

Euglycemic diabetic ketoacidosis caused by dapagliflozin

A case report

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Abstract

Rationale: Diabetic ketoacidosis is a serious and potentially life-threatening acute complication of diabetes mellitus (DM). Euglycemic diabetic ketoacidosis (eDKA) is however challenging to identify in the emergency department (ED) due to absence of marked hyperglycemia, often leading to delayed diagnosis and treatment. eDKA has been recently found to be associated with sodium-glucose cotransporter 2 (SGLT2) inhibitors, one of the newest classes of antidiabetics, though there are very limited reports implicating dapagliflozin as the offending agent in ED patients. Here we report a type 2 diabetic patient who presented to the ED with eDKA secondary to dapagliflozin administration.

Patient concerns: A 61-year-old Asian female with underlying type 2 DM presented to our ED with body weakness, dyspnea, nausea, vomiting, and mild abdominal pain for the past 2 days. These symptoms were preceded by poor oral intake for 1 week due to severe toothache. Dapagliflozin was recently added to her antidiabetic drug regimen of metformin and glibenclamide 2 weeks ago.

Diagnoses: Arterial blood gases showed a picture of severe metabolic acidosis with an elevated anion gap, while ketones were elevated in blood and positive in urine. Blood glucose was mildly elevated at 180 mg/dL. Serum lactate levels were normal. Our patient was thus diagnosed with eDKA.

Intervention: Our patient was promptly admitted to the intensive care unit and treated for eDKA through intravenous rehydration therapy with insulin infusion.

Outcomes: Serial blood gas analyses showed gradual resolution of the patient's ketoacidosis with normalized anion gap and clearance of serum ketones. She was discharged uneventfully on day 4, with permanent cessation of dapagliflozin administration.

Lessons: Life-threatening eDKA as a complication of dapagliflozin is a challenging and easily missed diagnosis in the ED. Such an ED presentation is very rare, nevertheless emergency physicians are reminded to consider the diagnosis of eDKA in a patient whose drug regimen includes any SGLT2 inhibitor, especially if the patient presents with nausea, vomiting, abdominal pain, dyspnea, lethargy, and is clinically dehydrated. These patients should then be investigated with ketone studies and blood gas analyses regardless of blood glucose levels for prompt diagnosis and treatment.

Abbreviations: DKA = diabetic ketoacidosis, DM = diabetes mellitus, ED = emergency department, eDKA = euglycemic diabetic ketoacidosis, EP = emergency physician, ICU = intensive care unit, SGLT2 = sodium-glucose cotransporter 2.

Keywords: dapagliflozin, emergency department (ED), euglycemic diabetic ketoacidosis (eDKA), sodium-glucose cotransporter 2 (SGLT2) inhibitors, type 2 diabetes mellitus (DM)

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Y-MC and C-JS are the first authors and contributed equally to this article.

Ethical approval: This case report was approved by the Institutional Review Board of Chang Gung Medical Foundation (IRB number 201700317B0). Informed consent was also obtained from the patient.

The authors have no conflicts of interest to disclose.

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1. Introduction

Diabetic ketoacidosis (DKA), a serious and potentially life-threatening acute complication of diabetes mellitus (DM), is characterized by ketoacidosis and hyperglycemia. Euglycemic DKA (eDKA), however, presents with a plasma glucose of <200 mg/dL,^[1] and is therefore challenging to identify in the emergency department (ED). Absence of marked hyperglycemia in the patient often leads to delayed diagnosis. Besides being reported in type 1 diabetic patients and pregnant women, eDKA has also recently been found to be associated with sodium-glucose cotransporter 2 (SGLT2) inhibitors, one of the newest classes of antidiabetic medications that achieve glycemic control by inhibiting renal glucose reabsorption and promoting glycosuria. Earlier reports of SGLT2 inhibitor-related eDKA have mostly centered around canagliflozin, ipragliflozin, and empagliflozin,^[2] with very limited reports of dapagliflozin as the offending drug in ED patients.^[3,4] Here we report a type 2 diabetic patient who presented to the ED with eDKA secondary to the administration of dapagliflozin (FORXIGA; AstraZeneca, Indiana). This report

reinforces to emergency physicians (EPs) the fact that though very rare, patients on dapagliflozin can present to the ED atypically in a state of DKA with relative normoglycemia, resulting in EPs unacquainted with SGLT2 inhibitors and its associated life-threatening complications missing or delaying the diagnosis of eDKA.

2. Case report

A 61-year-old Asian female with underlying type 2 DM presented to our ED with body weakness, dyspnea, nausea, vomiting, and mild abdominal pain for the past 2 days. These symptoms were preceded by poor oral intake for 1 week due to severe toothache. The patient had no fever, chills, alcohol intake, nor history of operation. She has had type 2 DM for the past 10 years, previously treated with a combination of metformin 1g twice daily and glibenclamide 10mg twice daily, with dapagliflozin 10 mg once daily being added to the regimen 2 weeks ago. Vital signs at presentation were: temperature 36.1°C, pulse rate 127 beats/min, respiratory rate 28 breaths/min, blood pressure 153/89 mm Hg. She was ill looking, noted to have Kussmaul breathing, and was moderately dehydrated with sunken eyes, dry oral mucosa, and poor skin turgor. Auscultation of the lungs revealed no significant findings. Arterial blood gases showed a picture of severe metabolic acidosis with an elevated anion gap (pH 6.986, CO₂ 20.9 mm Hg, HCO₃⁻ 7.0 mEq/L, anion gap 20 mEq/L), though blood sugar was found to be mildly elevated (180.0 mg/dL). Blood ketones were found to be elevated at 8.0 mmol/L, urine was positive for ketones, and serum lactate levels were normal (9.0 mg/dL). Renal function test revealed serum blood urea nitrogen of 25 mg/dL and serum creatinine of 0.8 mg/dL. She was promptly admitted to the intensive care unit (ICU) and treated for eDKA through intravenous rehydration therapy with insulin infusion. Serial blood gas analyses showed gradual resolution of her ketoacidosis with normalized anion gap and clearance of serum ketones. The patient was discharged from the ICU on day 2 and the general ward on day 4 uneventfully, with permanent cessation of dapagliflozin administration.

3. Discussion

Dapagliflozin is a selective SGLT2 inhibitor approved by the U.S. Food and Drug Administration in January 2014 to treat DM, either as a single treatment or in combination with other antidiabetics.^[5] Experiences with dapagliflozin-associated eDKA in the ED are still very limited.^[3,4] Being rarely observed in type 2 DM, eDKA can prove to be a diagnostic challenge for EPs unfamiliar with this class of antidiabetics, especially since ketone studies and blood gas analyses are not part of the standard workup for diabetic patients in the ED. Seemingly normal blood glucose levels may also convey a false impression of the patient's clinical stability, leading to a lower triage priority and delayed treatment.

DKA is classically defined as presence of the triad of hyperglycemia (>250 mg/dL), ketosis, and anion-gap acidosis. eDKA is then DKA without marked hyperglycemia.^[6] Indeed, our patient had ketoacidosis (blood pH 6.986, blood ketones 8.0 mmol/L), yet blood sugar levels of 180.0 mg/dL are far below the usual means of that in the "traditional" DKA—the diagnosis would thus have been missed if we had ruled out DKA based on the absence of marked hyperglycemia.

eDKA in type 1 diabetic patients is primarily due to reduced carbohydrate availability with concomitant reduction in insulin

dosage. eDKA in our patient, a type 2 diabetic lady on dapagliflozin, however has a different pathophysiology—SGLT2 inhibition caused a sharp spike in the urinary excretion of glucose in our patient. Plasma glucose concentrations subsequently fell, further exacerbated by her poor oral intake for the past 1 week. Since insulin release is dependent on glucose, pancreatic release of insulin decreased correspondingly; our patient did not have exogenous insulin injections either. Reduced inhibition by insulin, coupled with decreased SGLT2-mediated glucose transport into α -cells, then led to significant increase in plasma glucagon levels. These shifts in hormones enabled gluconeogenesis in the liver and augmented endogenous glucose production. Paradoxically, insulin sensitivity ultimately improved, limiting the rise in our patient's plasma glucose concentration.^[7]

While these changes in our patient's glucose homeostasis were ongoing, insulin deficiency caused a concurrent increase in lipolysis from her peripheral fat tissues, releasing free fatty acids. These fatty acids were subsequently converted into acetyl-CoA via beta-oxidation by hepatic mitochondria, and acetyl-CoA molecules entered the ketogenic metabolic cycle to produce acetoacetic acid. Acetoacetic acid was then reduced to beta-hydroxybutyric acid; accumulation of these two acids resulted in an elevated anion gap metabolic acidosis. Acetoacetic acid was also decarboxylated to acetone, a ketone body which served as an alternative energy source for our patient in her state of reduced intracellular glucose availability secondary to insulin deficiency.^[1] All these metabolic processes thus ultimately manifested as eDKA.

Decreased oral intake, as seen in our patient, is a risk factor for SGLT2 inhibitor-related eDKA. Other possible precipitants include alcohol intake, surgery or perioperative preparations, insulin reduction or cessation, infections, hepatic or renal impairments, acute coronary events, and pancreatitis.^[3,6,8]

4. Conclusion

We report a case of life-threatening eDKA as a complication of dapagliflozin, a challenging and easily missed diagnosis in the ED. Such an ED presentation is very rare, nevertheless EPs are reminded to consider the diagnosis of eDKA in a patient whose drug regimen includes any SGLT2 inhibitor, especially if the patient presents with nausea, vomiting, abdominal pain, dyspnea, lethargy, and is clinically dehydrated. These patients should then be investigated with ketone studies and blood gas analyses regardless of blood glucose levels for prompt diagnosis and treatment. Patients started on SGLT2 inhibitors can also be counseled to perform urine dipstick tests to check for ketones should they feel unwell, and seek medical treatment immediately if positive.

Author contributions

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