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SCIENTIFIC LETTERS

Canagliflozin induced diabetic ketoacidosis☆

Cetoacidosis diabética asociada a tratamiento con canagliflozina

We report the case of a 60-year-old Spanish male usually resident abroad, diagnosed with type 1 diabetes mellitus (T1DM) in 1992, with no associated vascular complications and with metabolic control, with mean HbA1c levels of 7.5–8% in the previous years. He was on basal-bolus insulin therapy consisting of insulin glargine 30 UI/day plus insulin glulisine 8 UI before breakfast, 18 UI before lunch, and 18 UI before dinner (total dose, 74 UI, 0.9 UI/kg of weight). The patient also had HBP treated with enalapril 20 mg and hypercholesterolemia on treatment with simvastatin 10 mg. His endocrinologist prescribed him, in addition to his regular insulin therapy, canagliflozin 100 mg/day, which he started during his holidays in Spain. The patient noted a rapid decrease in blood glucose and gradually reduced his insulin dose to 24 U of insulin glargine and 5 U of insulin glulisine before breakfast, 8 U before lunch, and 10 U before dinner (total dose, 47 U, 0.6 U/kg of weight). Thirteen days after treatment start and after drinking heavily the night before, patient had profuse vomiting and epigastric pain in the morning, and had a blood glucose level of 130 mg/dL and ketonemia higher than 3 mmol/L. Although the patient adequately interpreted ketonemia as a risk, he performed no correction with insulin because his glucose levels were normal. Due to persistent gastrointestinal intolerance, he ate nothing and used no insulin for 24 h, after which he attended the emergency room. A physical examination found a heart rate of 114 bpm, a respiratory rate of 25 rpm, and blood pressure of 140/78 mmHg, no signs of rehydration and a good level of consciousness. The results of laboratory tests at the emergency room were as follows: blood glucose, 499 mg/dL; urea, 77 mg/dL; creatinine, 1.58 mg/dL; Na, 140 mEq/L; K, 5.5 mEq/L; ketonuria 3+; capillary β-hydroxybutyrate, 9 mmol/L; pH 7; bicarbonate, 11 mmol/L; and the anion gap, 30. Liver function tests and lipase levels were normal. Based on a diagnosis of moderate diabetic ketoacidosis (DKA), intensive fluid therapy and intravenous insulin administration were started, achieving a normalization of the blood glucose level, the negativization of ketonemia, and the correction of metabolic acidosis in 12 h. The gastrointestinal symptoms disappeared, which allowed for the resumption of subcutaneous insulin. The patient remained asymptomatic and was discharged at 72 h on his regular insulin regimen. Canagliflozin was discontinued.

Type 2 sodium-glucose cotransporter (SGLT2) inhibitors are oral antidiabetic drugs (OADs) whose mechanism of action is the reduction of the renal reabsorption of glucose in order to increase its urinary excretion, thus reducing plasma glucose levels. They are indicated for the treatment of type 2 DM, alone or associated with other OADs or insulin. In different clinical development studies, SGLT2 inhibitors have been shown to improve blood glucose control, and have also achieved weight loss and blood pressure reduction. The efficacy and safety of SGLT2 inhibitors in type 1 DM is being tested in phase 3 clinical trials, with preliminary data[1] showing improved blood glucose control and decreased insulin requirements. There are three active ingredients currently on the market, dapagliflozin, canagliflozin, and empagliflozin, of which the first has been available in Spain since December 2013, while the other two have been available since 2015.

In May 2015, the US Food and Drug Administration (FDA), and subsequently the European Medicines Agency (EMA), issued an alert regarding the association of these drugs with the occurrence of DKA, of which 101 cases had been reported worldwide (0.5 cases per million population/year). DKA induced by SGLT2 inhibitors is characterized by blood glucose levels less than 250 mg/dL, while the remaining laboratory profile (metabolic acidosis with an elevated anion gap, elevated ketonemia and ketonuria) is as usual in typical DKA. The mean time to DKA occurrence from the start of treatment with SGLT2 inhibitors is 15 days (range, 1–175 days). In one third of the cases reported, the patients had type 1 DM (a non-approved indication of SGLT2 inhibitors). Predisposing factors such as infection, decreased calorie and fluid intake, or insulin dose reduction and alcohol consumption, were identified in half the cases.

DKA occurs when there is a deficit of glucose as an energy substrate in relation to insulin deficiency. The body resorts to the beta-oxidation of fatty acids as an alternative source of energy, which leads to ketone production (β-hydroxybutyrate) and, consequently, metabolic acidosis.

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The pathophysiology of DKA caused by SGLT2 inhibitors differs in several aspects from that of classical DKA[2,3]:

- DKA occurs with lower glucose levels (blood glucose <250 mg/dL) due to the greater renal losses of glucose induced by SGLT2 inhibitors. The decrease in the amount of glucose available as an energy substrate is the main causal mechanism. The decreased renal elimination of ketone bodies due to the stimulation of their tubular reabsorption is also involved in the genesis of DKA.
- DKA develops with slightly decreased insulin levels (mild insulinopenia); these occur as compensation when blood glucose levels decrease (relative insulinopenia), and are not an essential pathophysiological element.
- Elevated glucagon levels appear upon the stimulation of glucagon secretion by pancreatic α-cells which express SGLT2 receptors. The participation of SGLT2 inhibitors in the regulation of glucagon gene expression and in gluconeogenesis has recently been shown.[4] There is also an indirect mechanism, i.e. an increased insulin/glucagon ratio after the decrease in insulin levels.

To sum up, the reported patient with T1DM experienced moderate DKA associated with the use of canagliflozin after 13 days of treatment and triggered by alcohol consumption. Blood glucose levels were initially normal, but insulin discontinuation combined with decreased food intake promoted the subsequent development of DKA with overt hyperglycemia.

DKA is a serious complication. Few cases of DKA have been reported in patients treated with SGLT2 inhibitors, and the atypical presentation already discussed should be emphasized. Health care professionals should inform patients treated with SGLT2 inhibitors about the symptoms of DKA and the need for consulting their doctor if they occur. In these cases, the measurement of ketonemia should be performed irrespective of blood glucose levels. The most recent statement issued by the EMA[5] recommends for patients being treated with SGLT2 inhibitors the temporary interruption of treatment in the event of surgery or severe intercurrent disease. It also advises that patients be informed regarding the risk situations that may predispose them to ketoacidosis, such as intake restriction, severe dehydration, alcohol abuse, or increased insulin requirements due to infection.

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False overt hyperthyroidism by interference in immunoassay☆

Falso hipertiroidismo franco por interferencia en inmunoanálisis

Despite the great advances in the sensitivity and specificity of laboratory methods, cases with significant clinical-biochemical discrepancies still occur in some patients. A case of technical interference in the laboratory is reported below.

This was a 38-year-old male patient with a history of X-linked adrenoleukodystrophy (XLAD), confirmed by genetic study and fatty acid tests. Laboratory tests and clinical signs were also consistent with adrenal insufficiency. Since diagnosis the patient had received treatment with low-dose hydrocortisone, 15 mg daily in two divided doses, and was asymptomatic. He had been clinically monitored by the endocrinology department of our hospital since 2010. The patient had participated in different clinical trials for patients with XLAD, in which he received different antioxidant drugs. In January 2016, thyroid function tests showed a thyroid-stimulating hormone level of 0.07 mcU/mL (reference range: 0.30–5 mcU/mL) and a free thyroxine level of 3.89 ng/dL (reference range: 0.93–1.7 ng/dL). The patient denied any clinical symptom of hyperthyroidism, and the physical examination was normal.

Because of the clinical-biochemical discordance, the patient was asked about the treatment he was receiving, and reported that he was participating in a clinical trial with biotin (300 mg/day). The references consulted confirmed that biotin may interfere with laboratory tests using antibodies (Ab) or antigens (Ag) conjugated with biotin in their reactions. This was the case in the initial results of

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