

Severe hypercalcemia and hypernatremia in a patient treated with canagliflozin

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Summary

Drugs that inhibit the sodium-glucose co-transporter-2 (SGLT2) are an exciting novel, insulin-independent treatment for diabetes that block glucose reabsorption from the proximal tubules of the kidney, leading to increased glucose excretion and lower blood glucose levels. Inhibition of SGLT2 activity also reduces sodium reabsorption, which together with glycosuria produces a mild diuretic effect with the potential for dehydration and hyperkalemia. We report on a 60-year-old man with uncontrolled type 2 diabetes treated with insulin, glimepiride, metformin and canagliflozin, who was admitted with altered mental status after a syncopal episode. He had a 1-week history of ingestion of Tums for heartburn followed by poor appetite and lethargy. Laboratory work-up showed acute kidney injury, diabetic ketoacidosis (DKA), and parathyroid hormone-independent severe hypercalcemia of 17.4 mg/dl. DKA resolved with insulin treatment, and saline hydration led to improvement in hypercalcemia and renal function over 48 h, but was accompanied by a rapid increase in the serum sodium concentration from 129 to 162 mmol/l despite changing fluids to 0.45% saline. Urine studies were consistent with osmotic diuresis. Hypernatremia was slowly corrected with hypotonic fluids, with improvement in his mental status over the next 2 days. This is the first report of hypercalcemia associated with the use of a SGLT2 inhibitor. Although the exact mechanism is unknown, canagliflozin may predispose to hypercalcemia in patients ingesting excessive calcium because of dehydration from osmotic diuresis, with reduced calcium excretion and possible increased intestinal calcium absorption. Saline therapy and osmotic diuresis may lead to hypernatremia from electrolyte-free water loss.

Learning points:

- Canagliflozin, an SGLT2 inhibitor, may cause hypercalcemia in susceptible patients.
- Although the exact mechanisms are unknown, dehydration from osmotic diuresis and increased intestinal calcium absorption play a role.
- Close monitoring of serum calcium levels is recommended in patients treated with SGLT2 inhibitors who are elderly, have established hypercalcemia, or take oral calcium supplements.
- Saline therapy and osmotic diuresis may lead to hypernatremia from electrolyte-free water loss in susceptible patients.

Background

Sodium-glucose co-transporter-2 (SGLT2) inhibitors are a novel, insulin-independent treatment for diabetes that block glucose absorption in the proximal tubules of the kidney, increasing glucose excretion and lowering blood glucose levels. The European Medicines Agency (EMA) and

the U.S. Food and Drug Administration have approved canagliflozin and dapagliflozin. Empagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, and ertugliflozin have completed or are in phase III trials (1). Known side effects of canagliflozin include genital mycotic infections,



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urinary tract infections, and dehydration especially in the elderly (1) (2) (3). Hyperkalemia was the most common electrolyte abnormality in phase III trials, with non-significant changes in calcium and sodium levels (4). We present a patient with type 2 diabetes (T2DM) treated with canagliflozin who developed severe hypercalcemia and subsequent hyponatremia following excessive calcium ingestion and diabetic ketoacidosis.

Case presentation

A 60-year-old man with T2DM treated with insulin, glimepiride, metformin and canagliflozin, as well as primary hypothyroidism and hypertension, was admitted to the hospital with altered mental status after a syncopal episode. He had ingested 8–10 Tums daily for heartburn for 1 week, followed by poor appetite and lethargy. Past medical records revealed normocalcemia and normal renal function.

Investigation

He had severe hypercalcemia of 17.4 mg/dl (reference range 8.9–10.3), a high blood urea nitrogen level of 37 mg/dl (reference range 6–20), high creatinine of 1.91 mg/dl (reference range 0.64–1.27), low normal phosphorus of 2.7 mg/dl (reference range 2.7–4.7), elevated glucose of 407 mg/dl (reference range 70–100), low bicarbonate of 12.1 mmol/l (reference range 24–28), and an elevated β -hydroxy butyrate level of 9.2 mmol/l (reference range 0.02–0.27), indicating diabetic ketoacidosis. Further work up included low levels of parathyroid hormone (PTH) of 11 pg/ml (reference range 12–88), 25-hydroxy vitamin D of 24 ng/ml (reference range 30–100), 1,25-dihydroxy-vitamin D of 13 pg/dl (reference range 18–72), and a normal level of thyroid-stimulating hormone of 1.54 μ U/ml (reference range 0.5–5.7); serum protein electrophoresis, and parathyroid hormone-related protein of 22 pg/ml (reference range 14–27).

Treatment

The patient was treated with calcitonin and pamidronate, i.v. hydration with normal saline, and i.v. followed by s.c. insulin, with resolution of diabetic ketoacidosis over 24 h.

Outcome and follow-up

Hypercalcemia and renal function improved over 48 h, but the serum sodium concentration increased from 129

to 162 mmol/l despite changing i.v. fluids to 0.45% saline (Fig. 1). Unexpectedly, the urine sodium was <10 meq/l, with high urine glucose (>1000 mg/dl) and osmolality (782 mOsm/kg) indicating osmotic diuresis. Serum osmolality was 352 mOsm/kg. Hyponatremia slowly corrected with hypotonic i.v. fluids and free water through a nasogastric tube with improvement in his mental status over 2 days. Urinary glucose excretion, 4 days after discontinuation of canagliflozin, remained elevated at >1000 mg/dl even with resolution of hyperglycemia. Urine output was ~2 l/day throughout.

Discussion

Canagliflozin was the first SGLT2 inhibitor approved for treatment of T2DM, and the experience is the greatest with this drug. This class of drugs has recently gained attention due to a unique insulin-independent mechanism of action, weight loss, low risk of hypoglycemia, and oral route of administration. The most common side effects are genital mycotic infections (vaginal yeast infection/vulvovaginal candidiasis) and urinary tract infections. The osmotic diuresis of SGLT2 inhibitors can also cause a reduction in intravascular volume leading to orthostatic hypotension (1) (2) (3). Phase three studies showed small potassium elevations especially in patients with reduced glomerular filtration rate (GFR) (3). To our knowledge, hypercalcemia has not been reported as a side effect.

We propose a multi-factorial mechanism for the hypercalcemia in our case. First, he ingested excessive calcium. Second, osmotic diuresis, poor oral intake and hyperglycemia led to dehydration, which exacerbated hypercalcemia. Hypercalcemia has been reported in DKA in a child with severe metabolic acidosis, acute renal failure and rhabdomyolysis. DKA may contribute to

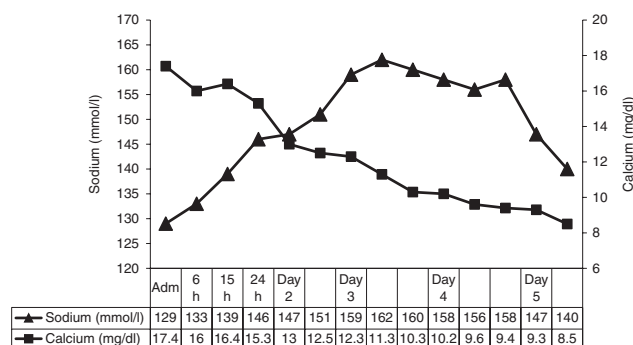


Figure 1
Sodium and calcium levels during hospitalization.

hypercalcemia due to severe metabolic acidosis along with insulin deficiency (5). Lastly, intestinal and urinary calcium absorption may have been increased due to inhibition of SGLT1 by the drug. In preclinical studies, canagliflozin reduced PTH and calcitriol levels, and increased urinary calcium excretion, indicating a tendency for PTH-independent hypercalcemia. This was explained by inhibition of intestinal SGLT1 leading to carbohydrate malabsorption followed by decreased pH and increased absorption of calcium. In clinical studies, however, although canagliflozin transiently reduced intestinal glucose absorption, there was no malabsorption based on tracer studies and the hydrogen breath test. No significant effects on serum calcium, PTH, calcitriol or urinary calcium excretion were observed in phase I and II trials (3) (6). In a phase III study, although no significant differences were found in serum calcium levels, hypercalcemia or a >10% increase in serum calcium was seen in 0.7, 1.0 and 1.5% of patients treated with placebo, or canagliflozin 100 mg or 300 mg, respectively, and 2, 0.9 and 0.9% of those with low GFR (4).

Severe hyponatremia following saline hydration may be due to osmotic diuresis, which can cause hyponatremic dehydration due to electrolyte-free water loss (7) and possibly secondary hyperaldosteronism from intravascular volume depletion. Hyponatremia at presentation has been reported in children with DKA. Continued loss of hypotonic urine is thought to cause increase in sodium concentrations and severe dehydration when the process of osmotic diuresis is prolonged (8). Also, hyperglycemia and hyperinsulinemia have been shown to increase sodium levels by activating red cell sodium-hydrogen antiporter (9). The mechanism by which SGLT2 inhibitors affect free water loss deserves further study.

Conclusion

This is the first report of hypercalcemia associated with a SGLT2 inhibitor. Although the exact mechanisms are unclear, these drugs may predispose to hypercalcemia. Saline therapy and osmotic diuresis may lead to hyponatremia from electrolyte-free water loss.

Note added in proof

After this paper was accepted for publication, the U.S. Food and Drug Administration (FDA) issued a warning that SGLT2 inhibitors may lead to ketoacidosis in patients with type 2 diabetes.

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.

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Patient consent

Written informed consent has been obtained from the patient for publication of the submitted article and accompanying images.

Author contribution statement

A Kaur: Manuscript writing and Endocrinology fellow involved in patient care during the hospitalization. S J Winters: Manuscript review and the consultant endocrinologist.

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