

Clinical Controversies in Heart Failure Diuresis

Bri Jansma, PharmD
PGY1 Pharmacy Resident
Sanford USD Medical Center
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• I have had no financial relationship over the past 12 months with any commercial sponsor with a vested interest in this presentation

Learning Objectives: Pharmacists

- Identify differences between loop diuretic agents.
- Compare and contrast loop diuretic administration techniques.
- Define diuretic resistance and its role in therapy.
- Describe several adjunct therapies, including mechanism of action and strengths or limitations.

Learning Objectives: Pharmacy Technicians

- Identify differences between loop diuretic agents.
- Compare and contrast loop diuretic administration techniques.
- Recognize medications that may be given concomitantly with loop diuretics in diuretic-resistant patients.

Introduction

- >90% of patients admitted for heart failure receive loop diuretics
- Roles of diuretic therapy:
 - Acute decompensation
 - Chronic maintenance of euvolemic state
- No proven long-term mortality benefit; however, provides symptomatic benefits
- Lack of strong evidence
 - Guidelines: Class I Recommendation with Level B or C Evidence

Yancy CW, et al. 2013 ACCF/AHA guidelines. Circulation. 2013;128:180-102
Parisekowi P, et al. 2016 ESC guidelines. Eur Heart J. 2016;37:129-200

Fine Balance

Advantages	Disadvantages
peripheral edema	Hypotension
pulmonary congestion	Azotemia
jugular vein distention	Fluid and electrolyte depletion
Symptomatic Benefits	Resistance development

Palazzuoli A, et al. Curr Drug Targets 2015;16(11):1246-53

Loop Diuretics

Loop Diuretic	Oral Bioavailability (%)	Elimination Half-life in Normal Individuals (hrs)	Elimination Half-life in Cirrhosis (hrs)	Elimination Half-life in CKD (hrs)	Elimination Half-life in CHF (hrs)	Usual Dose Range (mg/day) (doses/day)
Torsemide	80-100	3-4	8	4.5	6	5-100 (1-2)
Furosemide	10-100	1.5-2.0	2.5	2.8	2.7	40-240 (2-3)
Bumetanide	80-100	1	2.3	1.6	1.3	0.5-4.0 (2-3)

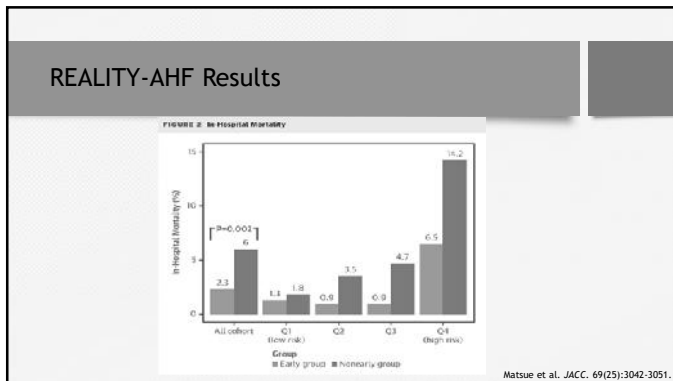
Palazzuoli A, et al. *Curr Drug Targets* 2015;16(11):1246-53

Door-to-Furosemide (D2F)

REALITY-AHF

- Prospective, multicenter, observational cohort study
- Assess the association between time to loop diuretic treatment and clinical outcome in AHF
- Door-to-furosemide (D2F): time from ED arrival to first IV furosemide injection
 - Early treatment group: <60 min

Matsue et al. *JACC*. 69(25):3042-3051.

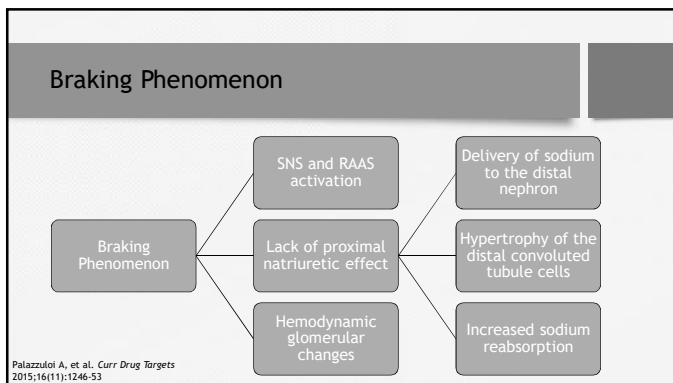


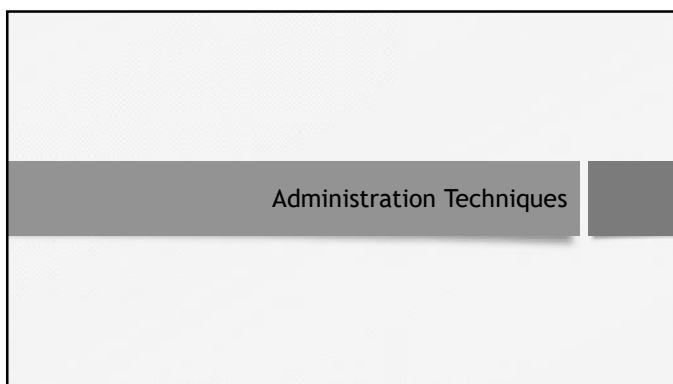
Diuretic Resistance

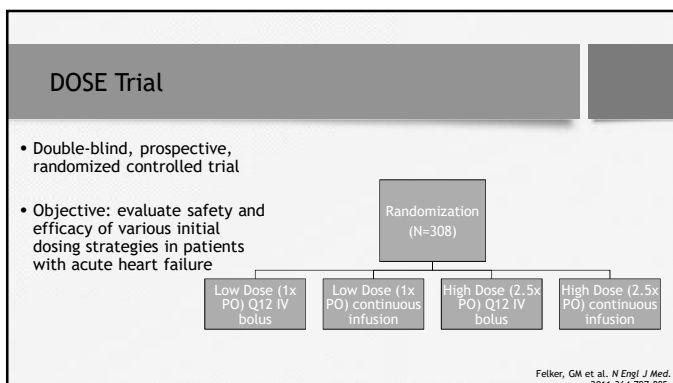
Definition: failure of diuretics to achieve decongestion despite the use of maximal recommended doses

Ellison DH, Felker GM. NEJM 2017;377:1964-75.

- ### Diuretic Resistance
- Contributing Factors to Diuretic Resistance**
- Inadequate dose of diuretic
 - Non-adherence
 - High sodium intake
 - absorption secondary to gut edema
 - Impaired diuretic secretion into tubule lumen (CKD, age, NSAIDs, probenecid)
 - Nephrotic syndrome
 - Antinatriuretic drugs: NSAIDs, antihypertensives
 - Low renal blood flow
 - Nephron remodeling
 - Neurohormonal activation
 - Hypoproteinemia
 - Hypotension
- Ellison DH, Felker GM. NEJM 2017;377:1964-75.







Results: Primary Endpoints

- Q12 hour bolus versus continuous infusion:
 - Global symptom relief: p= 0.47
 - Change in renal function: p= 0.45
- Low intensity versus high intensity dosing:
 - Global symptom relief: p= 0.06
 - Change in renal function: p= 0.21

Felker, GM et al. *N Engl J Med.* 2011;364:797-805

Results: Secondary Endpoints

	Q12 hour	Continuous	P value
Dyspnea VAS AUC at 72 hour	4456	4699	0.36
% free from congestion at 72 hour	14%	15%	0.78
Net volume loss at 72 hour (mL)	4237	4249	0.89
% treatment failure	38	39	0.88
% with Cr increase >0.3 mg/dL within 72 hours	17	19	0.64
LOS, days (median)	5	5	0.97

Felker, GM et al. *N Engl J Med.* 2011;364:797-805


Results: Secondary Endpoints

	Low Dose	High Dose	P value
Dyspnea VAS AUC at 72 hour	4478	4668	0.041
% free from congestion at 72 hour	11%	18%	0.091
Net volume loss at 72 hour (mL)	3575	4899	0.001
% treatment failure	37	40	0.56
% with Cr increase >0.3 within 72 hours	14	23	0.041
LOS, days (median)	6	5	0.55

Felker, GM et al. *N Engl J Med.* 2011;364:797-805

DOSE Trial Conclusions

- No significant difference in symptom relief or change in renal function for:
 - Low intensity versus high intensity
 - Q12 hour bolus versus continuous infusion



Fetker, GM et al. *N Engl J Med.* 2011;364:297-305.

Caveats

- Population size did not meet power
- No loading dose prior to continuous infusion
- Initial rates of continuous infusion lower than typically recommended (In both high- and low-dose populations)
- % of population with diuretic resistance: unknown
- Mean SCr: 1.5 mg/dL

Elison DH, Fetker GM. *NEJM* 2017;377:1964-75.

ACC/AHA HF Guidelines: Hospitalized Patients

IB: Patients with HF admitted with evidence of significant fluid overload should be promptly treated with IV loop diuretics to reduce morbidity.

IB: If patients are already receiving loop diuretic therapy, the IV dose should equal or exceed their chronic PO daily dose and should be given as either intermittent boluses or continuous infusion.

Yancy CW, et al. 2013 ACCF/AHA guidelines. *Circulation*. 2013;128:1880-930.

Adjunct Therapy

Adjunct Therapy

- Several suggested options
- May induce diuresis in refractory patients
- Overall, long-term safety, morbidity, and mortality are still unknown

Thiazide Adjunct Therapy

Sequential Nephron Blockade

- Thiazide + Loop Diuretic
- Mechanism:
 - Block NaCl reabsorption
 - "Synergy"
- Concerns:
 - Unclear literature
 - Increased risk of AEs
- Timing?

Ellison DH, Felker GM. NEJM 2017;377:1964-75.

Sequential Nephron Blockade in Literature: Hydrochlorothiazide versus chlorothiazide

- Single-center, retrospective review
- Hydrochlorothiazide or chlorothiazide background IV furosemide
- UO increased in both groups
- More significant increase with chlorothiazide
- Electrolyte disturbances common in both groups

Kissling KT, Pickworth KK. Pharmacotherapy 2014. 34(8):882.

Sequential Nephron Blockade in Literature: Chlorothiazide versus metolazone

- Retrospective cohort study at a large urban academic medical center
- IV chlorothiazide versus PO metolazone
- Net UO improved to a similar degree with both agents
- Adverse event rates similar

Shulenberg CE et al. Pharmacotherapy 2016. 36(8):852-60.

Sequential Nephron Blockade Tips

- Administer thiazide -30 min prior to loop
- Requires closer monitoring
 - Electrolytes
 - Serum creatinine
 - Hypotension

ACC/AHA HF Guidelines: Hospitalized Patients

IIA, B: If inadequate diuresis and symptom relief, it is reasonable to consider intensifying the regimen using either: higher doses of IV diuretics or adding a second diuretic (i.e. thiazide)

Yancy CW, et al. 2013 ACCF/AHA guidelines. *Circulation*. 2013;128:1810-52

Low-Dose Dopamine Adjunct Therapy

Dopamine

- Dopamine: Dose-dependent mechanism of action
 - Low dose: selective to dopamine receptors
 - Promotes renal vasodilation

Chen HH, et al. JAMA 2013;310:2533-43

Dopamine: ROSE AHF Trial

- Renal Optimization Strategies Evaluation in Acute Heart Failure
 - Low dose dopamine (2 mcg/kg/min) versus placebo N=183
 - Primary Endpoints:
 - Cumulative 72 hr urine output
 - Change in serum cystatin-C over 72 hr
 - Did not enhance decongestion or improve renal function.
 - No change in mortality or HF readmission endpoints.

Chen HH, et al. JAMA 2013;310:2533-43

ACC/AHA HF Guidelines

IIB, B: Low-dose dopamine + loop diuretic may be considered to improve diuresis and better preserve renal function and perfusion.

Yancy CW, et al. 2013 ACCF/AHA guidelines. Circulation. 2013;128:1876-92

Albumin Adjunct Therapy

Albumin

- Loop diuretic efficacy dependent on serum albumin concentrations
 - >90-95% protein bound
 - Hypoalbuminemia: volume of distribution \rightarrow diuretic concentration to kidney
- Kitsios *et al.* 2014 *Journal of Critical Care* meta-analysis
 - Urine output
 - <8 hours: statistically significant
 - 24 hours: not statistically significant
 - Effect was transient
 - Single dose albumin did not impact overall daily fluid balance
 - Overall conclusion: cumulative evidence does not support routine use

Other Approaches/Future Directions ?

- Tolvaptan
- Subcutaneous administration of furosemide
- Hypertonic saline + high dose loop diuretic
- Extracorporeal ultrafiltration

Elison DH, Felker GM. NEJM 2017;377:1964-75.

Conclusions

- Despite a variety of published literature, optimal diuretic strategies remain controversial
- Several factors contribute to diuretic resistance
 - Keep an eye out for possible interventions
 - Patient education
- Judicious monitoring required

Pharmacist: Assessment Question #1

- Which of the following is true?
 - A) Continuous infusions of loop diuretics have consistently been shown to have statistical significance over IV bolus injections in urine output and change in SCr.
 - B) Per the HF guidelines, hospitalized patients requiring increased diuresis and being started on parenteral loop diuretics should receive a dose equal to or exceeding their home oral dose.
 - C) None of the above.

Pharmacist: Assessment Question #2

- Compared to patients without significant comorbidities, CHF patients' loop diuretic half-lives are likely _____.
 - A) Prolonged
 - B) Shortened
 - C) CHF has no impact on diuretic half-lives

Pharmacist: Assessment Question #3

- Which of the following is NOT associated with increased risk for diuretic resistance?
 - A) NSAIDs
 - B) High sodium intake
 - C) Gut edema
 - D) Low sodium intake

Pharmacist: Assessment Question #4

- True or False: Concomitant albumin administration increases urine output, but the effect is transient.

Technicians: Assessment Question #1

- Which loop diuretic's absorption is most impacted by food?
 - A) Furosemide
 - B) Torsemide
 - C) Bumetanide
 - D) Loop diuretics' absorption are not impacted by food

Technicians: Assessment Question #2

- Which of the following is an approved route of administration?
 - A) Furosemide can be given subcutaneously.
 - B) Bumetanide can be given intravenously.
 - C) Both of the above.
 - D) None of the above.

Technicians: Assessment Question #3

- True or False: Metolazone may be given as an add-on therapy to furosemide in patients with diuretic resistance.

Questions?

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