Euglycemic diabetic ketoacidosis in type 2 diabetes mellitus treated with sodium-glucose cotransporter 2 inhibitors. A report on two cases

Antonio Burgio,[1] Maurizio Alletto,[1] Salvatore Amico,[2] Umberto Castiglione,[1] Giovanni Fulco,[1] Concetta Groppuso,[1] Gianfranco Gruttadauria,[1] Susanna Salvaggio,[1] Aulo Di Grande,[2] Federico Vancheri[1]

[1]Internal Medicine, S. Elia Hospital, Caltanissetta; [2]Emergency Department, S. Elia Hospital, Caltanissetta, Italy

ABSTRACT

Sodium-glucose cotransporter 2 inhibitors are a new second-line medication in the management of hyperglycemia in type 2 diabetes. These drugs can be associated with the development of diabetic ketoacidosis (DKA) with normal or moderately increased blood glucose levels. This is a life-threatening clinical condition termed euglycemic DKA (euDKA), of which the diagnosis can be delayed due to the relative euglycemia. We report on two patients with type 2 diabetes who presented to the Emergency Department with malaise, nausea and vomiting. Both patients had been taking dapagliflozin for at least six months. A risk factor for the development of ketoacidosis, namely heavy alcohol consumption, was found in one of the patients. Arterial blood gas analysis showed severe metabolic acidosis with increased anion gap, positive serum and urine ketones and normal arterial lactate. The patients were treated in Internal Medicine with intravenous fluids, insulin, sodium bicarbonate and potassium. Dapagliflozin was stopped. Both patients recovered uneventfully. Even in the absence of significant hyperglycemia, accurate interpretation of arterial blood gas analysis and serum ketones should lead to correct diagnosis of euDKA.

Introduction

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a new class of antihyperglycemic medications for the treatment of patients with type 2 diabetes mellitus (T2DM).[1-4] These agents decrease the concentration of blood glucose independently of insulin secretion through the inhibition of sodium-glucose cotransporter 2, which is responsible for more than 80% of renal glucose reabsorption in the proximal tubuli, thereby increasing urinary glucose excretion.[5] The agents also increase glucagon levels and ketone renal reabsorption, leading to an increased blood concentration of ketone bodies.[6] In addition, these drugs have been reported to decrease the risk of major cardiovascular events and to slow the progression of diabetic kidney disease.[7-9] SGTL2 inhibitors are a second-line treatment after metformin, or a first-line treatment in patients unable to tolerate metformin. Three molecules are currently in use: canagliflozin, dapagliflozin and empagliflozin.

These drugs may induce the development of diabetic ketoacidosis (DKA) in the absence of significantly elevated blood glucose level. This condition is termed euglycemic DKA (euDKA), was first described in 1973[10] and is defined as a metabolic state comprising three components: increased anion-gap metabolic acidosis, positive serum and urine ketones, and blood glucose levels <250 mg/dL.[11,12]

Although rare, this is a serious clinical condition, of which the diagnosis may be delayed or missed due to the relative euglycemia.

In May 2015, the U.S. Food and Drug Administration (FDA) released a warning concerning a potential increased risk of DKA in patients taking SGLT2 inhibitors, followed one month later by the European Medicine Agency.[13,14] FDA also identified potential triggering factors such as intercurrent illness, reduced fluid and food intake, reduced insulin dose and history of alcohol intake. As a consequence of the risk of euDKA, patients with latent autoimmune diabetes of

Correspondence: Federico Vancheri, Internal Medicine, S. Elia Hospital, Viale Luigi Monaco 1, 93100 Caltanissetta, Italy.
E-mail: fvanche@tin.it

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adulthood (LADA), both type 1 and type 2 diabetes, chronic consumption of alcohol, acute illness, or patients undergoing surgery, should be informed about the possibility of this potential life-threatening complication when taking SGLT2 inhibitors.[15]

We describe two patients with T2DM presenting with euDKA associated with the use of SGTL2 inhibitors.

Case Reports

Case #1

A 47-year-old woman with T2DM for seven years, normal weight [body mass index (BMI) 22], presented to the Emergency Department (ED) with vomiting, anorexia and malaise. She reported alcohol abuse at home in the last two days. The day before hospital admission she had developed muscle weakness and dysarthria. Her medical history included HIV positivity and anxious-depressive syndrome. She had been taking long-acting insulin plus metformin (2 g/die) with the addition of an SGLT2 inhibitor (dapagliflozin 10 mg) for the previous six months.

On admission, she appeared volume depleted. Physical examination showed dry mucosal membranes, absence of axillary sweat, blood pressure 120/60 mmHg, heart rate 90/min, respiratory rate 22/min, temperature 37°C. Blood glucose was 220 mg/dL (12.2 mmol/L). Serum ketones were positive. Arterial blood gas analysis performed 30 min after her arrival showed a severe metabolic acidosis with reduced plasma bicarbonate and increased anion gap (pH 7.09, HCO_3 4.0 mmol/L, anion gap 33.5, pCO_2 13.2 mmHg, normal lactic acid. The patient was admitted to the Internal Medicine ward with the diagnosis of DKA. The patient was treated with 500 mL/h of isotonic saline for the first 8 h, parenteral administration of 8 U.I/h of regular insulin, and parenteral administration of 10 mEq/h of potassium. The bicarbonate infusion was calculated as bicarbonate deficit using the formula:

HCO_3 deficit = 0.6 × weight (kg) ×
(optimal HCO_3 – measured HCO_3).

The bicarbonate deficit was restored in three hours by the administration of intravenous sodium bicarbonate and stopped at pH ≥7.2. The effect of therapy was regularly checked every hour for six hours and every two hours thereafter. The DKA resolved in about 36 h. Dapagliflozin was discontinued and the patient was discharged on an insulin basal bolus regimen. In the subsequent weeks there was no recurrence of DKA.

Case #2

Patient #2 was a 50-year-old woman with T2DM for nine years, normal weight, clinical history of uterine leiomyoma with metrorrhagic cycles, atrioventricular nodal reentrant tachycardia treated with radiofrequency catheter ablation, and aneurysm of the interatrial septum with small left to right shunt. She presented to the ED because of vague symptoms of general weakness, malaise, nausea and vomiting during the last three days. Her regular medications included metformin 850 mg three times a day. Because of uncontrolled blood sugar, as evidenced by high hemoglobin A1C (HbA1c) levels (9.1%), in 2016 dapagliflozin 5 mg once daily was started.

On admission, the physical examination showed blood pressure 115/60 mmHg, pulse rate 96 beats/min, oxygen saturation of pulse oximetry measurement 98%, Kussmaul breathing pattern, no lower extremity edema or jugular venous distention, temperature 36.1°C. Laboratory results showed glycemia 190 mg/dL (10.5 mmol/L), creatinine 0.64 mg/dL, glomerular filtration rate estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation 104, mild hyponatremia 133 mmol/L, serum potassium 3.84 mmol/L, serum osmolality 294 mosm/kg, macrocytic anemia (hemoglobin 8.2 g/dL, mean corpuscular volume 106), leukopenia (3900 cells/mm^3), severe thrombocytopenia (28,000 cells/mm^3), and a slight increase of C-reactive protein (8.4).

Urine analysis showed glycosuria (1000 mg/dL), ketonuria (>80 mg/dL), microalbuminuria (30 mg/dL) and no evidence of infection.

Blood gas analysis showed severe metabolic acidosis with increased anion gap (pH 7.21, pCO_2 19.1 mmHg, HCO_3 7.6 mmol/L, BE –18.3 mmol/L, anion gap 20 mmol/L) and normal levels of lactate (9 mg/dL). Testing for toxic alcohols including methanol, ethylene glycol and diethylene glycol was negative.

Chest radiography and ultrasound of the abdomen were normal.

The clinical and laboratory picture of the patient appeared to be euDKA induced by dapagliflozin. Dapagliflozin treatment was stopped and the patient was treated with intravenous fluid, insulin with dextrose and bicarbonate.

Despite this therapy, laboratory tests after a few hours of treatment showed no improvement. Hemodialysis was started with progressive improvement of blood gas analysis values (pH 7.37, pCO_2 29.1 mmHg, HCO_3 16.6 mmol/L, BE –7.76 mmol/L, anion gap 12 mmol/L) and normal lactate (8 mg/dL).

The patient was admitted to the Internal Medicine ward to continue the treatment with insulin and intravenous hydration until the resolution of the metabolic acidosis. The patient was discharged with the diagnosis of euDKA induced by dapagliflozin.

Discussion

DKA is a potentially life-threatening complication of T1DM although it can also rarely occur in patients with T2DM under stressful conditions such as infections or trauma. DKA develops as a result of absolute e/o relative insulin deficiency with subsequent lipolysis, increased free fatty acids, a subsequent increase in glucagon level, and therefore, production of ketone bodies. Hyperglycemia, usually higher than 300 mg/dL, is a key diagnostic criterion of DKA.[16]

The clinical presentation and laboratory values of the two patients were highly suggestive of DKA, although they had T2DM in which the development of DKA is unusual. In addition, glycemic levels were only mildly elevated. It is usually reported that the absence of severe hyperglycemia may delay the diagnosis of euDKA. However, when uremia or exogenous acid intoxication are excluded, the correct interpretation of blood and urine ketones, and the increased anion gap, with normal or reduced bicarbonate and lactate, should lead to the diagnosis of euDKA.

The pathophysiologic mechanism of DKA in patients taking SGTL2 inhibitors is different from that of patients with type-1 diabetes. The decrease of glucose level in the fasting and postprandial state induced by persistent glycosuria triggers a sequence of metabolic changes consisting of a reduction in insulin production from beta cells, alfa-cells stimulation and an increase in plasma glucagon concentration.[17,18] In addition, SGLT2 inhibitors may decrease the renal clearance of ketone bodies, further increasing the concentration of ketone in the body. These mechanisms in combination lead to the production of ketone bodies in the presence of normal or mildly elevated blood glucose levels (<250 mg/dL) (Figure 1).[19-22]

The risk of developing DKA in patients with T2DM taking SGTL2 inhibitors is low, although it has not been fully defined. Randomized drug development studies in T2DM patients showed that the incidence of DKA was 0.07% (12 events in 17,596 patients) in the SGTL2-treated group compared to 0.03% (two events in 6909 patients) in the comparator group.[23] The analysis of the FDA Adverse Event Reporting System (FAERS) showed a seven-fold increase of the risk of acidosis in T2DM patients treated with SGTL2 inhibitors.[24] On the other hand, retrospective observational studies did not find any statistically significant difference in DKA incidence between T2DM patients treated with SGTL2 inhibitors and patients treated with other drugs.[25,26]

The available evidence supports the notion that SGLT2 inhibitor-associated DKA is rare, is usually triggered by known precipitants, and can be prevented.[27] According to the current guidelines,[28] patients with at least two of the following factors: BMI <25, age of diabetes onset younger than 50 years, personal or family history of autoimmune disease or acute symptoms such as polyuria or polydipsia, should be screened for C-peptide level and anti-glutamic-acid-decarboxylase antibody titer. Once LADA is diagnosed, treatment with SGLT2 inhibitors should be avoided or performed with caution under close monitoring to reduce the risk of DKA.[29] Treatment

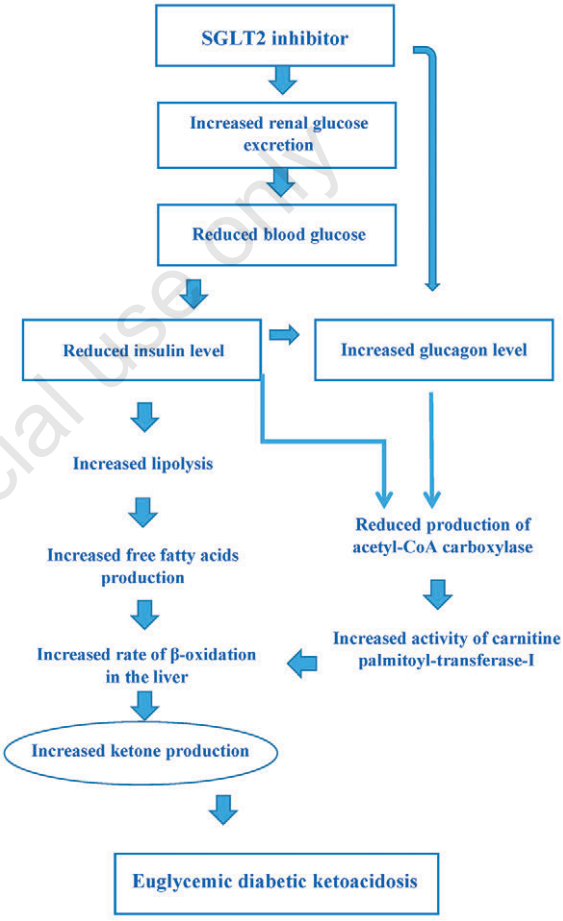

Figure 1. Possible mechanisms whereby sodium-glucose cotransporter 2 (SGLT2) inhibitors might induce euglycemic diabetic ketoacidosis. SGLT2 inhibitors lower blood glucose by increasing renal glucose excretion. As a consequence, insulin secretion is reduced. This results in an increase in the production of ketone bodies, through a lowering of insulin antilipolytic activity, stimulation of free fatty acids production, and the oxidation of these acids by the liver. The secretion of glucagon may be increased both by a direct effect of SGLT2 on pancreatic cells or by the reduced insulin secretion. Glucagon stimulates the activity of carnitine palmitoyl-transferase-I, which increases the rate of β-oxidation of free fatty acids in the liver, thus contributing to the increased production of ketone bodies. *Modified from Ogawa and Sakaguchi, 2016.*[17]

with SGTL2 inhibitors should be stopped 24 h before elective surgery, planned invasive procedures, or anticipated stressful physical activity. Excessive alcohol intake and a very low carbohydrate diet, both potentially ketogenic factors, can precipitate DKA. Reduction of insulin dose is another precipitating factor. It is recommended that patients taking SGLT2 inhibitors should avoid stopping insulin or excessively decreasing the dose.[17]

Conclusions

SGLT2 inhibitors are effective antihyperglycemic drugs. Although SGTL2 inhibitor-associated euDKA is rare, it represents a life-threatening event. Rapid recognition is based on the correct interpretation of serum ketones, bicarbonate level and anion gap, even in the absence of significant hyperglycemia. Effective prevention is feasible through accurate selection of patients to treat.

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