REVIEW

ROGER M. MILLS, MD*
Clinical Cardiology Section, Department of Cardiovascular Medicine, The Cleveland Clinic.

ROBERT E. HOBBS, MD*
Kaufman Center for Heart Failure, Department of Cardiovascular Medicine, The Cleveland Clinic

How to use nesiritide in treating decompensated heart failure

ABSTRACT

Nesiritide (Natrecor), a synthetic formulation of B-type natriuretic peptide (BNP), is the first new parenteral agent to be approved for treating heart failure in more than a decade. In patients hospitalized with decompensated congestive heart failure, nesiritide promptly reduces pulmonary capillary wedge pressure, pulmonary arterial pressure, right atrial pressure, and systemic vascular resistance, resulting in clinical improvement.

KEY POINTS

Nesiritide is indicated for patients with decompensated heart failure, New York Heart Association class IV, who have dyspnea at rest or with minimal activities and clinical evidence of fluid overload.

Patients should not receive nesiritide if they have undergone excessive diuresis and present "cold and dry" with low cardiac output and relative hypotension, or if they have aortic stenosis, hypertrophic cardiomyopathy, or cardiogenic shock.

The recommended dosage of nesiritide is a 2 µg/kg intravenous bolus, followed by an infusion of 0.01 µg/kg/minute.

In a large clinical trial, nesiritide was more effective and better tolerated than nitroglycerin. It also has clinical advantages over nitroprusside, dobutamine, and milrinone.

*The authors have indicated that they are on the speakers' bureau of Scios Inc.

NESIRITIDE (Natrecor) has many advantages over parenteral vasodilators and inotropic agents currently used in treating decompensated heart failure, being more effective and better tolerated, allowing patients to continue their usual medications while in the hospital, and not automatically requiring invasive monitoring.

This paper reviews the pharmacology and clinical use of nesiritide, the first new parenteral agent to gain approval from the US Food and Drug Administration for heart failure treatment in more than a decade.

WHAT IS NESIRITIDE?

Nesiritide is a peptide measuring 32 amino acids in length that is identical in structure to endogenous human B-type natriuretic peptide (BNP), formerly known as "brain natriuretic peptide" because it was first discovered in the brain of pigs. Nesiritide is now synthesized using recombinant DNA technology.

In the body, BNP is expressed by ventricular myocytes in response to pressure-volume overloading of the ventricles, and it has vasodilating and natriuretic actions that counter the vasoconstricting and fluid-retaining effects of the renin-angiotensin system. The counter-regulatory effects of BNP are beneficial in heart failure.[1,2]

Extensive clinical trials have confirmed that nesiritide (synthetic BNP) produces prompt hemodynamic and clinical improvement in patients with decompensated congestive heart failure.[3–11]

HOW DOES NESIRITIDE ACT?

Nesiritide binds to the A-type natriuretic peptide receptor on the surface of vascular smooth

muscle and endothelial cells and produces vasodilation through a guanosine monophosphate pathway. It is inactivated by a clearance receptor located on the cell surface and also by neutral endopeptidase cleavage. The vasodilatory effects do not depend on endothelial cells, cyclic adenosine monophosphate, or beta-adrenergic receptors, and clearance does not depend on renal or hepatic function.[2]

When given to patients in heart failure, nesiritide reduces pulmonary capillary wedge pressure, pulmonary arterial pressure, right atrial pressure, and systemic vascular resistance. This results in an increase in cardiac output involving several mechanisms, including redistribution of mitral regurgitant flow, improved subendocardial perfusion, and reflex vasodilation. The pulmonary capillary wedge pressure usually decreases within 15 minutes after bolus administration, and beneficial effects are maintained without tachyphylaxis during prolonged infusion (several days).

Nesiritide has modest intrinsic natriuretic and diuretic effects. However, the hemodynamic improvement associated with nesiritide therapy substantially enhances the effects of loop diuretics.

The elimination half-life of nesiritide is 18 to 20 minutes, and its hemodynamic effects dissipate entirely within 2 to 4 hours after stopping an infusion.

WHO IS A CANDIDATE FOR NESIRITIDE THERAPY?

Nesiritide is indicated for patients with decompensated heart failure, ie, in New York Heart Association (NYHA) class IV, who have dyspnea at rest or with minimal activities and clinical evidence of fluid overload (TABLE 1).

For practical purposes, we define "decompensated heart failure" as a sustained deterioration in function of at least one NYHA class, usually associated with evidence of total body salt and water overload, including neck vein distention, rales, hepatojugular reflux, and edema. Patients with these abnormalities are candidates for nesiritide.

In contrast, patients who have been "over-diuresed" and present "cold and dry" with low cardiac output and relative hypotension are not candidates for parenteral vasodilators. These patients require careful volume optimization, often with hemodynamic monitoring and inotropic support. In addition, patients with aortic stenosis, hypertrophic cardiomyopathy, or cardiogenic shock are not candidates for nesiritide therapy.

TABLE 1

Signs and symptoms of decompensated heart failure

Low perfusion
- Hypotension
- Cool extremities
- Narrow pulse pressure
- Sleepiness, obtundation
- Elevated blood urea nitrogen, creatinine
- Hyponatremia

Congestion
- Orthopnea, paroxysmal nocturnal dyspnea
- Neck vein distention
- Ascites, edema
- Hepatic tenderness
- Hepatojugular reflux
- Rales

HOW IS NESIRITIDE GIVEN?

Nesiritide is available only in parenteral form. It is given by the peripheral intravenous route with a loading bolus followed by a continuous infusion.

In the recently completed Vasodilation in the Management of Congestive Heart Failure (VMAC) trial,[11] the investigators used a 2 µg/kg intravenous bolus of nesiritide, followed by a fixed-dose intravenous infusion at 0.01 µg/kg/minute.

In earlier studies,[6–9] infusions at higher doses (up to 0.03 µg/kg/minute) did not produce additional hemodynamic benefit and were associated with higher rates of hypotension.

IS HEMODYNAMIC MONITORING REQUIRED?

Most patients do not require invasive hemodynamic monitoring. Of the 489 patients

Nesiritide clearance does not depend on renal or hepatic function

TABLE 2

Nesiritide vs nitroglycerin and nitroprusside

	NESIRITIDE	NITRO-GLYCERIN	NITRO-PRUSSIDE
Induces tachyphylaxis	No	Yes	No
Toxic	No	No	Yes
Causes hypotension	Yes	Yes	Yes
Requires special handling	No	Yes	Yes
Requires invasive monitoring	No	No	Yes
Causes headache	Yes	Yes	No

TABLE 3

Nesiritide vs dobutamine and milrinone

	NESIRITIDE	DOBUTAMINE	MILRINONE
Inotropic	No	Yes	Yes
Chronotropic	No	Yes	No
Vasodilating	Yes	No	Yes
Diuretic	Yes	No	No
Arrhythmogenic	No	Yes	Yes
Increases myocardial oxygen consumption	No	Yes	±

enrolled in the VMAC trial, 243 were treated without invasive monitoring. Treatment based on clinical evaluation, without right heart catheterization, proved safe and effective.[11]

Nesiritide therapy does not worsen cardiac arrhythmias.[10] However, because arrhythmia is frequent in heart failure patients, continuous electrocardiographic monitoring is recommended whenever decompensated patients require hospital admission. Since neither a right heart catheter nor an arterial line is required to monitor therapy, patients can receive nesiritide on a telemetry unit with frequent monitoring of vital signs.

WHAT ABOUT OTHER HEART FAILURE MEDICATIONS?

Almost 80% of hospital admissions for decompensated heart failure involve patients with previously diagnosed and treated heart failure. Often, the reason the patient goes into decompensation and needs to be admitted is that he or she was not compliant with the prescribed medical program.

During nesiritide therapy, baseline therapy with beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers (ARBs) can continue and may be modified as necessary.

We generally use modest intravenous doses of loop diuretics (usually furosemide) to help mobilize excess salt and water. High-dose diuretic therapy, when given with nesiritide, may result in intravascular volume depletion, hypotension, prerenal azotemia, and stimulation of the renin-angiotensin-aldosterone system.

If the decompensated patient has not been receiving beta-blocker therapy, these drugs should not be started until stable euvolemia has been achieved.

HOW DOES NESIRITIDE COMPARE WITH OTHER PARENTERAL DRUGS?

For practical purposes, there are four other parenteral agents (in addition to intravenous diuretics) used to treat decompensated heart failure: two vasodilators (nitroprusside and nitroglycerin) and two inotropic agents (dobutamine and milrinone).

Nitroprusside is extremely potent, and requires very careful monitoring of arterial pressure. In addition, accumulation of toxic metabolites limits its long-term use.

Dobutamine and milrinone both have the drawback of exacerbating arrhythmias, and dobutamine alone does not decrease wedge pressure significantly. TABLE 2 and TABLE 3 provide comparisons of these drugs with nesiritide.

Because of these issues, nitroglycerin was chosen as the agent for comparison with nesiritide in the Vasodilation in the Management of Congestive Heart Failure (VMAC) trial. This study found nesiritide to be more effective than nitroglycerin, based on more rapid improvement in pulmonary capillary wedge pressure and sustained benefit over 24 hours. Nesiritide was also better tolerated, with fewer side effects.[11]

HOW LONG CAN NESIRITIDE INFUSIONS BE CONTINUED?

The duration of therapy in the VMAC trial extended up to 48 hours, and sustained effect over that time has been well documented. Individual investigators have used much longer infusions, but the evidence is anecdotal.

Except in very unusual situations, patients should improve rapidly with nesiritide, and continued standard oral therapies, including ACE inhibitors, diuretics, and beta-blockers (if these were part of the patient's usual program) should be adequate for management within a day or two. In fact, failure to respond to nesiritide within 24 to 36 hours should prompt consideration of invasive hemodynamic monitoring.

WHAT ABOUT SIDE EFFECTS?

In the VMAC trial,[11] 8% of patients receiving nesiritide reported headaches, compared with 20% of patients receiving intravenous nitroglycerin.

Asymptomatic hypotension occurred in 8% of patients receiving either drug, and symptomatic hypotension occurred in 4% of patients receiving nesiritide vs 5% of patients receiving nitroglycerin.[11] Hypotension occurred more frequently in patients receiving nesiritide in other trials, in which higher doses were used. In rare cases, hypotension may be prolonged or may require intravascular volume expansion.

In our experience in clinical trials, overdiuresis has been the primary factor provoking hypotension with nesiritide. Diuretic doses should be adjusted downward when nesiritide infusions are used.

Nesiritide does not exacerbate arrhythmias or ischemia and does not generate toxic metabolites. Tolerance or hypersensitivity to the agent has not been observed.

HOW ABOUT COST?

The cost of nesiritide is approximately $375 per day of treatment for an average-sized patient. This is similar to milrinone, but more expensive than dobutamine, nitroprusside, and nitroglycerin.

Drugs are only a small part of hospital costs in heart failure

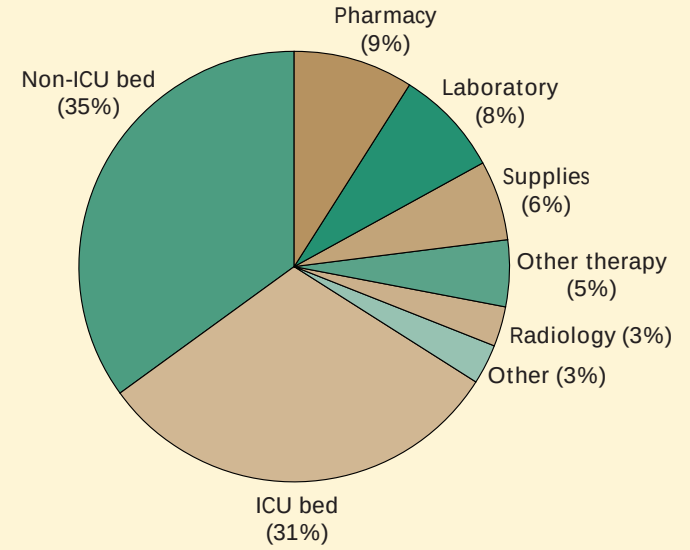

FIGURE 1. Hospital costs by cost center for heart failure (DRG 127) based on 1998 Medicare MEDPAR data.

Pharmacy charges, however, constitute only a fraction of heart failure hospitalization costs (FIGURE 1). Since patients treated with nesiritide infusion can be treated on a regular telemetry floor and do not require expensive intensive care unit management, hospitals may realize a net saving from using the drug. In addition, because baseline oral medications may be continued during the infusion, the overall hospital stay may be shortened.

When giving nesiritide, keep diuretic doses low

WHERE DOES NESIRITIDE FIT IN HEART FAILURE MANAGEMENT?

Current estimates suggest that about 80% of heart failure admissions are due to decompensation in patients with known chronic heart failure. The most common causes for these episodes include noncompliance with prescribed medications, dietary indiscretion, emotional stress, arrhythmias, or exacerbation of comorbid illnesses.

In most cases, the decompensated patient is salt-overloaded and water-overloaded. The reactivation of the renin-angiotensin system,

worsening of subendocardial ischemia, and exacerbation of functional mitral regurgitation that occur in this setting can be more effectively managed with vasodilator therapy and modest diuresis than with high-dose diuretics alone. In these patients, we expect that nesiritide will be a first-line agent for rapid hemodynamic and symptomatic treatment.

REFERENCES

1. **Chen HH, Burnett JC.** The natriuretic peptides in heart failure: diagnostic and therapeutic potentials. Proc Assoc Amer Physicians 1999; 111:406–416.
2. **Boland DG, Abraham WT.** Natriuretic peptides in heart failure. Congestive Heart Fail 1998; Mar/April:23–33.
3. **Hobbs RE, Miller LW, Bott-Silverman C, et al.** Hemodynamic effects of a single intravenous injection of synthetic human brain natriuretic peptide in patients with heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 1996; 78:896–901.
4. **Abraham WT, Lowes BD, Ferguson DA, et al.** Systemic hemodynamic, neurohormonal and renal effects of a steady-state infusion of human brain natriuretic peptide in patients with hemodynamically decompensated heart failure. J Card Fail 1998; 4:37–44.
5. **Marcus LS, Hart D, Packer M, et al.** Hemodynamic and renal excretory effects of human brain natriuretic peptide infusion in patients with congestive heart failure: a double-blind, placebo-controlled, randomized crossover trial. Circulation 1996; 96:3184–3189.
6. **Mills RM JR, Lejemtel TH, Horton DP, et al.** Sustained hemodynamic effects of an infusion of nesiritide (human B-type natriuretic peptide) in heart failure. J Am Coll Cardiol 1999; 34:155–162.
7. **Lejemtel TH, Bourge RC, Johnson AD, et al.** Recombinant human B-type natriuretic peptide improves symptoms and hemodynamics in patients with acutely decompensated CHF [abstract]. J Am Coll Cardiol 1998; 31(suppl A):83A.
8. **Elkayam U, Neibaur M, Haught WH, Horton DP.** Safety study of nesiritide (human B-type natriuretic peptide) for the treatment of hospitalized patients with acutely decompensated CHF [abstract]. J Card Fail 1998; 4(suppl 1):40.
9. **Colucci WS, Elkayam U, Horton DP, et al.** Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated heart failure. N Engl J Med 2000; 343:246–253.
10. **Burger AJ, Horton DP, Elkayam U, et al.** Nesiritide is not associated with the proarrhythmic effects of dobutamine in the treatment of decompensated congestive heart failure: The PRECEDENT Study [abstract]. J Card Fail 1999; 5:49.
11. **Young JB, Abraham WT, Stevenson LW, et al.** The VMAC Trial: vasodilation in the management of acute congestive heart failure. Presented at the 2000 American Heart Association Annual Scientific Sessions, November 2000; New Orleans, LA.

ADDRESS: *Roger M. Mills, MD, Department of Cardiovascular Medicine, F15, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail millsr@ccf.org.*