Efficacy of Subcutaneous Versus Intravenous Administration of Furosemide in Patients With Worsening Heart Failure

The Devil Is in the Details

We are in the midst of a heart failure (HF) epidemic, with major clinical and economic consequences for health care delivery (1), with symptomatic congestion in acute decompensated HF (ADHF) being a major driving factor for hospitalizations. To this end, the proof-of-concept study by Gilotra et al. (2) comparing the efficacy of a single, fixed-dose subcutaneous (SC) infusion of furosemide versus a bolus of a clinician-determined dose of intravenous (IV) furosemide in patients with ADHF, attempts a novel approach toward achieving reliable and cost-effective decongestion. Decompensated HF is not a 48-h illness amenable to a quick fix with IV therapy (3); thus, a novel opportunity to break the vicious cycle of congestion preceding hospitalization rests on the details of diuretic kinetics in this backdrop. The wide variation in bioavailability of oral furosemide in HF is well established and limits effective diuresis in ADHF (4). Although the pharmacokinetics of SC furosemide administration have been studied in healthy volunteers and patients with stable HF as outlined by Gilotra et al. (2), the kinetics of SC furosemide in overtly congested patients with ADHF may be different and need to be defined. To understand loop diuretic pharmacokinetics with SC administration, measurement of urinary furosemide concentrations is key in establishing the patterns of loop diuretic delivery in the urine, both in steady-state HF and ADHF (5). Additionally, mapping out SC furosemide pharmacokinetics in ADHF along with a noninvasive method of quantifying congestion, such as bio-impedance plethysmography, may be useful in understanding the degree of plasma refill occurring in response to this form of therapy. From a clinical perspective, the higher degree of natriuresis with SC furosemide infusion is encouraging, yet the rates of 30-d hospitalization for HF in this analysis were still high despite outpatient rescue IV diuretic therapy (52% in the SC group vs. 42% in the IV group, $p = 0.55$). This may be a consequence of the phenomenon of “diuretic braking” with both SC and IV administration of a short-acting loop diuretic such as furosemide, and raises the question as to whether subcutaneous use of a long-acting drug such as torsemide might be more effective and resource friendly. We believe that factoring these aspects into future studies exploring efficacy of SC loop diuretic therapies will help determine the optimal drug choice and method of delivery, thus potentially reducing the morbidity and mortality associated with HF.

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We thank Drs. Rangaswami and McCullough for their interest in our work (1) and the use of subcutaneous furosemide in patients with heart failure. Decompensated heart failure is indeed more than simply an acute event, and we agree with the authors that an understanding of diuretic kinetics throughout the continuum of heart failure (from stable state to subtle congestion to overt decompensation) is important.

The pharmacokinetics of subcutaneous furosemide have been described in both normal healthy volunteers (2) and in patients with chronic New York Heart Association functional class II heart failure subjects (3). Although it would be of interest to further study the kinetics in overtly congested patients as Drs. Rangaswami and McCullough recommend, we find it compelling that the administration of 1 dose of subcutaneous furosemide resulted in significant diuresis in such congested patients in our clinic who carried a high risk of hospitalization. This experience alone justifies consideration of this novel method of diuresis to avoid the costs and inconvenience of intravenous therapy via infusion clinics or hospitals. The letter writers also suggest study of subcutaneously delivered torsemide. Although we agree to the appeal of advantages seen with torsemide when comparing oral formulations (4), we found that subcutaneous furosemide, with its more consistent drug delivery (over 5 h) and better bioavailability, already resulted in a prolonged hourly urine output rate compared with intravenous furosemide. It is possible that a subcutaneous formulation of torsemide would produce such an extended prolonged effect that it may be a hindrance to patient quality of life. Further evaluation of subcutaneous furosemide is needed to assess its usefulness in the longer term (i.e., multiple consecutive doses) treatment of congestion. We find of interest the methods that the letter writers suggest, such as urinary furosemide measurements and correlation with noninvasive hemodynamic monitoring, and these may help in the future to guide dosing strategies. Last, we found a high rate of 30-day hospitalization after diuretic therapy; however, we believe this finding to be due to selection bias of high-risk patients as well as only 1-time dosing of the subcutaneous diuretic. Further study of the ability to prevent hospitalizations for heart failure via a multiple dose strategy and the use of a correlate to congestion to guide dosing is warranted.

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REFERENCES

Mechanisms of Discrepancy Between Pulmonary Artery Wedge Pressure and Left Ventricular End-Diastolic Pressure in Heart Failure With Preserved Ejection Fraction

We read with great interest the article by Mascherauer et al. (1), in which the relationship between mean pulmonary artery wedge pressure (PAWP) and left ventricular end-diastolic pressure (LVEDP) was