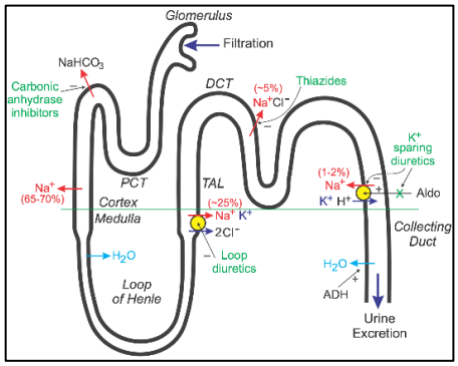
Clinical Pharmacology & Toxicology Pearl of the Week

~Part 3 - Hypertension Series: Thiazide and Thiazide-like Diuretics~



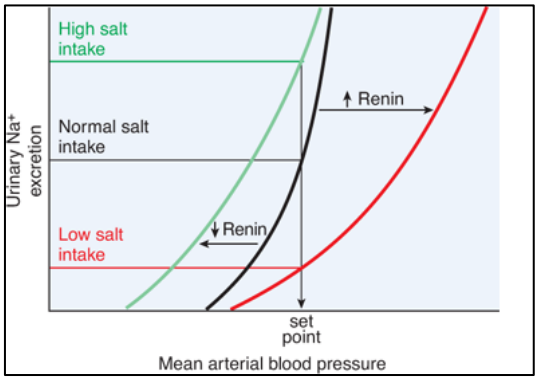
Thiazide and thiazide-like diuretics are a class of diuretics that predominantly operate at the distal convoluted tubule (DCT)

- 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)

Mechanisms of action:



- ✓ Renin release is mediated by: Baro-receptors in afferent arteriole, Beta-1 stimulation, and the macula densa (Senses distal convoluted tubule sodium-chloride concentration)
- ✓ Thiazide-induced inhibition of the sodium-chloride co-transporter (NaCC) in the distal convoluted tubule → natriuresis and mild diuresis
- ✓ Mild diuresis and drop in the extra-cellular fluid volume (200-300cc) → Typically offset by increase in Renin (RAAS) system
- ✓ Natriuresis: increases the slope of the pressure-natriuresis curve (see right) → Impaired absorption of sodium and chloride due to thiazide → higher sodium-chloride concentrations in distal convoluted tubule → sensed by macula densa → decreased renin-signal → vasodilation + sustained natriuresis → drop in blood pressure
- ✓ Promotes calcium reabsorption (increased calcium movement though the TRPV5 calcium channel in DCT)
- ✓ Other mechanisms (proposed):
  - Direct vessel vaso-dilation (inhibiting epithelial ATP, or potassium channels)
  - Weak carbonic anhydrase activity (promotes diuresis)

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.)
- ✓ Given macula-densa mechanism, 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:

- ✓ Metabolic derangements (Hypokalemia, hyponatremia, metabolic acidosis, hyperuricemia)
- ✓ Dehydration (rarely solely due to the thiazide itself)
- ✓ Metabolic derangements: Hyperglycemia, hypercalcemia, hypertriglycidemia (mechanism unclear; but decreased efficacy of insulin and sulfonylureas)
- ✓ Other side effects: vertigo, nausea, photosensitivity, Steven-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.

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:

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