Tolerability and Efficacy of High-Dose Furosemide and Small-Volume Hypertonic Saline Solution in Refractory Congestive Heart Failure

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ABSTRACT

Thirty patients aged 65–85 years, with refractory New York Heart Association (NYHA) class IV congestive heart failure (CHF) were treated with an intravenous infusion of furosemide (250–2000 mg/d) and small-volume hypertonic saline solution (150 mL of 1.4–4.6% NaCl) twice a day for 6 to12 days. A daily fluid oral intake of 1000 mL and previous cardiac therapy were maintained. Clinical signs and symptoms of CHF, such as dyspnea, edema and weakness, improved, as did severity of illness as defined by NYHA class. The infusion was well tolerated. After a 12-month follow-up, 24 patients (80%) were alive and in the NYHA class assigned on discharge from the hospital. This therapeutic combination is effective and well tolerated and should represent an innovative approach to the management of refractory CHF.

Keywords: furosemide; hypertonic saline solution; refractory congestive heart failure

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INTRODUCTION

The management of patients with advanced congestive heart failure (CHF) typically involves restriction of sodium intake and physical activity and pharmacotherapy with digoxin, diuretics, and angiotensin-converting enzyme (ACE) inhibitors.[1-4] Potent loop diuretics have long been accepted as first-line treatment of severe heart failure and significant fluid retention.[5,6]

A lack of response to furosemide is common, however, particularly in elderly patients with advanced disease. Age-related renal impairment, concomitant therapies that may affect renal function,[7,8] CHF-induced changes in gastrointestinal absorption and motility,[9] and reduced splanchnic blood flow[10,11] contribute to the unreliability of this agent.

Proposed options for countering diuretic resistance include increased doses or use of a constant infusion, a combination of different classes of diuretics, and concomitant infusion of dopamine to enhance renal blood flow and potentiate diuretic activity.[12-14]

Several studies have demonstrated the efficacy of hypertonic saline solution (HSS) in restoring the compromised central hemodynamics and peripheral organ blood flow characteristic of traumatic or septic shock.[15-17] Mechanisms of action to explain such efficacy were direct myocardial stimulation with maintenance of high cardiac output, increase of intravascular volume and subsequent peripheral arterial vasodilation, reduction in edema and sympathetic tone, and increased renal blood flow.[18-23]

In light of this information, we hypothesized that the intravenous infusion of high doses of furosemide together with small-volume HSS would be an effective treatment in patients with refractory CHF.

PATIENTS AND METHODS

Thirty hospitalized patients (20 men, 10 women), 65 to 85 years of age with refractory CHF of various etiologies were enrolled (Table 1).

By definition,[1] all patients had uncompensated heart failure (dyspnea, weakness, lower-extremity or generalized edema), were in New York Heart Association (NYHA) functional class IV, and were unresponsive to high oral doses of furosemide, ACE inhibitors, digoxin, and nitrates. Additional inclusion criteria were left ventricular ejection fraction of 35% or less, serum creatinine less than 2 mg/dL, reduced diuresis, and low natriuresis despite established treatments.

Each patient provided written consent before entering the study.

At entry, all patients underwent a complete physical examination that included a careful check for signs and symptoms of CHF, body weight (in the morning before breakfast), arterial blood pressure (mean of three measurements), and heart rate.

All these parameters and the amount of diuresis were measured daily. Each day, fasting blood samples were taken for determination of routine laboratory values, and total urine output was collected for measurement of sodium, potassium, and chloride. Laboratory tests were continued until a state of clinical compensation was achieved. Chest X-ray, electrocardiogram, and M-B mode echocardiogram were performed at baseline and on hospital discharge.

Table 1. Baseline Characteristics

Patient No.	Sex	Age, y	CHF Etiology	LVEF, %	Diuresis, mL/24 h	NaU, mEq/24 h
1	F	68	CAD + AF	35	450	45
2	F	72	CAD + AF	30	500	40
3	M	69	CAD + AF	32	350	55
4	F	85	HHD	35	450	65
5	M	84	CAD	27	350	45
6	M	82	HHD	35	500	60
7	M	60	CAD	35	850	85
8	F	84	HHD	35	500	50
9	F	71	CAD	30	400	60
10	F	84	CAD + AF	35	350	55
11	M	76	CAD	35	400	40
12	M	65	CAD	27	300	30
13	M	78	HHD	24	350	35
14	F	73	DCM	26	250	25
15	F	90	DCM	23	300	30
16	M	70	CAD	22	300	60
17	F	67	DCM	35	400	40
18	F	62	DCM	35	350	55
19	M	62	CAD	35	750	75
20	M	85	CAD	35	400	30
21	M	79	DCM	24	300	65
22	M	68	DCM	35	300	50
23	M	70	HHD	27	250	25
24	M	72	DCM	20	200	40
25	M	80	CAD	25	300	40
26	M	69	HHD	35	300	45
27	M	74	CAD	35	250	55
28	M	71	DCM	35	750	75
29	M	73	DCM	26	300	45
30	M	64	CAD	21	250	55
Mean±SD		73.5±7.9		30.3±5.3	390±155	49±15

CAD = coronary artery disease; AF = atrial fibrillation; HHD = Hypertensive heart disease; DCM = dilated cardiomyopathy; LVEF = left ventricular ejection fraction; NaII = natriuresis.

Each patient received a 30-minute intravenous infusion of furosemide (250–2000 mg/d) and HSS (150 mL of 1.4% to 4.6% sodium chloride) twice a day for 6 to 12 days.

The daily dosage of furosemide was adjusted according to diuresis, blood pressure values, and severity of signs and symptoms of CHF. The HSS concentration was modified as follows according to serum sodium values: ≤125 mEq/L-HSS concentration of 4.6%; 126 to 135 mEq/L-3.5%; >135 mEq/L-1.4% to 2.4%. Potassium chloride (20 to 40 mEq) was administered to prevent hypokalemia.

Once clinical compensation was obtained, the furosemide–HSS infusion was discontinued and replaced by oral administration of furosemide 250 to 500 mg/d and potassium supplementation; optimum CHF therapy was continued.

On hospital discharge, daily sodium intake was fixed at 120 mmoL with a fluid intake of 1000 mL. Patients were followed up weekly for the first 3 months after discharge and once a month for 9 months thereafter.

STATISTICAL ANALYSIS

Results are expressed as mean values ± SD. Statistical analysis was performed by means of the paired Student's *t* test for pre- and posttreatment data that did not differ significantly from normal; otherwise, the nonparametric paired Wilcoxon test was used.

RESULTS

Table 2 lists the components of the intravenous infusion and the duration of treatment.

After a mean of 8.5 days (range 6–12 days), rapid relief of dyspnea, fatigue, and weakness and regression of lower-extremity or generalized edema were evident in all patients. Twelve patients with generalized edema (ascites and pericardial and pleural effusions) experienced a complete remission that was clinically documented and confirmed by X-ray and echocardiography.

Change in NYHA functional class also occurred, further reflecting clinical improvement. From the initial class IV (inclusion criteria), 15 patients were in class IIA, 13 in class IIB, and 2 in class III at the time of discharge (Table 4).

Significant decreases in blood pressure ($P<.05$) were unaccompanied by symptomatic hypotension, and heart rate remained normal.

Significant increases were noted in mean daily diuresis ($P<.01$) and in levels of urinary ($P<.01$) and serum ($P<.05$) sodium and urinary potassium ($P<.05$) (Table 3). Serum potassium decreased significantly ($P<.05$), but all values remained within the normal range. Although serum uric acid concentrations were significantly increased after treatment, ($P<.05$) no patients reported symptoms of gout.

A significant weight loss ranging from 5 to 20 kg, ($P<.05$) was proportional to the increased volume of urine (Table 4).

Patients were discharged from the hospital after a mean stay of 12 days (range 8–15 days). During the 12-month follow-up, no patient was rehospitalized, and all remained in the NYHA class achieved at discharge.

Of the six deaths during the study, three were attributed to noncardiac events (bladder cancer, plasma cell myeloma, femoral fracture) (Table 4).

Table 2. Components and Duration of the Infusion

Patient No.	Furosemide, mg	HSS, %	Duration of Infusion, d
1	250–500	1.4–2.4	6
2	500–1000	1.4–3.5	12
3	500–1000	1.4–3.5	10
4	250–1000	1.4–2.4	11
5	250–1000	1.4–2.4	10
6	250–500	1.4–2.4	6
7	250–500	1.4–2.4	8
8	250–500	1.4–2.4	10
9	250–500	1.4–2.4	6
10	250–500	1.4–2.4	7
11	500–1000	1.4–2.4	6
12	250–500	1.4–2.4	6
13	250–500	1.4–2.4	7
14	500–1000	1.4–3.5	7
15	500–1000	1.4–2.4	6
16	250–500	1.4–2.4	6
17	500–1000	1.4–3.5	8
18	250–500	1.4	6
19	500–1000	1.4–2.4	11
20	250–500	1.4–2.4	12
21	250–500	1.4–2.4	10
22	250–500	1.4	8
23	250–500	1.4	6
24	250–1000	1.4–2.4	8
25	250–1000	1.4–3.5	12
26	500–2000	1.4–4.6	12
27	250–1000	1.4–3.5	11
28	500–2000	1.4–4.6	12
29	250–1000	1.4–2.4	8
30	500–2000	1.4–3.5	9

Table 3. Clinical and Laboratory Parameters Before and After Treatment*

	Before	After
Blood Pressure, mm Hg		
Systolic	142.0±23.8	121.7±12.7†
Diastolic	80.7±13.8	73.2±12.4†
Heart rate; beats/min	82.7±13.7	77.1±10.2†
Ejection fraction, %	30.3±5.3	32.1±6.4
Body weight, kg	73.8±9.1	63.8±8.8†
Diuresis, mL/24 h	390.0±155.0	2100.0±626.0‡
Serum sodium, mEq/L	135.9±6.8	142.2±3.8‡
Serum potassium, mEq/L	4.4±0.6	3.9±0.6†
Urinary sodium, mEq/24 h	49.0±15.0	198.0±28.0†
Urinary potassium, mEq/24 h	64.0±28.0	85.0±27.0†
Serum glucose, mg/dL	98.0±25.9	96.0±23.8
BUN, mg/dL	62.1±4.1	70.0±9.5†
Serum creatinine, mg/dL	1.6±0.05	1.4±0.07
Uric acid, mg/dL	6.7±2.6	8.6±3.2†
Serum albumin, g/dL	3.9±0.5	3.8±0.5

*Data are expressed as mean ± SD.
†$P<.05$.
‡$P<.01$.

DISCUSSION

Diuretics are the cornerstone of therapy for severe CHF, and their efficacy as well as shortcomings are well known.[1,4-5,6,11,24-27] The prime objective of diuretic use in these patients is to reduce salt and water retention, thereby improving the heart's pumping ability and reducing breathlessness, fatigue, and edema. The loop diuretic furosemide is the most frequently used compound in this class for CHF,[4-6] but resistance to its activity occurs frequently.[7-11] The overall response to loop diuretics depends on the time course and amount of drug reaching the kidney, particularly the pharmacodynamic reaction in the ascending limb of Henle's loop.[8] Because renal blood flow in advanced CHF is often reduced, the response to diuretics is progressively attenuated. Intravenous administration is preferable in these patients to overcome the decreased absorption of the orally administered drug.[1] Moreover, patients with CHF require higher concentrations of furosemide in the renal tubule to obtain an adequate natriuretic response, and the constant rate of drug delivery provided by an intravenous infusion may promote optimal diuretic treatment.[12]

Table 4. Effect of Treatment of Weight, NYHA Class, and Survival

Patient No.	Change in Weight, kg	Change in NYHA Class	Survival, months
1	5	IIa	12
2	15	IIb	12
3	13	IIb	12
4	20	IIb	6*
5	13	IIa	12
6	6	IIa	12
7	13	IIa	12
8	13	IIb	6*
9	6	IIb	12
10	8	IIa	12
11	6	III	4*
12	5	IIa	12
13	8	IIb	7*
14	7	III	8*
15	6	IIa	12
16	8	IIa	12
17	8	IIb	12
18	6	IIa	12
19	17	IIa	12
20	18	IIb	12
21	13	IIa	12
22	7	IIa	12
23	5	IIa	12
24	9	IIa	10*
25	10	IIb	12
26	12	IIb	12
27	9	IIb	12
28	13	IIb	12
29	7	IIa	12
30	11	IIb	12

*Deaths: patient no. 4, sudden death; no. 8, bladder cancer; no. 11, plasma cell myeloma; no. 13, stroke; no. 14, femoral-neck fracture; no. 24, sudden death.

The reduced renal blood flow also contributes to the sodium retention seen in patients with advanced CHF.[28] In fact, an increase in renal blood flow should be an important mechanism to re-establish natriuresis.

Intravenous infusion of HSS rapidly raises extracellular sodium concentration with a consequent rise in osmotic pressure, expansion of plasma volume, instantaneous mobilization of fluid into the vascular compartment, and increased renal blood flow.[15,18,29] The rapid expansion of extracellular fluid is responsible for the decreased plasma and peritubular oncotic pressure that, together with increased peritubular hydrostatic pressure, reduces proximal sodium reabsorption.[30] Simultaneous administration of furosemide at high doses enhances renal excretion of sodium and water that is facilitated by adequate concentrations in Henle's loop as a result of increased renal blood flow. Administration of HSS thus potentiates diuretic action and helps to overcome the established resistance to furosemide, with no need of doses exceeding 2 g/d. Consequently, significant electrolyte disturbances and other side effects, such as hypotension and tinnitus, are limited.

A salient finding in our study is 80% of patients were alive after 12 months. Moreover, no patients required re-admission to the hospital during the follow-up, all maintained their improved NYHA functional class.

It is possible that the therapeutic effects of this infusion are mediated not only by direct effects on renal hemodynamics, but also by neurohormonal modulation. Further investigation of this treatment might focus on changes in the renin-angiotensin-aldosterone system, vasopressin, atrial natriuretic peptide, and catecholamines in an assessment of long-term effects. Of note, patients were discharged on a normal-sodium diet. This may have contributed to the maintenance of clinical improvement by adding a counterbalance to activation of the renin-angiotension-aldosterone system so as to allow adequate diuretic action.

These results demonstrate that treatment with a combined intravenous infusion of furosemide and small-volume HSS is effective and well tolerated in patients with advanced and refractory CHF and may be a novel option in the management of this clinical challenge.

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