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Case Report

Euglycemic Diabetic Ketoacidosis Presenting as Chest Pain and Vomiting in a Patient taking SGLT-2 inhibitor

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Abstract:

Empagliflozin-induced Euglycemic Diabetic Ketoacidosis (EDKA) is a life-threatening metabolic emergency of Diabetes Mellitus. It is characterized by metabolic acidosis (i.e., pH <7.3 and Serum bicarbonate <15mEq/dl) with an increased anion gap, ketonemia and relatively normal serum glucose level. EDKA resembles Diabetic Keto Acidosis (DKA) but does not exhibit the typical high blood sugar levels. In EDKA, blood glucose is usually below 200 mg/dL. This condition is a diagnostic challenge as euglycemia masks the underlying diabetic ketoacidosis. Here we present a case of Empagliflozin-induced Euglycemic Diabetic Ketoacidosis presented with palpitation and several episodes of vomiting. The aim of this article is to create awareness among clinicians to consider this diagnosis in the differential, especially in the patients taking SGLT-2 inhibitors.

Keywords: *Euglycemic Diabetic Ketoacidosis, Empagliflozin, Diabetes Mellitus, SGLT-2 inhibitors.*

Introduction:

Empagliflozin is a sodium-glucose co-transporter-2 (SGLT-2) inhibitor that has been approved by Food and Drug Administration (FDA) for the treatment of type 2 Diabetic Mellitus since August 2014.[1] SGLT-2 inhibitors inhibit renal glucose re-absorption in proximal tubules through an insulin independent mechanism which increases urinary glucose excretion.[2]Recently, increasing studies showed that empagliflozin has a positive effect on the treatment of patients with established heart failure and type 2 diabetes mellitus.[3]

Case Report

A 42-year-old man presented at the emergency department with chest tightness, palpitation, nausea and multiple episodes of vomiting during last few hours. There was no radiation and was not related to exertion and other event. The vomiting was non bilious, non-bloody. There was no fever, abdominal pain and diarrhea was a known case of bronchial asthma and type 2 diabetes mellitus. For diabetes he was on oral medication linagliptin 5 mg and empagliflozin 25 mg for the last 6-7 months.

On examination,pulse was rapid and thready, BP was 90/50 mm Hg, temp 98.5°F, SpO_2 on room air was 94-95%. Patient was uncomfortable, oral mucosa was dry, abdomen was not distended, soft, and non-tender. Other physical examination was not remarkable.

ECG showed narrow complex tachycardia and patient was transferred to Coronary Care Unit (CCU). At CCU carotid message was given, but in the meantime patient became hemodynamically unstable. So, DC cardio-version (Synchronized) was done and sinus rhythm was restored. Initial investigation shows serum creatinine 1.88mg/dl, leukocytosis WBC count (29,000/mm^3), elevated lactate (9.5), normal blood osmolarity (282 m osmol/L), and euglycemia (156 mg/dL). Initially urinary ketone body was absent, procalcitonin and Troponin-I was normal.

Patient was treated with Intravenous (IV) fluids, and IV Sodibicarb but he was not improving and subsequent ABG shows persistent low pH, low bicarbonate and high anion gap. He became restless, respiratory rate increased, O_2 saturation was not maintained by face mask with 10L of O_2, so patient was intubated immediately and was put on mechanical ventilation.

At the same time for intractable acidosis, one session of hemodialysis was given to treat refractory high anion gap acidosis. But patient was not improving and still ABG showed high anion gap metabolic acidosis. Then IV fluid was started and insulin was started through syringe pump.

Table 1: Arterial blood gas analysis on different days

Day	Day 1	Later on D1	Day 3	Day 5	Day 9	Day 11	Day 28
pH	6.99	7.02	7.06	7.088	7.219	7.408	7.375
PCO_2	12.0	11.0	7.9	6.5	13.8	26.9	35.2
HCO_3	<3	2.4	2.3	2.0	5.7	20.4	20.8
Lactate	9.5	5.0	3.7	3.9	0.5	2.8	0.9
Anion gap	26.4	25.0	26.1	25.6	22.4	11.2	6.7

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Table 2: Serum electrolyte reports on different days

Day	Day 1	Day 3	Day 5	Day 13	Day 28
Na^+ (mmol/L)	139	142	139	141	140
K^+ (mmol/L)	3.7	2.5	4.5	3	3.9
Mg^{2+} (mmol/L)	1.8	_	0.8	1.8	2
PO_4^{3-} (mmol/L)	3	_	_	2.38	3.5

On ninth day, X-ray showed bilateral lung opacities and O_2 requirements was increasing, and patient became hemodynamically unstable. According to protocol, antibiotics were changed and inotropes were started. Then the patient improved and he was extubated. After 2 days of extubation, patient developed weakness in all four limbs, more on lower limbs, Muscle power was 1/5 in both lower limbs and 2/5 in both upper limbs. On biochemical analysis showed low serum Potassium (K^+), Magnesium (Mg^{2+}) and Phosphate (PO_4^{2-}). IV K^+, Mg^{2+} and PO_4^{2-} were given. Then the patient improved over weeks, and patient was discharged on day 29.

Discussion

Diabetic Ketoacidosis is defined by hyperglycemia (>250mg/dl), Ketoacidosis and anion gap acidosis.[4] Euglycemic Diabetic Ketoacidosis is characterized by severe metabolic acidosis (pH <7.3, HCO_3^-<18mEq/l), ketonemia, and blood glucose <250mg/dl .[5]

Typically, the onset of euglycemic diabetic ketoacidosis (eu-DKA) is triggered by factors such as strict dieting or starvation, pregnancy, alcohol intake, and the use of sodium-glucose cotransporter 2 inhibitors (SGLT-2is).[6]Three types of SGLT-2 are approved by FDA: Empagliflozin, Canagliflozin, and Dapagliflozin.[7] These inhibitors have demonstrated several therapeutic benefits for diabetic patients, including improved blood pressure management and enhanced glucose control. Additionally, they may offer protective effects for the heart and kidneys.However, since their introduction, numerous case reports have documented the occurrence of eu-DKA in patients treated with this drug class. [8-11]

Insulin secretion by pancreatic B cells is reduced by SGLT-2i by lowering blood glucose levels by increasing urinary glucose excretion. SGLT-2i act by blocking the transport proteins in the proximal tubule of the kidney which reabsorb glucose and sodium from urine independent of insulin leading to glucosuria and natriuresis. So, increase of counter-regulatory hormones such as glucagon, cortisol, epinephrine resulting on increase glucagon to insulin ratio.[12]

Due to SGLT-2i, the possible mechanism of Euglycemic Diabetic Ketoacidosis can be explained by decreasing the glucose level as well as decreasing insulin level, whereas glucagon is increased. As insulin starts to decrease, lipolysis is starts to increase along with FFA production. As a result, β-oxidation increases resulting in increased ketone body production which leads to eu-DKA. In the meantime, due to increased glucagon level and decreased insulin level, Acetyl-CoA (ACC) increases that leads to reducing the Carnitine palmitoyltransferase I (CPT-1) and β-oxidation is also increased which also produces ketone body that is responsible for eu-DKA.

Our patient presented with palpitation and vomiting, ECG showed supraventricular tachycardia, after restoration of sinus rhythm, Arterial Blood Gas (ABG) analysis was done which revealed High Anion Gap Metabolic Acidosis (HAGMA). But blood glucose was normal, urinary ketone body was absent. Later, we thought about Euglycemic Diabetic Ketoacidosis as patient gave history of taking SGLT-2i. Initially to correct refractory HAGMA intravenous sodium bi-carbonate was given, intermittent hemodialysis was done. After initiation of intravenous insulin therapy HAGMA was corrected. Septic shock with ventilator associated Pneumonia was complication of mechanical ventilation which was treated according to protocol.

The incidence of eu-DKA in type 2 diabetes patients using SGLT2 inhibitors is approximately 0.1%.[13] According to FDA data published in 2021, the median time to ketoacidosis after starting SGLT2 inhibitor therapy was 43 days.[14] Another case study indicated that 50% of patients who developed eu-DKA while on SGLT2 inhibitors had clear precipitating events, such as acute illness (e.g., infection and surgery), reduced oral intake, and decreased insulin doses.Fralick et al reported that type 2 diabetes patients on SGLT2 inhibitors are more than twice as likely to develop diabetic ketoacidosis within 180 days of follow-up compared to those on other oral hypoglycemic agents.[15]

Early involvement of a multidisciplinary team is crucial in managing this patient group. The primary focus of initial patient management is fluid resuscitation, as these patients often present with severe dehydration. Intravenous crystalloid fluids should be administered until the anion gap and acidosis are resolved.[16] In contrast to conventional DKA management, 5% dextrose should be added to the fluid resuscitation regime to avoid hypoglycemia and hasten the clearance of ketosis. An increase to 10% dextrose should be considered if ketoacidosis persists on 5% dextrose.Considering that patients with eu-DKA typically have blood glucose levels below 11.0 mmol/L (200 mg/dL), Modi et al recommend starting an insulin infusion at a rate of at least 0.02 to 0.05 units/kg/hr.[17]Blood glucose level should be assessed hourly at first and electrolytes monitored every 4 hours as intravenous supplementation of potassium, and other electrolytes may be required.Sodium bicarbonate infusions are not indicated, and their use in the setting of severe acidemia (pH less than 6.9) is controversial.[18] Patients on SGLT-2i should stop these medications immediately upon diagnosis and should not resume them until they have fully recovered from the acute illness.[19]

Conclusion

Due to cardioprotective effects of SGLT-2i nowadays it is commonly used for diabetic patients. Euglycemic DKA should be considered in the patient receiving a SGTT-2i who present with high anion gap metabolic acidosis even with normal blood glucose. Prompt recognition and early management is crucial for life saving. And electrolytic

imbalance like hypophosphatemia is common in DKA treated patient should be identified and treated early to reduce morbidity and mortality.

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