Severe Prolonged SGLT2i-induced Euglycemic Diabetic Ketoacidosis Refractory to Standard Therapy and Dialysis: Case Report and Literature Review

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ABSTRACT

Sodium-glucose cotransporter type 2 inhibitors (SGLT2i) are oral hypoglycemic agents that have insulin-independent glucose-lowering effects mediated by increasing the renal excretion of glucose by inhibiting the SGLT2-mediated renal glucose reabsorption. An increasingly recognized complication induced by SGLT2i is euglycemic diabetic ketoacidosis (eDKA). Here, we describe the case of a 26-year-old male patient with type 2 diabetes mellitus and morbid obesity. Prior to presentation he was on multiple oral hypoglycemic agents including SGLT2i. He developed life-threatening severe prolonged eDKA associated with SGLT2i (Canagliflozin), precipitated by adenovirus infection. The acidosis was not responding to standard DKA therapy and renal replacement therapy but was managed effectively with insulin titration based on capillary ketone measurements. After reviewing the literature on severe prolonged eDKA induced by SGLT2 and treatment modalities used, we present previously reported cases similar to ours.

Introduced in 2013, sodium-glucose cotransporter type 2 inhibitors (SGLT2i) are a relatively new class of drugs known for their glycemic and weight reduction effects, cardiovascular disease (CVD) risk reduction in type 2 diabetes mellitus (T2DM) patients, and renal protective effects in patients with chronic kidney disease. However, there are emergent risks associated with SGLT2i use. These include euglycemic diabetic ketoacidosis (eDKA), bone fractures, acute renal injury, Fournier's gangrene, and lower limbs amputations.[1]

In clinical trials with SGLT2i, eDKA rates ranged between 0.2 to 0.8 cases per 1000 patient-years among T2DM patients.[2] The tendency for underlying eDKA to accompany normal or near-normal glucose levels (< 13.9 mmol/L) may delay its recognition and management.[1] Precipitants of overt DKA include surgery, extensive exercise, myocardial infarction, stroke, severe infections, prolonged fasting, and other stressful physical and medical events.[2] Here, we described the case of a 26-year-old male patient with poorly controlled T2DM on multiple oral hypoglycemic agents, who developed life-threatening severe eDKA associated with SGLT2i use (canagliflozin). The acidosis was prolonged and refractory to standard DKA therapy and renal replacement therapy, but was managed effectively with insulin titration based on capillary ketone measurements.

CASE REPORT

A 26-year-old male presented to our hospital's emergency department in January 2020 with a four-hour history of agitation, shortness of breath, and abdominal pain. This was preceded by four days of fatigue, malaise, fever, and sore throat. He had recently joined the national military service. He was diagnosed with T2DM for seven years and was

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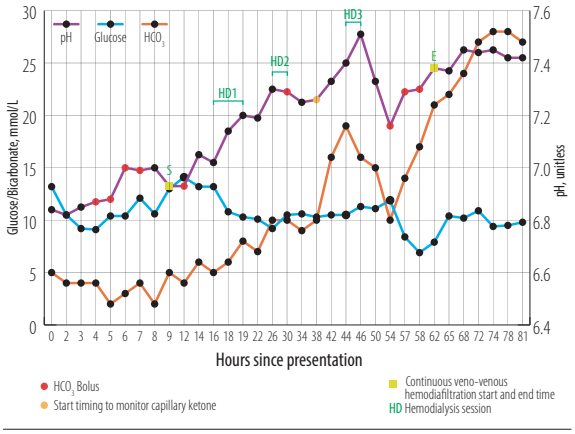

Figure 1: Changes in blood glucose, bicarbonate (HCO_3), and pH since presentation and timings of renal replacement therapy.

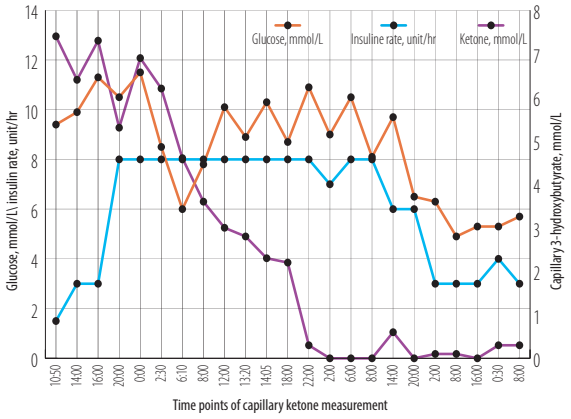

Figure 2: Insulin infusion rates compared with the levels of glucose and capillary ketones.

being treated in another institute and maintained on multiple oral hypoglycemic agents of which he could recall only metformin by name. He reported no history of recent travel. Physical examination was remarkable for dry oral mucosa. He was in distress, febrile (38.5 °C), tachycardic (110 beats per minute), tachypneic (28 breaths per minute), and had low blood pressure (110/50 mmHg) despite having received 2 L of normal saline prior to presentation. The patient was also morbidly obese with BMI of 41.52 kg/m^2 (120 kg; 170 cm). He had non-exudative pharyngitis. Chest examination revealed shallow deep breathing and bilateral vesicular breathing without added sounds. Cardiac exam was normal apart from sinus tachycardia. There was mild epigastric tenderness and other systemic examination was unremarkable.

Initial investigations revealed mild hyperglycemia (13.6 mmol/L), severe metabolic acidosis with bicarbonate level of 4 mmol/L, venous blood pH of 6.84, and high anion gap of 34. Urine ketone level was high (15 mmol/L) while lactic acid was normal at 2 mmol/L. The patient also had leukocytosis with white blood count of 29 × 10^9/L, hemoglobin of 16.4 g/L and platelet count of 350 × 10^9/L. His C-reactive protein at 64 (≤ 5) g/L, and procalcitonin at 2.3 (≤ 0.5) ng/mL were at elevated levels. The toxicology screen for alcohol and illicit drugs was negative. The following were within normal limits: sodium (135 mmol/L), potassium (3.8 mmol/L), creatinine (85 µmol /L), and urea (4 mmol/L). He had no rhabdomyolysis with normal total creatinine kinase of 223 IU/L. Serum osmolality was elevated at 315 mOsm/kg. Liver function and thyroid tests were normal.

Based on the above, broad-spectrum antibiotic therapy was started and diabetic ketoacidosis protocol was initiated with 10 units of insulin bolus followed by insulin infusion. Despite another five liters of crystalloid fluid, the patient's pH remained the same. Therefore, sodium bicarbonate ($NaHCO_3$) was infused intermittently (initial total of 250 mL of 8.4% $NaHCO_3$; nonetheless pH remained static around 6.99 [Figure 1]. Within a few hours of presentation, the patient developed respiratory distress and required assisted ventilation. As recommended by the nephrology specialist, renal replacement therapy (RRT) was initiated.

Point of care inpatient ketone measurement facility was not available in our hospital and the insulin rate was titrated based on serial glucose measurements which was well controlled with insulin infusion at the rate of one unit per hour. Basal insulin was started on the second day of admission along with insulin infusion.

After 18 hours from presentation, the patient's family brought in his home medications, which included daily gliclazide 120 mg, canagliflozin 300 mg, pioglitazone 30 mg, liraglutide 1.8 mg injection, and metformin/sitagliptin (1000/50 mg) twice daily. It was reported that he had uncontrolled diabetes and had refused to start insulin despite his primary physician's recommendations. Later, it was revealed that he was on canagliflozin (an SGLT2i) 300 mg daily for the preceding three years.

Thirty-eight hours after presentation, serial capillary blood ketone measurements using the FreeStyleOptium ketone meter (Precision Xceed!; Abbott Diabetes Care, Maidenhead, UK) was initiated to titrate insulin infusion rate along

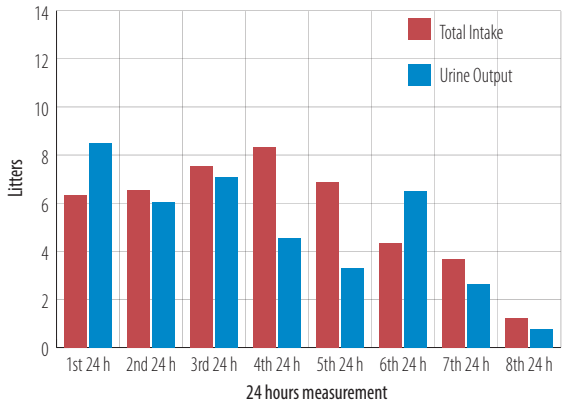

Figure 3: Total fluid intake and urine output.

with escalation of both dextrose and intravenous potassium replacement aiming for ketosis clearance [Figure 2]. The patient received a total of three sessions of intermittent hemodialysis (three hours each) and continuous veno-venous hemodiafiltration (CVVHDF) at 30 mL/kg/hour starting before first dialysis session and continued in between and after the last dialysis session [Figure 1]. In between, he required more $NaHCO_3$ boluses as well [Figure 1]. It took 62 hours to correct metabolic acidosis and thereby close the anion gap by means of RRT and changing the base of titration of insulin rate to capillary ketone levels.

On day four of hospitalization, the patient was extubated. On day five, he was shifted to basal bolus regimen. Though eDKA had resolved, ketonemia (> 0.6 mmol/L) was persistent till day 12. Prior to knowing his home medications, and in view of the refractory nature of the severe metabolic acidosis, metabolic team was consulted to rule out the possibility of inborn metabolic errors. Urine organic acid profile revealed peaks of 2-ketoisovaleric acid, acetoacetic acid, 3-OH butyric acid, and 2-OH isovaleric acid, suggestive of ketosis and advanced catabolism. In addition to that, he was noticed to have significant diuresis during the first 24 hours of presentation [Figure 3].

Further investigations including blood, sputum, and urine cultures were negative. Influenza screen, Strep A, HIV, and hepatitis B and C were also negative. Respiratory viral panel MDX was positive for adenovirus. Chest x-ray was normal initially. HbA_{1C} was 13.3%. C-peptide was 0.11 nmol/L, Anti IA2, GAD antibodies, and insulin antibodies were negative.

The patient's hospital stay was complicated with provoked femoral line site deep venous thrombosis and pulmonary embolism which was managed with anticoagulants. At discharge, he had spent 16 days in hospital.

DISCUSSION

SGLT2i are a class of oral glucose-lowering agents, first marketed in 2013. Thereafter, many reports emerged suggesting that SGLT2i increased the risk of eDKA. In 2015, US Food and Drug Administration (FDA) issued a drug safety communication that warned of an increased risk of eDKA associated with all SGLT2i class of drugs.[3] The FDA also identified potential eDKA triggering factors such as intercurrent illness, lower food and fluid intake, reduced insulin doses, and history of alcohol consumption.

A study using a large claims database in the USA found that the incidence of DKA within 180 days following initiation of SGLT2i was 2.2-fold higher than with dipeptidyl peptidase-4 inhibitors, the latter of which have no known association with eDKA.[4] From reports to the US FDA's Adverse Event Reporting System, Fadini et al,[5] found that higher proportional reporting ratios of 7.9 (95% CI: 7.5–8.4) for DKA in reports that mentioned SGLT2i compared to those without SGLT2i and having a diabetes indication and was higher for type 1 diabetes.

In cardiovascular outcome trials (CVOTs), the proportion of patients with reported diabetic ketoacidosis was similar in the SGLT2i and placebo groups for empagliflozin (EMPA-REG OUTCOME) and canagliflozin (CANVAS program), but it was higher for dapagliflozin (DECALRE-TIMI 58) with hazard ratio of 2.18 (95% CI: 1.10–4.30; $p = 0.02$).[1]

Limenta et al,[6] provided demographic and baseline laboratory investigation profiles of 20 DKA cases associated with SGLT2i that had been reported to the Health Sciences Authority, Singapore. Apart from the difference in blood glucose levels, there were no noted differences in the profiles of typical and euglycemic DKA cases. However, no data was provided regarding the duration of DKA resolution and intensive care unit (ICU) stay.[6]

A recent Korean study reported that patients using SGLT2i needed longer ICU stays than non-users (4 days vs. 2 days; $p = 0.019$). It also showed that on average DKA episodes developed

Table 1: Reported cases of severe prolonged euglycemic diabetic ketoacidosis(eDKA) with sodium glucose cotransporter type 2 inhibitors (SGLT2i) use and modalities of treatment.

Authors	Diabetes type + Other medications	SGLT2i	Precipitating factor	BMI (kg/m^2)	Glucose (mmol/L)	Bicarbonate (mmol/L)	Anion gap (mEq/L)	Ketone (mmol/L)	pH	Treatment	Comment	Duration of metabolic acidosis
Current report	26 y/o, male T2DM for seven years + multiple OHAs (poorly controlled)	Canagliflozin 300 mg	Infection	41.5	13.6	4.0	34.0	Urine ketone 3+ (15)	6.84	Insulin infusion + NaHCO3 + 3 hemodialysis sessions + CVVHDF	Intubation+ Ketonemia persisted for total 12 days	62 hours
Sloan et al, 2018[11]	63 y/o, male T2DM for 23 years + on mixed insulin	Canagliflozin seven months before presentation	Silent myocardial infarction and diverticulitis	27.2	13.3	8.0	–	5.2	7.15	Fixed and variable insulin infusion rates	Ketonemia persisted for total 12 days	five days of IV insulin
Maadarani et al, 2016[12]	44 y/o, male T2DM for eight years + insulin glargine and glimepiride	Dapagliflozin 5 mg one month before presentation	No identifiable factor	31.0	7.9	6.0	35.0	10.0	7.01	Insulin infusion up to 10 units/hour + NaHCO3 + eight hours CVVH	.	48 hours
Gelaye et al, 2016[13]	54 y/o, male T1DM + insulin glargine	Canagliflozin 300 mg three years before presentation	Postoperative day 2 laparoscopic appendectomy	–	7.9	9.0	37.0	12.4	7.06	Insulin infusion up to 10 units/hour + NaHCO3 infusion + hemodialysis	Intubation + Fomepizole	72 hours
Rafey et al, 2019[14]	44 y/o, male T2DM for five years+ GLP-1 agonist (poorly controlled)	Canagliflozin 300 mg	Postop day 6 post C5-C7 cervical decompression	38.8	9.4	44.8	33.8	4.3	7.10	Insulin infusion + basal insulin		92 hours
Rafey et al, 2019[14]	59 y/o, female T2DM for 17 years + basal bolus insulin (poorly controlled)	Empagliflozin 25 mg five months before presentation	Postop day 3 elective laparoscopic right partial nephrectomy	39.0	12.3	9.3	32.0	4.8	7.23	Insulin infusion	Stopping DKA protocol after 28 hours after normalization of glucose and pH lead to relapse	92 hours
Nappi et al, 2019[15]	67 y/o, female T2DM for five years + metformin	Empaglilozin 25 mg one month before presentation with low calories intake	NA	21.5	16.6	1.8	31.0	After 12 hours urine ketone 80 mg/dL	6.91	Insulin infusion + NaHCO3 + two days hemodialysis		1 week
Yeo et al, 2018[16]	23 y/o, female T2DM + metformin	Dapagliflozin 10 mg two years	Hypertri-glyceridemia induced pancreatitis	–	8.2	1.8	NA	Urine ketones 2+	7.03	Conservative DKA management + CRRT for two days		NA

T2DM: Type 2 diabetes mellitus; OHAs: Oral hypoglycemic agents; T1DM: Type 1 diabetes mellitus; GLP-1: Glucagon-like peptide 1; CVVH: Continuous veno-venous hemofiltration; CVVHDF: Continuous veno-venous hemodiafiltration; CRRT: Continuous renal replacement therapy.

after 124 days (range: 7–380 days) of starting SGLT2i.[7]

Several retrospective studies reported that in the absence of SLGT2i, biochemical resolution of DKA took place in 11–12 hrs.[8] The longer duration of SLGT2i-associated DKA is not emphasized in current management guidelines and has not been widely described in the literature. One reason could be that the majority of reported cases were managed successfully with standard DKA protocol and the time taken for DKA resolution was less of a research priority.

On the other hand, the impact of morbid obesity on DKA outcomes has been highlighted by a few retrospective studies. Elsheikh et al,[9] reported increased mortality associated with morbid obesity in patients with DKA with an adjusted odds ratio (AOR) of 1.37 (95% CI: 1.18–1.61, but not obesity with lower BMI in the range 30–40.[9] Similarly, Mudgal et al,[10] large-scale study found that morbidly obese DKA patients had higher mortality than those without morbid obesity (0.72% vs. 0.38%; AOR = 1.85; $p = 0.040$). The study also reported that obese DKA patients had longer hospital stays (3.79 vs. 3.14 days, $p < 0.001$) than their non-obese counterparts. It is worth mentioning that in the Korean study, there was no difference in BMI between SGLT2i users and nonusers.[7]

In Table 1, we have summarized seven reported cases with characteristics similar to ours. Like in those cases, our patient's insulin infusion rate was high and the duration prolonged. Ketones are cleared faster if the insulin infusion rate is based on serum ketone levels rather than on serum glucose. In the present case this shift was made at a later stage. Early adoption of this, strategy will also prevent recurrence of ketoacidosis in the recovery phase.

As in the other cases in Table 1, RRT was required for our patient. Whether to base the titration of insulin infusion rate on serum ketones from the start of the DKA protocol—as it may correct the acidosis faster and hold the need for RRT—is worth considering for future cases. However, in previous reported cases, despite delivering insulin at rates as high as 10 units/h, RRT was still needed. Such persistently high acidosis may be due to the action of SGLT2i, which is implicated in multiple pathophysiological processes, such as reduced pancreatic insulin secretion, increased glucagon secretion by direct stimulation of alpha pancreatic cells, increased conversion of fatty acids to ketone bodies by beta-oxidation in the liver (lipolysis), as well as increased ketone and acetoacetate reabsorption in renal tubules leading to reduced renal ketone excretion.[17]

CONCLUSION

With the expanding list of indications and use of SLGT2i, it is worth being aware of the special characteristics of DKA in presence of this class of drugs, and the importance of rapid clearance of ketosis by means of higher insulin infusion rates linked to the patient's serum ketone levels.

Disclosure

The authors declare no conflicts of interest. Written consent was obtained from the patient.

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