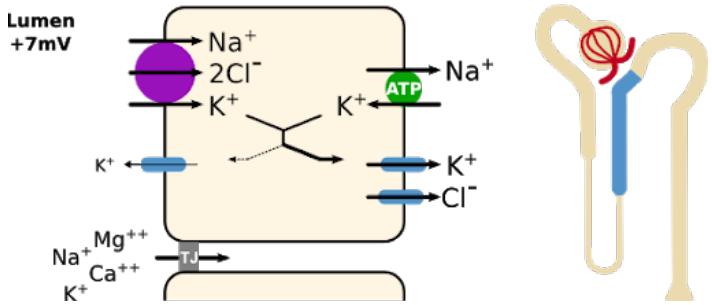
Clinical Pharmacology & Toxicology Pearl of the Week

~Antihypertensives, Part 6: Loop diuretics ~

- Mechanism of Action:
    - Primary effect is blockade of the Na+/K+/2 Cl- cotransporter.
    - This cotransporter is located predominantly on the thick ascending loop of Henle.



- Common understanding is that furosemide is used for its *natriuretic* effect. This is important for management of fluid overload and in chronic heart failure patients; but there are additional effects which have implications for acute care medicine.

- Additional Mechanisms of Action:
    - MOA #1: Loop Diuretic (blocks Na+-K+-2Cl- symporter in the loop of Henle)
        - End effect: Natriuresis (gets rid of Na+)/ Preload and Afterload Reduction
        - Time to effect: ~25 minutes
    - MOA #2: Promotes Prostaglandin Synthesis/Release in Vascular Endothelium
        - End effect: Venodilation/Preload reduction
        - Time to effect: ~5 minutes
    - MOA #3: Induction of Nitric Oxide Synthesis in Vascular Endothelium
        - End effect: Venodilation (mediated by bradykinin release)/Preload reduction
        - Time to effect: ~5 minutes
    - MOA #4: Promotes Prostaglandin Synthesis/Release in Bronchi
        - End effect: Bronchodilation/Improvement of dyspnea
        - Time to effect: ~5 minutes

- Narrative Review:

  The immediate effect of furosemide is that it increases venous compliance (meaning the veins can hold more fluid) and causes venodilation. Venodilation occurs from an increase in nitric oxide (NO) synthesis and prostaglandin (PGE) synthesis and is a direct mechanism of action of furosemide. This same increase in NO and PGE also acts at the pulmonary level and cause bronchodilation. Thus, the IMMEDIATE effect of furosemide is to decrease LVEDP and then induce NATURESIS 30 minutes post drug administration. Note: we are

unaware of any studies looking at the other mechanisms of furosemide as it relates to management of CHF or other respiratory illnesses.

Pharmacokinetics:

- Oral Bioavailability
  - Furosemide averages 50% oral bioavailability but is *widely variable* from 10-100%.
    - IV to PO conversion is very roughly 1:2.
    - Hypoalbuminemia will further limit drug bioavailability.
  - Bumetanide and Torsemide have oral bioavailability >80%
    - IV to PO conversion is approximately 1:1).
  - Peak drug concentrations are reached within 0.5-2 hours.

- Peak Action
  - Following an IV dose, peak action occurs after 30 minutes (for both furosemide and bumetanide).

- Half-life
  - Furosemide has a longer half-life than bumetanide, an alternative diuretic with the same MOA.
  - Furosemide is metabolized by the kidney.
    - Leading to a longer half-life of furosemide in patients with renal dysfunction.
  - Bumetanide is metabolized in the liver.
    - Leading to a longer half-life for bumetanide's in patients with hepatic dysfunction.
  - Note: Bumentanide is a US medication.

- Entry into the tubule
  - Loop diuretics have high albumin binding (>90%), so they aren't freely filtered into the tubule. In order to enter the nephron lumen, they must be actively *secreted* in the proximal tubule via organic anion transporters (OATs).
  - Secretion is impaired in uremia due to *competition* for organic anion transporters with other organic anions which accumulate in renal failure. For this reason, metabolic acidosis also impairs tubular secretion.

Pharmacodynamics:

- Furosemide exhibits a *ceiling effect*.
  - Beyond a certain dose additional drug won't increase the diuretic effect.
  - Note that higher doses might have a more *prolonged* effect.
- Higher doses are generally required in renal failure and in patients chronically exposed to furosemide.

- The starting dose doesn't particularly matter.
    - Reasonable choices might be:
        - Patients on chronic oral furosemide: Give an IV dose equal to or a bit higher than the patient's home oral furosemide dose.
        - Patients not on chronic furosemide: Give a dose between 20-80 mg IV depending on the renal function & acuity of the situation.
- The key is *empiric dose titration*.
    - If there is no result in 30-60 minutes, *keep doubling the dose* until the patient responds (or until you reach a dose of ~240 mg furosemide).
        - This rapid dose-titration should empirically define an effective furosemide dose.
        - The target urine output following an effective dose is >100-150 ml/hour.

Adverse Effects/Toxicity:

1. Magnesium, and Calcium wasting.
    - Mg2+ and Ca2+ are reabsorbed between cells in the thick ascending loop of Henle.
        - Reabsorption is driven by a lumen-positive electrochemical gradient.
        - Loop diuretics reduce this electrochemical gradient.
    - Furosemide was once used as a treatment for hypercalcemia, but not common anymore.

2. Contraction Alkalosis

3. Blockade of NaCl entry into the macula densa (which normally occurs via the NKCC2 channel).
    - Blockage of tubulo-glomerular feedback.
        - This ultimately leads to renal vasodilation (via increases in prostaglandin E2).
        - This is potentially beneficial.
    - Increased renin production:
        - This increases Angiotensin II levels (which may increase blood pressure and potentially defend the glomerular perfusion). In patients with chronic heart failure this has historically been proposed to cause arterial constriction via AT1 receptor and ultimately increase LVEDP . However, clinically this seems to be an insignificant effect. One theory for why this is not observed is that the AT1 effects are outweighed by AT2-receptor binding which induce predominantly arterial and venodilatory effects.
        - This also increases aldosterone levels (which may increase sodium retention by the distal nephron, potentially impairing further diuresis).

- Note: Patients with an allergy to sulfa *antibiotics* can safely receive loop diuretics.

- Adverse Effects:
    - Hyperglycemia
    - Hyperuricemia
    - Hypocalcaemia
    - Hypokalemia
    - Hypomagnesemia
    - Hypertriglyceridemia
    - Orthostatic hypotension
    - Pruritis
    - Steven Johnson Syndrome / Toxic Epidermal Necrolysis
    - Anaphylaxis

- Toxicity: no true toxic dose documented.
- Dosing is reported as ***titration to effect***
- Ensure mindfulness re: indication and risk of AKI secondary to furosemide.

Take Home Points:

- ✓ Furosemide is not purely a natriuresis agent.
- ✓ Variety of immediate mechanisms that target decreased LVEDP.
- ✓ No mortality effect for CHF from a natriuresis perspective but other MOA yet to be studied.
- ✓ In acute heart failure management, peripheral IV furosemide is preferred compared to central administration as it leads to better venodilation effects (more surface area to interact with endothelium).

References:

1. Dikshit K et al., Renal and extrarenal hemodynamic effects of furosemide in congestive heart failure after acute myocardial infarction. N Engl J Med. 1973 May 24;288(21):1087-90.
2. Bourland WA et al., The role of the kidney in the early nondiuretic action of furosemide to reduce elevated left atrial pressure in the hypervolemic dog. J Pharmacol Exp Ther. 1977 Jul;202(1):221-9.
3. Pickkers P et al., Direct vascular effects of furosemide in humans. Circulation. 1997 Sep 16;96(6):1847-52.
4. Wiemer G et al., Furosemide enhances the release of endothelial kinins, nitric oxide and prostacyclin. J Pharmacol Exp Ther. 1994 Dec;271(3):1611-5.
5. Almirall JJ, Dolman CS, Eidelman DH. Furosemide-induced bronchodilation in the rat bronchus: evidence of a role for prostaglandins. Lung. 1997;175(3):155-63.
6. Baan J, Chang PC, Vermeij P, Pfaffendorf M, van Zweiten PA. Venoconstriction by angiotensin II in the human forearm is inhibited by losartan but not by nicardipine. J Cardiovasc Pharmacol. 1998;31:50–55.
7. Newby DE, Masamouri S, Johnston NR, Boon NA, Webb DJ. Endogenous angiotensin II contributes to basal peripheral vascular tone in sodium deplete but not sodium replete man. Cardoivasc Res. 1997;36:268–275.
8. Newby DE, Goodfield NER, Flapan AD, Boon NA, Fox KAA, Webb DJ. Regulation of peripheral vascular tone in patients with heart failure: contribution of angiotensin II. Heart. 1998;80:134–141.

9. Scheuer DA, Perrone MH. Angiotensin type 2 receptors mediate depressor phase of biphasic pressure response to angiotensin. Am J Physiol. 1993;33:R917–R923.
10. Hein L, Barsh GS, Pratt RE, Dzau VJ, Kobilka BK. Behavioural and cardiovascular effects of disrupting the angiotensin type-2 receptor gene in mice. Nature. 1995;377:744–747.
11. Ichiki T, Labosky PA, Shiota C, et al. Effects on blood pressure and exploratory behaviour of mice lacking angiotensin type-2 receptor. Nature. 1995;377:748–750.

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.

Created: February 26, 2021

Reviewed: March 11, 2025