New Diabetes Medications Raise New Perioperative Concerns for the Anesthesiologist

Jennifer A. DeCou, MD, and Stephen H. Sams, MD

Anesthesiologists increasingly care for patients with diabetes perioperatively. The importance of optimal glucose management to reduce the incidence of complications in patients with diabetes is well established. Perioperative management to maintain relatively normal blood glucose levels is complex, given the broad variety of medications used to treat relative or absolute insulin deficiency. In this issue, Peacock et al introduce the anesthesiologist to a newer class of antidiabetes medications, the sodium glucose cotransporter 2 inhibitors (SGLT2i), and review the unique considerations for patients taking these agents perioperatively.

PHARMACOLOGY AND USE OF SGLT2i

In the United States alone, diabetes affects an estimated 29.1 million individuals, representing approximately 9.3% of its population. Almost 40% of American adults have prediabetes, which places them at high risk of developing diabetes during their lifespan. Given the concurrent rise of adult obesity and the aging population, the incidence of diabetes will likely approach 1 in 3 adults within the next 35 years. Anesthesiologists can expect to encounter patients with this disease process more frequently during the perioperative period. Due to intensive efforts at new drug development for treating diabetes, anesthesiologists frequently care for patients taking new medications with novel mechanisms of action used to manage this disease. Between the years 2000 and 2012, the US Food & Drug Administration (FDA) approved 22 insulin and diabetes drugs, many of which were aimed at treating type 2 diabetes. Within just the past 3 years, 15 drugs have been approved. Between 2013 and 2014, the US FDA approved the use of 3 SGLT2i, including canagliflozin, dapagliflozin, and empagliflozin for type 2 diabetes. Anesthesiologists must understand the unique characteristics of these drugs to safely care for patients taking them in the perioperative period. Peacock et al provide the critical education needed for safe management of these patients.

The “gliflozins” are SGLT2i, which increase urinary glucose excretion, leading to net glucose loss and decreased plasma glucose levels. Normally, glucose is filtered from the blood into the kidneys and is then reabsorbed in the S1 segment of the proximal tubule. This normal glucose reabsorption allows the body to minimize glucose loss and conserve calories. The glucose transporter-2 and SGLT2 are responsible for approximately 90% of the glucose reabsorption in the kidney, with most of the renal glucose reabsorption mediated by the SGLT2. Canagliflozin, and other drugs in this class, selectively inhibit SGLT2, leading to reduced reabsorption of glucose and the excretion of glucose in the urine. One major advantage of this class of medication is that its glucose-lowering effects are primarily independent of insulin. Despite a small increase in urinary tract infections, this once daily oral medication is generally well tolerated by patients and is associated with a low incidence of hypoglycemia and serious adverse events. The EMPA-REG OUTCOME study demonstrated that an SGLT2i (empagliflozin) could reduce major adverse cardiovascular events, heart failure admissions, cardiovascular mortality, and overall mortality for high-risk patients with cardiovascular disease when given in combination with standard care. Despite the clear evidence of efficacy, the SGLT2i create new management challenges for anesthesiologists. Historically, the presence of glucose in the urine has been used as an indicator of the degree of control of diabetes. The unique mechanism of action of these drugs, however, requires readjustment of expectations and monitoring because glucosuria is the foundation of the mechanism of action of this class of medication.

PERIOPERATIVE CONSIDERATIONS FOR ANESTHESIOLOGISTS

When anesthesiologists encounter a patient with diabetes presenting for surgery with an SGLT2i on the medication list, a few new things should be considered (Table). SGLT2i affect the process of osmotic diuresis and natriuresis via their mechanism of action and can lead to subsequent intravascular volume contraction. This contraction could lead to intraoperative hemodynamic instability, especially in those patient populations with other comorbidities that may result in baseline-compensated hypovolemia. Special attention should therefore be given to patients who have low systolic and/or diastolic blood pressure at baseline, the elderly population, patients on other diuretic medications, patients on medications that interfere with the
SGLT2i can increase risk of hypoglycemia when used in conjunction with insulin. SGLT2i can change drug metabolism and drugs interactions (ex rifampin and digoxin).

In the SGLT2 cardiovascular outcome trial EMPA-REG, the frequency of DKA was <0.1%. Although rare, the diagnosis may be missed or delayed in those presenting with only mild or moderate hyperglycemia, as is the case with patients on SGLT2i-induced glucosuria.

The pathophysiology of DKA typically begins with an absolute or a relative insulin deficiency. It can be classically defined as including hyperglycemia (typically 350–800 mg/dL), acidosis (venous pH <7.3 or a bicarbonate level <15 mmol/L), serum ketonemia (β-hydroxybutyrate >300 micromol/L) ketonuria, and glycosuria. In general, DKA is a rare but recognized finding in patients with type 2 diabetes. However, in patients on SGLT2i, euglycemic DKA may develop as a result of the SGLT2-induced glucosuria, the increased lipid oxidation and lipolysis, the increased mobilization of free fatty acids, and the predisposition to ketogenesis. This process is worsened if there is less access to carbohydrates and decreased insulin, which then increases ketones, nausea, and volume depletion. The off-label use of SGLT2i in patients with type 1 diabetes may also slightly increase the rare risk of euglycemic DKA. In addition, the FDA identified triggering factors such as concurrent illness, reduced food and fluid intake, reduced insulin doses, and history of alcohol intake. Because a patient in the perioperative period is likely to be both fasting and have a reduced insulin dose, it is prudent that an anesthesiologist who encounters such a patient who appears unwell (with symptoms suggesting DKA, as described above) should consider monitoring for acidosis, ketonuria, or ketonemia.

In the article 1, the recommendation is made to consider holding SGLT1 inhibitors 1 day before surgery in the fasting patient. This is important and appropriate advice given that the terminal half-life of canagliflozin, depending on the dose, is between 10 and 13 hours, and urinary glucose excretion can last slightly longer than 24 hours.

**CONCLUSIONS**

In general, SGLT2 are safe, effective medications used in the treatment of patients with type 2 diabetes. Anesthesiologists are well equipped to handle the potential for relative intravascular volume depletion, the low risk of hypoglycemia (when used in combination with other medications), and the potential for hyperkalemia.

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**Table. Perioperative Considerations for Anesthesiologists With Patients on SGLT2i for Type 2 Diabetes**

<table>
<thead>
<tr>
<th>SGLT2i Effects Perioperatively</th>
<th>Patient Considerations, Impact, and Management Recommendations</th>
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<tbody>
<tr>
<td>SGLT2i causes diuresis and natriuresis leading to potential intravascular volume contraction</td>
<td>Intraoperative hemodynamic instability especially in more susceptible patient populations. Lower threshold for more advanced monitoring depending on length and severity of expected fluid shifts.</td>
</tr>
<tr>
<td>SGLT2i can increase risk of hypoglycemia when used in conjunction with insulin</td>
<td>Higher risk of perioperative hypoglycemia and subsequent complications. Strict adherence to guidelines for glucose monitoring.</td>
</tr>
<tr>
<td>SGLT2i impact electrolyte imbalances, in particular, the potential for hyperkalemia</td>
<td>Monitor for signs and symptoms of hyperkalemia. Consider perioperative laboratory monitoring, particularly in those with renal failure and/or taking ACEi/ARBs.</td>
</tr>
<tr>
<td>SGLT2i can change drug metabolism and drugs interactions (ex rifampin and digoxin)</td>
<td>Potential need to adjust doses of concurrent drugs. Monitoring for signs and symptoms of subtherapeutic or toxic drug levels.</td>
</tr>
<tr>
<td>SGLT2i associated with increased risk of eDKA</td>
<td>Consider eDKA in patients presenting with classic DKA signs/symptoms or with triggering factors. Monitor for acidosis, ketonuria, or ketonemia.</td>
</tr>
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</table>

**Abbreviations:** ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blockers; eDKA, euglycemic diabetic ketoacidosis; SGLT2i, sodium glucose cotransporter 2 inhibitors.

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renin-angiotensin-aldosterone system, and patients with impaired renal function. Patients in these categories may be more likely to have hemodynamic instability intraoperatively. This instability can generally be alleviated by evidence-based appropriate fluid resuscitation and careful monitoring of intravascular fluid status during the anesthetic. When caring for a patient with these risk factors and who is taking an SGLT2i, having a lower threshold for more advanced intravascular monitoring might be indicated, depending on the length and likelihood of large intravascular volume shifts and/or potential blood loss. Urine output can be misleading in these patients and should not be used to guide fluid therapy.

Because SGLT2i do not work by increasing insulin levels and are completely independent of insulin for their glucose-lowering ability, they are unlikely to cause hypoglycemia when used alone. However, when used with another medication, such as insulin or insulin secretagogues, the risk of hypoglycemia increases. As with all patients with diabetes mellitus, perioperative blood glucose monitoring is indicated to reduce the overall risk and should be practiced in accordance with standard guidelines for intraoperative glucose monitoring.

SGLT2i can be associated with hyperkalemia, given the mild diuresis associated with their renal site of action and potential effects on electrolyte balance. This is particularly important for patients with renal failure or those who are taking angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.

SGLT2i can decrease the efficacy of uridine 5′-diphospho-glucuronosyltransferase enzyme-inducing drugs such as rifampin, and increasing the dose may be necessary. Mean peak digoxin drug concentration is increased when taking angiotensin-converting enzyme inhibitors and history of alcohol intake. Because a patient in the perioperative period is likely to be both fasting and have a reduced insulin dose, it is prudent that an anesthesiologist who encounters such a patient who appears unwell (with symptoms suggesting DKA, as described above) should consider monitoring for acidosis, ketonuria, or ketonemia.

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therapy), and the small risk of hyperkalemia (in patients predisposed to this condition). What the anesthesiologist does not want to miss is the rare complication of euglycemic DKA with its accompanying metabolic derangement and electrolyte disturbances in patients taking SGLT2i. While it is appropriate to maintain a low index of suspicion the majority of the time, the small risk may be increased in those patients with β cell destruction, type 1 diabetes, or concurrent illness. The perioperative fasting state may be a time when such patients are particularly vulnerable and require an anesthesiologist to be vigilant in the care of diabetes.

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REFERENCES