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The Maryland Poison Center's Monthly Update: News, Advances, Information

Euglycemic DKA from SGLT2 inhibitors

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are newer medications prescribed for patients with type 2 diabetes and heart failure. Some examples include empagliflozin, canagliflozin, and dapagliflozin. One unique adverse effect associated with SGLT2i's is diabetic ketoacidosis (DKA). In some instances, this can occur in the absence of significant elevations of blood glucose levels and has been termed euglycemic DKA (eDKA).

eDKA occurs because SGLT2i's reduce the blood sugar without increasing glucose utilization. This is because they induce a rapid increase in urinary glucose excretion. The agents may also have direct effects of stimulating ketogenesis and glucagon release. The body needs to compensate for a reduction in available fuel and the net result of these processes is increased free-fatty acid oxidation and ketone body production that occurs in the absence of hyperglycemia.

Despite differences in pathophysiology, the clinical presentation of eDKA and its management are nearly identical to that of traditional DKA. Patients can present with significant nausea, vomiting, and abdominal pain along with alterations in mental status. Electrolyte abnormalities and an elevated anion gap metabolic acidosis are common. Mainstays of therapy include intravenous fluid resuscitation, electrolyte correction, insulin, and early dextrose supplementation to prevent hypoglycemia. Despite the lack of overt hyperglycemia, insulin is still required to suppress glucagon activity, which is ultimately responsible for ongoing ketogenesis.

It is important to be able to identify patients at risk of developing eDKA to ensure it can be prevented or treated early. eDKA is not necessarily a consequence of acute SGLT2i overdose, but rather an adverse effect that may develop with therapeutic use in certain circumstances. Events that can precipitate eDKA include acute illness, surgical procedures, trauma, dehydration, low carbohydrate intake, reduced or insufficient insulin dosing, and excessive alcohol intake. One or more of these risk factors are often present in cases of SGLT2i eDKA. In the inpatient setting, it may be appropriate to hold SGLT2i therapy for patients undergoing surgical procedures or until acute illness has resolved. Holding therapy for a longer time period (up to 3 days) prior to surgery would take into account these agents' elimination half-lives (between 10-12 hours) and would ensure that a majority of the drug would have been eliminated from the body. It should be noted that a small number of cases have described patients developing eDKA days to weeks after SGLT2i therapy had been discontinued. High degrees of protein binding or increased elimination half-lives in patients with kidney disease may be implicated, but a definitive explanation for this phenomenon has yet to be identified.

Include eDKA as part of your differential for an elevated anion gap metabolic acidosis, especially in critically ill or post-operative patients that have a history of recent SGLT2i therapy. Arterial pH and serum beta-hydroxybutyrate levels can be measured to help confirm the diagnosis.

Did you know?

Not all ketone tests are created equally

Most urine ketone tests utilize the Legal reaction, which produces a purple color change when acetoacetate is added to nitroprusside in an alkaline medium. These tests will detect acetoacetate and sometimes acetone but not beta-hydroxybutyrate. Urine ketone tests are also semi-quantitative and do not provide real-time ketone measurement since their results reflect the average concentration in the urine since the time of last void.

Serum ketone testing can be ordered to provide quantitative, real-time measurements of ketones in plasma. Many of these tests measure for beta-hydroxybutyrate.

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