Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 44, No. 6, 2004
ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2004.06.046

EDITORIAL COMMENT

Furosemide in the Long-Term Management of Heart Failure

The Good, the Bad, and the Uncertain*

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When it was introduced some 35 years ago, furosemide, a potent loop diuretic, altered the practice of medicine. Administered intravenously, it provided a rapid natriuresis and diuresis that proved lifesaving to persons with acute pulmonary edema. It eliminated the need for rotating tourniquets and phlebotomy. Furosemide was next incorporated into the long-term management of heart failure, where its efficacy (and safety) would be presumed but never systematically addressed. It is entrenched in today's suggested standard of care for chronic cardiac failure. The aim of this commentary is to overview its use while raising awareness of potential adverse effects.

See page 1307

CONGESTIVE HEART FAILURE (CHF) AND FUROSEMIDE (THE GOOD)

Congestive heart failure is a clinical syndrome based on a constellation of signs and symptoms that arise from congested organs and hypoperfused tissues. Its appearance is rooted in a salt-avid state, where Na^+ retention (e.g., urinary Na^+/K^+ <1.0) is based on an activation of the circulating renin-angiotensin-aldosterone system (RAAS), whose effector hormones overwhelm the action of natriuretic peptides (1). When Na^+ retention exceeds Na^+ excretion, intravascular volume rises followed by an expansion of extravascular volume to collectively eventuate in signs and symptoms of CHF. In patients with untreated CHF, plasma and extracellular volumes are each increased by >30%, whereas plasma renin activity and aldosterone (ALDO) are >5 times control values (2). Patients with untreated CHF or those with treated but persistent CHF cannot be euvolemic. Euvolemic patients who report exertional dyspnea after climbing several flights of stairs do not have CHF. Furosemide is used in patients with CHF to enhance urinary Na^+ excretion with the target of reestablishing and maintaining Na^+ balance and euvolemia.

Integral to the safe use of furosemide in CHF is the regular surveillance of serum electrolytes, including Mg^{2+}. Serum K^+ should be maintained between 4.0 and 5.0 mEq/l while Mg^{2+} at ≥2.0 mEq/l. A small oral dose of spironolactone (25 mg) in combination with furosemide minimizes the risk of hypokalemia and hypomagnesemia. The utility of spironolactone, an ALDO receptor antagonist, in combination with furosemide and an angiotensin-converting enzyme (ACE) inhibitor, has proven efficacy in reducing morbid and mortal events in heart failure (3). However, this regimen must only be used when renal function is not significantly impaired (i.e., serum creatinine of <2.0 mg/dl). By monitoring electrolytes regularly and eliminating supplemental K^+, the potential for hyperkalemia is minimized. In the Studies Of Left Ventricular Dysfunction (SOLVD) and compared with other diuretics, K^+-sparing diuretics were associated with reduced risk of death from or hospitalization for progressive heart failure or all-cause cardiovascular-related death (4).

Not all patients with left ventricular systolic and/or diastolic dysfunction have RAAS activation and, hence, they can be asymptomatic, or compensated, without urinary Na^+ retention (Na^+/K^+ ratio >1.0). Indeed, resting plasma renin activity is normal in persons without signs and symptoms of CHF despite reduced ejection fraction (EF) (5). However, such persons are salt-sensitive with an inability to adequately excrete a dietary salt load secondary to reduced renal vasodilator and functional reserves (6). This exquisite sensitivity may be related to auto-/paracrine properties of angiotensin (Ang)-II produced within the kidneys and/or to impaired responsiveness to natriuretic peptides. An exaggerated activation of the RAAS during upright physical activity (7) would adversely influence urinary Na^+ excretion throughout the day despite normal resting plasma renin. An ACE inhibitor overcomes this salt sensitivity. Angiotensin-converting enzyme inhibition is a proven standard of care for asymptomatic and symptomatic persons with left ventricular systolic dysfunction.

In chronic cardiac failure, reduced EF neither predicts cardiac output nor that fraction of systemic blood flow apportioned to the kidneys. Accordingly, EF gauges neither renal blood flow nor RAAS activation and, therefore, it does not predict the clinical severity of failure, the presence of CHF, or the need for a diuretic. This is evidenced by patients enrolled in the SOLVD, where all patients had an EF <35%: those randomized to the prevention arm of the trial were asymptomatic, and those enrolled in the treatment arm were symptomatic.

Despite ACE inhibition, excessive dietary salt in a salt-sensitive individual may mandate the short-term use of or a larger-than-usual dose of furosemide to maintain or reestablish euvolemia. Other such circumstances arise when marked RAAS activation occurs with prolonged ambulation or with upright posture in the setting of high ambient temperatures, where skeletal muscle and cutaneous vasodilatation, respectively, compromise renal blood flow. To maintain a constant filtration fraction, the kidneys must

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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receive 20% of cardiac output. With the reduction in systemic blood flow that accompanies heart failure, its enhanced apportionment to skeletal muscle and skin occurs at the expense of renal perfusion and leads to RAAS activation. The long-term use of furosemide and short-term adjustments in furosemide dosage in each individual patient must be determined by the physician's clinical judgment.

POTENTIAL ADVERSE EFFECTS OF FUROSEMIDE (THE BAD AND THE UNCERTAIN)

RAAS activation. Angiotensin-converting enzyme inhibition attenuates but does not eliminate the formation of and associated biologic activity of circulating RAAS effector hormones. Recurrent elevations in plasma Ang-II occur through mechanisms independent of ACE whereas adrenal ALDO production is regulated by factors other than Ang-II (1). Used in excessive dosage, furosemide can cause a contraction of intravascular volume, the hemodynamic signal accounting for RAAS activation, together with a reduction in compensatory natriuretic peptides. Plasma renin activity was increased in a subset of asymptomatic patients enrolled in the SOLVD who were receiving a diuretic (5). The introduction of diuretics in previously untreated, euvolemic patients without CHF who report exertional dyspnea (this is not CHF) leads to intravascular volume contraction and RAAS activation at rest and during exercise (8), which should normalize after furosemide withdrawal.

Urinary Mg^{2+} and Ca^{2+} excretion. In addition to promoting the excretion of Na^+, K^+, and Cl^- that can lead to a hypokalemic, hypochloremic metabolic alkalosis, less well-recognized properties of furosemide include its augmentation of urinary Mg^{2+} and Ca^{2+} excretion. The majority of Mg^{2+} resorption occurs within the kidneys. A large fraction of Mg^{2+} is passively transported in the cortical thick ascending limb of Henle. Furosemide interferes with Mg^{2+} resorption, as well as Ca^+ and phosphate transport. Aldosterone also promotes Mg^{2+} and Ca^{2+} excretion at target tissues that include kidney and colon (9,10). When the hypermagnesuria and hypercalciuria that accompany chronic elevations in plasma ALDO (inappropriate for dietary Na^+ intake) are sustained, a loss of bone mineral density could ensue. Together, furosemide-mediated and ALDO-mediated increments in urinary Mg^{2+}, Ca^{2+}, and phosphate excretion could therefore have far-reaching effects on systemic tissues (vide infra).

The CHF syndrome is accompanied by a systemic illness that features oxi/nitrosative stress; a "storm" of such circulating proinflammatory cytokines as interleukin-6 and tumor necrosis factor-alpha; and a progressive wasting of lean tissue, fat, and bone mass that eventuates in cardiac cachexia (11). Neurohormonal activation may be solely responsible for this disorder. It is uncertain whether furosemide is contributory. Furosemide-induced urinary Ca^{2+} excretion could lead to a reduction in ionized Ca^{2+}, which activates the parathyroids to produce parathyroid hormone (PTH). Parathyroid hormone, in turn, stimulates the kidneys to elaborate $1,25(OH)_2D_3$, an active metabolite of vitamin D. Together, these hormones seek to preserve plasma Ca^{2+} homeostasis through the respective increased resorption of Ca^{2+} from bone and increased gastrointestinal absorption of Ca^{2+}. Bone loss can be a consequence of this scenario. Moderate and marked reductions in bone mineral density, respectively expressed as osteopenia and osteoporosis, together with elevated PTH, are found in patients with advanced symptomatic heart failure awaiting cardiac transplantation and having a history of long-term furosemide usage (11,12).

Intracellular cations. Another potential adverse outcome to furosemide-induced urinary Mg^{2+} and Ca^{2+} excretion is a reduction in cytosolic free Mg^{2+} ($[Mg^{2+}]_i$), the biologically active component of this all-important intracellular divalent cation, that leads to intracellular Ca^{2+} loading and induction of oxi/nitrosative stress. In peripheral blood mononuclear cells (i.e., circulating lymphocytes and monocytes), a reduction in $[Mg^{2+}]_i$ with Ca^{2+} loading contributes to an activation of these cells and a proinflammatory vascular phenotype of the coronary and systemic vasculature (13–15). In the case of the heart, the resultant perivascular/interstitial fibrosis serves as substrate for abnormal vasomotor reactivity, arrhythmias, and ventricular dysfunction. Fibrous tissue, its cellular composition, and their expression of bone morphogenic proteins, together with PTH-mediated and $1,25(OH)_2D_3$-mediated mobilization of Ca^{2+} from bone and gut, respectively, may predispose to tissue calcification. Nephrocalcinosis is known to accompany furosemide treatment. Chronic, inappropriate (relative to dietary Na^+) levels of plasma ALDO are accompanied by increased urinary Ca^{2+} and Mg^{2+} excretion and parathyroid hypersecretion (9,10,16).

Aldosterone and furosemide therefore could have additive effects that contribute to the progressive nature of CHF. In this issue of the *Journal*, McCurley et al. (17) report on a randomized controlled (vs. saline) trial with intramuscular furosemide (1 mg/kg) conducted in a porcine model of rapid pacing-induced ventricular dysfunction. Furosemide was initiated coincident with the onset of pacing and when animals were euvolemic and without CHF. This regimen accelerated the appearance of contractile and metabolic features of heart failure. Included was a reduction in echocardiographic left ventricular fractional shortening to implicate impaired myocardial contractility that was evident at week 3 of pacing (vs. week 5 in placebo controls). Unlike controls, there appeared an early (week 2) and persistent elevation in plasma ALDO, which could interfere with myocardial norepinephrine reuptake (18) and over the course of time reduce ventricular shortening. Moreover, and as noted earlier, ALDO promotes iterations in intracellular and extracellular concentrations of Mg^{2+} and Ca^{2+} that perturb enzymatic reactions they regulate. For example, $[Mg^{2+}]_i$ inhibits a Na^+/Ca^{2+} exchanger. In the furosemide-treated group of pigs, where urinary Mg^{2+} is likely increased and ALDO/Na^+ would reduce $[Mg^{2+}]_i$, increased Na^+/Ca^{2+} exchanger currents were found in

JACC Vol. 44, No. 6, 2004
September 15, 2004:1308–10

isolated cardiomyocytes together with a blunted responsiveness to isoproterenol despite elevations in plasma norepinephrine that were comparable with placebo-treated animals. These findings led the authors to implicate inefficient cardiomyocyte Ca^{2+} cycling. This important study draws attention to the potential detrimental effects of using a potent loop diuretic in the setting of normal intravascular and extravascular volumes.

Thiamine deficiency. Thiamine deficiency is another factor that can contribute to a reduction in myocardial contractility during furosemide treatment. It occurs through a nonspecific, flow-dependent urinary excretion of vitamin B_1. This applies to usual daily doses of furosemide. More than 90% of patients receiving at least 80 mg and >50% receiving 40 mg were found to have laboratory evidence of thiamine deficiency (19). Supplemental thiamine corrects this deficiency and improves echocardiographic EF (20).

CLOSING REMARKS

Loop diuretics, such as furosemide, can be lifesaving for the person with acute pulmonary edema. Their judicious long-term use can prove effective in achieving euvolemia in the salt-avid individual. However, these potent agents have never been systematically validated as safe and efficacious in the long-term management of chronic cardiac failure.

It must be recognized that such agents can do harm. For example, furosemide-mediated hypermagnesuria and hypercalciuria, when sustained, could have profound effects on the intracellular concentrations of these cations and all-important biologic reactions and responses they govern in such diverse tissues as the heart, immune system, and bone. Could it be that in seeking to preserve extracellular Mg^{2+} and Ca^{2+} homeostasis in this setting, the accompanying elevations in circulating PTH and $1,25(OH)_2D_3$ lead to a systemic illness that features the induction of oxi/nitrosative stress, a proinflammatory cytokine phenotype, and a wasting of tissues, including bone? Could this illness be rooted in secondary hyperparathyroidism? In turn, would these calcitrophic hormones contribute to the progressive nature and inexorable downhill clinical course that can accompany chronic cardiac failure? Is it possible that regimens involving putatively safer, non-loop diuretics would prove effective in maintaining euvolemia in salt-sensitive and salt-avid persons?

Investigator-initiated, hypothesis-driven research conducted in a mode of discovery, such as that reported herein by McCurley et al. (17), holds the promise to answering these and other questions.

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REFERENCES

1. Weber KT. Aldosterone in congestive heart failure. N Engl J Med 2001;345:1689–97.
2. Anand IS, Ferrari R, Kalra GS, Wahi PL, Poole-Wilson PA, Harris PC. Edema of cardiac origin: studies of body water and sodium, renal function, hemodynamic indexes, and plasma hormones in untreated congestive cardiac failure. Circulation 1989;80:299–305.
3. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999; 341:709–17.
4. Domanski M, Norman J, Pitt B, Haigney M, Hanlon S, Peyster E. Diuretic use, progressive heart failure, and death in patients in the Studies Of Left Ventricular Dysfunction (SOLVD). J Am Coll Cardiol 2003;42:705–8.
5. Francis GS, Benedict C, Johnstone DE, et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure: a substudy of the Studies Of Left Ventricular Dysfunction (SOLVD). Circulation 1990;82:1724–9.
6. Volpe M, Tritto C, DeLuca N, et al. Abnormalities of sodium handling and of cardiovascular adaptations during high salt diet in patients with mild heart failure. Circulation 1993;88:1620–7.
7. Kirlin PC, Grekin R, Das S, Ballor E, Johnson T, Pitt B. Neurohumoral activation during exercise in congestive heart failure. Am J Med 1986;81:623–9.
8. Bayliss J, Norell M, Canepa-Anson R, Sutton G, Poole-Wilson P. Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics. Br Heart J 1987;57:17–22.
9. Horton R, Biglieri EG. Effect of aldosterone on the metabolism of magnesium. J Clin Endocrinol Metab 1962;22:1187–92.
10. Massry SG, Coburn JW, Chapman LW, Kleeman CR. The effect of long-term desoxycorticosterone acetate administration on the renal excretion of calcium and magnesium. J Lab Clin Med 1968;71:212–9.
11. Anker SD, Clark AL, Teixeira MM, Hellewell PG, Coats AJ. Loss of bone mineral in patients with cachexia due to chronic heart failure. Am J Cardiol 1999;83:612–5.
12. Shane E, Mancini D, Aaronson K, et al. Bone mass, vitamin D deficiency, and hyperparathyroidism in congestive heart failure. Am J Med 1997;103:197–207.
13. Weglicki WB, Dickens BF, Wagner TL, Chmielinska JJ, Phillips TM. Immunoregulation by neuropeptides in magnesium deficiency: ex vivo effect of enhanced substance P production on circulating T lymphocytes from magnesium-deficient mice. Magn Res 1996;9:3–11.
14. Delva P, Pastori C, Degan M, Montesi G, Brazzarola P, Lechi A. Intralymphocyte free magnesium in patients with primary aldosteronism: aldosterone and lymphocyte magnesium homeostasis. Hypertension 2000;35:113–7.
15. Ahokas RA, Warrington KJ, Gerling IC, et al. Aldosteronism and peripheral blood mononuclear cell activation. A neuroendocrine-immune interface. Circ Res 2003;93:e124–35.
16. Resnick LM, Laragh JH. Calcium metabolism and parathyroid function in primary aldosteronism. Am J Med 1985;78:385–90.
17. McCurley JM, Hanlon SU, Wei S-k, Wedam EF, Michalski M, Haigney MC. Furosemide and the progression of left ventricular dysfunction in experimental heart failure. J Am Coll Cardiol 2004;44: 1301–7.
18. Barr CS, Lang CC, Hanson J, Arnott M, Kennedy N, Struthers AD. Effects of adding spironolactone to an angiotensin-converting enzyme inhibitor in chronic congestive heart failure secondary to coronary artery disease. Am J Cardiol 1995;76:1259–65.
19. Seligmann H, Halkin H, Rauchfleisch S, et al. Thiamine deficiency in patients with congestive heart failure receiving long-term furosemide therapy: a pilot study. Am J Med 1991;91:151–5.
20. Shimon I, Almog S, Vered Z, et al. Improved left ventricular function after thiamine supplementation in patients with congestive heart failure receiving long-term furosemide therapy. Am J Med 1995;98: 485–90.