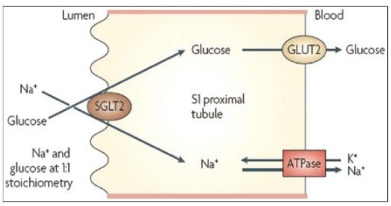
Clinical Pharmacology & Toxicology Pearl of the Week

~ SGLT2 Inhibitors and Euglycemic DKA ~



- ✓ SGLT-2 is a sodium-glucose cotransporter found in the renal tubules where it is responsible for ~90% of the glucose reabsorption
- ✓ The precursor to SGLT2 inhibitors, "Phlorizin", was isolated from the bark of apple trees in 1835
- ✓ SGLT2 inhibitors are approved for T2DM and are used off-label in T1DM
- ✓ They are indicated as second-line add-on therapy for T2DM in Canada and the USA, specifically in those who have established cardiovascular disease
- ✓ The incidence of euglycemic DKA (EDKA) is reported as ≤0.1%, however this is likely an underestimate as recognition of EDKA as a complication of SGLT2i use is rising
- ✓ SGLT2-inhibitors are postulated to cause EDKA by ↓ blood sugar, ↓ endogenous insulin secretion, ↑ glucagon secretion → subsequent lipolysis and increased ketone production
- ✓ Risk factors for euglycemic DKA in those on an SGLT2i include:
  - Increased insulin requirement (illnesses and surgery)
  - Insulin deficiency
  - Severe dehydration
  - Decreased carbohydrate intake
  - Excessive alcohol consumption
- ✓ Diagnostic criteria include:
  - Serum pH ≤ 7.3
  - Serum bicarbonate ≤ 15
  - Anion gap > 12
  - Ketones in serum or urine
- ✓ Treatment involves early recognition along with the following:
  - Correction of dehydration
  - Correction of electrolyte abnormalities, specifically hyper/hypoK
  - Consideration of insulin therapy in severe cases
  - Maintenance of a glucose of 12-15 mmol until the anion gap is closed
  - SGLT2 inhibitor should be held immediately
- ✓ SGLT2i continuation depends on whether there was a precipitating risk factor identified or not – if no obvious reason for EDKA, then the SGLT2i should be discontinued permanently.
- ✓ Patients should be counseled regarding sick day rules (table 1)

Box 1: Canadian Diabetes Association "NO FIGS" sick day protocol[3]

Prevention of diabetic ketoacidosis among patients with type 2 diabetes mellitus who are taking a sodium–glucose cotransporter-2 (SGLT-2) inhibitor

- **N**o symptoms, do not check for ketones
- **O**nly when symptomatic*, check for ketones†, even if blood glucose is relatively low (i.e., < 14 mmol/L)
- **F**luid maintenance (mineral drinks to replace ongoing electrolyte losses in the urine)
- **I**nsulin supplementation (may need regular insulin with a sliding scale coverage, or basal intermediate or long-acting insulin)
- **G**lucose and carbohydrate intake to allow for adequate insulin dosing
- **S**GLT-2 inhibitor therapy placed on hold until ketoacidosis has resolved and the precipitant has been removed; at which time the SGLT-2 inhibitor may be restarted; if no precipitant is identified, do not restart SGLT-2 inhibitor

*Nausea, vomiting, abdominal pain, tiredness, hyperventilation or Kussmaul breathing, somnolence and confusion.

†Serum ketone detection may be preferred over urine ketone detection.

Table 1: SGLT2i Sick Day protocol

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 9am-5pm. The on-call physician is listed in ROCA. Click **HERE** for clinical issues the CP service can assist with.

The Poison and Drug Information Service (**PADIS**) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414, and select option 1.

References can be found by scanning the QR code with a smartphone camera: