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

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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 DDP-4 inhibitor (DDP-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-hydroxybutirate 3.2 mmol/L and lactate 1.1 mmol/L. The estimated osmolarity 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 × 10³ µL and platelet count 253 × 10³ µL. Two days after hospitalisation the patient developed an acute kidney failure. 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...
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. Due to the change of the
antihyperglycemic agents there was no improvement in glycemic
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
contracted with SGLT2i. 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 x 10^3/µl and platelet count 253 x 10^3/µl. Liver function tests,
C-reactive protein, troponins were negative. The urine smear showed
erythrocytura, 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.
Cephoxinetine 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, PO2 16.6 mmHg, bicarbonate 11.0 mmol/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 erythrocytura. The haemoglobin
dropped to 11.4 g/dL and the white blood cell count gradually
decreased to 11.1 x 10^9/µL. 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 angiotensine 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 marked 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

**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       |
| pO2 (mmHg)         | 117.4    | 75-100          |
| pCO2 (mmHg)        | 11.7     | 13.9            |
| Bicarbonate (mmol/L)| 1.8   | 22-26           |
| Ketonuria (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 (mg/dL)| 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 (mg/dL)    | 8.1      | 8.6-10.1        |
| Osmolality (mOsm/Kg)| 300.25| Aug-16         |
| Anion Gap (mEq/L)  | 26.7     | 1.0-10.0        |
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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