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Case Report

Empagliflozin-Induced Euglycemic Diabetic Ketoacidosis After Esophagectomy

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Introduction

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are widely prescribed to patients with type 2 diabetes mellitus (T2DM), and were FDA approved in 2013. SGLT2i treatment has become commonplace. The American Diabetes Association (ADA) recommends their use as a second-line agent after metformin in patients with T2DM, or as a first-line agent in those who cannot tolerate metformin [1]. SGLT2i act by disrupting renal glucose resorption in the proximal tubule, increasing urinary glucose excretion, which lowers plasma glucose levels and HbA1c. Unlike other antihyperglycemic agents, SGLT2i do not interfere with endogenous glucose production nor stimulate insulin release. For this reason, this class has an attractive safety profile with substantially decreased risk of major hypoglycemic events [2].

However, SGLT2i still bear risk. Glucose homeostasis is shifted toward a starvation-like state [3], which may induce severe ketoacidosis [4]. In contrast to classical diabetic ketoacidosis (DKA), prompt diagnosis can be challenging because patients unexpectedly remain euglycemic [5]. In classical DKA, the insulin deficit leads to glucose underutilization and inappropriately high blood glucose levels, which then creates an increase in lipolysis [6]. The subsequent increase in free fatty acids and excess glucagon promotes hepatic free fatty acid oxidation and ketone body production [6].

The pathogenesis of euglycemic DKA (euDKA) differs, as circulating glucose levels are reduced. By increasing urinary glucose excretion and lowering blood glucose level, SGLTi cause a decline in endogenous insulin secretion from pancreatic cells and can lead to DKA despite euglycemia [7]. Additionally, there is a burden of evidence that SGLT2i act independently on pancreatic cells to stimulate glucagon production, further increasing hepatic ketogenesis [7]. SGLT2i additionally contribute to euDKA by increasing renal tubular absorption of ketone bodies; this confounds measurement of urine ketone bodies and makes the diagnosis of DKA even more elusive [8].

Here, we report a patient developing euDKA after esophagectomy due to preoperative empagliflozin exposure. The high prevalence of T2DM, the increasing prescribing rates of SGLT2i, and prolonged interruption of enteral nutrition during perioperative periods, all make euDKA an important differential diagnosis for anesthesiologists. Written HIPAA authorization was obtained from the patient.

Case Description

A 72-year-old gentleman with type 2 diabetes mellitus and esophageal adenocarcinoma underwent an elective transhiatal esophagectomy. He was maintained on dual antihyperglycemic therapy with metformin and empagliflozin (SGLT2i). As per surgical protocol, the patient was kept strictly nil per os (NPO) for 2 days after surgery. On postoperative day (POD) 2, the patient became progressively hyperpneic to a respiratory rate of 30 bpm. Arterial blood gas analysis revealed pH 7.32, PaCO2 16 mmHg,

and bicarbonate 8.2 mmol/L. Serum biochemistry demonstrated Na 141 mEq/L and Cl 105 mEq/L, revealing a high anion gap metabolic acidosis with respiratory compensation. Further workup revealed lactate 0.42 mmol/L, urine ketones 20 mg/dL, serum beta hydroxybutyric acid > 4.5 mmol/L, and a low serum glucose level of 76 mg/dL. Empagliflozin-induced euDKA was suspected. Intravenous glucose infusion with insulin drip was started. Within 12 hours of treatment initiation, serum glucose increased to 180 mg/dL and metabolic acidosis resolved – pH 7.49, PaCO2 36 mmHg, HCO3 27.8 mmol/L. Enteral nutrition was reestablished on POD 4 and patient was transitioned to an insulin sliding scale. The patient was discharged on POD 13 without any recurrence of ketoacidosis or residual acid-base disorders.

Discussion

Diabetic patients taking SGLT2i are predisposed to euDKA during the perioperative period. Diagnosis and initiation of treatment for SGLT2i-associated DKA may be delayed because of the euglycemic nature of the ketoacidosis. This contrasts with the typical hyperglycemia associated with DKA. SGLT2i have a rapid oral absorption and a long elimination half-life that can range from approximately 10 to 24 hours [9]. This pharmacokinetic profile lends to the current guidelines regarding perioperative management of SGLT2i. Cessation of SGLT2i 72 hours pre-operatively is recommended in elective surgical patients, and resumption only 24 hours after oral intake has returned to normal. EuDKA must be recognized during this period of prolonged fasting [10].

Presenting symptoms of euDKA are similar to those seen in traditional DKA: abdominal pain, nausea, vomiting, fatigue or dyspnea are the most common [11]. Low serum bicarbonate and positive urine ketones can be suggestive of DKA, but these measures are unreliable during SGLT2i use11. Parameters that more accurately diagnose euDKA are acidemia (pH <7.3), high anion gap (>10), and elevated β-hydroxybutyrate level (≥40 mg/dL in adults). Additionally, the American Association of Clinical Endocrinologists (AACE) recommends direct measurement of blood ketones to confirm the presence of euDKA [11].

As with classical DKA, treatment of euDKA requires expeditious initiation of fluid replacement and insulin infusion with glucose supplementation to restore acid-base and glucose homeostasis. Any agents that can contribute to ketogenesis, such as SGLT2i, should be promptly discontinued. The ADA now recommends initiating fluid resuscitation with 1-1.5 L/hr of isotonic fluids during the first 1 to 2 hours [12]. Delivering insulin therapy prior to fluid replacement may exacerbate an already severe dehydration state; continuous insulin infusion should be initiated only following IV hydration at a rate of 0.05 to 0.1 U/kg/hr12. Insulin should also be delayed until serum potassium level is greater than 3.3 mEq/L. Serum potassium should be carefully monitored and repleted intravenously as necessary [13]. Since serum glucose in euDKA is, by definition, less than 250 mg/dL, it is imperative to supplement 5% dextrose to the initial fluids to avoid hypoglycemia and curtail ketone formation [14]. No prospective randomized study has shown bicarbonate therapy to confer any benefit in DKA patients with a pH ≥ 6.9; the use of bicarbonate in this context is not supported [15].

The case described here stresses the importance of clinical vigilance in the perioperative period for patients taking SGLT2i. Early assessment of arterial blood gas and serum ketones is cardinal, as euglycemic status does not exclude the diagnosis of ketoacidosis. Resuscitative measures with isotonic solutions and insulin infusion will normalize the metabolic embarrassment. Expeditious diagnosis and treatment normalized our critically ill patient and served as a lesson for this rare presentation of this perilous disease process.

Conflict of Interest

None.

Acknowledgement

None.

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