'Euglycemic' Ketoacidosis in a Patient With Type 2 Diabetes Being Treated With Canagliflozin

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ABSTRACT

Objective: Canagliflozin is a sodium-glucose co-transporter 2 (SGLT-2) inhibitor, one of a class of novel antiglycemic agents that are gaining in popularity in the treatment of diabetes.

Methods: We describe a case in which a patient experienced difficult-to-treat metabolic ketoacidosis in the setting of canagliflozin use.

Results: A 52-year-old man with type 2 diabetes mellitus developed profound ketoacidosis without overt hyperglycemia while taking canagliflozin. Despite initiation of an insulin infusion, the metabolic acidosis persisted for 3 days.

Conclusion: Treatment with canagliflozin was associated with development of euglycemic ketoacidosis.

INTRODUCTION

Diabetic ketoacidosis (DKA) is a type of metabolic acidosis in which patients present with marked hyperglycemia, elevated anion gap acidosis and elevated plasma ketones.[1] "Euglycemic" DKA is an uncommon form of diabetic ketoacidosis without overt hyperglycemia (glucose ≤200 mg/dl).[2,3] It may occur in the setting of reduced caloric intake, alcohol use, or inadequate dosing of insulin, and can go unrecognized at initial presentation.[4,5] We report a case of euglycemic DKA in a patient who was taking canagliflozin, a sodium-glucose co-transporter 2 (SGLT-2) inhibitor. The patient had profound acidosis and ketosis, but blood glucose levels that were not overtly elevated. He was treated with a continuous insulin infusion and the metabolic acidosis slowly resolved. This case highlights an uncommon presentation of a common problem. As SGLT-2 inhibitors become more widely used, clinicians need to be familiar with this unusual complication.

CASE PRESENTATION

A 52-year-old man presented to an outside community hospital after experiencing somnolence and fatigue for several days. Three days before admission, the patient had started quetiapine for treatment of depression and insomnia. He subsequently developed fatigue, confusion, and nausea. On the day of admission, a family friend found him sleepy but responsive and called paramedics. At the hospital, the patient reported fatigue, nausea, abdominal pain, headache, and back pain.

The patient's medical history was remarkable for depression and anxiety, chronic low back pain, and traumatic brain injury resulting from a work accident 5 years previous. He had a history of type 2 diabetes, hypertension, obesity, and paroxysmal atrial flutter. His medications included aspirin (81 mg daily), canagliflozin (100 mg daily), glipizide (10 mg twice daily), metformin (1000 mg twice daily), furosemide (40 mg daily), lisinopril (10 mg daily), metoprolol tartrate (50 mg twice daily), simvastatin (20 mg daily), quetiapine (300 mg once daily), amphetamine-dextroamphetamine (20 mg twice daily), lorazepam (2 mg every 6 hours as needed for anxiety), and oxycodone controlled-release (60 mg 3 times daily). Canagliflozin was started 3 months prior to his admission. He was a former smoker, having quit 7 years previously. He did not currently drink alcohol or use intravenous drugs. He had been receiving disability payments for 5 years due to a work injury and lived alone.

On examination, his oral temperature was 37.9°C; heart rate was 90 beats per minute (BPM); blood pressure 142/68 mmHg; respiratory rate 16 breaths per minute; oxygen saturation was 94% on ambient air; and height, weight, and body mass index were 1.68 m, 131 kg, and 46.7, respectively. His exam was remarkable for somnolence. There was nonfocal tender-

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ness of the abdomen without distension. No masses or organomegaly were noted. Laboratory studies are reported in Table 1. The patient was admitted, placed on telemetry, and the quetiapine was stopped. The other preadmission antiglycemic and antihypertensive medications, including metformin, glipizide, and canagliflozin, were continued on the same schedule. In addition, amphetamine-dextroamphetamine was continued but oxycodone and lorazepam were held.

The patient was administered intravenous normal saline at 100 ml/hour for 2 days, and had a brief initial improvement at the outside hospital. After 3 days, he developed progressive altered mentation and confusion. Laboratory studies were repeated and he was found to have new onset metabolic acidosis (Table 1). He was transferred and admitted to the intensive care unit of a community teaching hospital. The patient was afebrile, with a heart rate of 95 bpm, blood pressure 116/75 mmHg, and oxygen saturation 97% on ambient air. Physical examination revealed a restless adult male with a disheveled appearance. He was arousable to voice but his utterances were inappropriate. The cardiac examination was notable for an irregularly irregular rhythm, without murmur or gallop. The abdomen was distended with positive bowel sounds, and there was mild, nonfocal abdominal tenderness but no rebound, guarding, or palpable masses. There were no focal deficits on neurological examination. Repeat serum chemistries and laboratory testing are listed in Tables 1 and 2. All oral antiglycemic medications were stopped on transfer, and the patient was started on an insulin infusion. He also was treated with dextrose and half normal saline infusion with added bicarbonate and potassium for presumed diabetic ketoacidosis in a euglycemic state.

During the first 24 hours, the patient remained hemodynamically stable. He developed compensatory respiratory alkalosis without ventilator assistance. His cognition improved. Despite the continuous insulin infusion, he remained acidotic and had an elevated anion gap. Metformin did not appear to contribute to the development of metabolic acidosis as there was no evidence of lactic acidosis and renal function was normal. Toxins associated with the development of metabolic acidosis were not found in the serum. The beta-hydroxybutyrate level was elevated. Most of the recorded glucose levels ranged from 100 mg/dl to 200 mg/dl during this time. (Figure). On the second hospital day after transfer, between 48 and 72 hours after the patient's last dose of canagliflozin, the anion gap and serum beta-hydroxybutyrate levels normalized. The dextrose and bicarbonate infusions were stopped. His mentation and physical strength improved substantially. GAD65 antibodies were undetectable, and the c-peptide level was in the normal range (Table 2). On the third hospital day after transfer, the patient was transitioned to a subcutaneous insulin regimen and transferred to a general medical floor.

Table 1. Laboratory Data

Variable	Reference Range, Adults†	Day 1, Outside Hospital	Day 3, Outside Hospital	On Admission (Day 1), This Hospital	Day 3, This Hospital
Hematocrit (%)	41.0-53.0	45.0	45.7	42.4	40.8
Hemoglobin (g/dl)	13.5-17.5	—	16.3	14.1	14.0
White-cell count (per mm^3)	4500-11,000	14800	9800	6100	10900
Platelet count (per mm^3)	150,000-400,000	227,000	166,000	158,000	185,000
Glucose (mg/dL)	77-99	248	158	146	157
Sodium (mmol/liter)	136-145	140	128	131	142
Potassium (mmol/liter)	3.5-5.1	4.7	4.5	4.2	3.1
Chloride (mmol/liter)	98-107	103	106	109	108
Carbon dioxide (mmol/liter)	21-32	19	6	<5	22
Creatinine (mg/dL)	0.6-1.3	0.9	1.2	1.2	0.7
Alkaline phosphatase (U/liter)	50-136	129	134	133	
Aspartate aminotransferase (U/liter)	15-37	39	36	36	
Alanine aminotransferase (U/liter)	4-65	59	46	42	
Lactic acid (mmol/L)	05-2.2	2.5		1.4	
Betahydroxybutyrate (mmol/L)	0.02-0.27			6.46	0.50
Urinalysis					
pH	5.0-8.0			5.0	
Specific gravity	1.003-1.030			1.021	
Urine protein	Negative			2+	
Urine ketones	Negative			2+	
Urine glucose	Negative			3+	

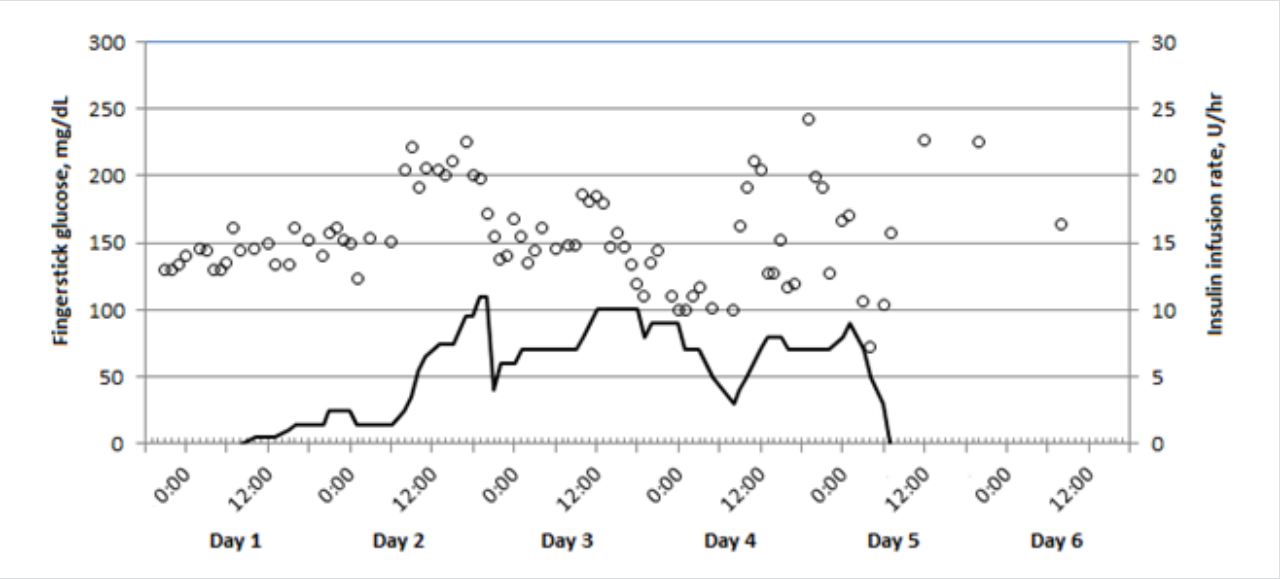
Table 2. Laboratory Data

Variable	Reference Range, Adults†	On Admission, This Hospital
Volatile Acids		
Methanol (mg/dL)		Negative
Isopropanol (mg/dL)		Negative
Ethylene glycol (mg/dL)		Negative
D-lactic acid	0.0-0.25	0.0
Glutamic acid decarboxylase antibody (IU/mL)	0.0-5.0	<5.0
C-peptide (ng/mL)	0.8-3.5	1.1
Blood Gases and Oximetry		
pH	7.35-7.45	7.13
paO^2 (mmHg)	80-100	107
$paCO^2$ (mmHg)	35-45	17
bicarbonate (mmol/L)	20-26	6
Osmolality, blood (mOsm/kg)	285-295	297
Osmolality, urine (mOsm/kg)		622

DISCUSSION

Sodium glucose transporter 2 (SGLT-2) inhibitors are a novel treatment for diabetes. SGLT-2 is the chief among a family of transmembrane proteins responsible for glucose reabsorption in

Figure. Blood Glucose After Transfer



Point-of-care and serum glucose measurements for the patient after transfer from the outside community hospital, where serum glucose measurements were 248 mg/dL at admission and 158 mg/dL at transfer. Open circles represent blood glucose measurements, and solid line represents insulin infusion rate.

the proximal renal tubule. Inhibition of SGLT-2 activity has been shown to decrease renal glucose reabsorption, leading to excretion of glucose in the urine and lowering of blood glucose levels and hemoglobin A1c.[6] Since 2013, three SGLT-2 inhibitors have been approved by the Food and Drug Administration (FDA) for use in the United States: canagliflozin, dapagliflozin, and empagliflozin. In early 2015, these agents were included in the joint American Diabetes Association and European Association for the Study of Diabetes revised position statement on management of hyperglycemia.[7] Later the same year, a randomized clinical trial of empagliflozin in patients with type 2 diabetes and pre-existing cardiovascular disease demonstrated a reduction in primary outcome of a composite of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke.[8]

Euglycemic ketoacidosis is a rare form of DKA that is typified by mild elevation in glucose levels in conjunction with metabolic acidosis. It has been reported to occur with inadequate calorie ingestion, alcohol use, or reduced insulin dosing.[2-5] Recently, the FDA issued a warning regarding an association between the development of ketoacidosis and use of SGLT-2 inhibitors.[9] Shortly after, Peters et al reported a case series in which treatment with SGLT-2 inhibitors was associated with the development of euglycemic ketoacidosis in 9 patients.[10] They described 2 individuals with type 2 diabetes who experienced euglycemic DKA postoperatively and 7 patients with type 1 diabetes. The latter group either had a reduction in caloric intake, reduced insulin dose, or had alcohol intake that preceded the development of euglycemic DKA.

The patient we describe had type 2 diabetes and had poor intake of food before and after his initial admission. Polypharmacy was notable in this case, and the patient recently had started on an atypical antipsychotic. Atypical antipsychotic medications, including quetiapine, have been reported to precipitate diabetic ketoacidosis in rare circumstances.[11,12] However, to our knowledge, none of the atypical antipsychotic medications have ever been reported to cause euglycemic ketoacidosis, and in the current case, quetiapine was stopped upon admission to the first hospital. Therefore, we suspect it is possible, but unlikely, that quetiapine was a contributing factor in the development of euglycemic ketoacidosis in this case. Similarly, amphetamine-dextroamphetamine and the other medications the patient had been treated with have not been reported to cause ketoacidosis. The patient had a mild elevation in the lactic acid level upon admission to the first hospital (day 1). This was thought to be a nonspecific elevation rather than to metformin-induced lactic acidosis as the repeat lactic acid level on day 1 following hospital transfer was normal despite the patient being treated with metformin until the transfer took place.

Another notable feature of this case is that the resolution of acidosis took 3 days after initiation of insulin infusion. Despite prompt initiation of insulin therapy, the patient's blood glucose was only mildly elevated during the first 48 hours after transfer, and clinicians participating in the patient's care were hesitant to depart from the hospital insulin infusion protocol out of concern that higher insulin infusion rates would result in hypoglycemia. It is not certain that more aggressive insulin

treatment initially would have hastened resolution of acidemia, but we wish to highlight the unexpectedly slow time course of recovery according to traditional DKA management pathways as recommended by the American Association of Clinical Endocrinologists (AACE) special panel.[13] This may have been due in part to the long half-life of canagliflozin, which had been continued for 3 days during the first hospitalization, prior to transfer.

The etiology of SGLT-2 inhibitor induced-euglycemic ketoacidosis is uncertain. SGLT transporter-2 inhibition in the kidney leads to increased glycosuria and secondarily to decreased plasma glucose levels. This may lead to a reduction in insulin secretion over time. During times of stress (eg, during and after surgery, during caloric restriction, or with infections) the relative insulinopenia may contribute to increased ketone body formation by the liver and predispose to the development of metabolic acidosis in certain patients.

The AACE recently convened a special panel to review the safety of SGLT-2 inhibitors in the context of its new safety reports which stated that "the prevalence of DKA is infrequent and the risk-benefit ratio overwhelmingly favors continued use of SGLT2 inhibitors."[13] The panel made additional recommendations to consider stopping SGLT-2 inhibitors at least 24 hours prior to elective surgery and during physiologic stress, measurement of beta-hydroxybutyrate for diagnosis of SGLT-2 inhibitor associated DKA, and treatment of SGLT-2 inhibitor associated DKA with traditional DKA protocols.

Many hospitals restrict or prohibit use of oral antiglycemic agents because of the risk of acute renal insufficiency and other conditions that can lead to metabolic derangements, including metabolic acidosis. There is also a higher risk of hypoglycemia with use of oral agents in the hospital because of skipped or missed meals and worsening renal function. Due to these factors, many institutions have policies whereby insulin is the only antiglycemic medication available for treatment of hyperglycemia or diabetes.

CONCLUSION

Euglycemic ketoacidosis recently has been recognized as an uncommon adverse event associated with use of SGLT-2 inhibitors. Salient aspects of the case are that the patient had type 2 diabetes and developed ketoacidosis with euglycemia while taking canagliflozin. This case demonstrates that euglycemic ketoacidosis can occur during treatment with canagliflozin and potentially with other SGLT-2 inhibitors. It is possible but unlikely that quetiapine played a role in the development of the euglycemic ketoacidosis in this vignette. Secondly, the use of oral antiglycemic medications in the hospital should be restricted to avoid untoward complications in patients treated for hyperglycemia and diabetes.

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