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SGLT2-Inhibitor induced euglycemic ketoacidosis in acute surgical patients

Aaron M. Hawkins, Richard V. Jackson, Hayden White, Deepak L. Vardesh

ABSTRACT

Introduction: A significant adverse effect of sodium-glucose co-transporter 2 (SGLT2) inhibitors is euglycaemic ketoacidosis. This is of particular significance for surgeons as the combination of long periods of fasting, surgical stress and reduced insulin dosing in acute surgical patients leaves them at an increased risk for developing euglycemic ketoacidosis. This case series reports the adverse reaction to empagliflozin, canagliflozin and dapagliflozin in four acute surgical patients. Case Series: Case 1: A 43-year-old female underwent elective total abdominal hysterectomy, bilateralsalpingectomy and incisional hernia repair, on a background of type 2 diabetes mellitus (T2DM) treated with metformin, insulin and empagliflozin. She developed significant euglycaemic ketoacidosis complicated by sepsis and a rectus abdominushaematoma. Case 2: A 70-year-old female with acute cholecystitis on a background of T2DM treated with metformin, insulin and canagliflozin. She developed euglycemic ketoacidosis after a 12-hour fast and 24-hour without her usual insulin. Case 3: A 45-year- old female admitted for cholelithiasis and subsequent cholecystectomy on a background of T2DM treated with metformin and dapagliflozin. She developed euglycemic ketoacidosis day-1 post procedure. Case 4: A 49-year-old female who presented with a right thigh abscess and fever, requiring incision and drainage, on a background of T2DM managed with metformin and dapagliflozin. She developed euglycemic ketoacidosis after an extended period of fasting. Conclusion: Given the increasing use of SGLT2 inhibitors and the unique combination of risk factors present for surgical patients, it is important that surgeons are familiar with this condition and able to diagnose and treat it early.

Keywords: Euglycemic ketoacidosis, Sodium-glucose co-transporter 2 (SGLT2) inhibitors, Type 2 diabetes mellitus (T2DM)

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INTRODUCTION

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a new class of oral hypoglycemics. The commonly used drugs in this class in Australia are dapagliflozin, canagliflozin and empagliflozin. In addition to serum glucose control, their cardioprotective, renoprotective,

blood pressure control and weight loss benefits have led to increasing the use of drug in the community. A significant adverse effect that has been reported is euglycemic ketoacidosis. This is of particular significance to surgeons as the combination of long periods of fasting, surgical stress and reduced insulin dosing in acute surgical patients increases their risk of developing euglycaemic ketoacidosis [1–6].

This report presents four acute surgical patients who developed euglycaemic ketoacidosis and explores the importance of early recognition of the condition by surgical teams.

CASE SERIES

Case 1

A 43-year-old female presented for elective total abdominal hysterectomy, bilateral salpingectomy and incisional hernia repair. This was on a background of type 2 diabetes mellitus, hypercholesterolemia and hypertension. Her medications included sitagliptin 100 mg daily, metformin 1000 mg daily, rosuvastatin 10 mg daily, telmisartan 40 mg daily and empagliflozin 25 mg daily. She was fasted from midnight and underwent the procedure in the morning with no complications. The patient was on a clear fluid diet to begin with and upgraded to a free fluid diet the following day at dinner. She continued to receive all her medications including her oral hypoglycemic agents during the perioperative period. On the second postoperative day, she developed significant anemia with a hemoglobin drop from 10.5 to 6.9 g/dL. Computed tomography (CT) imaging of her abdomen revealed a large rectus abdominis hematoma. The patient was again fasted, transfused one unit of packed red blood cells and underwent a laparotomy the following morning during which 1.5 L of blood was drained from the hematoma. There was no evidence of active bleeding.

Postoperatively, the patient required noradrenaline to maintain her blood pressure and was transferred to the ICU. At this point she was noted to have a metabolic acidosis with a pH of 7.02, HCO_3 5 mEq/L, and base excess of 24.6 mEq/L. Blood glucose was only 181.98 mg/dL and ketones 33.12 mg/dL. Serum Ppotassium was 3.1 mEq/L and phosphate was as low as <0.31 mg/dL. A diagnosis of SGLT-2i induced euglycemic ketoacidosis was suspected. Empagliflozin was ceased, insulin and dextrose infusion commenced as well as aggressive intravenous electrolyte replacement and total parenteral nutrition at 30 mL/h. She then became febrile with signs of systemic inflammatory response syndrome (SIRS), requiring ongoing vasopressor, and was commenced on intravenous piperacillin-tazobactam for presumed sepsis. Over the next 24 hours, the patient's ketosis and acidosis resolved, though she developed polyuria with urine output of up to 600 mL/h, associated with glycosuria. She needed significant potassium and phosphate replacement intravenously of up to 20 mEq/hr and 124 mg/hr respectively. Insulin/dextrose infusion was continued for a further 48 hours with intravenous electrolyte replacement before her urine output and electrolytes improved. In total, she received a total of 23 L of intravenous 5% dextrose in 72 hours, with associated urine output of 27 L over that time. Urine dipstick showed significant glycosuria. Unfortunately, no formal urinary glucose, potassium or phosphate testing was performed. Renal function was normal throughout the admission. The patient was subsequently discharged on post-operative day-7. Empagliflozin was permanently ceased.

Case 2

A 70-year-old female presented with acute cholecystitis. This was on a background of hypertension, dyslipidaemia and type 2 diabetes mellitus. Her diabetes treatment consisted of metformin 1700 mg mane and 850 mg nocte, insulin aspart/aspart-protamine 30/70 formulation 24 units mane and 20 units nocte and canagliflozin 300 mg daily. She had an acute kidney injury (AKI) (kidney disease: improving global outcomes guideline stage 1) on admission with her serum creatinine of 1.11 mg/dL, resolving back to her baseline of 0.74 mg/dL within 48 hours [7]. The patient spent 12 hours nil-by-mouth on her admission day, followed by a clear fluid diet overnight. The patient was not charted insulin for the first day of admission during her fasting state. On her second day of admission it was noted that the patient had a high anion gap metabolic acidosis with a pH of 7.27, despite blood glucose levels ranging from 180–270 mg/dL. Further investigation revealed serum ketones of 20.92 mg/dL. An insulin infusion was commenced, successfully returning the ketones level to normal. Canagliflozin was ceased and the patient advised to avoid SGLT2 inhibitors in the future.

Case 3

A 45-year-old female presented with cholelithiasis and underwent an uncomplicated cholecystectomy. This was on a background of hypertension, dyslipidemia, bell's palsy and type 2 diabetes mellitus with normal renal function. Treatment for diabetes mellitus consisted of metformin and dapagliflozin 10 mg daily. Day-1 postsurgery, the patient developed sinus tachycardia up to 150 bpm, and in the emergency call that followed it was discovered she had a high anion gap metabolic acidosis with a pH 7.19, bicarb 8 mEq/L and ketones 34.86 mg/dL, despite a blood glucose level 144 mg/dL. The patient was commenced on an insulin infusion and the ketoacidosis subsequently resolved. The patient was subsequently commenced on regular insulin and dapagliflozin was ceased permanently.

Case 4

A 49-year-old female presented with a right thigh abscess, fevers and systemic inflammatory response syndrome (SIRS). Her background history was significant for type 2 diabetes mellitus, dyslipidaemia, and a prolactin secreting pituitary microadenoma that had been inactive since 2011 with normal prolactin levels on no treatment. Medications include pregabalin, metformin and dapagliflozin 10 mg daily. The patient required incision and drainage in theatre with two subsequent returns to theatre for further debridement. Over the first 48 hours in hospital, the patient spent 36 hours nil-by-mouth. Day-1 following her third procedure in 48 hours, a high anion gap metabolic acidosis was noted with a pH 7.30 and ketones 25.56 mg/dL, despite a serum glucose 205.2 mg/dL. The patient was commenced on an insulin infusion and the ketoacidosis resolved. The abscess required no further surgical management, resolving with five days of oral amoxicillin/clavulanic acid 875/125 mg BD. Her dapagliflozin was ceased and she was discharged on regular insulin and metformin for ongoing diabetic management.

DISCUSSION

SGLT2 inhibitors

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a relatively new addition to the ever-growing arsenal for type 2 diabetes mellitus treatment. This class of drug lowers serum glucose level by increasing urinary glucose excretion [2]. The sodium glucose co-transporter 2 (SGLT2) is expressed in the proximal tubule of the kidneys. It plays a major role in reabsorption of glucose, responsible for reabsorption of as much as 90% of filtered glucose [8]. As the name suggests, this new drug class inhibits the SGLT2 transporter, reducing glucose reabsorption and thereby lowering serum glucose [2]. The use of drug class has been increasing since their introduction in 2013. Prescriptions for dapagliflozin, the most commonly prescribed SGLT2 inhibitor in Australia, through the Australian pharmaceutical Benefits Scheme, have increased from around 62,838 in 2014 to 290,783 in 2015 [9, 10].

A major advantage of SGLT2 inhibitors over other oral hypoglycemic medications is their systemic benefit in addition to serum glucose lowering. They have been shown to be associated with both reduced systolic blood pressure and significant weight loss in patients. Recently, a large study published in a academic journal demonstrated that patients taking empagliflozin, when compared to placebo, had significantly lower death rates from cardiovascular causes and reduced hospitalization from heart failure [5]. In addition to the cardioprotective benefits, evidence is emerging that use of SGLT2 inhibitors slow the progression of renal disease in patients with type 2 diabetes mellitus [6]. Given these benefits, we are likely to see growing numbers of patients being prescribed SGLT2 inhibitors in the coming years.

While an exciting prospect in the treatment of diabetes mellitus, it is important to be aware of the potential adverse effects of SGLT2 inhibitors. Patients taking SGLT2 inhibitors are at higher risk of genitourinary infections and symptomatic hypotension [11, 12]. In addition to this, reports have been emerging of an association with euglycemic ketoacidosis, the subject of this report [1, 2].

SGLT2 inhibitors and euglycemic ketoacidosis

As SGLT2 inhibitors became more commonly used, reports began to emerge of patients developing euglycemic ketoacidosis precipitated by the medication. These presentations varied from reversible and relatively asymptomatic to severe and symptomatic reactions [3]. In May 2015, the United States Food and Drug Administration (FDA) issued an official warning that SGLT2 inhibitors have the potential for euglycemic ketoacidosis [13].

The mechanism for this adverse reaction is multifactorial. The reduction in serum glucose and therefore reduction in serum insulin secretion leads to decreased carbohydrate oxidation and increased lipid oxidation [2]. In addition to this, SGLT2 inhibitors increase serum glucagon levels, both indirectly via reduced inhibition through insulin and directly via action on the SGLT2 transporter present on pancreatic alpha cells [2]. This influence on insulin and glucagon levels is central to the development of ketoacidosis. The SGLT2

Table 1: Blood pathology results: comparison of results at time of presentation to results at discharge

Case	BSL (mg/dL)	On Presentation				On Discharge				HbA1c %	Date
		Bicarb (mEq/L)	Ketones (mg/dL)	pH	Lactate (mg/dL)	Bicarb (mEq/L)	Ketones (mg/dL)	pH	Lactate (mg/dL)		
1	181.8	5	33.12	7.02	12.61	22	0.0	7.48	6.31	-	April 2017
2	273.6	10	20.92	7.27	17.12	25	5.81	7.36	7.21	-	Sept 2016
3	135	10	32.54	7.19	12.61	27	0.58	7.40	7.21	8.0	May 2016
4	205.2	14	25.56	7.30	7.21	26	1.74	7.39	11.71	10.4	July 2016

inhibitors likely also predispose to the development of ketoacidosis indirectly through suppression of renal ketone oxidation [2].

Our Cases

The four cases presented in this report have some significant differences in presentation, severity and management issues. Case 1 was clearly the most severe, requiring a four day intensive care admission, though the case was also complicated by sepsis and an abdominal hematoma. In each case, the ketosis and acidosis resolved within 24 hours of ceasing the SGLT-2 inhibitor and commencing insulin/dextrose infusion. Case 1, however, differed from the others in the extended period of polyuria and electrolyte disturbances in the form of hypokalemia and hypophosphatemia.

We hypothesize that the significant hypokalemia and hypophosphatemia in Case 1 was caused by a combination of intracellular shift secondary to the extended period of insulin infusion as well as urinary loss of potassium and phosphate. Unfortunately, urinary electrolytes were not measured to confirm this theory.

The cause for the extended period of polyuria is less clear. Empagliflozin was administered until day two post-procedure, with the final dose given the day prior to her ICU admission. Empagliflozin has been shown to have an extended effect on urinary glucose excretion (UGE) when compared to dapagliflozin and canagliflozin [14]. Though the half-life of empagliflozin in the serum is only 10–19 hours, UGE is maintained long after plasma concentrations diminish [15]. While plasma empagliflozin concentrations peak 2 hours post dose, UGE peaks 7 hours post dose and only reduces to a third by 60 hours. However, by 60 hours post dose the plasma concentrations of empagliflozin are less than a 50th of maximum [14]. This shows that empagliflozin's tissue effect of inhibition of SGLT2 action continues well beyond its virtual elimination from the blood. It is likely that this prolonged effect of empagliflozin on UGE, couple with the large volumes of intravenous dextrose, resulted in an osmotic diuresis.

While euglycemic ketoacidosis has been reported in patients not taking SGLT2 inhibitors in the past, it is an exceedingly rare condition in type 2 diabetes mellitus and SGLT2 inhibitors are by far the most commonly reported cause. The presentations in these cases are consistent with previously reported cases of SGLT2 inhibitors induced euglycaemic ketoacidosis, however a different previously unreported cause cannot be completely excluded.

Contributing factors

Risk factors or scenarios that may precipitate the above adverse reactions are important to recognize, allowing early diagnosis and treatment. Insulin deficiency is a major precipitating factor, and the most common scenario for this is a reduction in exogenous insulin dose by either the patient or health practitioner [3]. Case 2 illustrated an example of this. The surgical patient was kept nil by mouth for an extended period, with her insulin dose initially withheld and then restarted at a reduced dose. This accelerates the process of ketogenesis, as discussed above. A second, related, risk factor for development of euglycemic ketoacidosis is restriction of carbohydrate availability [3]. This can occur in situations of inter-current illness or, significantly in the cases discussed, prolonged fasting and surgical stress [2, 3, 16].

A classic acute surgical patient will often unavoidably experience extended periods of fasting and reduced insulin dosing combined with the stress of both the presenting condition and potentially surgery. For this reason, the perioperative period could be considered a perfect storm for precipitating euglycemic ketoacidosis. Early recognition of the condition by surgeons will become increasingly important as the use of this new drug-class becomes more prevalent.

Recognizing and managing the problem

The clinical presentation of euglycemic ketoacidosis is often fairly non-specific. Patients may complain of abdominal pain, nausea, vomiting, lethargy and malaise [17]. All of these are common symptoms for other surgical conditions, making diagnosis more difficult. More severe presentations may involve significant clinical dehydration and mental obtundation [17]. An arterial or venous blood gas, looking especially at pH and lactate level, should be taken. Blood ketones should be measured as well, even with normal or only slightly raised blood glucose.

Once the diagnosis is established, the SGLT2 inhibitor should be ceased and the patient commenced on an insulin infusion with adequate fluid resuscitation [18]. Electrolyte disturbances are common and should be corrected accordingly [18].

CONCLUSION

Given the increasing use of sodium-glucose co-transporter 2 inhibitors and the unique combination of risk factors that surgical patients commonly possess, it is important that surgeons are familiar with the condition of euglycaemic ketoacidosis caused by these drugs and are able to diagnose and treat it early. This report presents four cases of SGLT2 inhibitor induced euglycaemic ketoacidosis in surgical patients and explores the significance of the condition in surgical patients.

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Author Contributions

Aaron Matthew Hawkins – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Richard V Jackson – Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Hayden White – Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Deepak L Vardesh – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

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