The Effects of Furosemide Dose Reduction on Glomerular Filtration Rate in Stable Systolic Heart Failure

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To the Editor

Loop diuretics are effective and necessary to improve hemodynamics and relieve congestion in subjects with systolic heart failure (HF) and fluid overload. In contrast, in compensated/non-congested patients with left ventricular systolic dysfunction, reports suggest negative consequences of chronic loop diuretic therapy on the progression of HF (1,2). Others and we have also reported that in compensated HF patients, loop diuretic therapy has deleterious neurohumoral and renal hemodynamic effects such as renal vasoconstriction and activation of the renin angiotensin aldosterone system (1,3). The adverse renal effects of chronic loop diuretic therapy are significant as renal function is one of the most important predictors of prognosis in HF (4). Therefore, interventions aimed at improving or avoiding deterioration in renal function are critically important. The objective of the current study was to define the effects of decreasing furosemide, the most commonly prescribed loop diuretic, on renal function in compensated systolic HF patients with and without underlying renal insufficiency. We hypothesized that furosemide dose reduction would improve glomerular filtration rate (GFR) and decrease neurohumoral activation without adverse effects or a deterioration in functional status.

Outpatients with an ejection fraction less than 40 percent with (n=19) and without (n=13) renal insufficiency [defined as GFR less than 60 ml/min/1.73m^2] were enrolled. Inclusion criteria included stable New York Heart Association class II/III symptoms and stable cardiovascular medications for 3 months prior to study enrollment. Exclusion criteria included renal artery stenosis (greater than 50%), moderate or greater valvular disease, myocardial infarction or unstable angina or hospitalization within 6 months prior to enrollment, prior hemodialysis, and subjects on any other diuretic beyond furosemide. Subjects with a serum sodium of <125 mEq/dL or >150 mEq/dL or serum potassium of <3.5 mEq/dL or >5.5 were also excluded. This study was approved by the Mayo Foundation Institutional Review Board and was performed at the General Clinical Research Center at Mayo Clinic, Rochester, Minnesota (*ClinicalTrials.gov Identifier:* NCT00982423).

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After enrollment subjects were monitored for 3 weeks to ensure clinical stability on their clinically prescribed furosemide and cardiovascular medication doses. Subjects then underwent a baseline assessment of iothalamate GFR, para-amino-hippurate renal plasma flow, functional status (6 minute walk and Minnesota Living with HF Score), and natriuretic peptide and renin-angiotensin-aldosterone systems. Following this assessment subjects were instructed to reduce their furosemide dose and, if taken, potassium supplementation by 50 percent for three weeks. Electrolytes and creatinine were checked at 1 week following dose reduction. Subjects were instructed to weigh daily and provided the following weight-based dose adjustment algorithm: 1) Gain of < 2 pounds: no change in daily furosemide dose; 2) Gain of 2–3 pounds: double furosemide dose and potassium supplementation (if taken) for one day; 3) Gain of 3–4 pounds: double furosemide dose and potassium supplementation (if taken) for two days; and 4) Gain of > 4 pounds: call the investigator who will decide the extra dose of the furosemide and potassium supplementation. Seven subjects (37%) in the reduced GFR group and 5 subjects (38%) in the preserved GFR group increased their furosemide dose for 1 to 3 days according to the weight-based algorithm during the 3 weeks of furosemide reduction. Daily furosemide doses were reduced to 66 ± 9 mg (from 119 ± 14 mg) in the reduced GFR group and to 57 ± 8 mg (from 102 ± 13 mg) in the preserved GFR group. (Table 1) After 3 weeks of furosemide reduction, subjects returned for the same comprehensive assessment as was performed at baseline. Following this assessment, subjects resumed their pre-study doses of furosemide.

Our results highlight a differential response to furosemide reduction among subjects with reduced versus preserved GFR (Table 1). GFR increased from 42 ± 3 to 50 ± 4 ml/min/1.73m^2 in subjects with reduced GFR at baseline (p=0.02) (relative GFR increase 19%) whereas there was no change in the preserved GFR group (77 ± 3 to 73 ± 5 ml/min/1.73m^2, p=0.18). Atrial natriuretic peptide (ANP) significantly increased with furosemide reduction in the reduced GFR group (233 ± 48 to 291 ± 60 pg/ml, p=0.01). There was also a trend for an increase in plasma cGMP (p=0.07), the second messenger of ANP, following furosemide reduction in the reduced GFR group. We did not observe a change in angiotensin II or aldosterone with furosemide reduction although there was a signal for decreased renin activation in both groups. Importantly, there was no change in weight or functional status following furosemide reduction. Further, there were no adverse events including hospitalization, emergency room visits, or unplanned outpatient visits in either group.

These results demonstrate furosemide reduction in subjects with stable systolic heart failure and underlying renal dysfunction is safe and associated with an improvement in GFR without a change in volume or functional status. Combined with previous reports (1,3), these data suggest that furosemide may adversely affect GFR in stable HF subjects in the presence of underlying renal insufficiency. The etiology of the improved renal function associated with furosemide reduction may be secondary to greater activation of ANP which is well established to improve renal function via cGMP activation. The etiology of the increase in ANP may be in part due correction of intravascular volume contraction following furosemide reduction, leading to increased atrial stretch and release of ANP. Also, it has previously been noted that furosemide activates renin via multiple mechanisms (5) and in the current study there was a trend for decreased renin with furosemide reduction. Reduced

renin activation following furosemide reduction may in part account for the increase in GFR.

As it is well established that renal function is one of the single most predictive marker for adverse outcomes in HF and in an era of continued poor HF outcomes and a lack of new HF therapeutics in over a decade, a simple intervention which improves renal function deserves greater attention. Further prospective randomized controlled studies are warranted to determine if systematic reduction of furosemide doses in stable systolic HF subjects with renal dysfunction translates into improved clinical outcomes.

Acknowledgments

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Table 1

Baseline characteristics and neurohumoral, hemodynamic, and functional status assessment before and after furosemide dose reduction among stable heart failure patients

	Reduced GFR (n=19) (<60 ml/min/1.73m^2)		Preserved GFR (n=13) (60 ml/min/1.73m^2)	
Age, years	76±2[*]		68±3	
Female, n (percent)	6 (32)		4 (31)	
Coronary artery disease, n (percent)	12 (63)		6 (46)	
Diabetes mellitus, n (percent)	4 (21)		4 (31)	
Hypertension, n (percent)	10 (53)		5 (38)	
Hyperlipidemia, n (percent)	12 (63)		10 (77)	
Ejection Fraction, n (percent)	29±2		33±1	
Beta Blocker, n (percent)	17 (89)		13 (100)	
ACEi/ARB, n (percent)	13 (68)		12 (92)	
Aldosterone Antagonist, n (percent)	5 (26)		4 (31)	
Nitrates/Hydralazine n (percent)	7 (37)		2 (15)	
	Baseline Dose Furosemide	*Reduced Dose Furosemide*	*Baseline Dose Furosemide*	*Reduced Dose Furosemide*
Lasix Dose, mg per day	119±14[*]	66±9[†]	102±13	57±8[†]
Weight, kilograms	81±17	81±16	91±12	91±13
Glomerular Filtration Rate (ml/min)	42±3[*]	50±4[†]	77±3	73±5
Plasma Renal Flow (ml/min)	198±20	214±21	304±19	293±23
Atrial Natriuretic Peptide	233±48	291±60[†]	168±44	163±34
Plasma cGMP (pg/ml)	5.7±0.8	7.0±1.0[‡]	5.0±0.9	4.6±0.7
Plasma Renin Activity (ng/mL/hr)	2.1±0.8	1.4±0.5	4.3±2.0	2.7±1.1
Angiotensin II (pg/mL)	3.1±0.7	3.2±0.9	3.3±0.6	3.4±1.0
Aldosterone (ng/dL)	4.9±0.6	4.9±0.6	7.9±1.8	7.6±1.3
6 Minute Walk (meters)	327±20	336±23	428±30	419±32
Minnesota Living with HF Score	25±4	25±5	29±4	29±4
Systolic Blood Pressure (mm Hg)	117±5	121±5	114±4	114±4
Diastolic Blood Pressure (mm Hg)	67±2	68±2	70±2	70±3
Heart Rate (beats per minute)	67±2	66±2	66±3	68±4

Continuous variables compared using and paired (within group) t-test. Categorical variables compared using Chi-Square.

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; GFR, glomerular filtration rate; HF, heart failure

[*] p<0.05 vs. Normal GFR, student's t-test

[†] p<0.05 vs. Baseline Dose Furosemide, paired t-test

[‡]p=0.075 vs. Baseline Dose Furosemide, paired t-test