Impact of Nesiritide on Renal Function in Patients With Acute Decompensated Heart Failure and Pre-Existing Renal Dysfunction

A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Ronald M. Witteles, MD,* David Kao, MD,* Dianne Christopherson, PhD, RN,* Kelly Matsuda, PHARMD,* Randall H. Vagelos, MD, FACC,* Donald Schreiber, MD,†‡ Michael B. Fowler, MB, FACC*

Stanford and Palo Alto, California

Objectives

Our purpose was to evaluate the impact of nesiritide on renal function in patients with acute decompensated heart failure and baseline renal dysfunction.

Background

Although nesiritide is approved for the treatment of acute decompensated heart failure, retrospective analyses have raised concerns that it may cause worsened renal function. To date, no randomized clinical trials have prospectively evaluated this issue.

Methods

Consecutive patients with acute decompensated heart failure and baseline renal dysfunction were enrolled in this randomized, double-blind, placebo-controlled clinical trial. Subjects were randomized to receive nesiritide (0.01 μg/kg/min with or without a 2 μg/kg bolus) or placebo (5% dextrose in water) for 48 h in addition to their usual care. Predefined primary end points of the trial were a rise in serum creatinine by ≥20% and change in serum creatinine.

Results

Seventy-five patients were enrolled (39 nesiritide, 36 placebo). The groups had similar baseline age (74.9 vs. 75.5 years, respectively), blood pressure (123/64 vs. 125/64 mm Hg) and serum creatinine (1.82 vs. 1.86 mg/dl). There were no significant differences in the incidence of a 20% creatinine rise (23% vs. 25%) or in the change in serum creatinine (0.05 vs. 0.05 mg/dl). There were no significant differences in the secondary end points of change in weight (−2.19 vs. −1.58 kg), intravenous furosemide (125 vs. 107 mg), discontinuation of the infusion due to hypotension (13% vs. 6%), or 30-day death/hospital readmission (33% vs. 25%).

Conclusions

In this randomized, double-blind, placebo-controlled clinical trial, nesiritide had no impact on renal function in patients with acute decompensated heart failure. (BNP-CARDS trial; http://www.clinicaltrials.gov/ct/show/NCT00186329?order=1; NCT00186329) (J Am Coll Cardiol 2007;50:1835–40) © 2007 by the American College of Cardiology Foundation

One of the main challenges in the treatment of acute decompensated heart failure (ADHF) is worsened renal function. Renal dysfunction independently predicts a worse outcome in heart failure in general and ADHF in particular (1–12). Importantly, it is during the treatment period for ADHF when the effects are most significant, as a decline in renal function during ADHF therapy is a worse prognostic factor than the presence of baseline renal dysfunction (6–8,10–12). Loop diuretics, the mainstay of therapy for ADHF, are associated with worsened renal function, acti-

See page 1841

From the *Division of Cardiovascular Medicine, †Department of Emergency Medicine, Stanford University School of Medicine, Stanford, California; and the ‡Palo Alto Veterans Administration Hospital, Palo Alto, California. This trial was an investigator-initiated study funded by Scios, Inc. Dr. Fowler has received consulting fees/honoraria from Scios, and Drs. Fowler and Schreiber have received research support from Scios.

Manuscript received February 12, 2007; revised manuscript received March 26, 2007, accepted March 28, 2007.
Nesiritide (human recombinant B-type natriuretic peptide), approved by the Food and Drug Administration in 2001, became the first new therapy for ADHF in 14 years. Although its primary mechanism of action is as a systemic and pulmonary vasodilator, it has multiple effects on the kidneys, including promoting natriuresis, diuresis, and inhibiting the renin-angiotensin-aldosterone axis (21–23). Previous studies evaluating non–heart failure patients and stable heart failure outpatients have demonstrated mixed results regarding the effect of nesiritide on glomerular filtration rate (GFR), with some studies suggesting an improvement in GFR (even partially attenuating the negative effects of loop diuretics) and others showing no impact (21,24–30).

Although nesiritide’s effect on renal function was not a primary end point in prior trials, a meta-analysis published in 2005 found that treatment with nesiritide may be associated with worsened renal function (31). This study largely accounted for a dramatic decrease (up to 64%) in the clinical use of nesiritide for the treatment of ADHF (32). Despite this controversy and the importance of renal dysfunction in heart failure outcomes, no study of nesiritide administration on renal function in a population including patients with ADHF and pre-existing renal dysfunction in a prospective, randomized, double-blind, placebo-controlled clinical trial.

Methods

The BNP-CARDS (B-Type Natriuretic Peptide in Cardiorenal Decompensation Syndrome) trial was performed from March 1, 2004, to August 31, 2006, at Stanford University Hospital and from February 1, 2006, to August 31, 2006, at the Palo Alto Veterans Administration Hospital. All newly admitted inpatients during those periods with a primary diagnosis of ADHF were screened for the trial. Further inclusion criteria included a calculated GFR (using the Cockcroft-Gault formula) between 15 to 60 ml/min (changed from 15 to 50 ml/min in December 2004 to be consistent with the published definition of “moderate renal impairment”), and age ≥18 years (34,35). Exclusion criteria included baseline hypotension (systolic blood pressure <90 mm Hg), hemodynamically significant aortic stenosis, need for intravenous (IV) vasodilator therapy, admission to an intensive care unit, history of cardiac transplantation, allergy to nesiritide, and prior enrollment in the trial. Subjects were enrolled within 12 h of hospital admission. The protocol was approved by the human subjects committees at both study sites.

After written informed consent was obtained, patients were randomized in a 1:1 fashion to receive a fixed-dose nesiritide infusion (2 μg/kg IV bolus followed by a continuous infusion at 0.01 μg/kg/min for 48 h) or matching placebo (5% dextrose in water mimicking the same dosing). Randomization was performed by the research pharmacist at each site using a random number generator. The bolus could be held at the discretion of the treating physician (separate from the study investigators) if there was clinical concern for the development of significant hypotension, usually for baseline systolic blood pressure 90 to 109 mm Hg. The remainder of the medications administered to the patient (including diuretics) was at the discretion of the treating physician. Patients were monitored for adverse reactions to nesiritide, including hypotension. The infusion was discontinued at the discretion of the treating physician if the subject developed symptomatic hypotension. Serum creatinine was measured daily during the infusion. All clinicians and study personnel were blinded to the subject’s randomization.

The predefined primary end points of the trial were:

1. A significant decline in renal function (defined as a peak serum creatinine increase of ≥20% at any time during the first 7 days of hospitalization compared with the admission creatinine).
2. Change in serum creatinine from the admission value to discharge and/or day 7 of hospitalization, whichever was sooner.

Secondary end points included net negative diuresis ≥1 l/day while on the infusion; change in weight during the infusion; need to discontinue the infusion due to hypotension; total diuretic use while receiving the infusion; median length of stay; death or rehospitalization within 30 days; and resource utilization—defined by need for dialysis, intensive care monitoring, pulmonary artery catheterization, and intubation. Results were analyzed by Student t test and chi-square analysis, as appropriate. The study had 80% power at an alpha of 0.05 to detect a 28% relative difference in the first primary end point assuming a 25% event rate, and to detect a creatinine difference of 0.20 mg/dl in the second primary end point assuming a standard deviation of 0.30 mg/dl. Data were analyzed in an intention-to-treat fashion.

Results

Of 514 consecutive patients admitted with ADHF, 75 met inclusion/exclusion criteria and provided informed consent.

The baseline characteristics of the 2 groups were similar (Table 1). In particular, average age and serum creatinine were very similar between the 2 groups. A large portion of patients in each group (46% in the nesiritide group, 50% of the placebo group) were over 79 years of age.
There was no difference in the primary end points of renal dysfunction—either a ≥20% increase in serum creatinine, or the change in creatinine from the admission value (Fig. 1, Table 2). There was no significant difference in net weight loss or net fluid balance between the 2 groups, with slight trends for more weight loss/net negative fluid balance in the nesiritide group balanced by a trend toward higher doses of diuretics administered to that group. There were no gender-based differences in the results in either group.

Table 1 Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Nesiritide (n = 39)</th>
<th>Placebo (n = 36)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (yrs)</td>
<td>74.9</td>
<td>75.5</td>
<td>0.85</td>
</tr>
<tr>
<td>% male</td>
<td>67</td>
<td>61</td>
<td>0.62</td>
</tr>
<tr>
<td>Admission creatinine (mg/dl)</td>
<td>1.82</td>
<td>1.86</td>
<td>0.79</td>
</tr>
<tr>
<td>Admission GFR (ml/min, estimated)</td>
<td>35</td>
<td>33</td>
<td>0.48</td>
</tr>
<tr>
<td>% systolic dysfunction (LVEF &lt;45%)</td>
<td>55</td>
<td>62</td>
<td>0.58</td>
</tr>
<tr>
<td>Outpatient furosemide dose (mg/day)</td>
<td>65</td>
<td>55</td>
<td>0.50</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>123</td>
<td>125</td>
<td>0.77</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>64</td>
<td>64</td>
<td>0.87</td>
</tr>
<tr>
<td>% of patients taking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>72</td>
<td>58</td>
<td>0.22</td>
</tr>
<tr>
<td>ACE-I and/or ARB</td>
<td>51</td>
<td>47</td>
<td>0.73</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>15</td>
<td>11</td>
<td>0.59</td>
</tr>
<tr>
<td>Digoxin</td>
<td>28</td>
<td>25</td>
<td>0.75</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>21</td>
<td>6</td>
<td>0.06</td>
</tr>
<tr>
<td>Calcium blocker</td>
<td>23</td>
<td>25</td>
<td>0.85</td>
</tr>
<tr>
<td>Long-acting nitrate</td>
<td>23</td>
<td>28</td>
<td>0.64</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>5</td>
<td>25</td>
<td>0.02</td>
</tr>
<tr>
<td>History of (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>90</td>
<td>89</td>
<td>0.90</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>77</td>
<td>56</td>
<td>0.0499</td>
</tr>
<tr>
<td>COPD</td>
<td>26</td>
<td>19</td>
<td>0.52</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>56</td>
<td>44</td>
<td>0.30</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>44</td>
<td>36</td>
<td>0.51</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>8</td>
<td>19</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Values in bold indicate statistical significance.

Table 2 Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nesiritide (n = 39)</th>
<th>Placebo (n = 36)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in creatinine (mg/dl)</td>
<td>–0.05</td>
<td>0.05</td>
<td>0.46</td>
</tr>
<tr>
<td>Diuresis &gt;1 l/24 h (%)</td>
<td>49</td>
<td>48</td>
<td>0.91</td>
</tr>
<tr>
<td>Length of stay (median days)</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Length of stay (mean days)</td>
<td>5.85</td>
<td>5.67</td>
<td>0.91</td>
</tr>
<tr>
<td>Weight loss (kg)</td>
<td>2.19</td>
<td>1.58</td>
<td>0.26</td>
</tr>
<tr>
<td>Net fluid balance (l)</td>
<td>–1.99</td>
<td>–1.90</td>
<td>0.86</td>
</tr>
<tr>
<td>IV furosemide during infusion (mg)</td>
<td>124.5</td>
<td>106.7</td>
<td>0.53</td>
</tr>
<tr>
<td>Oral furosemide during infusion (mg)</td>
<td>34.8</td>
<td>28.8</td>
<td>0.45</td>
</tr>
</tbody>
</table>

There were no statistically significant differences in complications/adverse outcomes between the 2 groups, although there was a nonsignificant trend for the infusion being stopped more frequently in the nesiritide group due to hypotension (Table 3). Systolic and diastolic blood pressures trended lower in the nesiritide group at almost all time points, with significantly lower values than in the placebo group at 3, 6, and 12 h (Fig. 2).

Thirty-five percent of subjects had their bolus held by the treating physician (33% randomized to nesiritide, 36% randomized to placebo, p = NS). Subjects who received a bolus had higher baseline systolic blood pressures than subjects who had the bolus withheld (132 vs. 110 mm Hg, p < 0.0001). Subjects who received a nesiritide bolus had a nonsignificant trend (p = 0.15) toward a larger drop in systolic blood pressure 1 h after the infusion started (8.6 mm Hg) than those who had the bolus held (–0.9 mm Hg). There was no significant association between receiving a bolus and any of the predefined end points.

Discussion

The main finding of this study was that, in a cohort of patients with baseline renal insufficiency and ADHF, administration of nesiritide in addition to standard therapy did not result in worsened renal function. Importantly, administration of nesiritide did not protect against the development of renal dysfunction either. Therefore, whereas nesiritide appears to be safe in this population of patients from a renal standpoint, this trial provided no evidence for a therapeutic role to protect renal function.

One possible explanation for the disparate findings between this and previous studies is the use of a bolus dose. In
most previous studies, a 2-μg/kg IV bolus dose was adminis-
tered to patients, as per the protocol in the VMAC
(Vasodilation in the Management of Acute Congestive
Heart Failure) trial (36). The majority of the VMAC trial
population consisted of patients who, in the clinicians’
judgment, required a pulmonary artery catheter for manage-
ment before being enrolled in the trial (36). Their clinical
characteristics—an average pulmonary capillary wedge pres-
sure of 28 mm Hg, an average systemic vascular resistance
of over 1,400 dynes/s/cm$^5$, and the clinical need for a pulmo-
nary artery catheter—were such that a large bolus of a
vasodilator might be desirable. This represents a very
different population from many ADHF patients, who rarely
require a pulmonary artery catheter and who can usually
afford the 1 to 2 h necessary to gradually reach steady-state
concentration of the drug. Indeed, for a drug with a half-life
of approximately 20 min, steady-state concentrations are
reached relatively quickly with the continuous IV infusion
without administering a bolus. It is certainly conceivable
that any positive or neutral effects of nesiritide on GFR
might be overcomplicated by significant hypotension occurring
with the bolus dose, possibly accounting for some of the
worsened renal function seen in other retrospective analyses.

The recently published NAPA (Nesiritide Administered
Peri-Anesthesia in Patients Undergoing Cardiac Surgery)
trial found that peripheric use of nesiritide in patients
with left ventricular dysfunction undergoing coronary artery
bypass grafting protected against renal dysfunction and was
notable for the fact that a bolus dose was not included in the
protocol (37). The patients in the NAPA trial were very
different from those evaluated in our trial, most notably
because the NAPA trial cohort did not evaluate patients
with ADHF (for whom nesiritide is Food and Drug
Administration approved). Although only 1 of the 5 sub-
jects in our study who had the nesiritide infusion discon-
tinued due to hypotension received a bolus, this is likely a
reflection of the fact that the group who received the bolus
had significantly higher baseline blood pressure than the
group who had the bolus withheld. Receiving a nesiritide
bolus was associated with a trend toward developing a larger
drop in systolic blood pressure at 1 h in our study.

A second difference between our trial and other studies is
the dose of nesiritide infusion used. In our trial, all patients
randomized to the nesiritide arm received the recommended
starting dose of 0.01 μg/kg/min, a dose that retrospective
analyses have found to be more consistent with a neutral or
positive effect on renal function (38,39). Past studies have
used doses between 0.01 and 0.06 μg/kg/min, with higher
doses leading to more hypotension and more reports of
worsened renal function (31,36,39).

Another possible difference between the results of our
trial and observations from previous trials is the timing
when the nesiritide infusion was initiated. In our study, all
patients were started within 12 h of hospitalization, before
they might have otherwise been aggressively diuresed with
loop diuretics. This earlier administration may have con-
tributed to a lower incidence of hypotension, and may have
also prevented up-regulation of the renin-angiotensin-
aldosterone system otherwise associated with loop diuretic
administration (14–16,19,20).

A final important difference between our study and earlier
trials is the makeup of the study population. Our trial
design, which targeted all consecutive patients who met
entry criteria, was intended to yield a patient population
representative of admissions for heart failure in the general
population—and not surprisingly included many patients of
advanced age (48% of patients were >79 years of age) and
many patients with heart failure with preserved systolic
function (42%). This is opposed to a mean age of 61 years
and only 15% of patients with a left ventricular ejection
fraction >40% in the VMAC trial (36). Importantly, older
average age and higher prevalence of preserved systolic
function are both characteristics of the “cardiorenal” patient
(3,6,7,11).

Patients in the nesiritide group did develop significantly
lower systolic and diastolic blood pressure, with a trend
favoring the infusion needing to be discontinued for hypo-
tension more frequently. Despite this lower blood pressure,
patients in the nesiritide group did not develop worsened
renal dysfunction. A possible explanation may be the bal-
ance of “direct” and “indirect” effects of natriuretic peptides
on renal function. Direct effects of natriuretic peptides serve
to increase GFR by relaxing renal mesangial cells, dilating
the afferent renal artery, and constricting the efferent
renal arteriole; indirect effects serve to decrease GFR by
inhibiting the renin-angiotensin-aldosterone and sympa-
thetic axes and by lowering systemic blood pressures and
circulating blood volume (21,40–43). It is likely the balance
of these direct and indirect effects that causes GFR to
increase, decrease, or stay the same in individual patients. In
our cohort of patients with nesiritide administered per our
protocol, the net effect on GFR was neutral.
There were several important limitations to this study. Although this represents the largest randomized trial to prospectively evaluate the effect of nesiritide on renal function in ADHF, the number of participants still could allow for a type II error. A large treatment effect on the primary end points is unlikely given the lack of even a trend in either direction, but a smaller and potentially clinically relevant effect is still possible. Another limitation to this trial was the exclusion of important subgroups of ADHF patients, including those needing intensive care and those requiring IV vasodilator therapy; the results of this trial certainly do not exclude a potentially important effect of nesiritide (positive or negative) on renal function in those patients. Finally, although our trial was not powered to evaluate mortality and hospital readmission, there were nonsignificant trends observed in favor of placebo. Due to the relatively small sample size, the lack of statistical significance does not rule out differences in these outcomes.

Conclusions

The results of this prospective, randomized, double-blind, placebo-controlled clinical trial indicate that nesiritide therapy does not cause or prevent worsened renal function in patients with ADHF and pre-existing renal dysfunction. Data regarding the renal effects of nesiritide therapy in other patient populations, and effects on other clinical end points, await the result of other randomized trials.

Reprint requests and correspondence: Dr. Ronald M. Witteles, Division of Cardiovascular Medicine, Stanford University School of Medicine, 300 Pasteur Drive, Falk CVRC, Stanford, California 94305. E-mail: witteles@stanford.edu.

REFERENCES