Nesiritide Treatment for Acute Decompensated Heart Failure

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There are approximately 1.1 million hospitalizations for acute decompensated heart failure (ADHF) in the United States each year.[1] Despite recent advances, the management of these patients remains problematic. Approximately 4% of these patients will die during the index hospitalization, and 20% will succumb within 6 months of hospitalization.[2,3] Approximately 45% will be rehospitalized within 12 months of discharge.[4]

The Heart Failure Society of America (HFSA) has recently published comprehensive guidelines to aid in the management of these patients.[5] According to these guidelines, as well as to the 2005 European Society of Cardiology (ESC) guidelines, symptomatic improvement is an important treatment goal.[4,5] However, the latest data from the National Acute Decompensated Heart Failure Registry (ADHERE®) indicate that only 50% of patients are asymptomatic at the time of discharge.[6] Improving this rate will require more aggressive strategies for in-hospital management.

Acknowledgment: Dr. Burger has received research grants from Scios Inc. and is on the Scios speakers' bureau, but he has received no remuneration for the authorship of this article. Scios Inc. provided editorial and technical support for the development of this article.

Therapeutic options for ADHF include intravenous (IV) diuretics, vasodilators, and inotropic agents.[4,5] According to published guidelines, loop diuretics, either alone or in combination with vasodilators, are indicated as initial therapy for patients with evidence of fluid overload and adequate blood pressure.[4,5] Diuretics provide symptomatic relief in patients with signs and symptoms of fluid overload. However, they may produce adverse effects including electrolyte/metabolic abnormalities, reduced renal perfusion, and worsening renal function in susceptible individuals, and decreased cardiac output and increased systemic vascular resistance as a result of excessive diuresis. Vasodilators reduce filling pressures, indirectly increase cardiac output, and improve congestive symptoms.[5] Excessive or inappropriate vasodilation can lead to hypotension and changes in renal function. Inotropic agents augment myocardial contractility and improve short-term hemodynamics. However, they can cause arrhythmias and worsen ischemia. Current HFSA/ESC guidelines recommend that use of inotropic agents be limited to patients who have diminished peripheral perfusion or end-organ dysfunction and systolic blood pressure less than 90 mm Hg or symptomatic hypotension despite adequate filling pressures, and to patients who are unresponsive to vasodilators.[4,5] For the majority of these agents, there is little evidence from large, randomized, controlled trials to guide therapy.

Clinical Significance of Endogenous B-Type Natriuretic Peptide in ADHF

B-type natriuretic peptide (BNP) is an endogenous cardiac hormone with salt and water regulatory properties that antagonize the effects of the renin-angiotensin-aldosterone system and the sympathetic nervous system.[7-9] BNP has a direct relaxant effect on human vascular tissue, producing balanced vasodilation. It reduces mean arterial pressure, pulmonary capillary wedge pressure, pulmonary artery pressure, right atrial pressure, and systemic vascular resistance, with a resultant increase in cardiac output.[7-10] BNP improves coronary blood flow[11] and, unlike other vasodilators, inhibits neurohormonal activation.[7,8,12,13] However, the effects of BNP are often blunted in patients with advanced heart failure due to a variety of factors, including receptor interference by angiotensin II and faulty processing of the prohormone.[9,14]

Nesiritide in the Management of ADHF

HFSA guidelines recommend that IV vasodilator therapy (nesiritide, nitroglycerin, or nitroprusside) may be added to diuretic therapy for rapid symptomatic improvement in patients with ADHF who do not have symptomatic hypotension (Section 12.15).[5] Frequent blood pressure monitoring is recommended with these agents, and the dosage should be decreased or discontinued if symptomatic hypotension develops.

Administration of human recombinant BNP (nesiritide) at doses from 0.01 μg/kg/min to 0.03 μg/kg/min increases plasma BNP levels by 3-fold to 6-fold in ADHF patients. Nesiritide is indicated for ADHF patients with dyspnea at rest or with minimal activity, based on data from the Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial, which found nesiritide to be superior to the standard of care. Although the VMAC trial was not powered to evaluate the efficacy of nesiritide versus nitroglycerin, it does allow for important comparisons of each vasodilator relative to placebo plus standard therapy. In this trial, at the 3-hour time point, nesiritide plus standard therapy significantly reduced pulmonary capillary wedge pressure, mean pulmonary artery pressure, right atrial pressure, and systolic blood pressure, whereas nitroglycerin significantly reduced only systolic blood pressure relative to patients on placebo plus standard therapy.[15] Similarly, at the 3-hour primary endpoint, symptoms of patient-reported dyspnea were significantly improved in nesiritide subjects relative to placebo ($P = .03$).

A recent evaluation of ADHERE® data found that, compared with patients who had nesiritide initiated "late" (median 15.5 hours after hospital arrival), patients who had nesiritide initiated "early" (median 2.8 hours after hospital arrival) had a shorter mean duration of hospitalization (5.4 vs 6.9 days; $P < .001$) and were less likely to require transfer to the intensive care unit from another inpatient unit (odds ratio, 0.301; 95% confidence interval [CI], 0.206-0.440).[16] The results of this analysis are limited by the constraints of observational data, and no direct causal relationship can be established.

Chronic renal insufficiency is a common comorbidity in patients with heart failure. Approximately 20% of patients in the VMAC trial and 30% of patients in ADHERE® had renal insufficiency.[6,15] These patients may be nonresponsive or only partially responsive to treatment despite aggressive diuretic use.[17] HFSA guidelines recommend that IV vasodilator therapy, including nesiritide, may be added when patients have not adequately responded to an aggressive trial of diuretics and standard oral therapies (Section 12.17).[5] In clinical evaluations, the effects of nesiritide on pulmonary capillary wedge pressure, cardiac index, and systolic blood pressure in patients with chronic renal insufficiency were not significantly different than those in patients with normal renal function.[18] Since the most important mechanisms by which nesiritide is eliminated do not involve the kidney, dose adjustment is not required in these patients.[18]

In clinical trials, when nesiritide was initiated at doses higher than 0.01 μg/kg/min (0.015 μg/kg/min and 0.03 μg/kg/min), there was an increased rate of elevated serum creatinine (SCr) over baseline compared with standard therapies, although the rate of acute renal failure and need for dialysis was not increased (2.5% vs 2.2%; $P = .71$).[18,19] In the VMAC trial, using the approved 0.01 μg/kg/min infusion starting dose, 38 of 268 nesiritide subjects (14%) and 25 of 212 nitroglycerin subjects (12%) experienced an acute increase in SCr of more than 0.5 mg/dL during hospitalization.[20] Mean SCr values through day 30 for both treatment groups in VMAC patients with and without renal insufficiency are represented in Figure 1. VMAC was not designed to compare SCr changes between treatment groups or subpopulations.

In an analysis of 5 nesiritide trials that collected SCr data, patients who had an increase in SCr greater than 0.5 mg/dL at any time through 30 days had a corresponding mortality rate of 7.3% when treated with nesiritide and 13% when treated with standard therapies (Figure 2).[21] Unadjusted mortality data from all 7 randomized clinical trials conducted with nesiritide in patients with heart failure show a crude 30-day mortality rate of 5.5% for nesiritide-treated patients compared with 4.3% for control patients receiving standard therapies.

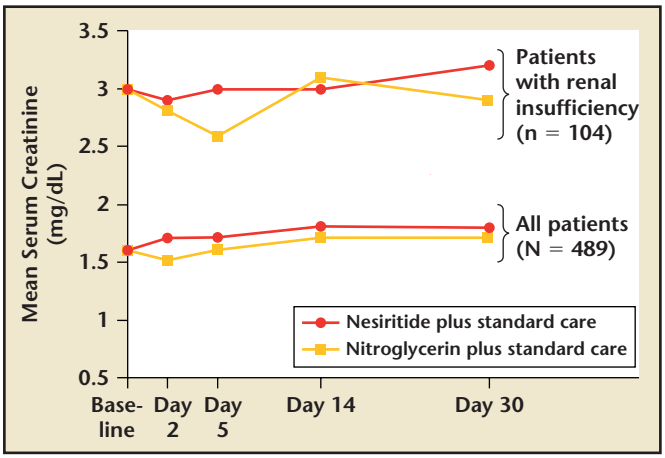

Figure 1. *Mean serum creatinine (SCr) in the Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial in all patients (N = 489) and in the subgroup of patients with baseline renal insufficiency (defined as baseline SCr ≥ 2.0 mg/dL, n = 104). The study drug was discontinued following 24 to 48 hours of treatment in the majority of patients in VMAC.*

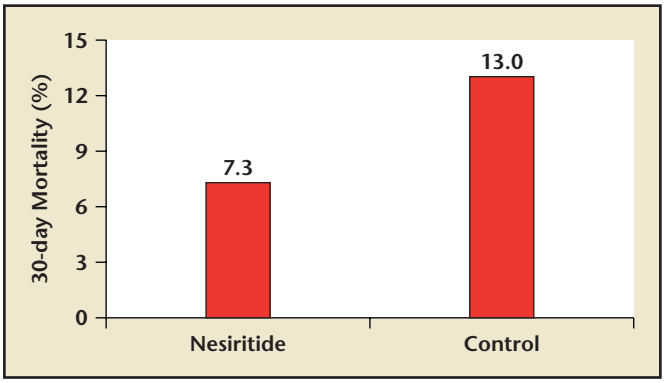

Figure 2. *Thirty-day mortality in patients with serum creatinine increases of more than 0.5 mg/dL who were treated with nesiritide or standard therapy, based on a pooled analysis of 5 trials.[21]*

Mortality rates at 180 days are 21.5% and 20.7%, respectively.[18,22] A retrospective analysis of data for 65,000 patients from ADHERE® showed an in-hospital mortality odds ratio of 0.94 (95% CI, 0.77-1.16; P = .58) for nesiritide compared to nitroglycerin, after adjusting for baseline differences in risk factors and propensity score.[23] Because the information presented above exists as either unadjusted data from clinical trials not designed to formally assess mortality as an endpoint or as observational data with known limitations, it is inconclusive. To date, there is not enough information to know about the effect of nesiritide on mortality.

Working Toward Best Practice

ADHERE® data suggest that most patients with ADHF may not be receiving optimal treatment.[6] Overall, 51% of patients in ADHERE® had either a weight gain or a weight loss of less than 5 pounds during their hospitalization, and only 50% were asymptomatic at the time of discharge.[6] HFSA and ESC guidelines cite the value of IV vasodilator therapy for symptomatic improvement in combination with diuretics, and ADHERE® data suggest that many patients with ADHF are eligible for this treatment.[4-6] At hospital presentation, 89% of patients in ADHERE® had dyspnea (34% at rest), and only 2% were ineligible for vasodilator therapy based on systolic hypotension (< 90 mm Hg).[6] Despite this, nesiritide and nitroglycerin were used in only 13% and 9% of patients, respectively, whereas 62% of patients received IV diuretic monotherapy.[6]

Nesiritide is recombinant human BNP, a cardiac regulatory hormone with important vasodilatory properties. Nesiritide is indicated for the treatment of ADHF patients with dyspnea at rest or with minimal exertion.[18] Its use is consistent with current HFSA and ESC guidelines recognizing the importance of IV vasodilator therapy for symptomatic relief. When added to standard care, nesiritide is superior to placebo in lowering pulmonary capillary wedge pressure and improving patient-reported dyspnea.[18] ■

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Previews in Cardiovascular Medicine highlights topics of interest to cardiologists and is supported by the companies that sponsor publication of this journal; the material has not been reviewed by the Medical and Contributing Editors.

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