Empagliflozin-Induced Euglycemic Diabetic Ketoacidosis in Type 2 Diabetes Mellitus

Sir,

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a new class of antihyperglycemic medications that inhibit sodium-dependent glucose uptake in the kidneys and promote glycosuria. Here, we describe a case of euglycemic diabetic ketoacidosis (EuDKA) due to empagliflozin in a patient with type 2 diabetes mellitus (T2DM) to increase physicians’ awareness and to avoid delays in the recognition of this serious side effect.

A 61-year-old male with T2DM presented to the emergency department with HbA1c of 8.7%. He was on insulin Mixtard® 70/30 (45 U) twice a day subcutaneously and on a combination of sitagliptin 50 mg, metformin 1 g twice a day and empagliflozin 10 mg daily, the dosage of which was increased to 25 mg daily 5 days prior to his acute presentation. The patient presented to the emergency room complaining of diffuse abdominal pain, decreased oral intake, nausea and vomiting. He was afebrile and hemodynamically stable. He had mild tenderness all over the abdomen. The rest of the physical examination was unremarkable.

Laboratory testing revealed a serum glucose of 11.8 mmol/L (3.9–6.9 mmol/L), a serum bicarbonate of 13 mmol/L (22–31 mmol/L), a high anion gap of 27 mmol/L, a pH of 7.21, a PCO$_2$ of 3.8 kPa (4.6–6 kPa), lactate of 2.5 mmol/L (0.05–2.00 mmol/L) and 4+ ketones in the urine. Serum electrolytes, blood urea nitrogen, creatinine, lipase, amylase, liver function tests and complete blood count were within normal limits. The cardiac enzymes and electrocardiogram were negative for any cardiac ischemia. The septic workup was negative. The patient was admitted as a case of EuDKA secondary to empagliflozin, as no other precipitating factor for his diabetic ketoacidosis (DKA) could be identified. The patient was started on continuous intravenous hydration and insulin infusion. His acidosis resolved and anion gap closed within the first 24 h of presentation, and intravenous fluids and insulin infusion were discontinued on day 3. The patient was discharged on gliclazide 30 mg daily, metformin extended release 1 g daily and insulin 70/30 (30 U) twice daily.

DKA and EuDKA are rare serious adverse effects of the SGLT2 inhibitors.[1] The Cardiovascular Outcome Trial for empagliflozin (EMPA-REG™) reported an incidence of DKA in <0.1% of the participants, with no difference between EMPA and placebo groups.[2] However, the occurrence of DKA with the use of SGLT2 inhibitor in Type 1 diabetes mellitus (T1DM) patients is 9.4% and <0.2% in patients with T2DM.[3] In fact, the United States Food and Drug Administration and the European Medicines Agency have published a formal warning regarding this potential complication in T1DM and T2DM.[4,5]

Our patient presented within a short period of time (5 days) after his empagliflozin dose was increased from 10 to 25 mg. Patients should not be re-challenged with SGLT2 inhibitor treatment after episodes of ketoacidosis. It is important to check ketonuria and ketonemia at any time a patient treated by SGLT2 inhibitor is unwell, regardless of the glucose levels. There is not enough evidence in the literature to recommend regular monitoring of ketones in patients with T2DM taking a SGLT2 inhibitor.

**Declaration of patient consent**

The author certify that they have obtained all appropriate patient consent for publication in the Journal.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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