Euglycemic diabetic ketoacidosis associated with SGLT2 inhibitor use in non-type 1 diabetes mellitus

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Abstract

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have been associated with the development of euglycemic diabetic ketoacidosis (EuDKA), a potentially life threatening condition with an indolent presentation. The rates of EuDKA in clinical trial patients with Type 2 Diabetes (T2D) was under 1%, but there is increasing recognition of this complication in hospitalized patients. This report shares our experience of five cases of non-T1D associated EuDKA during an inpatient hospitalization over an 8-month period between October 2015 and June 2016. In our series, two patients had Type 2 Diabetes (T2D) and three had pancreatogenic diabetes, with one presenting post-Whipple’s resection of a pancreatic cyst and two others with acute pancreatitis. The median time to DKA from last dose of SGLT2 inhibitor was 2 days (range 0.75-6). Glucosuria (>1000 mg/dL) with euglycemia was present at diagnosis in all patients and persisted for up to 12 days after discontinuation of the drug. All patients were treated with dextrose and IV or SubQ insulin, depending on the severity of the acidemia. The time to resolution of acidemia was 0.5-4 days. Based on our clinical experience, current recommendations to stop SGLT-2 Inhibitors 24 hours prior to a surgery with a prolonged NPO are not adequate. Additionally, risks can also be minimized by administering basal insulin and empiric dextrose in at risk hospitalized patients who are NPO, despite normal blood sugars.

Keywords: Diabetes, SGLT-2 Inhibitors, DKA, Euglycemic DKA

Background

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have been associated with the development of Euglycemic Diabetic Ketoacidosis (EuDKA), a potentially life threatening condition with an indolent presentation. The initial case series published comprised mostly of people with Type 1 Diabetes (T1D) and there is increasing recognition of this complication in patients with non-T1D [1-3]. The rates of EuDKA in clinical trial patients with T1D are estimated to be up to 6% and in those with T2DM, under 1% [2,4].

Objective

To report on our hospital’s experience with SGLT2 inhibitor-associated euglycemic DKA in five patients with non-T1D and provide evidence for a relationship between early case detection and rapid resolution of acidemia.

Methods and Findings

A retrospective chart review was performed after obtaining approval from our Institutional Review Board. Five patients with non-T1D were identified as developing SGLT2 inhibitor associated EuDKA during an inpatient hospitalization over an 8-month period between October 2015 and June 2016. EuDKA was defined by the presence of an anion gap metabolic acidosis (Anion gap ≥ 12, serum bicarbonate level <19 mmol/L) and ketosis (serum beta hydroxybutyrate [B-OHB] ≥ 3 mmol/L) without marked hyperglycemia (blood glucose <250 mg/dL).

Patient demographics and clinical findings are summarized in Table 1. Two patients had Type 2 Diabetes (T2D). Three had pancreatogenic diabetes with one presenting post-Whipple's resection of a pancreatic cyst and two others with acute pancreatitis. The median age of the patients was 64 years (range 56-65), median duration of diabetes was 15 years, and median duration of SGLT2 inhibitor use was 6 months (range 1-18 mos). Four patients were receiving canagliflozin and one empagliflozin. Median time to DKA from last dose of SGLT2 inhibitor was 2 days (range 0.75-6). Median time to DKA from a precipitating event of pancreatic insult and/or fasting restriction (NPO) was 2 days (range 1-4). Median B-OHB level at diagnosis of EuDKA was 5.3 mmol/L (range 3.3-5.9), and median blood glucose was 112 mg/dL (range 73-208). Glucosuria (>1000 mg/dL) with euglycemia was present at diagnosis in all patients and was used to evaluate for drug effect. Glucosuria persisted for up to 12 days following the pre-hospital discontinuation of SGLT2 inhibitor use for one patient on the maximum dose of canagliflozin and up to 6 days in patients on lower drug doses. Management with insulin and dextrose infusion led to resolution of DKA after 0.5-4 days. Based on our clinical experience, current recommendations to stop SGLT-2 Inhibitors 24 hours prior to a surgery with a prolonged NPO are not adequate. Additionally, risks can also be minimized by administering basal insulin and empiric dextrose in at risk hospitalized patients who are NPO, despite normal blood sugars.

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rates were not adjusted below 0.02 units/kg/hr and the time on the insulin infusion was shortened. Beginning with the third patient, all patients were transitioned to basal insulin once DKA resolved (defined as HCO3 >18 mmol/L and anion gap <10), as glucosuria persisted. The time to diagnosis of EuDKA from the identified precipitant was correlated to the time to resolution of DKA (r=0.89; p<0.05).

**Discussion and Conclusion**

Widely recognized risk factors for SGLT2I- associated EuDKA include starvation, surgery, sepsis, excessive alcohol intake, and reduced subcutaneous insulin dose in patients on insulin therapy [5]. Hospitalization for pancreatic disease likely represent an additional risk factor beyond these. Proposed mechanisms of DKA in the setting of SGLT2I therapy include alterations in balance between gluconeogenesis and ketogenesis. SGLT2I through increasing urinary glucose excretion, reduces insulin secretion from pancreatic β-cells. These medications also have direct effects on pancreatic alpha cells, leading to increased glucagon release and the kidney, leading to enhanced tubular reabsorption of ketones through the electromechanical gradient generated by SGLT2I- induced inhibition of sodium reabsorption [6-9].

EuDKA risk can be minimized by earlier discontinuation of SGLT2 inhibitor therapy prior to a planned surgery with a prolonged post-operative NPO and during an episode of acute illness. There are currently no perioperative consensus guidelines for management of patients on SGLT inhibitors. Initial professional society recommendations were to stop SGLT-2 inhibitors for at least 24 hours pre-operatively [10]. A 2016 recommendation from an expert panel, after a review of the early literature, suggested stopping these drugs 3 days prior to surgery [11]. Recommendations from anesthesiology groups differ as well, with recommendations to hold these medications for 24-48, but more frequently 72 hours [12-14]. Based on our clinical experience, we would recommend stopping these drugs at least 3 and when possible up to 7 days prior to surgery. Prompt recognition of EuDKA can lower morbidity and should involve monitoring the basic metabolic panel and glucose in fasting, peri and post-operative patients, and patients admitted with pancreatitis who were on an SGLT2 inhibitor. Patients with worsening acidemia, regardless of blood glucose level, should have an assessment of serum ketones, pH, and a urinalysis for glucosuria to evaluate for EuDKA. Ongoing catabolism can be addressed by providing insulin (subQ or IV depending on severity of the acidemia) and dextrose or nutritional therapy even when blood glucose is “on-target” for a hospitalized patient. Although in most recent case series, patients’ initial treatment is IV insulin, in our experience subQ insulin can be used effectively and safely, especially in patients with mild EuDKA [13-15]. Risk for EuDKA can also be minimized by administering basal insulin and empiric dextrose in hospitalized patients who are NPO, despite normal blood sugars that might incline physicians and other providers to hold basal insulin.

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References


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