COMMENT ON ROSENSTOCK AND FERRANNINI

Euglycemic Diabetic Ketoacidosis: A Predictable, Detectable, and Preventable Safety Concern With SGLT2 Inhibitors. Diabetes Care 2015;38:1638–1642

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I felt uneasy about the assessment by Rosenstock and Ferrannini (1) that euglycemic diabetic ketoacidosis (euDKA) associated with sodium–glucose cotransporter 2 inhibitor (SGLT2i) therapy is predictable.

My patient got up, ate breakfast, and went to work only to become symptomatic later that morning. By that evening she was in the intensive care unit with arterial pH 6.8 and β-hydroxybutyrate 9.95 mmol/L (normal range 0.02–0.27) associated with blood glucose 182 mg%, creatinine 0.84 mg%, and lactate 1.4 mmol/L (0.05–2.2) and with negative results on salicylates, acetaminophen, ethylene glycol, lipase, blood cultures, transaminase, human chorionic gonadotropin, and toxicology screening. She was not known to have any of the precipitating factors, such as alcohol use, which have been described in the literature on this topic. One month previously she had been characterized as having type 2 diabetes with a fasting blood sugar of 236 mg%; insulin, 15.5 μIU/L; C-peptide, 3.1 ng/mL; GAD antibody, <1 (0.0–1.5); and HOMA2, 32 %B and 3.2 insulin resistance.

Two weeks before the event, her medicines had been changed from sitagliptin, metformin, and glipizide to sitagliptin, metformin, and dapagliflozin. She had declined a prescription for basal insulin glargine. Moderate ketonuria in a routine urinalysis at a visit prior to this change of therapy was attributed to therapeutic restriction of dietary carbohydrate and was not considered important at the time in an asymptomatic person with type 2 diabetes. She had been diagnosed with type 2 diabetes 14 years previously at age 23 at a weight of 211 lbs and had never seen an endocrinologist. Following the change of therapy to include SGLT2i, her blood glucose levels fell into a range <200 mg%.

The swiftness and severity of such metabolically overwhelming hyperketonemia could not have been anticipated in view of her relatively healthy baseline insulin and C-peptide. C-peptide levels were low or undetectable in most of the cases of euDKA reported by Erondu et al. (2). The experience with my case makes it difficult to accept the notion that euDKA associated with SGLT2i is predictable.

Peters et al. (3), in discussing their cases of euDKA, wrote "patients are generally asymptomatic until they have developed euDKA" and suggested the "only way to ensure timely recognition would be to use daily urine or blood ketone testing." But is this practice justified or likely to win compliance for such a rare event? Preliminary symptoms of a mild nature may indicate the beginning of euDKA in some patients, but the possibility of abrupt onset, as seen in my case, remains highly concerning. Perhaps people who have experienced this complication are those who were able to drastically curb dietary carbohydrate intake. We may need to advise keeping carbohydrate >40 g per meal in addition to restricting alcohol when prescribing SGLT2i therapy.

Perhaps some disproportionate increment of serum β-hydroxybutyrate not detected in the nitroprusside test would give a warning that the patient is "sliding toward euDKA" (1) prior to the emergence of symptoms. Given the importance of this class of drugs in clinical practice, I am confident that observant clinicians will find ways to manage this important safety concern.

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References

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