Clinical Investigations

Insufficient Natriuretic Response to Continuous Intravenous Furosemide Is Associated With Poor Long-Term Outcomes in Acute Decompensated Heart Failure

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ABSTRACT

Background: Treatment of acute decompensated heart failure (ADHF) with loop diuretics, such as furosemide, is frequently complicated by insufficient urine sodium excretion. We hypothesize that insufficient natriuretic response to diuretic therapy, characterized by lower urine sodium (U_{Na}) and urine furosemide, is associated with subsequent inadequate decongestion, worsening renal function, and adverse long term events.

Methods and Results: We enrolled 52 consecutive patients with ADHF and measured serum and urine sodium (U_{Na}), urine creatinine (U_{Cr}), and urine furosemide ($U_{Furosemide}$) levels on a spot sample taken after treatment with continuous intravenous furosemide, and followed clinical and renal variables as well as adverse long-term clinical outcomes (death, rehospitalizations, and cardiac transplantation). We observed similar correlations between U_{Na}:$U_{Furosemide}$ ratio and U_{Na} and fractional excretion of sodium (FE_{Na}) with 24-hour net urine output ($r = 0.52-0.64$, all $P < .01$) and 24-hour weight loss ($r = 0.44-0.56$; all $P < .01$). Interestingly, FE_{Na} (but not U_{Na} or U_{Na}:$U_{Furosemide}$) were influenced by estimated glomerular filtration rate (eGFR). We observed an association between lower U_{Na}:$U_{Furosemide}$ with greater likelihood of worsening renal function (hazard ratio [HR] 3.01; $P = .02$) and poorer adverse clinical outcomes (HR 1.63, $P = .008$) after adjusting for age and eGFR. Meanwhile, both diminished weight loss and net fluid output over 24 hours of continuous intravenous furosemide were observed when U_{Na}:$U_{Furosemide}$ ratios were <2 mmol/mg or when U_{Na} <50 mmol.

Conclusion: In patients with ADHF receiving continuous furosemide infusion, impaired natriuretic response to furosemide is associated with greater likelihood of worsening renal function and future adverse long-term outcomes, independently from and incrementally with decreasing intrinsic glomerular filtration. (*J Cardiac Fail 2014;20:392–399*)

Key Words: Acute decompensated heart failure, furosemide, urine sodium, natriuresis.

Loop diuretics are the first-line agents for amelioration of symptoms and restoration of volume status in the treatment of acute decompensated heart failure (ADHF).[1] However, a subset of patients treated for ADHF fail to elicit effective diuresis with loop diuretics despite persistent congestion. There have been several postulates to this so-called "diuretic resistance" phenomenon.[2,3] First, the presence of heart failure has been shown to shift the loop diuretic

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dose-response curve down and to the right, with the same dose of diuretics producing an attenuated response in heart failure patients compared with normal control subjects.[4,5] Second, loop diuretics have been shown to indirectly reduce renal blood flow by activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS), thereby leading to a further increase in tubular sodium absorption. The reduced renal blood flow itself may cause decreased diuretic delivery because it is predominantly secreted at the tubular level, and tubular resistance to the diuretic can be induced by the neurohormonal activation.[6] Third, loop diuretic exposure has been shown to cause hypertrophy of distal tubular epithelial cells with enhanced distal sodium absorption.[7] Although in most cases, health care providers determine effective diuretic dosing via assessment of urine output and weight loss over the course of treatment with loop diuretics, few simple bedside measures are reliable in determining real-time diuretic effectiveness.[8]

We investigated the clinical significance of the natriuretic response to loop diuretic therapy in terms of the development of adverse clinical outcomes, and examined the clinical utility of measuring spot urine electrolytes as potential bedside tools to determine the effectiveness of decongestion strategies during continuous intravenous loop diuretic therapy.

Methods

Study Population

We prospectively enrolled consecutive subjects ≥18 years old who were admitted to the hospital with a clinical diagnosis of acute decompensated heart failure, including evidence of fluid overload (≥2+ lower extremity edema, presence of pulmonary edema or pleural effusion on chest radiograph, jugular venous distention, worsening dyspnea, orthopnea, paroxysmal nocturnal dyspnea, or ascites, or increase in body weight from baseline that was attributed to fluid retention). We included only those receiving a continuous infusion of furosemide for 3−24 hours at the discretion of the treating physician, owing to the need to establish a steady-state systemic level of furosemide to reliably assess natriuretic response via the measurement of urinary furosemide by spot collection. The purpose was to identify a patient while congestion is still present and effective diuresis is still occurring yet long enough for furosemide to achieve relatively steady state at the urinary level. We excluded subjects who were unable to provide informed consent or comply with study protocol, who were on renal replacement therapy or anuric at the time of enrollment, or whose hospital discharge was anticipated within the next 24 hours.

Study Design

This was a single-center, observational, prospective cohort study approved by the Cleveland Clinic Institutional Review Board. All subjects provided written informed consent. Treatment of heart failure, including diuretic dosing, was based on standard of care as determined by the treating physician independently from the study. Although not specified for the study, all patients were put on a low-sodium (2 g) cardiac diet as the institution's standard of care for heart failure admissions. In addition to this, diabetics were put on diabetic diet. Weight loss was calculated by subtracting the weight value 24 hours after the urine samples were measured from the weight on the day of first urine sample measurement (baseline). Forty-eight-hour and 72-hour total net fluid balance from baseline were also assessed. Glomerular filtration rate was estimated (eGFR) by the Modified Diet and Renal Disease equation. Patients were followed for 5 days or until discharge after enrollment, and electronic medical record follow-up of adverse long-term outcomes were tracked as a secondary end point until study completion (August 2010).

Assay Measurements

Urine sodium (U_{Na}) concentration from spot urine samples was measured by ion-selective electrode, and urine creatinine (U_{Cr}) was measured by enzymatic assay within the Cleveland Clinic Reference Laboratory. Urinary furosemide ($U_{Furosemide}$) from spot urine samples was assessed by NMS Labs (Willow Grove, Pennsylvania) with the use of high-performance liquid chromatography. We defined the natriuretic response to furosemide as the ratio of U_{Na} to $U_{Furosemide}$, expressed as mmol/mg. Fractional excretion of sodium (FE_{Na}) was calculated as: $(U_{Na} \times S_{Cr})/(U_{Cr} \times S_{Na}) \times 100\%$ (where S_{Cr} and S_{Na} are serum concentration of creatinine and sodium, respectively). Worsening renal function (WRF) was defined as a rise in serum creatinine of ≥0.3 mg/dL from day 1 to day 5 after enrollment into the study. Baseline B-type natriuretic peptide (BNP) levels were measured with the use of the Abbott Architect ci8200 platform (Abbott Laboratories, Abbott Park, Illinois). Physicians providing care for the patients were blinded from the assay results derived from this study. Ratio of U_{Na}:$U_{Furosemide}$ was analyzed independently, and the results were not available to the treating physicians.

Statistical Analysis

Continuous variables were summarized as mean ± standard deviation (SD) if normally distributed, and as median and interquartile range (IQR) if nonnormally distributed. Normality was assessed by the Shapiro-Wilk *W* test. Categoric variables were summarized as proportions and frequencies. Spearman rank correlation method was used as a nonparametric measure of association for correlations between urinary electrolytes and clinical characteristics and laboratory indices. The Wilcoxon rank-sum or Kruskal-Wallis tests were used to compare differences in urinary electrolytes and nonnormally distributed variables across clinical categories, whereas Student *t*-test or 1-way analysis of variance were used to compare differences in normally distributed variables across clinical categories. Proportions were compared with the use of contingency table analysis. The logistic regression analysis determining the odds ratio of worsening renal function (defined as a rise in serum creatinine of ≥0.3 mg/dL) associated with U_{Na}:$U_{Furosemide}$ was a nominal logistic regression analysis with an effect likelihood ratio test. In multivariable logistic regression, age and eGFR were added as covariates with U_{Na}:$U_{Furosemide}$, and tests and confidence intervals on odds ratios were again likelihood ratio based in a nominal logistic regression. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated through logistic regression analysis and evaluated according to the likelihood ratio test. Kaplan-Meier survival plots were calculated from baseline to time of all-cause mortality, cardiac transplantation, or heart failure rehospitalization. The Cox proportional hazards regression model was used to analyze time to all-cause mortality, cardiac transplantation, or heart failure rehospitalization associated with decreasing urinary analyte levels