University Hospitals of Leicester NHS
NHS Trust

Perioperative Management of Patients on Sodium Glucose Co-Transporter-2 (SGLT2) Inhibitors Medications

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KEY WORDS

Sodium Glucose Co-Transporter-2 Inhibitors, Euglycemic Ketoacidosis, Postoperative ketoacidosis, Diabetes mellitus, Heart failure

1. INTRODUCTION AND OVERVIEW

1.1. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are a relatively new generation of oral glucose-lowering agents used in the treatment of type 2 diabetes mellitus (T2DM). In addition to lowering blood sugar, several prominent trials have demonstrated renal and cardiovascular benefits. There are many forms of SGLT2 Inhibitors. The following table lists the different SGLT2 inhibitors available in the UK market.

Generic name	Brand name
Dapagliflozin	Forxiga
Canagliflozin	Invokana
Empagliflozin	Jardiance
Ertugliflozin	Steglatro

There are three medications that have an SGLT2 inhibitor and metformin in one tablet, which decreases the amount of glucose produced by the body. They are:

Generic name	Brand name
Dapagliflozin + metformin	Xigduo
Canagliflozin + metformin	Vokanamet
Empagliflozin + metformin	Synjardy

And there are two medications that have an SGLT2 inhibitors and a **DDP-4 inhibitor** in one tablet. They are:

Generic name	Brand name
Empagliflozin + linagliptin	Glyxambi
Dapagliflozin + saxagliptin	Qtern

1.2. SGLT-2 inhibitors work by blocking the low-affinity, high-capacity SGLT2 protein located in the proximal convoluted tubule of the nephron. This leads to reducing plasma glucose levels by promoting glucosuria by primarily inhibiting renal reabsorption of glucose. The mechanism is unique compared with all other glucose-lowering agents as it does not interfere with endogenous insulin or incretin pathways.

1.3. The potential complications are: polyurea, dehydration, UTI, bone fragility, and hypotension.

1.4. SGLT-2 inhibitors predispose patients to euglycaemic diabetic ketoacidosis (EDKA), particularly during times of physiologic stress, including fasting and surgery. The mechanism of which is not clearly understood. According to the handbook of peri-operative medicine, 2016; The advice is:

- Pre-operatively, do not take on day of surgery. If a patient is likely to miss more than one meal consider starting a variable rate intravenous insulin infusion.
- The manufacturers of the SGLT2 inhibitors are unable to provide any advice about their use in the perioperative period; However, they do advise temporary interruption of treatment in patients with volume depletion.
- The European Medicine Agency (EMA) recommend temporarily stopping SGLT2 inhibitors in patients undergoing major surgery.
- Post-operatively, recommence when the next dose is due if the patient is eating and drinking normally, is not receiving variable rate intravenous insulin infusion, and is not dehydrated.
- Combination products Omit on day of surgery, restart as above unless metformin monograph advises otherwise.

In March 2020, the MHRA published the following safety alert regarding the use of SGLT2 Inhibitors for hospitalised patients. The alert says:

- interrupt sodium-glucose co-transporter 2 (SGLT2) inhibitor treatment in patients who are hospitalised for major surgical procedures or acute serious medical illnesses
- monitor ketones during this period – measurement of blood ketone levels is preferred to urine
- restart treatment with the SGLT2 inhibitor once ketone values are normal and the patient's condition has stabilised
- report suspected adverse drug reactions to SGLT2 inhibitors to the Yellow Card Scheme

1.5. The atypical features of SAPKA and delayed presentation raise concerns regarding timely diagnosis. Symptoms like nausea, vomiting, tachypnoea, and abdominal pain are common in the post-operative period anyway. That makes the diagnosis even more tricky.

1.6. In our trust, a few complications, mainly EDKA have been reported. This was due to the fact that SLGT2-inhibitors were not stopped preoperatively. That led to metabolic acidosis, re-admission to ITU, and prolongation in hospital length of stay.

1.7. This policy is formulated to assist in perioperative and critical care management of patients who are on (SGLT2) inhibitors drugs to avoid these complications.

2. POLICY SCOPE

2.1. This guideline applies to all hospital health care professionals who are involved in the care of patients treated with SLGT2 inhibitors medications; Especially in the perioperative period. This includes doctors, nurses, and clinical pharmacists in

different specialities like, Diabetes (endocrine), Anaesthetists, Surgeons, Cardiologists, nephrologists, surgical wards, pre-op assessment teams, and ITU.

2.2. This guideline applies for all patients > 16 years who are on SGLT2-inhibitors medication preoperatively and going for elective or emergency surgical procedures.

2.3. It also applies for these patients who will be admitted to ICU either postoperatively or for other medical emergency reasons.

2.4. This policy includes patients who are admitted to hospital as a ward-based care and do not require any surgical interventions, especially if they are admitted for acute serious medical condition.

2.5. This guideline does not cover patients taking insulin or other oral hypoglycaemic medications

3. DEFINITIONS AND ABBREVIATIONS

3.1. Euglycemic diabetic ketoacidosis (e DKA) is an uncommon but life-threatening condition which may be defined as DKA in the setting of a serum glucose level of < 14 mmol/L.

3.2. sodium-glucose co-transporter 2 (SGLT2) inhibitors are a novel class of anti-hyperglycaemic agents which include Canagliflozin, Dapagliflozin, Empagliflozin, and Ertugliflozin

3.3. variable rate intravenous insulin infusion (VRIII)

3.4. Sodium Glucose Co-transporter 2 Inhibitors associated perioperative ketoacidosis (SAPKA)

4. ROLES, WHO DOES WHAT

4.1 Responsibilities within the Organisation

a) Identify the Board Director Lead – The author of this policy.

b) This policy is to be implemented by all staff who have direct contact with patients who might be on this group of medications (SGLT2) Inhibitors.

c) If a staff member is not sure what to do, they can seek advice from the nurse in charge, or the responsible doctor if available.

d) This policy is to be supported by ITAPS, Surgical specialities, medi
Pre-op assessment teams, CDU, AMU, and A&E teams.

5. RECOMMENDATIONS, STANDARDS AND PROCEDURAL STATEMENTS

Perioperative issues during continuing using of SGLT2 inhibitors

5.1. Risk of Euglycemic diabetic ketoacidosis e DKA or SAPKA.

5.2. increased risk of post-operative urinary tract infection and delayed wound healing

5.3. Risk of volume depletion, hypotension and / or electrolyte disturbances

For elective procedures, the following measures must take place:

- Discontinue of treatment with the SGLT2 inhibitors for at least 3 days for Canagliflozin, Dapagliflozin, Empagliflozin, and 4 days for Ertugliflozin before elective surgeries. Temporary cessation is unlikely to adversely affect heart failure or diabetes management. Resume the medication only when the patient is not de-hydrated and back to their normal eating/drinking habits.

- For combination drugs like Dapagliflozin/Metformin (Xigduo), Empagliflozin/Metformin (Synjardy), or Empagliflozin/Linagliptin (Glyxambi), It is worth considering changing the medication to a monotherapy; to Metformin (in case of Xigduo or Synjardy), or Linagliptin (in case of Glyxambi) for 3 days pre-op then resuming the combination drug when the patient starts eating and drinking as normal post-operatively.
- Consider postponing major surgeries if a patient continues receiving SGLT2 inhibitors preoperatively.
- This is particularly important if patients require a surgery with reduce caloric intake or liver reduction diet.
- bariatric surgery patients seem to be at an increased risk of SAPKA.
- Minor surgical procedures, such as day surgery, may not require any temporary cessation of SGLT2i medication
- SGLT2i medication must not be commenced until achieving adequate oral intake
- Blood glucose must be monitored until eating habits and food intake stabilises
- Avoiding the use of dexamethasone
- Commence VRIII perioperatively where indicated
- Ensure emergency treatment of hypoglycaemia is prescribed
- Ensure rapid acting insulin is prescribed if not on VRIII.

For emergency surgeries and patients who require ICU admission, the following measures must take place:

- Withhold SGLT-2 inhibitors on admission to hospital
- Monitor capillary blood glucose (CBG) levels closely
- Treatment of any hypoglycaemia as per trust guidelines.

The Hospital Management of Hypoglycaemia in adults with Diabetes Mellitus (DM) Guidelines. Trust Ref: B41/2011

- Check ketones in the blood not urine on a daily basis at a minimum.
- Commence VRIII where indicated
- Resume the SGLT2 Inhibitor when the patient starts eating and drinking normally and there are no signs of dehydration post-operatively.

Emergency admission for non-surgical reason e.g.: pneumonia, sepsis, diarrhoea, vomiting, fever, dehydration …etc

- Stop SGLT2 inhibitors until the dehydration is better. Pragmatically 3 days after the patients feeling better and back to regular feeding.

TREATMENT OF EUGLYCEMIC DIABETIC KETOACIDOSIS (E DKA). REFER TO UHL DKA TRUST GUIDELINES. TRUST REF. B66/2011

- **e DKA should be considered when a patient has:** An anion gap metabolic acidosis and pH <7.3, Elevated ketones in the blood, A blood glucose <14 mmol/L
- perioperative e DKA is likely to be under-recognised

Step 1— stop inciting medications

- SGLT2 inhibitors should be discontinued as soon as e DKA is diagnosed

Step 2—Start Fluid Replacement with Monitoring of Electrolytes and Ketones

- 1 L/hour to 1.5 L/hour of normal saline or lactated Ringer's solution during the first 1 to 2 hours of fluid resuscitation
- Treatment with IV fluid supplementation should continue until the anion gap closes and acidosis has resolved

- Ketones and electrolytes should be monitored hourly and every 2 hours, respectively
- urine ketones are not a reliable indicator in detecting e DKA
- This should be continued till blood ketones are <0.6 mmol/L and electrolytes are stabilized
- Sodium bicarbonate infusion is not indicated.

Step 3—Start Continuous Insulin Infusion

- Starting at a rate of 0.05 Unit/kg/hour to 0.1 Unit/kg/hour with serum potassium levels >3.3 mEq/L
- If hypokalaemia is present, insulin therapy should be delayed until potassium normalizes
- Adequate monitoring of potassium levels should be conducted every 2 hours until electrolyte stabilization
- Once EDKA has resolved, the patient may be started on SC long-acting insulin and premeal rapid-acting insulin to control BG
- The insulin infusion should be continued for at least 1 hour after SC insulin is given.

Step 4—Start Glucose Administration

- Glucose 5% should be added to fluids
- If ketoacidosis persists dextrose 10% may be used

6. EDUCATION AND TRAINING REQUIREMENTS

6.1. It is the responsibility of ITAPS service to educate all healthcare professionals who involve in the management of these patients perioperatively about this guideline.

6.2. It is important to educate all clinical team members about the clinical features of e DKA for early diagnosis and treatment to avoid its complications.

6.3. For, TREATMENT OF EUGLYCEMIC DIABETIC KETOACIDOSIS (E DKA). REFER TO UHL DKA TRUST GUIDELINES. TRUST REF. B66/2011

6.4. All clinical staff members who are working in any location within UHL would be expected to seek senior advice or advice from the diabetes team if they were unsure of how to manage a patient with type 2 diabetes with SGLT2 inhibitors.

7. MONITORING AND AUDIT CRITERIA

7.1. All Policies must include details of audit standards or key performance indicators that will be used for monitoring compliance and effectiveness and the frequency of monitoring / audit. These must be set out in the Policy Monitoring table set out below.

6.6. Key indicators should relate to the aims and objectives of the policy and be based on policy standards

6.7. The monitoring table must also identify who is responsible for conducting and or leading the monitoring, the methodology to be used and process for reviewing results and taking action to improve performance where appropriate.

6.8. Advice on the most effective methodology, both in terms of measuring the success of the document and using the minimum resources in doing so, can be sought from the Clinical Audit Team.

Element to be monitored	Lead	Tool	Frequency	Reporting arrangements Who or what committee will the completed report go to.
Auditing The compliance with the policy. For example; How many patients developed eDKA while on SGLT2 Inhibitors.	ITAPS Quality and Safety Lead	Data Collection	Every 2 years	ITAPS Quality and Safety Committee

8. RELATED GUIDELINES

The related international guidelines and other relevant papers are those listed below:

1- 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes: Developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC).

2- FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections (fda.gov). 2022.

3- https://www.acc.org/Latest-in-Cardiology/Articles/2022/10/07/17/21/Preoperative-Cessation-of-SGLT2i

4- https://www.uptodate.com/contents/sodium-glucose-cotransporter-2-inhibitors-for-the-treatment-of-hyperglycemia-in-type-2-diabetes-

mellitus?search=sglt2%20inhibitors&source=search_result&selectedTitle=2~123&usage_type=default&display_rank=1

5- https://www.gov.uk/drug-safety-update/sglt2-inhibitors-updated-advice-on-the-risk-of-diabetic-ketoacidosis

6- https://www.medscape.com/viewarticle/927047

7- https://www.ukcpa-periophandbook.co.uk/medicine-monographs/sodium-glucose-co-transporter-2-sglt-2-inhibitors

8- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8813019/

9. REFERENCES

1. Plewa MC, Bryant M, King-Thiele R. Euglycemic Diabetic Ketoacidosis (Stat Pearls [Internet]). 2022. Available at: https://www.ncbi.nlm.nih.gov/books/NBK554570/. Accessed 09/01/2022.
2. Lam DWH. Euglycemic Diabetic Ketoacidosis in the Modern Era (youtube.com) 2018. Available at: https://www.youtube.com/watch?v=-UNimRawMHg. Accessed 09/01/2022.
3. Wang KM, Isom RT. SGLT2-inhibitor induced euglycemic diabetic ketoacidosis: a case report." Kidney Med 2020;2:218-221.
4. Nasa P, Chaudhary S, Shrivastava PK, Singh A. Euglycemic diabetic ketoacidosis: A missed diagnosis. World J Diabetes. 2021 May 15;12(5):514-523. [PMC free article] [PubMed]
5. Wazir S, Shittu S, Dukhan K, Sharief M, Beer S, Malik W, Alansari L. Euglycemic diabetic ketoacidosis in pregnancy with COVID-19: A case report and literature review. Clin Case Rep. 2022 Apr;10(4):e05680. [PMC free article] [PubMed]

6. Kalra S, Singh V, Nagrale D. Sodium-glucose cotransporter-2 inhibition and the glomerulus: A review. Adv Ther. 2016;33:1502–18.

7. Burke KR, Schumacher CA, Harpe SE. SGLT2 inhibitors: a systematic review of diabetic ketoacidosis and related risk factors in the primary literature. Pharmacotherapy 2017; 37: 187e94

8. Meyer EJ, Gabb G, Jesudason D. SGLT2 inhibitor-associated euglycemic diabetic ketoacidosis: a South Australian clinical case series and Australian spontaneous adverse event notifications. Diabetes Care 2018; 41: e47e9

9. Venkatesan Thiruvenkatarajan, Emily Jane Meyer, Nagesh Nanjappa, Roelof M. Van Wijk and David Jesudason, British Journal of Anaesthesia, 123 (1): 27e36 (2019)

10. Sleiwah A, McBride M, Black CE. Euglycemic ketoacidosis: a potential new hazard to plastic surgery day case and inpatient procedures. BMJ Case Rep August 9;2017. https://doi.org/10.1136/bcr-2017-220253.

11. Maraka S, Kearns AE, Kittah NE, O'Keeffe DT. Recurrent euglycemic diabetic ketoacidosis after discontinuation of sodium-glucose cotransporter 2 inhibitor. Diabetes Res Clin Pract 2016; 118: 77e8

12. Tan H, Acharya S. Perioperative cessation of sodium glucose cotransporter-2 inhibitors: 72 hours or seven days? Anaesth Intensive Care 2018; 46: 425

13. Sodium-Glucose Cotransporter 2 inhibitors-associated perioperative ketoacidosis: a systematic review of case reports. Journal of Anaesthesia 2023, 37:465-473. Published online: 27 February 2023.

14. Multicentre prospective observational study of sodium-glucose cotransporter-2 inhibitor-associated postoperative ketoacidosis: the SAPKA study protocol. BMJ Open, 10.1136/bmjopen-2021-049592. 23-November-2021