

Diabetic Ketoacidosis Linked with Sodium Glucose Co-Transporter 2 Inhibitors in an Elderly Patient with Type 2 Diabetes

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Abstract

Objective: To report an episode of diabetic ketoacidosis and acute kidney failure in a patient with type 2 diabetes (T2DM) recently initiated a sodium-glucose co-transporter 2 inhibitor (SGLT-2i) and a DPP-4 inhibitor (DPP-4i).

Methods: We describe the clinical presentation, laboratory data and management of an elderly T2DM patient with diabetic ketoacidosis.

Results: A 80 year-old T2DM female presented with, fatigue, nausea, recurrent vomiting, muscle pain, malaise and shortness of breath three weeks after initiation of dapagliflozin 5 mg and sitagliptin 100 mg. On admission to the emergency department, the patient was hypotensive, and rapidly became comatose. The glucose concentration was 398 mg/dL, Na 135 mmol/L, K 4.1 mmol/L, pH 6.8, and bicarbonate 1.8 mmol/L, blood urea nitrogen 22.8 mg/dL, creatinine 0.96 mg/dL, beta-hydroxybutyrate 3.2 mmol/L and lactate 1.1 mmol/L. The estimated osmolality was 300.25 mOsm/L and the anion gap 26.7 mEq/L. C-reactive protein was <2.5 mg/L. Urine sample was normal and urine culture was negative. Hemoglobin was 12.6 g/dL; leucocyte count was $21.0 \times 10^3 \mu\text{L}$ and platelet count $253 \times 10^3 \mu\text{L}$. Two days after hospitalisation the patient developed an acute kidney failure and anemia. The patient was treated with balanced electrolyte solutions, continuous insulin infusion and IV antibiotics and dapagliflozin was discontinued. Diabetic ketoacidosis resolved in 48 hours and the acute kidney failure in 6 days. The patient was discharged 10 days after admission with a basal bolus regimen with insulin analogues.

Conclusions: This elderly patient with long lasting type 2 diabetes treated with SGLT-2i developed diabetic ketoacidosis and acute kidney failure. This complication occurred associated with dietary derangements and lack of insulin treatment. Each medication change needs a very clear indication; otherwise it adds more risk to the patient than benefit. When prescribing SGLT2i in diabetics, physician must assure diabetes education, an adequate insulin provision and strict monitoring of glucose and urine ketones.

Keywords: Diabetes ketoacidosis; Type 1 diabetes; SGLT2 inhibitors

Introduction

Diabetic Ketoacidosis (DKA) is a serious and potentially life-threatening condition, which mainly occurs in Type 1 Diabetes Mellitus (T1DM). In T2DM, DKA may appear particularly in the presence of insulin deficiency associated with increased insulin requirements. SGLT-2i is novel anti-hyperglycaemic agents, which block glucose reabsorption in the proximal renal tubule enhancing urinary glucose excretion and lowering plasma glucose concentrations with few side effects [1-4]. These agents have been indicated as monotherapy, or combined with other oral agents, as well with insulin for the treatment of T2DM patients [5]. In T2DM, SGLT2i reduces fasting, postprandial glucose and HbA1c levels between 0.3 to 1.2% with low rates of hypoglycaemia [6].

Besides from its glucose lowering effects, these drugs induce weight loss between 1.5-3.0 kg, and add positive effects on blood pressure,

uric acid levels, cardiovascular mortality and renal benefits in high-risk patients with T2DM [7-9].

Adverse effects of SGLT2i include genital fungal and urinary tract infections [9,10]. Special attention must be paid when prescribing this medication to frail patients who are more susceptible to postural hypotension, dehydration, and dizziness, for instance in those receiving diuretics [5]. The US Food and Drug Administration has delivered reports warning that usage of SGLT2 inhibitors may be linked with an augmented risk of DKA in both T1DM and T2DM patients [11]. This complication has been observed in the context of certain predisposing factors, which includes reduction in insulin provision, infections, surgery, alcohol intake and dietary derangements [11-16].

Case Presentation

An 80 year-old female non-obese T2DM with hypertension, dyslipidaemia and peripheral neuropathy developed DKA while

Table 1: Pertinent Laboratory Results in the patient with DKA.

Case	Initial	Reference value
Glycemia (mg/dL)	398	70-100
pH	6.8	7.35-7.45
pO ₂ (mmHg)	117.4	75-100
pCO ₂ (mmHg)	11.7	13.9
Bicarbonate (mmol/L)	1.8	22-26
Ketoneuria (mg/dL)	150	0
Beta hydroxybutyrate (mmol/L)	3.2	less than 0.6
Lactate (mmol/L)	1.1	1.0-1.7
BUN (mg/dL)	22.8	7.9-20.1
Creatinine	0.96	0.62-1.3
Na (mEq/L)	135	135-145
K (mEq/L)	4.1	3.5-5.1
Chloride (mEq/L)	106.5	98-107
Calcium	8.1	8.6-10.1
Osmolality (mOsm/Kg)	300.25	Aug-16
Anion Gap (mEq/L)	26.7	1.0-10.0

traveling in a cruise-ship through the Caribbean. Three weeks before during a medical evaluation performed by a general doctor, her usual treatment, which consisted of glimepiride and metformin, was changed to sitagliptin 100 mg and dapagliflozin 5 mg because the glycosylated haemoglobin A1c was 10.3%. The patient also received losartan 50 mg and simvastatin 20 mg daily. With the change of the antihyperglycemic agents there was no improvement in glycaemic control. However, the patient was able to maintain normal daily routine activities. While in the ship the patient decided to eat salads, meats, drank water, sugar free refreshments and occasionally alcoholic beverages. Twelve hours before admission the patient presented epigastric pain, nausea, vomiting, malaise, fatigue and muscle pain. The patient gradually became hypotensive and comatose. She was treated with two litres of saline solutions. In the evening of that day the patient was airlifted to the Emergency Department of a General Hospital in San José, Costa Rica. On arrival at the public general hospital the heart rate was 120 beats per minute, respiratory frequency 16/min with profound respiration. The patient was a febrile and her blood pressure was 108/65 mmHg. Heart sounds were rhythmic and lungs were clear. The abdomen was soft without masses with normal peristaltic movements. Haemoglobin was 12.6 g/dL, leucocyte count was $21.0 \times 10^3 \mu\text{L}$ and platelet count $253 \times 10^3 \mu\text{L}$. Liver function tests, C-reactive protein, troponins were negative. The urine smear showed erythrocyturia, abundant bacteria and 10 leucocytes per field. Urine and blood cultures became negative. The electrocardiogram, thorax X rays and abdominal ultrasound were unremarkable. Table 1 illustrates the initial arterial blood gases, electrolytes and renal function tests. Dapagliflozin, losartan and simvastatin were discontinued. The patient continued receiving 1 litre of balanced electrolyte solutions each 8 hours, and a continuous insulin infusion for two more days. Cephoxitine 2 g each 12 hours was initiated due to the suspicion of a urinary infection. The metabolic acidosis reverted in 48 hours (pH 7.42, pCO₂ 16.6 mmHg, bicarbonate 11.0 mmo/L) and glycemia ranged between 180 to 230 mg/dL. Intravenous insulin infusion was discontinued and subcutaneous human insulin was initiated. On the second day the patient developed hypokalemia and acute kidney failure. The blood urea nitrogen and creatinine concentrations increased to 43.0 mg/dL and 2.6 mg/dL, respectively. Another urine smear showed few granular casts and erythrocyturia. The haemoglobin

dropped to 11.4 g/dL and the white blood cell count gradually decreased to $11.1 \times 10^3 \mu\text{L}$. Five days later when the patient was stable she was referred to Hospital CIMA for further management where a basal bolus regimen with insulin analogues was started. The renal function gradually normalized and the haemoglobin increased. Also, the C-peptide level was of 1.13 ng/mL (0.9-7.10) with a concomitant glucose level of 150 mg/dL.

Discussion and Conclusion

This elderly fragile patient with long lasting T2DM recently treated with SGLT-2i developed DKA. Myocardial infarction, heart failure, acute intra-abdominal infection was not documented. At presentation the patient had severe metabolic acidosis, and hemodynamic instability. These conditions resolved within 48 hours with insulin and fluid replacement therapy [17]. However, while the patient was still in the local hospital, hypokalaemia, anemia and acute kidney failure occurred. Hypokalaemia was clearly the result of inadequate potassium replacement. As the patient was not anemic before admission and there was no evidence of bleeding during this acute episode, dilution of haemoglobin was likely the cause of the reduction in hematologic parameters. The acute kidney failure was probably due to hypovolemia aggravated by the angiotensin II blocker. These agents in the presence of volume depletion can prolong hypotension and may contribute to kidney failure. In addition, since infections can precipitate DKA [17] the physician's in-charge of the patient in the local hospital considered reasonable to employ antibiotics.

We received the patient at Hospital CIMA after 5 days of treatment when most the acute complications were resolved. She was discharged 5 days later receiving a basal bolus regimen with insulin analogues, continued with her usual antihypertensive and lipid lowering treatment. Regular contact with the patient and her family has been maintained over the last 6 months.

SGLT2 inhibitors improve glycemic control by inhibiting glucose reabsorption at the proximal renal tubule [1-4]. SGLT-2i also reduces glucose stimulated insulin secretion and diminishes insulin concentrations [1-4]. In response to a lower insulin inhibition and suppression of SGLT2 receptors found in the alpha cells, glucagon concentrations increase [18,19]. Alterations in insulin/glucagon ratio can lead to exaggerated lipolysis from adipose tissue and increased ketogenesis [19-21]. Under these conditions, diabetic patients receiving SGLT2i have an increased the risk for DKA [18-21]. Of note, during the two weeks prior to the trip, when the patient was receiving the new medications, no improvements in glucose control were observed. However she remained clinically stable. In this case, based on the pathophysiology of DKA associated with SGLT-2i [18-21], it seems unlikely that the DPP-4i had a role in the development of DKA. DKA was conceivable precipitated by reduction in carbohydrate intake, prolonged fasting and ethanol intake in the background of insulin deficiency, as the C-peptide concentration was not elevated in the presence of hyperglycemia.

We recently reported a case of DKA in a type 1 diabetic male in whom insulin provision was markedly reduced after initiation of SGLT2 [22,17]. SGLT2i-associated DKA could occur at any duration of SGLT2i use [22,23] as it was seen in our case report.

DKA associated with SGLT-2i is uncommon. A meta-analysis of randomized controlled clinical trials reported an unimportant effect of the medications on the presence of DKA. After the initial warning made by the FDA the incidence of SGLT2i-associated DKA were less than 1/1000 in controlled trials and 1.6/1000 person-years in cohort studies and a recently a report of nationwide population based cohort

from Korea, the risk of hospitalization for DKA was not increased in those treated with SGLT2 inhibitor vs DPP4 users [22,23].

It is important to highlight that polypharmacy in the elderly, especially with borderline renal or hepatic function and an unknown pharmacologic interaction increases the risk of complications [24-26]. Furthermore, particular attention must be exercised to avoid liquid overload and a careful replacement of electrolytes in elderly patients with DKA [17].

Finally, care must be paid when fragile T2DM patients change their prescription and in particular if SGLT-2 are involved in this change. In such cases it is recommended that patients must report any suspicious manifestation of DKA and to monitor ketone levels if they become sick [25].

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