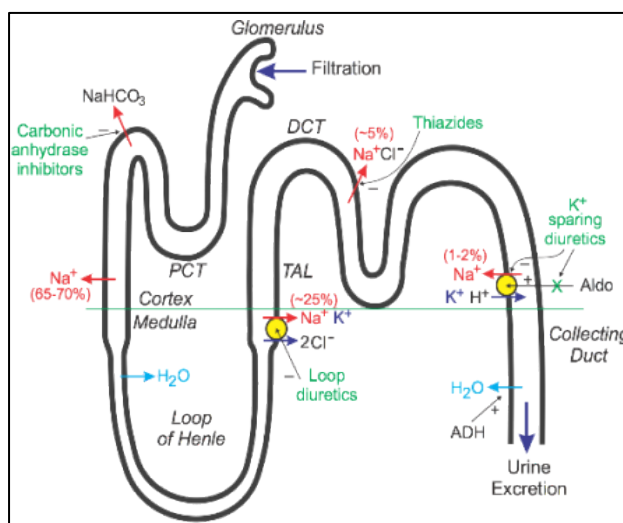




Clinical Pharmacology & Toxicology Pearl of the Week

~Antihypertensives, Part 3: Thiazide and Thiazide-like Diuretics~

- ✓ Thiazide and thiazide-like diuretics are a class of diuretics that predominantly operate at the distal convoluted tubule (DCT)
- ✓ Thiazide diuretics: hydrochlorothiazide
- ✓ Thiazide-like diuretics: chlorthalidone, metolazone, indapamide
- ✓ Indications:
 - Treatment of hypertension
 - Off-label: Edema, calcium nephrolithiasis, nephrogenic diabetes insipidus, augmented effect of loop diuretics (Lasix + metolazone)



How to use/Combinations:

- ✓ Thiazide/Thiazide-like diuretics are first line therapy for simple hypertension (The data to support this comes from the ALLHAT trial; see [Hypertension Canada](#) for complete hypertension guidelines.)
- ✓ Thiazides work additively when combined with agents to block RAAS system: B-blockers, ACEi/ARB, mineralocorticoid receptor antagonists.

Pharmacokinetics:

Drug:	Bioavailability (%)	Plasma Half-Life (hrs)	Metabolism	Elimination
Hydrochlorothiazide	~70%	2.5	non-metabolized	40-80% renal
Chlorthalidone	~65%	~47	non-metabolized	65% renal
Indapamide	~93%	~14	extensively metabolized by CYP3A4	60-70% renal

- ✓ Thiazides have a **flat** dose-response curve: This means that further increasing the dose beyond the target dose provides **no** further drop in blood pressure but significantly increases the risk for adverse side effects.

- ✓ Chlorthalidone is approximately 1.5-2x as potent as hydrochlorothiazide, therefore a dose of 12.5 mg chlorthalidone is equivalent to 25 mg of HCTZ; chlorthalidone should not be dosed higher than 25 mg, as the increased incidence of electrolyte abnormalities significantly outweighs any further blood pressure lowering effect.

Adverse Effects/Toxicity:

- ✓ Dehydration (rarely solely due to the thiazide itself)
- ✓ Metabolic derangements (Hypokalemia, hyponatremia, metabolic acidosis, hyperuricemia, hyperglycemia, hypercalcemia, hypertriglyceridemia (mechanism unclear; but decreased efficacy of insulin and sulfonylureas))
- ✓ Other side effects: vertigo, nausea, photosensitivity, Stevens-Johnson Syndrome/TEN
- ✓ Toxicity:
 - Metabolic derangements leading and subsequent cardiovascular instability
 - Hypotension
 - CNS depression (Rare and mostly in children)

Take home points:

- ✓ First line in simple hypertension
- ✓ Work additively with other agents that target RAAS system (B-blockers, ACEi/ARB, MRAs)
- ✓ Flat dose-response curve (for blood pressure)
 - Higher doses lead to more side-effects and electrolyte disturbances without added benefit of blood pressure lowering effect.

References:

1. Reilly RF, Jackson EK. Regulation of Renal Function and Vascular Volume. In: Brunton LL, Chabner BA, Knollmann BC. eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12e. McGraw-Hill
2. Benowitz NL. Antihypertensive Agents. In: Katzung BG. eds. *Basic & Clinical Pharmacology*, 14e. McGraw-Hill
3. Drugbank: <https://go.drugbank.com/drugs/DB00381>
4. Micromedex: <https://www.micromedexsolutions-com.ahs.idm.oclc.org>
5. Indiana University Department of Medicine Clinical Pharmacology - Flockhart Tables: <https://drug-interactions.medicine.iu.edu/MainTable.aspx>

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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