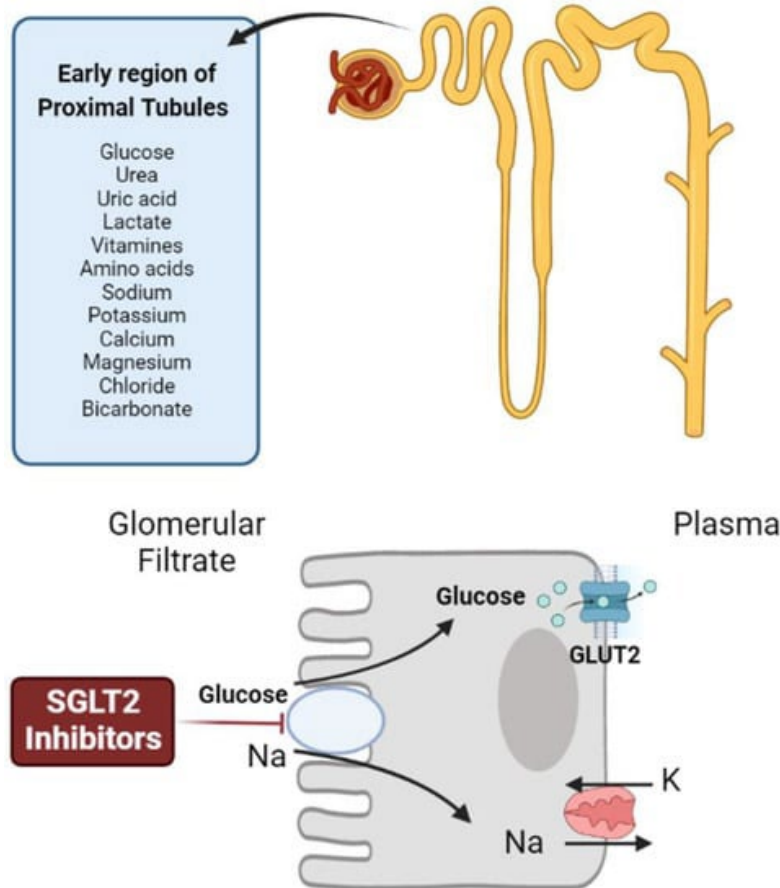




Clinical Pharmacology & Toxicology Pearl of the Week ~SGLT-2 inhibitors~

- ❖ Approximately 90% of filtered glucose in the kidney is re-absorbed by the low-affinity and high-capacity sodium-glucose co-transporter-2 (SGLT-2) and glucose transporter-2 (GLUT-2) located in the first segment of the proximal convoluted tubule.
- ❖ SGLT-2 inhibitors work by inhibiting glucose uptake in the proximal convoluted tubule of the kidney.



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Indications for Use:

- Type II Diabetes Mellitus
- Studies show benefit of SGLT-2 inhibitors, specifically Canagliflozin and Dapagliflozin, in delaying progression to end stage renal disease and reduction of cardiovascular events in patients (cardiovascular death, MI, or stroke)
 - o Seen in both diabetic patients and non-diabetic patients (DAPA-CKD) with chronic kidney disease
- Further benefits demonstrated in patients with heart failure with reduced ejection fraction in preventing hospitalizations in four large trials with or without diabetes

	Canagliflozin	Empagliflozin	Dapagliflozin
Absorption	Bioavailability 65%	Bioavailability 78%	Bioavailability 78%
		Peak plasma concentration 1.5 hours	Peak plasma concentration 1 hour
	Studies show no effect on pharmacokinetics with co-administration of high fat meal		
Distribution	Volume of distribution 83.5L	Volume of distribution 73.8L	Volume of distribution 118L
	Plasma protein binding = 99%	Plasma protein binding = 86%	Plasma protein binding = 91%
Metabolism	Metabolized by O-glucuronidation by UGT 1A9 and UGT 2B4.	Metabolized via glucuronidation	Primarily metabolized by glucuronidation by UGT 1A9
	No active metabolites	No active metabolites	No active metabolites
	Half-life: 10-13 hours	Half-life: 12 hours	Half-life: 13.8 hours
Elimination	41% unchanged in feces 33% in urine as metabolites	41% unchanged in feces 54% eliminated in urine	75% unchanged in urine 21% in feces
Dosage Forms	100 mg daily 300 mg daily	10 mg daily 25 mg daily	5mg daily 10 mg daily
Dosage Considerations	GFR > 60 ml/min: No dosage adjustment GFR 30-60ml/min:100 mg PO Daily GFR <30 <ul style="list-style-type: none"> - Urinary albumin > 300 mg/d: do not initiate, but may continue if previously started - Urinary albumin < 300 mg/d: manufacturer labelling indicates not to initiate, some off-label use at 100 mg daily 	Manufacturer recommends not initiating with GFR below 45 ml/min and discontinue if persistently below this GFR but newer studies showing cardiac and renal benefits in patients with diabetic CKD below this GFR	Manufacturer recommends not initiating with GFR below 45 ml/min but newer studies showing benefits in patients with diabetic CKD below this GFR

Drug interactions	<p>Caution when using with UGT 1A9 inducers such as Rifampin which may decrease plasma concentrations of SGLT-2 inhibitors</p> <p>Tyrosine Kinase inhibitors (e.g. Sunitinib, Lapatinib) inhibit UGT 1A9 and may increase plasma levels of SGLT-2 inhibitors</p> <p>Acetaminophen is metabolized largely UGT 1A6 and to a lesser extent by UGT 1A9. However, studies have not shown any alteration in clearance of acetaminophen with concomitant SGLT-2 inhibitor use</p>
Adverse Effects	<p>Genitourinary infections, euglycemic DKA, Fournier's gangrene, lower limb amputation (Canagliflozin warning), bladder cancer (Dapagliflozin warning)</p>

Summary:

- SGLT-2 inhibitors work by inhibition of glucose uptake in the proximal convoluted tubule
- Primary indication for use is in T2DM but studies also show benefits in terms of cardiovascular outcomes in patients with chronic kidney disease
- Three commercially available SGLT-2 inhibitors in Canada, no significant difference in their pharmacokinetics and pharmacodynamics
- Caution when using SGLT-2 inhibitors with medications that are substrates, inducers, or inhibitors of UGT 1A9 enzymes

References

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7. Zhang, N., Liu, Y. & Jeong, H. Drug-Drug Interaction Potentials of Tyrosine Kinase Inhibitors via Inhibition of UDP-Glucuronosyltransferases. *Sci Rep* 5, 17778 (2015).

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, Specialist Link and through RAAPID. 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.

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