Nesiritide Does Not Improve Renal Function in Patients With Chronic Heart Failure and Worsening Serum Creatinine

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Background—Nesiritide (synthetic human brain natriuretic peptide) is approved for the treatment of symptomatic heart failure. However, studies of brain natriuretic peptide in patients with heart failure have come to conflicting conclusions about effects on glomerular filtration rate (GFR), effective renal plasma flow, natriuresis, and diuresis.

Methods and Results—To identify a population at high risk of renal dysfunction with conventional treatment, we selected patients with a creatinine level increased from baseline (within 6 months). We examined the effects of nesiritide on GFR (measured by iothalamate clearance), renal plasma flow (measured by para-amino hippurate clearance), urinary sodium excretion, and urine output in a double-blind, placebo-controlled, crossover study. Patients received nesiritide (2 μg/kg IV bolus followed by an infusion of 0.01 μg/kg per minute) or placebo for 24 hours on consecutive days. Nesiritide and placebo data were compared by repeated-measures analysis and Student t test. We studied 15 patients with a recent mean baseline creatinine of 1.5 ± 0.4 mg/dL and serum creatinine of 1.8 ± 0.8 mg/dL on admission to the study. There were no differences in GFR, effective renal plasma flow, urine output, or sodium excretion for any time interval or for the entire 24-hour period between the nesiritide and placebo study days. For 24 hours, urine output was 113 ± 51 mL/h with placebo and 110 ± 56 mL/h with nesiritide. GFR during placebo was 40.9 ± 25.9 mL/min and with nesiritide was 40.9 ± 25.8.

Conclusions—Nesiritide did not improve renal function in patients with decompensated heart failure, mild chronic renal insufficiency, and renal function that had worsened compared with baseline. The lack of effect may be related to renal insufficiency, hemodynamic alterations, sodium balance, severity of heart failure, or drug dose. Understanding the importance of these issues will permit effective and appropriate use of nesiritide. (Circulation. 2004;110:1620-1625.)

Key Words: heart failure ■ kidney ■ creatinine ■ natriuretic peptides ■ kidney failure

Decompensated congestive heart failure (CHF), a common cause of hospitalization, is frequently associated with a hemodynamically mediated increased serum creatinine concentration. There are many reasons to be concerned about this worsening renal function. Renal dysfunction can prevent adequate diuresis and thereby hamper symptomatic relief. It also may lead to reluctance by physicians to prescribe or optimally dose beneficial medications, including ACE inhibitors and diuretics.

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Renal function also has prognostic importance; the greater the renal impairment, the worse is the clinical outcome of patients with CHF. Among hospitalized CHF patients, an increase in serum creatinine is one of the most powerful predictors of poor survival.

Nesiritide (synthetic human brain natriuretic peptide [BNP]) is an agent approved for the treatment of symptomatic CHF. It is a vasodilator, with proven efficacy to decrease pulmonary capillary wedge pressure and improve self-reported dyspnea. There are also suggestions that BNP might have renal effects. In some studies, BNP has been shown to increase natriuresis and diuresis, but this has not been observed universally. Similarly, studies of BNP have come to conflicting conclusions about the effects on glomerular filtration rate (GFR) or renal plasma flow. The extent of the renal effects of nesiritide when given in therapeutic doses to decompensated CHF patients is uncertain.

We therefore sought to evaluate the renal effects of nesiritide in patients hospitalized for worsening CHF. To identify a patient population with high risk of renal dysfunction with conventional treatment, we selected patients with a creatinine level increased from their individual baseline. In this group of high-risk patients for whom a renally active drug would have clinical benefit, we examined the effects of...
nesiritide on GFR, effective renal plasma flow (ERPF), urinary sodium excretion, and urine output in a double-blind, placebo-controlled, crossover study.

Methods

Patient Sample
Fifteen patients with decompensated CHF who were volume overloaded and required hospital admission were enrolled in the study. Patients were required to have a plasma creatinine concentration greater than their baseline by $\geq 0.2$ mg/dL and $\geq 10\%$. All patients were classified as NYHA class II to IV CHF and had an ejection fraction $< 40\%$. Patients requiring parenteral vasoactive therapy, including dobutamine, milrinone, dopamine, nitroglycerin, or nitroprusside, were excluded from the study. Additional exclusion criteria were renal deterioration suspected to be unrelated to CHF, NSAID use in the 24 hours before study entry, intravenous radiocontrast administration within 72 hours of study entry, systolic blood pressure $< 90$ mm Hg, current dialysis, serum creatinine $> 5.0$ mg/dL, clinically significant aortic or mitral stenosis, and hypersensitivity to nesiritide or any of its formulation components. All patients provided informed consent, and the Human Research Protections Office of the University of Maryland approved the protocol.

Study End Points
The primary end point was the effect of nesiritide on GFR compared with placebo from 21 to 24 hours of each infusion period. This end point was chosen because it would demonstrate the effect of nesiritide at the end of a 24-hour infusion with minimal carryover effect from the previous day. Secondary end points included the effects of nesiritide on GFR, ERPF, urine output, and urinary sodium excretion at 0 to 3, 3 to 6, 6 to 21, 21 to 24, and 0 to 24 hours of the nesiritide infusion compared with placebo.

Procedure
Patients received 24-hour infusions of placebo or nesiritide in a randomized, double-blind, crossover design over 2 consecutive 24-hour periods while receiving a 2-g sodium diet. The patient’s weight on the second day was required to be within 1 kg of the first day’s weight in order that changes in intravascular volume would not affect renal function. Nesiritide was administered as a 2-$\mu$g/kg IV bolus followed by a continuous infusion of 0.01 $\mu$g/kg per minute, the recommended and US Food and Drug Administration–approved dose.

GFR and ERPF
Three hours before drug infusion, patients received a bolus of 200 mg para-amino hippurate (PAH) and 456 mg iothalamate administered over 5 minutes. A constant-rate infusion of PAH and iothalamate was then started immediately and continued through the end of the study. The infusion rate was determined by the patient’s estimated GFR and calculated to achieve steady-state plasma concentrations of 15 to 20 mg/L.

GFR was determined by the clearance of iothalamate, and ERPF was determined by the clearance of PAH. Plasma and urine concentrations of iothalamate and PAH were measured for each sample by high-performance liquid chromatography. Urinary clearance for each interval was calculated as Clearance $= (Ae^{-y})/(\text{AUC}^{-y})$, where $Ae^{-y}$ is the amount of iothalamate or PAH recovered in urine from time $x$ to $y$, and $\text{AUC}^{-y}$ is the area under the plasma concentration–time profile for iothalamate or PAH from time $x$ to $y$. Plasma clearance ($CL_p$) was also determined and is reported for the 24-hour period. It was calculated as $CL_p = K_d \times V_o$, where $K_d$ is the elimination rate constant and $V_o$ is the volume of distribution, both obtained by 1-compartment modeling methods, as previously described.

Urinary sodium was measured for each sample by standard laboratory procedures.

Time Course
PAH/iothalamate infusions were initiated 3 hours before the administration of nesiritide or placebo. Blood samples were obtained at $-3, 0, 3, 6, 21,$ and 24 hours during each drug infusion period. Blood samples were centrifuged within 15 minutes of collection. The resulting plasma was frozen until analyzed. Urine aliquots were obtained at each time point from the total urine output during that time period. Patients were not required to have urinary catheters. Patients without catheters were asked to urinate at the end of each collection period. Urine samples were frozen until analyzed. Total urine output was measured and recorded for each period.

GFR and ERPF were assessed for the first 3 hours after drug initiation, the next 3, the next 15, and the final 3 hours. This permitted assessment of the short-term effects on renal function as well as effects after 1 day of treatment.

Concomitant Medications
Cardiovascular medications, including intravenous and oral diuretics, $\beta$-blockers, digoxin, and ACE inhibitors, were given at the 6-hour time point on both study days. Doses were kept constant from the day before the start of the study through the end of the study. The diuretic dose was chosen to maintain a neutral fluid balance.

Urine Measurements
All patients underwent the crossover of study drug infusion. Several patients had missing data. In all cases, both the missing data and the matched data from placebo or active infusion were excluded from analysis. All decisions about exclusion of data were made before unblinding of the data. When data were unavailable for a 3-hour period, these patients were included in the 24-hour analysis because of the minimal impact of a single 3-hour period. Urine samples for 2 patients were not evaluable for GFR and ERPF during the 6- to 21-hour time period. These patients were excluded from the 24-hour GFR and ERPF evaluation by urinary clearance. In addition to determination of renal function by urinary clearance, therefore, analysis for the 24-hour GFR and ERPF was calculated by plasma clearance modeling. The reported 24-hour GFR and ERPF data are derived from plasma clearance for these 2 patients. Two additional patients could not be evaluated for GFR and ERPF because of missing blood samples, but urine output and sodium excretion were accurately measured.

Statistical Analysis
All values are reported as mean$\pm$SD. A general linear model repeated-measures analysis was used to compare groups. To increase sensitivity, a Student 2-tailed paired t test was also used to compare placebo and active drug values for each individual time point. We calculated 95% CIs. Analyses were done on SPSS, version 11.5.0.

Power calculations showed that 15 patients would have been sufficient to have 80% power to detect a 13% improvement in GFR (assuming a mean initial GFR of 50 and SD of 7), with a probability value of $< 0.05$.

Results

Baseline Characteristics
Patient characteristics are listed in the Table. All patients were classified as NYHA class III ($n = 8$) or class IV ($n = 7$) CHF. At the time of enrollment, 93% of patients exhibited clinical evidence of fluid overload (elevated jugular venous pressure in 60%, rales in 63%, peripheral edema in 93%). Mean ejection fraction was $22\pm 5\%$. Arterial pressure at baseline was $115\pm 17/66\pm 9$ mm Hg.

Baseline creatinine (within the past 6 months) was $1.5\pm 0.4$ mg/dL. At enrollment, the mean creatinine was $1.8\pm 0.8$ mg/dL, and calculated GFR was $44\pm 18$ mL/min by the Modification of Diet in Renal Disease (MDRD) formula:
Baseline Characteristics (n=15)

<table>
<thead>
<tr>
<th>Age, y</th>
<th>64.6±15 (range, 36–82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
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</tr>
<tr>
<td>Race, white/black</td>
<td>11/4</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td>115/66±17/9</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>79±16 (range, 60–112)</td>
</tr>
<tr>
<td>Baseline creatinine, mg/dL</td>
<td>1.5±0.4 (range, 0.9–2.4)</td>
</tr>
<tr>
<td>Enrollment creatinine, mg/dL</td>
<td>1.8±0.8 (range, 1.1–3.1)</td>
</tr>
<tr>
<td>Baseline GFR, mL/(kg·1.73 m²) (estimated by MDRD formula)</td>
<td>57±18 (range, 28–87)</td>
</tr>
<tr>
<td>Enrollment GFR, mL/(kg·1.73 m²) (estimated by MDRD formula)</td>
<td>44±18 (range, 14–77)</td>
</tr>
<tr>
<td>NYHA class, n (%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>8 (53)</td>
</tr>
<tr>
<td>IV</td>
<td>7 (46)</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>22±5 (range, 12–30)</td>
</tr>
<tr>
<td>Heart failure etiology, n (%)</td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>8 (53)</td>
</tr>
<tr>
<td>Nonischemic</td>
<td>7 (46)</td>
</tr>
<tr>
<td>Chronic medications, n (%)</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor/angiotensin receptor blocker</td>
<td>15 (100)</td>
</tr>
<tr>
<td>β-Adrenergic blocker</td>
<td>10 (66)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>13 (87)</td>
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<tr>
<td>Spironolactone</td>
<td>9 (60)</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>15 (100)</td>
</tr>
<tr>
<td>Isosorbide mononitrate</td>
<td>6 (40)</td>
</tr>
</tbody>
</table>

Data are mean ± SD unless indicated otherwise.

GFR = 186 × (S_c)⁻¹.¹³⁴ × (Age)⁻⁰.²⁰³ × (0.742 if female) × (1.210 if black), where S_c is serum creatinine.

Chronic cardiovascular medications used by patients included β-adrenergic blockers (66%), ACE inhibitors or angiotensin receptor blockers (100%), isosorbide mononitrate (40%), digoxin (87%), spironolactone (60%), and loop-type diuretics (100%).

All patients received daily doses of furosemide. Eleven patients received intravenous furosemide (140±60 mg; range, 60 to 240 mg). Four patients received oral furosemide: 2 received 40 mg, 1 received 80 mg, and 1 received 400 mg. The mean weight of the patients on the day before the study was 92.1±23.2 kg. The weight decreased by 0.7±1.4 kg on the morning before the first day of the study and by 0.5±1.4 kg on the morning of the second day.

Urine Output and Sodium Excretion

There was no significant difference in urine output during nesiritide infusion compared with placebo at any time point or for the entire 24-hour period (P=0.95 by repeated-measures analysis) (Figure 1). Urine flow rates for the first and second 3-hour periods were 72±31 and 75±53 mL/h with placebo infusion and 68±32 and 89±76 mL/h with nesiritide infusion, respectively. Urine output during the 6- to 21-hour time period was 133±63 mL/h with placebo and 125±72 mL/h with nesiritide (P=0.6). The urine output during this time period reflects the effect of loop diuretics, which were administered after the 6-hour collection period.

Urine output from 21 to 24 hours was 95±79 mL/h with placebo and 94±100 mL/h with nesiritide infusion (P=0.9). For the entire 24-hour period, urine output was 113±51 mL/h with placebo infusion and 110±56 mL/h with nesiritide infusion (P=0.72). The difference in urine output between nesiritide and placebo over 24 hours was −3±3.7 mL/h (95% CI, −24 to 17).

There was no significant difference in sodium excretion between days (P=0.36). For the entire 24-hour period, sodium excretion with placebo infusion was 8.5±7.2 mmol/l compared with 8.3±6.9 mmol/l with nesiritide infusion (P=0.89). Sodium excretion changed by −0.19±5.2 mmol/l (95% CI, −3.1 to 2.7) with nesiritide (Figure 2). For the 6- to 21-hour period after administration of furosemide, sodium excretion was 9.9±8.2 mmol/l with placebo and 9.8±8.6 mmol/l with nesiritide infusion (P=0.94). As with the data for urine output, there was also no significant difference in sodium excretion during the time periods of 0 to 3, 3 to 6, and 21 to 24 hours.

GFR and ERPF

Comparison of GFR during placebo and nesiritide infusion revealed no significant difference during any of the individual time periods or the entire 24 hours (P=0.09 by repeated-measures analysis) (Figure 3). GFR during placebo and nesiritide infusions for the time period 21 to 24 hours was 44.9±27.9 and 38.3±21.3 mL/min, respectively. For 0 to 3 hours, it was 43.4±31.4 and 41.7±31.1 mL/min (P=0.64),...
respectively. For the 3- to 6-hour time period, GFR was 48.5 ± 30.3 with placebo and 42.5 ± 24.8 with nesiritide (P = 0.17). For the entire 24-hour period, GFR (as determined by urinary clearance) during placebo infusion was 41.1 ± 25.5 mL/min and with nesiritide infusion was 40.9 ± 25.9 (P = 0.93). GFR changed by −0.2 ± 9.5 mL/min (95% CI, −5.9 to 5.5).

With the use of the plasma clearance model, GFR during the 24-hour period of placebo infusion was 42.7 ± 18.27 mL/min, and during nesiritide infusion GFR was 41.3 ± 18.4 mL/min (P = 0.25). This confirms the consistency of plasma and urinary clearance models.

There was no significant change in ERPF with nesiritide infusion compared with placebo (P = 0.09) (Figure 4). For the 24-hour periods, average ERPF was 160 ± 66 mL/min for placebo and 143 ± 65 mL/min for nesiritide (P = 0.10). With nesiritide, ERPF changed by −17 ± 35 (95% CI, −39 to 4). There was also no difference during the time periods from 0 to 3, 3 to 6, 6 to 21, and 21 to 24 hours.

Baseline characteristics of patients, including renal function, demographics, and blood pressure, did not affect the response to nesiritide.

Discussion

This study was unable to demonstrate any effect of a 24-hour infusion of nesiritide on urine output, sodium excretion, GFR, or ERPF in a group of patients with decompensated CHF and an acute decline in renal function. These individuals often present a treatment challenge because diuresis is hampered by the need to balance renal function effects against the desire for further diuresis. Inotropic agents, including dobutamine and milrinone, are often used in patients whose renal function is impaired in large part as a result of decreased renal flow. Use of inotropic medications, however, is complicated by possible adverse hemodynamic effects, arrhythmias, and a strong association with increased morbidity and mortality. Thus, a drug that increases urine output while improving or preserving renal function would be extremely valuable in patients similar to the subjects of the present study. Unfortunately, nesiritide at the doses used did not have this effect.

GFR and ERPF

There was clearly no improvement in GFR in the present study. Indeed, at some time points the GFR during the nesiritide infusion was (nonsignificantly) worse than that during placebo infusion. The lack of improvement in GFR is consistent with numerous previous studies that have demonstrated no change in GFR or creatinine clearance in patients with CHF. Human studies that have demonstrated improved GFR have generally evaluated a small number of normal individuals. Even these studies, however, have not necessarily demonstrated improved ERPF.

Nesiritide appears to exert hemodynamic effects in patients with both CHF and renal dysfunction (although the effects may be quantitatively different from those seen in normal individuals). Clinically, CHF patients with an elevated creatinine concentration had a response similar to those with normal renal function in the Vasodilation in the Acute Management of CHF trial. Notably, this occurred even in patients with minimal urine output, which emphasizes the importance of the vascular actions of nesiritide. Although this study found a slight (0.2 mg/dL) decrease in serum creatinine, no conclusion can be made about renal function in this small, retrospective analysis with insensitive end points.

One canine pacing model of CHF demonstrated improved GFR with nesiritide. This occurred only with high doses (10 pmol/kg per minute) of the drug, which suggests that there might be a dose-response curve and that only doses above those approved by the US Food and Drug Administration exert renal actions.

Diuresis with loop diuretics can decrease GFR, and agents that directly affect the renal vasculature might permit maintenance of renal perfusion despite diuresis. There are no studies, however, evaluating whether nesiritide can maintain renal function in the face of increased diuresis. Some data suggest that diuresis associated with nesiritide may lead to deterioration in GFR. A recent study by Tang et al. reported at the 2004 annual meeting of the American College of Cardiology, evaluated the hemodynamic effects of high-volume diuresis in conjunction with nesiritide. It revealed that 15% of patients had a >50% reduction in GFR, as estimated by the Cockcroft-Gault formula. In another study of 7 patients (with relatively high mean arterial pressure and normal renal function), creatinine clearance was worse after infusion of human BNP than in the period before infusion. The effects of nesiritide on renal function in the face of aggressive diuresis will need to be formally tested.
As with GFR, there was no difference in ERPF during nesiritide infusion compared with placebo. This confirms previous data showing no change in ERPF in patients with CHF.\textsuperscript{13,14} Although afferent and efferent renal arteriolar vasodilatation might be expected to lead to increased ERPF, the vasodilator properties of nesiritide might decrease blood pressure and counteract these direct actions.\textsuperscript{11,21}

### Urine Output

We were unable to demonstrate any difference in urine output or sodium excretion between the infusion periods. Our data are consistent with previous studies that demonstrated no difference in urine output, sodium excretion, or both\textsuperscript{12–14} with clinically used doses of nesiritide in CHF patients. This has occurred even when hemodynamic changes were documented. As with the GFR results, the lack of diuretic and natriuretic effect may have been secondary to the doses used. Studies that have detected increased urine output, sodium excretion, or both in CHF patients often have used higher doses of nesiritide.\textsuperscript{11} The dose used in the present study was the dose used in the pivotal trials, and the present study indicates that this dose does not have a marked diuretic effect in decompensated CHF patients.

Another possible cause of the present findings relates to the patient population. Good data exist that demonstrate increased urinary sodium in normal individuals. When normal individuals were given BNP at doses causing serum concentrations similar to that seen in mild CHF, BNP induced a 2-fold increase in sodium excretion.\textsuperscript{7} Both natriuresis and diuresis have been reported with nesiritide in normal individuals.\textsuperscript{8} Similar doses in patients with CHF, however, might result in a very different response. Some data support the notion that patients with CHF have a different response to BNP than do normal individuals. In one study the absolute increase in urinary sodium excretion was much lower in CHF patients (27 μmol/min) than in control subjects (190 μmol/min). The distal fractional reabsorption of sodium decreased significantly less in CHF patients than in control subjects.\textsuperscript{14} Even the vascular effects may differ in CHF patients and controls.\textsuperscript{16}

The use of loop diuretics in previous studies has been heterogeneous, but it has been suggested that patients receiving nesiritide might need and receive less diuretic treatment to achieve similar urine output and/or sodium excretion.\textsuperscript{5,22} In the present study all patients received loop diuretics at the beginning of the 6- to 21-hour time period. Although doses varied from patient to patient, the dose on the 2 study days was unchanged. We did not detect a difference in urine output or sodium excretion during nesiritide or placebo infusions despite the same doses of diuretics. Both groups demonstrated the same (and expected) marked increase in urine production and sodium excretion after furosemide administration.

### Limitations

We studied only 15 patients and did not have the power to detect small differences in GFR, ERPF, or urine output. However, our findings are unlikely to be related to the power of the study because there was no trend at any time toward improved renal function with nesiritide. The study was powerful enough to exclude clinically important changes in this patient population. The 95% CIs show a maximum possible effect of only 15% on urine output and 13% on GFR for the 24-hour period. Even these effects would not be expected to change clinical outcomes.

The patients evaluated in this study had both an elevated baseline creatinine (1.5 mg/dL) and a recent deterioration in renal function (creatinine on entry of 1.8 mg/dL); 13 of the 15 patients had mild to moderate chronic renal insufficiency. Thus, the present findings could be related to either (or both or neither) of these abnormalities.

Because we did not use urinary catheters, urine collections may have been incomplete and the data not as precise as desired. However, plasma disappearance of the markers showed no difference between groups, as did the large volume collections between 6 and 21 hours (at which time the effects of incomplete urination should be minimal). In addition, previous studies of similar populations have been able to detect drug effects.\textsuperscript{19} Thus, we believe that the techniques used in this study should not have markedly affected the results.

In conclusion, nesiritide did not improve renal function in patients with decompensated CHF, mild chronic renal insufficiency, and renal function that had worsened compared with baseline. These patient characteristics need to be evaluated to determine their importance as causes of the lack of renal effects of nesiritide. Whether baseline renal insufficiency, acute worsening of renal function, or severity or chronicity of CHF affects the renal response to nesiritide is unknown. Similarly, these patients may need higher drug doses. Understanding the importance of these issues will permit effective and appropriate use of nesiritide.

### References


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