Canagliflozin-associated severe hyponatremia: a rare and potentially adverse effect?

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Summary

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) induce osmotic diuresis by inhibiting the proximal renal tubular reabsorption of the filtered glucose load, which in turn can occasionally lead to severe dehydration and hypotension amidst other adverse effects. We present a case of a 49-year-old man with type 2 diabetes mellitus (T2D) on canagliflozin, a SGLT2i. The patient was brought to the emergency room following a motor vehicle accident. He was confused and had an altered mental status. His blood alcohol and urine toxicology screens were negative. Initial investigations revealed that he had severe hyponatremia with euglycemic ketoacidosis. The adverse condition was reversed with close monitoring and timely management, and the patient was eventually discharged. This is the first report to suggest hyponatremia as a potentially serious adverse effect following SGLT2i therapy. Its impact on the renal tubule handling of sodium and water is not yet well characterized. While further studies are warranted to understand better the pathophysiological mechanisms associated with SGLT2i-induced adverse effects, timely dose reduction or perhaps even its temporary discontinuation may be recommended to prevent complications.

Learning points:

- Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are usually well-tolerated, but some serious adverse effects have been documented.
- Our case report suggests hyponatremia as a potential, rare side effect of SGLT2i and makes physicians aware of the occurrence of such life-threatening but preventable complications.
- Timely and close monitoring of the patient, with temporary discontinuation of this drug, may be recommended towards effective management.
- Studies demonstrating a comprehensive understanding of SGLT2i-related electrolyte derangements are warranted.

Background

Type 2 diabetes mellitus (T2D) is a chronic metabolic disorder associated with hyperglycemia that eventually leads to micro- and macro-vascular complications resulting in target organ damage (1). Sodium-glucose cotransporter-2 inhibitors (SGLT2i – canagliflozin, dapagliflozin, empagliflozin, etc.) are relatively new anti-diabetic medications that target the sodium-glucose cotransporter-2 in the proximal convoluted tubule. They...
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DOI: 10.1530/EDM-21-0035

https://edm.bioscientifica.com/

exhibit their antihyperglycemic effects in an insulin-independent manner.

Accumulating evidence from major trials demonstrates that SGLT2i are potent cardio- and nephroprotective agents, offering reductions of up to 38% in cardiovascular mortality, 35% in heart failure hospitalization, 45% in the progression of renal disease, and 30% in all-cause mortality (2). Because of its beneficial effect on cardiovascular hemodynamics, SGLT2i, particularly dapagliflozin, has been recently approved by the Food and Drug Administration for heart failure treatment, even in patients without diabetes.

While SGLT2i are usually well-tolerated, adverse effects of this class include urinary frequency, dehydration, genitourinary tract infections, and, rarely, euglycemic diabetic ketoacidosis (DKA) (3). Hyponatremia is a common disorder in the elderly, but we present a unique case of a middle-aged man with a history of T2D on canagliflozin. He was brought to the emergency room (ER) with altered mental status in the setting of severe hyponatremia, managed with timely intervention, and eventually discharged.

Case presentation

A 49-year-old man with a medical history significant for T2D and hypertension was brought into the ER as a trauma notification after a motor vehicle accident. On the day of hospitalization, he had consumed one gallon of water for an outpatient urine toxicology screen (for pre-employment process). He developed acute onset dizziness and altered sensorium while driving that resulted in the accident. He also developed acute urinary retention. Of note, he was experiencing episodic postural dizziness since the initiation of canagliflozin for his diabetes (a month prior to his presentation). His home medications included insulin glargine 10 units daily, metformin 1000 mg twice daily, canagliflozin 100 mg daily, lisinopril 5 mg daily, simvastatin 10 mg daily, and ranitidine 150 mg twice daily. In the ER, he was confused and slightly lethargic but easily arousable and oriented only to himself. His initial Glasgow Coma Scale was 14. The patient’s initial triage vitals were stable (heart rate at 95 bpm, blood pressure 134/82 mmHg, afebrile, and unlabored breathing). There was no evidence of external physical injuries except the examination significant for suprapubic fullness along with tenderness. A Foley catheter was inserted in the ER, and 3 L of clear yellow urine were drained. He had remained confused and drowsy for the first 12 h upon his arrival at the hospital.

Table 1 Laboratory results of the patient during hospitalization.

| Biochemical parameters          | Day 1 | Day 2 | Day of discharge | Reference range          |
|---------------------------------|-------|-------|------------------|--------------------------|
| Serum sodium                    | 118   | 117   | 137              | 135–145 mEq/L            |
| Serum potassium                 | 3.9   | 4.6   | 4                | 3.5–5.0 mEq/L            |
| Serum chloride                  | 74    | 78    | 96               | 98–108 mEq/L             |
| Serum bicarbonate               | 17.1  | 16.4  | 25.8             | 24–30 mEq/L              |
| Blood urea nitrogen             | 20    | 19    | 23               | 5–26 mg/dL               |
| Serum creatinine                | 0.7   | 0.7   | 0.8              | 1–1.5 mg/dL              |
| Serum glucose                   | 187   | 178   | 240              | 70–105 mg/dL             |
| Anion gap                       | 26.9  | 22.6  | 15.2             | ≤13.9 mEq/L              |
| Serum osmolality                | 248   | 224   |                  | 275–295 mOsm/Kg          |
| Serum anti-diuretic hormone (ADH)| 9.1   |       |                  | < 4.3 pg/mL              |
| Serum ketone (qualitative)      | Trace |       |                  |                          |
| TSH                             | 1.08  |       |                  | 0.47–6.90 mIU/L          |
| HbA1c                           | 8.2%  |       |                  | <5.7%                    |
| Urine osmolality                | 632   | 224   | <20              | 50–1200 mOsm/kg          |
| Urine sodium                    | 70    | <20   | <20              | 32–176 mEq/L             |
| Urine potassium                 | 32    | 5     | 9                | 25–125 mEq/L             |
| Urine chloride                  | 32    | <20   | <20              | 110–250 mmolL            |
| Urine creatinine                | 31    | 19    | 51               | 25–350 mg/dL             |
| Urine osmolar excretion         | ~2400 mOsm/12 h | | | |
| Urine drug screen               | Negative | | | |
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(Ref range: 24–30 mEq/L), anion gap (AG) 26.9 mEq/L (Ref range: ≤ 13.9 mEq/L), and serum glucose 187 mg/dL (Ref range: 70–105 mg/dL). Serum osmolality was 248 mOsm/kg (Ref range: 275–295 mOsm/Kg) with positive serum ketones (qualitative assessment). Antidiuretic hormone (ADH) concentration on the day of admission was 9.1 pg/mL (Reference value < 4.3 pg/mL). Urine analysis for glucose was noted to be > 1500 mg/dL. While in the ER, in the setting of his acute altered mental status, a urine toxicology screen was performed to rule out drug intoxication, which was unremarkable. He was found to have severe symptomatic hyponatremia, and euglycemic DKA attributed to his altered sensorium. The diagnosis of euglycemic DKA was established based on elevated AG, reduced serum bicarbonate, and a serum qualitative assessment showing positive ketones in the setting of canagliflozin use.

**Treatment**

While in ER, 3% hypertonic saline was administered via a triple lumen central venous catheter, and the patient was admitted to the medical intensive care unit for further management. Hypertonic saline was stopped intermittently because of rapid sodium correction. His mental status returned to baseline by day 2 at the hospital, and serial blood workups showed rapid sodium correction from 117 to 131 mEq/L within 12 h (Fig. 1). Dextrose (5%) water with serial vasopressin injections was administered for this overcorrection. Initial urine studies on day 1 showed the osmolality of 632 mOsm/kg with urine sodium of 70 mEq/L and chloride of 32 mEq/L. His urine osmole excretion was ~ 2400 mOsm in 24 h. After 3 days of hospitalization, his serum sodium level was normalized. Euglycemic DKA was managed concurrently with intravenous insulin. Interestingly, he continued to have euglycemic glycosuria 5 days after his hospitalization, despite discontinuing canagliflozin, although he was no longer in ketoacidosis.

**Outcome and follow-up**

He was discharged home with temporary discontinuation of canagliflozin and to follow-up as an outpatient for his diabetes care.

**Discussion**

Despite the recent findings that demonstrate the efficacy and benefits of SGLT2i, our report is the first to suggest the development of hyponatremia as another potentially rare and adverse side effect. SGLT2i are oral hypoglycemic agents that inhibit the SGLT-2 protein expressed in the S1 segment of the early proximal convoluted tubules, responsible for 90% of glucose reabsorption (1). SGLT2i can cause as much as 40–80 g/day of urinary glucose loss with normal blood glucose levels, leading to osmotic diuresis and, to a lesser extent causing natriuresis as a direct effect (4). This can constrict the extracellular fluid compartment, triggering the activation of the renin-angiotensin-aldosterone axis and increasing ADH production (5).

Three potential interacting mechanisms are likely to have contributed to our patient’s presentation: (i) osmotic diuresis secondary to SGLT2i use, (ii) appropriately elevated ADH likely triggered by hypovolemia from massive osmotic diuresis, and (iii) excess free water intake in a short period with ongoing osmotic diuresis. As this was our patient’s index visit to the hospital, a pre-hospitalization HbA1c concentration was unavailable. However, the HbA1c measured during his hospitalization

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**Figure 1**

Serum sodium trend of the patient during hospitalization.
was 8.2%, indicating suboptimal glycemic control with an average blood glucose concentration of around 190 mg/dL. In addition, the urine glucose concentration of >1500 mg/dL demonstrated the glucosuric effects of SGLT2i. The patient was noted to have urinary osmole excretion of ~2400 mOsm in 24 h, confirming the diagnosis of osmotic diuresis. ADH concentration on admission was also significantly elevated to 9.1 pg/mL. Although there was no overt clinical evidence of dehydration, including dry mucous membrane, hypotension, tachycardia, and end-organ hypoperfusion, it is evident from history that he did have episodes of postural dizziness, likely pointing towards orthostatic hypotension. The lack of objective evidence for dehydration could likely be in the setting of excess free water intake. We do not believe that his severe hyponatremia was primarily because of excess free water intake since the intake of 3 L of free water in this 70 kg man with acute urinary retention would have decreased the serum sodium to ~125 mEq/L, assuming a baseline of 135 mEq/L. He was not known to have SIADH or hyponatremia in the past; however, we did not have a baseline serum sodium within 48 h of his presentation. It has been shown in the literature that acute urinary retention with bladder distention can precipitate SIADH but usually resolves once the bladder is decompressed. In our patient, despite catheterization, his serum sodium remained low. Instead, it worsened to 117 mEq/L on day 2 of hospitalization (Table 1). Furthermore, the initial urine assessment showed a spot urine sodium concentration of 70 mEq/L, still alluding to the possibility of an underlying SIADH vs natriuretic effects of SGLT2i. However, prompt discontinuation of canagliflozin and initiation of treatment led to an immediate correction of urine sodium to <20 mEq/L (on day 2), indicating a clinical scenario consistent with osmotic diuresis and not SIADH. As far as urinary retention was concerned, the patient did not have any prior history of enlarged prostate or voiding difficulties. Polyuria may have precipitated acute urinary retention secondary to ongoing diuresis and free water intake, unmasking the underlying bladder outlet obstruction. We believe that our patient’s persistent severe hyponatremia was primarily driven by significant osmotic diuresis with appropriate ADH secretion from SGLT2i potentiated by acute bladder distention. He was discharged with temporary discontinuation of canagliflozin, but he failed to follow up as an outpatient.

The Food and Drug Administration has issued warnings on urinary tract infections and ketoacidosis with SGLT2i (6). Based on clinical trials, hyponatremia with SGLT2i is not reported as a significant adverse effect. Literature elucidating the effects of this class of medication on renal sodium and water handling is minimal. As glucosuria leads to osmotic diuresis and consequently increased free water excretion, the recent completion of the SAND and the DIVE trials has provided interesting data for the hypothesis that SGLT2i may help SIADH patients without significant adverse effects (7, 8). However, these studies’ key limitations, including the absence of free-water clearance measurements, a very short treatment period, and the possibility of undiagnosed heart failures, suggest caution in using SGLT2i for SIADH (2).

SGLT2i is used as an add-on therapy and, in recent times, has increasingly been used as a first-line treatment for T2D and in treating heart failure patients even without diabetes (9, 10). Given its multiple cardiovascular and metabolic benefits, it is also vital to understand the physiology of its various adverse effects, including euglycemic DKA and osmotic diuresis, as these could potentially lead to severe electrolyte disturbances. However, studies demonstrating a comprehensive understanding of SGLT2i-related electrolyte derangements are warranted. Any indication of symptoms suggestive of volume depletion and excessive osmotic diuresis should prompt appropriate evaluation and careful consideration of dose reduction or even temporary discontinuation of the medication. Though our case report has its limitation in establishing a direct causal link between SGLT2i and hyponatremia, it presents a unique observation of a potential rare side effect of the drug that we believe would benefit clinicians.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
This work did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Patient consent
Every attempt was made to contact patient or family to obtain consent however we were unable to reach patient or family to obtain consent. As discussed with the journal, this report ensures presenting “de-identified patient data.” The journal editorial office approved this before submission.

Author contribution statement
M D designed the study and wrote the first draft; S N revised the draft and edited the paper; I M helped in data interpretation; S M conceptualized and supervised the study.
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