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Diabetic euglycemic ketoacidosis induced by oral antidiabetics type SGLT2i

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ABSTRACT

Euglycemic diabetic ketoacidosis (euglycemic DKA) is a serious complication of diabetes, which can occur in some patients treated with oral antidiabetics called sodium-glucose co-transporter 2 inhibitors (SGLT2i). This group of drugs works by increasing renal excretion of sodium and glucose, thereby lowering blood glucose levels.

Euglycemic DKA is characterized by having blood glucose levels in the normal range, usually below 200 mg/dL (11 mmol/L), which complicates early diagnosis.

We present the case of a 67-year-old patient with type 2 diabetes mellitus, treated with metformin and empagliflozin, who was admitted to the Intensive Care Unit in a coma with severe ketoacidotic decompensation.

INTRODUCTION

Classic diabetic ketoacidosis (DKA) is one of the most serious complications of diabetes. It is accompanied by hyperglycemia, metabolic acidosis, and increased ketone bodies in the blood and urine [1][2]. In a subgroup of patients, blood glucose is in the normal range or at the high limit, with values below 200 mg/dL (11 mmol/L), associated with an elevated metabolic anion gap and positive ketones. This clinical manifestation is defined as euglycemic diabetic ketoacidosis (euglycemic DKA). [3]

Conditions that can cause euglycemic DKA are: prolonged fasting, dehydration, excessive alcohol consumption, salicylate overdose, lactic acidosis, reduced insulin doses, viral or bacterial infections, tricyclic antidepressant overdose, renal tubular acidosis, starvation, glycogen storage disorders, and SGLT2i treatment. [4]

The glyphlozin family (SGLT2i), is a group of oral hypoglycemic drugs, which are used in the treatment of type 2 diabetes. Included in this group are dapagliflozin, cangliflozin and empagliflozin. These drugs were authorized in 2012 by the FDA and the EMA and are recommended as second-line therapy associated with insulin and other oral antidiabetics, such as metformin, as they improve glycemic control [5].

CLINICAL CASE

A 67-year-old male was found unconsciously in his home by his son with a drooping corner of the mouth to the right side. His son referred hyporexia of several days.

On arrival of emergency services, the patient was still unconscious: Glasgow Coma Scale (ECG) 4/15, blood pressure (BP) 197/136 mmHg, heart rate (HR) 127 l.p.m., O2 saturation 97%. Orotracheal intubation was performed after sedation of the patient. Serotherapy was initiated followed by noradrenaline perfusion for arterial hypotension. He was transferred to the referral hospital and admitted to the Intensive Care Unit (ICU).

It should be noted that his past medical history showed remarkable high blood pressure, diabetes mellitus type 2 (DMT2) and dyslipidemia along with chronic obstructive pulmonary disease (COPD), transient ischemic attacks (TIAs) with cardioembolic profile, former heavy drinker, no Q Killip I NSTEMI (non-ST-segment elevation myocardial infarction) and depressive syndrome. Up to the moment of hospital admission, the patient was receiving treatment with several drugs, which were disulfiram, bronchodilators, lansoprazole, paroxetine, metmorfim and empagliflozin, lorazepam, rosuvastatin, adiro and olmesartan/amlodipine.

In the ICU the patient presented poor general condition with a decreased level of consciousness (ECG 3/15), hypotensive, tachycardia and tachypnea, asthenic habit, distal coldness, and dryness of mucous membranes.

Biochemistry tests were requested highlighting: glucose 191 mg/dL (10.6 mmol/L), urea 83 mg/dL (13.82 mmol/L), creatinine 1.54 mg/dL (0.14 mmol/L) (glomerular filtrate CKD-EPI 46 mL/min/1.73m^2), ultrasensitive troponin I 533 ng/L, phosphorus 7.6 mg/dL (2.45 mmol/L), magnesium 1.1 mg/dL (0.45 mmol/L), serum osmolarity 327 mOsm/Kg and osmol gap 43, remaining tests were normal. The hemogram showed 15.4× 10^9/L leukocytes, hemoglobin 13.1 g/dL (8.13 mmol/L) and 187000 platelets, with coagulation of no clinical significance. In Elemental and sediment stood out: glucose (4+) and ketone bodies (4+).

The gasometry displayed severe metabolic acidosis with a pH of 6.92, bicarbonate of 7.7 mmol/L, pCO2 of 41 mmHg, pO2 119 mmHg and an excess of bases of -24.8 mmol/L (ABLflex 800 Radiometer®).

The patient was monitored and a right central venous catheter was placed. Due to hypotension

and poor distal perfusion, noradrenaline and intense fluid therapy were continued, associating bicarbonate for severe metabolic acidosis, together with calcium and magnesium (Table 1: Timeline laboratory tests).

After reaching a certain hemodynamic stability, a cranial *computerized axial tomography (CAT)* was requested, in which bilateral and symmetrical hypodensity of both lenticular nuclei with expansive effect was detected due to volume increase, suggesting toxic/metabolic etiology.

With the suspicion of coma of possible toxic/metabolic origin, a complementary study was carried out. Toxics in urine were negative. In the cooximetry the patient presented: carboxyhemoglobin 0.7% and methemoglobin 1.6%, ruling out poisoning by toxins and CO.

Given the symptoms of metabolic acidosis with elevated anion gap (osmol gap 43 on admission), normal lactate (1.8 mmol/L), and the patient's history, alcohol poisoning was suspected. Nephrologists decided to administer hemodialysis. After the first session the patient maintained a Glasgow of 3/15, correct renal function, good diuresis rhythm and persistence of acidosis. Sample for ethanol and methanol determinations was sent to the laboratory, being within the reference range (day of admission and the following day), which rules out alcohol intoxication.

The patient needed insulin perfusion in dextran on the 3rd day of admission to the ICU, which corrected acidosis (negative ketone bodies in urine), but the patient's poor neurological response ECG: 3/15.

Once the ingestion of toxins (drugs of abuse, ethanol, methanol, salicylates, CO...) had been ruled out, the symptoms could correspond to euglycemic ketoacidosis due to empagliflozin. For its diagnosis, levels of β-hydroxybutyrate were determined in serum with a result of 103.7 mg/dL (9.96 mmol/L) (reference value <3.1 mg/dL ó < 0.3 mmol/L), improving ketoacidosis with the administration of insulin and the suspension of antidiabetic treatment from the beginning. No neurological changes at any time on the Glasgow scale.

Finally, the poor evolution and prognosis of the patient's baseline situation led to exitus on the 8th day of admission to the ICU.

DISCUSSION

Euglycemic DKA is a rare entity, which occurs with blood glucose levels below 200 mg/dL (11 mmol/L). There are several possible etiologies, with the recent use of SGLT2i being one of the triggering mechanisms. [6]

These drugs inhibit the reabsorption of sodium and glucose in the proximal and distal renal tubules, with increased glycosuria and natriuresis, thus decreasing the concentration of plasma glucose [7].The amount of glucose eliminated by the kidney through this mechanism depends on the concentration of glucose in the blood and the glomerular filtration rate.

In addition to their hypoglycemic effect, SGLT2i have other beneficial effects such as weight and blood pressure reduction, and may help prevent heart disease due to plasma volume depletion.

Glycosuria and hypoglycemia caused by SGLT2i reduce insulin secretion in pancreatic β cells and promote glucagon production. These changes in insulin and glucagon promote lipolysis and thus the production of free fatty acids, which are metabolized to ketone bodies (acetoacetate and β-hydroxybutyrate) in the liver by β-oxidation. [8], [9], [10]

Euglycemic DKA in patients being treated with SGLT2i, poses a challenge to the physician because of the few or non-specific symptoms: nausea, vomiting, abdominal pain, anorexia, polydipsia, dyspnea, confusion, normal blood glucose values, and ketoacidosis. [6] The diagnosis of this entity is sometimes late, delaying the patient's

Table 1 Timeline of laboratory tests

	Basal	1 day	2 day	3 day	4 day	5 day	6 day	7 day	8 day	Reference ranges
Markers of severe metabolic acidosis										
pH	6.92	7.3	7.38	7.33	7.34	7.29	7.40	7.44	7.46	7.35 - 7.45
Bicarbonate mmol/L	7.9	9.3	12.7	15.3	21.9	21.3	25.5	24.9	26.6	21 - 26
Base excess mmol/L	-24.8	-16	-19	-9	-3.2	-3.6	0.7	0.7	3.1	-2.5 - 2.5
Lactate mmol/L	1.8	2.8	0.6	0.7	0.6	0.6	0.7	1.4	0.6	0.5 - 2
Clinical Chemical										
Glucose mg/dL (mmol/L)	191 (10.6)	128 (7.10)	116 (6.44)	237 (13.15)	195 (10.82)	208 (11.54)	191 (10.60)	161 (8.94)	171 (9.49)	74 - 109 (4.1 - 6.1)
Urea mg/dL (mmol/L)	83 (13.82)	70 (11.65)	44 (7.32)	79 (13.14)	94 (15.64)	85 (14.15)	74 (12.31)	74 (12.31)	72 (11.98)	19 - 49 (3.16 - 8.16)
Creatinine mg/dL (mmol/L)	1.54 (0.14)	1.20 (0.11)	0.85 (0.08)	0.90 (0.08)	1.04 (0.09)	.76 (0.07)	0.68 (0.06)	0.73 (0.07)	0.70 (0.06)	0.72 - 1.18 (0.063 - 0.10)
Calcium mg/dL (mmol/L)	7 (1.77)	7.6 (1.89)	8.3 (2.07)	9.0 (2.25)	8.6 (2.12)	8.3 (2.07)	8.4 (2.10)	8.1 (2.02)	7.7 (1.92)	8.4 - 10.4 (2.1 - 2.6)
Magnesium mg/dL (mmol/L)	1.1 (0.45)	1.7 (0.70)	1.4 (0.58)	1.7 (0.70)	1.6 (0.66)	1.4 (0.58)	1.3 (0.53)	1.4 (0.58)	1.7 (0.70)	1.6 - 2.5 (0.7 - 1.03)
Phosphorus mg/dL (mmol/L)	7.6 (2.45)	4.4 (1.42)	3.9 (1.26)	1.8 (0.58)	2.1 (0.68)		2.6 (0.84)	2.8 (0.90)	3.1 (1.00)	2.4 - 5.1 (0.8 -1.65)
Urine analysis										
Glucose	4+			4+						-
Ketone bodies	4 +			±						-

treatment, most of the time due to exclusion. [4] The temporary cessation of SGLT2i, hydration, frequent carbohydrate intake and administration of insulin boluses, together with the administration of bicarbonate, allows the control of ketoacidosis in 12 hours, although most severe cases necessitate several days of care in the ICU. [5], [8].

In the case described, due to the patient's poor condition and personal history, a diagnosis of toxic/metabolic coma (toxins, CO, salicylates, methanol) was made. Once this diagnosis was dismissed, the possibility of treatment with SGLT2i (emplagliflozin) was assessed as the cause of the severe ketoacidosis that he presented (very high osmol gap), confirming the new diagnosis with the result of β-hydroxybutyrate in serum days after his admission. The outcome of this case is a result of the severe decompensation he presented upon arrival at the hospital, his diagnosis by exclusion and delay in treatment.

Euglycemic DKA due to SGLT2i is extremely uncommon, with an estimated incidence of 2 out of every 10,000 patients treated with these drugs. It can sometimes go unnoticed, making it an under-diagnosed entity. Euglycemic DKA is more common in patients treated with dapagliflozin than with empagliflozin. [9]

Patients treated with SGLT2i are recommended to make follow-up appointments with their physician, to be aware of possible complications, and to periodically have ketone bodies in blood or urine (test strips) measured (it is important to note that when these levels are high, the patient should report to the emergency department). [11]

LEARNING POINTS

- Euglycemic DKA is a rare and dangerous adverse effect of SGLT2i type drugs.
- The use of SGLT2i is indicated only in type 2 diabetics; its use in insulin-dependent diabetics multiplies the risk of euglycemic DKA.
- The determination of a pH lower than 7.2 together with glycemias lower than 200 mg/dL (11 mmol/L) and ketonuria are the main biochemical indicators of euglycemic DKA.
- In patients treated with SGLT2i, the determination of ketonuria is recommended as a screening procedure.

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