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Case Report..

A Rare Case of Euglycemic Ketoacidosis

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ABSTRACT

Euglycemic diabetic ketoacidosis (DKA) is an acute life-threatening clinical emergency characterized by ketoacidosis with either normal plasma glucose or near normal degree of hyperglycemia. We described a case of male Saudi 36 year old presented at Accident and Emergency department, AlNoor hospital, Makkah, Saudi Arabia with nausea, vomiting, polyurea, and excessive thirst with haziness of vision and decreased vision sharpness, a short period after starting Empagliflozin therapy. His plasma glucose was <100 mg/dl, VBG pH was 7.18 with low HCO3 and ketones were positive. He was diagnosed as Euglycemic DKA. The patient was managed in intensive care unit by DKA protocol and asked to stop Empagliflozin. After discharge, the patient felt better as his general condition as well as his catabolic manifestations were improved.

Keywords: Empagliflozin, Euglycemic, Diabetic Ketoacidosis.

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INTRODUCTION

Diabetic ketoacidosis (DKA) is a life-threatening acute diabetic complication, mainly affects type 1 patients; however, it can be triggered by trauma, pregnancy, starvation, alcohol use, infection, fasting before surgeries without dextrose or acute coronary syndrome in type 2 patients.[1] DKA is characterized by a triad of hyperglycemia (plasma glucose > 14 mmol/L), metabolic acidosis and ketonemia.[2,3]

Euglycemic DKA is characterized by ketoacidosis (pH < 7.3 or serum bicarbonate < 18 mmol/L) with either normal plasma glucose or near normal degree of hyperglycemia (11-14 mmol/L).[4] It is considered as an acute life-threatening clinical emergency, as the absence of hyperglycemia delays its diagnosis in intensive care units or emergency departments.[5]

Empagliflozin is one of the sodium-glucose co-transporter inhibitors (SGLT-2i) that has been approved since 2014 for the type 2 diabetes therapy by the Food and Drug Administration (FDA).[6] Its mechanism of action depends mainly on glycosuria resulted from inhibition of glucose uptake in proximal tubules[7], which might lead to dehydration.[8] However, it may result in DKA with mild to moderate elevation of blood glucose level.[9] The rate of SGLT-2i-associated DKA had a rate ranged between 0.16 and 0.76 insults per 1,000 type 2 DM patient years.[10]

CASE DESCRIPTION

This is a male Saudi 36 year old newly married working in administrative job patient. He started to notice an increase in voiding of urine that even woke him up from sleep along with increase desire of water drinking, all started one month before attending hospital Accident and Emergency department. Later on, the patient noticed haziness of vision with decreased vision sharpness. After a few days, he attended a private laboratory and did glycated hemoglobin which surprisingly showed 13.7% and his plasma glucose was >300 mg/dl. He consulted health care provider who advised him to start Empagliflozin, one of the Sodium Glucose transporters-2 inhibitor, as 10 mg/day+ MetforminXR 1500 mg/day as well as statin and vitamin D replacement. For 5 days, his self-monitor blood glucose (SMBG) was in range of 80-150 mg/dl and this was associated with increased blurring of vision. Next day, he started to feel nausea, abdominal pain and acidity. Later, he vomited and attended private clinic and his plasma glucose was <100 mg/dl, given intravenous fluid and discharge home. At night, his complains continued and he visited the Accident and Emergency department of Al-Noor specialist hospital. His blood glucose was 108 mg/dl, VBG pH 7.18 with low HCO3 and ketones positive.

The patient was admitted as a case of Euglycemic ketoacidosis mostly due to sodium glucose co-transporters 2 inhibitor "SGLT-2 inhibitor", Newly diagnosed diabetes of type 1 (T1DM), with a family history of grandmother diabetes mellitus type 2 (T2DM). Drug history indicated that the patients were on Metformin XR 1500 mg/day, Empagliflozin 10 mg/day and Atorvastatin 10 mg/day. His weight was 72.7 kg while his height was 1.72 meter and body mass index (BMI) was 24.5 kg/m^2 and waist circumference was 103 cm. Regarding vital signs, pulse was 80, blood pressure was 130/80 m/Hg, oxygen saturation was 98% and body temperature was 36.8 ˚C.

Patient presented to Accident and Emergency department with polyuria, polydipsia, blurring of vision and muscle cramps. His plasma glucose was 5.9 mmol/l = 106 mg/dl, venous blood gases (VBG) pH 7.15, bicarbonate (HCO3) was 8.7 meq/l pco2 was 25 mmhg, sodium was 153 meq/l, potassium was 3.5 meq/l, chloride was 100, Anion gap was 44. Amylase was normal. His blood urea nitrogen/creatinine was normal. Liver enzymes are normal. Intensive care unit (ICU) team consulted and accepted admission under ICU care. Sequential blood glucose was 3.0 mmol/l- 2.8 mmol/l – 14.3 mmol/l – 16.9 mmol/l –5.4 mmol/l – 2.27 mmol/l – 3.0 mmol/l – 3.3 mmol/l then 16.9 mmol/l lastly 5.1 mmol/l while sequential VBG pH was 7.15-7.15- 7.27-7.35, sequential Anion gap was 44-24-13 and sequential HCO3 was 8.7-8.7- 21 meq/l.

Patient was managed in ICU by DKA protocol but was suffering from persistent low blood glucose which was managed by shifting fluid from dextrose 5% to dextrose 10% after which his blood glucose was corrected, and acidosis started to improve and recovered from acidosis. Patient started on basal insulin as Determir insulin as 10 units/SQ/day/once daily, later shifted to medical ward and started on aspart 6 units/tid/SQ.

Patient was advised to stop empagliflozin as it is possibly the precipitating factor of his euglycemic ketoacidosis. Patient was discharged on Determir 12 units/SQ/day/O. D, aspart 6 units/tid/SQ/day and diabetes education given- insulin titration education given and followed up in clinic. After discharge, the patient was feeling better as his general condition was improved and his catabolic manifestations as polyuria, polydipsia and blurring of vision was also improved.

Our final diagnosis was Euglycemic Ketoacidosis precipitated by sodium glucose co-transporters 2 inhibitor, Empagliflozin.

DISCUSSION

SGLT2 inhibitors are oral antihyperglycemic medications of insulin-independent class, which act by decreasing the re-absorption of glucose in the proximal tubule of the kidney and mediate re-absorption of 90% of the filtered glucose load, causing urinary glucose excretion and consequently lowered elevated blood glucose levels in type 2 diabetic patients. Additionally, through this mechanism of action, they decrease blood pressure and weight.[11]

Diabetic ketoacidosis is a metabolic disorder characterized by hyperglycemia, acidosis, and ketonuria, which usually occurs in diabetic patients when insulin levels are too low. In the absence of insulin, lipolysis is stimulated instead of glycogenolysis for energy production, consequently increasing ketone levels followed by their accumulation in the blood leading to acidosis.[12]

Euglycemic diabetic ketoacidosis is a relatively very rare complication of SGLT2 inhibitor use, however, it can result in a life-threatening insult, especially if not diagnosed early.[13] In the present case report, patient presented with metabolic acidosis, ketonemia, however, the blood glucose was <100 mg/dl. Diabetic ketoacidosis mostly accompanied by high blood glucose levels.[14]

It is essential to remind that SGLT2 inhibitor–associated ketoacidosis presents with euglycemia or slightly elevated glucose blood concentrations delayed the diagnosis and treatment of ketoacidosis. Some of risk factors for developing ketoacidosis in patients treated with SGLT2 inhibitors were identified including previous history of DKA, high hemoglobin A1C (>10%), recent hypoglycemia, and low baseline serum bicarbonate levels[15] or therapy with pioglitazone in addition to SGLT2 inhibitor[16], as thiazolidinediones, including pioglitazone, can induce fluid retention.[17]

Risk of ketoacidosis is increased among SGLT2 treated patients, thfrom fatbe explained by several mechanisms including the fact that SGLT2 inhibitors decrease the level of blood glucose level by an insulin-independent mechanism, enhance the rates of lipolysis in adipose tissue and ketogenesis in the liver, increase plasma glucagon levels, acting directly on pancreatic α-cells to increase pre-proglucagon gene expression, and also decrease renal clearance of ketone bodies.[18] The level of ketone body increased in patients treated with SGLT2 inhibitor, so it is vital to emphasize that failing myocardium in diabetic heart patients to optimally use traditional substrates (free fatty acid, glucose) but can use ketone bodies as an alternative for energy production, This shifting of metabolism from fat/glucose oxidation to ketone bodies in patients treated with SGLT2 inhibitors improves myocardial and renal function.[15]

Therefore, in case of having nausea, vomiting, or malaise in patients taking SGLT2 inhibitors, rapid diagnostic screening is vital. Serum ketones and arterial blood gases analysis should be done immediately in any patient presenting with aforementioned symptoms, and if acidosis is confirmed, SGLT2 inhibitors should be stopped.

In conclusion, euglycemic DKA should be a diagnosis of exclusion, after exclusion of other reasons for high anion gap metabolic acidosis. It is very important for physicians to have a high level of suspicion for euglycemic ketoacidosis in diabetic patients treated with SGLT-2i, particularly those with atypical initial presentation. In this study, we present a case of empagliflozin-induced euglycemic ketoacidosis in a patient with T2DM.

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