Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are relatively new antidiabetic drugs, which have been recently approved for heart failure treatment. Although treatment interruption is recommended 3 to 4 days before surgery, it is unclear whether SGLT-2 inhibitors should be discontinued when prescribed for heart failure treatment. We describe a case of postoperative ketoacidosis with hypoglycemia in an 83-year-old woman who took dapagliflozin for heart failure and underwent transcatheter aortic valve replacement. She was nondiabetic and took dapagliflozin on the day of the procedure. This case suggests the need to discontinue SGLT-2 inhibitors ahead of the day of surgery when used for heart failure.

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**GLOSSARY**

ABG = arterial blood gas; PaCO₂ = partial arterial carbon dioxide pressure; PCI = percutaneous coronary intervention; SGLT-2 = sodium-glucose cotransporter-2; TAVR = transcatheter aortic valve replacement; CARE = case report; DKA = diabetic ketoacidosis

**CASE DESCRIPTION**

An 83-year-old woman presented to our hospital with dyspnea on exertion and lower leg edema. The patient had a history of mitral valve replacement, pacemaker implantation for sick sinus syndrome, and persistent atrial fibrillation. She had been prescribed warfarin (2 mg/d), aspirin (100 mg/ every other day), candesartan (4 mg/d), and propafenone (300 mg/d). Ultrasound echocardiography revealed severe aortic valve stenosis and reduced left ventricular ejection fraction (30%). Coronary angiography showed 90% left anterior descending coronary artery stenosis. Dapagliflozin (10 mg/d) and spironolactone (25 mg/d) were administered to treat heart failure, and percutaneous coronary intervention (PCI) followed by TAVR was scheduled. Medical history also included chronic kidney disease (stage 2), cerebral infarction, rheumatoid arthritis, and idiopathic pneumonitis. Three weeks after her presentation, PCI was performed successfully.

TAVR was performed 7 weeks after PCI. Preoperative laboratory testing showed decreased estimated glomerular filtration rate (64.6 mL/min). Hemoglobin A1c was 5.4%. Urine glucose (4+) and ketones (±) were positive. The patient had diarrhea 6 days before TAVR. However, it subsided on the next day, and she had no change in her dietary habits. Laboratory testing obtained 2 days before surgery showed no abnormalities in serum electrolyte and albumin concentrations.

On the day of surgery, the patient fasted after midnight with only a sip of water with her morning medications. She took her dapagliflozin on the morning of surgery and entered the operating room at 2 pm. TAVR was performed uneventfully under general anesthesia. During the 99-minute procedure, 8 g of glucose was given by administering 800 mL of acetate Ringer’s solution with 1% glucose. After emergence from anesthesia, the patient was transferred to the intensive care unit. Postoperative arterial blood gas...
(ABG) showed decreased bicarbonate level (19.4 mmol/L), and urinalysis showed ketonuria (ketones 2+) and glucosuria (2+). Although blood pH (7.36), partial arterial carbon dioxide pressure (Paco2, 35.2 mm Hg), lactic acid (0.6 mg/dL), and anion gap (14.9 mmol/L) were almost in normal ranges, the blood glucose concentration was low (56 mg/dL), which was overlooked. The patient showed no symptoms associated with hypoglycemia and was stable with no remarkable events.

The ABG results obtained on the next morning (approximately 12 hours after intensive care unit admission) revealed a metabolic acidosis with hypoglycemia (pH, 7.265; Paco2, 36.3 mm Hg; bicarbonate, 15.9 mmol/L; anion gap, 13.8 mmol/L; glucose, 52 mg/dL; and lactic acid, 0.6 mmol/L). Laboratory testing of venous blood also showed low glucose concentrations (39 mg/dL). Urinalysis showed ketonuria (4+) and glucosuria (2+). During the 12-hour postoperative period, the patient received 420 mL of normal saline and drank 250 mL of water with a urinary output of 1310 mL. Although the patient remained asymptomatic, 10 g of glucose was administered intravenously, and after 2 hours, ABG results showed a slight improvement of metabolic acidosis (pH, 7.317; Paco2, 31.2 mm Hg; bicarbonate, 15.5 mmol/L; anion gap, 16.1 mmol/L; and lactic acid, 0.6 mmol/L), but glucose concentration remained low (70 mg/dL). The patient resumed eating that morning, and dapagliflozin was simultaneously discontinued. Blood glucose concentrations were monitored until postoperative day 5, and no further hypoglycemia developed (Table). The patient was discharged on postoperative day 9.

DISCUSSION

SGLT-2 inhibitors lower blood glucose concentrations independent of insulin by inhibiting urine glucose reabsorption in the proximal tubule in the kidney and promote glucose excretion. Recently, SGLT-2 inhibitors have been approved for the treatment of chronic heart failure with reduced ejection fraction in adults with and without type 2 diabetes. Over the last few years, there has been an increasing number of reports of patients with type 2 diabetes treated with these medications who develop severe acidosis during the perioperative period. In 2020, a safety label for SGLT-2 inhibitors was changed to recommend withholding them for at least 3 days and ertugliflozin for at least 4 days before surgery based on their pharmacological half-lives because of increased risk of perioperative euglycemic ketoacidosis in diabetic patients. However, the optimal duration of interruption is debated. Moreover, no evidence is available to inform us when these drugs should be discontinued before surgery when prescribed for heart failure. In these patients, discontinuation of the drug may be deleterious to heart failure management.

In the present case, the patient took her dapagliflozin on the day of surgery and developed ketoacidosis on postoperative day 1. Although the ketoacidosis observed in this case seemed to be triggered by persistent hypoglycemia, dapagliflozin might have contributed to some extent, as it shifts substrate utilization from carbohydrates to lipids, resulting in ketogenesis. During the perioperative period, blood glucose concentration decreased significantly (19.4 mmol/L) and remained low (56 mg/dL). Urinalysis showed ketonuria (ketones 2+) and glucosuria (2+). Although laboratory testing of venous blood showed low glucose concentrations (39 mg/dL), blood pH (7.265), partial arterial carbon dioxide pressure (Paco2, 36.3 mm Hg), lactic acid (0.6 mg/dL), and anion gap (14.9 mmol/L) were almost in normal ranges. The patient remained asymptomatic, and 10 g of glucose was administered intravenously. ABG results revealed a metabolic acidosis with hypoglycemia (pH, 7.265; Paco2, 36.3 mm Hg; bicarbonate, 15.9 mmol/L; anion gap, 13.8 mmol/L; glucose, 52 mg/dL; and lactic acid, 0.6 mmol/L). The patient resumed eating that morning, and dapagliflozin was simultaneously discontinued. Blood glucose concentrations were monitored until postoperative day 5, and no further hypoglycemia developed (Table). The patient was discharged on postoperative day 9.

**Table. Concentrations of Blood Glucose, Urine Glucose, and Urine Ketones Before and After the Procedure**

| Postoperative days | –1 | –2 | –3 | –4 | –5 | –6 | –7 | –1 | –2 | –3 | –4 | –5 | –6 | –7 | –1 | –2 | –3 | –4 | –5 | –6 | –7 |
|--------------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Blood glucose mg/dL | 102| 71 | 71 | 71 | 71 | 71 | 71 | 71 | 71 | 71 | 71 | 71 | 71 | 71 | 71 | 71 | 71 | 71 | 71 | 71 | 71 |
| Urine glucose – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Urine ketones – | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |

Abbreviations: PCI, percutaneous coronary intervention; TAVR, transcatheter aortic valve replacement.
concentrations are commonly unchanged or elevated by surgical stress. Furthermore, hypoglycemia is rare in persons without drug-treated diabetes. While SGLT-2 inhibitors promote urine glucose excretion, they are believed to prevent hypoglycemia by increasing endogenous glucose production by stimulating hepatic gluconeogenesis. Previous studies have suggested that dapagliflozin does not increase the risk of hypoglycemia compared to placebo outside the perioperative setting. However, it is unclear whether normal blood glucose concentrations are maintained during perioperative fasting with dapagliflozin treatment. After undergoing PCI 2 months earlier, the patient did not develop hypoglycemia or ketoacidosis. PCI was performed in the morning without general anesthesia, and she ate her lunch after the procedure. On the other hand, the perioperative fasting period for TAVR lasted over 24 hours. SGLT-2 inhibitors are associated with an increased risk of hypoglycemia when administered with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Although the patient had taken an angiotensin receptor blocker (candesartan), it is unlikely that the combination of dapagliflozin and candesartan alone caused hypoglycemia, as she had taken these medications when she underwent PCI. Since the patient is nondiabetic with no history of hypoglycemia, it is likely that the effect of perioperative fasting on blood glucose concentrations was enhanced by dapagliflozin. Although the patient had diarrhea 6 days before surgery, it is unclear whether diarrhea contributed to hypoglycemia or ketoacidosis development, as it subsided after only 1 day. Furthermore, the patient was likely dehydrated perioperatively, as postoperative urine output was greater than fluid intake. In heart failure patients, diuretics are often continued on the day of surgery. SGLT-2 inhibitors increase urine output, and the simultaneous use of diuretics and SGLT-2 inhibitors may enhance the risk of dehydration. Dehydration is a potential risk factor for SGLT-2 inhibitor-associated ketoacidosis. Although the exact etiology of hypoglycemia and ketoacidosis is still unclear, a combination of dehydration and starvation combined with dapagliflozin might have contributed to the adverse event. While it is unclear whether dapagliflozin should be discontinued before surgery in patients using this drug for heart failure, this case suggests the need for drug disruption in these patients.

In conclusion, clinicians should be aware of the risk of SGLT-2-associated hypoglycemia and ketoacidosis in perioperative settings in nondiabetic patients taking these drugs for heart failure, especially in the presence of precipitating factors. If SGLT-2 inhibitor treatment is continued during the perioperative period, measuring capillary or blood ketone concentrations as well as blood glucose concentrations is recommended. If DKA is suspected, acid-base determination is needed.  

**DISCLOSURE**

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