Case Report

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Euglycaemic Ketoacidosis: An Overlooked Cause of Symptoms Suggestive of Bowel Obstruction in SGLT2 Inhibitor Users

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Abstract

Euglycaemic ketoacidosis (EDKA) is a rare, life-threatening complication of sodium-glucose co-transporter 2 (SGLT-2) inhibitors. With their increasing use in the management of type 2 diabetes(T2DM) and heart failure due to long-term beneficial effects, the incidence of this complication is on the rise. We report a case of a 44-year-old female with T2DM on multiple oral hypoglycaemic agents, including empagliflozin, who developed EDKA during intercurrent illness.

Keywords: Euglycaemic DKA, severe acidosis, SGLT2 inhibitors

Introduction

SGLT2 inhibitors were approved by the Food and Drug Administration (FDA) in 2013 for the treatment of type 2 diabetes mellitus (T2DM). They act through the inhibition of SGLT 2 transmembrane proteins (receptors) expressed on the apical cells of proximal convoluted tubules (PCT), which results in the inhibition of glucose reabsorption in PCT and facilitates its excretion in urine [1]. Due to their long-term beneficial effect, their use has gained popularity in the recent past. However, the FDA has cautioned against life-threatening complications of EDKA. It is defined by the triad of high anion gap metabolic acidosis, high serum and urine ketones, and a blood glucose level of less than 250 mg/dL [1,2].

Case history

A 44-year-old female was admitted with abdominal pain, vomiting and fever. She didn't open her bowel for 3 days, but she passed flatus. No history of substance abuse or drug overdose. She had a history of diabetes and dyslipidaemia for a two-year duration. The drug history revealed that she is on maximum doses of metformin, gliclazide and sitagliptin. Also, she has been taking empagliflozin 10mg daily for a year. For dyslipidaemia, she was taking Atorvastatin.

On examination, she was coherent but was ill-looking and dehydrated. She was afebrile with a blood pressure of 160/90 mmHg, pulse rate was 108 beats per minute. Examination of cardiovascular, respiratory, neurological and gastrointestinal systems were normal except for mild abdominal tenderness. She was reviewed by the surgical team and the working diagnosis of intestinal obstruction was made.

Her random blood sugar on admission was 240 mg/dl. A complete blood count revealed white cells were 17360/mm^3 with normal haemoglobin and platelets. Renal functions, Serum amylase and urine test were normal. Liver function was normal, but C-reactive protein was 60 mg/dl. Electrocardiogram revealed sinus tachycardia, and troponin I was negative. The imaging studies (chest and abdominal radiography and ultrasound of the abdomen) didn't show any abnormalities.

While in the surgical ward, the patient's clinical condition worsened, and the medical team was called to review the patient. On further assessment, her arterial blood gas analysis revealed high anion gap metabolic acidosis with normal lactate levels (pH- 7.03, pCO2- 12 mmHg, HCO3- 3.2mmol/L, lactate- 0.6mmol/L, anion gap -32). Her urine ketone body was positive. Her clinical picture and investigations have confirmed the diagnosis of euglycaemic DKA

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Emphagliflozin was stopped since admission. She was managed with normal saline, soluble insulin infusion and intravenous potassium chloride as per diabetic ketoacidosis protocol. Also, she was given intravenous bicarbonate. Third-generation cephalosporin was started to cover sepsis focus. It took about 52 hours to resolve acidosis. She improved rapidly and went home on day six with Mixtard insulin.

Discussion

SGLT2 inhibitors are a new class of oral hypoglycaemic agents. Their use is recommended by the United States FDA as the second-line drug after metformin for glycaemic control. According to the American Diabetes Association (ADA) 2022 guideline, it was used as the first line pharmacological therapy for type 2 diabetes (usually with metformin), especially in patients with chronic kidney disease, stroke, or Heart failure.[2,3] However, in 2015, the FDA cautioned that their use is associated with serious adverse drug events of EDKA. [4]

EDKA was first described in 1973. In later years, reports said that approximately 2.6% - 3.2% of cases of DKA presented with euglycaemia. However, there is evidence of an increasing trend from early reports of EDKA as the use of SGLT2 inhibitors increases. [2]

The mechanism for the development of EDKA is the switch from carbohydrate to fat metabolism due to carbohydrate depletion secondary to renal glycosuria leads to low serum glucose and increased glucagon/ insulin ratio which stimulates lipolysis and promotes ketogenesis in the liver. Furthermore, they also increase renal absorption of ketone bodies. [1]

Any condition that results in decreased glucose availability or decreased glucose production, decreased insulin secretion, increased counter-regulatory hormone production and increased glucagon/insulin ratio can cause EDKA. The common causes are SGLT2 inhibitors, pregnancy, infection, prolonged fasting, prolonged physical exercise, and ketogenic diets. [5] Most cases published in the literature have reported that the patient who are on SGLT2 inhibitors develops EDKA in the early part of initiation[3] however our patient was on emphagliflozin for up to one year. Infection and decreased oral intake with vomiting might have precipitated EDKA in our patient. To reduce the risk of EDKA the treatment should be stopped in patients who are on SGLT2 inhibitors and have other risk factors for DKA. "Sick day rule" should be explained to patients in detail[2] The half-life of SGLT2 inhibitors ranges from 11-13 hrs. Hence it is recommended by the FDA to stop these drugs for 72 hrs (five half-lives) to get eliminated from the body. Patients of renal failure may take up to eleven half-lives for drug elimination. [3.4]

Clinically, it presents like conventional DKA with nausea, vomiting, abdominal pain, weakness and fatigue. Kussmaul breathing may be observed due to metabolic acidosis. However, our patient did not develop kussmaul breathing even though she had significant acidosis. Hypotension, tachycardia, dryness of mucous membranes and skin, and a reduced skin turgor may also be observed due to dehydration. Rarely neurological features are present in more severe cases of metabolic acidosis.[5] Patients with DM who present with these symptoms but do not have hyperglycaemia and if they are on SGLT2 inhibitors should be investigated for EDKA. The blood glucose in EDKA is considered as less than 250mg/dl.

Our case highlights having a high index of suspicion for the development of EDKA in patients on SGLT2 inhibitors. As patients with EDKA have normal or near-normal blood glucose levels, it may be falsely reassuring for clinicians. Therefore, it is recommended to do an ABG and ketone body test at the bedside to avoid the pitfalls. For unknown reasons, our patient was not severely ill even with a PH of 7.03. Her main complaint was abdominal pain and on-and-off vomiting even during the hospital stay. In the low-resource settings where serum ketone body measurements are not available at the bed site or arterial blood gas analysis is limited the clinical suspicion of EDKA will prevent delay in diagnosis, unnecessary investigations and mortality. Unexplained high anion gap metabolic

acidosis even with a normal glucose level should prompt the clinician to exclude this complication.

Conclusion

This case report adds to the existing evidence in the literature supporting the relationship between the use of SGLT2 inhibitors and EDKA. This report also highlights the importance of patient education on "sick-day-rule". It may be challenging to diagnose this condition in the absence of hyperglycaemia as seen in typical DKA. We recommend that any patients who are on SGLT 2 inhibitors having abdominal pain should be off from SGLT 2 inhibitors immediately irrespective of the blood glucose levels. Moreover, ketone body assessment as well as ABG analysis should be performed at the bedside before proceeding to further investigations. Also, the low threshold to start insulin infusion and follow the protocol of DKA management in such patients should not be delayed even if the blood glucose levels are not high and the bedside side ketone body assessment and ABG are not available.

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