

## Diuretics in HF

- Diuretics are commonly used despite the lack of evidence for survival benefit.
- Diuretics can relieve symptoms in patient with HF which are the result of excessive fluid retention.
- Diuretics are classified based on their site of action.

### Loop Diuretics

- Block the Na-K-2Cl cotransporter at the luminal side of the thick ascending limb of the loop of Henle.
- Result in ↑Na excretion, ↑K excretion, ↑Cl excretion.

#### Pharmacokinetic

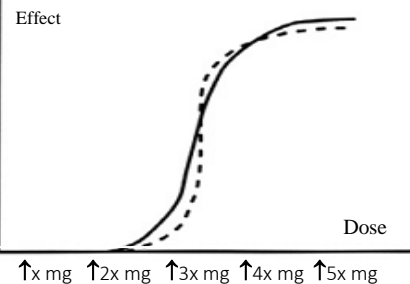
- Varied absorption, albumin bound.
- All loop diuretics have the same efficacy (when administered in comparable doses, they exert comparable effects).
- Onset = 30 - 60 mins.

**Table 5. Intravenous Diuretic Medications Useful for the Treatment of Severe Heart Failure**

Drug	Initial Dose	Maximum Single Dose
<b>Loop Diuretics</b>		
Bumetanide	1.0 mg	4 to 8 mg
Furosemide	40 mg	160 to 200 mg
Torsemide	10 mg	100 to 200 mg
<b>IV Infusions</b>		
Bumetanide	1-mg IV load then 0.5 to 2 mg per hour infusion	
Furosemide	40-mg IV load then 10 to 40 mg per hour infusion	
Torsemide	20-mg IV load then 5 to 20 mg per hour infusion	

ACC/AHA HF guideline 2009

Pharmacokinetics of loop diuretics (Ann Pharmacother 2009;43:1836)			
Property	Furosemide	Torsemide	Bumetanide
Bioavailability	50% varied 10-100%	80-100%	80-100%
Half-life (T1/2)	1.5-2 hrs	3-4 hrs	1 hr
interval	OD, BID, TID	Daily	TID, QID
Duration of action	6-8 hrs	12-14 hrs	4-6 hrs
Estimate cost (baht)	40 po ฿1-4 500 po ฿3-30 20 iv ฿7 250 iv ฿140	10 po ฿19	1 po ฿3 2 iv ฿40
Equivalence dose	40 mg oral = 20 mg IV	= 20 mg oral	= 1 mg oral = 1 mg IV



**DOSE trial:** (NEJM 2011;364:797)

- Double blind RCT of furosemide in pts with HF (N=308)
- 2x2 factorial:
  - High-dose (2.5x home dose) vs. low-dose (1x home dose)
  - IV bolus vs. IV continuous infusion
- At 72 hours:
  - 1° endpoints: no statistic significant difference in patients' global assessment of symptoms or in Δ renal function in any group.
  - 2° endpoints: High-dose was associated with greater wt loss, net volume loss, ↑ number of pt c WRF(>0.3), ↓ dyspnea.

#### Pharmacodynamics: (Brater. Semin Nephrol 2011;31:483-494)

- Loop diuretic has a sigmoid dose-response curve.
- Not response until reaching a threshold dose.
- Once the plateau is reached, the higher doses do not cause a much greater response.
- Once the plateau is reached, if more fluid loss is needed, the drug should be given more frequently.

#### Clinical pearl

- Varied in absorption of furosemide = unreliable dosing.
- Adverse effect: Ototoxic, hypoK, hyperUric (gout), hyperglycemia, hypoMg.
- Diuretics decrease intravascular volume. Patient may develop relative hypovolemic if capillary refill rate is abnormal

### Diuretic Resistant (ter Maaten. Nat.Rev.Cardiol 2015;12:184-192)

- First, rule out poor compliance to medications, salt or fluid restriction.
- If suboptimal dose or bioavailability:
  - Increase doses, if not reaching response dose.
  - Increase frequency, if already at response dose.
  - Switch to a drug that has better bioavailability (torsemide or bumetanide), if given orally.
  - Switch to IV form, switch to IV continuous infusion.
- Adding second diuretics eg. thiazide, spironolactone, tolvaptan.
- Ultrafiltration: Greater control of fluid removal rate but no greater weight loss when compared to diuretics and more adverse effect (CARRESS-HF NEJM2012).

### Adding Second Diuretics

#### Thiazide

- Block the Na-Cl symporter at the distal tubule.
- Synergy effect in patient with chronic use of loop diuretic because loop cause ↑[Na] reabsorption in distal tubule and secondary tubule hypertrophy.
- Suggested dose: HCTZ 50-100 mg oral daily.
- Traditionally given 30 mins before furosemide.
- S/E: HypoK, hypoNa.

#### Spironolactone

- An aldosterone blocker
- Work at the collecting duct.
- A low dose - as guideline recommendation for chronic HFREF management to improve survival, does not have diuretic effect. Need 50-75 mg/day to reach natriuretic effect.
- S/E: 2% serious hyperK, 10% gynecomastia.

#### Tolvaptan (EVEREST JAMA2007)

- A vasopressin antagonist
- Block the V2 receptor in the collecting tubule → ↑water excretion "aquaresis"
- Starting dose: 7.5 - 15 mg oral daily.
- In patients with ADHF, adding tolvaptan improved weight loss and congestion (dyspnea, orthopnea, JVD, edema, rales) in first few days to wk but no effect on long-term mortality or rehospitalization.
- S/E: 6% dry mouth, 14% thirst, 1.5% hyperNa (mean ↑ of 4 mEq/L). Minimal effect on hemodynamics, K, and Cr. Contraindicate in ↑AST/ALT
- Patient must not on fluid restriction when using tolvaptan.

#### Clinical pearl

- Alternative strategies (limited evidence) include acetazolamide, mannitol and hypertonic saline.
- Neither low dose dopamine nor nesiritide can improve urine output or renal function in patient with AHF and diuretic resistant (ROSE JAMA2013).

