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, including withholding medications that may result in a decline in renal function, or have reduced clearance
    - **SAD MANS** = sulfonylureas, ACE inhibitors, diuretics/direct renin inhibitors, metformin, ARBs, NSAIDS, SGLT-2 inhibitors

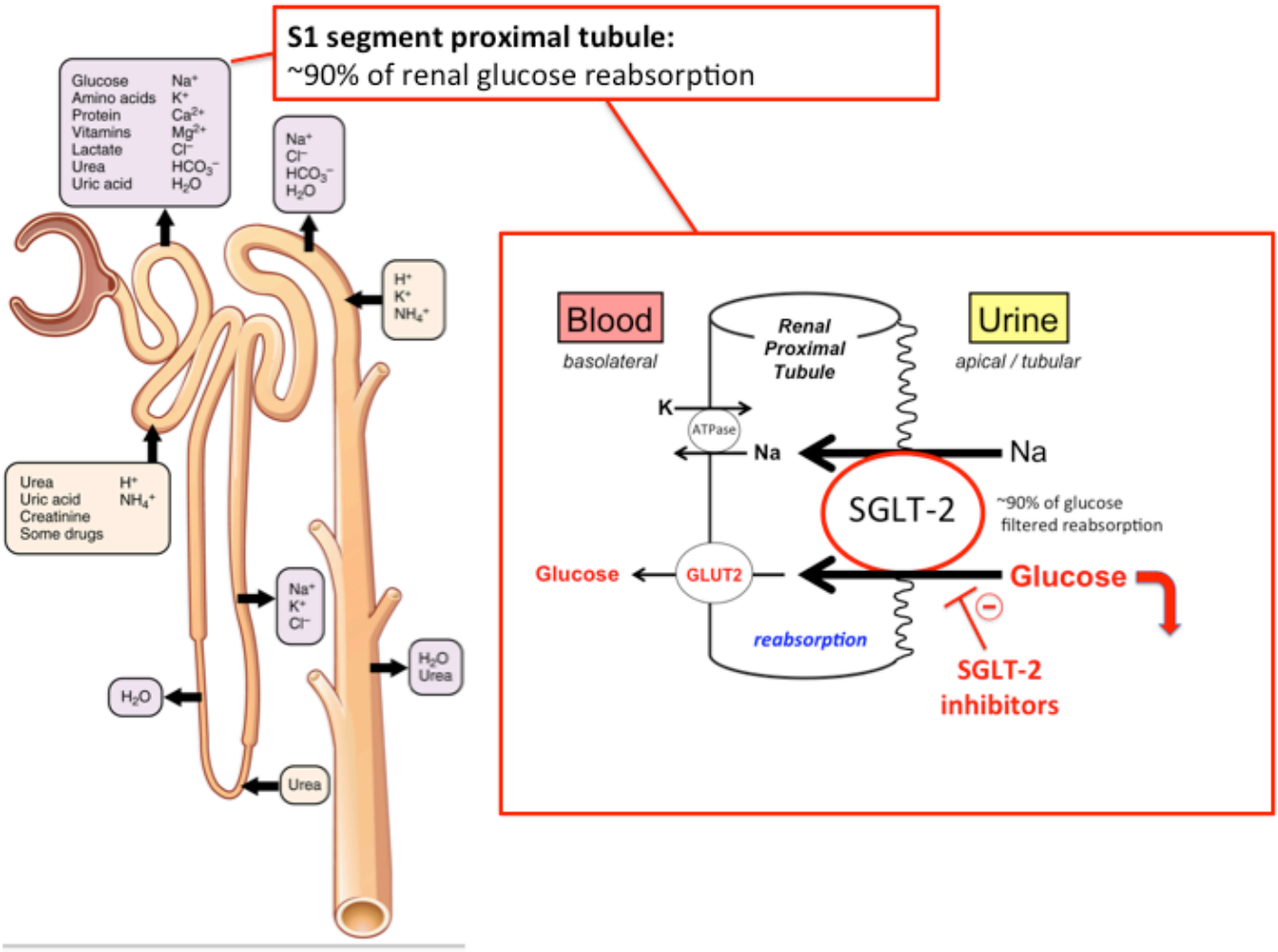
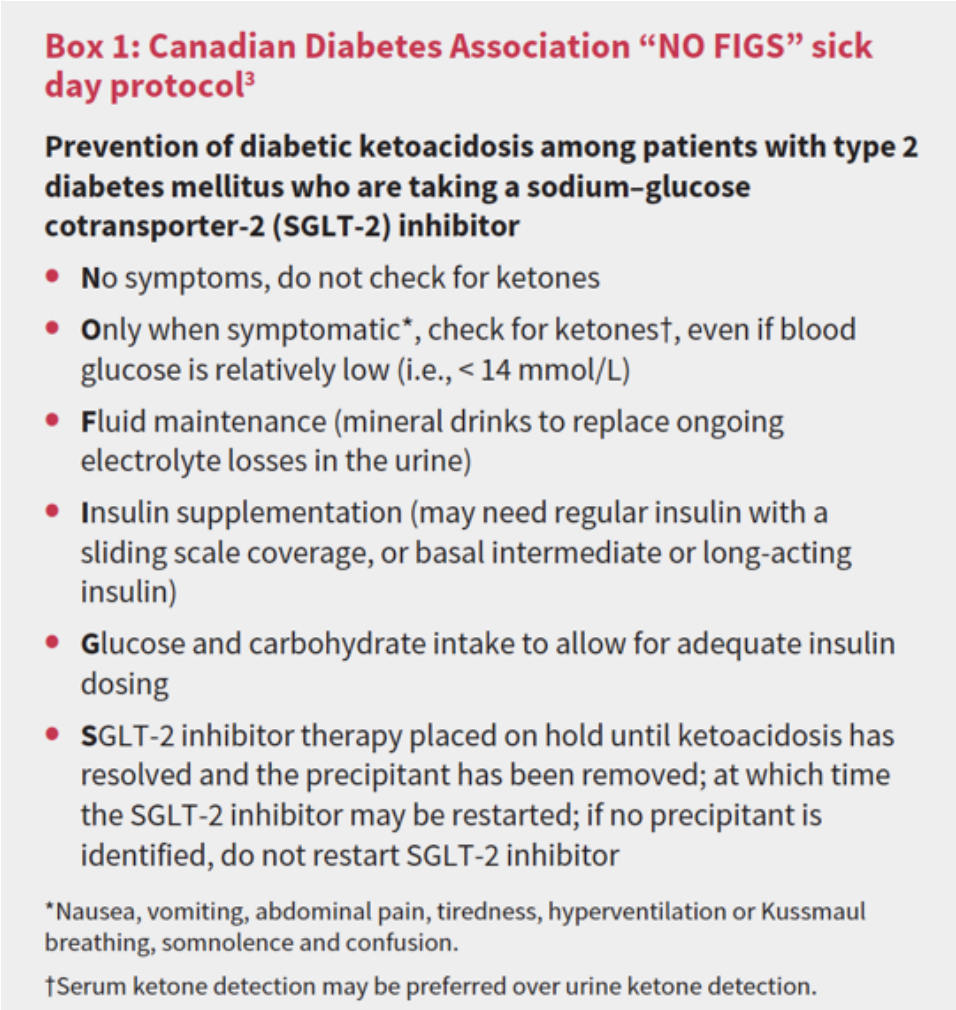


Figure. Mechanism of Action of SGLT-2 inhibitors.

From https://tmedweb.tulane.edu/pharmwiki/doku.php/sglt-2_inhibitors



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.

Figure. CDA sick day protocol.

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The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral and Specialist Link. You can also find us in the Alberta Referral Directory (ARD) by searching "Pharmacology" from the ARD home page. Click HERE for more details about the service.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

More CPT Pearls of the Week can be found HERE.

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