CASE REPORT

Euglycaemic diabetic ketoacidosis in a patient with type 2 diabetes started on empagliflozin

Owais Rashid,¹ Saad Farooq,¹ Zareen Kiran,¹ Najmul Islam²¹Aga Khan University, Karachi, Sindh, Pakistan²Department of Endocrinology, The Aga Khan University Hospital, Karachi, Sindh, Pakistan

Correspondence to

Dr Owais Rashid, owais.rashid@aku.edu

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SUMMARY

Diabetes ketoacidosis (DKA) is largely associated with type 1 diabetes and has hyperglycaemia as a cardinal feature. We discuss the case of a 42-year-old man, a patient with type 2 diabetes, who presented to the emergency room, with nausea, vomiting and abdominal pain. He had recently changed his diabetes medications and started on an SGLT2 inhibitor (empagliflozin) along with metformin, pioglitazone, liraglutide and self-adjusted exogenous insulin. DKA was suspected in the wake of clinical examination and lab findings but glucose levels were below the cut-off for DKA; therefore, he was diagnosed with euglycaemic DKA. He was successfully managed with intravenous hydration and insulin infusion. We discuss the link of SGLT2 inhibitors with DKA and the pathophysiology behind euglycaemic DKA.

BACKGROUND

SGLT2 inhibitors are a newer class of antidiabetic drugs that work by decreasing the absorption of glucose in the kidney by inhibiting sodium-dependent glucose uptake. This increases the loss of glucose in the urine. This is a case documenting one of the rarer side effects of treatment with SGLT2 inhibitors, especially empagliflozin. Diabetic ketoacidosis (DKA) usually presents as a triad of hyperglycaemia, increased anion-gap acidosis and ketosis.¹ With the widespread usage of SGLT2 inhibitors, the incidence of DKA is likely to increase and diagnosis may be missed in the presence of euglycaemia. Therefore, physicians need to be cautious about this side effect and the novel presentation of DKA in the setting of SGLT2 inhibitor usage.

CASE PRESENTATION

A 42-year-old man, a patient with type 2 diabetes for 7 years, presented with nausea, vomiting and upper abdominal pain/discomfort for the past 4 days. Before the start of these symptoms, he had, for 6 years, been taking injection glargine, 40 units and injection aspart, 12 units, before breakfast, 18 units before lunch and 24 units before dinner along with metformin XR 750 mg twice daily for his diabetes. His sugars were well controlled with an glycated haemoglobin (HbA1c) of 7.1% in January 2016. He visited a doctor in the USA for his increasing insulin requirements and was advised to change to metformin 1000 mg twice daily and to start empagliflozin 25 mg once a day. He was also advised to add pioglitazone 30 mg and liraglutide 0.6 mg gradually along with self-adjusted insulin doses. The patient started empagliflozin 25 mg initially along with glargine and aspart in

the usual daily doses with dramatic improvement in his blood sugars the next day (fasting blood sugar around 70 mg/dL). However, he started having nausea and abdominal discomfort, and therefore reduced his glargine dose to half (20 units), decreased the insulin aspart before each meal and continued metformin and empagliflozin 25 mg the next day. His symptoms of nausea and upper abdominal discomfort persisted while his blood sugars remained controlled. His sugars improved to the extent that he stopped the insulin glargine on the third day, but continued insulin aspart, metformin and empagliflozin, and started pioglitazone 30 mg once daily. His nausea and upper abdominal discomfort/pain continued to worry him. On the fourth day following the start of empagliflozin, he also started injection liraglutide 0.6 mg as advised by his doctor, for weight loss, and continued insulin aspart, metformin and empagliflozin. He continued to have worsening of his symptoms and after 4 days of using empagliflozin 25 mg and metformin 1000 mg, 2 days of using pioglitazone 30 mg and one dose of injection liraglutide 0.6 mg, he was presented to the emergency room, with nausea, vomiting and upper abdominal pain.

INVESTIGATIONS

His labs showed a random blood glucose level of 202 mg/dL, arterial blood gases; pH 7.15, PCO₂ 19.50, HCO₃ 7.5, urinary ketones were 2+ve, electrolytes: Na 133 mmol/L, K 4.5 mmol/L, chloride 98 mmol/L, HCO₃ 10.1 mmol/L and an anion gap of 24.9. Additional labs showed troponin I values of <0.006 and 0.005 performed twice (cut-off >0.04), white cell count of 7.8×10⁹/L, amylase 52 (28–100), lipase 91(6–51), no growth on blood cultures, liver function tests: total bilirubin 0.6 mg/dL, serum glutamic-pyruvic transaminase 26 IU/L, γ-glutamyl transpeptidase 15 IU/L and alkaline phosphatase of 103 IU/L (table 1).

DIFFERENTIAL DIAGNOSIS

- Diabetic ketoacidosis
- Acute pancreatitis
- Lactic acidosis

TREATMENT

The patient was diagnosed as a case of euglycaemic diabetic ketoacidosis secondary to empagliflozin, as no other precipitating factor for his diabetic ketoacidosis could be identified. He was managed with continuous insulin infusion, hydration and discontinuation of all his previous medications. After his acidosis got better and he started eating, a basal

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Table 1 Lab investigations

Labs	Values	Normal range
Blood glucose (mg/dL)	202	(80–160)
Arterial pH	7.15	(7.35–7.45)
Arterial pCO ₂ (torr)	19.50	(35–48)
Arterial bicarbonate	7.50	(19–24)
Urinary ketones	+2	0
Sodium (mmol/L)	133	(136–145)
Potassium (mmol/L)	4.50	(3.5–5.1)
Chloride (mmol/L)	98	(98–107)
Bicarbonate (mmol/L)	10.1	(20–31)
Anion gap (mEq/L)	24.9	(8–16)
Troponin I (ng/mL)	<0.006	(<0.01)
White cell count×10 ⁹ /L	7.8	(4–10)
Amylase (IU/L)	52	(28–100)
Lipase (IU/L)	91	(6–51)
Total bilirubin (mg/dL)	0.6	(0.3–1.9)
SGPT (IU/L)	26	(<45)
GGT (IU/L)	15	(6–50)
Alkaline phosphatase (IU/L)	103	(50–100)

GGT, γ -glutamyl transpeptidase; SGPT, serum glutamic-pyruvic transaminase.

bolus regimen with insulin glargine and aspart was started. The patient was discharged on the basal bolus regimen and asked to follow-up in clinic with self-monitoring of blood glucose. He was advised not to restart empagliflozin.

OUTCOME AND FOLLOW-UP

The patient remained stable on follow-up after 1 week and all his symptoms resolved completely.

DISCUSSION

Several changes were made concurrently in our patient's drug regimen, which is not recommended and is unwise as this may lead to poor compliance, more side effects and inferior glucose control. In our patient, metformin, liraglutide and empagliflozin can all cause nausea, vomiting and abdominal pain, but only the latter has been linked to euglycaemic DKA.

Empagliflozin is an SGLT2 inhibitor. These medications dramatically reduce blood glucose and HbA1c. Added benefits include promotion of weight loss, lowered blood pressures, decreased hypoglycaemic episodes and a lower exogenous insulin requirement.² These benefits may make them useful even in type 1 diabetes though they are not yet Food and Drug Administration approved for this purpose.

Although SGLT2 inhibitors are relatively safe drugs, they have been linked to side effects such as urinary tract infections, genital mycotic infections and volume depletion, also, diabetic ketoacidosis has been observed in rare instances.^{3–4} It is surprising that the major finding of DKA, increased blood glucose levels, was not found in our patient; however, a lot of the reported cases of DKA with SGLT2 inhibitors have had a similar presentation of euglycaemia.^{5–6}

According to a study by the European Medicines Agency, a total of 101 cases of DKA were reported in patients with T2D treated with SGLT2 inhibitors; 63 were reported with canagliflozin, 34 with dapagliflozin and only 4 with empagliflozin, hence empagliflozin is the SGLT2 inhibitor least linked with the development of DKA. In spite of high anion gap acidosis and increased plasma ketones, several patients with DKA also had relatively normal plasma glucose levels.⁷ Roach and Skierczynski⁶ also

described euglycaemic DKA during treatment with empagliflozin in a woman who had blood glucose of 161 mg/dL.

This rarer form of DKA may well be due to under-recognition and under-reporting, but an altered physiological process may be at fault as well. Normally, in DKA, insulin deficiency or resistance results in a surge of counter regulatory hormones, for example, glucagon. This results in severe hyperglycaemia and a shift of metabolic fuel to fatty acids. Oxidation of fatty acids causes the production of ketones, which subsequently leads to DKA.¹ In our patient, the SGLT2 inhibitor may have caused a massive loss of glucose in the urine resulting in euglycaemia, decreased glucose dependent insulin release and subsequent DKA. Furthermore, DKA was probably augmented by the decreased amount of exogenous insulin. Moreover, lactic acidosis in DKA might also have developed as suggested by Cox *et al.*⁸ Since our patient was on high doses of metformin and might have been dehydrated, this may have led to enhanced acidosis.

Although SGLT2 inhibitors increase glucose excretion in the urine, this beneficial effect may be counterbalanced by their stimulation of endogenous glucose production and increased glucagon secretion. The exact mechanism of this effect is as yet unknown but it may have a relation with the SGLT2 receptor found on pancreatic α cells. Thus these drugs may act as glucagon secretagogues by inhibiting this SGLT2 receptor thereby augmenting DKA.⁹

Patient's perspective

This episode was one of the worst experiences of my life and I think I am very lucky to come out alive. I never thought a simple medication could cause my family and me so much trouble. I partly blame my doctor, who should have guided me more about this side effect so I could have made a more informed decision. Initially, I was very happy with the drug because it decreased my insulin requirement, but then I had to be hospitalised because of the side effect it caused. I have now decided to only take medicines that have been tried and tested and to not take newer medications because this episode has made me very distrustful of any new medicine.

Learning points

- It is unwise to make several changes simultaneously in the drug regimen of a patient with type 2 diabetes as this may not only lead to poorer compliance but also result in more side effects, especially hypoglycaemia.
- SGLT2 inhibitors are highly useful drugs but may predispose to diabetic ketoacidosis (DKA), therefore physicians must be cautious when prescribing them to patients.
- Exogenous insulin should never be drastically decreased as it may precipitate DKA.
- Patients on SGLT2 inhibitors should be counselled to urgently seek medical attention in case they develop symptoms suggestive of DKA, for example, nausea, vomiting, abdominal pain, etc.
- DKA-prone individuals should not be prescribed SGLT2 inhibitors especially if the patient experiences repeated infections, dehydration, vomiting, diarrhoea, or trauma or is about to undergo surgery.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Diabetic Ketoacidosis: practice essentials, background, pathophysiology [Internet]. Emedicine.medscape.com. 2016 [cited 6 March 2016]. <http://emedicine.medscape.com/article/118361-overview>
- 2 John M, Gopinath D, Jagesh R. Sodium-glucose cotransporter 2 inhibitors with insulin in type 2 diabetes: clinical perspectives. *Indian J Endocrinol Metab* 2016;20:22.
- 3 Vasilakou D, Karagiannis T, Athanasiadou E, *et al*. Sodium–glucose cotransporter 2 inhibitors for type 2 diabetes. *Ann Intern Med* 2013;159:262.
- 4 FDA. FDA Briefing Document. NDA 204042 Invokana (Canagliflozin) Tablets. 2013. [http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/](http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM334550.pdf) Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM334550.pdf (accessed 6 Mar 2016).
- 5 Storgaard H, Bagger JI, Knop FK, *et al*. Diabetic ketoacidosis in a patient with type 2 diabetes after initiation of sodium-glucose cotransporter 2 inhibitor treatment. *Basic Clin Pharmacol Toxicol* 2015;118:168–70.
- 6 Roach P, Skierczynski P. Euglycemic diabetic ketoacidosis in a patient with type 2 diabetes after treatment with empagliflozin. *Diabetes Care* 2015;39:e3.
- 7 EMA. Review of Diabetes Medicines Called SGLT2 Inhibitors Started: risk of diabetic ketoacidosis to be examined. 2016. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/SGLT2_inhibitors__20/Procedure_started/WC500187926.pdf (accessed 6 Mar 2016).
- 8 Cox K, Cocchi MN, Saliccioli JD, *et al*. Prevalence and significance of lactic acidosis in diabetic ketoacidosis. *J Crit Care* 2012;27:132–7.
- 9 Bonner C, Kerr-Conte J, Gmyr V, *et al*. Inhibition of the glucose transporter SGLT2 with dapagliflozin in pancreatic alpha cells triggers glucagon secretion. *Nat Med* 2015;21:512–17.

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