Severe Euglycaemic Ketoacidosis with SGLT2 Inhibitor Use in the Perioperative Period

Background

Sodium-glucose co-transporter-2 (SGLT2) inhibitors ("gliflozins") are oral medications that act by promoting glucose excretion in urine and are used in the treatment of Type 2 Diabetes Mellitus.[1,5,6]

There have been recent reports of patients with type 2 diabetes who are taking these medications developing euglycaemic diabetic ketoacidosis (euDKA) leading to severe acidemia requiring ICU/HDU admission during the perioperative period.[2,6]

The clinical chemistry features of euDKA include:

- Acidemia: plasma pH < 7.3
  - Metabolic Acidosis - Standard Base excess < -5 mmol/L
  - plasma bicarbonate < 15 mmol/L
- Wide anion gap: anion gap > 12mmol/L (albumin corrected)
- Normal or mildly increased plasma glucose: glucose < 14 mmol/L
- Increased plasma ketones
- Urinary ketones may be normal or increased.

Possible triggers for euDKA include:

- restricted dietary intake (e.g. fasted)
- surgery
- dehydration
- active infection.

Cases of ketoacidosis with SGLT2i use in type 1 diabetes have also been reported in clinical trials.[3]

One possible mechanism for the atypical situation of diabetic ketoacidosis in patients with type 2 diabetes is that SGLT2 inhibitors blunt insulin production in the face of stress hormones leading to increased ketotic metabolism.

Features

DKA should be considered in patients taking SGLT2i who:

- Develop drowsiness, abdominal pain, nausea, vomiting, fatigue or unexplained deterioration or acidosis
- Have fingerprick ketone (or blood beta-hydroxybutyrate) levels >0.6 in the perioperative period, or >1.5 at any other times
- Have metabolic acidosis on VBG or ABG.

Note:

1. normal plasma glucose levels do not exclude the diagnosis
2. normal urine ketones do not exclude the diagnosis
3. Lactic acidosis is an important differential diagnosis but may also precipitate euDKA.

SLGT2 inhibitor agents include DAPAGLIFLOZIN (Forxiga®), EMPAGLIFLOZIN (Jardiance®), CANAGLIFLOZIN (Invokana® - available in New Zealand but not in Australia), or a combination with metformin (Xigduo®, Jardiamet®).

Recommendations for Practice

SGLT2i be ceased up to 3 days pre-operatively or in other physically stressful situations (the two days prior to surgery and the day of surgery). This may require an increase in other glucose lowering agents during this time.

Strongly consider postponing non-urgent surgery if SGLT2 inhibitors have not been ceased 3 days prior to surgery, and blood ketones are >0.6, or where HbA1c is >9.0%, as these are indicators of insulin insufficiency, and a high 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 a SGLT2i prior to surgery.

If the blood ketone level is >0.6mmol/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 the anaesthetist should be contacted to perform an URGENT ABG or VBG to measure the Base Excess.

Contact the treating medical officer or endocrinologist or physician on-call for assistance for blood ketone level >1.5 in any patients on these medications.

euDKA should be treated as a medical emergency.

All patients with euDKA should also receive a review by the endocrinologist or physician on-call. If required contact your referral tertiary hospital for advice.

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 effects of withholding SGLT2 inhibitors (and metformin if on combined medication) on glycaemic control.

For more major procedures, SGLT2i should only be restart post-operatively when the patient is eating and drinking and close to discharge (usually 3-5 days post-surgery).

Resources

1. Risk of Diabetic Ketoacidosis after Initiation of an SGLT2 Inhibitor. Fralick M, Schneeweiss S, Patorno E. New England Journal of Medicine. 2017;376(23):2300–2.
2. Euglycaemic diabetic ketoacidosis in patients using sodium-glucose co-transporter 2 inhibitors. Isaacs M, Tonks KT, Greenfield JR. Intern Med J. 2017 Jun;47(6):701-704. doi: 10.1111/imj.13442.
3. Diabetic ketoacidosis with canagliflozin, a sodium-glucose cotransporter 2 inhibitor, in patients with type 1 diabetes. Peters AL , Henry RR, Thakkar P, Tong C, Alba M. Diabetes Care. 2016; 39(4):532-8
4. 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
5. **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.
6. Sodium-glucose cotransporter-2 inhibitors (SGLT-2i) in the perioperative setting. Peacock SC, Lovshin, JA Can J Anesth/J Can Anesth (2018) 65:143–147