

CASE REPORT

EUGLYCEMIC DIABETIC KETOACIDOSIS AND SEVERE ACUTE KIDNEY INJURY SECONDARY TO OFF LABEL USE OF SODIUM GLUCOSE COTRANSPORTER-2 INHIBITOR IN A TYPE-1 DIABETIC PATIENT

Hassan Tahir, Adil Wani, Vistasp Daruwalla, Nour Daboul, Jahnavi Sagi

Department of Internal Medicine, Temple University/Conemaugh Memorial Hospital, Johnstown-USA

Sodium glucose Cotransporter-2 (SGLT2) inhibitors are a new class of drug approved for the treatment of type-2 diabetes; however they are also increasingly used off label in type-1 diabetic patients. SGLT2 Inhibitors work by increasing glucose excretion in urine. Euglycemic diabetic ketoacidosis (DKA) is potentially life threatening side effect as patients have normal glucose and minimal symptoms thus delaying diagnosis and treatment. Our case report highlights the risk of using SGLT2 inhibitors in type-1 diabetes and also supports the need for long term studies to define clear efficacy and complications of SGLT 2 inhibitors in both type-1 and type 2 diabetes mellitus.

Keywords: Euglycemic DKA, SGLT2 Inhibitor, Type 1 Diabetes, canagliflozin

J Ayub Med Coll Abbottabad 2015;27(4):923-4

INTRODUCTION

Diabetic ketoacidosis (DKA) for long has been the hallmark of type-1 diabetes mellitus (T1DM). Euglycemic DKA has been defined as glucose levels <180 mg/dl and metabolic acidosis (serum bicarbonate <10 mEq/L).¹ Sodium-glucose cotransporter 2 (SGLT2) inhibitors, though FDA approved for type 2 diabetes mellitus (DM) only, are increasing being used off label as an adjunctive therapy to insulin in type-1 diabetics. Euglycemic DKA is a life threatening complication seen in both Types of diabetes mellitus, but its risk is much higher in T1DM as DKA is more commonly associated with T1DM. We present a rare case of true euglycemic DKA and severe acute kidney injury requiring renal replacement therapy in a T1DM secondary to a SGLT 2 inhibitor (canagliflozin).

CASE REPORT

A 29 year old Caucasian male with a past medical history significant for type 1 diabetes mellitus confirmed with an elevated level of antibodies to glutamic acid decarboxylase (GAD), came in with nausea and vomiting for the last three days. He denied any fever, chills or cold symptoms. His home medications comprised of lantus 20 units at night and metformin 1000 mg daily. He was recently started on canagliflozin for uncontrolled hyperglycemia and high HbA1c (9.1).

On admission his vitals were BP 130/85 mmHg, heart rate 130bpm, respiratory rate 29 and saturation 99% on room air. On examination he was alert and oriented to time, place and person. Laboratory findings demonstrated metabolic acidosis with a pH of 6.92, pCO₂ of 29 mm/hg, HCO₃ of 1.7 meq/L along with an anion gap of 23. His serum glucose level measured 177mg/dl while urine glucose level was 500 mg/dl along with urine ketone levels greater than 150 mg/dl. A diagnosis of euglycemic DKA was made. Leukocytosis with a count of 19,700 cm³ without bandemia was noted but blood, urine and sputum cultures were negative for any infection. Patient was initially treated with intravenous fluid resuscitation with bicarbonate and weight based subcutaneous insulin. Repeat ABGs showed worsening acidosis with pH of 6.85, pCO₂ of 8 mmhg, HCO₃ of 1.3 meq/L. Patient also had oliguric acute kidney injury with a creatinine of 4.5 mg/dl and a GFR of 16 ml/min. His condition gradually worsened, he was tachypneic with a respiratory rate of 42, lethargic and nonresponsive. He was intubated and transferred to the intensive care unit for further management. He was started on insulin and bicarbonate drip, which improved his metabolic acidosis over time but his renal function gradually worsened to a point where he needed intermittent hemodialysis. Patient kidney function and respiratory status progressively improved and he was extubated on the day 6.

Table-1: Important labs from the date of admission to discharge

	0 hours	4 hours	8 hours	Day 2	Day 3	Day 4	Day 5	Day 6
pH	6.92	6.85	6.93	7.03	7.34	7.33	7.38	7.39
pCO₂	9	8	8	23	26	26	31	36
HCO₃	1.7	1.3	2	6	14	13	18	21
Glucose	178	110	264	195	219	182	137	126
Anion gap	30	25	16	13	6	10	11	12
Glucose	1.1	1.1	1.2	2.7	4.5	6.7	7.2	7.2
Creatinine	-	-	-	2.7	4.1	4.9	2.1	1.8

DISCUSSION

SGLT receptors present on the luminal side of proximal convoluted tubules transport glucose from luminal to intracellular space against the concentration gradient. The process is driven by Na^+/K^+ pump gradient. Two types of SGLT receptors exist in the tubule of which SGLT 2 is responsible for 90% of glucose absorption. SGLT-2 inhibitors decrease glucose reabsorption in the tubules and increase glucose urine excretion. SGLT2 inhibitors approved in the USA by FDA are Dapagliflozin, Canagliflozin and Empagliflozin. SGLT2 inhibitors, such as empagliflozin, have both basal and postprandial anti-hyperglycemic effects. Because induced increases in urinary glucose occur in a non-insulin-mediated manner, individuals with T1DM can potentially benefit from addition of this medication to achieve target glycemic control.² The preliminary studies with empagliflozin and dapagliflozin in T1DM individuals suggest that total insulin use can be decreased with use of these treatments.^{3,4} However, despite evidence of improved glycemic control in T1DM, SGLT 2 inhibitors are approved for T2DM only.

Patients with T1DM present with ketoacidosis in an insulin deficient state or secondary to stress and infection. Usually high blood sugar in the presence of symptoms prompts us to test for urine or blood ketones, thus leading to early diagnosis and management of DKA. Unexpected or persistent hyperglycaemia acts as a warning sign in such patients. Unfortunately, this warning sign is lost in type-1 diabetics taking SGLT2 inhibitors and euglycemic DKA ensue. In addition, patients tend to keep the insulin dose at the same level or even reduce it due to normal blood sugars, thus worsening the acidosis. Significant delay in Diagnosis and treatment makes euglycemic DKA one of the life threatening side effects of SGLT 2 inhibitors. Our patient had T1DM and SGLT 2 inhibitor was added to insulin and metformin for uncontrolled DM. Patient started having nausea and vomiting two weeks later and was found to have euglycemic DKA and acute kidney injury.

The effect of SGLT2 inhibition in individuals with T1DM leading to renal insufficiency is still unknown. Canagliflozin has been associated with a reduction in GFR in moderate renal impairment. Our patient was recently started on

canagliflozin was found to have profound kidney injury during DKA, necessitating the use of CRRT with intermittent hemodialysis. Hence decline in renal function during a ketotic episode in patients prescribed with SGLT2 inhibitors needs further investigation as ketosis is a major risk factor for increased morbidity and mortality in individuals with T1DM. Nasopharyngitis (26%) and genitourinary infections (14%) were most commonly documented in T1DM individuals who took empagliflozin, with 5% of subjects reporting ketoacidosis.⁴

CONCLUSIONS AND RECOMMENDATIONS

Off label use of SGLT2 inhibitor should be avoided in type 1 DM. If prescribed, then it should be used with extreme caution. Adequate patient counselling and close monitoring for sign and symptoms of ketosis is advisable in such cases.

Diabetic patients on SGLT 2 inhibitors are at increased risk of DKA even with normal blood glucose.

There should be a low threshold for checking urine or blood ketones in patients taking SGLT2 Inhibitors. This may help in early diagnosis.

SGLT2 inhibitors may cause kidney injury the cause of which is unknown. Further trials and studies are needed to truly determine safety of SGLT 2 inhibitor in T1DM.

ACKNOWLEDGEMENTS

We thank Prachi kalamkar and Shashank Dubey for their input in our case report.

Conflict of Interest: Authors declare no conflict of interests.

REFERENCES

- Jenkins D, Close CF, Krentz AJ, Natrass M, Wright AD. Euglycaemic diabetic ketoacidosis: does it exist? *Acta Diabetol* 1993;30(4):251-3.
- Lamos EM1, Younk LM, Davis SN. Empagliflozin, a sodium glucose co-transporter 2 inhibitor, in the treatment of type 1 diabetes. *Expert Opin Investig Drugs* 2014;23(6):875-82.
- Henry RR, Rosenstock J, Chalamandaris AG, Kasichyanula S, Bogle A, Griffen SC. Exploring the potential of dapagliflozin in type 1 diabetes: Phase 2a pilot study. *Diabetes* 2013;62(Suppl 1):Abstract 70-LB.
- Cherney DZ, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, *et al.* Renal hemodynamic effect of Sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation* 2014;129(5):587-97.

Address for Correspondence:

Hassan Tahir, Department of Internal Medicine, Temple University/Conemaugh Memorial Hospital, 1086 Franklin Street, Johnstown, PA 15905-USA

Email: hassantahir_01@hotmail.com