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NESIRITIDE: USE IN ACUTE DECOMPENSATED HEART FAILURE

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Introduction

Heart failure (HF) is a common clinical syndrome, affecting 4.9 million people in the United States (U.S.) in 2003. There are an additional 550,000 cases diagnosed each year with a mortality rate of approximately 50% within 5 years.[1] Acutely decompensated heart failure (ADHF) is characterized hemodynamically by elevated right and left ventricular filling pressures, decreased cardiac output, and increased systemic vascular resistance.[2] It is the primary diagnosis for close to one million hospital admissions annually in the U.S. and a secondary diagnosis for nearly two million more. The total cost of HF this year is projected to approach 26 billion dollars.

The in-hospital mortality rate for ADHF is 5 to 8%. This is sobering given that the rate of readmission is 20% at 30 days and 50% by 6 months.[2] While many guidelines exist for the treatment of different acute cardiovascular conditions including acute coronary syndromes, ischemic strokes, and life-threatening arrhythmias, major guidelines for the treatment of ADHF have not been published. Guidelines in existence only deal with the treatment of chronic HF.

Several classes of medications are available to treat ADHF. Examples include loop diuretics, such as furosemide (Lasix®) and torsemide (Demadex®), and vasodilators such as nitroglycerin and nesiritide (Natrecor®). Additionally, positive inotropes are approved for ADHF in patients with low cardiac output; these include dobutamine (Dobutrex®) and milrinone (Primacor®). (Table 1) Unfortunately, there is little evidence in the medical literature to help clinicians select from this list.

This article will discuss the pharmacology, pharmacokinetics, clinical trials and effects of nesiritide, the latest drug to be approved for ADHF.

Treatment:

ADHF has two physiologic components, central and peripheral congestion (i.e., volume overload) and poor cardiac output. Pharmacologic modalities usually target one or both of these components.

In patients with mild volume overload, intravenous (IV) diuretic therapy with a loop diuretic is preferred. Monitoring of diuretic efficacy is driven by urine output tempered by renal function. For patients with normal renal function, the goal urine output is $\geq$ 500 ml in the first 2 hours whereas an acceptable urine output in patients with serum creatinine > 2.5 mg/dl is 250 ml.[3] If the patient fails

INSIDE THIS ISSUE:

Table 1. Dosing recommendations for selected drugs used to treat ADHF.

Drug	Dose (start)	Titration
Furosemide	40 to 180 mg IV bolus	20-80 mg/hour via continuous infusion
Nitroglycerin	5-10 mcg/min continuous IV infusion	Increase by 5 mcg/min IV every 3–5 min until clinical response or 20 mcg/min reached. Then, increase by 10-20 mcg/min. Usual range = 5-100 mcg/min.
Nesiritide	2 mcg/kg IV bolus, followed by 0.01 mcg/kg/min continuous IV infusion	May be cautiously titrated by 0.005 mcg/kg/min at intervals no less than 3 hours, if clinically indicated. Maximum dose = 0.03 mcg/kg/min.
Dobutamine	0.5-1 mcg/kg/min continuous IV infusion	Increase every 5 to 15 minutes. Normal effective range 2-20 mcg/kg/min.
Milrinone	50 mcg/kg continuous IV infusion over 10 minutes as loading dose, followed by 0.375 mcg/kg/min	Usual maintenance dose = 0.5 mcg/kg/min. Maximum recommended dose is 0.75 mcg/kg/min

to attain adequate diuresis after the initial bolus, the previous dose may be doubled and should be administered within 2 to 4 hours of the first dose to induce more rapid diuresis. Alternatively, a continuous infusion can be initiated after the initial bolus. Electrolyte deficiencies are often associated with IV diuretics, and treatment can be complicated by hypotension, alkalosis, azotemia and renal dysfunction.

In patients with moderate to severe volume overload, the patient response to intravenous diuretics may be inadequate, especially if renal function is compromised. In this situation, a more aggressive pharmacological strategy is required. A diuretic in combination with a parenteral vasodilator is often effective in these patients if they have a systolic blood pressure > 90 mm Hg.[4] The addition of nesiritide or nitroglycerin to an intravenous diuretic may elicit a more rapid response. However, hypotension is often encountered with this regimen.

In patients with low cardiac output, use of an inotropic agent can be considered. It may be difficult to adequately diurese a patient with poor peripheral perfusion (i.e. low output). The phrase, "you must warm the patient up before they will dry out" is often cited, suggesting that peripheral perfusion must be restored before diuresis can be achieved. There are usually two factors affecting the selection of an inotrope. Namely, concomitant therapy with a beta-blocker and baseline blood pressure. In patients with low cardiac output (CO) and systolic BP (SBP) < 90 mm Hg the primary agent should be dobutamine. In patients with low CO and SBP > 90 mm Hg either dobutamine or the phosphodiesterase inhibitor, milrinone are reasonable options. If SBP is less than 90 or the patient is on a beta-blocker, milrinone is the drug of choice.[4] The rationale behind this is that phosphodiesterase inhibitors, referred to as "inodilators", may significantly lower BP, and dobutamine may be less effective if the $Beta_1$ receptor is blocked. Routine use of positive inotropes is discouraged since, despite symptomatic improvement, they are associated with decreased survival.

Pharmacology/Pharmacokinetics

Nesiritide is an intravenous, recombinant, purified preparation of human B-type natriuretic peptide (hBNP). Nesiritide is a naturally-occurring hormone produced primarily in the ventricles of the heart in response to increased wall stress that occurs from volume overload. Nesiritide produces balanced arterial and venous dilation, evidenced by reductions in systemic vascular resistance, systemic arterial pressure, pulmonary capillary wedge pressure (PCWP), right atrial pressure, and mean pulmonary arterial pressure. Nesiritide increases cardiac output and stroke volume, without increasing heart rate. It also has natriuretic actions, thereby promoting diuresis. Following IV administration in patients with HF, nesiritide exhibits biphasic elimination from the plasma. The mean initial elimination phase is approximately 2 minutes. The mean terminal elimination half-life of nesiritide is approximately 18 minutes; however, the pharmacodynamic onset and duration of action is much longer.

Table 2. Trials Comparing Nesiritide to other Agents in ADHF.

Trial	Acronym	Agents	Results
Young, et al. (2002)[6]	VMAC	nesiritide vs. nitroglycerin vs. placebo	PCWP: At 3 hours, -5.8 vs. -3.8, at 24 hours: -8.2 vs. -6.3, both favoring nesiritide
Burger, et al. (2002)[9]	PRECEDENT	nesiritide vs. dobutamine	Dobutamine: VT: 48 ± 205 PVBs: 69 ± 214 Nesiritide: Vtach: -5.6 ± 17 PVBs: -13 ± 83
Peacock, et al. (2003)[8]	PROACTION	nesiritide vs. standard care	Hospital readmission within 30 days reduced by 57% vs. Placebo
Silver, et al. (2002)[7]		nesiritide vs. dobutamine	Hospital readmission. Nesiritide: 4% Dobutamine: 13%
Yancy, et al. (2004)[12]	FUSION I	nesiritide vs. standard care	Death and hospitalization in high risk. Nesiritide: 52% Standard care: 78% Number of days alive and out of hospital (days). Nesiritide: 83 Standard care: 77

PCWP= Pulmonary capillary wedge pressure. PVB= Premature ventricualr beat. VT= Ventricular tachycardia.

The drug has an onset of action of 15 minutes with a duration of action of up to an hour or more.[5] After initiating the recommended dose, 60% of the 3-hour effect on PCWP reduction is achieved within 15 minutes, reaching 95% of the 3-hour effect within 1 hour. Approximately 70% of the 3-hour effect on SBP reduction is reached within 15 minutes.[9] Human BNP is cleared from the circulation via the following three independent mechanisms, listed in order of decreasing importance: 1) binding to cell surface clearance receptors with subsequent cellular internalization and lysosomal proteolysis; 2) proteolytic cleavage by endopeptidases, such as neutral endopeptidase; and 3) renal filtration.[5] There is no dose adjustment recommended in renal insufficiency, though cautious monitoring seems prudent given its partial renal clearance.

Because the effects of nesiritide are predictable and sustained at the recommended dosage, it does not commonly require dose titration or more invasive hemodynamic monitoring.[6] In comparison, tachyphylaxis can occur in patients receiving IV nitroglycerin, necessitating additional titration and higher doses. Frequent dose titration and the possibility of hypotension with other ADHF treatments often mandate that patients be treated in an intensive care unit (ICU). Nesiritide may not require intensive monitoring depending on the clinical situation; however, this population often require ICU care for other reasons.

Clinical Trials

The VMAC (Vasodilation in the Management of Acute Congestive Heart Failure)[6] trial evaluated the use of nesiritide in ADHF. The study was a randomized, double blind, placebo controlled trial comparing the use of IV nitroglycerin, nesiritide and placebo in patients suffering from dyspnea due to ADHF. There were 489 patients enrolled in the study. The primary end point was the absolute change in pulmonary capillary wedge pressure (PCWP) and patient self-evaluation of dyspnea from baseline to 3 hours after the start of nesiritide infusion. The secondary outcomes included a comparison of hemodynamic and clinical effects of nesiritide and nitroglycerin at 24 hours, global clinical status, and the overall safety profile. The study demonstrated a statistically significant reduction in PCWP among patients treated with nesiritide compared to nitroglycerin or placebo at 3 and 24 hours. Nesiritide reduced PCWP by -5.8 mm Hg and -8.2 mm Hg while nitroglycerin reduced it by -3.8 mm Hg and -6.3 mm Hg at 3 and 24 hours, respectively. The difference in PCWP was not statistically different at 48 hours. Nesiritide was associated with greater mean reductions in systolic and mean pulmonary arterial pressure than nitroglycerin at 3 hours. Nesiritide was better tolerated, with fewer

Table 3. Adverse Effects of Agents Used in ADHF.

Treatment	Common Adverse Effects
Diuretics	electrolyte disturbances (hypokalemia and hypomagnesaemia), hypotension, azotemia, contraction alkalosis
Nitroglycerin	dose-dependent hypotension, headache, sinus tahcycardia, nausea, vomiting, tolerance
Nesiritide	hypotension, syncope, headache, renal dysfunction, nausea, vomiting
Dobutamine	ventricular arrhythmias, tahcycardia, angina, palpitations, hypertension, nausea, vomiting, hypokalemia
Milrinone	ventricular arrhythmias, sudden cardiac death, angina, palpitations, atrial tachycardias, hypotension

patients reporting adverse events, primarily headache. The incidence of hypotension was similar; however, the duration of hypotension was longer with nesiritide due to a longer duration of action.

Studies evaluating patients with ADHF have reported a nonsignificant trend towards reduced readmission in patients treated with nesiritide compared with nitroglycerin or positive inotropes, including dobutamine.[6,7] In the VMAC trial,[6] the authors note that the 6 month readmission rate was 13% for nitroglycerin and 7% for nesiritide; however, VMAC was not powered to show statistical difference for this outcome. Similar results have been reported with nesiritide compared to dobutamine. Silver et al.[3], found a non-significant trend towards fewer rehospitalizations related to heart failure in patients treated with nesiritide (4% vs. 13%, p = 0.081). In the PROACTION (Prospective Randomized Outcomes Study of Acutely Decompensated Congestive Heart Failure Treated Initially as Outpatients with Natrecor) study, nesiritide reduced the rate of hospital readmission at 30 days by 57% compared with placebo; the change did not achieve statistical significance (p=0.058).[8]

Nesiritide may be safer than positive inotropes with respect to arrhythmogenicity.[9] The PRECEDENT (Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Nesiritide Therapy)[9] study demonstrated that dobutamine increases the incidence of ventricular tachycardia (VT) and ventricular ectopy when compared with nesiritide. (Table 2) On the other hand, the incidence of hypotension was lower with dobutamine. This multi-center, randomized, open-label, active-control trial compared the safety of low dose dobutamine ($\geq$ 5 mcg/kg/min) with 2 fixed doses of nesiritide (0.015 and 0.030 mcg/kg/min) in 255 patients. End points included mean heart rate, number of premature ventricular beats (PVBs) per hour, and repetitive beats per hour. Dobutamine significantly increased all measures of ventricular ectopy, while nesiritide reduced the rate of VT compared with baseline. Dobutamine increased the mean number of VT episodes per 24 hours by 48 $\pm$ 205 (P=0.001), repetitive ventricular beats by 15 $\pm$ 53 (P=0.001) and PVBs by 69 $\pm$ 214 (P=0.006). Dobutamine increased the heart rate by 5.1 $\pm$ 7.7 bpm (P<0.001). Nesiritide had significantly smaller effect on these parameters. Both agents resulted in similar improvements in signs and symptoms of HF. The adverse effects of positive inotropes and evidence of reduced survival have prompted the American Heart Association and American College of Cardiology to discourage the routine use of intermittent outpatient inotropic support in patients with severe HF (Class III recommendation).[10]

Results from FUSION I (Follow Up Serial Infusions Of Natrecor), a pilot trial designed to evaluate the safety and tolerability of weekly infusions of nesiritide when administered in the outpatient setting to patients with advanced HF who are at high risk for hospitalization, were recently pubished.[11,12] FUSION I was a multi-center (46 U.S. sites), randomized, open-label pilot study with three treatment arms enrolling a total of 210 patients. Patients were randomized to receive either standard care (usual long-term cardiac medications with or without IV inotropes) or serial infusions of either 0.005 or 0.01 μg/kg/min of nesiritide in addition to their usual long-term cardiac medications, excluding IV inotropes. Patients were further classified as low- or high-risk based on seven criteria (patients

with four or more of these criteria were considered high risk). All patients had weekly outpatient visits for 12 weeks. Nesiritide patients received a four- to six- hour infusion at each weekly visit. At the end of follow-up, the primary endpoint, the incidence of investigator-reported adverse events, was similar in all treatment arms. A subgroup analysis showed that patients in the higher risk stratum experienced a statistically significant reduction in death and hospitalization with nesiritide (52% vs. 78%; p=0.038). The number of days that patients were alive and out of the hospital also improved (67 vs. 77 days; p=0.027). Through week 12, 5% of nesiritide patients and 17% of standard care patients had died (p=0.079) at 12 weeks. While the results of this pilot study are encouraging, a larger trial demonstrating similar benefits in this population is necessary.

Dosage and Administration

The approved dose is 2 mcg/kg administered as an IV bolus, followed by a continuous IV infusion of 0.01 mcg/kg/min.[5] The dose can be slowly titrated, based on clinical response, to the maximum dose of 0.03 mcg/kg/min, although experience with doses greater than 0.01 mcg/kg/min is limited. Blood pressure must be monitored closely. If hypotension occurs, the dose should be reduced or discontinued. Once the patient is stabilized, the infusion should be restarted at a dose that is reduced by 30% (with no bolus administration). Hypotension can be prolonged, therefore, at higher doses a period of observation may be required even after drug discontinuation. The prolonged half-life also necessitates close attention to titration guidelines since rapid titration may provoke profound hypotension and renal failure.

Contraindications

Nesiritide is not recommended for patients in whom vasodilating agents are not appropriate, such as patients with significant valvular stenosis (aortic stenosis, mitral stenosis, idiopathic hypertrophic subaortic stenosis, valvular heart disease), restrictive or obstructive cardiomyopathy, constrictive pericarditis, pericardial tamponade or pericardial effusion, or other conditions in which cardiac output is dependent upon venous return, or for patients suspected to have low cardiac filling pressures.[5]

Adverse Effects

Side effects of nesiritide are a direct result of its mechanism of action. In separate clinical trials, the side-effect profile of nesiritide was lower than nitroglycerin and dobutamine. In VMAC,[6] the overall adverse event rate was lower for nesiritide than nitroglycerin (20% vs. 5%). The incidence of hypotension was similar in both groups (8%) with a longer duration of hypotension in the nesiritide group. PRECEDENT[9] compared the incidence of adverse effects between nesiritide and dobutamine. There was a statistically significant increase in the incidence of arrhythmias in patients receiving dobutamine. Nesiritide caused hypotension more often. Table 3 lists common adverse effects with ADHF treatments.

There is a lack of information about drug-interactions with nesiritide. No studies have been conducted in this area. Based on the mechanism of action, it is recommended that nesiritide not be given within 24 hours of the phosphodiesterase inhibitors, sildenafil, vardenafil, or tadalafil, since the risk of hypotension may be increased. Pharmacodynamic drug interactions are possible with any other treatment that lowers blood pressure. Nesiritide should be used cautiously in patients receiving antihypertensives, inodilators, or nitrates.

Cost

The retail cost of nesiritide is approximately 500 dollars for every 1.5 mg vial. The cost for a 70 kg

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patient would be 47 dollars for a loading dose of 2 mcg/kg and 336 dollars for a 24 hour infusion with an infusion rate of 0.010 mcg/kg/min. The acquisition cost of other medical treatments is considerably less than that of nesiritide. Many institutions reserve nesiritide for patients who fail to respond to conventional therapy with diuretics, inotropes, or nitroglycerin. Others suggest that the increased acquisition cost is offset by nesiritide's efficacy, which may permit early discharge and increased time to rehospitalization. However, this has not been clearly validated. In fact a recent analysis of the available data suggests that nesiritide is not more cost-effective than dobutamine in the acute setting. (Gerhard T, et al. Abstract #244E, American College of Clinical Pharmacy (ACCP), 2004 Annual Meeting, Dallas, TX) It is not clear whether nesiritide will be cost-effective in the outpatient setting, though the the data from FUSION suggesting that hospitalizations might be reduced is exciting.

Summary

ADHF is treated based on the severity of symptoms and other patient-specific considerations, such as concomitant illness, background therapy, and clinical parameters. In patients experiencing moderate to severe symptoms or those who are not responsive to IV diuretics, nesiritide represents an alternative to conventional vasodilators and positive inotropes. Nesiritide is administered as a fixed dose and with minimal titration. It relieves central congestion better than nitroglycerin, though symptomatic and clinical improvement was not different at 48 hours. Nesiritide is better tolerated than conventional therapies. It appears to cause less ventricular ectopy compared with inotropes, though the clinical significance of this observation has not been validated. The American College of Cardiology/ American Heart Association will release an updated HF guideline this fall that will, for the first time, devote a section to ADHF. Ongoing studies will further help clinicians identify the role of nesiritide in the acute and outpatient setting.[11]

References

1. Heart disease and stroke statistics-2004 update. American Heart Association. Available at www.americanheart.org.
2. Fonarow GC. Pharmacologic Therapies for Acutely Decompensated Heart Failure. Reviews in Cardiovascular Medicine. Rev Cardiovasc Med 2002;3 Suppl 4:S18-27.
3. Peacock WF 4th, Albert NM. Observation unit management of heart failure. Emerg Med Clin North Am 2001;19:209-32.
4. DiDomenico RJ, Park HY, Southworth MR, et al. Guidelines for Acute Decompensated Heart Failure Treatment. Ann of Pharmacother 2004; 38:649-660.
5. Clinical Pharmacol. Gold Standard Media; Aug. 2004.
6. VMAC Investigators. Intravenous nesiritide vs. nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. JAMA 2002;287:1531-40.
7. Silver MA, Horton DP, Ghali JK, et al. Effect of nesiritide versus dobutamine on short-term outcomes in the treatment of patients with acutely decompensated heart failure. J Am Coll Cardiol 2002;39:798-803.
8. Peacock WF, Emerman CL. Safety and efficacy of nesiritide in the treatment of decompensated heart failure in observation patients: the PROACTION trial (abstract). J Am Coll Cardiol 2003;41:336A.
9. Burger AJ, Horton DP, LeJemtel T, Ghali JK, Torre G, Dennish G, et al. Effect of nesiritide (B-type natriuretic peptide) and dobutamine on ventricular arrhythmias in the treatment of patients with acutely decompensated congestive heart failure: the PRECEDENT study. Am Heart J 2002;144:1102-8.
10. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2001;38:2101-13.
11. Press Release -- SCIOS. Las Vegas, NV and Fremont, CA - September 23, 2003.
12. Yancy CW, Saltzberg MT, Berkowitz RL, et al. Safety and feasibility of using serial infusions of nesiritide for heart failure in an outpatient setting (from the FUSION I trial). Am J Cardiol 2004;94:595-601.

New Drug Approvals

Trospium chloride tablets (Sanctura, Indevus) is an antimuscarinic (i.e., antispasmodic) agent indicated for the treatment of overactive bladder in patients with urinary incontinence, urgency, and urinary frequency. Like other antimuscarinics, it is contraindicated in patients with or at risk for urinary or gastric retention, uncontrolled narrow-angle glaucoma, or a hypersensitivity to its ingredients, including lactose. The recommended dosage is 20 mg twice daily, with each dose taken at least one hour before meals or on an empty stomach. Patients with a creatinine clearance <30 mL/min should receive a dosage of 20 mg once daily at bedtime; patients age 75 years or older may need to take 20 mg once daily. Sanctura is available as 20-mg tablets.