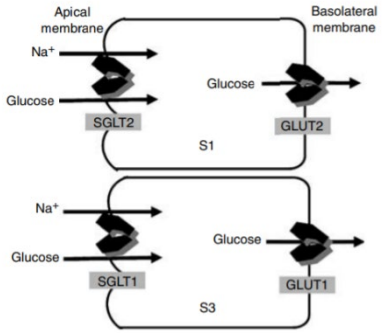
Clinical Pharmacology & Toxicology Pearl of the Week

Comparing 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

Current Indications for Use:

- Type II Diabetes Mellitus
- Recent studies (CREDENCE, DAPA-CKD) 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)
    - Seen in both diabetic patients (both CREDENCE and DAPA-CKD) 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
    - EMPA-REG, CANVAS, DELCARE-TIMI58, DAPA-HF
    -

	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 - 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	Caution when using with UGT 1A9 inducers such as Rifampin which may decrease plasma concentrations of SGLT-2 inhibitors Tyrosine Kinase inhibitors (e.g. Sunitinib, Lapatinib) inhibit UGT 1A9 and may increase plasma levels of SGLT-2 inhibitors 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
Adverse Effects	Genitourinary infections, euglycemic DKA, Fournier's gangrene, lower limb amputation (Canagliflozin warning), bladder cancer (Dapagliflozin warning)

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

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 with which the CP service can assist.

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

1. Canagliflozin. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com.

2. Empagliflozin. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com.

3. Dapagliflozin. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com.

4. Hsia DS, Grove O, Cefalu WT. An update on sodium-glucose co-transporter-2 inhibitors for the treatment of diabetes mellitus. *Curr Opin Endocrinol Diabetes Obes*. 2017;24(1):73-79. doi:10.1097/MED.0000000000000311.

5. Lee YJ, Lee YJ, Han HJ. Regulatory mechanisms of Na(+)/glucose cotransporters in renal proximal tubule cells. Kidney Int Suppl. 2007 Aug;(106):S27-35. doi: 10.1038/sj.ki.5002383. PMID: 17653207.

6. Tahara A, Takasu T, Yokono M, Imamura M, Kurosaki E. Characterization and comparison of sodium-glucose cotransporter 2 inhibitors in pharmacokinetics, pharmacodynamics, and pharmacologic effects. J Pharmacol Sci. 2016 Mar;130(3):159-69. doi: 10.1016/j.jphs.2016.02.003. Epub 2016 Feb 15. PMID: 26970780.

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). https://doi.org/10.1038/srep17778