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The catabolic triad: case report of fasting, major cardiac surgery and sodium–glucose co-transporter 2 inhibitors leading to perioperative euglycaemic ketoacidosis

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Abstract

Sodium-glucose co-transporter-2 inhibitors (SGLT2i) are novel oral hypoglycaemic agents. For patients with diabetes mellitus, without a prior history of myocardial infarction or atherosclerotic disease, SGLT2i have been shown to reduce incident heart failure and worsening renal function. SGLT2i therapy is increasing among patients presenting for cardiac surgery. However, the perioperative use of SGLT2i carries a significant risk of euglycaemic diabetic ketoacidosis, due to their catabolic mechanism of action. This case report demonstrates euglycaemic ketoacidosis post-coronary artery bypass grafting secondary to SGLT2i, highlighting the multiple risk factors and consequences of this iatrogenic complication.

Keywords: Euglycaemic Diabetic Ketoacidosis • Post cardiac surgery acidosis • SGLT2i • Sodium-glucose co-transporter-2 inhibitors

INTRODUCTION

Sodium-glucose co-transporter-2 inhibitors (SGLT2i) are novel oral hypoglycaemic agents, first marketed in 2012. SGLT2i's increase renal glucose excretion by decreasing glucose reabsorption in the proximal convoluted tubule. SGLT2i are catabolic (decrease insulin release) unlike most diabetic medications, which are anabolic (increased glucose uptake). These agents are second-line treatment for type 2 diabetes mellitus (T2DM) (Biguanides are first line) and have been shown to decrease cardiovascular events, body mass index and blood pressure in patients with T2DM [1]. Two studies, DAPA-HF (assessing dapagliflozin) and EMPEROR-Reduced (assessing empagliflozin) highlighted a decreased combined risk of cardiovascular death or hospitalization for heart failure in patients with reduced ejection fraction with or without diabetes in patients prescribed an SGLT2i [2, 3]. While these studies reported a low incidence of Euglycaemic Diabetic ketoacidosis (0.1%), it is a known complication, highlighted by the FDA warning in 2015 following 20 case reports of euglycaemic diabetic ketoacidosis (euDKA) between 2013 and 2015 [2].

CASE REPORT

We present the case of a 54-year-old male who underwent a surgically uncomplicated 3 vessel (2 vein and 1 arterial conduit) coronary artery bypass graft. His history was significant for T2DM maintained on biguanide therapy (metformin 500 mg base deficit) for several years. Dapagliflozin 5 mg OD (SGLT2i) was commenced 2 months preoperatively, to optimize his elevated HBA1C. SGLT2i therapy was withheld 24 h preoperatively. The patient was fasted from midnight on the evening prior to surgery (9 h).

The patient's post-induction arterial blood gas demonstrated a pH of 7.45 with a normal bicarbonate and glucose. However, in the early postoperative period, pH decreased with a marked base deficit (−7.7 mmol/l). Oxygen delivery (cardiac output × arterial oxygen content) was optimized but, despite this, his metabolic acidaemia deteriorated further (base deficit −15.8 mmol/l). Surrogates for adequate cardiac output including normal mentation, SvO_2 (68%) and arterial blood lactate (0.9 mmol/l), suggested a non-cardiac aetiology. He was tachypnoeic with a $PaCO_2$ of 2.9 KPa. His urine output was 450 ml/h for the first 2 h postoperatively with ongoing polyuria (>2 ml/kg/h) for 5 days. Serum/urinary ketones were 4.9 mmol/l and 3+, respectively. Serum glucose was normal (6.5 mmol/l). He had a significant parenteral potassium requirement (100 mmol of Potassium Chloride/day) in the initial 48 h postoperatively, attributed to urinary potassium loss.

A diagnosis of euDKA was made, and in consultation with endocrinology, treatment with insulin (6 units/h) and dextrose infusion was commenced. Figure 1 demonstrates the acid base balance over the 7 days in intensive care unit. At 65 h, dextrose and insulin infusions were stopped resulting in immediate re-emergence of ketoacidosis, demonstrating ongoing ketogenesis

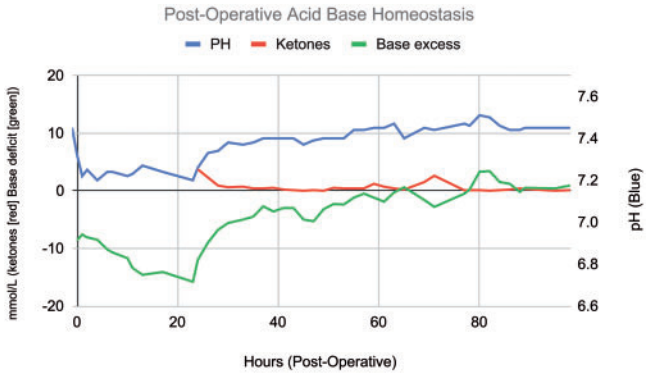

Figure 1: Postoperative acid base homeostasis.

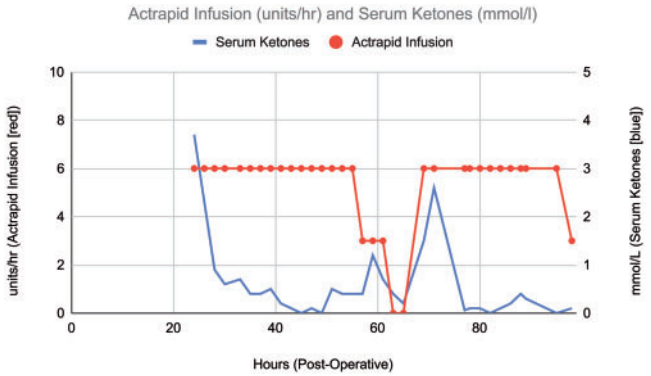

Figure 2: Actrapid infusion (units/h) and serum ketones (mmol/l).

in keeping with the prolonged terminal half-life of SGLT2i's (Figure 2). At 90 h postoperatively, the insulin and dextrose infusions were stopped. Oral intake and biguanide therapy were recommenced and the patient was discharged from the intensive care unit.

DISCUSSION

Cardiac surgery creates a milieu that predisposes patients to a catabolic state; a long fasting time, increased adrenergic activity and the hormonal stress response including elevated cortisol and glucagon levels. This is amplified by the concurrent use of SGLT2i, decreasing plasma glucose resulting in hypoinsulinaemia and euDKA. Hypoinsulinaemia is the cornerstone of ketogenesis, causing reduced glucose use, increased lipolysis and increased free fatty acid transport to the liver. Glucagon levels increase, leading to free fatty acid oxidation and ketosis. Polyuria, secondary to both ketosis and SGLT2i, results in significant electrolyte and volume flux. Diagnosis of euDKA is also challenging post-cardiac surgery due to the multiple possible aetiologies of acidaemia. The myocardium post-cardiac surgery is sensitive to pH, electrolyte and volume abnormalities, making euDKA particularly hazardous for these patients.

Recent evidence supporting the use of SGLT2i for T2DM and heart failure in patients with reduced ejection fraction with or without diabetes is likely to result in an increase in the number of patients presenting for cardiac surgery who are receiving SGLT2i therapy [1–3].

There is a lacking in consensus guidelines regarding perioperative management of SGLT2i [4]. We advise SGLT2i should ideally be stopped 5 days prior to elective cardiac surgery. This decision needs to be balanced against glycaemic control. Where preoperative cessation is not possible, carbohydrate drinks could be considered in the hours preoperatively, as used in enhanced recovery programmes to minimize starvation-induced catabolism. Postoperative nutritional intake should be highlighted on the daily intensive care unit handover. Prolonged fasting, reduced intake or unexplained acidosis should prompt measurement of ketones. In emergency surgery, extra vigilance with serum ketone monitoring and the early initiation of insulin and carbohydrate infusions when ketosis occurs.

Conflict of interest: none declared.

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