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CLINICAL RESEARCH

Subcutaneous Furosemide in Heart Failure

Pharmacokinetic Characteristics of a Newly Buffered Solution

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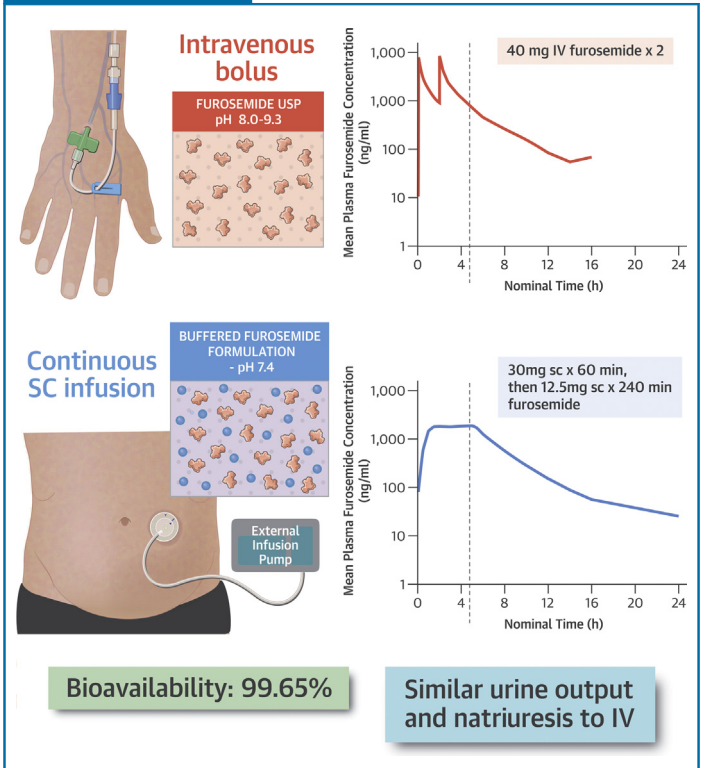
VISUAL ABSTRACT



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HIGHLIGHTS

- **Parenteral diuretics form the cornerstone of treatment of fluid overload in heart failure. The alkaline pH of furosemide USP precludes SC administration.**
- **A novel buffered formulation of furosemide (pH 7.4) was developed for SC infusion using a wearable patch pump.**
- **A 5-h biphasic SC infusion (30 mg in hour 1 followed by 12.5 mg/h for 4 h) of the novel formulation was tested in 2 clinical studies.**
- **Following SC administration, therapeutic levels of furosemide were reached within 30 min and maintained for up to 6 h. This resulted in complete bioavailability and equivalent diuresis when compared with 80 mg of intravenous furosemide.**
- **A novel strategy using SC administration of buffered furosemide is introduced for outpatient use, including self-administration at home. This may help to reduce the patient and economic burden of heart failure.**

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All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Basic to Translational Science* author instructions page.

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ABBREVIATIONS AND ACRONYMS

ANOVA = analysis of variance

AUC = area under the curve

AUC_∞ = plasma concentration to infinity

AUC_{last} = last measurable plasma concentration

CI = confidence interval

C_{max} = peak plasma concentration

HF = heart failure

IV = intravenous

LSM = least squares mean

SC = subcutaneous

$t_{½}$ = terminal phase elimination half-life

SUMMARY

Parenteral diuretics form the cornerstone of decongestion in heart failure. However, parenteral therapy routinely requires emergency room or inpatient care. A novel buffered furosemide formulation with neutral pH was developed to offer "hospital-strength" diuresis for outpatient use, including self-administration at home. Subcutaneous infusion using a biphasic delivery profile resulted in complete bioavailability (99.65%) and equivalent diuresis when compared with intravenous administration. Subcutaneous administration of buffered furosemide was well tolerated with no evidence of any drug-induced skin reactions. Subcutaneous infusion of buffered furosemide in the outpatient setting or home may help to reduce the burden of heart failure. (J Am Coll Cardiol Basic Trans Science 2018;■:■-■)

Heart failure (HF) is a chronic disease associated with considerable morbidity, mortality, and health care expenditures. According to the American College of Cardiology/American Heart Association, 5.7 million Americans were diagnosed with HF in 2012 (1), and this number is expected to increase 46% by 2030 (2). Patients with HF make up 11% of the Medicare population and are responsible for 34% of the total annual Medicare expenditures. Expenditures related to HF are expected to increase 127% by 2030 alone (2). It is noteworthy that the HF population constitutes 41.5%, 55.3%, and 49.5% of total Medicare inpatient admissions, readmissions, and admissions to skilled nursing facilities, respectively (3).

Although HF management has improved over the years, many patients experience repeated hospital admissions for fluid overload marked by worsening of congestive symptoms. Intravenous (IV) furosemide is the foundation of treatment for patients with decompensated HF (4). However, IV therapy may only be administered by a certified health care professional, typically done in emergency rooms or in a hospital setting, which limits more timely access and inherently drives up the cost of treatment.

There is a large gap between chronic oral diuretic therapy given at home versus IV diuretics administered in the naturally more expensive hospital setting. A potential intermediate step would be that of access to an "IV-like furosemide" for use outside the hospital. This would enable development of a new care model with access to a more predictable and/or intensive diuresis in the outpatient setting, thereby preventing (re-)hospitalizations and reducing length of hospital stay.

Several small studies have reported that furosemide administration via the subcutaneous (SC) route can result in significant diuresis in both healthy volunteers (5), as well as patients with advanced stage HF (6-9). However, furosemide is insoluble at physiological pH, and commercially available furosemide injectable products (furosemide injection USP or BP) have a pH of approximately 9.0. Alkaline products can cause significant irritation and discomfort, which currently precludes SC administration of available furosemide solutions.

A novel proprietary furosemide formulation was developed with a pH of 7.4 to minimize the risk of tissue irritation and discomfort. The aim of this report is to present the first pharmacokinetic and pharmacodynamic results of this novel furosemide formulation administered via the SC route using a biphasic delivery profile.

METHODS

SUBJECTS AND STUDY DESIGN. This article reports on 2 separate studies designed to: 1) characterize the pharmacokinetic profile of a novel formulation of furosemide administered SC and measure the resulting diuresis and natriuresis; and 2) estimate the bioavailability of SC furosemide compared with an equivalent dose of oral or IV furosemide in subjects with chronic stable HF.

In the first study, a first-in-man, proof-of-concept study (FUROPHARM-HF [Furosemide Pharmacodynamics and Pharmacokinetics After Subcutaneous or Oral Administration]; NCT02350725), eligible subjects (n = 10) were randomized (1:1) to receive 80 mg of oral furosemide (Lasix, Sanofi Belgium, Diegem, Belgium) or 80 mg (8 mg/ml in 10 ml) of a novel furosemide buffered solution administered SC with an external infusion pump using a biphasic pattern (30 mg over the first 60 min followed by 12.5 mg/h for 4 h). After a 14-day fluid re-equilibration washout, all subjects received the alternate treatment. Plasma furosemide levels were evaluated over 8 h.