CLINICAL VIGNETTE

SLGT-2 Inhibitor Induced Euglycemic Diabetic Ketoacidosis

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Case Report

An 80-year-old female was admitted to the hospital with acute cholecystitis. She presented to the emergency department (ED) with weakness, right upper quadrant abdominal pain, nausea, and vomiting. A Computed Tomography (CT) of the abdomen and pelvis showed a distended gallbladder with wall thickening and pericholecystic fluid stranding. She was noted to have tachycardia, but other vital signs were normal. She has a history of diabetes mellitus type 2, hypertension, and dyslipidemia. An accurate medication reconciliation on admission could not be completed because the patient was not feeling well enough to recount her medications and she received most of her medical care at an outside facility. The patient lives alone and is independent in her most of her activities of daily living, including medication management. The patient's family was unable to provide additional medication information. Per review of pharmacy records she was noted to have prescriptions for canagliflozin, dulaglutide, sitagliptin/metformin, repaglinide, quinapril, rosuvastatin, fenofibrate, mirabegron, famotidine, duloxetine, and calcitriol.

She was started on broad spectrum intravenous (IV) antibiotics and underwent open subtotal cholecystectomy with findings of a necrotic gallbladder. A drain was placed in the remnant gallbladder. On hospital day 2 (post-operative day 1) the patient was feeling well with expected post-operative pain. Her white blood cell count (WBC) improved from 23 to 16 (x10E3/uL). The surgical team recommended discontinuation of antibiotics and she started on a clear liquid diet which she tolerated well. She had difficulty tolerating side effects of IV hydromorphone and was transitioned to IV acetaminophen 1gm three times a day, which was successful in controlling her pain. Her glucose levels ranged from 162 mg/dL to 254 mg/dL. On hospital day 3 her WBC continued to improve to 13 and she remained hemodynamically stable. She was noted to have an increase in abdominal distention and changed back to nothing by mouth (NPO) status per the recommendation of the surgical team. Given her NPO status, her IV acetaminophen was extended for another 24 hours. Her glucose levels ranged from 131-150 mg/dL. On hospital day 4 (post-operative day 3) she developed emesis and tachycardia. An electrocardiogram (EKG), blood tests, chest radiograph (CXR), and IV fluids (IVF) were ordered. She appeared clinically well at this time, was alert, conversant and endorsed only mild, unchanged abdominal pain around the surgical site. On physical exam, her abdomen was soft, mildly tender to palpation around the surgical site, and without rebound or guarding. There was no erythema or purulence at the surgical site. Three hours later she screened positive for sepsis based on a nurse-driven sepsis screening protocol because of persistent tachycardia. Her lab tests showed a bicarbonate of 4 mmol/L, glucose of 210mg/dL, WBC of 15 x10E3/uL, and an anion gap of 30. A stat venous blood gas (VBG) showed a pH 6.9 and pCO2 of 24. Given severe acidemia she was transferred to the intensive care unit (ICU). Infection was the leading suspected cause of her clinical symptoms and an infectious evaluation including CXR, urinalysis, abdominal CT scan, and blood cultures were obtained and broad spectrum antibiotics were restarted. All tests were negative for infection and her blood lactate level returned normal at 13 mg/dL (nl 5-25 mg/dL). Urine ketones were +4, blood ketones were "small", and a beta-hydroxybutyrate was 139.2 mg/dL (<3 is normal). She was diagnosed with euglycemic diabetic ketoacidosis (DKA). An insulin drip was started, endocrinology was consulted, and her acidemia improved. She was eventually discharged to a skilled nursing facility for rehab. Her DKA was felt to be precipitated by her home sodium-glucose cotransporter-2 (SLGT) inhibitors, starvation from NPO status, post-operative state, and possible IV acetaminophen use.

Discussion

SLGT2 inhibitors have transformed diabetes management since they were first approved by the FDA in 2013. They inhibit renal reabsorption of glucose by blocking the sodium-glucose cotransporter in the proximal convoluted tubule in the kidney. This increases natriuresis and glucosuria, resulting in lower blood glucose levels.[1] Their benefits extend beyond blood glucose control. Studies have shown that SLGT2 inhibitors lead to a reduction in blood pressure and weight. They additionally preserve renal function, reduce the risk of heart failure decompensation and hospitalization, and reduce cardiovascular deaths.[2-6] This benefit even extends to heart failure patients with reduced EF (HFrEF) and chronic kidney disease (CKD) who are not diabetic.[7,8] These benefits have led to an increase in SLGT2 inhibitor prescriptions as well as more awareness of potential side effects. SLGT2 inhibitors can cause genital yeast infections, urinary frequency, and dehydration. Rare side effects include fractures, serious urinary tract infections, lower limb amputation and Fournier's gangrene.[9,10] In 2015 the FDA issued a warning that SLGT2 inhibitors may increase the risk of ketoacidosis after 73 cases were reported between March 2013 and May 2015. It was noted that identification and treat-

ment were delayed in many cases because blood glucose levels were not very elevated.

Euglycemic diabetic ketoacidosis (DKA) is defined as keto-acidosis with blood glucose levels less than 200-250mg/dl. It is an uncommon form of DKA and more likely to occur in patients with type 1 diabetes. Pregnancy and prolonged fasting are additional risk factors. It accounts for about 3% of DKA cases though is likely under-reported.[11] The risk of euglycemic DKA associated with SLGT-2 inhibitors varies in the literature likely due to its overall low incidence. Two reviews of adverse event registries showed that patients with type 2 diabetes on SLGT2 inhibitors had a 7-fold higher risk of developing DKA when compared to those taking dipeptidyl peptidase 4 (DPP-4) inhibitors and double the risk when compared to those taking glucagon-like peptide 1 (GLP-1) receptor agonists.[12,13] Euglycemic ketoacidosis accounted for 71% of cases of DKA in one of the reviews. A more recent multicenter retrospective cohort study reported almost 3-fold increased risk for DKA when compared to DDP-4 inhibitors.[14]

The mechanism of SLGT2 inhibitor induced ketoacidosis is not fully known. As blood glucose levels decrease with increased urinary glucose excretion, SLGT-2 inhibitors lead to reduced insulin secretion from pancreatic B-cells. This appears to promote lipid oxidation and ketogenesis. SLGT-2 inhibitors also increase glucagon secretion as a secondary effect of reduced insulin secretion or possibly as a direct effect on pancreatic alpha-cells.[15] Glucagon inhibits acetyl-CoA carboxylase which increase carnitine palmitoyltransferase–I (CPT-1) activity in the liver, leading to increased beta-oxidation of fatty acids in the mitochondria. When fatty acid oxidation increases, the liver converts the biproduct (acetoacetate) into ketone bodies.[16] The ongoing SLGT2 inhibitor medicated glucosuria prevents substantial hyperglycemia during ketogenesis. Finally, SLGT-2 inhibitors may mimic starvation conditions in the kidneys because they lower the glucose excretion threshold.[17] Canagliflozin appears to have the greatest risk of DKA compared to the other SLGT2 inhibitors likely due to its less selective inhibition of SGLT2/SGLT1. Canagliflozin may inhibit SGLT1, which is expressed in the small-intestine enterocytes which increases the risk of osmotic diarrhea and volume depletion, predisposing a person to DKA.[14] Canagliflozin also has a higher association of fractures and lower limb amputations.

While the absolute risk of euglycemic DKA is low in patient taking SLGT2 inhibitors, it is important for physicians to be aware of this possibility. DKA is a serious and life-threatening condition and delayed diagnosis could result in significant morbidity or mortality. The risk of misdiagnosis of euglycemic DKA is high as providers are often falsely reassured by relatively normal blood glucose levels and do not commonly encounter this condition. Inpatient providers, in particular, should monitor closely for acid base abnormalities in patients who take this medication and hold SLGT2 inhibitors on admission to the hospital. SLGT2 inhibitors are not recommended for patients with type 1 diabetes given the risk of DKA.

In March 2020, the FDA issued a new warning for patients on SLGT2 inhibitors undergoing surgery. The warning states:

"To lessen the risk of developing ketoacidosis after surgery, FDA has approved changes to the prescribing information for SGLT2 inhibitor diabetes medicines to recommend they be stopped temporarily before scheduled surgery. Canagliflozin, dapagliflozin, and empagliflozin should each be stopped at least three days before, and ertugliflozin should be stopped at least four days before scheduled surgery".[18]

The absence of substantial hyperglycemia delayed the diagnosis of DKA in this patient. The patient's metabolic derangements were incorrectly assumed to be an infectious complication of her surgery. In hindsight, the patient did exhibit classic clinical signs of DKA including nausea, abdominal pain, fatigue, and tachycardia. However, these clinical findings are not unusual in acute cholecystitis and the post-operative period. This patient also had other risk factors for DKA. Any acute illness can trigger DKA in a patient with diabetes. This patient also had prolonged NPO status due to concerns for a possible post-operative complication. This likely led to decreased glycogen stores, mimicking a starvation state. There was also reduced exogenous insulin ordered when the patient was NPO which may have further promoted ketogenesis. Finally, there are case reports of acetaminophen induced anion gap acidosis. Chronic therapeutic use can lead to an accumulation of 5-oxoproline, sometimes referred to as pyroglutamic acid.[19] Usually, the anion gap is quite high and it is often a diagnosis of exclusion. It's possible that 48hours of IV acetaminophen contributed to our patient's acidotic state. Confirmation of this diagnosis is via a serum 5-oxoproline level which is not widely available.

DKA is diagnosed by metabolic acidosis, hyperglycemia, and ketones in the urine or blood. Since glucose levels are normal or near normal in euglycemic DKA, a higher index of suspicion of this diagnosis is needed. Any patient who is chronically on an SLGT2 inhibitor with lab evidence of metabolic acidosis (pH <7.3 or serum bicarbonate <18mmol/L) should have urine ketones, serum ketones, and a B-hydroxybutyrate checked. The treatment of euglycemic DKA is the same as hyperglycemic DKA. Patients should be placed on an insulin drip and intravenous fluids with frequent monitoring of their acid-base status. Endocrinology consult is recommended.

There will likely be an increase in use of SLGT2 inhibitors over the next 5 years as physicians become more comfortable with the risks, benefits, and indications for this relatively new drug. Currently this medication is only prescribed to 20% of Medicare beneficiaries presumed to have type 2 diabetes[20] suggesting it is not being prescribed to its full potential to protect against cardiovascular and renal outcomes. It will also be prescribed more to non-diabetics with heart failure and CKD. In February 2022 the FDA expanded use of Empagliflozin to patients with heart failure with preserved left ventricular fraction with or without diabetes which will further expand the use. As SLGT2 inhibitors use increases, awareness

of the potential to cause euglycemic DKA will be even more important as its incidence will also increase.

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