PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #353
SUBCUTANEOUS DIURETICS FOR END-OF-LIFE MANAGEMENT OF HEART FAILURE
Ryan Jozwiak MD and Sean Marks MD

Background Diuretics are a mainstay of treating symptomatic volume overload in heart failure (HF), including at the end-of-life. For some patients, bowel edema from HF-related congestion can diminish the absorption and effectiveness of oral diuretics. Intravenous diuretics, however, are difficult to administer in an outpatient or hospice setting, which likely contributes to the frequent emergency department visits and hospitalizations in HF, even near the end-of-life (1). In this context, subcutaneous (SC) furosemide can be helpful. This *Fast Fact* reviews its use.

Clinical Context Although thiazide diuretics (e.g. hydrochlorothiazide, chlorthalidone, or metolazone) and potassium sparing diuretics (e.g. spironolactone) are established therapies for chronic HF, loop diuretics such as furosemide or bumetanide are the mainstay for acute or severe HF (2,3). Loop diuretics work via two mechanisms: an immediate veno-dilator effect as well as diuresis of fluid and electrolytes (2). Some HF patients enrolled in hospice develop refractory dyspnea, and swelling with resultant anxiety despite the use of opioids or benzodiazepines (4-6). SC furosemide, which is more easily administered at home than IV, has been proposed to help these patients.

Pharmacology Bumetanide has not been established as safe and/or effective subcutaneously, thus furosemide is the preferred SC diuretic. Typically, the IV furosemide formulation is given via a SC clysis line for continuous subcutaneous infusions (CSCI) or a SC butterfly needle for intermittent dosing. Hence, SC and IV costs are essentially equivalent. For patients with an indwelling IV catheter, there is little rationale to utilize SC over IV. Furosemide formulations come in 20 to 50 mL syringes with concentrations of 10 mg/ml. Current daily dose limits are based on available commercial syringes and are approximately 200-300 mg daily. This may change as the market for SC medications change (7).

- Onset of diuresis is 1-1.5 hours for oral; 30 minutes for SC; 5 minutes for IV furosemide. Therefore, if there is minimal urine output 1-2 hours after oral administration of furosemide, it is reasonable to consider a dose of parenteral furosemide in the setting of symptomatic dyspnea from HF (8).
- Diuretic effect is 6-8 hours for oral; 4 hours for SC; 2 hours for IV furosemide (9).
- For intermittent SC dosing, many experts recommend starting with an equivalent oral dose. For CSCI dosing, calculate the initial hourly dose from the previous daily oral dose (10, 11). E.g., someone receiving 100 mg/day of oral furosemide should receive 100 mg SC in 24 hours or 4 mg/hr CSCI.

Outcomes A human, pre-clinical, placebo-controlled trial demonstrated that furosemide has diuretic activity when administered SC (9). The clinical evidence for SC furosemide otherwise is in a handful of case reports and series. In a series of 43 consecutive end-stage HF patients prescribed CSCI by palliative care or hospice clinicians, CSCI was associated with a median weight loss of 5.6 kg and most patients avoided hospital admission and terminal breathlessness (10). A case series of HF patients who received intermittent SC furosemide demonstrated a prompt resolution of weight gain, breathlessness, and peripheral edema (4).

Side Effects & Safety Diuretics can cause intravascular volume depletion and kidney injury. Furosemide promotes diuresis of sodium, potassium, magnesium, and chloride which can lead to significant electrolyte abnormalities and subsequent risk for cardiac arrhythmia (7). Furosemide infusions have been associated with ototoxicity when used at doses >1600 mg daily or when used concurrently with a medication associated with ototoxicity (e.g. vancomycin) (7,12). Self-resolving dermatologic site reactions involving stinging/burning at the site of injection may occur in up to 23% receiving CSCI (9).

Controversies Clinicians should be cognizant of several unresolved clinical questions regarding the appropriate use of SC furosemide (11).

- In general, the data supporting the efficacy of SC furosemide is less robust than other SC palliative-based medications, e.g. SC use of opioids (11).
- Clinical debate remains regarding the need for serum monitoring of renal function and electrolyte abnormalities for dying HF patients receiving SC furosemide to prevent sentinel iatrogenic events

such as renal failure or cardiac arrhythmias. When prognosis is anticipated to be less than a month and goals of care are comfort, the rationale for serum lab monitoring may be less compelling.

- For patients who can still safely swallow oral medications, adjuvant oral diuretics such as chlorthalidone and metolazone may augment the effectiveness of SC furosemide (5,13).
- While empiric oral potassium supplementation has been associated with prolonged survival in those initiating furosemide use (14), there is no current literature supporting or arguing against the use of oral potassium in standard end-of-life diuretic use and supplementation may depend on goals of care.
- It remains unclear whether the optimal approach to utilizing SC is as a rescue therapy when clear signs of acute HF are apparent – e.g. breathlessness, peripheral edema – versus a preventative approach wherein intermittent SC furosemide doses are given in response to weight gain.

Conclusion In the setting of end-of-life HF management, there appears to be a role for the use of SC furosemide when oral treatment fails. While further research is needed, small clinical investigations have demonstrated effective diuresis and prevention of hospital admissions and hospice de-enrollment without significant adverse effects from SC furosemide.

References

1. Felker GM, O'Connor CM, Braunwald E. Loop diuretics in acute decompensated heart failure: Necessary? Evil? A necessary evil? *Circ Heart Fail.* 2009; 2:56-62.
2. McMurray JJV, Adamopoulos S, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *Eu J Heart Failure.* 2012; 14:803-69.
3. Hunt SA, Baker DW, et al. ACC/AHA Guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. *Circulation.* 2001; 104:2996-3007.
4. Farless, LB, et al. Intermittent subcutaneous furosemide: parenteral diuretic rescue for hospice patients with congestive heart failure resistant to oral diuretic. *Am J Hosp Palliative Medicine. 2013;* 30(8): 791-2.
5. Gadoud A, Jenkins SM, Hogg KJ. Palliative care for people with heart failure: summary of current evidence and future direction. *Palliative Med. 2018;* 27(9): 822-8.
6. Lum HD, et al. Availability of heart failure medications in hospice care. *Am J Hosp Pall Med. 2016;* 33(10) 924-8.
7. Carone L, et al . Furosemide. *J Pain Symptom Management. 2016;* 52(1)):144-150.
8. Oh SW, Han SY. Loop diuretics in clinical practice. *Electrolytes & Blood Pressure*. 2015; 13(1):17-21.
9. Verma AA. Diuretic effects of subcutaneous furosemide in human volunteers: a randomized pilot study. *Pharmacotherapy.* 2004; 38:544-9.
10. Zacharias H, et al. Is there a role for subcutaneous furosemide in the community and hospice management of end-stage heart failure? *Palliative Med. 2011;* 25(6):658-63.
11. Beattie JM, Johnson MJ. Subcutaneous furosemide in advanced heart failure: has clinical practice run ahead of the evidence base? *BMJ Supportive & Palliative Care*. 2012; 2:5-6.
12. Schwartz GH, et al. Ototoxicity induced by furosemide. *New Engl J Med.* 1970; 282(25):1413-14.
13. Cheng HWB, Sham MK, et al. Combination therapy with low-dose metolazone and furosemide: a "needleless" approach in managing refractory fluid in elderly renal failure patients under palliative care. *Intl Nephrol Urol.* 2014; 46(9):1809-13.
14. Leonard CE, et al. Empiric potassium supplementation and increased survival in users of loop diuretics. *PloS One*. 2014; 9(7):e102279.

Authors' Affiliation: Medical College of Wisconsin, Milwaukee, WI.

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