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EDITORIAL COMMENT

Innovation in Diuretic Therapy

The Missing Ingredient for Treating Worsening Heart Failure Outside the Hospital?*

Stephen J. Greene, MD,[a,b] G. Michael Felker, MD, MHS[a,b]

"Acute" or worsening heart failure (HF) has traditionally been synonymous with an episode of hospital-based care (1). Acute HF has also been hypothesized to be a distinct biological entity, a concept supported by biomarkers showing end-organ injury and outcomes data showing higher post-discharge mortality rates (2–4). However, with accumulating research, reconciling how a location of care (i.e., the hospital) could be consistently linked to a biological process (i.e., worsening heart failure [WHF]) has proven problematic (5). A generation of randomized controlled trials using short-term intravenous (IV) therapies given soon after presentation to the hospital has failed to improve long-term outcomes (6). Biomarker evidence of new end-organ injury (e.g., elevated troponin level) has been shown to be nonspecific to the hospitalized period (7). Perhaps most provocative, recent outcome data suggest that patients with WHF carry a similarly poor prognosis irrespective of whether they are hospitalized (8,9).

With data increasingly challenging the biological relevance of the hospital in WHF, hospitalization may be more simply viewed as a treatment strategy and health care resource rather than a biological event. In that respect, as clinicians, researchers, and health systems work to decrease the burden of HF hospitalizations, key questions must be increasingly considered: What makes the hospital care strategy so special? What are the specific unique features hospitalization brings to WHF care? Answers to these questions are fundamental to efforts toward offering comparable care in the outpatient setting.

Although hospitalization is undoubtedly necessary for many patients with WHF (e.g., cardiogenic shock, unstable arrhythmia), United States registry data suggest that >90% of patients receive IV diuretic agents, with most receiving no other IV therapy (10). Indeed, the most obviously "special" characteristic of the hospital may be that it offers the option to receive IV loop diuretic therapy, which is known to be more effective at managing congestion than escalating doses of oral diuretic agents (11). In many circumstances, decisions for hospital-based care may be driven more by the lack of an effective and readily accessible outpatient treatment option than by overt safety concerns. Despite the continued ubiquitous use of IV diuretic agents for episodes of WHF, there has been little change in IV diuretic therapy since furosemide's initial approval in 1966. In a world of rapid technological innovation, is there room to improve on IV furosemide?

In this context, development of subcutaneous (SC) furosemide has garnered increasing optimism as a safe and effective outpatient alternative to the traditional hospital-based IV diuretic strategy. In this issue of *JACC: Basic to Translational Science*, Sica et al. (12) present primary data from 2 small experiences testing biphasic delivery of a novel buffered SC

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From the [a]Duke Clinical Research Institute, Durham, North Carolina; and the [b]Division of Cardiology, Duke University Medical Center, Durham, North Carolina. Dr. Greene is supported by National Institutes of Health grant 5T32HL069749-14 and a Heart Failure Society of America/Emergency Medicine Foundation Acute Heart Failure Young Investigator Award funded by Novartis. Dr. Felker has received research funding from Otsuka, Novartis, Roche Diagnostics, Amgen, Merck, the American Heart Association, and the National Heart, Lung, and Blood Institute; and served as a consultant for Novartis, Roche Diagnostics, Amgen, Trevena, Cytokinetics, Madeleine, MyoKardia, Bristol-Myers Squibb, Stealth Biotherapeutics, and GlaxoSmithKline.

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furosemide formulation among patients with chronic HF. The first study randomized 10 patients in a first-in-human, proof-of-concept, crossover study designed to characterize the pharmacokinetic profile of the SC formulation. Following SC initiation, therapeutic plasma levels were reached within 30 min and were maintained in a narrow therapeutic range

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for the duration of administration. In contrast (and as consistent with prior data), plasma levels following oral furosemide dosing were highly variable, with intersubject variation between highest and lowest levels 70-fold different at 30 min and 10-fold different at 60 min, respectively (11). Compared with SC, oral furosemide resulted in a shorter duration at therapeutic plasma levels and less urine output. The second crossover study randomized 16 patients and aimed to define the bioavailability of SC furosemide versus IV. As compared with IV, peak plasma concentrations of SC were lower (geometric mean 1,990 ng/ml vs. 8,270 ng/ml), and time to peak was longer (median 4 h vs. 125 min), but therapeutic plasma levels were maintained longer with SC such that areas under plasma concentration curves were nearly identical, and absolute bioavailability was complete (>99%). Pharmacodynamic properties of SC and IV also appeared nearly identical, with very similar degrees of diuresis and natriuresis with either formulation. Safety and tolerability data across the 2 studies were reassuring, with minimal evidence of erythema and swelling at the site of SC injection.

Sica et al. (12) are to be congratulated for providing critical data defining the pharmacokinetic and pharmacodynamic profiles of this novel SC agent. Nonetheless, some limitations of this work should be acknowledged. First, the characteristics of the study patients must be carefully considered when generalizing these results. Specifically, patients were clinically stable with mild symptoms, and recent HF hospitalization was an exclusion. Similarly, the combination of a low maintenance diuretic dosage, relatively preserved baseline renal function, and relatively robust baseline blood pressure suggests absence of significant diuretic resistance in these cohorts. Second, study patients tended to have relatively mild elevations in body mass index, and patients with significant obesity were excluded. The feasibility and efficacy of SC delivery must be confirmed in patients with both significant obesity and cardiac cachexia. Third, although safety data were favorable, future studies must clarify the safety and tolerability of repeated long-term SC administration. Fourth, future studies are needed to prove the feasibility of an infusion pump apparatus suitable for home use. Not only must a pump prove its durability over repeated injections, but it must also be sufficiently simple to allow patients successful operation in the home and reliable administration of medication. Fifth, although these preliminary data for diuresis and natriuresis with SC therapy are encouraging, larger studies are needed to validate effects on decongestion and explore implications on subsequent risks of hospitalization and other clinical events.

Although some patients with WHF experience rapid clinical deterioration (e.g., “flash” pulmonary edema), most have gradually worsening congestion over a prolonged period (i.e., days to weeks), thus offering a potential window of time when outpatient providers are tasked with modifying therapy in hopes of restoring baseline status (13,14). Unfortunately, even if this window is recognized, the lack of effective and reliable outpatient therapy directly contributes to an enormous number of HF hospitalizations. For instance, furosemide is the most commonly used loop diuretic agent, and oral doses are frequently escalated in the presence of worsening symptoms (15). The inconsistent bioavailability of oral furosemide highlighted in the current study reaffirms that up-titration may be a flawed (or futile) strategy for many patients when dependable diuretic effects are required and the need for hospitalization hangs in the balance. In contrast, although study of SC furosemide remains at an early stage, the possibility of delivering an “IV equivalent” diuretic agent in the home could be transformative.

The findings from Sica et al. (12) are complementary to those of another recent report using the same buffered SC agent and biphasic delivery. In that single-center study by Gilotra et al. (16), 41 outpatients presenting with WHF were randomized to a single dose of SC versus IV furosemide. Despite a higher mean dose in the IV group (mean 123 mg), the 80-mg fixed SC dose performed well, resulting in similar urine output and weight loss and greater natriuresis (16). No instances of worsening renal function, severe electrolyte disturbance, or immediate or delayed skin irritation were seen in either arm of the study (16). Although all studies are small, the combined findings of Sica et al. (12) and Gilotra et al. (16) support the remarkable potential of SC furosemide to serve as a safe and effective IV substitute. As such, the larger SUBQ-HF (Subcutaneous Furosemide in Acute Decompensated Heart Failure) randomized trial (NCT03170219) is currently under way and designed to test this same buffered SC formulation,

in conjunction with a novel "patch pump" designed for home delivery, among patients with WHF. The trial will evaluate whether such an approach can shorten existing HF hospitalizations or avoid HF hospitalization altogether in selected patients. Specifically, the primary objective is to determine whether a strategy using SC furosemide treatment can improve the number of days alive and out of the hospital at 30 days, as compared with usual care. The relevance of this study endpoint for the hospitalized HF population should be emphasized; whereas expedited discharge obviously allows for more days out of the hospital "up front," absence of a downstream "cost" in excess rehospitalization days would signal significant patient-centered and economic benefits. Although results of the SUBQ-HF trial remain to be determined, the combined pharmacological and decongestion data from these smaller studies provide compelling plausibility for SC furosemide meeting the mark (12,16).

In summary, the contemporary armamentarium for the outpatient treatment of WHF remains limited and ill-equipped to handle the scope of the problem. As the public health and economic burdens of WHF continue to grow, it is imperative that the medical community develop safe and effective means of treating worsening congestion outside the hospital. Given the lack of evidence-based treatment strategies and the urgent unmet need, any therapeutic advancement in this space has the potential to fundamentally change HF care delivery. Innovation in diuretic therapy is clearly long overdue and may be the key missing ingredient for treating worsening HF outside the hospital.

ADDRESS FOR CORRESPONDENCE: Dr. G. Michael Felker, Duke Clinical Research Institute and Division of Cardiology, Duke University Medical Center, Box 3850, Durham, North Carolina 27710. E-mail: michael.felker@duke.edu.

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