DOI：10.6314/JIMT.201902_30(1).09 內科學誌 2019：30：47-50

Dapagliflozin-induced Postoperative Euglycemic Diabetic Ketoacidosis: Two Cases

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Abstract

The most common side effect of sodium–glucose co-transporter 2 (SGLT2) inhibitors is genital tract infections. However, a few case reports have shown that their use may induce postoperative euglycemic diabetic ketoacidosis (DKA). Herein, we report two cases of patients who received SGLT2 inhibitor dapagliflozin preoperatively; DKA developed a few days after the operation. To the best of our knowledge, these cases are the first and second reported cases of dapagliflozin-induced DKA after orthopedic surgery. We suggest changing the use of SGLT2 inhibitors to the use of insulin preoperatively and adequate fluid replacement to prevent this life-threatening complication. (J Intern Med Taiwan 2019; 30: 47-50)

Key Words: Diabetic ketoacidosis, Dapagliflozin, Sodium–glucose co-transporter 2 inhibitors

Medical history

Case 1

A 60-year-old woman was admitted to our hospital after falling. She had schizophrenia for decades without treatment. She had type 2 diabetes for 5 years with poor medication adherence, and her HbA1c was around 12-13%. Linagliptin/metformin (2.5/850 mg/day, twice) and dapagliflozin (10 mg/day) were added to her regimens for 1 month. On arrival, her vital signs were stable with no cardiopulmonary distress. Physical examination revealed tenderness over her lower back and limited range of motion of her left knee with tenderness and swelling; no neurologic deficit was observed. Blood biochemistry results included a glucose level of 293 mg/dL and normal kidney and liver functions. X-rays showed a fracture over the proximal end of the tibia and fibula and another fracture over the right calcaneus. L-spine computed tomography revealed a compression fracture of the L3 vertebral body. She underwent an open reduction with internal fixation for her left tibia fracture the on first day after admission. She had a negative input/output for several days. Spinal fusion with instrumentation and laminec-

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tomy were performed on the 9th day. She was afebrile and normotensive, and her blood glucose ranged from 116 to 182 mg/dL during the perioperative period. Progressive dyspnea developed starting on the 9th day. Studies revealed leukocytosis with left shift and normocytic anemia. The anion-gap acidosis with pH: 7.33, HCO_3^-: 12.4 mEq/L, and an anion gap: 21. Psychogenic dyspnea was initially suspected; thus, quetiapine (100 mg at bedtime) was prescribed. Her dyspnea worsened on the 11th day, and a pulmonologist was consulted. A repeat blood gas showed pH: 7.06, HCO_3^-: 2.0 mEq/L, and an anion gap: 24. Additionally, her lactate level was 0.9 mmol/L and serum ketone level was 5.6 mmol/L (Table 1). A chest x-ray showed increased infiltration over the right upper and middle lobe. Electrocardiography and cardiac enzymes were normal. She was diagnosed to have diabetic ketoacidosis and transferred to a medical intensive care unit (ICU). Insulin infusion was administered for 2 days, and then switched to neutral protamine Hagedorn (NPH, 70 units), followed by regular insulin (30 units). Ceftriaxone was administered for her pneumonia after verification through a susceptibility data. Her follow-up blood gas showed a pH: 7.50, HCO_3^-: 18.7 mEq/L, and serum ketone of 0.5 mmol/L. She was discharged on 21st day with NPH (70 units)/regular insulin (30 units).

Case 2

A 63-year-old woman was admitted to our hospital due to a left distal femoral bone and humeral bone fractures. She has type 2 diabetes for 8 years with HbA1c around 11%-12%. She was treated with glimepiride/metformin (4/1000 mg/day, twice) and dapagliflozin (10 mg/day) for several years. On arrival, her vital signs were heart rate: 130 bpm, respiratory rate: 28 rpm, body temperature: 36.2°C, and blood pressure: 153/83 mmHg. On physical examination, tenderness, swelling, and limited ROM over the left knee and shoulder were observed. Blood biochemistries results included glucose: 386 mg/dL and normal kidney and liver functions. X-rays showed a fracture over the left humeral neck and supracondylar region of the left distal femur. She underwent ORIF with external skeletal fixation for her left humerus fracture and ORIF with a plate for her left femur fracture on the first day of admission. The operation was uneventful with blood loss of 450 ml. She had mild chest pain on the second hospital day, which subsided after administration of nitroglycerin. She had negative input/output for 3 days. She developed dyspnea, dizziness, and vomiting on the 4th hospital day. Her vital signs included heart rate: 110 bpm, respiratory rate: 24 rpm, body temperature: 37.1°C, and blood pressure: 136/78 mmHg. Complete blood count revealed leukocytosis, normocytic anemia, and the cardiac enzymes were normal. Thus, blood transfusion was performed. Agitation and lower abdominal pain developed on the 5th hospital day. Physical examination showed respiratory failure. Her blood glucose levels during hospitalization ranged from 194 to 338 mg/dL. A blood gas analysis showed a pH: 7.15, HCO_3^-: 6.3 mEq/L, an anion gap: 23, and serum ketone level: 3.8 mmol/L (Table 2). ECG demonstrated sinus tachycardia. Chest x-ray revealed no active lung lesion. An endotracheal tube (ETT) intubation was performed, and she was transferred to our medical ICU. She was diagnosed with DKA, and

Table 1. A 60-year-old woman with DKA after orthopedic surgery

Serum ketone	5.6	mmol/L
Capillary blood glucose	116-182	mg/dL
Arterial blood gas		
pH	7.06	
$HCO3^-$	2	mEq/L
Anion gap	24	

Table 2. A 63-year-old woman with DKA after orthopedic surgery

Serum ketone	3.8	mmol/L
Capillary blood glucose	194-338	mg/dL
Arterial blood gas		
pH	7.15	
$HCO3^-$	6.3	mEq/L
Anion gap	23	

an insulin infusion was administrated from the 4th to 6th hospital day, and then switched to NPH (70 units)/ regular insulin (30 units). No obvious infection source was noted, and empirical antibiotic with ceftriaxone was used for 3 days. The follow-up blood gas analysis was within normal limits, and the serum ketone level was 1.1 mmol/L. ETT was removed on the 8th hospital day, and the patient was transferred to the regular ward 2 days later. She was discharged on the 15th hospital day with NPH (70 units)/regular insulin (30 units).

Discussion

DKA develops promptly, and most patients may not be aware of this disease. Common symptoms of DKA are vomiting, abdominal pain, and weakness as well as symptoms of hyperglycemia, including polydipsia, polyuria, and polyphagia. Signs on physical examination are Kussmaul respirations, tachycardia, and dry skin turgor. The precipitating factors of DKA include infection, omission or an inadequate dose of insulin, and intercurrent illness, such as myocardial infarction, pancreatitis, and cerebrovascular accident[1]. DKA associated with the use of sodium-glucose cotransporter 2 (SGLT2) inhibitors may have a somewhat different mechanism from usual DKA. There are two possible mechanisms: (1) a reduced insulin level and (2) an increased glucagon level. SGLT2 inhibitors decrease blood glucose levels by promoting urinary glucose excretion, resulting in reduced insulin secretion from the pancreas. Decreased antilipolytic activity ensues with stimulation of the production of free fatty acids, which are converted to ketone bodies in the liver. SGLT2 inhibitors are also active in pancreatic α cells, and glucagon secretion increases[2]. SGLT2 inhibitors enhance the use of fat (lipolysis), while sparing carbohydrates from being the energy resource for cells [3].

In a recent systemic review, a total of 34 cases have been reported with SGLT2 inhibitor-associated DKA, mostly with the use of canagliflozin (26 patients) and dapagliflozin (5 patients). These patients were characterized by low blood glucose levels (average blood glucose, 265.6 ± 140.7 mg/dL), and DKA was often caused by a precipitating factor (recent major surgery or decreased or discontinued insulin)[4]. A case series in South Australia showed 13 cases of SGLT2 inhibitor-related DKA, and 9 cases were related to the use of dapagliflozin[5]. None of these dapagliflozin-related DKA were predisposed by surgery. With respect to other SGLT-2 inhibitor-associated DKA, most patients underwent major abdominal surgery, including pancreatectomy[6], abdominoplasty[7], and bariatric surgery[8, 9]; only one patient had orthopedic surgery of the knee[10].

Patients with diabetes treated with SGLT2 inhibitors who also underwent a major operation experience prolonged fasting, which may predispose them to ketosis. Additionally, SGLT 2 inhibitors have a modest diuretic effect, which superimposes with volume depletion such as blood loss from surgery to aggravate DKA. Minor operations may also induce DKA! Herein, we have reported two cases of dapagliflozin-induced postoperative DKA. To the best of our knowledge, these cases are the first and second reported cases of dapagliflozin-induced DKA after orthopedic surgery (one patient underwent spinal fusion and ORIF and the other patient underwent only ORIF).

The guideline of American Diabetes Association in 2017 suggests withholding metformin 24 h before surgery and any other oral hypoglycemic agents the morning of surgery or procedure. Moreover, shift to half of the NPH dose or 60%–80% doses of a long-acting analog or pump basal insulin is suggested[11]. The half-life of SGLT2 inhibitor is 11–13 h. Thus, we suggested withholding SGLT2 inhibitor 2–3 days (3–5 half-life) before the surgery. And adequate fluid replacement should be performed to prevent SGLT2 inhibitor-induced DKA.

DKA is a life-threatening complication of type 2 diabetes. The most common side effect of the use of SGLT2 inhibitors is genital tract infections; however, SGLT2 inhibitor-induced DKA may also occur postoperatively. Additionally, it may be accompanied by lower-than-anticipated glucose levels, making the

diagnosis difficult. Orthopedists should be aware of the possibility of this complication. We suggest switching the use of SGLT2 inhibitor to the use of insulin and performing adequate fluid replacement perioperatively and to restart the inhibitor while strictly controlling serum blood glucose levels after the operation. Future studies should examine the relationship between surgery and SGLT2 inhibitor-induced DKA.

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Dapagliflozin 引起術後正常血糖之糖尿病酮酸中毒：兩例個案報告暨文獻回顧

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摘 要

使用鈉-葡萄糖共轉運蛋白2 (SGLT2)抑制劑的最常見副作用是生殖道感染。然而，一些個案報告顯示它們的使用可能引起術後正常糖尿病酮酸中毒。在此，我們報告了2例術前接受SGLT2抑製制劑dapagliflozin的患者；糖尿病酮酸中毒在手術後幾天發生。據我們所知，這些個案是第一次和第二次報告的dapagliflozin引起的骨科手術後糖尿病酮酸中毒的個案。我們建議將術前SGLT2抑制劑改為胰島素以及適度的水分補充以預防這種危及生命的併發症。