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Case Report

A Case of SGLT2 Inhibitor-Associated Euglycemic Diabetic Ketoacidosis Following Coronary Artery Bypass Surgery

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ABSTRACT

Objective: Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a novel group of oral hypoglycemic agents with multiple proven beneficial effects. However, their use has been associated with euglycemic diabetic ketoacidosis (DKA), typically triggered by risk factors such as acute illness, surgery, and decreased calorie intake. Therefore, it is recommended that patients discontinue SGLT2 inhibitors at least 24 hours before surgery to minimize this risk. We report a case of a postoperative euglycemic DKA in a patient who had discontinued SGLT2 inhibitor therapy 48 hours prior to surgery.
Methods: We describe the clinical course of a patient with type 2 diabetes mellitus on empagliflozin therapy who was referred for coronary artery bypass graft surgery.
Results: A 60-year-old man with type 2 diabetes mellitus developed euglycemic DKA a few hours after coronary artery bypass graft surgery. Laboratory results showed acute postoperative elevated anion gap metabolic acidosis with normal glucose and elevated blood ketone levels. It was later revealed that the patient was treated as an outpatient with empagliflozin; the last dose was taken 48 hours prior to his procedure.
Conclusion: Euglycemic DKA can occur postoperatively in patients with a history of SGLT2 inhibitor use, even 48 hours after the discontinuation of therapy. This case highlights the need to revisit the recommended time to discontinue these agents, specifically prior to major surgery, because their pharmacokinetic effects may persist after 24 hours of discontinuation, putting patients at risk for postoperative euglycemic DKA.

Introduction

By 2014, and within 2 years, 3 sodium-glucose cotransporter 2 (SGLT2) inhibitors, namely canagliflozin, dapagliflozin, and empagliflozin, were approved by the U.S. Food and Drug Administration as a novel class of medications for the treatment of diabetes mellitus (DM). SGLT2 inhibitors lower serum glucose levels by blocking glucose reabsorption in the kidneys through a mechanism independent of insulin.[1,2] Multiple studies have revealed that this class of medications reduces the risk of hypoglycemia, promotes weight loss, reduces cardiovascular risk, and slows the progression of albuminuria, which has resulted in a significant increase in their use over the past few years.[3,4] In the U.S., SGLT2 inhibitors are only approved for the treatment of type 2 DM due to safety concerns in type 1 DM. However, off-label use in type 1 DM is common.[5] SGLT2 inhibitors have been associated with an increased risk of diabetic ketoacidosis (DKA), which is characteristically associated with paradoxical normal or slightly elevated serum glucose levels, referred to as euglycemic DKA. Between March 2013 and June 2014, 20 cases of SGLT2-related euglycemic DKA were reported, causing the U.S. Food and Drug Administration to issue a safety warning.[5,6]

Some described precipitating factors for SGLT2 inhibitor-related euglycemic DKA include acute illness, surgery, a low-calorie intake, and excessive alcohol use.[1,3,4] Therefore, the American Association of Clinical Endocrinologists and the American College of Endocrinology advise that patients who are to undergo surgery should stop taking their SGLT2 inhibitors at least 24 hours before surgery to reduce the risk of euglycemic DKA in the postoperative period.[5]

We report a case of euglycemic DKA occurring postoperatively in a patient who stopped SGLT2 inhibitor therapy 48 hours before surgery.

Abbreviations: CABG, coronary artery bypass graft; DKA, diabetic ketoacidosis; DM, diabetes mellitus; SGLT2, sodium-glucose cotransporter 2 inhibitor.

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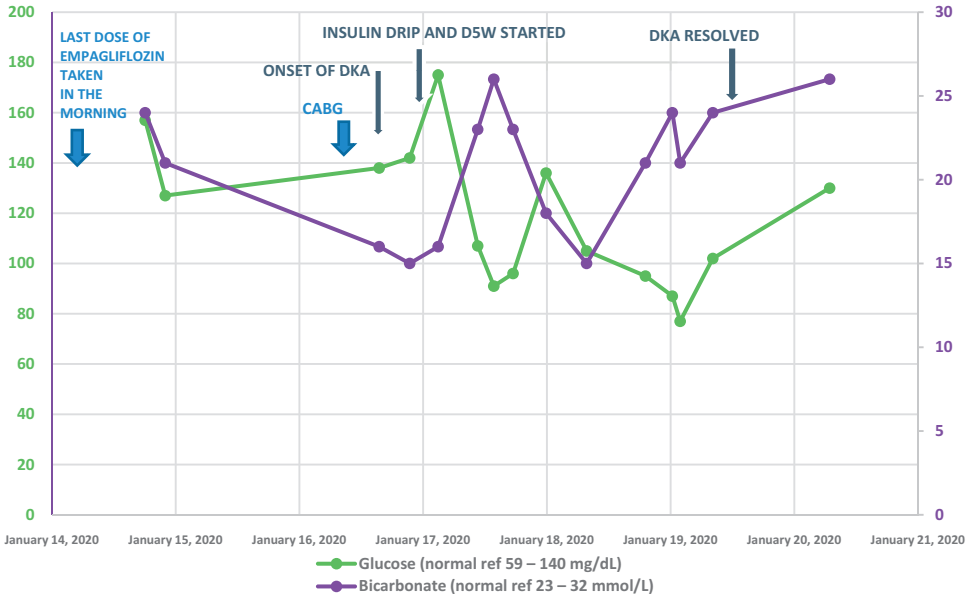

Fig. Trend of bicarbonate and glucose levels from the onset of diabetic ketoacidosis to the initiation of insulin drip/D5W infusion, and the resolution of ketoacidosis.

Case Report

A 60-year-old man was referred to our hospital for coronary artery bypass graft (CABG) surgery following cardiac catheterization at the referring hospital, which revealed triple-vessel disease. His medical history was significant for coronary artery disease, hypercholesterolemia, and type 2 DM diagnosed 15 years previously. He was taking glimepiride (2 mg twice daily), metformin (1000 mg twice daily), subcutaneous semaglutide (0.25 mg weekly), and empagliflozin (10 mg orally daily). The latter 2 medications were started around a year prior to presentation at our hospital but were not on the medication list that he provided on admission.

On arrival at our hospital, he was asymptomatic, and vital signs were within normal limits. Laboratory testing revealed a white blood cell count of 7.6 K/μL (reference range: 4.8-10.8 K/μL), hemoglobin of 14.6 g/dL (14-18 g/dL), serum glucose of 157 mg/dL (59-140 mg/dL), bicarbonate of 24 mmol/L (23-32 mmol/L), anion gap of 12 mmol/L (3-11 mmol/L), troponin of 0.09 ng/mL (0.00-0.02 ng/mL), and glycated hemoglobin of 9.6% (81 mmol/mol). Urinalysis revealed glucosuria of >1000 mg/dL and ketonuria of 15 mg/dL. His oral antihyperglycemic medications were withheld, and he was placed on a subcutaneous insulin regimen for inpatient glucose control.

On the third day (around 42 hours) of admission, the patient underwent CABG surgery. Within just a few hours following surgery, the patient developed elevated anion gap metabolic acidosis with an arterial pH of 7.275, a reduced bicarbonate level of 15 mmol/L, and an increased anion gap of 25 mmol/L. The serum glucose level was normal, at 138 mg/dL (59-140 mg/dL), but the β-hydroxybutyric acid level, which was measured to evaluate the etiology of the acidosis, was elevated at 6.52 mmol/L (0.02-0.27 mmol/L). Hence, a diagnosis of euglycemic DKA was made, and the patient was started on an intravenous insulin drip with an infusion of 5% dextrose in water. He also required transient 24-hour intravenous norepinephrine for hypotension. Ketoacidosis resolved over the next 2 days (Fig.), and he transitioned to subcutaneous insulin (ie, basal and premeal insulin) with adequate glycemic control.

The etiology of elevated anion gap metabolic acidosis was initially unclear considering the patient's normal glucose level, normal kidney function test results, normal lactic acid level, and negative results for acetaminophen, salicylate, and blood alcohol. Elevated ketone levels and the history, subsequently obtained, of home SGLT2 inhibitor therapy helped to establish the diagnosis of euglycemic DKA. Further investigation revealed that the patient had been on Invokana (canagliflozin) for many years and was switched to Jardiance (empagliflozin) about a year before presentation at our hospital. His last dose of Jardiance was the morning of his transfer to our hospital, which was about 48 hours before the CABG surgery. The remainder of his hospital stay was uneventful. At discharge, he was educated on the need to discontinue SGLT2 inhibitors at least 3 days before any procedure requiring prolonged fasting.

Discussion

Most cases of SGLT2 inhibitor-related euglycemic DKA seem to have a precipitating factor. Common scenarios include infection, surgery, reduction or discontinuation of insulin, decreased oral intake, dehydration, and excessive alcohol use.[1,3,4] A major cardiothoracic procedure, along with prolonged fasting on the day of surgery, were likely precipitants of the euglycemic DKA in our patient.

The precise mechanism by which SGLT2 inhibitors induce euglycemic DKA is not fully understood. A possible explanation is that SGLT2 inhibitors lower serum glucose levels through the inhibition of glucose reabsorption in the kidneys, leading to decreased insulin release and increased glucagon secretion by the pancreatic cells, both of which stimulate the production of ketones via the beta-oxidation of free fatty acids in the liver.[1,4,7] Additionally, SGLT2 inhibitors directly stimulate glucagon release from the pancreas, which feeds back to more ketone production.[4,7] In normal physiology, glucose stimulation of insulin release by beta cells, coupled with subsequent insulin-induced inhibition of glucagon secretion, leads to a high insulin-to-glucagon ratio in the pancreatic venous flow and portal circulation, promoting glycogenesis. The renal glucose loss observed with SGLT2 inhibitors decreases insulin stimulation and the insulin-to-glucagon ratio, leading to decreased glycogenesis, and in the setting of prolonged glucose deprivation, increased gluconeogenesis and glycogenolysis. The lack of circulating glucose results in an increased production of ketoacids. Another possible mechanism of ketoacidosis is an SGLT2

inhibitor-induced starvation state that results in increased renal reabsorption of ketone bodies.[1,4] Eventually, there will be a buildup of ketosis in the presence of lower glucose levels, which is exacerbated in acute stress or when there is a low availability of carbohydrates.

The American Association of Clinical Endocrinologists and the American College of Endocrinology recommend discontinuing SGLT2 inhibitors at least 24 hours before elective surgery.[5] However, because the SGLT2 inhibitors' half-lives range from 11 to 17 hours, their pharmacodynamic effects may persist despite discontinuing the medication.[3] Our patient stopped empagliflozin intake 48 hours before his CABG but still developed postoperative euglycemic DKA. Another factor that could lower the threshold of euglycemic DKA could be the anticipated stress levels associated with the procedure, which are typically extremely elevated in cardiothoracic surgeries.

A delay in diagnosing euglycemic DKA is common because of the normal to mildly elevated glucose levels (eg, 138 mg/dL in our patient). It also becomes more challenging in the postoperative period, during which direct surgical complications can be mistaken as the cause of acidosis and may lead to unnecessary interventions.[3] The diagnosis was also more challenging in our patient because the history of SGLT2 inhibitor use was not obtained on admission, which emphasizes the importance of a detailed medication history.

More studies are needed to guide the optimal timing of the discontinuation of these agents before elective procedures to reduce the risk of developing euglycemic DKA. An interesting finding in our patient was the presence of significant glycosuria despite normal blood glucose levels on admission. This discordance is probably indicative of a persisting SGLT2 inhibitor effect and possible increased risk of acidosis in a fasting state. A teaching point of our case would be to highlight to providers the alarming nature of persistent glycosuria in a patient treated with an SGLT2 inhibitor and undergoing a procedure. Whether glycosuria is reflecting uncontrolled hyperglycemia or a persistent SGLT2 receptor blockade, it should warrant close monitoring of glucose levels and acid-base status following a prolonged fasting state or procedure.

Conclusion

Euglycemic DKA can occur postoperatively in patients with a history of SGLT2 inhibitor use, even 48 hours after discontinuing therapy. With the rapidly expanding use of SGLT2 inhibitors to include, in addition to diabetes, cardiac and renal indications, both providers and patients should be aware of this complication and should consider discontinuing SGLT2 inhibitors at least 48 to 72 hours prior to major surgery. Persistent glycosuria, despite discontinuation of the medication, should warrant closer monitoring for metabolic acidosis following procedures. Detailed medication history and testing for ketones in the blood are imperative to prevent a delay in insulin therapy. Preventive perioperative therapy with both glucose and insulin in patients recently treated with SGLT2 inhibitors might be an effective strategy.

Disclosure

The authors have no multiplicity of interest to disclose.

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