



Diabetic Ketoacidosis, Lactic Acidosis and Alcoholic Acidosis in a Type 2 Diabetic Male: Synergic Effects of SGLT-2 Inhibitors with Heavy Alcohol Consumption

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Abstract

Objective: To report a Type 2 Diabetic (T2DM) heavy drinker patient who developed Euglycemic Diabetic Ketoacidosis (eDKA), Lactic Acidosis (LA) and Alcohol Ketoacidosis (AKA) chronically treated with a sodium-glucose co-transporter 2 SGLT2 inhibitor (SGLT-2i) and metformin.

Methods: We describe the clinical presentation and management of a 62-year-old T2DM male with eDKA, LA and AKD while taking empagliflozin and metformin.

Results: The patient presented to the emergency department with nausea, vomiting, myalgia and malaise at the end of a binge of alcohol ingestion. Body mass index was 27.9 kg/m² and blood pressure 120/80 mmHg. Baseline glucose concentration was 129 mg/dL, sodium 124 mmol/L, potassium 4.2 mmol/L, chloride 94.6 mmol/L, blood urea nitrogen 14.4 mg/dL, creatinine 0.75 mg/dL, pH 7.27, PO₂ 104.4 mmHg, PCO₂ 20.5 mmHg, bicarbonate of 9.4 mmol/L, beta-hydroxybutyrate 7.81 mmol/L and lactate 25.1 mg/dL. The estimated osmolality was 269.5 mOsm/L and the anion gap was 20 mEq/L. The patient received intravenous saline solutions, insulin infusion at 0.5 U/hour for 12 hours and had an oral feeding. During hospitalization glucose levels were kept between 90-156 mg/dL, metabolic acidosis and electrolyte abnormalities reverted within four hours. The patient was discharged with a DPP-4 inhibitor and metformin.

Conclusions: This T2DM non-insulin requiring patient chronically treated with SGLT-2i developed eDKA, LA and AKA after a binge of alcohol ingestion. Heavy ethanol intake combined with SGLT-2i induced biochemical alterations leading to a combined metabolic acidosis.

Keywords

Diabetes Ketoacidosis; Alcoholic Ketoacidosis; Lactic Acidosis; Alcohol Abuse; Type 2 Diabetes; SGLT2 Inhibitors

Abbreviations

eDKA: Euglycemic Diabetes Ketoacidosis; LA: Lactic Acidosis; HbA1c: Glycosylated Hemoglobin A1c; SGLT 2i: Sodium-Glucose Co-Transporter Inhibitors

Introduction

The introduction of SGLT2i broadened the therapeutic spectrum in the management of type 2 diabetes [1-3]. In addition to the effects on glucose control, these agents have cardiovascular and renal benefits [4-7]. Adverse effects of SGLT2i include genital infections, dehydration and must be used with caution in elderly patients receiving diuretics [8]. Associated with their use is increased risk of eDKA, although a rare complication, it can be serious [8-13]. eDKA can occur in the context of certain predisposing factors such as infections, surgery, prolonged fasting and reduction in insulin administration [8-13]. The pathophysiology of this complication involves an imbalance in the insulin/glucagon ratio, which leads to an uncontrolled ketone bodies production [14,15].

On the other hand, AKA happens in patients with chronic alcoholism after a binge of alcohol consumption and food deprivation. Frequently, patients with AKA present with starvation and dehydration 1-2 days after stopping alcohol intake [16,17]. Moreover, Lactic Acidosis (LA) can occur in patients with acute ethanol intoxication [18]. Recently, Schwetz et al presented a case series of metformin associated LA and eDKA, one of such patients with renal failure was receiving SGLT-2i [19].

We report a unique case of a T2DM patient, who developed to combined metabolic acidosis after a binge of alcohol intake while being treated with SGLT-2i.

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Variables	Before	After	Reference value
Glycemia (mg/dL)	129	135	70-200
pH	7.27	7.32	7.35-7.45
pO ₂ (mmHg)	104.4	90.7	83.0-100.0
pCO ₂ (mmHg)	20.5	22.9	32.0-45.0
Bicarbonate (mmol/L)	9.2	11.6	22-26
Ketonuria	150	150	Neg
Beta OH hydroxybutyrate (mmol/L)	7.81	NA	< 0.6
Lactate (mg/dL)	25.1	12.2	5.4-12.6
Sodium (mmol/L)	124	133.3	135-145
Chloride (mmol/L)	95.9	100.3	101-109
Potassium (mmol/L)	4.2	4.75	3.5-5.1
BUN (mg/dL)	14.4	13	7.9-20.1
Creatinine (mg/dL)	0.75	0.8	0.81-1.4
Anion Gap (mEq/L)	20.2	21.4	3.0-11.0

Table 1: Pertinent laboratory results in a heavy drinker T2DM patient treated with empagliflozin/metformin

Case Presentation

A 62-year-old T2DM male patient was admitted into the hospital due to a 2-days history of nausea, vomiting, myalgia and malaise. Type 2 diabetes and mixed dyslipidemia were diagnosed 2 years before, during a routine evaluation. He had been treated with empagliflozin/metformin 12.5/1000 mg twice a day and simvastatin/ezetimibe 10/40 mg with excellent adherence. Also, he performed exercise 5 days a week and have eaten properly. His previous history revealed that he quit smoking 2 years ago, but drinks alcoholic beverages daily. He had normal liver, renal and thyroid function tests; the stress electrocardiogram was negative and the coronary artery calcium score was 507 Angaston units (80th percentile). The HbA1c ranged from 6.7 to 7.0 % over the last 12 months and the lipid levels performed 3 months before showing a total cholesterol of 168 mg/dL, triglycerides 354 mg/dL, HDL cholesterol 37 mg/dL and the LDL cholesterol 60 mg/dL.

Two weeks before admission the patient increased alcohol ingestion to half a liter of whisky and several beers daily and at the same time he had normal eating patterns. Two days before admission due to nausea and vomiting, he stopped alcohol intake and fasted for 24 hours while taking empagliflozin. On admission the patient was sober, breathing normally with a respiratory frequency of 12/min. Fruity smell was not noticed. Body mass index was 27.9 kg/m², blood pressure was 120/80 mmHg, without a postural drop in blood pressure, heart rate was 80/min and had dry tongue. The rest of the physical examination was unremarkable. Table 1 illustrates fasting glucose, renal function tests, electrolytes, ketonuria, arterial blood gases, lactate, beta hydroxybutyrate, osmolality, and the anion gap. Hematocrit and leukocyte count were normal, amylase was 47.8 U/L, AST 84 U/L, ALT 56 U/L and GGT 136 U/L. Total cholesterol, triglycerides and HDL cholesterol concentrations were: 184, 237 and 53 mg/dL, respectively. HbA1c was 7.8 % and the C-peptide concentration was 0.9 ng/mL. He was hospitalized for 24 hours and received four liters of IV saline solution, an IV insulin infusion at a rate of 0.5 U/hour, esomeprazole 40 mg IV, diazepam 10 mg twice a day and vitamin B complex. While in the hospital, he had oral feeding, and the glucose levels were kept between 90-156 mg/dL. The metabolic acidosis were resolved in six hours as shown in Table 1. The patient was discharged with a DPP-4 inhibitor and metformin 24 hours later.

Discussion

We describe the combined presentation of eDKA, LA and AKA

in a heavy drinker and overweight T2DM patient. The patient complained of nausea, vomiting, malaise and myalgia after stopping a binge of alcohol consumption. There was no evidence of infection, cardiovascular or respiratory complications and had a normal blood pressure. Upon admission, the glucose level was 129 mg/dL and the C-peptide concentration was within the normal range.

Our patient presented with metabolic acidosis characterized by raised anion gap, elevation of beta hydroxybutyrate and lactic acid, in the absence of over hyperglycemia. The glycosuria effect of SGLT-2i conjointly with prolonged fasting and impaired gluconeogenesis seen with ethanol intake may explain why this patient had mild elevation in fasting glucose concentrations, condition consistent with the diagnosis of eDKA [9,10].

The association of SGLT-2i with eDKA is an uncommon adverse effect, which has been described in both type 1 and type 2 diabetes linked to a number of predisposing factors including infection, cardiovascular events, surgery, prolonged fasting, usually in the setting of a reduction of insulin administration [8-13]. The mechanisms implicated in the development of eDKA associated with SGLT-2i treatment are not fully understood, but may be related to an imbalance between insulin and the counter-regulatory hormones including glucagon, cortisol and catecholamine. As a result of such changes, adipose tissue lipolysis increases and ketogenesis is stimulated [14,15].

Meanwhile, AKA is commonly seen in malnourished patients with chronic alcoholism who have a history of a superimpose binge alcohol ingestion [16,17]. This condition is caused by the combined effects of alcohol and starvation on carbohydrate metabolism. With alcohol ingestion the NADH/NAD ratio increases and acetoacetate and acetic acid are generated [17-22]. The later may be utilized for energy or converted to acetyl-CoA which can be oxidized in the Krebs cycle. Acetyl-CoA can also be metabolized into triglycerides, or redirect to the ketogenesis pathway forming acetoacetic acid, beta-hydroxybutyric acid and acetone [17-22].

As indicated above, in AKA, the prolonged periods of ethanol ingestion reduce carbohydrates and protein stores and may directly stimulate lipolysis. Vomiting associated with ethanol cause volume depletion and this, in turn leads to an increase in sympathetic responses. Furthermore, cortisol, adrenaline, growth hormone and glucagon levels rise and insulin production decreases [17-23].

In our case both conditions, DKA and AKD prompted metabolic pathways redirecting flues to ketogenesis and eventually to ketoacidosis. Additionally, the metabolism of ethanol results in an augmented lactate and glycerol production [18,19]. Lactic acidosis can occur as a result of a high hepatic NADH/NAD ratio, diverting pyruvate catabolism towards lactate and also impair gluconeogenesis [18,19]. In our case, whether metformin could have played a role in the elevation of lactic acid is uncertain. Lactic acidosis associated with metformin has been described in patients with renal insufficiency taking SGLT-2 [19], none of these were present in our patient. Thus, it is unlikely that lactic acidosis due to metformin could have played an important role in our patient.

This case illustrates the combined effects of metabolic derangement that gradually occurred at the end of a two-week binge of alcohol intake and fasting in the presence of SGLT-2i exposure. The relative contribution of each factor, namely, alcohol binge, starvation and SGLT-2i therapy is difficult to establish. It is feasible that the synergic effects of all these metabolic alterations ended in the combined metabolic acidosis.

The patient was treated with volume replacement and although he was normoglycemic and there was no evidence of insulin deficiency, we decided to infuse small amounts of regular insulin intravenously to help revert the metabolic pathways which lead to acidosis. The effects of this intervention resulted in a rapid normalization in lactate concentrations, a rise in pH and bicarbonate levels after only four hours of treatment.

We conclude that physicians must be aware of the risk of DKA, LA and AKA to active drinking T2DM patients treated with SGLT-2i.

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