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RESEARCH ARTICLE

A CASE REPORT: EUGLYCEMIC DIABETIC KETOACIDOSIS PRESENTING AS SEVERE ABDOMINAL PAIN AND UPPER GASTROINTESTINAL BLEED IN A PATIENT STARTED ON SGLT2 INHIBITOR.

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ABSTRACT

EuDKA caused by SGLT2 inhibitors is thought to be rare but real entity. Sodium-glucose co-transporter-2 (SGLT-2) inhibitors are a relatively new class of oral antidiabetics for type 2 DM with renal and cardio protective benefits and acceptable safety profile. Although they are considered to be safe but US FDA issued a warning on use of SGLT-2 inhibitors about the risk of ketoacidosis. It is advised to health care professionals to consider the risk of EuDKA in patients who developed nausea, vomiting, abdominal pain, tiredness and difficulty in breathing while using it these drugs. We report a case of 52-year-old male recently diagnosed with type 2 diabetes developed EuDKA after 7 days of starting Empagliflozin therapy. The unique features in our case were presentation with severe pain abdomen and signs of peritonitis along with upper GI bleed. Very few cases have been reported in literature with such presentation. There was no precipitant factor like fever, sepsis, post-operative setting, fasting and decreased carbohydrate intake described in literature in our case. Use of SGLT2 inhibitors in catabolic state might be the precipitant factor in our case.

INTRODUCTION

Euglycemic diabetic ketoacidosis (EuDKA) was first described by Munro et al. in 1973 in type 1 DM with severe ketoacidosis, plasma bicarbonate of 10 mEq/l or less, with the blood glucose less than 300 mg/dl. (1) There are many causes of EuDKA in diabetics like decreased carbohydrate intake with increased insulin dose, psychological stress, pregnancy, ketogenic diet and alcohol. (2) EuDKA caused by SGLT2 inhibitors is thought to be rare but real entity. Sodium-glucose co-transporter-2 (SGLT-2) inhibitors are a relatively new class of oral antidiabetics for type 2 DM with renal and cardio protective benefits and acceptable safety profile. They prevent glucose reabsorption from the proximal renal tubules by inhibiting sodium-glucose transporter 2. (3) Although they are considered to be safe but the data regarding their long-term safety is scarce. US FDA issued a warning on use of SGLT-2 inhibitors about the risk of ketoacidosis and advised health care professionals to consider this risk in patients who developed nausea, vomiting, abdominal pain, tiredness and difficulty in breathing while using it (4).

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EuDKA is a known side effect of all the classes of these drugs, but it is most common with canagliflozin, followed by empagliflozin and dapagliflozin (100%, 77%, and 48.3%, respectively). Infection (32.6%) was found to be the most common trigger for EuDKA, followed by insulin non-compliance (13.7%) (5) Empagliflozin which was the offender drug in our case, got FDA approval in August 2014 by the Food and Drug Administration (FDA) with a plasma half-life of 13 hours. It is metabolized mainly by the liver. It should be out of the system in three days, according to its half-life. In our case ketosis persisted for 5 days after discontinuing empagliflozin Pujaraetal also experienced persistent ketosis and glycosuria eight days after discontinuing dapagliflozin (7). High protein binding or decreased eGFR might explain the prolonged effect of these drugs (8). We report a case of 52-year-old male recently diagnosed with type 2 diabetes developed EuDKA after 7 days of starting Empagliflozin therapy. The unique features in our case were presentation with severe pain abdomen and signs of peritonitis along with upper GI bleed. Very few cases have been reported in literature with such presentation. There was no precipitant factor like fever, sepsis, post-operative setting, fasting and decreased carbohydrate intake described in literature. Use of SGLT2 inhibitors in catabolic state might be the cause of precipitation of EuDKA induced pain abdomen in our case.

Diagnosis in critical care setting sometimes may become challenging in absence of awareness of this adverse effect of SGLT-2 inhibitor. Hence increased awareness and education is required regarding SGLT-2 inhibitor induced EuDKAto promptly diagnose and treat this condition.

CASE REPORT: 52-year-old male presented in emergency with history of multiple episodes of vomiting, one episode of hematemesis and severe pain abdomen for last one day. There is no history of fever. He had been recently diagnosed with type 2 diabetes.

Abdominalexamination revealed diffuse abdominal tenderness with guarding and no rigidity. Bowel sounds were absent. Rest of the systemic examination was unremarkable. At the time of admission: white cell count was 7950mm3 with 80% neutrophils, Hb 8gm%, platelets 1.7 lacs, Serum creatinine was 1.2mg/dl and urea 48 mg/dl. Electrolytes including sodium, potassium and calcium values were within the normal range. Liver function tests including albumin, bilirubin and transaminases were in normal limit. Amylase and lipase were normal.

Table 1. **Findings at the time of admission and follow up are summarized**

Parameter	Reference range	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6
PH (%)	7.35-7.45	7.25	7.25	7.36	7.42	7.43	7.42
PaCO2 (mm Hg)	35-45	28	35.3	41.6	34.4	32.6	41.1
HCO3 (mmol/\L)	22-26	14	14.9	23	22.1	21.5	25.5
Anion gap	8-12	15.9	18	22.7	11.5	9.3	7.1
Blood glucose (mg/dl)	70-100	220	194	190	170	130	98
Sodium (mmol/L)	135-155	139	142	135	130	131	134
Serum lactate (mmol/L)	0.50-1.50	0.6	1.0	2.05	1.32	0.90	0.6
Urine Glucose	Negative	Positive	Positive	Positive	Positive	Positive	Negative
Urine Ketones (mg/ dl)	0-<5	Positive (20)	Positive (80)	Positive (80)	Positive (80)	Positive (40)	Negative
HbA1c (%)	<5.7	8.9	-	-	-	-	-
Hb (gm/dl)	13.0-17.0	8.7	8.9	9.8	9.4	8.8	8.7
WBC Total (/cu/mm)	4000-10000	7950	8270	11750	8490	7350	6540
Platelet Count (mm^3) (lakhs\cu.mm)	1.5-4.1	1.74	1.40	1.63	1.65	1.40	1.6
PCV (%)	40-50	25.1	28.5	29.4	29.1	26.3	26.1
MCV (FL)	83-101	81.5	86.1	82.4	83.1	81.8	81.5
Urea (mg\dl)	19.2-42.8	48	45	33	28	27	26
S. Creatinine (mg/dl)	0.66-1.25	1.2	1.2	1.0..	0.7	0.7	0.7
S.Na (mmol\L)	135-155	139	142	135	130	131	134
S.K* (mmol\L)	3.5-5.5	4.6	4.2	4	3.6	3.2	3.8
PT (INR)	12.4-14.8/0.89-1.13	13.2/13.6/0.97	-	-	-	-	-
S. BIL Total (mg\dl)	0.2-1.3	1.7	-	-	-	-	-
S. BIL Direct (mg\dl)	0.0-0.4	0.0	-	-	-	-	-
S. BIL IN Direct (mg\dl)	0.0-1.1	1.7	-	-	-	-	-
SGOT (U\L)	17-59	37	-	-	-	-	-
SGPT (U\L)	21-72	55	-	-	-	-	-
S. ALK Phosphatase /SGGT (U\L)	38-126	84	-	-	-	-	-
S. Protein (gm\dl)	6.3-8.2	7.3	-	-	-	-	-
S. Albumin (gm\dl)	3.5-5.0	4.4	-	-	-	-	-
S. Globulin (gm\dl)	2.0-4.1	2.9	-	-	-	-	-
S.A/G Ratio	1.0-2.1	1.5	-	-	-	-	-
PCT (ng/ml)	<0.5	.08	-	-	-	-	-
NT Pro- BNP (pg/ml)	<125	25	-	-	-	-	-
AMYLASE / LIPASE	30-110/23-300	56/234	-	-	-	-	-
Trop-T (ng/ml)/ CKMB (IU/L)	0-0.01/5-25	Negative	-	-	-	-	-
Fever Panel		Negative	-	-	-	-	-

At the time of diagnosis, he had polyurea, polyphagia, polydipsia and significant weight loss suggestive of highly uncontrolled sugars with catabolic state. HBA1c was 8.9% at the time of diagnosis. He was started on multiple antidiabetic drugs including metformin, glimepiride and empagliflozin 7 days before the hospital admission by some local practitioner. There is also history of alcohol intake though he denies recent intake in last one week after the diagnosis. There is no significant past medical history of hypertension, CAD, BA, COPD. There is also no history of any over the counter drug intake. On examination patient was in severe pain and looked very anxious. He was conscious and oriented. BP was 140 / 90mm of Hg. Heart rate was 150 beats per minute, Spo2 was 98%on room air, Respiratory rate was 24 breaths per minute and temperature was 98.8degree Fahrenheit.

HbA1C was 8.9%. Arterial blood gas revealed metabolic acidosis, with a pH of 7.25, HCO3 14 mmol/L, PCO2: 28mmHg, anion gap: 15.9 mEq/L and lactate0.6 mmol/L suggestive of high anion gap metabolic acidosis with normal lactates. Urine ketonesand urine glucose were positive. Cause of high anion gap acidosis was contributed to ketoacidosis. Presence of ketoacidosis, marked glucosuria in presence of moderated hyperglycaemia with history of Empagliflozin use clinched diagnosis of Euglycemia ketoacidosis. CT abdomen revealed prominent colonic loops with faecal impaction and no evidence of perforation peritonitis. CT abdominal angiographic study was also normal ruled out possibility of mesenteric ischemia. UGI endoscopy revealed presence of erosive oesophagitis and gastritis for which APC was done.

Electrocardiogram showed sinus tachycardia at 150 beats per minute. Chest X-ray was normal. 2 D echo was normal LV ejection fraction. As there was no other significant cause of pain abdomen, by excluding all etiologies like pancreatitis, perforation peritonitis, mesenteric ischemia etc, pain abdomen was contributed to Eu DKA precipitated with use of SGLT2inhibitor. Patient was started on infusion of normal saline and IV insulin infusion. All oral antidiabetics including Empagliflozin was stopped. Patient was kept nil orally. Serial monitoring of Blood sugars, urine ketones and arterial blood gas were done. Insulin infusion was continued till next 3 days until the anion gap closed and bicarbonate levels normalized. Intravenous glucose infusion was required intermittently to facilitate insulin infusion therapy for correction of ketoacidosis, especially when sugars were below 200 mg /dl. For abdominal pain he required multimodal analgesia with IV fentanyl infusion, IV paracetamol and use of transcutaneous patch of opioids. It took almost 3 days for pain abdomen to settle down partially and to wean him off the parenteral infusion of fentanyl. He was started on clear liquids to start with after 3 days when ABG improved and anion gap closed. He tolerated low volume of clear liquids for 24 hours and started passing flatus. On 5th day he tolerated the soft diet and his ketones became negative. He had good bowel sounds and complete relief in pain abdomen with no further requirement of analgesics on day 6 and advised to shift to room and discharged on 7th day with advice of self-monitoring of glucose at home and basal bolus insulin therapy. He was advised not to restart SGLT2 inhibitor in immediate post recovery period and to follow up in endocrinology OPD for further optimization of his sugars.

DISCUSSION

Euglycemic diabetic ketoacidosis (EuDKA) is supposed to be a rareadverse effect of sodium-glucose cotransporter 2 (SGLT2) inhibitors but likely underrecognized and underreported. (9) SGLT2 inhibitors are widely used drug now a days for treatment of type 2 Diabetes because of its cardiovascular and renal benefits. Data from various randomized controlled clinical trials are constant with the hypothesis that SGLT2 inhibitors cause a 2 to 4-fold increase in the risk of ketoacidosis (10). Vulvovaginitis, balanoposthitis, volume depletion and AKI are well known and common side effects. Euglycemic ketoacidosis though considered to be a rare complication but if not identified and treated timely can lead to serious outcomes. (11). EuDKA can be a missed diagnosis because of nonspecific symptoms and signs along with absence of severe hyperglycaemia. Hence critical care physicians as well as other speciality doctors like gastroenterologist, surgeons, physicians and nephrologists should be aware of this complication of SGLT2 inhibitors while dealing with critically ill patients with unexplained high anion gap acidosis along with history of intake of intake of these medications. In the same context FDA in May 2015 also gave the warning on its use in perioperative setting (4).

Euglycemic diabetic ketoacidosis is a clinical syndrome can occur in both type 1 and type 2 diabetes mellitus with presence of euglycemia or moderate hyperglycaemia (blood glucose less than 250 mg/dL), high anion gap metabolic acidosis (arterial pH less than 7.3, serum bicarbonate less than 18 mEq/L) and ketonemia. (12). There is Increase in urinary glucose excretion which in turn leads to a decrease in glycaemic level resulting in the reduction of endogenous insulin secretion and increased glucagon levels. Increase glucagon to insulin ratio will cause lipolysis and production of free fatty acids (FFAs) which gets converted into ketone bodies leading to ketoacidosis (13). Though there are many studies and case reports available of EuDKA induced by SGLT2 inhibitors but there are some unique features in our case. Our case presented with severe pain abdomen and upper GI bleed with marked tenderness and guarding all over the abdomen and absent bowel sounds suggestive of Acute Abdomen at the time of presentation. EuDKA presented as acute abdomen mimicking peritonitis and upper GI bleed has been reported occasionally in some case reports. In literature sometimes it is also called as diabetic pseudo peritonitis. (14, 15). The usual symptoms are nonspecific like nausea, anorexia, vomiting, pain abdomen, dehydration, increase thirst, excessive fatigue, weakness, dyspnoea and altered sensorium (16). Lack of awareness of this entity sometimes lead to overzealous investigations to find the cause of pain and unwanted surgeries. The pathogenesis of abdominal pain caused by Eu-DKA has been explained with multiple mechanisms. Gastrointestinal smooth muscle dysfunction, paralytic ileus and acute gastric dilation can occur due electrolyte disturbances such as hypokalaemia and hypocalcaemia. Increased free fatty acids can cause impaired pancreatic circulation, pancreatic swelling and exudates causing peritoneal irritation. Hypoxia, acidosis anddecreased PH of gastric juice will disrupt the integrity of the gastrointestinal mucosa causing severe acute gastritis, a plausible explanation for GI bleed. Gastric mucosal petechial haemorrhages and upper GI bleed has been described in DKA but has not reported with Eu DKA (17). Potential predisposing factors for SGLT-2 inhibitor-associated Eu-DKA are acute illnesses such as urinary tract infection, dietary restrictions or fasting, surgical stress, use of alcohol, diffuse paralytic ileus etc. In our case no such clear precipitant factor was present. Our patient recently diagnosed with uncontrolled diagnosed diabetes and HBA1c of 8.9%. He was in catabolic state and losing weight at the time of diagnosis Use of SGLT2 inhibitors with lower body mass index and decreased glycogen stores can sometimes predispose them for development of EUDKA (18). Plausible theories which are relevant to our case may be genetic sensitivity, low body mass index, decreased glycogen stores and decreased insulin level due to glucotoxicity of beta cells (19).It has also been seen that the duration of SGLT2 use has no relevance to the risk of development of EuDKA. It can occur with time of onset ranging from 1 day to 1 year (median 43 days). In our case it occurred within seven days of its use (20). Treatment of SGLT-2 inhibitor-associated Eu-DKA is similar to management of conventional DKAexcept for the prompt discontinuation of SGLT-2 inhibitors. Other treatments include IV fluids, IV insulin administration, and electrolyte correction, supportive and symptomatic care. Insulin drip should be continued until the anion gap closes and bicarbonate levels normalize. Intravenous glucose may be needed to facilitate theadministration of the large amounts of insulin which is required to correct the ketoacidosis (21). For prevention, these medications should be discontinued during the sick days and minimum of three days before major surgical procedures. These drugs preferably should not be used in critical care setting. (22),though the exact time of restarting these medications is not clear in literature but it should not be restarted in immediate post recovery period. (23)

CONCLUSION

It should be stressed that appropriate patient selection for SGLT-2 inhibitors and the increased awareness of their rare side-effect is necessary to prevent any untoward outcomes. Importantly, more needs to be done to increase awareness of this rare but potentially fatal condition of EuDKA amongst primary care/ER and critical care physicians. Patients should be carefully selected with appropriate indications for SGLT-2inhibitors. EuDKA is an under recognized and possibly fatal adverse effect of SGLT-2 inhibitors; hence, measurements of serum ketones should be done whenever a patient taking SGTL-2 inhibitors gets sick. Though it is important to do the detailed workup for acute abdomen, but knowing the entity will help further in reducing unnecessary testing and surgery. Knowing this entity also helps in better management to fullness with lot of conviction, better prognostication of patient and his family members.

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