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Subcutaneous furosemide for the treatment of heart failure: a state-of-the art review

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Abstract
The prevalence of heart failure (HF) is on the rise. By 2030, over eight million Americans (46% increase from current prevalence) will have heart failure. In the USA, approximately 30 billion dollars is spent annually on heart failure and this number will likely double in 2030. Thus, HF represents a significant economic burden. Acute decompensated heart failure (ADHF) is a clinical spectrum, which refers to increasing symptoms and signs of heart failure prompting an emergency room visit or hospitalization. In ADHF, inpatient administration of intravenous diuretic is the standard of care due to the variability in the absorption of oral diuretics. Within 30 days, 25–30% of these patients are readmitted with recurrent ADHF. Recent efforts have focused in reducing HF readmission, and thereby decreasing costs; hence, innovative outpatient treatment options have emerged. Subcutaneous furosemide use will potentially overcome the need to place intravenous lines, reduce associated expenses, and enable management of ADHF at home. This review presents data on the pharmacodynamics and pharmacokinetics of subcutaneous furosemide, scientific evidence on the use of this therapy in the palliative and hospice population, and its experimental use as an outpatient therapy and/or as a bridge from inpatient to home.

Keywords Subcutaneous · Furosemide · Heart failure · At-home treatment · Palliative care

Introduction

The prevalence of heart failure (HF) is estimated around 6.5 million people and is expected to increase to eight million by the year 2030. HF is responsible for one million hospitalizations annually. Each year, there are 650,000 new cases [1]. In the USA, approximately 30 billion dollars is spent annually on heart failure and this number will likely double in 2030. This represents a significant economic burden on the health care system. Acute decompensated heart failure (ADHF) is a clinical spectrum which refers to increasing symptoms and signs of heart failure prompting an emergency room visit or hospitalization. Readmission rates at 30 days and 6 months are estimated to be 25% and 50% respectively. Since October 2012, the Hospital Readmissions Reduction Program (HRRP) has mandated public reporting of readmission rates which resulted in financial penalties for hospitals with higher readmission rates. Among Medicare beneficiaries, heart failure is the leading cause of readmissions and a major contributor to penalties [2].

When patients present with signs of ADHF, the bioavailability of oral medications is unpredictable (20–90% for furosemide) [3, 4]; hence, parenteral diuretic therapy is the mainstay of treatment. Intravenous therapy requires the placement of intravenous lines by a health care practitioner with associated maintenance expense and inherent risk for infections and thrombosis. A novel approach to reduce heart failure readmissions is the use of subcutaneous (SC) furosemide for ADHF.

The emergence of subcutaneous furosemide

The mechanism of action of furosemide is through the inhibition of sodium and chloride reabsorption in the proximal and distal tubules as well as the loop of Henle. Furosemide has been available since the 1960s and is commonly administered via oral, intravenous (IV), or intramuscular formulations. Subcutaneous furosemide offers the possibility of avoiding IV line placement and/or inpatient admission for parenteral diuresis. Conventional furosemide is alkaline (pH 8.5 to 9),

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causing irritation to the skin. To combat this side effect, a proprietary isotonic furosemide (pH 7.0 to 7.8) for subcutaneous use has been developed. Ten milliliters of the buffered solution (Cook Pharmica, Bloomington, IN, USA) which contains 8 mg/mL of furosemide is delivered subcutaneously.

SC Pharmaceuticals Inc., (Burlington, MA) has developed a preprogrammed infusor (FUROSCIX Infusor) for the delivery of SC furosemide. FUROSCIX Infusor is a two-component design, which combines a reusable activator and a cost-effective single-use cartridge (Fig. 1). The cartridge contains a micro-piston pump, size 27 gauge needle, drug reservoir, and adhesive backing. A total of 80 mg of furosemide is delivered subcutaneously over 5 h (30 mg in hour 1, then 12.5 mg/h over the next 4 h).

Pharmacokinetic and pharmacodynamics of subcutaneous furosemide

SC furosemide was initially tested in seven healthy adult mongrel dogs. In a prospective randomized crossover study, SC administration was associated with comparable urine output as oral or intravenous administration (calculated total dose of 2 mg/kg). The peak urine output at 1 h was higher in the IV furosemide group (260 mL/h) compared to SC furosemide (242 mL/h), and the urine output returned to baseline later with the SC furosemide (4 h vs 2 h) than IV furosemide. Continuous IV infusion maintained a stable urine output throughout the 8-h study [5].

The utility of SC furosemide has been shown in a variety of clinical settings (Table 1). The bioavailability of the SC furosemide was demonstrated in twelve healthy volunteers [6]. These volunteers were randomized to SC furosemide or normal saline. The volunteers were injected with 20 mg of SC furosemide (2 mL) or an equivalent volume of normal saline on days 3 and 5. The efficacy of the SC diuretic was confirmed by a statistically significant increase in the total urine output (SC furosemide, 1430 vs normal saline, 459 mL), natriuresis (SC furosemide, 134 meq/L vs normal saline, 29 meq/L), and a faster time to initial void (SC furosemide, 30 min vs normal saline, 221 min) [6].

Recently, Sica et al. [9] investigated the bioavailability of SC furosemide in comparison with an equivalent oral furosemide dose in the FUROPHARM-HF (Furosemide Pharmacodynamics and Pharmacokinetics after Subcutaneous or Oral Administration) trial. Ten eligible New York Heart Association (NYHA) functional class II patients were randomized to receive oral furosemide (80 mg) or SC furosemide (30-mg bolus over 1 h, followed by 12.5 mg/h for 4 h using a biphasic external infusion pump). Crossover to the alternate treatment occurred after 14 days of fluid re-equilibration. Therapeutic plasma furosemide was achieved in 30 min (range 617 to 1548 ng/mL) and maintained for 5 h for SC furosemide. A wide variation of oral furosemide (range, 43 to 2989 ng/mL) was present at 30 min. Total urine output was 1550 mL after oral administration compared to 1833 mL after SC delivery [9].

Similarly, 16 patients with chronic congestive heart failure were randomized (1:1) to receive 80 mg of furosemide administered IV (40 mg over 2 min then another 40 mg, 2 h later) or 80 mg SC with the an external infusion pump using the same protocol described above [9]. A 7-day washout re-equilibration was achieved prior to the crossover to the alternate treatment.

Compared to IV furosemide (8270 ng/mL), SC furosemide resulted in lower mean peak plasma concentrations (1990 ng/mL). However, urine output after IV furosemide and SC furosemide was comparable at 8 h (2,718 ± 654 mL and 2663 ± 1021 mL respectively) and at 24 h (3,672 ± 740 mL and 3614 ± 1045 mL respectively) [9]. SC furosemide achieved a therapeutic level for 6 h and quantifiable levels for 24 h and bioavailability was found to be 99.6%.

Fig. 1 The sc2Wear™ Furosemide Infusor. Comprised of two components: **a** the single-use disposable cartridge, which serves as a drug reservoir and has the size 27-gauge retractable needle which delivers the furosemide; **b** the reusable activator controlled with a rechargeable battery which drives the pump. The base plate of the disposable cartridge with adhesive backing is attached to the abdomen for drug elution

Table 1 Studies involving the use of SC furosemide

Author (year)	Type of study	Population	Size (*n*)	Dose	Duration (days)	Results	Site reactions
Verma et al. (2004) [6]	Single-center, randomized, double-blind crossover pilot study	Healthy volunteers	12	20 mg (2 mL) on days 3 and 5	5	SC furosemide vs placebo UO, 1430 ± 504 mL vs 459 ± 279 mL Volume of initial void, 432 ± 178 mL vs 218 ± 130 mL Urine sodium, 134 ± 31 mL vs 29 ± 17 mL	11/12 patients with stinging and burning sensation at injection site
Zacharias et al. 2011 [12]	Retrospective	Hospice	32 advanced congestive heart failure patients	40–250 mg daily SC furosemide, infusion	2–48	15 dying patients—symptom resolution 26/28 (93%) avoided hospital admission	NA
Galindo-Ocana et al. 2013 [7]	Retrospective	Advanced heart failure patients	44 (17 received SC furosemide)	160 mg/day SC infusion (range, 99–250 mg/day)	8–16	Median survival, 26.51 days (10.8–253.51 days)	NA
Austin et al. (2013) [8]	Non-randomized	Outpatient end-stage HF	25 (14 IV, 11 SC)	Oral equivalent dose given	< 7 ($n = 8$) > ($n = 3$)	IV treatment resulted in significant reduction (1.6 cm) of mean calf circumference	NA
Gilotra et al. (2018) [17]	Randomized controlled (phase II trial)	Outpatient NYHA II–IV	40 (IV 19, SC 21)	SC furosemide 80 mg over 5 h (fixed dose)	–	IV vs SC furosemide 6 h UO (1636 mL vs 1514 mL; $p = 0.7$) Weight loss (− 1.5 ± 1.1 kg vs − 1.5 ± 1.2 kg, p—0.95)	0
Sica et al. (2018) [9] FUROPHARM-HF	Randomized prospective trial (crossover)	NYHA II	10	80 mg of furosemide oral and SC (given over 5 h)	8 h	Therapeutic plasma furosemide was achieved in 30 min (range 617 to 1548 ng/mL) for SC furosemide and maintained for 5 h. There was a wide variation of oral furosemide (range of 43 to 2989 ng/mL) at 30 min	1 patient with transient erythema, 8 with minimal erythema, 6 with minimal swelling
Sica et al. (2018) [9] PK/PD Pivotal study	Randomized controlled trial (crossover)	Stable heart failure patients	16	80 mg SC furosemide over 5 h	1	SC furosemide bioavailability was 99.6% and a therapeutic level of 6 h maintained IV vs SC furosemide Urine output at 8 h (2,718 ± 654 mL vs 2663 ± 1021 mL) Urine output at 24 h (3,672 ± 740 mL vs 3614 ± 1045 mL)	No evidence of any drug-induced skin reactions

Clinical application to hospice and palliative care patients

Symptom relief is the cornerstone of a successful palliative care and hospice practice. End-stage heart failure patients arrive at the end of life with significant symptom burden of shortness of breath, fatigue, and edema, which is often difficult to manage. Continuous subcutaneous infusions are commonly used in palliative care to relieve symptoms. However, most of this experience is with opioids and benzodiazepines, with some case reports of SC furosemide usage in palliative care and hospice populations. Over three decades ago, Goenaga et al. [10] demonstrated the effectiveness of SC furosemide in a hospice cohort. Three patients were treated with continuous infusion while five were treated with intermittent boluses with doses ranging from 40 to 140 mg. The clinical utility of subcutaneous furosemide was similarly demonstrated in two end-stage heart failure patients treated palliatively. Both patients were transitioned back to an oral diuretic within days [11].

In a retrospective review of 32 advanced heart failure subjects on a palliative-cardiology service who received a continuous subcutaneous infusion, 93% (26/28) of patients avoided re-hospitalization. The 15 terminal patients (out of the 32) in this review were free of symptoms prior to death [12]. A retrospective observational study conducted between 2008 and 2012 evaluated patients treated with SC furosemide (17 patients) and IV furosemide (27 patients). Fifteen out of the 17 families treated with SC furosemide expressed satisfaction with the management of symptoms [13]. The number of hospitalizations and emergency room consults were comparable. In a recent report, the palliative use of SC furosemide was effective in a renal transplant patient with anasarca [14]. Due to difficulty in obtaining venous access, 250 mg of furosemide was given subcutaneously over 24 h with urine output of 400 mL to 1000 mL per day. Although the patient died 5 days later, his edema was significantly reduced with improvement in symptoms.

Ambulatory management with SC furosemide

As discussed earlier, IV furosemide is the standard of care in ADHF because of its consistent bioavailability. Due to patient preference and efforts to decrease healthcare costs, ambulatory management of patients in ADHF is desirable. The efficacy of IV furosemide has been demonstrated in the ambulatory setting [15]. Ambulatory management of ADHF with SC furosemide was initially shown by Zatarain-Nicola et al. [16], who treated 24 patients with SC furosemide via a continuous flow and non-electric pump attached to the abdominal or chest tissue. Patients were treated for 4–5 days for an endpoint of improved functional status or achievement of dry weight. Significant weight loss (mean of 2.09 kg, $p < 0.001$) was noted without any significant changes in serum creatinine, sodium, or potassium. Recently, forty NYHA class II–IV patients were randomized to IV furosemide (1:1 conversion of outpatient oral and IV dose to a maximum of 160 mg) or SC furosemide (30 mg within 1 h, then 12.5 mg/h for 4 h). The mean 6-h urine output (IV, 1636 mL vs SC, 1514 mL; $p = 0.7$) and weight loss (IV, -1.5 ± 1.1 kg vs SC, -1.5 ± 1.2 kg, p—0.95) were comparable between both modalities of furosemide administration [17]. SC furosemide caused a comparable diuresis to the IV furosemide despite an overall lower dose and there was lack of difference in 30-day readmission rates.

Our group is currently investigating the clinical utility of SC furosemide in patients presenting with early signs of volume overload (NCT03359161) to an outpatient cardiology clinic. Patients who qualify for the SQUEESE HF Trial (SubQ fUrosEmide EaSEs Heart Failure) will be sent home with the FUROCIX infusor to self-administer 80 mg of SC furosemide daily for three continuous days. To ensure safety, visiting nurses will make home visits to draw labs, perform clinical reassessments, and reinforce teaching on heart failure management and device usage. The study will evaluate the effectiveness of the device and assess its safety. The primary outcomes to be measured include weight loss between visits, reduction in nt-pro BNP, 30-day survival rate, 30-day hospitalization rate for heart failure or heart failure-related medical events, discontinuation of treatment due to adverse events, and proportion of patients who require an additional 4 days of at-home treatment.

The FREEDOM–HF (Furoscix Real-World Evaluation for Decreasing Hospital Admissions in Heart Failure, NCT03458325) is also evaluating the ambulatory use of SC furosemide in patients who present to the emergency room with decompensated heart failure. On presentation to the emergency room, patients will be sent home with FUROSCIX. This cohort will be compared to a propensity-matched historical inpatient cohort treated with intravenous furosemide for < 72 h. The study plans to compare the HF-attributable direct medical costs.

Inpatient management with SC furosemide

The standardized care for ADHF in the inpatient setting is to use an intravenous diuretic, transition patients to oral diuretics, and then discharge them home with outpatient follow-up. The SUBQ-HF Trial is a multicenter, phase II trial (NCT03170219) which will randomize 300 patients to standard of care (inpatient IV furosemide) or the SC furosemide. The SC furosemide cohort will be divided into two pathways: Pathway 1 (early discharge)—the patient is admitted and then undergoes SC furosemide device teaching followed by discharge within 24 h; pathway 2 (admission avoidance)—the patient will be sent home from the emergency room or clinic after device teaching. The SC furosemide arm will receive 80 mg of furosemide injection over 5 h daily or twice daily based on their diuretic requirements for 1–7 days. The primary endpoint will measure days alive and out of hospital between randomization and day

30. Secondary outcomes will include medical cost from randomization to 30 days, 30-day heart failure readmission, and patient safety as measured by adverse events.

Challenges of SC furosemide

Although there are reported cases of SC furosemide in Europe as outlined above, its use in the USA is still considered experimental. The data so far from the clinical trials must be interpreted with caution. The economic impact of SC furosemide compared to IV furosemide is unknown. From our experience from the SQUEESE HF Trial, patients and their caregivers have not had any significant difficulty in the use of the SC infusion pump. However, this could be due to selection bias from enrolling patients or caregivers who demonstrate a good understanding of how to manage the pump from home. The use of this technology in the vulnerable heart failure cohort (geriatric, pregnant, adults with disability among others) will need to be investigated.

Patients with significant obesity and end-stage kidney disease are generally excluded so the pharmacodynamics and kinetics in such patients are unknown. Also, the variation in response of extreme anasarca and cachectic patients need to be investigated further. Conventional furosemide is irritating to the skin due to its alkalinity (pH of 8.5 to 9). The local side effects that have been reported include stinging, burning, swelling, and/or erythema at the injection site. As shown by Gilotra et al. [17] these dermatological adverse events can be eliminated with the use of a buffered solution. As patients are transitioned to home-based treatment with SC furosemide, concerns will include consideration of how to safely address electrolyte imbalances or hypotension due to fluid balance shifts.

Conclusion

Subcutaneous furosemide has emerged as a pivotal therapeutic option for acute decompensated heart failure. If validated in large-scale randomized control trials, this therapy may lead to a paradigm shift whereby ADHF patients can be managed in the outpatient setting.

Compliance with ethical standards

This article does not contain any studies with human participants performed by any of the authors.

Conflict of interest None of the authors has any conflict of interest related to the contents of this manuscript. Lana Tsao has received research grant from SC Pharmaceuticals Inc. (developers of the proprietary furosemide infusor) for an ongoing clinical trial. None of the coauthors have any disclosures to make.

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