Case Report

Empagliflozin induced euglycemic diabetic ketoacidosis. A case reports

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ABSTRACT

Introduction: Diabetic ketoacidosis (DKA) is one of the most serious acute complications of diabetes. Its defining features are hyperglycemia and ketoacidosis. Euglycemic DKA (EDKA) affects patients whose serum glucose levels are within the normal range. The use of sodium-glucose cotransporter 2 (SGLT2) inhibitors is one of the newly identified risks for this condition.
Case presentation: A 75-year-old woman with type 2 diabetes mellitus presented to our emergency department with decreased consciousness and decreased oral intake for two days. She had been diagnosed with a cerebrovascular accident for 12 days, and empagliflozin was added to her medications. Laboratory evaluation revealed metabolic acidosis, despite a minimally elevated serum glucose concentration. The patient was admitted to the intensive care unit with EDKA secondary to empagliflozin and treated with intravenous rehydration therapy and intravenous insulin infusion.
Conclusions: Empagliflozin (SGLT2 inhibitor) is a new anti-hyperglycemic medication that is associated with an increased risk of DKA. Several patients present with normal or minimally elevated serum glucose concentration, which frequently leads to a delay in diagnosis. EDKA should be considered when evaluating a patient with unexplained metabolic acidosis while taking an SGLT2 inhibitor, and SGLT2 inhibitors should be discontinued if acidosis is confirmed.

1. Introduction

Diabetic ketoacidosis (DKA) is one of the most significant and acute consequences of diabetes. Its defining features are hyperglycemia and ketoacidosis [1]. Euglycemic DKA (EDKA) refers to a state in which a patient's serum glucose concentration is within the normal range (euglycemic means that the patient's plasma glucose concentration is less than 250 mg/dl) [2]. The normal blood glucose concentration in EDKA prevents patients and doctors from immediately recognizing this issue. The use of sodium-glucose cotransporter 2 (SGLT2) inhibitors is a newly found risk for this illness [3,4].

The study aims to present a case with Empagliflozin-Induced Euglycemic Diabetic Ketoacidosis. The report has been written in line with SCARE 2020 guidelines [5].

2. Case presentation

A 75-year-old woman with a 15-year history of type 2 diabetes had poor control with oral hypoglycemic agents, including metformin and insulin Mixtard 70/30 (15 U) twice a day. She has positive family history of type 2 diabetes. She was recently diagnosed with a cerebrovascular accident (CVA) and discharged with empagliflozin, aspirin, and atorvastatin treatment 12 days before her acute presentation.

She was brought to the emergency department by her family because of decreased consciousness and decreased oral intake for two days. There were no preceding cardiovascular, respiratory, or gastrointestinal symptoms. She had no fever, sore throat, cough, headache, chest pain, syncope, diarrhea, vomiting, or urinary problems. She denied a history of chronic abdominal pain, weight loss, thyroid disease, ischemic heart disease, or recent travel.

Physical examination revealed a presentation temperature of 36.3 °C, pulse rate of 110 beats/min, respiratory rate of 28 breaths/min, and blood pressure of 110/89 mmHg. She was moderately dehydrated, with dry oral mucosa and poor skin turgor. The chest examination results were normal, and the other examination findings were unremarkable.

Owing to the patient's state at presentation, a non-enhanced computed tomography scan of the head showed no intracranial pathologies. Chest radiography, urine culture, and a full septic workup were performed. The patient tested negative for signs of infection. The cardiac enzyme concentrations and electrocardiogram results were negative.

Venous blood gas showed a pH of 7.12, pCO$_2$ of 38 mmHg, HCO$_3$ of 12, sodium of 149 mmol/L, potassium of 3.6 mmol/L, glucose of 185 mg/dl, and lactate of 2.4 mmol/L. The initial biochemistry showed serum sodium of 139 meq/L, potassium of 5 meq/L, chloride of 102 meq/L, albumin of 43.5 g/L, and serum glucose of 190 mg/dl. The corrected sodium was calculated to be 140 meq/L, the anion gap was 25, serum osmolality was 288 mOsm/kg, and urine ketone was positive +3.

The patient was admitted to the intensive care unit with EDKA secondary to empagliflozin use, as no other precipitating factor could be identified.

The patient was treated with intravenous insulin infusion and intravenous rehydration therapy. Repeated blood gas analyses demonstrated gradual resolution of the ketoacidosis, with a normalized anion gap and elimination of the serum ketones. The patient was discharged and placed on metformin extended release of 1 g daily and insulin 70/30 (20 U) twice daily.

3. Discussion

Empagliflozin is an SGLT2 inhibitor. It increases urinary glucose excretion, which decreases blood sugar concentrations. Recent research has demonstrated that SGLT2 inhibitors provide cardiorenal advantages unrelated to glycemic control [6–8]. The popularity of this medicine has increased as a result of these findings, particularly in patients with cardiorenal comorbidities [6–8]. One of the profound adverse effects of EDKA remains a concern. Patients with diabetes treated with SGLT2 inhibitors experience EDKA episodes more frequently when their body mass index is lower and glycogen stores are decreased [3]. It has been demonstrated that the duration of use has no relevance to the risk of EDKA associated with SGLT2 inhibitors [9–11].

The mechanism of action of SGLT2 inhibitors is to promote excretion and block glucose reabsorption from the proximal convoluted tubule. The loss of urinary glucose results in a state of carbohydrate starvation and volume depletion, increasing the glucagon/insulin ratio and leading to a state of severe dehydration and ketosis [3].

Additionally, SGLT2 inhibitors enhance the release of glucagon from the pancreas, which worsens the existing glucagon/insulin imbalance. They also inhibit the ability of the kidneys to remove beta-hydroxybutyrate and acetoacetate [12–15]. Owing to the loss of urine glucose and SGLT2 inhibitor-induced hypoinsulinemia, euglycemia is preserved [4,11,12]. SGLT2 inhibitors also improve ketone reabsorption [9,14].

The symptoms of EDKA induced by SGLT2 inhibitors are similar to those of DKA. However, EDKA patients typically do not have the same severity of dehydration symptoms as other DKA patients [16,17–19]. Any patient using SGLT2 inhibitors who experiences nausea, vomiting, or fatigue should have their serum ketones assessed, and SGLT2 inhibitors should be discontinued if acidosis is present.

The management of EDKA caused by SGLT2 inhibitor use is similar to that of DKA but with caution for the absence of hyperglycemia. Ideally, isotonic saline should be administered for resuscitation. This should be followed by ongoing intravenous insulin infusion at a rate of 0.02–0.05 units/kg/h [6]. To prevent hypoglycemia, dextrose-containing fluids should be started at the same time as the insulin infusion. Throughout the treatment, the serum glucose and electrolyte concentrations were monitored. The presence of two of the following conditions indicates the resolution of EDKA: a serum bicarbonate concentration of 15 mmol/L, an anion gap of 12 mmol/L, or a venous pH of >7.3 [6].

4. Conclusions

A novel family of antihyperglycemic drugs, known as SGLT2 inhibitors, have been shown to significantly lower the risk of cardiovascular disease and kidney problems in people with type 2 diabetes mellitus. Their use seems to increase the risk of DKA. Several cases present with euglycemia, which frequently leads to delayed diagnosis.

Euglycemia is a common feature in several patients and frequently causes delays in diagnosis. When assessing a patient who is on an SGLT2 inhibitor and has unexplained metabolic acidosis, EDKA should be considered. If acidosis is observed, SGLT2 inhibitors should be discontinued.

Ethical approval

This is a case report, therefore, Approval is not necessary for case report in our locality.

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Author's contribution

Waleed M.Altowayan: follow up the patient, writing the manuscript and final approval of the manuscript and he is the corresponding author.

Declaration of competing interest

The authors report no conflicts of interest.

Trial registry number

1. Name of the registry: NA.
2. Unique Identifying number or registration ID: NA.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): NA.

Guarantor

Waleed Altowayan is the Guarantor of submission.

Consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2022.104879.

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