

Pharmacy & Therapeutics Committee
Natreacor (nesiritide)
11/2001

Recommendations:

- Nesiritide is recommended to be added to the formulary for use in patients who have failed or are intolerant to nitroglycerin, nitroprusside, dobutamine and/or milrinone. It is not recommended as a first line agent as it has not been proven to be a superior agent and is much more expensive than other FDA approved agents. As additional studies become available nesiritide's formulary status will be re-reviewed.
- A cardiology consult is recommended for all patients receiving nesiritide.
- A system wide drug usage evaluation is recommended.
- The Committee recommends that the above recommendations be presented to cardiology.

Findings:

- *Nesiritide is indicated for intravenous treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity.*
- Nesiritide is structurally identical to human (B) brain-type natriuretic peptide (hBNP) and is derived from E. coli using recombinant DNA technology.
- Nesiritide has the same 32 amino acid sequence as the endogenous peptide produced by the ventricular myocardium in response to increased cardiac volume and pressure overload.
- Nesiritide mimics the body's endogenous hormone B-type Natriuretic Peptide (BNP) with endogenous levels increasing by 3 fold with the recommended dose (0.01 mcg/kg/min).
- Nesiritide promotes sodium excretion, and vasodilation of venous, arterial and coronary vessels. It decreases preload/afterload without increasing heart rate while suppressing the renin-angiotensin-aldosterone axis and norepinephrine in doses higher (0.015-0.5 mcg/kg/min) than recommended in the package insert (0.01 mcg/kg/min). Cardiac index increases secondary to afterload reduction. Tachyphylaxis was not demonstrated with infusions up to 48 hours for either NTG or nesiritide. Nesiritide appears to cause renal efferent arteriolar vasoconstriction.
- Hypotension is the dose limiting side effect and last for several hours (2.2 hours) after the infusion is discontinued and is dose related. The incidence of symptomatic hypotension is increased by concurrent use of oral ACEI (6% versus 1%). If symptomatic hypotension occurs stop the infusion and restart at a dose reduced by 30%.
- There is limited experience with administering nesiritide longer than 48 hours (170 patients).
- Nausea and vomiting appear to be dose related.
- Studies have not been demonstrated decreased arrhythmias related mortality versus other agents.
- Nesiritide has not demonstrated a decrease in mortality versus other agents.
- Nesiritide has not been studied in combination with IV vasodilators such as milrinone, IV ACE inhibitors, nitroglycerin, and nitroprusside.
- FDA approved inotropics for short-term treatment of CHF includes dobutamine and milrinone.
- *Approximately 28% of CHF cases admitted to Bon Secours Richmond hospitals are given one of the following: dobutamine (52%), milrinone (Primacor)(15%), nitroglycerin (32%), or nitroprusside (<1%).*
- *The average cost per case was Dobutamine \$40, milrinone \$550, and nitroglycerine \$5.*

Cautions:

- Nesiritide should be avoided in patients with cardiogenic shock, systolic blood pressure < 90 mm Hg or in patients with low cardiac filling pressures.
- Nesiritide may cause renal impairment in patients with severe CHF.

Cost Analysis

- Nesiritide is supplied as a 1.5-mg vial, which cost \$372.40. Nesiritide is 2-6 times more expensive than equivalent doses of dobutamine, 2 times more expensive than equivalent doses of milrinone, and 50 times more expensive than nitroglycerin.
- Cost per day of Therapy:

Drug Cost per day of therapy for 70 kg Patient						
Nesiritide	0.01 mcg/kg/min	\$372	0.02 mcg/kg/min	\$744	0.03 mcg/kg/min	\$1116
Milrinone	0.375 mcg/kg/min	\$239	0.5 mcg/kg/min	\$359	0.75 mcg/kg/min	\$478
Dobutamine	2 mcg/kg/min	\$177	5 mcg/kg/min	\$177	10 mcg/kg/min	\$353
Nitroglycerin	50 mcg/min	\$7	100 mcg/min	\$11	200 mcg/min	\$21

Pharmacokinetics

- T_{1/2} 18-22 minutes
- The pharmacodynamic half-life is approximately 1 hour.
- V_{ss} 0.19 l/kg
- Clearance 9.2 ml/min/kg is proportional to weight.

- Elimination by:
 - binding to cell surface and cellular internalization and lysosomal proteolysis
 - proteolytic cleavage by peptide endopeptidases on vascular luminal surfaces
 - renal filtration

Dosing and administration

- Loading dose 2 mcg/kg bolus over 1 minute (from the infusion bag)
- Continuous infusion 0.01 mcg/kg/min
- If symptomatic hypotension occurs stop the infusion and restart at a dose reduced by 30%.
 - Dosage increases of 0.005 mcg/kg/min after a bolus of 1 mcg/kg/min were made no more frequently than every 3 hours, up to a maximum dose of 0.03 mcg/kg/min, were made in 23 patient in the VMAC trial if SBP \geq 100 and PCWP \geq 20 mm Hg.
- Renal dosage adjustment is not necessary
- Add 1.5 mg to 250 ml of D5W, NS, D5-1/2NS, or D5-1/4NS, expires in 24 hours.
- Endogenous levels increase by 3-6 fold with infusion doses ranging form 0.01 to 0.03 mcg/kg/min
- Do not shake the vial

Studies

- VMAC (unpublished): randomized, double-blinded study of hemodynamic and clinical effects of nesiritide (2 mcg/kg bolus, 0.01 mcg/kg/min up to 0.03 mcg/kg/min (50% of catheterized patients) versus nitroglycerin (no protocol for titration, physician discretion) added to standard therapy (including dobutamine and dopamine) infusion for symptomatic decompensated CHF. Primary endpoint PCWP with approximately 50% of the patients catheterized and patient self-evaluation. Patient could not receive other intravenous vasodilators. Patients with ACS, diastolic dysfunction, arrhythmias, or hepatic or renal insufficiency were NOT excluded. *There was unequal randomization of patients on dobutamine or dopamine in the NTG and nesiritide groups (more in nesiritide groups), which could invalidate the finds of the study. Mortality rates at one and six months were not significantly different for patients receiving nesiritide versus nitroglycerin (6 months: 25.1% versus 20.8%).*

VMAC Trial: Mean Hemodynamic Change from Baseline after 3 hours of Therapy			
Effects at 3 hours	Placebo (n=62)	Nitroglycerin (n=60)	Natrecor (n=124)
PCWP (mm Hg)	(baseline 27.7 \Rightarrow 25.7) -2 \pm 4.2	(baseline 28 \Rightarrow 24.2) -3.8 \pm 5.3	(baseline 27.8 \Rightarrow 21.9) -5.8 \pm 6.5 (p < 0.05)
Right atrial pressure (mm Hg)	0	-2.6	-3.1 (p < 0.05)
Cardiac index (L/min/M ²)	0	0.2	0.1
Mean pulmonary artery pressure (mm Hg)	-1.1	-2.5	-5.4 (p < 0.05)
Systemic vascular resistance (dynes/sec/cm ⁵)	-44	-105	-144
Systolic blood pressure (mm Hg)*	-2.5	-5.7 (p < 0.05)	-5.6 (p < 0.05)
Urine Output		1279 \pm 1455	1257 \pm 1657

P values are versus baseline

*Based on all treated subjects: placebo n=142, NTG n=143, Nesiritide n=204

VMAC Hemodynamic Effects by Nitroglycerin Dose Subgroups During Placebo Controlled Period						
Parameter		Nitroglycerin (mcg/minute)				
Change in PCWP (mm Hg)	All NTG	\leq 30	30-60	\geq 60	Nesiritide 0.01 mcg/kg/min	Placebo
1 hour	-2.8 \pm 4.1 (n=58)	-2.4 \pm 4.3 (n=44)	-2.9 \pm 2.9 (n=8)	-5.2 \pm 4.3 (n=6)	-5.5 \pm 6.3 (n=121)	-1.5 \pm 4.8 (n=62)
3 hours	-3.8 \pm 5.3 (n=59)	-3.4 \pm 5.4 (n=43)	-2.3 \pm 2.7 (n=6)	-6.6 \pm 5 (n=10)	-5.8 \pm 6.5 (n=121)	-2 \pm 4.2 (n=62)
Change in SBP (mm Hg)						
1 hour	-4 \pm 13 (n=60)	-3.2 \pm 12.4 (n=47)	-2.4 \pm 6.7 (n=7)	-11.7 \pm 21 (n=6)	-3 \pm 11.9 (n=124)	-0.1 \pm 11.8 (n=62)
3 hours	-3.8 \pm 14.4 (n=60)	-4 \pm 14.3 (n=44)	-2.3 \pm 13.9 (n=6)	-6.6 \pm 15.3 (n=10)	-4.9 \pm 12.2 (n=124)	-2 \pm 10.8 (n=62)

Note all standard deviations are very large and results are not statistically significant.

Efficacy Study

Randomized, double-blinded, placebo-controlled study of two doses of nesiritide as a continuous infusion in patients with decompensated CHF (Scios Study 704.325). Colucci WS. Intravenous Nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. NEJM 2000;343:246:53

Inclusion criteria: symptomatic decompensated CHF, PCWP \geq 18 mm Hg, CI \leq 2.7 l/min/m², SBP \geq 90 mm Hg. Loading dose of 0.6 mcg/kg and then 0.03 mcg/kg/min or 0.3 mcg/kg then 0.015 mcg/kg/min (*note these doses are not FDA approved*) or placebo for the first 6 hours, then unblinded and placebo patients were started on standard care. Nesiritide patients either continued nesiritide or were switched to standard care.

Mean ABSOLUTE \pm SD (Percentage) Changes from Baseline after 6 Hours (Scios 704.325)			
P < 0.001 for 1 st 5 rows compared to placebo			
Hemodynamic Endpoints	Placebo (n=42) Standard Therapy	0.015 mcg/kg/min (<i>Dose not FDA approved</i>) (n=43)	0.03 mcg/kg/min (<i>Dose not FDA approved</i>) (n=42)
PCWP mm Hg	+ 2 \pm 7.2 (+ 9%)	- 6 \pm 7.2 (- 21%)	-9.6 \pm 6.2 (-35%)
MRAP mm Hg	+ 0.4 \pm 4.6 (+ 8%)	-2.6 \pm 4.4 (- 12%)	-5.1 \pm 4.7 (-39%)
SVR dynes/sec/cm ⁵	+ 161 \pm 481 (+ 13%)	-247 \pm 492 (-13%)	-347 \pm 499 (-18%)
CI L/min/m ²	- 0.1 \pm 0.47 (- 4%)	+0.2 \pm 0.49 (+16%)	+0.4 \pm 0.69 (+27%)
SBP mm Hg	+ 0.3 \pm 11 (0%)	-4.4 \pm 10.2 (-4%)	-9.3 \pm 12.6 (-7%)
Symptomatic Hypotension	0	1 (2.3%)	2 (4.8%)
Study Drug Stopped 2 nd \downarrow BP			1
Study Drop Out Due to ADR	1	1	3
Length of Hospitalization	No Difference (company data on file)		
Readmission after discharge through day 21			
Mortality			

Comparative Trial

A randomized, *open-label*, active-controlled, multicenter phase III safety study of two doses of nesiritide hBNP administered as a continuous infusion in the treatment of decompensated CHF. (Scios 704.326)

Nesiritide 0.3 mcg/kg bolus followed by 0.015 mcg/kg/min infusion or 0.06 mcg/kg bolus followed by 0.03 mcg/kg/min infusion or standard care (parenteral vasoactive agent: dobutamine, milrinone, NTG, or sodium nitroprusside). *Of the patients receiving nesiritide 0.015 and 0.03 mcg/kg/min, 17% and 24 % received an additional IV vasoactive drug, most commonly dobutamine.*

Subject Self-Assessment of Global Clinical Status (% Better or Markedly Better) Scios 704.326			
	Nesiritide 0.015 mcg/kg/min n=?	Nesiritide 0.03 mcg/kg/min N=?	Standard care N=?
6 hours	67%	60%	64%
24 hours	84%	77%	80%
Last Available	88%	86%	89%
Hypotension Symptomatic	11%	17%	4%
Study Drug Stopped 2 nd \downarrow BP	5	10	0
Drop out from study due ADR	1		

Resource Utilization and Outcomes Compared to Dobutamine Scios 704.326			
	Nesiritide 0.015 mcg/kg/min (n=103)	0.03 mcg/kg/min (n=100)	Dobutamine (n=58 of 102 randomized to standard care regimen)
Median Length of Stay (days)	6	5	5
Median Total Length of all Vasoactive Infusion Therapy (hours)	42.4	41.3	48
CHF readmission	4%	4%	13%
6 month mortality	18%	24%	31%

Statistical significance is not included, as the dobutamine group is a subgroup of the randomized standard care regimen. The analysis of a subgroup violates statistical rules.

Significantly more patients taking dobutamine had a prior MI, p= 0.03

Prospective Open labeled Randomized evaluation of cardiac ectopy with dobutamine (5 mcg/kg/min) or nesiritide (0.015 or 0.03 mcg/kg/min) therapy (Scios 704.329) Precedent Trial Abstract Only. Conclusions: The majority of patients continue their baseline rhythm, approximately 80%.

Scios 704.329 Change from baseline 24 hour Holter tape to treatment 24 hour Holter tape			
Endpoint	Dobutamine (n=83)	Nesiritide	
		0.015 mcg/kg/min (n=84)	0.03 mcg/kg/min (n=79)
Average Heart Rate (bpm) Mean + SD Median (25 th , 75 th percentile)	+ 5 ± 8 +4 (-2,+10)	-1 ± 6 -1 (-5, +3) p < 0.001	+1 ± 7 + 1 (-3, +5) p 0.002
Average Hourly PVB's Mean + SD Median (25 th , 75 th percentile)	+ 69 ± 214 4 (-7, +107)	-13 ± 83 -1 (-24, +3) p 0.001	-5 ± 96 -1 (-29, +5) p 0.002
Average Hourly Repetitive Beats Mean + SD Median (25 th , 75 th percentile)	+15 ± 53 0 (0, +7)	-5 ± 19 0 (-2,0) p < 0.001	+ 3 ± 34 -0 (-1,0) p 0.001
Mortality		2%	

P values are versus dobutamine

Teerlink JR. Ambulatory Ventricular Arrhythmias in Patients With Heart Failure Do Not Specifically predict an Increased Risk of Sudden Death. *Circulation* 2000;101:40-46

BACKGROUND: Ventricular arrhythmias are a frequent finding in congestive heart failure (CHF) patients and a cause of concern for physicians caring for them. Previous studies have reached conflicting conclusions regarding the importance of ventricular arrhythmias as predictors of sudden death in patients with CHF. This study examined the independent predictive value of ventricular arrhythmias for sudden death and all-cause mortality in PROMISE (Prospective Randomized Milrinone Survival Evaluation). METHODS AND RESULTS: Ventricular arrhythmias were analyzed and quantified by use of prespecified criteria on baseline ambulatory ECGs from 1080 patients with New York Heart Association (NYHA) class III/IV symptoms and a left ventricular ejection fraction \leq 35% enrolled in PROMISE. The relationship of ventricular arrhythmias and other clinical parameters to overall mortality and sudden death classified by an independent, blinded mortality committee was determined. There were 290 deaths, of which 139 were classified as sudden. Of the several measures of ventricular ectopy that were univariate predictors, the frequency of nonsustained ventricular tachycardia (NSVT) was the most powerful predictor and remained a significant independent predictor when included with other clinical variables in multivariate models of both sudden death mortality and non-sudden death mortality. However, multiple logistic analysis with models including the clinical variables with and without the NSVT variable demonstrated that the frequency of NSVT did not add significant information beyond the clinical variables. CONCLUSIONS: This study demonstrates that ventricular arrhythmias do not specifically predict sudden death in patients with moderate-to-severe heart failure. Thus, the finding of asymptomatic NSVT on ambulatory ECG does not identify specific candidates for antiarrhythmic or device therapy.

References:

1. Wilson SC, Intravenous Nesiritide, a natriuretic Peptide, in the Treatment of Decompensated Congestive Heart Failure. *N Engl J Med* 2000;343:246-53.
2. Burger AJ, Comparison of the Occurrence of Ventricular Arrhythmias in Patients with Acutely Decompensated Congestive Heart Failure Receiving Dobutamine Versus Nesiritide Therapy. *Am J Cardiol* 2001;88:35-39.
3. Mills, RM. Sustained Hemodynamic Effects of an Infusion of Nesiritide (Human b-Type Natriuretic Peptide) in Heart Failure. *J Am Coll Cardiol* 1999;34:155-62.
4. VMAC TRIAL "Vasodilation in the Management of Acute Heart Failure", SCIOS STUDY 704.339)
5. PRECEDENT TRIAL "Prospective, Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natreacor Therapy", SCIOS STUDY 704.329.
6. A Randomized, Double-blinded, Placebo-controlled Study of Two Doses of Natreacor hBNP Administered as a Continuous Infusion in Patients with Decompensated CHF, SCIOUS STUDY 704.325
7. A Randomized, open-label, Active-Controlled, Multicenter Phase III Safety Study of Two Doses Of Natreacor hBNP administered as a Continuous Infusion in the Treatment of Decompensated CHF, SCIOS STUDY 704.326
8. Hobbs RE, An update on Nesiritide for treatment of Decompensated Heart Failure.
9. Nesiritide for Decompensated Congestive Heart Failure, *The Medical Letter* 2001;43:100-101

Drug	Dose	HR	MAP	PAOP	CO	SVR
Dopamine	0.5-3 mcg/kg/min	0	0	0	0/+	-
	3-10 mcg/kg/min	+	+	0	+	0
	> 10 mcg/kg/min	+	+	+	+	+
Dobutamine	2.5-20 mcg/kg/min	0/+	0	-	+	-
Amrinone	5-10 mcg/kg/min	0/+	0/-	-	+	-
Milrinone	0.375-0.75 mcg/kg/min	0/+	0/-	-	+	-
Nitroprusside	0.25-3 mg/kg/min	0/+	0/-	-	+	-
Nitroglycerin	5-200 mcg/min	0/+	0/-	-	0/+	0/-
Furosemide	20-80 mg q4-6h	0	0	-	0	0
Enalapril	1.25-2.5 mg q6-8h	0	0/-	-	+	+

		PCWP	CO	SVR
Vasodilators	Nitroprusside	↓↓↓	↑	↓↓↓
	Nitroglycerine	↓↓↓	↑	↓↓↓
	Nesiritide	↓↓↓	↑↑	↓↓↓
Inotropics	Dobutamine	↓	↑↑	NC
Inodilators	Milrinone	↓↓↓	↑↑	↓↓↓

Reference: ???

Studies

Dobutamine

Oliva F. Intermittent 6-month low-dose dobutamine infusion in severe heart failure: DICE Multicenter Trial. AM Heart J 1999; 138:247-53. Multicenter randomized controlled open trial of 38 patients in patient with NYHA III-IV with $CI \leq 2.2$ and $EF \leq 30$. Randomize to placebo or dobutamine 2.5 mcg/kg/min for 48 hours once a week, maximum dose 5 mcg/kg/min for 72 hours once a week. Average age 65 years, (36-79) NYHA III 17/, NYHA IV 21. Baseline and two week 24 hour Holter was monitored Exclusion criteria history of malignant arrhythmias w/o an automatic defibrillator in place. Patients underwent a dobutamine titration test and

were excluded if HR > 110 beats/min or new appearance of AF, ventricular ectopic > 6 per minute, or sustained VT. Low-dose dobutamine was well tolerated.

Baseline Dobutamine Dose titration curve			
Dobutamine Dose	Heart Rate	Cardiac Index	Pulmonary Wedge Pressure
Baseline	78	1.9	23.5
2.5 mcg/kg/min	83	2.2	21
5 mcg/kg/min	87	2.4	20.5
7.5 mcg/kg/min	89	2.6	19.5

	Dobutamine (n=19)	Placebo (n=19)
Hospitalizations any cause	11/19	17/19
Hospitalizations with worsening CHF	7/11	11/17
Death	5/19	3/19
Time to first cardiovascular death or hospitalization from any cause	No difference p=0.91	

Kishore JH. Home Inotropic Therapy in Advance Heart Failure. Chest 1997;112:1298-1303. Retrospective study to assess the effect of home IV inotropic therapy in NYHA IV patients on the overall cost of care. Drugs uses: dobutamine 71% (17/24), milrinone 17% (4/24), combination 8% (2/24), milrinone plus dobutamine and dopamine 4% (1/24). Home IV inotropic therapy reduces hospital admissions, length of stay, and cost of care and improves functional class in patients with advanced heart failure.

Tolerance may develop with dobutamine infusions after as little as 72 hours of IV therapy. Intermittent infusion durations of 48 hours minimize the risk. Dobutamine significantly increases cardiac output and decreases PCWP, RAP, systemic and pulmonary vascular resistances.