CLINICAL VIGNETTE

Euglycemic Diabetic Ketoacidosis following Initiation of Sodium-Glucose Cotransporter 2 Inhibitor

Laura King, DO

A 44-year-old male with type 2 diabetes diagnosed five years prior, mixed hyperlipidemia, and hepatic steatosis presented for diabetes follow up with his primary care doctor. Routine labs were checked, and HgbA1c was elevated at 8.7%, increased from previous levels of 8.1% three months prior, and 7.2% one year prior. The patient was taking metformin 1,000 mg BID. Due to increasing HgbA1c level despite medication adherence and healthy diet and exercise, additional diabetic treatment was discussed. A mutual decision was made to start daily empagliflozin 10 mg. Approximately two weeks after starting empagliflozin, the patient returned after noting mood swings, insomnia, low back and flank pain. The patient was instructed to hold the medication given these new symptoms, and a basic metabolic panel was ordered to assess kidney function, and check electrolyte, anion gap, and glucose levels.

The next day, prior to the patient completing the lab ordered, he presented to the emergency department (ED) with nausea, vomiting, and poor PO intake in addition to worsening of the previously noted symptoms. In the ED, labs revealed leukocytosis (WBC 22.9 x10E3/uL) (N 4.5-10 x 10^3 cells/uL), hyponatremia (Na 131 mmol/L) (N 136-144 mmol/L), hyperglycemia (229 mg/dL) (N 64-100 mg/dL), high creatinine (1.81 mg/dL) (N 0.8-2.3 mg/dL), high anion gap (20 mmol/L) (N 4-12 mmol/L), high beta hydroxybutyrate (6.21 mmol/L) (N <0.5 mmol/L), normal lactic acid (1.4 mmol/L) (N 0.5-2.2 mmol/L), low bicarbonate (total CO2 8 mmol/L) (N 23-29 mmol/L, and arterial blood gas (ABG) with low pH 7.19. Chest x-ray showed no acute cardiopulmonary process. He was started on intravenous (IV) fluids, insulin drip, and empiric antibiotics. He was admitted to the intensive care unit (ICU) for further management of diabetic ketoacidosis protocol. His labs normalized, including resolution of acute kidney injury and normalization of anion gap. He was titrated off of IV insulin. His COVID-19 test came back positive, although the patient did not require any treatment as he never developed any hypoxia or respiratory symptoms. He was discharged from the hospital on insulin glargine and empagliflozin was discontinued.

Post hospital discharge, he established care with an endocrinologist for further management of his type 2 diabetes. His diabetes was well controlled with further titration of insulin glargine and continuation of metformin, with his HgA1c going down to 6.3%.

Discussion

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are primarily used for management of type 2 diabetes. Their mechanism of action involves increasing urinary excretion of glucose by inhibiting proximal tubular reabsorption of glucose in the kidney. In addition to their efficacy in the treatment of diabetes, they have also been shown to be beneficial in decreasing the progression of diabetic kidney disease as well as reducing the risk of cardiovascular events. However, SGLT2 inhibitors are the only group of diabetes medications that increase risk for diabetic ketoacidosis (DKA).[1]

DKA is diagnosed by a combination of hyperglycemia, anion gap metabolic acidosis, and ketonemia. Most commonly, the serum glucose is between 350 to 500 mg/dL, although it may exceed 1,000 mg/dL in some cases.[2] It is distinguished from other causes of high anion gap acidosis by ruling out lactic acidosis associated with metformin. Euglycemic DKA may be seen in cases where the glucose is less than 250 mg/dL and is commonly seen in patients who have been treated with insulin prior to arriving in the ER, pregnant women, patients with poor oral intake, and with SGLT2 inhibitors.[2] The relatively normal glucose in these cases can sometimes cause a delay in diagnosis of DKA.

Although DKA is not a common adverse event in patients treated with SGLT2 inhibitors, the FDA issued a warning in May 2015 that this drug class may increase DKA risk.[3] One cohort study reported a twofold increased risk of DKA with SLGT2 inhibitors compared to GLP1 receptor agonists.[4] Similarly, an analysis of a claims database from commercially insured patients in the United States reported rates of DKA in patients who had initiated SGLT2 inhibitors was approximately twice of patients initiated on DPP4 inhibitors.[5] Proposed mechanisms for causing DKA include promoting glucagon secretion and a decrease in the renal and urinary clearance of ketone bodies.[3] The highest risk of DKA was associated with canagliflozin, followed by empagliflozin, and lowest with dapagliflozin.[2]

SGLT2 inhibitors are generally recommended as the second-line drug after metformin for type 2 diabetes treatment due to their additional cardiovascular and renal benefits, despite increased risk of DKA. Some studies have associated SGLT2 inhibitors with an increased risk of amputation, bone fracture, and urinary tract infections. However, one meta-analysis sug-

gested that in patients with type 2 diabetes and a high cardiovascular disease risk, the substantial cardiovascular and renal benefits of SGLT2 outweighed the risk of DKA and amputation, with an overall favorable risk/benefit ratio for SGLT2 treatment.[6]

While the benefits of SGLT2 inhibitors in the treatment of type 2 diabetes are significant and the overall risk of DKA is small, it is important that physicians treating patients with SGLT2 inhibitors remain vigilant for serious adverse effects such a DKA and to warn patients of signs and symptoms to look out for. The recognition that DKA can occur with a near normal glucose is also important to recognize to avoid misdiagnosis and treatment delays.

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