

Diabetes Insipidus Induced by Sodium-Glucose Cotransporter-2 Inhibitor Treatment

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Abstract: The patient was a 56-year-old woman with schizophrenia and diabetes mellitus who had been prescribed risperidone and an SGLT2 inhibitor. The patient's son found her in her home in an unconscious state after two days of fever. On arrival, her Glasgow Coma Scale score was E3V4M6. She had a blood pressure of 144/122 mmHg, a heart rate of 163 beats per minute (BPM), a respiratory rate of 22 breaths per minute, and a body temperature of 41.1°C. She was diagnosed with urosepsis with hyperglycemia, glucosuria and dehydration a massive infusion of lactate Ringer solution was administered. As a result, her heart rate decreased to 102 BPM and her consciousness improved. After admission to the intensive-care unit, she underwent intermittent antibiotic treatment and received a continuous infusion of insulin without an SGLT2 inhibitor to control her blood glucose level to <200 mg/dl. However, her urinary glucose level remained at 4+, and her urinary volume increased to >3000 ml per day with a gradual increase in hyponatremia and heart rate, she also developed a consciousness disturbance; this required aggressive fluid resuscitation. From the 5th day, her urinary volume decreased gradually. After obtaining a normal daily urinary volume with normal vital signs, and the improvement of her urinary tract infection, she was discharged on foot. We reported the first case of diabetes insipidus induced by an SGLT2 inhibitor. Physicians should consider the possible development of diabetes insipidus when treating patients using SGLT2 inhibitors.

Keywords: diabetes insipidus; sodium-glucose cotransporter-2 inhibitor; dehydration

INTRODUCTION

Sodium-glucose cotransporter (SGLT2) inhibitors are a new class of drugs that work by inhibiting the renal tubular reabsorption of sodium and glucose. This allows us to take advantage of glycosuria (glucose excretion) while the patient remains relatively euglycemic [1]. These inhibitors may also reduce insulin secretion with blood glucose levels that remain close to the normal range due to the blockade of glucose reabsorption at the renal proximal tubule [1]. SGLT2 inhibitors are thought to be safe drugs with minimal side effects [2]. We herein report a case in which diabetes insipidus was induced by sodium-glucose cotransporter-2 inhibitor treatment.

CASE REPORT

The patient was a 56-year-old woman with schizophrenia and diabetes mellitus who had been prescribed risperidone and an SGLT2 inhibitor. The patient's son found her in her home in an unconscious state after two days of fever. On arrival, her Glasgow Coma Scale score was E3V4M6. She had a blood pressure of 144/122 mmHg, a heart rate of 163 beats per minute (BPM), a respiratory rate of 22 breaths per

minute, an SpO₂ of 95% (under 5L/min oxygen) and a body temperature of 41.1°C. A physical examination revealed systemic redness and tremor at all extremities. A venous gas analysis revealed the following: pH, 7.47; PCO₂, 29.2 mmHg; PO₂, 48.1 mmHg; HCO₃⁻, 21.2 mmol/l; and base excess level, -0.9 mmol/l. An electrocardiogram showed sinus tachycardia. An ultrasound study revealed hyper-dynamic cardiac wall motion and the collapse of the inferior vena cava diameter. The main findings of a blood analysis were as follows: white blood cell count, 6,900/μl; hemoglobin, 14.2 g/dl; platelet count, 19.7 × 10⁴/μl; total protein, 7.0 g/dl; glucose, 402 mg/dl; aspartate aminotransferase, 27 IU/L; alanine aminotransferase, 26 IU/L; gamma-glutamyltransferase, 57 IU/L; blood urea nitrogen, 18.4 mg/dl; creatinine, 0.88 mg/dl; creatinine phosphokinase, 116 IU/L; sodium, 133 mEq/L; chloride, 96 mEq/L; potassium, 4.4 mEq/L; c-reactive protein, 21.8 mg/dl; activated partial thromboplastin time, 19.2 (27.4) s; and international normalized ratio of prothrombin time, 1.08. A urinalysis revealed the following findings: protein, 1+; glucose, 4+; occult blood, +; and leukocyte, +. Whole-body computed tomography (CT) revealed no specific findings. She

was diagnosed with urosepsis with hyperglycemia, glucosuria and dehydration a massive infusion of lactate Ringer solution was administered. As a result, her heart rate decreased to 102 BPM and her consciousness improved. After admission to the intensive-care unit, she underwent intermittent antibiotic treatment and received a continuous infusion of insulin without an SGLT2 inhibitor to control her blood glucose level to <200 mg/dl. However, her urinary glucose level remained at 4+ (over 1000 mg/dl), and her urinary volume increased to >3000 ml per day with a gradual increase in hypernatremia (maximum, 173 on the 4th hospital day) and heart rate, she also developed a consciousness disturbance; this required aggressive fluid resuscitation. An infusion of vasopressin failed to control her urinary volume. She was temporarily treated with thiazide diuretics to control nephrogenic diabetes insipidus but this was ineffective. From the 5th day, her urinary volume decreased gradually. After obtaining a normal daily urinary volume with normal vital signs, and the improvement of her urinary tract infection, which was induced by *Escherichia coli*, she was discharged on foot. She returned to her home on the thirteenth hospital day.

DISCUSSION

This is the first reported of the induction of diabetes insipidus by an SGLT2 inhibitor. Kim et al reported no clinically meaningful changes in the serum electrolyte and creatine levels, or in the estimated glomerular filtration rate of patients treated with SGLT2 inhibitors. In previous studies, patients treated with dapagliflozin (an SGLT2 inhibitor) were reported to show a small increase in their 24-hour urine volume (107–470 mL above baseline) at the end of the study [3-5]. Furthermore, the hematocrit levels of a small number of patients showed a minor increase (1.5–2.9% from baseline) [3]. The glucosuria induced by SGLT2 is known to cause osmotic diuresis, which is followed by an increase in the urinary volume. In contrast, our case showed a significant increase in her daily urinary volume, dehydration, and life threatening hypernatremia [6, 7]. This might have occurred due to an idiosyncratic response to the SGLT2 inhibitor and/or because of drug interactions between SGLT2 and the psychogenic drug that was used to treat the patient's schizophrenia. Although there has been a report on the induction of diabetes insipidus by lithium, our patient was treated with resperione [8]. In the present case, vasopressin and thiazide diuretics failed to control the patient's diabetes insipidus; however, the condition showed spontaneous improvement, probably due to the internal metabolism and excretion of the SGLT2 inhibitor. Similarly to the present case, other studies have reported a relationship between the induction of glucosuria by SGLT2 and urinary tract infection [9, 10].

CONCLUSION

We reported the first case of diabetes insipidus induced by an SGLT2 inhibitor. Physicians

should consider the possible development of diabetes insipidus when treating patients using SGLT2 inhibitors.

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