AUSTRALIAN DIABETES SOCIETY

ALERT

Severe Euglycaemic Ketoacidosis with SGLT2 Inhibitor Use in the Perioperative Period

Background

Sodium-glucose co-transporter-2 inhibitors (SGLT2i) are oral medications that promote glucose excretion in the urine for the treatment of type 2 diabetes. SGLT2i may also be used off-label for the treatment of type 1 diabetes.[1,5,6]

- There have been recent reports of patients with type 2 diabetes who are taking these medications developing severe acidosis requiring ICU/HDU admission during the peri-operative period.[2,6]
- Cases of ketoacidosis with SGLT2i use in type 1 diabetes have also been reported in clinical trials.[3]
- They carry a risk of severe diabetic ketoacidosis (DKA) with near normal or only mildly elevated blood glucose levels.
- The risk was increased if the patient has been fasting or had very restricted dietary intake, had undergone a surgical procedure, was dehydrated or had active infection.
- The ketosis was only detected by blood ketone testing.

Note: these agents may also reduce urinary ketone excretion so that urine ketone testing may be unreliable.

Features

DKA should be considered in patients taking SGLT2i who:

- Develop abdominal pain, nausea, vomiting, fatigue or unexplained acidosis – a normal plasma glucose level does not exclude the diagnosis.
- have fingerprick ketone (or blood beta-hydroxybutyrate) levels >0.6 mmol/L in the perioperative period or >1.5 mmol/L at any other time
- have low pH on VBG or ABG, and low bicarbonate with a high anion gap, indicating metabolic acidosis

Note: Severe ketosis may exist even where BGL is <16 mmol/L

SGLT2i agents include dapagliflozin (Forxiga), empagliflozin (Jardiance), or a combination with metformin (Xigduo, Jardiamet)

Recommendations for Practice

- SGLT2i be ceased at least 3 days pre-operatively (2 days prior to surgery and the day of surgery) or in other physically stressful situations. This may require an increase in other glucose-lowering drugs during this time.
- Strongly consider postponing non-urgent surgery if SGLT2 inhibitors have not been ceased prior to surgery and either blood ketones are >0.6 mmol/L, or HbA1c is >9.0%, as these are indicators of insulin insufficiency and a higher risk of DKA.
- Routinely check both blood glucose and blood ketone levels in the perioperative period if the patient is unwell or is fasting or has limited oral intake, and has been on an SGLT2i prior to surgery.
- If the blood ketone level is >0.6 mmol/L in an unwell pre- or peri-operative patient or >1.5 mmol/L in all other unwell inpatients who have been on an SGLT2i, the treating medical officer and, where relevant, anaesthetist, should be contacted to perform an URGENT VBG to measure the pH
- It is strongly recommended that all patients with DKA are reviewed by an endocrinologist or physician on-call. If required contact your referral tertiary hospital for advice.
- SGLT2i should only be restarted post-operatively when the patient is eating and drinking and close to discharge (usually 3-5 days post-surgery).
- Patients who have day surgery/procedures should only recommence SGLT2i if on full oral intake. It may be prudent to consider delaying recommencement of SGLT2i for a further 24 hours though consideration should also be given to the impact of withholding these agents (and metformin if on combined medication) on glycaemic control.
- Check blood glucose and blood ketone levels if patient has been taking an SGLT2i (prior to or following surgery) and is unwell in the week following surgery.

Resources

1. 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. published ahead of print February 13, 2018, doi:10.2337/dc17-1721. Open access article, http://care.diabetesjournals.org/content/early/2018/02/07/dc17-1721?papetoc
2. Peacock SC, Lovshin, JA Can J. Sodium-glucose cotransporter-2 inhibitors (SGLT-2i) in the perioperative setting. Anesth/J Can Anesth. 2018; 65:143–147
3. Isaacs M, Tonks KT, Greenfield JR. Euglycaemic diabetic ketoacidosis in patients using sodium-glucose co-transporter 2 inhibitors. Intern Med J. 2017 Jun; 47(6):701-704.
4. Fralick M, Schneeweiss S, Patorno E. Risk of Diabetic Ketoacidosis after Initiation of an SGLT2 Inhibitor. New England Journal of Medicine. 2017; 376(23):2300–2.
5. Peters AL, Henry RR, Thakkar P, Tong C, Alba M. Diabetic ketoacidosis with canagliflozin, a sodium-glucose cotransporter 2 inhibitor, in patients with type 1 diabetes. Diabetes Care. 2016; 39(4):532-8.
6. European Medicines Agency. Review of diabetes medicines called SGLT2 inhibitors started: risk of diabetic ketoacidosis to be examined [Internet], 12 June 2015. Available from http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/SGLT2_inhibitors__20/Procedure_started/WC500187926.pdf.
7. AACE/ACE Position Statement American Association Of Clinical Endocrinologists and American College of Endocrinology Position Statement on the Association of SGLT-2 Inhibitors And Diabetic Ketoacidosis. Endocrine Practice: June 2016, Vol. 22, No. 6, pp. 753-762.