Euglycemic ketoacidosis following a single dose of empagliflozin

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ABSTRACT
Sodium-glucose co-transporter 2 (SGLT-2) inhibitors have recently joined the therapeutic armamentarium for the treatment of diabetes mellitus. SGLT-2 inhibitors, as monotherapy or in combination with other medications, have a favorable effect on hemoglobin A1C concentrations. However, a growing number of reports have described ketoacidosis as a complication following prolonged SGLT-2 inhibitor therapy. We report a case of SGLT-2 inhibitor associated ketoacidosis in a patient following a single first dose of empagliflozin.

KEYWORDS
Empagliflozin side-effects; ketoacidosis; SGLT-2 inhibitors

Introduction
The World Health Organization reports that the prevalence of diabetes mellitus (DM) for adults over 18 years of age has increased from 4.7% to 8.5% over the past three decades [1] and is continuously trending upwards. Approximately 9.3% of the population of the U.S.A. has DM, and 37% are pre-diabetic [2], with a projected prevalence of DM between 1 in 3–5 adults by the year 2050 [3]. DM not only affects the major organs of the body at a cellular level but also affects the macro and microvasculature of vital organs throughout the body, potentially leading to vascular, cerebral, retinal, cardiovascular, and renal complications [2]. While a number of treatment options have been proposed over the decades for the treatment of DM, diet and consistent physical exercise remain the first line strategy [1,2]. Several treatment modalities have emerged in recent years [4–6]. The U.S. Food and Drug Administration (FDA) approved empagliflozin in August 2014 as an adjunct to diet and physical exercise to assist in attaining optimal glycemic control [7].

Although not recommended for patients with type 1 DM, sodium-glucose co-transporter 2 (SGLT-2) inhibitors appear to be useful in the treatment of type 2 DM [8]. SGLT-2 inhibitor treatment may occur either as monotherapy or in addition to conventional treatment with insulin, sulfonylureas, or metformin [9–11]. With the exception of mild side effects of nausea, vomiting, abdominal pain, and lethargy, SGLT-2 inhibitors have thus far been generally well tolerated by diabetic patients.

Between March 2013 and May 2015, the FDA Adverse Event Reporting System (AERS) received 73 reports of acidosis associated with SGLT-2 inhibitor use. Nearly all of these cases required emergency department visits for the treatment of ketoacidosis, and all reported cases of ketoacidosis occurred in patients on stable, regular doses of SGLT-2 inhibitors usually over a period of weeks to months [8].

We report a case of ketoacidosis following a single first dose of empagliflozin.

Case report
A 25-year-old male presented to the emergency department with complaints of diffuse body cramping, light-headedness, and sweating for four hours. He had been feeling tired and generally unwell for the previous two weeks. Eight weeks before presentation, he started metformin 500 mg twice daily for newly diagnosed DM with a dose increase to 1000 mg twice daily four weeks before presentation. His primary care provider added empagliflozin (10 mg daily) as a combination therapy with metformin to help achieve glycemic control. The patient indicated that he had only begun the empagliflozin the day prior to his ED presentation and had only used one dose of the drug prior to presentation. He denied any current alcohol or illicit drug use.

On presentation, he was awake, alert, and oriented to person, time, place, and situation. He appeared to be weak and diaphoretic. The initial vital signs were temperature 97.4 degree F, blood pressure 127/64 mm Hg, pulse 88 beats per minute, respiratory rate 18 breaths per minute, and oxygen saturation 100% on room air. The physical examination was otherwise unremarkable, and an initial electrocardiogram was normal.
The initial blood glucose concentration was 223 mg/dL. Further laboratory investigations revealed a white blood cell count of $14.6 \times 10^3$/mm$^3$, lactate 3.6 mmol/L, sodium 137 mmol/L, chloride 96 mmol/L, and bicarbonate 11 mmol/L. The calculated anion gap was 30. His beta-hydroxybutyrate concentration was 100.3 mg/dL or 9.6 mmol/L (normal value = 0.2–2.81 mg/dL or <0.2 mmol/L).

Treatment commenced with intravenous normal saline followed by insulin infusion at 0.5 units/hour and 5% dextrose in normal saline (D5NS) infusion. The anion gap declined from 30 mEq/L to 15 mEq/L over a period of 24 hours. The intravenous insulin was converted to the subcutaneous administration of long acting insulin. The patient continued to improve and was discharged from the hospital after 76 hours on both short- and long-acting insulin and with follow up by the Endocrinology service. The patient received strict instructions to avoid empagliflozin or other SGLT-2 inhibitor class drugs.

**Discussion**

Empagliflozin is a member of the SGLT-2 inhibitor class of medications that was approved for the treatment of DM on 1 August 2014 [7]. The mechanism of action for SGLT-2 inhibitors blocks SGLT-2 transporter at proximal renal tubules [12–14]. This results in decreased absorption of glucose and sodium with resultant glucosuria. This drug appears to be generally safe and well tolerated [10–12] with associated reductions in HbA1C in diabetic patients [10]. Further benefits reported by the FDA include reduction of cardiovascular mortality in adults with DM II [15]. However, reports of ketoacidosis soon followed FDA approval [8,16,17]. Most cases have involved euglycemic ketoacidosis in patients taking canagliflozin 300 mg [17,18] and empagliflozin 25 mg [19].

The pathophysiology of euglycemic ketoacidosis associated with SGLT-2 inhibitor appears to involve decreased insulin production and increased glucagon production. These in turn result in lipolysis with increased fatty acid production and the subsequent oxidation of free fatty acids with ketone body formation [17–20]. The mainstay of treatment includes intravenous fluid and insulin administration to increase uptake of glucose by peripheral tissues as well as to decrease gluconeogenesis and ketogenesis, thus closing the anion gap.

The risk of ketoacidosis with empagliflozin appears to be dose-dependent [16]. In this case, we report the presentation of euglycemic ketoacidosis after a single 10 mg dose of empagliflozin.

We used the Naranjo score to determine the probability that empagliflozin caused ketoacidosis in this case [21]. The calculated Naranjo score is 7 based upon previous conclusive reports on ketoacidosis secondary to SGLT-2 inhibitors (+1); the adverse event appeared after a single dose of empagliflozin (+2) and improved after the drug was discontinued (+1); no other alternate causes of the event were identified (+2) and laboratory investigations were consistent with euglycemic ketoacidosis (+1). According to the Naranjo adverse drug reaction probability scale, a score between 5 and 8 indicates that the untoward reaction was “probably due to the drug” [21]. We concluded that metformin associated lactacidosis (MALA) was unlikely since the patient had minimally elevated lactate compared to the typically high lactate concentration in MALA [22]. The physiologic effects of empagliflozin on insulin, glucagon, and free fatty acid production after acute use of empagliflozin [19] likely explains the sudden onset of ketoacidosis after a single dose.

**Conclusion**

We report a case of ketoacidosis following a single dose of empagliflozin (10 mg). Clinicians prescribing empagliflozin must maintain a high level of suspicion for ketoacidosis and educate patients on the need to seek emergency medical attention for symptoms consistent with that entity. Future research should clarify the risk factors that may predispose diabetic patients to empagliflozin-associated ketoacidosis.

**Disclosure statement**

The authors report no conflict of interest.

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**References**

[1] World Health Organization. Global report on diabetes. Geneva: World Health Organization; 2016 [cited 2017 Jul 31]. Available from: http://www.who.int/diabetes/global-report/en/

[2] Centers for Disease Control and Prevention. National diabetes statistics report: estimates of diabetes and its burden in the United States. Center for Disease Control and Prevention; 2014 [cited 2017 Jul 31]. Available from: https://www.cdc.gov/diabetes/pdfs/library/diabetesreportcard2014.pdf

[3] Boyle JP, Thompson TJ, Gregg EW, et al. Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and pre-diabetes prevalence. Popul Health Metrics. 2010;8:29. DOI:10.1186/1478-7954-8-29
[4] Middleton J. The effect of case management on glycemic control in patients with type 2 diabetes. Case Manag. 2003;14(6):43–47. DOI:10.1016/S1061925903002650

[5] American Diabetes Association. Standards of medical care in diabetes – 2009. Diabet Care. 2009 Jan;Suppl 1: S1–S2, 32. Available from: https://doi.org/10.2337/dc09-S001

[6] American Diabetes Association. Executive summary: standards of medical care in diabetes – 2013. Diabet Care. 2013;Suppl 1: S4–S10, 36. Available from: https://doi.org/10.2337/dc13-S004

[7] U.S. Food and Drug Administration. FDA approves Jardiance to treat type 2 diabetes. Press Release. 2014 Aug 1 [cited 2016 Aug 10]. Available from: www.fda.gov/NewsEvents/PressAnnouncements/ucm407637.htm

[8] U.S. Food and Drug Administration. FDA drug safety communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood. Safety Announcement. 2015 [cited 2017 Jul 31]. Available from: https://www.fda.gov/Drugs/DrugSafety/ucm446845.htm

[9] Hansing H, Merker L, Seewaldt-Becker E, et al. on behalf of the EMPA-REG METSU Trial Investigators. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes. A 24-week, randomized, double-blind, placebo-controlled trial. Diabet Care. 2013;36(11):3396–3404. DOI:10.2337/dc12-2673

[10] Pieber TR, Famulla S, Eilbracht J, et al. Empagliflozin as adjunct to insulin in patients with type 1 diabetes: a 4-week, randomized, placebo controlled trial (EASE-1). Diabet Obes Metab. 2015;17(10):928–935. DOI:10.1111/dom.12494

[11] Roden M, Merker L, Christiansen AV, et al. Safety, tolerability and effects on cardiometabolic risk factors of empagliflozin monotherapy in drug-naive patients with type 2 diabetes: a double-blind extension of a Phase III randomized controlled trial. Cardiovasc Diabetol. 2015;14:154. DOI:10.1186/s12933-015-0314-0

[12] DeFronzo RA, Davidson JA, Del Prato S. The role of the kidneys in glucose homeostasis: a new path towards normalizing glycaemia. Diabet Obes Metab. 2012;14:5–14. DOI:10.1111/j.1463-1326.2011.01511.x

[13] Hedrington MS, Davis SN. The role of empagliflozin in the management of type 2 diabetes by patient profile. Ther Clin Risk Manage. 2015;11:739–749. DOI:10.2147/TCRM.S71762

[14] Baker WL, Smyth LR, Riche DM, et al. Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: a systematic review and meta-analysis. J Am Soc Hypertens. 2014;8:262–275. DOI:10.1016/j.jash.2014.01.007

[15] U.S. Food and Drug Administration. FDA approves Jardiance to reduce cardiovascular death in adults with type 2 diabetes. FDA News Release. 2016 Dec 2 [cited 2017 Jul 31]. Available from: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm531517.htm.

[16] Nishimura R, Tanaka Y, Koikawa K, et al. Effect of empagliflozin monotherapy on postprandial glucose and 24-hour glucose variability in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled, 4-week study. Cardiovasc Diabetol. 2015;14:11. DOI:10.1186/s12933-014-0169-9

[17] Peters AL, Buschur EO, Buse JB, et al. Euglycemic diabetic ketoacidosis: a potential complication of treatment with sodium-glucose cotransporter 2 inhibition. Diabet Care. 2015;38(9):1687–1693. DOI:10.2337/dc15-0843

[18] Chai PR, Bonney C, Blohm E, et al. Canagliflozin-associated diabetic ketoacidosis: a case report. Toxicol Commun. 2017;1:2–5. DOI:10.1080/24734306.2017.1331604

[19] Ferrannini E, Muscelli E, Frascerra S, et al. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. J Clin Invest. 2014;124:499–508. DOI:10.1172/JCI72227

[20] Ogawa W, Sakaguchi K. Euglycemic diabetic ketoacidosis induced by SGLT2 inhibitors: possible mechanism and contributing factors. J Diabet Invest. 2016;7(2):135–138. DOI:10.1111/jdi.12401

[21] Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239–245. DOI:10.1038/clpt.1981.154.154.

[22] Friescke S, Abel P, Roser M, et al. Outcome of severe lactic acidosis associated with metformin accumulation. Crit Care. 2010;14(6):R226. DOI:10.1186/cc9376. Epub 2010 Dec 20.