CLINICAL VIGNETTE

Drug Induced Euglycemic Diabetic Ketoacidosis

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A 39-year-old man presented to the emergency department (ED) with a seven-day history of epigastric pain. He described the pain as moderate, non-radiating and worse with eating. He also noted nausea, with three episodes of non-bloody, non-bilious emesis. There was no history of trauma or similar symptoms in the past. His previous medical history was significant for type 2 diabetes mellitus (DM), mild peripheral neuropathy and hypercholesterolemia. He had undergone a treadmill stress test in the prior year for non-specific chest pain, which was negative. He denied fevers, chills, cough, urinary tract related symptoms or any prior episodes of pancreatitis, peptic ulcer disease or gastritis. He denied any alcohol consumption in the preceding few months and was a non-smoker. His family history was significant for coronary artery disease in both his mother and maternal grandfather. He was taking metformin 500 mg po bid, canagliflozin 300 mg po daily and pravastatin 10 mg po qhs. He denied taking aspirin; he did not have any symptoms of depression or suicidal ideation.

The vital signs were a blood pressure 150/87 mm Hg; heart rate 125 beats per minute; respiratory rate 26 breaths per minute; temperature of 36.5 °C; and 99% oxygen saturation on room air. He had an unremarkable head, eyes, ears, nose and throat exam. His pulmonary exam was normal other than tachypnea and his cardiac exam only significant for sinus tachycardia. The abdomen was soft, with mild tenderness in the epigastrium, without guarding or rebound. The remainder of the physical exam, including the extremities and neurologic evaluation, were normal.

His initial complete blood count was significant for a white cell count of 17/uL; and hemoglobin of 18.6 g/dL. The BMP was remarkable for a glucose of 198 mg/dL, sodium of 137 mmol/L, chloride of 101 mmol and a bicarbonate of 10 mmol/L. The blood urea nitrogen, creatinine and potassium were normal. His anion gap was elevated at 26. The urinalysis was remarkable for 20 mg/dL of ketones and a glucose of 300 mg/dL. Amylase and lipase were both within the normal range but serum acetone was elevated. The ECG revealed ST segment depression in the lateral leads. Additional studies included an elevated serum beta-hydroxybutyrate and a lactic acid level of 1.1 mmol/L. Arterial blood gas revealed a pH of 7.12 and a PaCO2 of 18. His Troponin I was initially 0.02 but trended up to 0.45.

He was diagnosed with diabetic ketoacidosis (DKA) and non-ST elevation myocardial infarction. A side effect profile check of his medications identified patients using metformin and canaglifozin [sodium-glucose cotransporter-2 (SGLT2) inhibitors] at increased risk for DKA with relative euglycemia. His oral hypoglycemic agents were stopped; he was treated with IV insulin and intravenous dextrose 5% at 125 cc/hour. The anion gap eventually decreased to 12 with absence of ketones in his urine. His non-ST elevation myocardial infarction was treated with aspirin, clopidigrel, carvedilol as well as enoxaparin. Cardiac catheterization revealed triple vessel coronary disease with moderate left ventricular dysfunction. He ultimately underwent a coronary artery bypass graft.

Discussion

In our case, euglycemic DKA was most likely due to the canagliflozin which has been associated with DKA and relative normoglycemia in both type 1 and type 2 diabetics.[1] Euglycemic DKA is now defined as DKA in the presence of blood glucose levels < 200 mg/dL.[2] Euglycemic DKA develops much more commonly in type 1 diabetics. At present SGLT2 inhibitor medications are only indicated for treating type 2 DM but have been used in type 1 patients off label. Prior to the inclusion of the SGLT2 inhibitors, causes of euglycemic DKA included partial treatment of DKA with insulin, starvation, excessive alcohol intake, inhibition of gluconeogenesis, and in pregnancy.[3] SGLT2 inhibitors lower blood glucose levels by increasing urinary glucose excretion. This is achieved by lowering the renal threshold for glucose excretion in a dose-dependent manner. This in turn leads to reduced insulin secretion from pancreatic beta-cells. The body responds by lowering the antilipolytic activity of insulin and stimulating free fatty acids, which are then converted to ketone bodies in the liver. SGLT2 inhibitors are also associated with an increase in glucagon production. The lowering of the insulin-to-glucagon ratio further stimulates lipolysis and increases circulating free fatty acids and lipid oxygenation.[4] The added stress response from the myocardial infarction in our patient may also have contributed to his metabolic perturbation.

A meta-analysis of canaglifozin trials found the incidence of DKA of 0.52 for 100mg and 0.76 for 300 mg per 1000 patient-years.[5] Most cases of SGLT2 inhibitor DKA have only mild or moderate increases in blood glucose levels which is mainly due to excretion of glucose in urine. In this case, DKA was associated with a low blood glucose as well. His DKA was likely triggered by reduced oral intake due to gastroparesis and exacerbated by calorie loss through canaglifozin induced glycosuria. Our patient was also taking metformin and combined

metformin-associated lactic acidosis and euglycemic keto-acidosis has been described.[6] In the rare cases where this has been reported, the metformin was associated with lactic acidosis and invariably associated with significant renal insufficiency. As our patient had both normal renal function and a normal lactic acid level, it is very unlikely that metformin was a contributing factor.

In conclusion, the incidence of diabetes mellitus in the United States is increasing. Non-Insulin hypoglycemic agents are increasingly used to treat patients who don't respond to lifestyle modification and metformin mono-therapy. Euglycemic diabetic ketoacidosis is rare but internists should have a higher index of suspicion in patients taking SGLT2 inhibitors.

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Submitted April 25, 2019