was 2,050 mg/dL, 10.5%, 46.1 mg/dL, and 3.4 mg/dL, respectively. His level of sodium, potassium, chlorine, calcium, phosphorus, carbon dioxide, C-reactive protein, serum osmotic pressure, and fasting C-peptide was 120.3 mEq/L, 6.2 mEq/L, 86 mEq/L, 10.1 mg/dL, 4.6 mg/dL, 28.3 mmol/L, 0.2 mg/dL (normal range: 0~0.5 mg/dL), 412 mOsm/kg, and 5.6 ng/mL, respectively. His urine ketone level was negative and his urinary osmotic pressure was 542 mOsm/kg. Inaddition, the results of a blood test and urine test were in normal ranges (Table 1). There was no abnormal finding in chest and abdominal X-rays. There was no specific finding except for left ventricular hypertrophy in the electrocardiogram and mild fatty liver in the abdominal ultrasonography. He was diagnosed with acute renal failure accompanying hyperosmolar hyperglygemic syndrome in consideration of the above symptoms and started to receive fluid and insulin treatment. On the second day of hospitalization, his blood sugar level was maintained at 200~400 mg/dL. Hyposthenia, anorexia, and dizziness he had complained of improved and there was no evidence of fever or infection and therefore antibiotics were not used. On the third day, his creatinine level recovered to 1.1 mg/dL and blood sugar management was well maintained. Therefore, on the fourth day, treatment was converted to subcutaneous insulin infusion and multiple doses of insulin regimen (36 units of Insulin Detemir before breakfast, and 12 units of insulin NovoRapid before every breakfast) and then he was discharged. Thereafter, he received ambulatory care; treatment was changed into combined administration of 30 units of Detemir, 1000mg/day of metformin, and 100mg/day of vildaglpitin. His level of HbA1C in two months and five months after discharge from our hospital was 8.2 % and 5.2%, respectively. Therefore, administration of insulin was stopped, and he took 1000mg/day of metformin and 100 mg/day of sitagliptin only.

DISCUSSION

SGLT2 inhibitors decrease absorption of glucose in the kidneys, cause excretion, and lower blood sugar level. In many cases, patients with diabetes mellitus also are obese and have high blood pressure. Given that blood sugar targets and blood sugar lowering strategies focus on personalized ones for each patient in the recommendation guideline announced recently, SGLT2 inhibitors have gained attention because of their effects in promoting weight loss and lowering blood pressure in addition to blood sugar lowering effects.[1] SGLT2 inhibitors are totally different from existing diabetes mellitus agents in terms of mechanism of action and are expected to add a blood sugar lowering function to the existing treatment of type 2 diabetes mellitus.

Table 1.

Varible	Value
Physical examination	
Age(y)	59
Height(cm)	178.4
Body mass index(kg/m2)	33.0
Routine complete blood cell	
White blood cell(/mm3)	12,210
Hemoglobin(g/dL)	15.3
Platelet(/mm3)	264,000
Blood chemistry	
Sodium(mEq/L)	120.3
Potassium(mEq/L)	6.2
Chloride(mEq/L)	86
Blood urea nitrogen(mg/dL)	46.1
Creatinine(mg/dL)	3.4
Glucose(mg/dL)	2,050
Glycosylated hemoglobin(%)	10.5
Calcium(mg/dL)	10.1
Phosphorus(mg/dL)	4.6
Total CO2(mmol/L)	28.3
C-reactive protein(mg/dL)	0.2
Serum osmolarity(mOsm/kg)	412
C-peptide(ng/mL)	5.6
Urinalysis	
pH	5
Glucose	3+
Ketone body	-
Occult blood	-
White blood cell(esterase)	-
Nitrate	-

Hyperosmolar hyperglygemic syndrome is one of the acute complications of diabetes mellitus, and unlike diabetic ketoacidosis, it occurs mainly among type 2 diabetes mellitus patients. It is characterized by severe hyperglycemia (〉 600 mg/dL) and hyperosmosis (〉 320 mOsm/L) without ketoacidosis; failure to sufficiently ingest water together with serious osmotic dieresis and the resulting damage to renal functions decreases excretion of glucose, triggering even more serious hyperglycemia—in other words, a vicious circle.[6] The older the patient, the lower the average arterial

pressure of the patient, the higher the level of plasma osmotic pressure and the concentration of crreatinine, the worse the prognosis of the patient; it is known that the mortality rate is 11% despite active treatment.[7] The most common factor for hyperosmolar hyperglygemic syndrome is an infection and it also may be caused by a stroke, myocardial infarction, a trauma, and drugs like steroid agents or diuretics.[8] Dehydration, hyperglycemia, and electrolyte disorders should be corrected and at the same time their cause should be clarified and treated.[9]

The patient of this case visited our hospital with the level of blood sugar and effective osmotic pressure at 2,050 mg/dL and 412 mOsm/L, respectively, and with urine ketone level negative and the condition of hyperosmolar hyperglygemic syndrome. There was no special factor triggering his condition of hyperosmolar hyperglygemic syndrome and therefore it was estimated that administration of the SGLT2 inhibitor as a single agent from three months ago was related. Therefore, administration of dapagliflozin was stopped and fluid regimen and intravenous insulin injection were applied and the patient exhibited a recovery from the second day.

In relation to the SGLT2 inhibitor with regard to this patient, the pathogenesis of hyperosmolar hyperglygemic syndrome is not clear but two factors are thought to have a role in bringing on his condition. First, the major mechanism of metformin is inhibition of glucose generation in the liver, and it is estimated that a vicious circle was triggered in which glucosuria resulting from cessation of taking metformin and administration of a SGlT2 inhibitor increased glyconeogenesis in the liver and the accompanying osmotic dieresis triggered dehydration and damage to renal functions, lowering excretion of glucose as urine, which in turn triggered the even more severe hyperglycemia.

Second, it is estimated that the effect of increasing appetite caused by dapagliflozin and cessation of administration of metformin increased food intake, triggering severe hyperglycemia, and dehydration and degradation of renal functions that occurred due to the diuretic effect, which in turn lowered excretion of glucose in urine, resulting in hyperosmolar hyperglygemic syndrome. In addition, he frequently drank sodas, coffee drinks high in calories, and fruit juice due to the increase in appetite after taking dapagliflozin. Suzuki et al.[10] reported that in an animal experiment, the subject's appetite increased by 10 percent after administration of tofogliflozin. Hiromi[11] reported on a case where a patient stopped taking a SGLT2 inhibitor due to feelings of hunger and there was an increase in the subject's weight after the subject changed medication from liraglutide to a SGLT2 inhibitor for weight loss purposes. Ferrannini et al.[12] reported that the actual weight loss was smaller than what was expected from the glucose excretion effect by a SGLT2 inhibitor and this was because of the increase in energy intake that was linked to glucose excretion.

The patient of this case was diagnosed with type 2 diabetes mellitus ten years ago and took metfor-

min as a single agent, thereby controlling well blood sugar. For the additional effect of weight loss, the combined administration of metformin and a SGLT2 inhibitor was commenced from six months ago. His blood sugar was well controlled during this period of combined drug administration. Given the details of this case where, after cessation of metformin and conversion to taking a SCLT2 inhibitor as a single agent three months ago, the patient's desire for sugar intake was heightened and his cravings for food and dehydration commenced, which resulted in hyperosmolar hyperglygemic syndrome accompanying acute kidney damage rather than any loss in weight loss, it is considered important that a clinician be aware of these facts. Switching from taking a SGLT2 inhibitor as a single agent after cessation of long-term administration of metformin can lead to intrinsic glyconeogenesis increases in the liver and increased appetite that brings on hyperglycemia and this can result in osmotic dieresis with the possibility of dehydration. Careful observation is needed with regard to drug interaction when an oral hypoglycemic agent has been administered and then there is a switch to a SGLT2 inhibitor as a single agent.

If the patient of this case had reduced insulin secretion function with no accompaniment of acute renal damage, his condition may have been expressed in the form of acidemia including ketoacidosis that occurred after administration with a SGLT2 inhibitor.[4] However, his insulin secretion function was relatively preserved with the accompaniment of acute renal damage, and therefore it is estimated that sugar excretion into urine was not effectively done and as a result hyperosmolar hyperglygemic syndrome occurred.

In hyperosmolar hyperglygemic syndrome, the diagnosis of its cause and its treatment have decisive influence on its prognosis and therefore its cause should be discovered through precise physical examination, current history, past history, and findings in the laboratory. Whether a SGLT2 inhibitor was administered should be carefully considered caution when investigating the cause of hyperosmolar hyperglygemic syndrome. Hereby, the authors experienced a patient with hyperosmolar hyperglygemic syndrome that occurred after taking a SGLT2 inhibitor and therefore made a report on this case in conjunction with an examination of the relevant literature.

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