LETTER TO THE EDITOR

Perioperative Implication of Sodium-glucose Cotransporter-2 Inhibitor in a Patient Following Major Surgery

Sonali Vadi[1], Vidhyadhar Lad[2], Dheeraj Kapoor[3]

Abstract

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are the second line of therapy in diabetes mellitus type 2. They are frequently coprescribed with other noninsulin glucose-lowering medications. Diabetic ketoacidosis (DKA) with lower-than-anticipated glucose levels is an important SGLT2i-related adverse effect in postoperative patients. This case highlights the need for increased postoperative surveillance of patients on this group of medications. Ketonuria was managed with short-acting insulin infusion with dextrose-containing intravenous fluid, as a part of the ongoing intensive care treatment to which the patient responded well. Awareness of DKA with lower-than-anticipated glucose levels is an important clinical challenge, an entity that can be confused in the setting of major and complex surgeries. The frequency of this arcane and underreported diagnosis in the perioperative setting is unknown.

Keywords: Diabetic ketoacidosis with lower-than-anticipated glucose levels, Perioperative medicine, Sodium-glucose cotransporter-2 inhibitors.

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Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are being hailed for their cardiovascular and renal protective effects. In view of evidence of a reduction in hospitalization for heart failure, cardiovascular-related deaths, and all-cause mortality, they are increasingly prescribed in patients with diabetes mellitus type 2 with cardiovascular disease. Diabetic ketoacidosis (DKA) with lower-than-anticipated glucose levels is an important SGLT2i-related adverse effect in postoperative patients. Decisions regarding discontinuation and restarting medications in the perioperative period are complex issues. Herein we highlight the need for increased postoperative surveillance of patients on this group of medications.

A 56-year-old male, known hypertensive, sleep apnea, and diabetes mellitus type 2 (Acarbose—since a year and Metformin, Liraglutide, Lantus insulin, and Dapagliflozin—since 5 years) was hospitalized for coronary artery bypass grafting. His body mass index was at 41 kg/m^2. Acarbose was taken 72 hours prior, and Metformin and Dapagliflozin were last taken 48 hours prior to the day of surgery. Preoperative blood glucose control was managed by intravenously administered customized scaled short-acting insulin. Intraoperative course was uneventful. He did not receive any steroids. Postoperative hemodynamics were stable. He complained of excessive thirst postoperatively. Arterial blood gas revealed metabolic acidosis. Given no other causes of metabolic acidosis and a medication history of SGLT2i, urine ketones were checked and reported "large." His capillary blood glucose levels ranged from a minimum 107 mg/dL to maximum of 280 mg/dL. (Table 1) This was managed as DKA with lower-than-anticipated glucose levels. Postoperative urinary glucose was 2245 mg/dL. Subsequently, his beta-hydroxybutyrate levels came positive at 0.81 mmol/L. Stabilized, he was discharged on subcutaneous short and long-acting insulin. On follow-up, his fasting blood glucose and postprandial blood glucose have been under control with negative urine ketones.

[1]Department of Intensive Care Medicine, Kokilaben Dhirubhai Ambani Hospital and Medical Research Center, Mumbai, Maharashtra, India

[2]Department of Cardiovascular Surgery, Kokilaben Dhirubhai Ambani Hospital and Medical Research Center, Mumbai, Maharashtra, India

[3]Department of Endocrinology, Kokilaben Dhirubhai Ambani Hospital and Medical Research Center, Mumbai, Maharashtra, India

Corresponding Author: Sonali Vadi, Department of Intensive Care Medicine, Kokilaben Dhirubhai Ambani Hospital and Medical Research Center, Mumbai, Maharashtra, India, Phone: +91 22-4269-6969 e-mail: sonalivadi@hotmail.com

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Inadequate clearance of SGLT2i and the stress of major surgery are precipitating factors for DKA with lower-than-normal glucose levels. An important point to remember is that SGLT2i aid reabsorption of ketone bodies. Consequent ketoacidosis may not be accompanied by ketonuria.[1] SGLT2i causes glucosuria with a resultant reduction in insulin secretion and use. This leads to a reduction in insulin to glucagon ratio. Insulin requirements are masked. Hence, reduction in dose or discontinuation of insulin after major surgery should be avoided.[2] SGLT2i-related urinary glucose losses may persist for several days.[3] All oral hypoglycemic agents are conventionally withheld on the day of surgery. This may not hold true for the SGLT2i group of medication. American Association of Clinical Endocrinologists and American College of Endocrinology recommend withholding SGLT2i for at least 24 hours prior to any event that may precipitate DKA, to be

Table 1: Biochemical parameters, clinical trends during intensive care unit stay

Postoperative ICU day	*Time*	*pH (range: 7.35–7.45)*	*HCO_3- (range: 22–26 mEq/L)*	*Lactate*	*Anion gap (range: 1–10)*	*Lowest and highest fingerstick glucose levels in 24 hours (mg/dL)*	*Urine ketones*	*Serum beta-hydroxybutyric acid (range: 0.02–0.27 mmol/L)*	*Intake/ output (in 24 hours)*	*Human actrapid insulin (units/24 hours)*
0	1504	7.37	23.5	1.47	14.1	107; 225	—	—	3090/3620	—
	2200	7.33	17.6	1.67	17.6					
	0300	7.26	15.6	1.63	19.3					
1	0600	7.33	16.5	2.2	18.8	145; 249	Large	0.81	3870/4340	48
	1430	7.33	17.6	2.24	16.9					
	2300	7.42	23.3	1.23	5.8					
2	0600	7.44	21.6	1.39	1.6	152; 222	Moderate	—	2960/2750	40
	1800	7.40	23.7	1.24	9.4					
3	0800	7.45	22.3	1.2	9.5	167; 242	Large	—	3000/2730	27
4	0800	7.37	22.2	1.26	14.1	120; 280	Moderate	—	2950/2700	27
5	0600	7.39	22	2.55		145; 202	Large	—	600/450	—

restarted once the patient has resumed normal diet, while Food and Drug Administration[4] recommends withholding for 3 days prior to surgery. Half-life of SGLT2i is 11 to 13 hours. However, their pharmacodynamic effects may persist beyond the five half-lives[2] with glucosuria and ketonemia seen up to 9 to 10 days post-SGLT2i discontinuation.[5] Hence, it would be prudent to withhold this group of medication for more than 5 days preoperatively, requiring coordination among the surgical, anesthesia, endocrinology, and intensive care unit teams. Perioperative monitoring of acid–base and ketone status is mandatory, with monitoring to be continued until the postoperative stress is resolved. SGLT2i may be reintroduced once the oral intake is resumed to normal.

Awareness of DKA with lower-than-anticipated glucose levels is an important clinical challenge, an entity that can be confused in the setting of major and complex surgeries. The frequency of this arcane and underreported diagnosis in the perioperative setting is unknown. Patients with diabetes mellitus on SGLT2i, who develop metabolic acidosis, need to be knowingly investigated for DKA with lower-than-anticipated glucose levels. The optimal timing of discontinuation of SGLT2i's preoperatively is undetermined but definitely needs to be longer than several of their elimination half-lives. We suggest withholding SGLT2i for at least 7 days prior to major surgery. Knowledge of the existence of this entity in the "real world" clinical practice with vigilance in its diagnosis by astute postoperative surveillance will help to identify more cases, thus influencing outcomes.

Orcid

Sonali Vadi https://orcid.org/0000-0002-7341-2407
Vidhyadhar Lad https://orcid.org/0000-0002-5368-8756
Dheeraj Kapoor https://orcid.org/0000-0003-0369-3319

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