Ketoacidosis with SGLT-2 Inhibitor and Ketogenic Diet: A Case Study

Mercedez D. Bernard D.O., Karen L. Schafer, D.O.

Comanche County Memorial Hospital

Abstract

This case study illustrates the importance of obtaining dietary history and supplying dietary education for patients on sodium-glucose cotransporter-2 (SGLT2) inhibitors. In this case, the presumed diagnosis of pure diabetic ketoacidosis (DKA) is confounded by the persistence of anion gap metabolic acidosis despite correction of glucose and electrolyte abnormalities. Only after obtaining the dietary history could the etiology for the persistent ketoacidosis be elicited. Frank discussion with the patient regarding his dietary intake and additional diabetic education allowed shared decision making for the physician and patient regarding medication regime. The patient had successful weight loss and improved glucose control while on a lowâ€“carbohydrate diet. Due to his reluctance to discontinue the low-carbohydrate diet, SGLT2 inhibitors were discontinued. SGLT2 inhibitors have many benefits for diabetic patients and have been a successful adjunct to the treatment of diabetes; however, patient selection and dietary education when initiating these medications is imperative.

Introduction

Among the new pharmaceutical treatments for type 2 diabetes are the SGLT2 inhibitors. This relatively new class of drugs inhibits proximal tubular reabsorption of glucose thereby increasing the urinary excretion of glucose. Anticipated drops in A1C can be approximately 0.7-1% when these medications are taken reliably with metformin.[1] Other suggested benefits of the SGLT 2 inhibitors include weight reduction, lowering of blood pressure, decreased cardiovascular risk (canagliflozin and empagliflozin), and reduction of glomerular hyperfiltration in type 1 diabetics.[2-5] These desirable effects and tolerability of the medications have catapulted the SGLT2 inhibitors to popularity among physicians and patients alike. However, these likable medications have not been without flaws. In May 2015 the Food and Drug Administration (FDA) added additional warnings to the labels of SGLT2 inhibitors in regards to increased risk for ketoacidosis as well as serious urinary tract infections.[6] In 2016 additional warnings regarding increased risk for amputations were added.[7]

Concomitantly, there has been a substantial rise in the use of â€œketogenicâ€ diets and â€œlow-carbohydrateâ€ diets by many with type 2 diabetics. When strictly adhered to, these low carbohydrate diets can potentially stimulate multiple mechanisms leading to ketoacidosis. Increases in lactate due to starvation can enhance hepatic ketogenesis, fat-rich meals can enhance alpha-cell secretion of glucagon and lower insulin concentrations, and fatty acid concentration

can rise due to lack of carbohydrate-induced inhibition of beta-oxidation of fatty acids.[8,9] Euglycemic ketoacidosis in non diabetic patients has been described in the literature when patients adhere tightly to these diets.[8-10] This case presentation highlights the dangers of engaging in a ketogenic diet while on an SGLT2 inhibitor.

Case Presentation

A 46-year-old male presented to the emergency department with a four day history of body aches, cough, and chills. On the day of presentation, the patient had also developed nausea, vomiting, and abdominal pain. A check of his blood glucose at home yielded too high to register on his glucometer and he promptly reported to the emergency department for further evaluation. His past medical history was significant for recent exposure to the flu, type 2 diabetes, hypertension, and obesity (body mass index of 41 kg/m2). The patientâ€™s medication list included amlodipine, irbesartan, metoprolol, and canagliflozin/metformin.

On presentation, the patient was alert and conversational. Vital signs were normal with the exception of mild tachypnea with a respiratory rate of 22 respirations per minute. He was afebrile and appeared euvolemic. Initial laboratory studies revealed a high anion gap metabolic acidosis with a pH of 6.9, serum anion gap of 42 mEq/L, and hyperglycemia with a serum glucose of 567 mg/dL. Additional labs were significant for serum potassium of 6.9 mEq/L, serum ketonemia, serum creatinine of 2.3 mg/dL, and serum lactic acid of 4.7 mmol/L. Urinalysis revealed ketonuria and glucosuria but was otherwise unremarkable.

The patient was diagnosed with diabetic ketoacidosis and intravenous fluids and intravenous insulin were initiated. He was subsequently admitted to the ICU. His oral diabetic medication (canagliflozin/metformin) was discontinued while DKA protocol was initiated.

Within the first twelve hours following initiation of medical management, the patientâ€™s electrolyte abnormalities, acute kidney injury, and lactic acidosis resolved. However, despite continued intravenous fluid and insulin administration, the patient remained in persistent ketoacidosis with elevated anion gap despite euglycemia for greater than 48 hours into his hospital admission.

Due to concern for persistent ketoacidosis despite medical management, additional causes for anion gap metabolic acidosis were considered. The patient denied alcohol use, ingestion of acetaminophen, salicylates, or other potential toxins. However, the patient did admit to following a strict ketogenic diet (less than forty grams of carbohydrates per day) with subsequent 28 pound weight loss in the six weeks prior to his presentation. Furthermore, he admitted that he was recently switched from metformin monotherapy to canagliflozin/metformin in the last month.

Due to persistently elevated serum betahydroxybutyrate in conjunction with rapid weight loss and adherence to a low carbohydrate diet, diet-associated ketoacidosis was felt to be the primary contributing factor to the patientâ€™s persistent ketoacidosis. A diabetic educator was consulted for further evaluation and dietary counseling.

A diabetic diet was ordered with careful monitoring of labs and telemetry for refeeding

syndrome. The patient was transitioned to subcutaneous insulin. The patientâ€™s serum anion gap remained elevated. However, his symptoms had resolved and he requested discharge to home. Due to known reported cases of SGLT2 inhibitors precipitating ketoacidosis, canagliflozin/metformin was discontinued at discharge.11 The patient was agreeable to continued outpatient therapy with subcutaneous insulin. Arrangements were made for close follow up with his primary care physician for further lab monitoring and medication management. He was also instructed to discontinue his strict low carbohydrate diet and to follow carbohydrate counting as instructed per diabetic education. However, due to his successful weight loss on the low carbohydrate diet, the patient expressed his reluctance to change his diet.

Discussion

This case demonstrates the challenges of managing DKA in patients on SGLT2 inhibitors. This patient presented with classic symptoms of DKA. However, after appropriate treatment, anion gap metabolic acidosis remained. The remaining differential diagnosis for increased anion gap metabolic acidosis includes glycols, oxoproline, lactate, methanol, aspirin, and renal failure. The patient had none of these conditions. Low carbohydrate diets by themselves have been shown to cause ketoacidosis.[9,10] His history of consuming a low carbohydrate diet accompanied by the recent addition of an SGLT2 inhibitor suggests that this combination could be deadly.

We performed a PubMed data base search using MeSH headings: diabetic ketoacidosis, SGLT2 inhibitors, low carbohydrate diets, and ketogenic diets. Only one article was retrieved that discussed low carbohydrate diet and DKA associated with SGLT2 inhibitors.[13] Several studies demonstrated that certain medical conditions can exacerbate the development of DKA in conjunction with SGLT2 inhibitors. These medical conditions include recent insulin omission or dose reduction, severe acute illness, dehydration, extensive exercise, surgery, starvation, or excessive alcohol intake.[14] Our patient had none of these conditions. A low carbohydrate diet was implicated in only one case report, which involved a diabetic female with Prader-Willi syndrome.[13] After bariatric surgery there is often an exaggerated ketosis related to low carbohydrate intake.[15,16] This patient had no history of bariatric surgery. Our case illustrates the importance of obtaining a dietary history. In most of the current literature related to DKA or euglycemic ketoacidosis and its association with SGLT2 inhibitors, dietary history is missing. This was an average diabetic patient attempting to improve glycemic control through diet and exercise which was recommended by his primary care provider.

In the SGLT-2 inhibited patient, a loss or decrease of ingested carbohydrates via diet or fasting may precipitate a pronounced hepatic ketogenesis by increasing glucagon levels. Additional literature suggests that SGLT 2 inhibitors may also decrease the renal clearance of ketones.[11] While the exact association between SGLT-2 inhibitors and ketoacidosis is not clearly understood, in 2015 the FDA proceeded with a safety warning that SGLT-2 inhibitors may increase the risk of ketoacidosis.[6] We theorize that our patient had likely developed an underlying ketosis secondary to his strict low-carbohydrate diet and became further compromised with the addition of an SGLT2-inhibitor.

Patients that are motivated towards weight loss and improved blood glucose control may attempt strict carbohydrate restriction in order to obtain desired results. Ketogenic diets have been shown

to improve glucose control and provide improved weight loss when compared to low glycemic index diets in diabetic patients.[12] The success achieved with these diets make them popular among our diabetic and obese patients.

There are many benefits for patients that use SGLT2 inhibitors. However, appropriate patient selection is imperative and should be carefully considered by physicians. Patients on SGLT-2 inhibitors should be counseled to maintain a healthy, well-rounded diet and to discuss any changes in diet or exercise regimens with their provider prior to initiation. In particular, given the risk for ketoacidosis associated with SGLT-2 inhibitors, patients should be advised to avoid low carbohydrate or ketogenic diets.

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