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Dapagliflozin- Induced Severe Ketoacidosis Requiring Hemodialysis

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Abstract

The availability of novel classes of medication for the treatment of type 2 Diabetes mellitus (type 2 DM) provides doctors with options to choose individualized treatments based on patient and agent characteristics beyond metformin therapy, as per current guidelines. Independent of impaired beta-cell function and insulin resistance, sodium glucose cotransporter type 2 (SGLT2) inhibitors represent a different treatment strategy for reducing plasma glucose levels and glycosylated hemoglobin concentrations by increasing urinary glucose excretion through reduced renal glucose reabsorption. However, metabolic acidosis may arise with such novel drugs through a different mechanism, which can produce a life-threatening condition requiring hemodialysis. Here, we present the case of a 48-year-old male type 2 diabetic patient who presented with vague symptoms of general weakness, nausea, malaise and shortness of breath over several days. He was started on dapagliflozin one month before presentation. His lab test showed a near-normal level of glucose with severe anion gap metabolic acidosis and ketoacidosis, which was resistant to bicarbonate therapy and required hemodialysis. All of the findings were consistent with dapagliflozin-induced ketoacidosis.

Keywords

Dapagliflozin, SGLT2 inhibitors, Metabolic acidosis, Hemodialysis

Introduction

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a new oral hypoglycemic drugs class indicated for the treatment of type 2 diabetes mellitus. They increase the urinary excretion of glucose, as mechanism of action. Euglycemic diabetic ketoacidosis (DKA) is becoming a recognized complication of SGLT2 inhibitors [1]. The presentation is usually atypical, with normal blood sugar that may lead to a delay in diagnosis and management and hence, the severity at presentation. Management includes stopping the offending drug and administering intravenous fluid and insulin. Here, we present the case of a 48-year-old man who was admitted to the ICU with severe anion gap metabolic acidosis and ketoacidosis with normal glucose levels. The findings were consistent with dapagliflozin-induced ketoacidosis that required hemodialysis to close the anion gap.

Case History

A 48-year-old male patient with an eight-year history of Type 2 diabetes mellitus and a history of dyslipidemia presented to the emergency department with vague symptoms of general weakness, malaise, nausea, and shortness of breath of one week duration. He denies vomiting, fever, or diarrhea. His regular medications included metformin 1000 mg twice daily, glimepiride 4 mg once daily and insulin glargine 20 units at night. Because of uncontrolled blood sugar as evidenced by high hemoglobin A1C (HbA1c) levels of 10.9%, he was started on dapagliflozin 5 mg once daily one month before recent presentation to the emergency room (ER). He did not stop his insulin glargine (20 units once at night) but he stopped glimepiride by himself to reduce number of tablets that he is taking. He denied alcohol or nonprescription drug intake.

Physical examination was remarkable for obesity (body mass index 31 kg/m2), tachycardia (112 bpm), tachypnea (RR 28/minute), blood pressure (90/60) and dry oral mucosa. His oxygen saturation was 98% on room air. Chest examination was normal and the remainder of the examination was unremarkable.

On presentation, he had a blood glucose level of 142 mg/dL (normal 70-140) and normal kidney function (eGFR 103- estimated by CKD-EPI). He also had severe metabolic acidosis with a pH of 7.006 (normal 7.35-7.45), an anion gap of 35 (normal 8-16) and a serum bicarbonate level of 6 mmol/L (normal 22-28). His lactate level was normal and his hydroxybutyrate level was 10 mmol/L (normal 0.4-0.5 mmol/L). Serum sodium was 140 mEq/L, serum potassium of 4.5 mEq/L and serum osmolality 295 mosm/kg. Urine analysis showed no evidence of infection and urine electrolytes were within normal limit. Urine osmolality of 150 mosm/kg. WBC in complete blood count was 6.000 cells/mcL. C-reactive protein was in normal range (5 mg/L).

Testing for toxic alcohols including methanol, ethylene glycol and diethylene glycol was negative. There was no osmolar gap.

Given his severe anion gap metabolic acidosis and ketoacidosis with a euglycemic profile, he was admitted to the ICU and started on infusions of intravenous fluid, insulin (up to 10 units/hr) along with dextrose to prevent hypoglycemia (glucose was maintained around 100 mg/dl), and bicarbonate. His clinical status deteriorated and he became semiconscious with severe acidotic breathing. Lab tests after a few hours of treatment showed no improvement despite bicarbonate infusion. He received hemodialysis session of 8 hours (continuous veno-venous hemodiafiltration with dose of 30 mL/kg/h) until the acidosis was corrected. Based on the above finding of high anion gap metabolic acidosis, with no obvious precipitating factor of ketoacidosis like infection or starvation, euglycemic ketoacidosis

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induced by dapagliflozin was considered. Insulin treatment was continued until the ketones were cleared, while also maintaining the serum glucose levels. His anion gap normalized in 48 hours, with the improvement of both symptoms and laboratory data.

Discussion

Aiming for improved glycemic control with subsequent reduction of diabetic complications, sodium glucose cotransporter type 2 (SGLT2) inhibitors are a new class of medication introduced recently with a novel mechanism of action that addresses factors other than insulin resistance and beta cell dysfunction.

In glucose homeostasis, the kidney plays an important role through gluconeogenesis and reabsorption of filtered glucose [2]. The release of renal glucose is increased in both the postabsorptive and postprandial states in patients with type 2 DM [2-4]. Approximately 160 to 180 grams of glucose are filtered by the kidneys each day [5]. Using energy provided by a transmembrane sodium gradient, renal proximal tubules are responsible for 90% of glucose reabsorption, mediated by sodium glucose cotransporter 2 (SGLT2) [5,6].

Selective inhibition of SGLT2 in the renal proximal tubules promotes renal glucose excretion, thereby lowering plasma glucose levels without affecting other metabolic processes [7].

However, this class of medication has been associated with ketosis, ketoacidosis and diabetic ketoacidosis, mostly in the euglycemic state [8]. The absence of obvious hyperglycemia despite the development of ketoacidosis can lead to delayed diagnosis since the patients usually monitor serum glucose on a daily basis.

Several factors have been involved in the pathophysiologic mechanism of ketoacidosis with SGLT2 inhibitors, particularly the decreased insulin-glucagon ratio. The reduction of insulin secretion from pancreatic beta-cells that noted after SGLT2 inhibitors is a result of lowering blood glucose levels by increasing urinary glucose excretion. The decrease in blood insulin levels results in a reduction of the antilipolysis action of insulin and increase the production of free fatty acids, which are converted to ketone bodies by beta-oxidation in the liver [9]. Nonselective inhibitors of SGLT1/SGLT2 increase reabsorption of acetoacetate in the renal tubules by increasing the sodium concentration in the renal tubular fluid and thereby increasing ketone reabsorption, mediated by an electrochemical gradient [10]. Another factor of ketogenic effects of SGLT2 inhibitors can be explained by direct pancreatic stimulation. SGLT2 is expressed on alpha cells of pancreatic islets, which can lead to increased serum levels of glucagon post-administration [9]. The Possible triggering factors of SGLT2 inhibitors ketoacidosis that were identified in the case reports include urosepsis and infection, trauma, reduced fluid or caloric intake and decreased insulin dose [10]. Including hypoinsulinemia, other factors contribute to the development of high anion gap metabolic acidosis detected in case reports are acute renal failure, hypovolemia, history of alcohol intake, hypoxemia and reduced oral intake. Half of the cases did not identify a precipitating factor for DKA [11].

Iipragliflozin, dapagliflozin, luseogliflozin, tofogliflozin, canagliflozin and empagliflozin are the SGLT2 inhibitors on the market in Japan. A total of 28 cases of DKA or ketoacidosis had been reported till July 2015 [11]. All the cases had blood glucose levels under 200 mg/dL except for 2 cases with blood glucose levels over 300 mg/dL. One case had a history of distal pancreatectomy due to cystadenoma and another case occurred after an attack of pancreatitis [11].

The FDA Adverse Event Reporting System (FAERS) database reported 20 cases of diabetic ketoacidosis (DKA), ketoacidosis or ketosis in patients managed with SGLT-2 inhibitors in the period between March 2013 and June 6, 2014. Most of the DKA cases were reported in patients with type 2 DM. A high anion gap metabolic acidosis accompanied by elevated blood or urine ketones and normal glucose levels was reported in the majority of reported cases. The glucose levels were only mildly elevated at less than 200 mg/dL in some reports. These findings are not typical of diabetic ketoacidosis [1]. The European Medicines Agency had also reported 101 cases of ketoscidosis in patients treated with SGLT-2 inhibitors for type 2 DM worldwide as of May 19, 2015 [8]. According to several studies, the overall frequency of reported events suggestive of DKA was less than 0.1% [12]. Two weeks (range: 1 to 175 days), was the median time to onset of symptoms following enrollment in drug therapy [1].

A large adverse event analysis has been published, including 17,596 patients with DM II from randomized studies of canagliflozin through May 2011 [12]. The incidence of serious adverse events of DKA and related events was 0.07% (12 patients). All of the cases responded well to intravenous fluid and bicarbonate infusion. One case deteriorated and did not respond to treatment, but responded to hemodialysis [12].

The withdrawal of insulin or insulin secretagogues at the onset of treatment with an SGLT2 inhibitor, may appears to be a risk factor for the development of euglycemic DKA [13].

In our case, the traditional treatment of high anion gap metabolic ketoacidosis induced by dapagliflozin in a diabetic patient with a nearly normal level of serum glucose included Intravenous fluid, insulin infusion with backup dextrose and bicarbonate infusion for nearly 8-10 hours. Unfortunately, neither clinical or laboratory improvement was observed. However, as severe metabolic acidosis with delay response to treatment can become a life-threatening condition, hemodialysis was considered as an option to treat metabolic acidosis induced by dapagliflozin. After the session of hemodialysis, traditional treatment continued until the ketones were cleared while maintaining the serum glucose levels. His anion gap normalized in 48 hours with the improvement of both symptoms and laboratory data.

An atypical presentation of SGLT2 inhibitor-induced diabetic ketoacidosis with near-normal blood sugar can delay diagnosis and treatment. Healthcare professionals should, therefore, consider the possibility of ketoacidosis in patients taking SGLT2 inhibitors who have symptoms consistent with the acidosis even with near normal blood glucose. In our case, the patient developed nonspecific complaints of 1-week duration with laboratory results suggestive of high anion gap metabolic acidosis, ketoacidosis with almost normal serum glucose level and normal toxic alcohols level. These factors may contribute to the severity of the disease upon presentation to the hospital.

Learning Points

1. Physicians should consider the possibility of ketoacidosis in patients receiving SGLT2 inhibitors and presenting with suggestive symptoms even if blood sugar levels are not elevated.
2. The delay in diagnosing ketoacidosis in diabetic patient on SGLT2 inhibitors can be due to atypical presentation, including normal blood glucose level.
3. If the diagnosis is suspected or confirmed, treatment with SGLT2 inhibitors should be stopped immediately and should not be restarted unless another cause for the ketoacidosis is identified and resolved.

In severe cases of ketoacidosis induced by SGLT2 inhibitors, hemodialysis can be an option in addition to standard treatment.

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