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## Nesiritide

(Natreacor<sup>®</sup> - Scios)

### Summary

**Indication:** Nesiritide is indicated for the intravenous treatment of acutely decompensated heart failure in patients who have dyspnea at rest or with minimal exertion. It is not classified in any currently used drug classes and has both natriuretic and vasodilatory properties.

**Monitoring Parameters:** Patients should be monitored for the symptoms of acute congestive heart failure such as dyspnea and fatigue, as well as clinical readings such as pulmonary coronary wedge pressure, heart rate, cardiac index, and systolic blood pressure. Systolic blood pressure readings below 90 mm Hg warrant a decrease or discontinuation of nesiritide infusion. Potential adverse events that should be monitored are systemic hypotension and more rare electrolyte imbalances, such as hypokalemia and hypomagnesemia. Nesiritide should be avoided in patients with low cardiac filling pressures, valvular stenosis, restrictive or obstructive cardiomyopathy, or other conditions in which cardiac output is dependent on venous return.

**Dose:** The recommended dosing regimen for nesiritide is a 2 microgram/kg intravenous bolus, followed by an intravenous infusion of 0.01 mcg/kg/min. This infusion may then be modified based on blood pressure readings and patient response. Published studies have used infusion rates as high as 0.03 mcg/kg/min. Duration of infusion varies, but therapy with an infusion of 0.015 mcg/kg/min resulted in an average of 2.1 day treatment.

**Pediatrics:** The effectiveness and safety of nesiritide has not been established in pediatric populations. No pediatric patients were used in any of the studies reviewed and the youngest patient found in the reviewed literature was 33 years old.

**Geriatrics:** No overall difference in the effectiveness of nesiritide between younger and older patients has been established. Although nesiritide is renally cleared there was no established need for dosage decreases in patients with renal insufficiency. Dosages have, however, been adjusted for weight differences, as is seen in the dosing recommendations (mcg/kg/min).

**Pregnancy:** Category C: No animal reproductive studies have been conducted with nesiritide. It is also not known whether nesiritide can cause fetal harm when administered to pregnant women, or if it has the capacity to affect reproductive function. Nesiritide should be used during pregnancy only if

the potential benefit justifies any potential risk to the fetus.

**Breast Feeding:** The safety of use of nesiritide in nursing women has not been measured.

**Cost:** \$371.41 for a 1.5 mg vial. A bolus of 2 mcg/kg followed by 0.01 mcg/kg/min 24 hour infusion in a 70 kg patient would cost \$284.25.

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### Introduction

Congestive heart failure is a condition in which myocardial dysfunction creates an inability of the heart to circulate blood at a rate sufficient to meet the metabolic needs of peripheral tissues and organs.<sup>1,2,3</sup> Failure can be systolic and/or diastolic in nature and is the most common hospital discharge diagnosis in patients over the age of 65.<sup>1</sup> It is estimated that 2 million Americans have heart failure and that an additional 400,000 develop the condition each year.<sup>2</sup> Hospitalization for the primary treatment of heart failure occurs in 900,000 Americans each year, and an additional 1.8 million are treated for heart failure as a secondary condition.<sup>2,3</sup> There is an estimated mortality of 200,000 annually, and patients classified by the New York Heart Association scale as class IV have an annual mortality rate of 40-50%.<sup>2</sup> Heart failure is more common in men than in women, and the mean length of survival post-diagnosis is 1.7 years for men and 3.2 years for women. Death is often classified as sudden (20-50%) in these patients, implying that the underlying cause of death is likely ventricular arrhythmia.<sup>1</sup>

Heart failure is initiated by a decrease in heart function, usually caused by an acute myocardial infarction, prolonged stress due to hypertension or valvular dysfunction, toxins (as seen in alcohol abuse), or infection. This loss of function leads to a reduced filling of the heart and/or reduced contractility of the myocardium, creating a need for physiologic compensation.<sup>1,2</sup> Heart failure is often identifiable by its common symptoms of dyspnea and fatigue. The inability of the heart to create sufficient blood pressure throughout the body initiates various physiological response mechanisms that allow the heart to

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compensate for the decreased filling. As cardiac function decreases, three major compensatory mechanisms are enacted to maintain cardiac output. The first two occur almost immediately as an increase is seen in both sympathetic nervous system output (norepinephrine) and in pre-load, leading to increased stroke volume (Frank-Starling mechanism).<sup>1</sup> The third compensatory mechanism, ventricular hypertrophy, occurs over time, as the heart is forced to work harder than it would in normal conditions.<sup>1</sup> Cardiac volume and pressure increases caused by compensatory mechanisms in heart failure lead to the synthesis and excretion of human b (brain)-type natriuretic peptide (hBNP) by the left ventricle.<sup>4,5,6,7</sup> In this way, levels of natriuretic peptides, more specifically hBNP, serve as a sensitive marker indicative of heart failure and allow for the identification of asymptomatic heart failure. This physiological response to hBNP, or a synthetic version, may be beneficial in the treatment of heart failure.<sup>8</sup>

Compensation eventually results in cavitory dilation, elevated intracardiac pressures, decreased cardiac output and a diminished functional reserve. Compensation is effective at first, but often leads to fibrosis and a decrease in cardiac function, leading to decreased systolic function, increased diastolic pressures and ventricular dimensions, and continuous remodeling of myocardial architecture.<sup>2</sup> Eventually the compensatory mechanisms of the circulatory system and the heart itself are overwhelmed or exhausted and the heart fails.<sup>1,2</sup>

At times, patients with heart failure may experience periods of acute decompensation, typically identified by sudden onset of effort intolerance, dyspnea, and other presenting symptoms. This decompensation warrants acute medical treatment, the methods of which have changed very little in the last ten years.<sup>3</sup> These acute exacerbations of heart failure are currently treated with one or a combination of the following: vasodilators, inotropic agents, or diuretics either as monotherapy or in various combinations. Dopamine, dobutamine, nitroprusside, nitroglycerin, amrinone, milrinone and furosemide are the most common agents used in current therapies, each of which performs a function related to relieving the stress on the heart.<sup>1,2</sup> These agents, however, are not perfect by any means. One of the most prevalent concerns found in using the aforementioned agents is an increased tendency for arrhythmia. Natriuretic peptides, such as hBNP, have been shown to decrease pulmonary artery wedge pressure and mean arterial pressure and increase cardiac index (CI), urine volume and sodium excretion without a normally associated adverse neurohormonal activation.<sup>6,7</sup> The therapeutic advantage of hBNP to currently available vasodilators used in acutely decompensated congestive heart failure is its claimed ability to attenuate reflex responses with a lower propensity for causing arrhythmias.<sup>5</sup>

### Pharmacology/Pharmacokinetics

Nesiritide is an exogenous form of human b (brain)-type

natriuretic peptide (hBNP), a 32 amino acid peptide manufactured from *E. Coli* using recombinant DNA technology.<sup>4,9</sup> These levels serve as a sensitive marker for left ventricular dysfunction, as the role of this hormone, secreted mainly by the ventricle in response to vascular wall stress, is diuresis, natriuresis and vasodilation.<sup>4</sup> Human BNP binds to the guanylate cyclase receptor of vascular smooth muscle and endothelial cells, leading to the relaxation of smooth muscles through an increase in intracellular concentrations of guanosine 3',5'-cyclic monophosphate (cGMP).<sup>5,9</sup> Cyclic GMP acts as a second messenger to dilate veins and arteries.<sup>5,9</sup>

Nesiritide has a mean terminal elimination half-life of approximately 18 minutes, which is associated with approximately two thirds of the area-under-the-curve (AUC).<sup>5,9</sup> The drug has also been found to have biphasic distribution from the plasma.<sup>9</sup> In patients with CHF, the mean initial elimination phase is approximately 2 minutes. The mean volume of distribution in the central compartment is approximately 0.073 L/kg, the mean steady state volume of distribution is 0.19 L/kg, and the mean clearance is approximately 9.2 mL/kg.<sup>9</sup> At least 60% of 3-hour effect of nesiritide on pulmonary capillary wedge pressure occurs in 15 minutes after administration; 95% is found at one hour.<sup>5</sup> Elimination of hBNP occurs by three independent mechanisms. The first, and most prominent, method of elimination is through binding to cell surface clearance receptors followed by cellular internalization and lysosomal proteolysis.<sup>9</sup> The second is proteolytic cleavage by endopeptidases that are found on the vascular luminal surface, the kidneys and the lungs.<sup>8,9</sup> The third, and least prominent, mode of elimination is renal clearance.<sup>9</sup>

### Clinical trials

#### *Acutely Decompensated Congestive Heart Failure*

The efficacy of nesiritide was evaluated in an open-label, randomized, multi-center, active control trial in 305 patients (261 were included in the final analysis) with a history of congestive heart failure who presented with symptomatic, acutely decompensated congestive heart failure for which parenteral vasoactive therapy was deemed necessary.<sup>5</sup> Patients were randomly assigned to one of three groups for a maximum of seven days. These groups were monotherapy with a standard care agent (a single intravenous vasoactive drug routinely used for the management of decompensated heart failure including dobutamine, milrinone, nitroglycerin, dopamine and amrinone) (n=102), nesiritide 0.015 mcg/kg/min intravenous infusion after an intravenous bolus of 0.3 mcg/kg (n=103), and nesiritide 0.03 mcg/kg/min after an intravenous bolus of 0.6 mcg/kg (n=100). The study was masked with regard to the dose of nesiritide being administered, but not to the identity of the drug being given. Cardiac arrest (defined here as an unresponsive patient with no palpable pulse and no spontaneous respiration, requiring closed chest compression for response) and ven-

tricular tachycardia (VT; defined as three or more consecutive ventricular premature complexes with a rate of more than 100 beats per minute) were considered primary efficacy measures. Further differentiation was made between sustained VT (> 30 seconds) and non-sustained VT. Continuous clinical hemodynamic and electrocardiographic monitoring occurred throughout the drug infusion, and blood pressure, heart rate and respiratory rate were taken at baseline and every 15 minutes for 2 hours, every 30 minutes for 1 hour, at 4 and 5 hours and then at least every 4 hours thereafter. For the purpose of analysis, the group of 'standard therapy patients' was reduced to those receiving dobutamine (total sample size reduced from 305 to 261). No analysis was conducted on the groups receiving milrinone, nitroglycerin, dopamine or amrinone, as they were considerably smaller than the dobutamine group.<sup>7</sup>

Dobutamine dosing occurred at a mean of 4.3+/-1.5 mcg/kg/min and was increased to an average of 5.4+/-2.6 mcg/kg/min. Dose reductions occurred 50% of the time in dobutamine patients, compared to 17 and 18% with the low and high dose nesiritide groups, respectively. Total duration of vasoactive therapy was 3.7+/-4.1 days for the dobutamine group, 2.1+/-1.8 days for the low dose nesiritide group and 1.8+/-1.6 days for the higher dose nesiritide group. Addition of a second vasoactive medication was required in 20 (10%) of the nesiritide patients, while seven (12%) of the dobutamine patients needed additional medications. Cardiac arrest occurred in three (5%) of the dobutamine patients and none of the patients receiving nesiritide ( $p=0.011$ ). Sustained VT occurred in four (7%) dobutamine patients, two (2%) high-dose nesiritide patients, and no low-dose nesiritide patients ( $p=0.014$ ). Non-sustained VT occurred in 10 (17%) dobutamine patients, 17 (17%) of low-dose nesiritide patients and 6 (6%) of high-dose nesiritide patients ( $p=0.029$ ). Adverse effects were uncommon in both dobutamine and nesiritide. Hypokalemia occurred in 3% of all patients, regardless of therapy, and hypomagnesemia occurred in 3% of low-dose nesiritide, 1% of high-dose and no dobutamine patients. Symptomatic hypotension was found in 12% of those receiving low-dose nesiritide, 18% high-dose nesiritide and 5% dobutamine ( $p=0.061$ ). During the 21 day study period death occurred in 5 (9%) dobutamine patients, 6 (6%) low-dose nesiritide and 6 (6%) high-dose nesiritide patients.

In a randomized, double-blind, placebo-controlled trial, the short-term efficacy of nesiritide with regard to hemodynamic measures and symptoms was analyzed.<sup>6</sup> The primary endpoint in this study was the change from baseline in pulmonary capillary wedge pressure (PCWP) 6 hours after the start of therapy. Secondary endpoints were global clinical status, clinical symptoms and other hemodynamic measurements. Patients in the trial were assigned in equal numbers using blocks of 12 to the following treatment groups: placebo (D5W) bolus followed by constant intravenous placebo infusion,

nesiritide 0.3 mcg/kg IV followed by an infusion of 0.015 mcg/kg/min, and nesiritide 0.6mg/kg followed by 0.03 mcg/kg/min. The identities of treatment groups were revealed to investigators after 6 hours of infusion. In instances where systolic blood pressure dropped below 85 mm Hg, infusions were stopped and then resumed at 50% of the earlier dose once the blood pressure had stabilized at 90 mm Hg or greater. Global clinical status, as well as dyspnea and fatigue were assessed at baseline and at 6 hours. Global clinical status was rated independently by the investigator and the patient on a five-point scale (markedly better, better, no change, worse, markedly worse). Dyspnea and fatigue were each rated jointly by the patient and investigator on a three-point scale (improved, no change, worse). Three pulmonary capillary wedge pressure and cardiac index readings were taken before drug administration. Mean right arterial pressure, PCPW, cardiac index, pulmonary arterial pressures, systolic blood pressure and heart rate were recorded at 1.5, 3, 4.5 and 6 hours after the start of drug infusion. Plasma aldosterone and norepinephrine levels were taken at baseline and at 6 hours. Treatment was discontinued in five patients before 6 hours due to sustained VT (1, placebo group), worsening congestive heart failure (1, low-dose nesiritide), symptomatic hypotension and nausea, excessive decrease in PCWP, and oliguria (1 each, high-dose nesiritide).

Nesiritide administration led to dose-related decreases in PCWP of -6.0 +/-7.5mm Hg and -9.6+/-6.2 mm Hg for low- and high-dose nesiritide, respectively ( $p<0.001$ ). Right atrial pressure (-2.6+/-4.4 and -5.1+/-4.7 mm Hg,  $p<0.001$ ), systemic vascular resistance (-247+/-492 and -347+/-499 mm Hg,  $p<0.001$ ), and systolic blood pressure (-4.4+/-10.2 and -9.3 +/-12.6 mm Hg,  $p=0.001$ ) all had dose-related decreases upon administration of low- and high-dose nesiritide, respectively. A moderate increase was seen in the cardiac index (0.2+/-0.49 and 0.4+/-0.69,  $p<0.001$ ) and no change in the heart rate (-1.6+/-7.1 and 0.0+/-8.8,  $p=0.22$ ) was reported for the two doses of nesiritide. Global clinical status, as judged by the patient, improved 14% in the placebo group, 60% in the lower dose nesiritide group and 67% in the high dose group ( $p<0.001$ ). No change on global status was reported for 74% of the placebo group, 25% of the low dose group and 23% of the high dose group ( $p<0.001$ ). Global clinical status, as judged by the attending physician, improved in 5% of placebo patients, 55% of low-dose, and 77% of high-dose patients ( $p<0.001$ ). At baseline, 96% of all patients reported fatigue and 93% reported dyspnea. Dyspnea improved in 12%, 56% and 50% ( $p<0.001$ ) and fatigue improved in 5%, 32% and 38% of the patients in the placebo, low-dose nesiritide and high-dose nesiritide groups, respectively. Aldosterone levels increased 0.6 ng/dL, 2.5ng/dL and 1.6 ng/dL in the three groups and plasma norepinephrine levels did not change in any group.

A comparative, randomized trial was performed which compared nesiritide with standard intravenous agents in terms of efficacy and adverse events.<sup>6</sup> Patients were randomly assigned to three treatment groups. The groups were: standard therapy as determined by the attending physician (n=102), a loading dose of nesiritide of 0.3 mcg/kg followed by a constant intravenous infusion of 0.015 mcg/kg/min (n=103), and nesiritide 0.6 mcg/kg bolus followed by a constant intravenous infusion of 0.03 mcg/kg/min (n=100). The duration of treatment for each group was similar, with 68 to 73 % treated for one or two days, 14 to 21% treated for three to five days and 9 to 14 % treated for more than five days ( $p=0.42$ ). The most common adverse event in patients treated with nesiritide was dose-related hypotension with 4% of those receiving standard therapy, 11% of low-dose nesiritide and 17% of high-dose nesiritide patients reporting symptomatic hypotension ( $p=0.008$ ). Asymptomatic hypotension was reported in 7% of standard therapy, 12% of low-dose nesiritide and 24% of high-dose nesiritide patients ( $p=0.002$ ). Sustained ventricular tachycardia was not reported in any nesiritide patients and one standard patient. Non-sustained ventricular tachycardia was found in 8% of standard patients, 10% of low-dose nesiritide patients, and 1% of high-dose ( $p<0.02$ ). Bradycardia was not seen in any patients receiving standard therapy and 5 and 4% of those on low and high dose nesiritide ( $p=0.07$ ), respectively.

### Adverse effects

In clinical trials, nesiritide was generally well-tolerated. The most common adverse event was hypotension, 11% of patients receiving a 0.015-mcg/kg/min infusion and 17% of those receiving a 0.03 mcg/kg/min infusion experienced symptomatic hypotension. Asymptomatic hypotension was experienced at a rate of 12% and 24% in each group, respectively. Hypotension was not relieved immediately when the infusion was stopped and took an average of 2.2 hours to regain normotensive blood pressure readings, as compared to 0.7 hours with nitroglycerin.<sup>9</sup> Non-sustained ventricular tachycardia was experienced in 10% of patients receiving the lower infusion rate, while 1% of the higher infusion rate patients experienced such an event. Bradycardia was reported in 5% of low dose and 4% of high dose patients. Other notable adverse reactions reported in various trials of nesiritide include headache (8%), insomnia (6%), dizziness (5%) and nausea (9%).<sup>9</sup>

### Cost, dose, how supplied

The labeled dosing regimen for nesiritide is a 2 mcg/kg intravenous bolus, followed by an intravenous infusion of 0.01 mcg/kg/min. The rate may then be modified based on patient response. Published studies have used infusion rates as high as 0.03 mcg/kg/min. The duration of infusion varies, but in clinical trials therapy with an infusion of 0.015 mcg/kg/min resulted in an average of 2.1 days treatment.

Nesiritide is supplied in a single dose vial containing 1.5 mg of drug. The average wholesale price for a single 1.5 mg vial is \$371.41. The cost to treat a 70-kg patient for 24 hours is \$250. In contrast, the cost of dobutamine (10 mcg/kg/min) in the same 70-kg patient would be \$11.

### Conclusion

Nesiritide was approved with relatively few published trials. In these studies nesiritide was shown to be an effective agent for the treatment of patients with acutely decompensated heart failure. Nesiritide treatment was associated with improvements both in hemodynamic monitoring parameters and clinical impression scores. However, there are three areas which require further exploration before nesiritide is integrated into standard care. First, information is needed the impact of nesiritide on patient outcomes, such as survival, reduced hospitalization, and faster resolution of the acute failure. Second, additional studies are needed comparing nesiritide to standard care. Finally, more experience with the drug is required to determine the true extent of its hypotensive effect. Until this additional information is obtained, nesiritide should be reserved for patients who do not respond to or who are intolerant of standard therapies. At the University of Wisconsin Hospital and Clinics, nesiritide has been added to the formulary for a 6-month limited term and its use restricted to Cardiology and Critical Care services and to patients who meet one or the following criteria: (1) unacceptable hemodynamic response (urine output, dyspnea, blood pressure, heart rate) after 24 hours of therapy with high dose IV diuretics (>80 mg furosemide plus at least 2.5 mg PO metolazone) AND an IV inotrope (dobutamine at doses >5 mcg/kg/min or milrinone); OR (2) development of serious arrhythmias (VT or NSVT) on the above regimen; OR (3) recurrent hospitalizations (>2) and the need for inotropes despite state of the art outpatient CHF management (i.e., ACE-inhibitors, digoxin, beta-blockers, diuretics, spironolactone). ■

*References available on request.*