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A case report; Canagliflozin induced Diabetic Ketoacidosis

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Abstract

Canagliflozin is an SGLT2 inhibitor developed for the treatment of adults with T2DM (DM). Canagliflozin lowers the renal threshold for glucose and promote urinary glucose excretion. Euglycemic diabetic ketoacidosis is a post market warning in patients with type 1 diabetes and type 2 diabetes treated with SGLT-2 inhibitors. We report a case of 44-year-old male who was treated as a type 2 Diabetes Mellitus for 4 years presented to Emergency Department with history of Vomiting, Abdominal discomfort, Dry mouth and Polyuria. His medication regimen includes Canagliflozin, Insulin Detremir, Sitagliptin and Metformin. Further workup showed Eugylycemic Diabetic Ketoacidosis and successfully treated as per local DKA guidelines. As part of the work up, he tested positive for glutamic acid decarboxylase auto antibodies.

It is very important to be vigilant with the use of SGLT-2 inhibitors to decrease morbidity and potentially mortality particularly in patients with long-standing type 2 diabetes associated with marked β-cell insufficiency, type 1 diabetes mellitus, or latent autoimmune diabetes of adult onset.

Keywords

diabetic ketoacidosis; euglycemic diabetic ketoacidosis; SGLT2 inhibitors; canagliflozin

Abbreviations

DM: Daibetes Mellitus; T1DM: Type 1 Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus; SGLT-2: Sodium Glucose Transporter-2; EuDKA: Euglycemic Diabetic Ketoacidosis; DKA: Diabetic Ketoacidosis

Introduction

The increased risk of euglycemic diabetic ketoacidosis (euDKA) with sodium-glucose co transporter- 2 (SGLT-2) inhibitors is a post market warning that Food and Drug Administration (FDA) recently issued for patients with type 1 diabetes (T1DM) and type 2 diabetes (T2DM) using this new class of drugs [1]. The drugs are only approved for use in patients with T2DM. Recently some patients developed Ketoacidosis who were receiving SGLT-2 inhibitors [2]. We present a case of euDKA with SGLT-2 inhibitor and discuss the possible mechanisms leading to this event.

Case Description

A 44-year-old male who was initially diagnosed as a type 2 Diabetes Mellitus 4 years ago, presented to Emergency Department with history of Vomiting, Abdominal discomfort, Dry mouth and Polyuria. He denied fever, diarrhoea or sick contacts. His appetite was reduced and he admitted less eating and drinking. He denied alcohol consumption. The patient continued to take his medication

regimen which includes Canagliflozin 300mg of which was started one week prior to admission to the hospital. Other medications include Detremir insulin 12 units at night time, Sitagliptin 100 mg of, Metformin 1 gm twice a day. His Novorapid was stopped and insulin Detremir was reduced recently due to episodes of hypoglycaemia. On examination, he appeared ill and dehydrated. His vital signs demonstrated temperature of 36.4°C, blood pressure 104//52 mmhg, heart rate 102/min, respiratory rate 20/min and oxygen saturation of 98% on room air. Extremities showed no edema and his systemic examination was unremarkable including respiratory, cardiovascular, neurological and abdominal examination. His chest X-ray was unremarkable. Laboratory work up showed blood glucose level of 12 mmol, urea 9.6 mmol/L, creatinine 145 umol/L, sodium 136 mmol/L, potassium 5.2 mmol/L, White blood cells 23.8 x10^9/L, neutrophills 21.4 x10^9/L, hemoglobin 17 g/dl, platelets 242 x10^9/L, CRP 1.3 mg/L, total bilirubin 9 umol/L, ALT 22 U/L, gamma GT 18 U/L alkaline phosphatase 115 U/L, albumin 54 g/L, globulin 35 g/L. Blood gas analysis showed severe metabolic acidosis with PH of 6.97, anion gap of 37 mEq/L and bicarbonate of 7.8 mmol/L, lactate 1.4 mmol/L, serum ketones 6.3 mmol/L and urine ketones 4+.

He met the diagnostic criteria of DKA and was admitted in the intensive care unit. He was successfully treated as per local DKA guidelines and his Canagliflozin was stopped. His clinical status improved and was discharged home with basal bolus insulin regimen. No other trigger was found as there was no evidence of sepsis, trauma, acute cardiovascular event, alcohol or substance abuse. It was very likely related to Canagliflozin. His further workup showed normal Lipid profile and positive Glutamic Acid Decarboxylase auto antibodies. HbA1c was 10.3% (89mmol/mol).

Discussion

Canagliflozin and dapagliflozin are inhibitors of the sodium glucose cotransporter- 2 (SGLT-2) in the proximal renal tubule. This inhibition prevents the reabsorption of filtered glucose and results in glycosuria, which is accompanied by mild osmotic diuresis and modest weight loss [3]. Currently, these drugs are only licenced to use in type 2 Diabetes Mellitus. Off-label use of SGLT-2 inhibitors in the setting of T1DM is increasing [4,5], presumably due to the increase of obesity in those patients.

DKA is rare but life threatening complication of Diabetes. Recent evidence suggests that euglycemic DKA might occur not so infrequently in individuals treated with SGLT-2 inhibitors [6]. There have been more than 70 cases of euDKA with the use of SGLT2 inhibitors reported to the FDA since the release of the novel class of drug in the market in 2013 [1]. In May of 2015, the FDA released a warning announcement that the three currently approved SGLT2 inhibitors—canagliflozin, dapagliflozin, and empagliflozin—may lead to ketoacidosis in patients [7]. 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 [8].

Historically, euglycemic DKA develops mostly in individuals with type 1 DM and only rarely in those with type 2 DM. Euglycemic DKA is classically thought to be facilitated by partial treatment of DKA with exogenous insulin, food restriction, alcohol intake, inhibition of gluconeogenesis, and pregnancy. SGLT2 inhibitors lower blood glucose levels by increasing urinary glucose excretion, which reduces insulin secretion from pancreatic β-cells. This results in a lowering of the antilipolytic activity of insulin and stimulation of free fatty acids, which are converted to ketone bodies in the liver [9]. In addition,

evidence suggests that the administration of SGLT2 inhibitors stimulates the secretion of glucagon, which might be either a secondary effect mediated by the decrease in insulin secretion or a direct effect of SGLT2 inhibitors on pancreatic α-cells [6]. The lowering of the insulin-to-glucagon ratio further stimulates lipolysis and increases circulating free fatty acids and lipid oxygenation [10].

In cases of T1DM or latent autoimmune diabetes of adult onset (LADA), when starting SGLT-2 inhibitors, clinicians or patients often decrease the dose of insulin administered to minimize the risk of hypoglycaemia [5]. This results in a decrease in circulating insulin levels, which leads to an increase in lipolysis in adipose tissue and ketogenesis in the liver, and more circulating ketones in the body.

Our patient was diagnosed with T2DM several years prior to admission based on clinical background mainly based on his age. His short acting insulin was stopped and Long acting insulin was reduced due to frequent episodes of hypoglycemia and was started on Canagliflozin one week prior to admission. He had some common symptoms of DKA including abdominal discomfort and vomiting; though his work up did not show any source of infection. Septic screen was negative and his other investigations including chest X-ray, troponins, liver function tests and amylase were all normal. He had further workup done which showed positive GAD autoantibodies. He was diagnosed with LADA and recent use of SGLT-2 inhibitors placed him at high risk of developing euDKA.

EuDKA can be detected and easily prevented. Patients who are being treated with SGLT-2 inhibitors should be educated about the risk of euDKA. The most effective means of preventing SGLT2 inhibitor–associated DKA is to ensure that SGLT2 inhibitors are appropriately prescribed and are withheld during any situation that might precipitate DKA (eg, acute illness, surgery, dehydration, excessive alcohol intake) [11].

Conclusion

It was evident that recent use of SGLT-2 inhibitor led to development of Euglycemic Diabetic Ketoacidosis in our case. Recently, the FDA has been increasing awareness of potential euDKA caused by SGLT-2 inhibitors. However, it can still be prevented by appropriate triage of the patients, withholding of SGLT-2 inhibitors when necessary and proper counselling of the patients.

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