ALERT UPDATE January 2020

Periprocedural Diabetic Ketoacidosis (DKA) with SGLT2 Inhibitor Use

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. Note that SGLT2i are not approved for use in the management of type 1 diabetes in Australia or New Zealand, although they are sometimes used off-label in this setting.

- Over the last few years there has been an increasing number of reports of patients with type 2 diabetes who are taking these medications developing severe acidosis requiring ICU/HDU admission during the peri-operative period.
- SGLT2i carry a small but definite risk of severe diabetic ketoacidosis (DKA). Sometimes this DKA is associated with near normal or only mildly elevated blood glucose levels (i.e. euglycaemic ketoacidosis [euDKA]).
- The risk is increased if the patient has been fasting or has very restricted dietary intake, has undergone bowel preparation and/or a surgical procedure, is dehydrated or has an intercurrent illness such as active infection.
- Blood ketone testing is strongly recommended to detect and monitor DKA as urine ketone testing may be unreliable.
- The following is based on the best available evidence as of September 2019.

Clinicians should consider DKA/ euDKA in patients taking SGLT2i who have one or more of:

- symptoms of abdominal pain, nausea, vomiting, fatigue or metabolic acidosis – a normal or only modestly elevated plasma glucose level does not exclude the diagnosis.
- finger prick capillary blood ketone (or blood beta-hydroxybutyrate) levels >1.0 mmol/L with or without hyperglycaemia
- low (negative) base Excess (BE) < -5mmol/l indicating metabolic acidosis on arterial or venous blood gasses.

SGLT2i agents currently available in Australia include dapagliflozin (Forxiga), empagliflozin (Jardiance), and ertugliflozin (Steglatro), as well as fixed dose combinations with metformin (Xigduo, Jardiamet, Segluromet) or with gliptins (Glyxambi, Qtern, Steglujan).

SGLT2i agents currently registered in New Zealand include dapagliflozin (Forxiga), empagliflozin (Jardiance) and canagliflozoin (Invokana). N.B. Only dapagliflozin (Forxiga) is currently commercially available.

Advice for peri-procedural practice

- When commencing patients on SGLT2i, clinicians should inform patients about the risk of DKA associated with procedures, ideally with written information and management plans.
- For surgery and procedures requiring one or more days in hospital, and/or requiring 'bowel preparation' including colonoscopy, cease SGLT2i at least 3 days pre-procedure (2 days prior to surgery and the day of surgery/procedure). This may require increasing other glucose-lowering drugs during that time. If the SGLT2i is part of a fixed dose combination, this will lead to withdrawal of two glucose lowering drugs unless the second drug is continued separately.
- For day-stay procedures (including gastroscopy), SGLT2i can be stopped just for the day of procedure. However, fasting before and after the procedure should be minimised.

On admission

- If the patient is unwell: strongly consider postponing non-urgent procedures.
- Measure both blood glucose and blood ketone levels. If the patient is clinically well and ketones are < 1.0 mmol/L, proceed. Consider hourly blood glucose and blood ketone testing during procedure and 2 hourly following procedure until eating and drinking normally.
- If the SGLT2i has not been ceased for 3 days pre-procedure (2 days prior to surgery and the day of surgery) or has been taken on the day of day-surgery or the day procedure, the course of action depends on the urgency of the procedure combined with patient comorbidity, surgical factors, HbA1c, blood ketones, and base-excess (see table). *[Note HbA1c >9% or 75 mmol/mol is an indicator of insulin insufficiency and a higher risk of DKA in this setting.]*
- All patients on SGLT2i undergoing emergency surgery should be admitted post-procedure to a ward capable of managing diabetic ketoacidosis in collaboration with endocrinology and critical care.

- **At any point before, during or after a procedure, if the blood ketone level is >1.0 mmol/L in an unwell patient** who has been on an SGLT2i, take arterial or venous blood gases to measure the (standard) Base Excess (SBE). If ketones are > 1.0 mmol/L and base excess <-5 mmol/L the patient has presumed diabetic ketoacidosis, and if the blood sugar < 14 mmol/L, presumed euglycaemic diabetic ketoacidosis.
  - For a ward patient, or where there is no critical care expert, the rapid response (MET) team should be activated or an ICU contacted, and collaboration sought with endocrinology or general medicine.
  - In other critical care areas, anaesthetists or emergency medicine physicians should liaise with endocrinology and ICU. Management priorities include: rehydration; intravenous insulin (with added dextrose infusion if the BGL is <15mmol/l); hourly monitoring of blood glucose, ketones and blood gases with appropriate action to escalate or de-escalate treatment.
- All patients with DKA and euDKA should be reviewed by an endocrinologist or physician on-call and critical care specialists. If required, contact a tertiary hospital for expert advice.

Post procedure

- Restart SGLT2i post-operatively only when the patient is eating and drinking normally or close to discharge from hospital.
- Patients who have day surgery/procedures should only recommence SGLT2i if on full oral intake. Consider delaying recommencement of SGLT2i for a further 24 hours but also consider potential for hyperglycaemia.
- Provide patients with written advice to seek medical advice if unwell in the week following the procedure.

Table: Suggested Management of CLINICALLY WELL patients who have NOT ceased SGLT2i

Ketones	Base Excess	Comments
<1	> -5	**No ketosis and no metabolic acidosis.** Consider proceeding with day surgery: hourly monitoring of blood ketones during the procedure, and 2nd hourly following the procedure until eating and drinking normally or discharged. Provide the patient with written post-discharge advice. Where blood gas analysis is not available proceed only if added risk is consistent with goals of care. More extensive surgery requires considering goals of care and collaboration with endocrinology and critical care. Perioperative insulin and dextrose infusions may reduce risk.
>1	> -5	**Ketosis without metabolic acidosis.** Seek endocrinology or general medicine advice. Ketosis without acidosis may reflect starvation, particularly in patients with HbA1c < 9% (<75 mmol/mol). Consider proceeding, but with perioperative insulin and dextrose infusions to reduce risk of ketosis and acidosis (DKA).
>1	< -5	**Ketosis with metabolic acidosis.** Strongly consider postponing non-urgent surgery. Escalate care with endocrinology and critical care.

Footnote: Blood gas analysis is recommended to assess for presence of metabolic acidosis. Where blood gas analysis is not readily available, and the ketones are > 1.0 the procedure should not be performed.

Resources

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