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Diabetic Ketoacidosis Associated with Sodium-Glucose Cotransporter-2 (SGLT-2) Inhibitor Dapagliflozin in Type 2 Diabetes

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Abstract

Diabetic ketoacidosis (DKA) is a rare adverse effect associated with SGLT-2 inhibitors. We describe a case of a 61-year-old gentleman with Type 2 diabetes treated with twice daily Novomix 30 and metformin. He wanted to lose weight and therefore, the diabetes team in primary care transitioned him to oral anti-hyperglycaemic medications consisting of a combination of metformin, DPP4 inhibitor (sitagliptin) and SGLT-2 inhibitor (dapagliflozin). During a holiday, he developed viral gastroenteritis and was admitted to the local hospital with DKA. He was treated with fixed rate insulin infusion as per the DKA protocol and was discharged on insulin and metformin. The combination of the SGLT-2 inhibitor (dapagliflozin) and concomitant dehydration from the gastroenteritis pre-disposed the patient to DKA. Our case highlights the importance of reinforcing sick day guidance of SGLT-2 inhibitors at each clinical interaction with patients to mitigate against the risk of SGLT-2 inhibitor associated DKA. In addition, patients presenting to the hospital should undergo blood ketone testing regardless of the blood glucose levels, to exclude the possibility of euglycaemic ketoacidosis.

Keywords: Diabetic ketoacidosis; DKA; Sodium-glucose cotransporter-2 inhibitor; Dapagliflozin

Abbreviations: DKA: Diabetic Ketoacidosis; SGLT-2: Sodium-Glucose Cotransporter-2 Inhibitor; CKD: Chronic Kidney Disease; CVOT: Cardiovascular Outcome Trials; ASCVD: Atherosclerotic Cardiovascular Disease

Introduction

SGLT-2 inhibitors are effective glucose-lowering agents which have been shown to have cardio and reno-protective effects [1,2]. SGLT-2 inhibitors licensed in the UK are canagliflozin, dapagliflozin, empagliflozin and ertugliflozin [3-5]. SGLT-2 inhibitors lower plasma glucose by inhibiting Na+-glucose–coupled transport in the proximal tubule. In addition to their anti-hyperglycaemic effects, these agents have shown promising results regarding cardiovascular outcomes and progression of chronic kidney disease (CKD) [3-5].

SGLT-2 inhibitors are recommended as therapeutic options for glycaemic management in type 2 diabetes and in addition for cardiorenal risk reduction in people with established heart failure, atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease with albuminuria [6]. Importantly, the cardiorenal benefits are noted in people with and without diabetes [1,2]. However, a potential side effect of these medications is an increased risk of diabetic ketoacidosis in patients with both Type 1 and Type 2 diabetes [7,8]. Due to the high risk of DKA, dapagliflozin is no longer licenced as an adjunctive agent to insulin therapy in Type 1 diabetes [9]. DKA rates of 0.1–0.6% with SGLT-2 inhibitors were reported in the cardiovascular outcome trials (CVOTs) compared with <0.1–0.3% with placebo [6,10-13]. The heart failure and CKD outcome studies of SGLT-2 inhibitors reported very low rates of DKA with these agents [6,14-16].

In an analysis of 9225 safety reports of dapagliflozin in the European pharmacovigilance database (EudraVigilance), the DAPAgliflozin and KETOacidosis (DAPA-KETO) study reported 2406 cases of at least one DKA with Dapagliflozin [17]. Dapagliflozin was associated with a 12-fold (computed Reporting Odds Ratio (ROR) 12.07, 95%CI 11.67–13.81) and 7.6-fold (ROR 7.59, 95%CI 7.13–7.89) increased risk of DKA compared to DPP-4 inhibitors and insulin, respectively [17]. Furthermore, a 2.5-fold

(95%CI 1.16–5.21) risk of DKA was noted in a meta-analysis of randomized trials of SGLT-2 inhibitors compared with reference groups [18].

An analysis of DKA reports in the US Food and Drug Administration Adverse Event Reporting System (FAERS) found >2500 DKA reports in which SGLT-2 inhibitors were recorded as suspect or concomitant drugs [19]. The proportional reporting ratios (PRR), computed as the ratios of proportion of DKA in individuals on SGLT-2 inhibitors to the proportion of individuals not on SGLT-2 inhibitors, was 7.9-fold (95% CI 7.5, 8.4) higher in individuals with diabetes on SGLT-2 inhibitors compared to those not treated with SGLT-2 inhibitors. Importantly, DKA resulted in mortality of 1.54% individuals [19].

In some cases, SGLT-2 inhibitors may cause euglycaemic ketoacidosis, which can lead to a delay in diagnosis due to normal blood glucose levels [20]. SGLT-2 inhibitors lead to low concentrations of portal insulin due to the urinary glucose losses which coupled with the hyperglucagonaemia and the negative fluid balance may contribute to the development of ketosis [20]. This in turn leads to further elevations of the counter-regulatory hormones which increase insulin resistance, lipolysis and increasing ketogenesis [21-23].

Case Report

We report a case of SGLT-2 inhibitor induced severe DKA in a person living with Type 2 diabetes.

A 61- year-old man with a background of Type 2 Diabetes was admitted to the tertiary care hospital with symptoms of viral gastroenteritis which he had contracted during a holiday. His background was significant for mixed hyperlipidaemia, coronary heart disease and metabolic syndrome. He was diagnosed with Type 2 diabetes 11 years ago for which he was on Metformin, Sitagliptin and Dapagliflozin. He was previously on insulin, however felt that he was gaining weight on it, hence opted for oral medications. On presentation to ED, he was found to be in diabetic ketoacidosis (pH 7.27, CBG 17.7mmol/L, ketones 7.4mmol/L). His HbA1c was 118mmol/mol. He had acute kidney injury as a result of dehydration. He was initiated on fixed rate insulin infusion and IV fluids as per DKA protocol and all his oral anti-hyperglycaemic agents were held. The most likely cause of his DKA was determined to be the use of SGLT-2 inhibitor in the presence of dehydration from gastroenteritis. Once the DKA had resolved, he was commenced on subcutaneous insulin and Dapagliflozin was stopped indefinitely.

Discussion

SGLT-2 inhibitor associated DKA in individuals with diabetes can be a potentially life-threatening adverse event. To ensure safe prescribing of SGLT-2 inhibitors in people with diabetes, caution should be exercised in patients who may be at higher risk of DKA [3,5]. Importantly, some people diagnosed with type 2 diabetes may have an alternative type of diabetes such as a slowly progressing Type 1 diabetes, Latent Autoimmune Diabetes in Adults (LADA), secondary diabetes due antecedent damage to the pancreas (Type 3c diabetes) or ketosis-prone Type 2 diabetes with a reduced beta cell function. These individuals may be at a higher risk of DKA with SGLT-2 inhibitors which cause an increase in the glucagon: insulin ratio [3].

Risk factors for DKA include alcohol excess, fasting or decreased food intake, very-low-carbohydrate/ketogenic diets, strenuous exercise, severe dehydration, and increased insulin requirements due to intercurrent illness and dehydration. In addition, sudden reduction in insulin, acute serious medical illness or major surgery can precipitate DKA in people on SGLT-2 inhibitors. Furthermore, initiation of SGLT-2 inhibitors in insulinopaenic individuals with Type 2 diabetes, Latent autoimmune Diabetes of Adults (LADA) or secondary diabetes incorrectly diagnosed as 'Type 2' diabetes may be potentially associated with an increased risk of DKA [3,24].

To mitigate against the risk of DKA in people with diabetes, it is essential to avoid large initial reductions in total daily insulin dose particularly pertinent in those individuals who have been misclassified as having type 2 diabetes. It is imperative that patients should be advised about sick day guidance and that this should be reiterated at each clinical interaction with the patient [3]. Patients should be aware that they need to stop the treatment immediately and to seek urgent medical attention if they develop any symptoms or clinical features of DKA. Healthcare professionals should be aware of the need to check ketones in patients when they are unwell, even if the glucose level is normal, as they may have euglycemic ketoacidosis.

If DKA is confirmed, the SGLT-2 inhibitor should be stopped immediately. The DKA should be treated with intravenous insulin and rehydration according to the local protocols. In addition, if there is euglucaemia or only mild hyperglycaemia, 10% dextrose may be required to be initiated at the start of DKA treatment alongside the rehydration, to facilitate the clearance of ketones. This case highlights the need for pharmacovigilance and appropriate counselling of patients on SGLT-2 inhibitors, prior to starting therapy and at each clinical contact. It is essential that patients initiated on SGLT2 inhibitors are effectively counselled regarding sick day guidance and potential for development of DKA, which is a life-threatening diabetic emergency. Clinicians should be aware of the side effects and risks associated with the use of SGLT-2 inhibitors.

Raising the awareness of the importance of monitoring ketones in people who are acutely unwell may help decrease the incidence of this potentially life-threatening adverse effect. With the increased utilisation of SGLT-2 inhibitors across a range

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of indications, strategies for mitigating the risk of DKA, early detection and appropriate management of ketoacidosis, should it occur, needs to be embedded in the healthcare policies.

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