

## AUSTRALIAN DIABETES SOCIETY

### ALERT UPDATE AUGUST 2019

#### Diabetic Ketoacidosis (DKA) with SGLT2 Inhibitor Use, Particularly Perioperatively

##### 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, although they are sometimes used off-label in this setting.<sup>1,2,7,8,9</sup>

- There have been an increasing number of reports over the last few years of patients with type 2 diabetes who are taking these medications developing severe acidosis requiring ICU/HDU admission during the peri-operative period.<sup>1,3,4,8,9</sup>
- Cases of ketoacidosis with SGLT2i use in type 1 diabetes have also been reported in clinical trials.<sup>5</sup>
- SGLT2i carry a small but definite risk of severe diabetic ketoacidosis (DKA)<sup>10</sup>. Sometimes this is in association 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 be used in detecting and monitoring DKA as urine ketone testing may not be reliable under these circumstances.

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

##### Features

DKA/euDKA should be considered in patients taking SGLT2i who:

- Develop abdominal pain, nausea, vomiting, fatigue or unexplained acidosis – a normal or only modestly elevated plasma glucose level does not exclude the diagnosis.
- Have finger prick capillary blood ketone (or blood beta-hydroxybutyrate) levels >1.0 mmol/L in the perioperative period or >1.5 mmol/L at any other time
- Have low pH <7.3 on VBG or <7.35 ABG, and low bicarbonate <15mmol/L with a high anion gap >12, indicating metabolic acidosis

*Note: Severe ketosis may exist even when BGL is <11 mmol/L*

**SGLT2i agents** include dapagliflozin (Forxiga), empagliflozin (Jardiance), ertugliflozin (Steglatro) as well as fixed dose combinations with metformin (Xigduo, Jardiamet, Segluromet) or with DPP4 inhibitors (Glyxambi, Qtern, Steglujan).

## Recommendations for Practice

- When clinicians are commencing patients on SGLT2i, the patient should be informed about the risk of DKA. Ideally written information including potential risk factors, warning symptoms and a management plan should be given to the patient.
- Advise temporary cessation of SGLT2i with significant intercurrent illness.
- SGLT2i do not require cessation, excepting on day of procedure, for minor operations with short period of fasting (4 hours), with **no risk of dehydration** and with rapid resumption of normal food and fluid intake following the procedure.
- Cease SGLT2i at least 3 days pre-operatively (2 days prior to surgery and the day of surgery). This may require an increase in other glucose-lowering drugs during that time. It should be noted that if the SGLT2i is part of a fixed dose combination this will lead to withdrawal of two glucose lowering drugs.
- Routinely perform both blood glucose and blood ketone measures 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. Suggest hourly blood glucose and blood ketone testing during procedure and 2 hourly following procedure until eating and drinking normally.
- If the blood ketone level is  $>1.0$  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, or anaesthetist, should be contacted to perform an URGENT VBG to measure the pH.
  - **If pH  $<7.3$  on VBG and/or  $HCO_3 <15$**  the treating medical officer should manage the patient with rehydration as well as intravenous insulin-dextrose infusion. Blood glucose, ketones and VBG should be monitored hourly and if blood ketones do not begin to fall and pH is not restored, the insulin, and therefore dextrose infusion rate will need to be increased.
- If the SGLT2i has not been ceased prior to non-urgent surgery, then the course of action depends on HbA1c, blood ketone and pH levels:
  - HbA1c  $>9.0\%$ , irrespective of ketone and pH levels – strongly consider postponing non-urgent surgery because of higher risk of infection and prolonged hospital stay. HbA1c  $>9.0\%$  is also an indicator of insulin insufficiency and a higher risk of DKA.
  - Blood ketones  $>1.0$  mmol/L AND venous pH is  $<7.3$ , irrespective of HbA1c – strongly consider postponing non-urgent surgery.
  - HbA1c  $\leq 9.0\%$ , blood ketones  $>1.0$  mmol/L AND venous pH  $\geq 7.3$  – the elevated ketones may reflect starvation ketosis combined with effect of SGLT2i. Surgery could proceed but manage with intravenous insulin-dextrose infusion to treat the ketosis and prevent progression to ketoacidosis.
  - HbA1c  $\leq 9.0\%$ , blood ketones  $\leq 1.0$  mmol/L – can proceed to surgery with hourly monitoring of blood ketones during the procedure and second hourly following the procedure until eating and drinking normally or discharged.
- It is strongly recommended that all patients with DKA/euDKA are reviewed by an endocrinologist or physician on-call. If required, contact a tertiary hospital for expert advice.
- SGLT2i should only be restarted post-operatively 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. It may be prudent to consider delaying commencement of SGLT2i for a further 24 hours, with consideration given to the impact of withholding medication on glycaemic control.
- Advise the patient of need to check blood glucose and blood ketone levels if the patient has been taking an SGLT2i (prior to or following surgery) **and is unwell in the week following surgery**.

## Resources

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5. Isaacs M, Tonks KT, Greenfield JR. Euglycaemic diabetic ketoacidosis in patients using sodium-glucose co-transporter 2 inhibitors. *Intern Med J* 2017; 47:701-704.
6. Fralick M, Schneeweiss S, Patomo E. Risk of Diabetic Ketoacidosis after Initiation of an SGLT2 Inhibitor. *New England Journal of Medicine*. 2017; 376:2300–2302.
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10. 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*: 2016; 226:753-762.