Case Series

Sodium Glucose Transporter 2 Inhibitors and Diabetic Ketoacidosis in Three Patients with Diabetes: Underlying Causation

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Abstract

Sodium glucose transporter 2 inhibitors (SGLT2i) inhibit the reabsorption of glucose in the renal tubules reducing glycemia and increasing glucosuria. The increased glucosuria causes a shift in normal flora and colonization of pathogenic microorganisms leading to an increase in mycotic genital infections. Recent Food and Drug Administration reported cases of diabetic ketoacidosis (DKA) after initiation of SGLT2i probes the question of safety with such agents. The mechanisms of ketoacidosis and the breakdown of lipids are often misunderstood, and blame is placed on lack of insulin or on medications used to treat diabetes. However, many patients living with diabetes do not experience DKA if the proper treatment and management of concomitant comorbidities are addressed. After a retrospective chart review of 250 patients, three patients were identified with DKA while on SGLT2i, but for three distinct contrasting reasons. Assessment of the pharmacodynamics of SGLT2i and the pathophysiology of DKA infers that emphasis for prevention of SGLT2i-associated DKA should be placed on appropriate diagnosis, infection, and electrolyte abnormalities.

Keywords: Case series, diabetes, diabetic ketoacidosis, electrolyte abnormalities, latent autoimmune diabetes in adults, sodium glucose transporter 2 inhibitors

Introduction

The sodium glucose transporter 2 inhibitors (SGLT2i), such as canagliflozin, empagliflozin, and dapagliflozin, promote the renal excretion of glucose, and A1C is modified by the osmotic diuresis effect of the medication.[1] SGLT2i are commonly prescribed due to their ability to reduce weight and blood pressure, and lower the risk of hypoglycemia compared to sulfonylureas. Although SGLT2i use has become increasingly common (including advancing in therapy preference on the AACE/ACE algorithm), SGLT2i are not without limitation, particularly increased risk of infection.[2-4] A more recent finding is diabetic ketoacidosis (DKA). Around twenty atypical cases of acidosis were reported to the United States Food and Drug Administration (FDA) linking ketoacidosis with the SGLT2i class.[5,6] Underlying reasons for DKA with these SGLT2i has not been established. Therefore, the pharmacodynamics of SGLT2i combined with the pathophysiology of DKA was evaluated for causation.

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Methods

A retrospective chart review was conducted on patients started on SGLT2i and later presented with DKA. There are 2200 patients at Oxford Endocrinology Consultants (OEC), and 250 of these patients were referred to a pharmacist through a collaborative practice management. Charts of pharmacist-managed patients were reviewed. Three patients were identified as diagnosed with type 2 diabetes mellitus (T2DM), started on a SGLT2i, and presented to an

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emergency department (ED) with DKA. Medications, previous illnesses, and A1C were collected, as well as administration, titration, and pharmacological parameters to distinguish commonalities among patients. An extensive literature search was used to identify possible causes for DKA in the three cases found at OEC.

Results

Patient 1– appropriate diagnosis

Patient 1 was a 55-year-old Caucasian female initially diagnosed with T2DM in 2005 with an A1C of 8.9%. She was referred to OEC after presenting to the ED with nausea and vomiting in January 2015. She was diagnosed with DKA and admitted to the intensive care unit (ICU). After obtaining a medication history at OEC, it was discovered that monotherapy with canagliflozin was initiated 2 months before the DKA episode. The Naranjo score for this adverse drug reaction (ADR) was possible. After resolution of DKA, insulin detemir and insulin lispro were started while canagliflozin was discontinued. In the following months, metformin, linagliptin, and empagliflozin were gradually initiated in addition to insulin. The patient was diagnosed with latent autoimmune diabetes in adults (LADA) based on a C-peptide of 0.4 ng/mL in April 2015. The patient's average self-monitoring blood glucose decreased from 205 mg/dL to 155 mg/dL in 5 months with a slight improvement in A1C to 8.6%. The patient has not had another episode of DKA.

Patient 2– infection

Patient 2 was a 47-year-old Caucasian female initially diagnosed with T2DM in 2005 and her most recent A1C was 9.2%. She presented to the ED with DKA (blood glucose = 459 mg/dL CO_2 = 5, and pH = 6.9) in February 2014. On presentation of DKA, the patient was receiving metformin ER, liraglutide, and canagliflozin. Canagliflozin and fluconazole were added 6 days before ED presentation. The Naranjo score for this ADR was possible. In the ED, the patient was diagnosed with an underlying septic pneumonia. The patient was discharged on multi-daily insulin monotherapy with an A1C = 8% 2 months after discharge. Sitagliptin and metformin were added before the patient was lost-to-follow-up.

Patient 3– electrolyte abnormality

Patient 3 was a 56-year-old African–American female diagnosed with T2DM for an unknown duration with an A1C = 8.2%. The patient was admitted to the ICU with DKA in June 2014 after being started on dapagliflozin 2 months ago. The Naranjo score for this ADR was possible. The patient was also treated with glipizide and insulin glargine before admission. In the ED, the patient was diagnosed with an underlying electrolyte abnormality due to Fanconi syndrome. After resolution of DKA and discontinuation of dapagliflozin, the patient was started on saxagliptin.

Discussion

DKA occurs when the body does not have enough insulin to digest and utilize glucose, and the adipose tissue is catabolized to make energy instead, resulting in ketone formation.[7] SGLT functions by sodium following glucose and water following sodium through osmosis [Figure 1]. When SGLT2 is inhibited, the fluid and electrolytes are shifted and excreted in urine causing decreased blood volume hyperkalemia, and dehydration.[8,9] The addition of other medications that cause hyperkalemia (e.g., ACE inhibitors) may have an additive effect.[10] Dehydration and hyperkalemia are both predisposing factors for metabolic acidosis due to significant increase in anion gap with sodium loss.[7]

LADA is a genetic intermediate between type 1 diabetes mellitus (T1DM) and T2DM that is a slow progressing immune-mediated T1DM. DKA occurs more often in T1DM compared to T2DM due to insulin deficiency versus decreased insulin sensitivity. The diagnosis of the type of diabetes age of onset (e.g., >30 years), a low C-peptide (e.g., <0.51 ng/mL), insulin independence for <6 months after diagnosis, and/or the presence of circulating islet antibodies.[11] LADA is often misdiagnosed as T2DM due to advanced age at onset, and often LADA patients are not initiated on insulin secondary to T2DM algorithmic recommendations for initial oral therapy.[12] Patient 1 was not diagnosed with LADA before initiation of SGLT2i. The lack of exogenous insulin therapy contributed greatly to the onset of DKA in patient 1. Exposure to SGLT2i may have synergistically contributed to DKA in this patient. Interestingly, a different SGLT2i was initiated after insulin therapy without further DKA episodes.

Increased glucosuria causes a shift in normal flora and colonization of pathogenic microorganisms leading to an increase in mycotic genital infections, particularly candidiasis yeast and urinary tract infections.[9] Patients tend to lose glycemic control during infections leading to DKA.[9,13] Patient 2 is the quintessential example of infection leading to DKA. However, the addition of an SGLT2i cannot be overlooked in its contribution to infection for this patient.

Fanconi syndrome is a disorder of the proximal renal tubules (where sodium glucose transporters are located) that

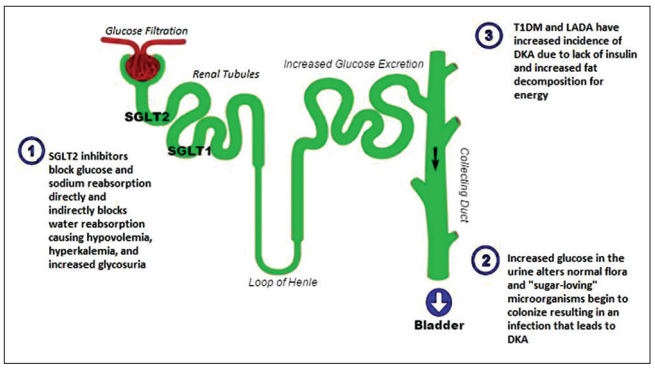

Figure 1: Mechanisms of diabetic ketoacidosis resulting from glucose transporter 2 inhibitors

results in excretion of excessive electrolytes and protein into the urine.[14] Electrolyte abnormality due to Faconi syndrome is possibly triggered by the SGLT2i use which can lead to dehydration and ketoacidosis. Patient 3 had undiagnosed Faconi syndrome and consequently exhibited symptoms of DKA following SGLT2i use.

Conclusion

DKA is a potential risk of taking the SGLT2i, and there appear to be three forewarnings that could aid in the assessment of DKA risk with SGLT2i.[2-4] Early and appropriate diagnosis of LADA may decrease the risk of hospitalization from DKA in patients started on SGLT2i without insulin therapy. SGLT2i use was safe in LADA when added to insulin therapy in this case series. The osmotic effects of these medications include: (1) increasing glucosuria, (2) causing electrolyte imbalances due to dehydration, (3) changing the normal flora, and (4) causing infection. Proper hydration, including taking SGLT2i with a glass of water, could reduce DKA incidence with SGLT2i.[10] Overly vigilant monitoring of infection, especially on SGLT2i initiation, may be warranted. It is important to rule out Faconi syndrome and other diseases that induce electrolyte abnormalities before SGLT2i initiation. Furthermore, preexisting electrolyte abnormalities must be corrected before initiation of SGLT2i.

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Conflicts of interest

There are no conflicts of interest.

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