Scientific letters

Subcutaneous Furosemide in Patients With Refractory Heart Failure

Furosemida subcutánea como tratamiento para pacientes con insuficiencia cardiaca refractaria

To the Editor,

Reports of subcutaneous (SC) furosemide used to treat heart failure (HF) are scarce and mainly involve small case series in which this administration route was used for decompensation with congestive symptoms during relatively short periods.[1–3] A recently published phase-II clinical trial[4] compared the efficacy of intravenous furosemide vs a new SC furosemide formulation for treating decompensated HF, and concluded that the new formulation is similar to the intravenous drug in terms of efficacy and safety. These results suggest that the new formulation may also be effective as long-term treatment for patients with chronic resistance to oral diuretics, who have few therapeutic options.

The main aim of this study was to determine the mid- and long-term effectiveness of HF treatment using SC furosemide infusion with elastomeric pumps, by comparing the hospitalization rates for HF during the year prior to inclusion and during follow-up. The secondary aims were to evaluate the weight reduction in patients with congestive symptoms, assess dry weight maintenance in euvolemic patients starting this therapy, and determine the safety of the intervention. Between December 2014 and March 2018, we recruited 16 consecutive patients with decompensated HF refractory to oral diuretic control and with at least 2 hospitalizations in the previous 6 months or requiring repeat intravenous administration. Severe adverse events were defined as infusion-related infections, local skin lesions leading to treatment discontinuation, and deterioration of renal function or hyperpotassemia requiring treatment. Local skin lesions not requiring specific treatment were considered mild adverse events.

Patient characteristics are shown in Table 1. In the year prior to starting SC furosemide, patients had a mean of a 3.2 ± 2.5 hospitalizations for HF, yielding a rate of 0.26 hospitalizations for decompensated HF/patient/mo of follow-up. All patients had been receiving high doses of oral furosemide (mean dose, 138.7 ± 41.1 mg/d; 9 patients [56.3%] took potassium-sparing diuretics and 7 [50.0%] thiazides). Treatment was started during a decompensation or while congestive symptoms persisted in 12 patients. Four patients started treatment while they were euvolemic, after achieving clinical stability with intravenous diuretics.

The mean duration of therapy with SC furosemide infusion was 159.6 ± 185.1 days. The initial furosemide dose was 234.2 ± 68.4 mg/d in congestive patients and 122.5 ± 15.0 mg/d in euvolemic patients. During follow-up, only 2 patients experienced a decompensation, with a predominance of signs of low cardiac output; both died during hospital admission. This implied a rate of 0.02 admissions/patient/mo of follow-up. In the remaining patients, there were no decompensations requiring intravenous diuretic administration or hospital admission.

Patients starting SC furosemide therapy with symptoms of congestion experienced weight loss of 2.6 ± 1.0 kg in the first 3 days and 0.4 ± 0.3 kg in the following days; this loss persisted at 30 days (Figure 1). Those starting SC furosemide after the congestive symptoms had been controlled showed only a slight weight loss.

In 2 patients, SC therapy could be discontinued at 39 and 77 days after initiation, with patients continuing on oral diuretics.

With regard to safety, 2 patients developed local complications (skin erosion without infection) that required treatment discontinuation, permanently in 1 patient and temporarily in the other. There were only 2 infectious complications, which resolved with antibiotics and did not require treatment withdrawal. No significant deterioration of renal function occurred, although there were some mild, transient creatinine increases.

In the group studied (patients attended in a heart failure unit with persistent decompensation attributed to ineffective oral diuretic therapy and requiring intermittent intravenous therapy), SC furosemide administration using elastomeric pumps was useful for decreasing the number of hospitalizations, improving the congestive symptoms, achieving weight reductions in congestive patients, and maintaining the dry weight in euvolemic patients. Adverse events were local and were related to lengthy periods of administration.

Although the number of patients studied is limited, we believe that these promising observations open a new line of investigation for the treatment of patients with refractory HF.

Table
Characteristics of Patients and Subcutaneous Furosemide Treatment

Patient	Age/ sex	Heart disease	LVEF	PASA > 55 mmHg	GF (mL/min)	Hospitalization for HF in the 12 previous mo	Emergency room stay for HF in the 12 previous mo	Status at the start of subcutaneous treatment	Days on treatment with subcutaneous furosemide	Initial dose*	Maintenance dose*	Initial NYHA	NYHA at 2 weeks	Reason for end of follow-up	Decompen-sations during follow-up	Vital status	Cause of death
1	91/M	Valvular	50	Yes	20	5	2	Congestive	56	250	50	IV	II	Death	0	Dead	Aspiration pneumonia
2	61/M	Ischemic	20	Yes	60	9	0	Congestive	19	350	250	IV	III	Death	0	Dead	Sudden cardiac death
3	71/M	Ischemic	25	Yes	20	0	0	Congestive	273	180	70	IV	III	Death	0	Dead	Sudden cardiac death
4	84/M	Ischemic	38	Yes	60	8	1	Congestive	177	250	180	III	II	Death	0	Dead	Respiratory sepsis
5	90/M	Ischemic	42	Yes	24	4	0	Congestive	77	250	60	III	II	Switch to oral	0	Dead	Sudden cardiac death
6	84/M	Ischemic	30	No	21	3	0	Congestive	82	215	110	III	II	Death	0	Dead	Overall deterioration
7	88/M	Ischemic	45	No	25	2	0	Congestive	658	215	110	III	II	Continuing	0	Alive	
8	68/M	Valvular	35	Yes	45	1	0	Congestive	35	360	140	IV	III	Death	1	Dead	Refractory HF
9	81/M	Ischemic	50	Yes	25	4	1	Euvolemic	114	110	110	III	II	Death	0	Dead	Renal sepsis
10	71/W	Idiopathic	20	Yes	25	3	1	Euvolemic	500	150	110	III	II	Continuing	0	Alive	
11	67/M	Ischemic	35	No	10	3	0	Congestive	124	250	200	IV	III	Death	0	Dead	Urinary sepsis
12	91/W	Valvular	55	Yes	11	0	0	Congestive	26	200	200	III	II	Local complications	1	Dead	Refractory HF
13	82/W	Idiopathic	28	Yes	35	2	1	Euvolemic	280	130	80	III	II	Continuing	0	Alive	
14	85/M	Valvular	34	Yes	24	2	0	Congestive	86	130	65	IV	II	Death	1	Dead	Refractory HF
15	55/W	Valvular	55	Yes	90	1	0	Euvolemic	15	100	65	III	III	Death	0	Dead	Sudden cardiac death
16	78/M	Idiopathic	25	Yes	63	2	0	Congestive	39	160	65	IV	II	Switch to oral	0	Alive	

GF, glomerular filtration; HF, heart failure; LVEF, left ventricular ejection fraction; M, man; NYHA, New York Heart Association functional class; PASP, pulmonary artery systolic pressure; W, woman
Two patients did not have hospital admissions, but they experienced decompensation that required intravenous furosemide administration.
* Initial and maintenance doses of subcutaneous furosemide (mg/d).

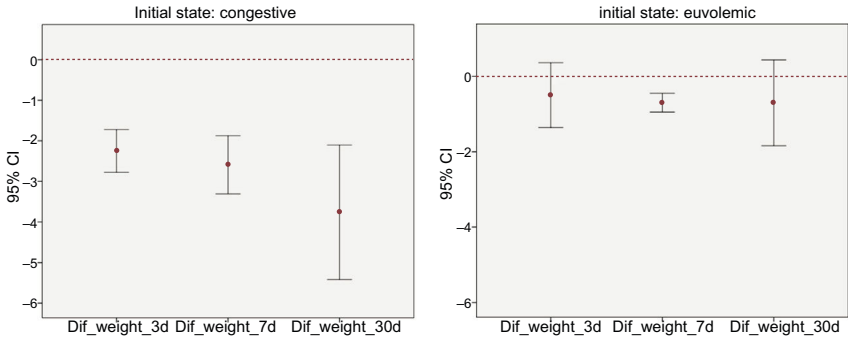

Figure. Mean weigh loss at 3 and 7 days and at 1 month after starting subcutaneous furosemide therapy in patients with congestive and euvolemic status, respectively. 95% CI, 95% confidence interval.

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Disseminated Infection Due to *Mycobacterium chimaera* After Aortic Valve Replacement

Infección por Mycobacterium chimaera *diseminada tras sustitución de válvula aórtica*

To the Editor,

A recent publication reported an international outbreak of *Mycobacterium chimaera* infection following heart surgery, through airborne transmission of the bacteria from the heater-cooler units (HCU) used during cardiopulmonary procedures.[1] Here, we describe a case of *M. chimaera* endocarditis on a prosthetic aortic valve.

A 51-year-old man was hospitalized in December 2011 for a 3-month history of abdominal pain, fever, hepatomegaly, and weight loss. Six months previously, he had undergone aortic valve replacement with a Mitroflow biologic prosthetic valve due to severe stenosis, with subsequent implantation of a DDD pacemaker to treat postoperative atrioventricular block. The initial analyses showed mild pancytopenia and abnormal liver enzyme levels (aspartate aminotransferase, 412 U/L; alanine aminotransferase, 389 U/L; alkaline phosphatase, 779 U/L; gamma-glutamyl transferase, 460 U/L; total bilirubin, 2.5 mg/dL). Transesophageal echocardiography depicted a 17 × 10-mm vegetation anchored in the noncoronary commissure of the aortic valve (Figure A). Amorphous granulomas were seen in liver and bone marrow biopsy specimens, and hematoxylin-eosin staining showed features indicative of hemophagocytosis (Figure B and C). In both specimens, *M. chimaera* was identified by polymerase chain reaction and culture, which prompted initiation of antibiotic treatment with rifampicin, ethambutol, clarithromycin, and amikacin. The patient required immunosuppressive therapy (etoposide, cyclosporine, and dexamethasone) to control the hemophagocytic syndrome (HPS), which resolved after some weeks of therapy. Two weeks later he experienced occlusion of the tibioperoneal artery due to an embolism (Figure D), in which *M. chimaera* was again identified (Figure E). In February 2012, the patient underwent Bentall-De Bono surgery to replace the bioprosthesis with a Sorin ART 21 LFA prosthesis, and the endocardial pacemaker with an ESPRIT DR epicardial device. In January 2013, the aortic tube graft with integrated valve had to be replaced with a 21-mm homograft due to dehiscence secondary to uncontrolled infection. The patient experienced an ischemic stroke in August 2013, and a new aortic vegetation was detected. In October 2015, 2 years after the last complication, the medication was withdrawn. The epicardial pacemaker generator was replaced in January 2017 because of battery depletion. The surgical wound from generator replacement showed exudation and lack of healing. Conventional cultures were negative, and finally, *M. chimaera* was identified by growth in specific media. Antibiotic treatment was reinitiated with azithromycin, rifabutin, and moxifloxacin. Positron emission tomography/computed tomography showed anomalous metabolic activity only at the pacemaker (Figure F). The absence of other metabolic foci in the examination indicated the possibility of complete cure by replacement of the infected system with another endocardial device. At the time of writing, the patient remains in treatment.

In 2015, another case of *M. chimaera* endocarditis was diagnosed in the center where the patient had undergone his first surgery. Samples were taken from the HCU (LivaNova PLC, formerly Sorin Group Deutschland GmbH) and from the hospital