CASE REPORT

The DKA that wasn’t: a case of euglycemic diabetic ketoacidosis due to empaglifoxin

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Abstract

Sodium glucose co-transporter (SGLT-2) inhibitor is a relatively new medication used to treat diabetes. At present, the Food and Drug Administration (FDA) has only approved three medications (canaglifoxin, dapaglifoxin and empaglifoxin) in this drug class for the management of Type 2 diabetes. In May 2015, the FDA issued a warning of ketoacidosis with use of this drug class. Risk factors for the development of ketoacidosis among patients who take SGLT-2 inhibitors include decrease carbohydrate intake/starvation, acute illness and decrease in insulin dose. When identified, immediate cessation of the medication and administration of glucose must be done, and in some instances, starting an insulin drip might be necessary. We present a case of a patient with diabetes mellitus being on empaglifoxin (SGLT-2 antagonist) who was admitted for acute cholecystitis. The hospital course was complicated by euglycemic diabetic ketoacidosis after being kept nothing per orem before a contemplated cholecystectomy.

INTRODUCTION

The management of diabetes has evolved since its discovery in 1910. A gamut of medications has become available to address the glycemic control among diabetics especially for Type 2 diabetics. Empaglifoxin is a sodium glucose co-transporter (SGLT-2) inhibitor that has been approved by the Food and Drug Administration (FDA) in August 2014. It has been the latest drug approved in the drug class since 2013. This case highlights a case of euglycemic ketoacidosis with the use of empaglifoxin.

CASE REPORT

A 61-year-old female presented to her primary care doctor with right upper quadrant abdominal pain for a day. Her only medical history is diabetes Type 2 maintained on empaglifoxin and diet controlled hypertension. Patient used to be on the combination of metformin–repaglinide but has been stopped 2 months prior to admission due to gastrointestinal side effects. She described the pain as right upper quadrant tightness, rated as 10 on a scale of 10 with occasional radiation to her back. Pain was also associated with nausea and vomiting. She was sent to the emergency department. An ultrasound of the abdomen was done which revealed evidence of acute calculous cholecystitis. She was placed on nothing per orem and was admitted for laparoscopic cholecystectomy. She was given intravenous fluids with normal saline.

On the second hospital day, her laboratory results revealed that her bicarbonate levels were 7 mmol/L with an anion gap of 18. An arterial blood gas showed a pH of 7.19 and a pCO2 of <20. Oxygen level was normal. She still had persistent abdominal pain at this time. At this time patient’s white blood cell count also increased from 13.9 × 10^3/mcl on admission to 22.6 × 10^3/mcl. Lactate level was normal. Serum beta hydroxybutyrate was elevated. Urinalysis also showed the presence of ketones and elevated urine glucose despite normal serum glucose (104 mg/dL).
The patient’s metabolic acidosis anion gap is attributed to ketoacidosis. This is likely due to her intake of empagliflozin. The patient being placed on NPO pre-operative likely further exacerbated the degree of ketosis that is brought about by the medication. She was given dextrose containing intravenous solution and insulin drip. The patient’s acid–base status improved in the next 48 hours. She had the laparoscopic cholecystectomy done successfully without any event.

**DISCUSSION**

SGLT-2 inhibitors are the first class of medications that act on the kidneys to optimize glycemic control. The kidneys play a pivotal role in the regulation of glycemic homeostasis. In majority, 90% of the filtered glucose is absorbed in the proximal convoluted tubule. SGLT-2 is a protein located in the proximal convoluted tubule involved in the reabsorption of glucose [1].

Canagliflozin, dapagliflozin and empagliflozin are the SGLT-2 inhibitors currently approved by the FDA. These medications have been extensively studied and have been shown to improve the cardiometabolic markers of diabetes mellitus Type 2 [2].

In May 2015, the FDA issued a warning with the use of SGLT-2 inhibitors. Post marketing surveillance of the drug shows reports of diabetic ketoacidosis. From March 2013 (Canagliflozin was approved) to May 2015, a total of 73 cases of ketoacidosis were identified with the use of SGLT-2 inhibitors (canagliflozin [n = 48], dapagliflozin [n = 21] and empagliflozin [n = 4]). Majority of the cases occurred among Type 2 diabetics [3].

Euglycemic diabetic ketoacidosis is characterized by the presence of metabolic acidosis (pH <7.3 and serum bicarbonate <18 mEq/L), ketosis and a blood glucose <200 mg/dL [4]. The human body produces a basal amount of glucose through gluconeogenesis and glycogenolysis even without any carbohydrate intake. This is the trigger for the basal insulin release by the pancreas. SGLT-2 inhibitors lower blood glucose by increasing urinary excretion of glucose. This fall in blood glucose decreases insulin secretion by the pancreas. This in turn leads to an increase of glucagon to insulin ratio. The end result is enhanced gluconeogenesis. This leads to increased ketogenesis hence the ketoacidosis [5]. Although Type 2 diabetics have been characterized by insulin resistance, the disease is also complicated by relative insulin deficiency making these patients prone in developing ketonemia [5,6] (Fig. 1).

SGLT-2 inhibitors are FDA approved to treat Type 2 diabetes. Off label use in Type 1 diabetics has been noted due to its favorable insulin independent glucose lowering and weight loss effects. However, the use of the medication in this patient population increases the side effect of ketoacidosis [7]. This emphasizes the importance of insulin deficiency as a central factor in the development of ketoacidosis with the use of SGLT-2 inhibitors.

Not all patients on SGLT-2 inhibitors develop ketonemia. Several risk factors have been elucidated to contribute to the development of ketoacidosis. This includes decrease in insulin or secretagogue dose, starvation or decrease in carbohydrate intake, acute illness, pregnancy and even alcohol intake [3,5,7-9] (Table 1).

In our patient, being placed on NPO prior to surgery without any glucose intake was the main driving force that lead to the development of ketoacidosis. This was also compounded by the active gallbladder infection that the patient had in the beginning. The patient took a dose of empagliflozin on Day 1 of admission. The temporal association with the intake of the medication and the development of ketoacidosis confirms the diagnosis.

Just like the case report of Gelaye et al., our patient was given an insulin drip with a dextrose containing solution [10]. Our patient needed 48 hours of insulin drip for the anion gap to normalize. A repeat urine test to check for urine glucose showed decreasing levels. This implies decreasing effect of empagliflozin. It has been recommended that patients on any SGLT-2 inhibitor who do not feel well must stop the medication.

Ketoacidosis as a complication of SGLT-2 inhibitor use is increasingly being recognized. Clinicians should be aware of this side effect as this new drug class for diabetics will likely be used more often in the near future. It is not uncommon for side effects as this to be identified only during the post marketing surveillance of a drug. Cases like this happen with any new drug released for patient consumption.

Labeling our case as euglycemic ‘diabetic’ ketoacidosis may be incongruous given that the pathophysiology of ketoacidosis from SGLT-2 inhibitor use is different from ketonemia due to diabetes. A drug-induced ketoacidosis may be more appropriate. Though proper nomenclature of this condition is yet to be determined, the management of DKA and SGLT-2 inhibitor ketoacidosis is similar. Insulin and dextrose are central to the management.

**Table 1: Risk factors for the development of ketoacidosis among SGLT-2 inhibitors use**

| Risk factor                      | Proposed mechanism                                      |
|---------------------------------|---------------------------------------------------------|
| Starvation/reduce in carbohydrate intake | Enhanced gluconeogenesis                               |
| Decrease in insulin/insulin secretagogue dose | Insulin deficiency that leads to increase in glucagon hence increased ketogenesis |
| Pregnancy                        | Insulin resistance, accelerated starvation, emesis      |
| Type 1 diabetes                  | Insulin deficiency makes it more prone to ketogenesis   |
| Acute illness                    | Increased counter regulatory hormones (Glucagon, cortisol, catecholamines) leading to gluconeogenesis |
Recognizing the risk factors is very important when evaluating patients on SGLT-2 inhibitors. Pre-operative glucose supplementation should be done. Avoiding abrupt changes in the patient’s insulin dose is likewise necessary. Probably the most important aspect of treating patients with this new medication is patient education.

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GUARANTOR
The authors accept full responsibility for the work, had access to the data and controlled the decision to publish.

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