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CASE REPORT

Euglycaemic diabetic ketoacidosis as a severe complication of dapagliflozin

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Abstract

Diabetic ketoacidosis (DKA) is a severe and potentially lethal complication of diabetes. The use of a relatively new class of antihyperglycaemic drugs, the SGLT2 inhibitors, can cause DKA, albeit with a different presentation compared to the 'classic' DKA. Therefore, since it might not be recognised at an early stage, awareness of this specific presentation of DKA as a complication of the use of SGLT2 inhibitors is important. In addition, the risk of dapagliflozin-induced DKA can be reduced by timely precautions, in particular around surgery or during fasting. We describe a case of dapagliflozin-associated DKA, and explain its underlying potential mechanisms.

Introduction

Diabetic ketoacidosis (DKA) is a severe and potentially life-threatening complication of diabetes.[1] It is commonly, but not exclusively, encountered in patients with type 1 diabetes mellitus, and usually the consequence of absolute insulin deficiency. Therefore, it is generally seen in untreated patients with de novo type 1 diabetes or in patients with insulin deficiency due problems with insulin administration, such as pump defects. However, DKA can also occur in patients with type 2 diabetes (DM2), in particular in those with long-term diabetes, who are almost insulin deficient.[2] Recently, a new mode of DKA was described, associated with the use of sodium-glucose-cotransporter-2 inhibitors (SGLT2 inhibitors) in the treatment of DM2.[3] In the past five years, the prescription of SGLT2 inhibitors in the Netherlands has increased more than 240%, from 1.4 million defined daily doses (DDDs) in 2016 to 4.8 million DDDs in 2020.[4] In this case report, we describe the development of severe DKA with shock in a patient with DM2 using dapagliflozin, and its underlying mechanism.

Case

A 76-year-old male with DM2 was admitted to intensive care unit with respiratory distress, shock and agitation. A few days earlier the patient had been admitted to the surgical ward because of an obstructive ileus caused by suspected carcinoma in the descending colon. He had undergone an acute laparotomy with the construction of a deviating double-loop transversostomy. Apart from oral medication for DM2, glimepiride, metformin, dapagliflozin and simvastatin, he was not taking any other medication. The long-term metabolic glucose regulation was quite good with a HbA1c level of 60 mmol/mol.

At admission to the surgical ward, the metformin and glimepiride were discontinued, whereas dapagliflozin and simvastatin were continued until the day of surgery.

Postoperatively, the patient remained fasting initially. The plasma glucose levels ranged from 4.8 to 11.2 perioperatively. Two days postoperatively, the patient developed shock with tachycardia and severe agitation in combination with tachypnoea (35/min) and respiratory distress. On physical examination he was afebrile (37.3 °C) and hypotensive (94/65 mmHg), with an increased respiratory rate of 35/min (Kussmaul pattern) in combination with sinus tachycardia with a pulse rate of 135/min. The peripheral circulation was poor and his extremities were cold.

Arterial blood gas analysis showed a metabolic acidosis with a pH of 7.02. Initially, the pCO_2 and bicarbonate levels were undetectable, causing a delay in treatment (*table 1*). Analysis of venous blood showed a bicarbonate concentration of 5 mmol/l, with a plasma lactate concentration of 1.4 mmol/l. Because of the respiratory insufficiency, a pulmonary embolism was initially considered to be part of the differential diagnosis. CT pulmonary angiography, however, showed no signs of emboli. In the upper abdomen free air was detected.

Table 1. Laboratory data at admission to the ICU

Haemoglobin	7.5	mmol/l
Erythrocytes	4.3	10^{12}/l
C-reactive protein	419	mg/l
Leukocytes	12.2	10^{9}/l
Thrombocytes	409	10^{9}/l
Prothrombin (INR)	1.0	INR
APTT screening	41	Sec
Fibrinogen	7.6	g/l
Bilirubin	<17	µmol/l
Alkaline phosphatase	90	U/l
Gamma GT	33	U/l
ASAT	25	U/l
ALAT	20	U/l
Lactate dehydrogenase	219	U/l
Urea	12.9	mmol/l
Creatinine	103	µmol/l
eGFR CKD-epi	61	ml/min/1.73 m^2
Osmolality	338	mosmol/kg
Sodium	148	mmol/l
Potassium	3.4	mmol/l
Chloride	114	mmol/l
Calcium	2.18	mmol/l
Phosphate	1.23	mmol/l
Magnesium	1.08	mmol/l
pH arterial	7.05	
pCO_2 arterial	<Memo>	kPa
Bicarbonate (arterial)	<Memo>	mmol/l
Base excess (arterial)	<Memo>	mmol/l
pO_2 (arterial)	18.2	kPa
O_2 saturation (arterial)	0.98	mol/mol
Albumin	26	g/l
Protein (total)	64	g/l
Glucose	13.6	mmol/l
Lactate	1.4	mmol/l

Based on this clinical development shortly after major surgery, sepsis due to intra-abdominal leakage was suspected, and the patient underwent an acute re-laparotomy. However, no abnormalities were found.

Further analysis of the metabolic acidosis revealed a high anion gap (29 mmol/l) and mild hyperglycaemia (13 mmol/l). Urine analysis showed the presence of ketones >5 mmol/l, in particular the 3-OH-hydroxybutyrate level was 5.2 mmol/l (N <0.3 mmol/l).

Based on these findings the diagnosis dapagliflozin-associated DKA was made, with just a mild level of hyperglycaemia. Although the mechanism of SGLT2-associated DKA is not fully understood, the clinical picture has been described previously as a complication of dapagliflozin. Dapagliflozin was discontinued immediately.

The DKA was treated according to the national guidelines with 2000 ml/24 h of intravenous glucose 10% and insulin 1 IU/h, in combination with suppletion of 10-20 ml/h of potassium chloride. Within hours, his clinical condition as well as the biochemical parameters improved. Eight hours after the initiation of the treatment, the plasma pH increased from 7.02 to 7.35. Around surgery and during the DKA, plasma glucose concentrations ranged from 9-13.5 mmol/l. After two days, the patient could be discharged in a good clinical condition.

Discussion

This case report describes a patient with DM2 and severe 'non-classic' DKA, which we consider a complication of the use of dapagliflozin in combination with ileus, and consequently surgery. SGLT2 inhibitors are a relatively new class of oral antihyperglycaemic agents. Recently the Dutch College of General Practitioners (NHG) standard for the treatment of DM2 was revised to the extent that the use of SGLT2 inhibitors has become even more prominent, in particular in patients with a high cardiovascular risk. Thus, an increase in the use of SGLT2 inhibitors is likely to occur.[5] SGLT2 inhibitors lower blood glucose by blocking the reabsorption of glucose in the proximal renal tubule, thereby promoting glycosuria. Thus, this process is insulin-independent since it relies purely on tubular filtration of glucose.[3] The most important side effects of dapagliflozin are hypoglycaemia if used in combination with sulfonylurea or insulin and genito-urethral infections due to glucosuria. In addition, the development of DKA has been reported before.

Although the exact mechanism of SGLT2-associated DKA is not fully understood, some postulations regarding its mechanisms have been made.[6] By reducing the plasma glucose concentration through the process of insulin-independent glucosuria, the secretion of insulin by pancreatic beta-cells is evenly reduced, thereby increasing a ketotic metabolic environment by stimulating lipolysis and ketogenesis. In addition, inhibition of SGLT2, which is present in the pancreatic alpha cells, possibly

increases the concentration of glucagon, the primary counter-regulatory hormone, causing an increase in the insulin-to-glucagon ratio, inducing ketogenesis and glycogenolysis.[6] The latter process may be part of the explanation of the mild hyperglycaemia in our patient.

Furthermore, most patients with end-stage DM2 lower their exogenous insulin dose after initiation of SGLT2 inhibitors, thereby further reducing the circulating insulin levels and putting them at even more risk of ketosis.[6] Since our patient was not using exogenous insulin, this mechanism could not have played a role. Nevertheless, in the light of the significantly increased use of SGLT2 inhibitors over the past few years, the incidence of DKA is relatively low, suggesting the need for additional factors to induce DKA. Since various pathophysiological mechanisms are postulated for the development of DKA by SGLT2 inhibitors, its potential causes are evenly multifactorial. Apart from 'spontaneous' development of DKA, a number of triggering factors have been described, such as gastrointestinal diseases, fasting, the use of a low-carb diet or after surgery.

Whereas 'the classic DKA' is generally accompanied by high or even extreme hyperglycaemia, SGLT2-associated DKA is usually accompanied by euglycaemia or, as in our case, only mild hyperglycaemia. The blood glucose level observed during DKA in patients on SGLT2 inhibitors occurs as a result of the balance between endogenous glucose production and renal glucose clearance. Thus, if the blood glucose concentration tends to increase by a relative lack of insulin, the excretion of glucose can increase substantially under the use of SGLT2 inhibitors, thereby causing relatively normal blood glucose concentrations. Other factors such as the presence of physical stress due to the surgical intervention may play an additional role.

In addition to metabolic dysregulation, the use of SGLT2 inhibitors can cause haemodynamic dysregulation as well.[7] By stimulating the secretion of sodium to the distal tube, the intra-glomerular pressure decreases.[3] In combination with osmotic diuresis, a decrease of the intravascular volume, low blood pressure and a lower preload and afterload of the heart can develop, which can lead to the development of 'shock', as in our case.

In daily practice it is important to realise that all SGLT2 inhibitor treated patients presenting with signs or symptoms of developing DKA, such as nausea and/or vomiting, should be monitored for DKA even during euglycaemia. It can be helpful to keep close track of the fluid balance in order to prevent dehydration. Particularly in situations of gastrointestinal diseases, fasting, postoperatively or during low-carb dieting, patients are prone to develop 'non-classic' DKA, as in the described case. Discontinuing the use of dapagliflozin preoperatively and/or during fasting could be considered. If DKA is diagnosed, the SGLT2 inhibitor should be discontinued, and the DKA should be treated according to traditional guidelines, which are similar to the treatment of 'classic DKA'.

In conclusion, doctors should be aware of the fact that SGLT2 inhibitors can cause DKA, even during euglycaemia, in particular in situations with low carbohydrate state such as after fasting or during severe illness, or postoperatively.

Disclosures

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Informed consent was obtained from the patient for the publication of this case report.

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