Fluctuation in Serum Sodium Levels Related to Ipragliflozin Administration in a Patient with Diabetic Nephropathy and Sequela of Traumatic Brain Injury

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Abstract

A 46-year-old diabetic man underwent the removal of a hematoma caused by traumatic brain injury. After surgery, severe hyponatremia occurred. The subsequent administration of NaCl and fludrocortisone improved his laboratory findings. The patient was transferred to our hospital, and his insulin therapy was replaced by teneligliptin. One week later, ipragliflozin treatment was initiated and induced an immediate increase in the serum sodium levels. NaCl and fludrocortisone were therefore discontinued. However, hyponatremia recurred after ipragliflozin withdrawal due to a urinary tract infection. NaCl and fludrocortisone were initiated again, and the laboratory data improved. We herein report a case of serum sodium fluctuation related to ipragliflozin administration.

Key words: SGLT2 inhibitor, electrolyte free-water clearance, CSWS, SIADH, DPP-4 inhibitor

Introduction

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have been recently developed (1, 2); they act by reducing renal glucose reabsorption in the proximal convoluted tubule, leading to increased urinary glucose excretion and subsequent reductions in plasma glucose and glycosylated hemoglobin (HbA1c) levels. In addition, SGLT2 inhibitors reduce body weight and blood pressure. Synergistic effects of the combination of SGLT2 inhibitors and other antidiabetic drugs are expected. Furthermore, SGLT2 inhibition reduces renal hyperfiltration presumably by modulating tubuloglomerular feedback mechanisms and is expected to demonstrate renoprotective effects similar to those of renin-angiotensin system blockers (3). Typical adverse effects include urinary and genital tract infections and volume depletion-related events, such as hypotension. Although there are few reports on the effects of SGLT2 inhibition on serum electrolytes (4), the incidence of adverse effects appears to be low. SGLT2 inhibitors may be effective in patients who cannot fully carry out diet therapy and exercise therapy.

We recently treated a diabetic patient who presented with dysregulation of the water-electrolyte (sodium) balance as a sequela of traumatic brain injury. Intensive insulin therapy (IIT) was replaced with oral antidiabetic drugs (OAD) by administering ipragliflozin for 8 weeks. To maintain his serum sodium level within the normal range, we controlled the administration of NaCl and fludrocortisone in conjunction with the administration of ipragliflozin.

In this report, we discuss the potential mechanisms behind serum sodium level fluctuations related to ipragliflozin administration by considering changes in the relative balance between circulating plasma volume and serum sodium levels. In addition, we discuss how changes to OAD therapy were possible in this case.
Case Report

A 46-year-old man fell down and hit his head badly. He was admitted to Y University Hospital in mid-December 2013. On admission, his Glasgow Coma Scale was 7 (E1V1 M5), and a neurological examination revealed right hemiparesis. A CT scan showed left acute epidural hematoma and traumatic subarachnoid hemorrhaging. The patient underwent evacuation of the hematoma. He had been diagnosed with diabetes mellitus in 2009, but did not receive any medical treatment. At the time of admission to Y University Hospital, his laboratory results revealed several abnormal values, including a blood glucose (BG) level of 419 mg/dL, an HbA1c level of 9.5%, a serum creatinine (sCr) concentration of 0.73 mg/dL, an estimated glomerular filtration rate (eGFR) of 98.6 mL/min/1.73 m², a sNa level of 133 mEq/L, a brain natriuretic peptide (BNP) level of 39.9 pg/mL, a body mass index of 23.5 kg/m², urinary glucose (-), urinary ketones (-), urinary protein (-), and urinary occult blood (-). Therefore, the patient was started on a diet of 1,800 kcal/day with 8 g of salt, and basal-bolus insulin analog therapy was continued, which included insulin glargine (24 units daily) and insulin aspart (8, 6, and 8 units before each meal). Fig. 1 shows the patient’s clinical course after admission. The patient had proliferative diabetic retinopathy (Fukuda classification B1) and diabetic nephropathy (The Japan Diabetes Society/Japanese Society of Nephrology classification stage 2). Seven-point BG profiles are shown in Fig. 2. Although the patient’s BG profile while under treatment with IIT was excellent on Day 5, we suggested a change from IIT to OAD in order to discharge him from the hospital and to enable him to resume work, and he agreed to this proposal.

When he entered our hospital, his Japan Coma Scale was 0-1, and ordinary conversation was possible. He could calculate the serial sevens subtraction test without error. Pretibial pitting edema was not observed. His laboratory results showed a BG level of 95 mg/dL, an HbA1c of 7.0%, a sCr of 0.68 mg/dL, an eGFR of 98.6 mL/min/1.73 m², a sNa of 133 mEq/L, a brain natriuretic peptide (BNP) level of 39.9 pg/mL, a body mass index of 23.5 kg/m², urinary glucose (-), urinary ketones (-), urinary protein (-), and urinary occult blood (-). Therefore, the patient was started on a diet of 1,800 kcal/day with 8 g of salt, and basal-bolus insulin analog therapy was continued, which included insulin glargine (24 units daily) and insulin aspart (8, 6, and 8 units before each meal). Fig. 1 shows the patient’s clinical course after admission. The patient had proliferative diabetic retinopathy (Fukuda classification B1) and diabetic nephropathy (The Japan Diabetes Society/Japanese Society of Nephrology classification stage 2). Seven-point BG profiles are shown in Fig. 2. Although the patient’s BG profile while under treatment with IIT was excellent on Day 5, we suggested a change from IIT to OAD in order to discharge him from the hospital and to enable him to resume work, and he agreed to this proposal.

The patient’s insulin dosage was decreased on Day 5 and finally discontinued on Day 8. In exchange, he was started on teneligliptin on Day 6. His BG profile on Day 13 indicated an overall status of hyperglycemia, with BG levels more than 200 mg/dL after breakfast and dinner (Fig. 2). On Day 14, his 24-hour urinary C-peptide excretion (UCPR) level was 7.3 μg/day. Therefore, the patient was started on ipragliflozin 50 mg once a day on Day 14. Glucosuria was

Figure 1. Clinical course of the patient after admission. Longitudinal changes in the blood glucose (BG), estimated glomerular filtration rate (eGFR), urinary glucose excretion (uGlu), body weight (BW), and serum sodium (sNa) levels are shown. Fluctuations in the sNa levels were observed not only immediately after starting an SGLT2 inhibitor, but also after the withdrawal of an SGLT2 inhibitor.
Hyponatremia is often observed after acute brain injuries such as subarachnoid hemorrhage and traumatic brain injury. CSWS and syndrome of inappropriate secretion of antidiuretic hormone (SIADH) are considered to be the two principal causes of hyponatremia in patients with acute brain injury (5). In this case, the sNa levels began to decrease two weeks after brain injury. Then, the patient’s laboratory results showed hyponatremia with massive urinary sodium excretion. However, the precise distinction between CSWS and SIADH is difficult to ascertain. At the onset of hyponatremia at Y University Hospital in the present case, laboratory tests revealed an elevated ratio of blood urea nitrogen/creatinine persisting for a few days, a slight increase in the serum potassium levels, and long-lasting hyponatremia. Unfortunately, we did not assess an accurate extracellular fluid status or arginine vasopressin (AVP) levels during his hospitalization period. However, the successive administration of both NaCl and fludrocortisone improved the sNa levels without restriction of the water intake. Furthermore, we observed an elevation of the plasma BNP levels, which is one of characteristics of CSWS (6). Therefore, we considered the possibility of CSWS as the cause of hyponatremia after brain injury in the present case (5, 6).

After transfer to our hospital, the patient’s sNa level fluctuated in relation to the administration of ipragliflozin. There are several potential mechanisms behind the fluctuations in sNa level. First, immediately after the patient was started on ipragliflozin (on Day 20), his sNa level and plasma osmolality level increased to 144 mEq/L and 301 mOsm/kg, respectively, alongside a weight decrease, BP decrease, and hematocrit level increase. Assessment of electrolyte free-water clearance (EFWC) may help to determine the mechanisms underlying the changes in the sNa level related to ipragliflozin administration (7, 8). As shown in Table, the modified electrolyte free-water clearance (MEFWC) was immediately observed. The trends for various laboratory values are shown in Table. His body weight (BW) was 70.5 kg at the time of starting ipragliflozin treatment, which decreased to 69.5 kg on Day 19. On Day 20, his BG levels at 10:00, 12:00, 18:00, and 20:00 decreased (Fig. 2); on the other hand, his sNa level increased to 144 mEq/L. On Day 28, his BW was 69 kg, and his sNa and uNa levels were 139 mEq/L and 103 mEq/L, respectively. We therefore decreased the NaCl dosage to 3 g/day. Thereafter, he was able to discontinue fludrocortisone on Day 35 and NaCl on Day 42. On Day 56, his BW and blood pressure (BP) decreased to 66.0 kg and 92/71 mmHg, respectively, and his BG profile generally improved, except for his BG level at 22:00.

On Day 59, the patient developed a fever. The cause of the fever was determined to be a urinary tract infection, which was treated by levofloxacin. On Day 72, the patient’s UCPR level increased to 23.8 μg/day; ipragliflozin was subsequently discontinued because it became obvious that he had a neurogenic bladder. Surprisingly, his sNa levels decreased to 121 mEq/L on Day 84. Brain magnetic resonance imaging on Day 85 demonstrated the disappearance of both the epidural hematoma and the subdural hematoma, and there was no evidence of hydrocephalus. Thereafter, hyponatremia with urinary sodium excretion persisted, and his sNa and uNa levels were 119 mEq/L and 60 mEq/L, respectively, on Day 91. Because the fluctuations in his sNa levels were considered to be related to ipragliflozin administration, the patient was re-started on NaCl and fludrocortisone on Day 91. Finally, on Day 96, the patient’s sNa, fasting BG, and HbA1c levels reached 134 mEq/L, 94 mg/dL, and 6.9%, respectively, and the patient was discharged on Day 100.

The patient discontinued NaCl therapy in early October following an outpatient visit. At his recent visit in late February 2015 (9 months after ipragliflozin withdrawal), his sNa, HbA1c, and eGFR levels were 133 mEq/L, 6.7%, and 83.2 mL/min/1.73 m², respectively, without any OAD besides teneligliptin.
The theoretical AVP secretion value was calculated by the following equation; 0.38 × (plasma osmolality - 280). The predicted AVP secretion value was calculated by the following equation; 1.7 × (urine osmolality/plasma osmolality).

**Note:** The asterisk (*) indicates the value on the nearest day.

Plasma osmolality was calculated by the following equation; 2 × sNa (mEq/L) + blood glucose/18 (mg/dL) + blood urea nitrogen/2.8 (mg/dL).

sustained effects on urinary glucose excretion and fasting plasma glucose over 12 weeks and a transient reduction in the plasma volume that is largely attenuated by week 12 (9). However, our case suggests fluctuations in the sNa levels according to SGLT2 inhibitor administration, not only immediately after starting an SGLT2 inhibitor, but also after the withdrawal of an SGLT2 inhibitor after 8 weeks of administration in patients with dysregulation of the water-electrolyte (sodium) balance.

DPP-4 inhibitors have been extensively used in recent years due to their efficacy and safety (1, 2, 10). In the present case, when treatment was changed from IIT to OAD, teneligliptin was initially administered alone. However, the patient’s BG profile indicated an overall hyperglycemic status with the highest glucose value seen after dinner (Fig. 2). Nevertheless, only 1 week after the initiation of the combination of ipragliflozin with teneligliptin, his overall BG profile improved. Endogenous insulin secretion measured by UCPR was low (7.3 μg/day) when teneligliptin was administered alone for 1 week. However, UCPR gradually increased after the addition of ipragliflozin, reaching 23.8 μg/day after 8 weeks of joint therapy. This clinical course suggests that replacement of IIT with OAD was appropriate for the patient. Recently, Takahara et al. reported that a four-week treatment with ipragliflozin improved the β-cell function and glucose levels in patients with type 2 diabetes mellitus, and these effects lasted even after discontinuance of ipragliflozin (11). In this case, an increase in UCPR was observed two weeks after starting ipragliflozin, however, it was several weeks before the UCPR levels increased to a sufficient level. We were unable to continue ipragliflozin due to his urinary tract infection and neurogenic bladder. However, his HbA1c value was 6.7% at a recent outpatient visit. Therefore, it is likely that even an eight-week treatment with ipragliflozin might offer benefits.

To the best of our knowledge, there are no case reports similar to the present case. Our case report also suggested that careful monitoring of the water-electrolyte balance may help to overcome potential adverse effects from SGLT2 inhibitor treatment.

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

References