

Comparison of the Occurrence of Ventricular Arrhythmias in Patients With Acutely Decompensated Congestive Heart Failure Receiving Dobutamine Versus Nesiritide Therapy

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Ventricular arrhythmias are common in patients with congestive heart failure (CHF) and may be exacerbated by positive inotropic therapy. Because human B-type natriuretic peptide (nesiritide), an arterial and venodilator, inhibits sympathetic activity, it may decrease the incidence of arrhythmias. Our investigation compares the arrhythmogenicity of dobutamine with nesiritide. A total of 305 patients with decompensated CHF requiring intravenous vasoactive therapy were randomized to receive standard therapy (n = 102) or nesiritide (0.015 $\mu\text{g}/\text{kg}/\text{min}$ [n = 103] or 0.030 $\mu\text{g}/\text{kg}/\text{min}$ [n = 100]) to gain additional data on the relative safety and efficacy of nesiritide compared with standard parenteral care. Dobutamine was chosen as the standard care agent in 58 subjects. During study drug infusion, all patients had continuous clinical hemodynamic and electrocardiographic monitoring. The dobutamine and ne-

siritide groups were similar with respect to baseline use of antiarrhythmic agents, including β blockers. Serious arrhythmias and the incidence of cardiac arrest were more common in patients who received dobutamine than in those taking nesiritide: sustained ventricular tachycardia, 4 (7%) versus 2 (1%), respectively (p = 0.014); nonsustained ventricular tachycardia, 10 (17%) versus 23 (11%), respectively (p = 0.029); cardiac arrest, 3 (5%) versus 0, respectively (p = 0.011). We conclude that among patients with decompensated CHF for whom dobutamine is selected as standard therapy, the incidence of serious ventricular arrhythmias and cardiac arrest is significantly greater than the incidence of these events in patients randomized to nesiritide.

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Human B-type natriuretic peptide (hBNP) is secreted predominantly by the ventricle¹ in response to ventricular wall stress (pressure or volume overload), and its level is substantially augmented in response to ventricular overload in congestive heart failure (CHF). hBNP is elevated in patients with various forms of heart failure including ischemic heart disease,² idiopathic dilated cardiomyopathy,^{1,3} hypertrophic cardiomyopathy,⁴ and isolated right ventricular failure.⁵ Furthermore, plasma concentrations of hBNP closely correlate with several clinical and hemodynamic indicators of disease severity.^{3,6} In the setting of heart failure, hBNP serves to unload the heart by virtue of its natriuretic and vasodilatory properties.^{6,7} Several studies have shown that infusion of

recombinant hBNP (nesiritide), which has a half-life of 18 minutes, is associated with favorable hemodynamic and natriuretic effects in patients with severe CHF.^{7,8} In addition to their natriuretic and vasorelaxant properties, natriuretic peptides exert an inhibitory effect on sympathetic activity in both normal subjects^{9,10} and in patients with CHF.¹¹ These observations suggest that the relative therapeutic merit of nesiritide in the setting of decompensated CHF may be to attenuate reflex sympathetic responses, which may, in turn, result in a lower propensity for arrhythmias. The present analysis examines the occurrence of complex ventricular arrhythmias during short-term dobutamine or nesiritide therapy in patients with acutely decompensated heart failure.

METHODS

This investigation was a randomized, active-control, multicenter trial designed to evaluate the efficacy and safety of intravenous nesiritide compared with standard therapy in patients with symptomatic acute CHF for whom inpatient parenteral vasoactive therapy was considered appropriate. Patients were randomized to standard care therapy consisting of a single parenteral vasoactive agent or nesiritide. The treatment assignment was open-label with respect to the standard care agent versus nesiritide, but was double-blinded to

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dose of nesiritide. The duration of therapy and the choice of a standard agent were at the attending physician's discretion. The primary end point of this analysis was the incidence of ventricular arrhythmias reported as adverse events during study drug infusion. The protocol was performed in agreement with the guidelines established in the Declaration of Helsinki and was approved by the institutional review board of the participating hospitals. Written informed consent was obtained from each patient before initiation of vasoactive therapy.

Eligibility and exclusion: Adults aged >18 years with a previous history of chronic CHF, who presented with symptomatic, acutely decompensated CHF for which parenteral vasoactive therapy was deemed necessary, were candidates for the study. Exclusion criteria included recent myocardial infarction within 48 hours, ongoing unstable angina, stroke within the past month, cardiogenic shock or prolonged hypotension (systolic blood pressure <90 mm Hg), contraindications for positive inotropic therapy (significant valvular aortic stenosis or obstructive cardiomyopathy), constrictive pericarditis, biopsy-proved active myocarditis, complex congenital heart disease, and primary pulmonary hypertension. Patients who were already being treated with parenteral vasoactive agents were excluded if they had received this therapy for >4 hours or for <4 hours if the current therapy could not be discontinued for the protocol-specified washout period (6 hours for milrinone and 30 minutes for nitroglycerin, nitroprusside, dobutamine, or dopamine).

Drug administration regimens: Eligible patients were randomly assigned to 1 of 3 treatment groups for a maximum of 7 days¹: standard care agent, defined as a single intravenous vasoactive drug routinely used for the management of decompensated heart failure (e.g., intravenous nitroglycerin, dobutamine, milrinone, or nitroprusside)²; nesiritide 0.015 $\mu\text{g}/\text{kg}/\text{min}$ after an intravenous loading dose of 0.3 $\mu\text{g}/\text{kg}$ ³; nesiritide 0.030 $\mu\text{g}/\text{kg}/\text{min}$ after an intravenous loading dose of 0.6 $\mu\text{g}/\text{kg}$.

During study drug infusion, all patients had continuous clinical hemodynamic and electrocardiographic monitoring. Blood pressure, heart rate, and respiratory rate were measured at baseline, every 15 minutes for 2 hours, every 30 minutes for 1 hour, at hours 4 and 5, and at least every 4 hours thereafter. At the discretion of the attending physician, the dose of all therapies could be modified and a second parenteral vasoactive drug could be added to, or substituted for, the initial study drug; however, nesiritide was discontinued if another vasodilator was added. Adjustments of the dose downward or discontinuation of the drug was permitted in the event of a clinically significant adverse reaction.

Definition of arrhythmic events: Spontaneous ventricular tachycardia (VT) was considered as ≥ 3 consecutive ventricular premature complexes with a rate >100 beats/min. VT terminating spontaneously within 30 seconds was classified as nonsustained VT. Sustained VT was considered as VT duration >30 seconds or

requiring emergency termination before that time because of hemodynamic compromise. Ventricular fibrillation was defined as a disorganized rhythm with no discrete QRS complexes discernible. Cardiac arrest required that the patient be unresponsive with no palpable pulse and no spontaneous respiration, and that closed chest compression was required before any patient response. Events were recorded with telemetry rhythm strip or 12-lead electrocardiogram and read by an experienced investigator.

Statistical analysis: The general analysis strategy was to test for nonspecific differences between the 3 treatment groups followed by pairwise comparisons of treatment groups. Continuous data were typically analyzed by the omnibus F test followed by pairwise contrasts, ordinal data by the Kruskal-Wallis test followed by pairwise 2-sample Wilcoxon procedures, and categorical data by Fisher's exact test followed by pairwise Fisher's exact test.

The comparability of treatment groups with respect to the demographic and baseline characteristics was assessed with the omnibus F test, the Kruskal-Wallis test, or the generalized Fisher exact test depending on the distribution of the variables.

For duration of treatment, pairwise comparisons of nesiritide versus dobutamine were examined using the 2-sample Wilcoxon test. For concomitant medications and adverse events, the 3 treatment groups were tested for nonspecific differences with generalized Fisher's exact test. Pairwise comparisons were examined using either the 2-sample Wilcoxon test or Fisher's test. All analysis results were obtained using SAS software, version 6.12 (SAS Inc., Cary, North Carolina).

RESULTS

Subject enrollment and baseline features: The study group consisted of 305 patients enrolled at 46 US clinical sites between January 7, 1997, and July 3, 1997; 102 patients received standard therapy, 103 received 0.015 $\mu\text{g}/\text{kg}/\text{min}$ of nesiritide, and 100 were given 0.030 $\mu\text{g}/\text{kg}/\text{min}$ of nesiritide. Of the 102 patients receiving standard therapy, dobutamine was the drug most often given for initial parenteral therapy (n = 58) followed by milrinone (n = 19), nitroglycerin (n = 18), dopamine (n = 6), and amrinone (n = 1). Therefore, we compared the arrhythmogenicity of dobutamine, the most frequently used standard agent chosen by the attending physicians in this trial, with the 2 nesiritide groups.

The clinical characteristics of the 261 patients who received dobutamine or nesiritide as initial therapy are listed in Table 1. The treatment groups were similar with respect to most baseline clinical variables. Significantly more patients taking dobutamine had a prior myocardial infarction than those taking nesiritide (p = 0.03), and there was a tendency for more of the patients taking dobutamine to be classified as having "ischemic cardiomyopathy."

Many patients enrolled in the study had a history of cardiac arrhythmias (Table 2) and 5% had an automatic implantable cardiac defibrillator. Consequently, 11% of all patients were receiving class III antiar-

Characteristics	Dobutamine (n = 58)	Nesiritide ($\mu\text{g}/\text{kg}/\text{min}$)		Overall p Value
		0.015 n = 103	0.030 n = 100	
Age (yrs)	65 \pm 14	63 \pm 14	65 \pm 12	0.520*
Men/women	76%/24%	65%/35%	67%/33%	0.361 [†]
Previous NYHA class				0.548 [‡]
Class II	4 (7%)	6 (6%)	11 (11%)	
Class III	30 (52%)	57 (55%)	52 (52%)	
Class IV	24 (41%)	40 (39%)	36 (36%)	
Previous MI	40 (69%)	51 (50%)	49 (49%)	0.030
Etiology of heart failure				0.029
Ischemic	39 (67%)	53 (51%)	54 (54%)	
Idiopathic	11 (19%)	27 (26%)	18 (18%)	
Hypertensive	0 (0%)	12 (12%)	9 (9%)	
Valvular	1 (2%)	3 (3%)	5 (5%)	
Alcohol induced	0 (0%)	2 (2%)	3 (3%)	
Diabetic cardiomyopathy	1 (2%)	2 (2%)	3 (3%)	
Drug induced	1 (2%)	0 (0%)	4 (4%)	
Unknown	5 (9%)	3 (3%)	2 (2%)	
Prior drug therapy				
Digoxin	34 (59%)	62 (60%)	61 (61%)	0.973
Diuretics	48 (83%)	82 (80%)	84 (84%)	0.716
ACE inhibitors	33 (57%)	67 (65%)	59 (59%)	0.507
All receptor antagonists	2 (3%)	6 (6%)	8 (8%)	0.538
Hydralazine	6 (10%)	4 (4%)	6 (6%)	0.254
Calcium antagonists	7 (12%)	18 (17%)	19 (19%)	0.543
Nonintravenous nitrates	29 (50%)	45 (44%)	54 (54%)	0.338
Other antihypertensives	1 (2%)	7 (7%)	4 (4%)	0.352

*Omnibus F test; [†]Fisher's exact test; [‡]Kruskal-Wallis test.
Data presented are mean \pm SD.
All = angiotensin II; ACE = angiotensin-converting enzyme; MI = myocardial infarction; NYHA = New York Heart Association.

Characteristics	Dobutamine (n = 58)	Nesiritide ($\mu\text{g}/\text{kg}/\text{min}$)		Overall p Value*
		0.015 n = 103	0.030 n = 100	
Class III antiarrhythmics	9 (16%)	11 (11%)	9 (9%)	0.451
Other antiarrhythmic agents	0 (0%)	2 (2%)	4 (4%)	0.278
β blockers	8 (14%)	11 (11%)	7 (7%)	0.359
Previous arrhythmic events				
Atrial fibrillation	28 (48%)	40 (39%)	37 (37%)	0.357
Nonsustained VT	15 (26%)	17 (17%)	23 (23%)	0.304
Sustained VT	4 (7%)	3 (3%)	15 (15%)	0.008
Sudden death	7 (12%)	2 (2%)	14 (14%)	0.002

*Fisher's exact test.

rhythmic agents before study drug administration. At the time of the study entry, patients in the 3 treatment groups did not differ significantly with regard to the use of antiarrhythmic agents or β blockers. However, patients randomized to nesiritide had a higher frequency of prior sustained VT or resuscitated sudden cardiac death ($p = 0.008$ and $p = 0.002$, respectively).

The total duration of parenteral vasoactive therapy was 3.7 ± 4.1 days for the dobutamine group, 2.1 ± 1.8 days for the $0.015 \mu\text{g}/\text{kg}/\text{min}$ nesiritide group ($p < 0.001$ compared with dobutamine), and 1.8 ± 1.6 days for the $0.030 \mu\text{g}/\text{kg}/\text{min}$ nesiritide group ($p < 0.001$ and $p = 0.14$ compared with dobutamine and

$0.015 \mu\text{g}/\text{kg}/\text{min}$ nesiritide, respectively). Dobutamine was infused at a mean starting dose of $4.3 \pm 1.5 \mu\text{g}/\text{kg}/\text{min}$ (range 2 to 12) and advanced to a mean of $5.4 \pm 2.6 \mu\text{g}/\text{kg}/\text{min}$ (range 2 to 16) during treatment. A decrease in the dobutamine dose was necessary more frequently than with either dose of nesiritide (50%, 17%, and 18%, respectively, $p < 0.001$).

Twenty patients (10%) enrolled in the nesiritide groups required the addition of a second vasoactive drug. In 17 of these patients, dobutamine was added (7 in the $0.015 \mu\text{g}/\text{kg}/\text{min}$ group and 10 in the $0.030 \mu\text{g}/\text{kg}/\text{min}$ group). Nesiritide was not available as a second drug to the dobutamine group, but 7 patients (12%) in the dobutamine group required a second inotrope (3 dopamine, 1 milrinone, and 3 dopamine and milrinone).

Effect of vasoactive therapy on ventricular arrhythmias: Ventricular arrhythmias occurred more frequently in patients treated with dobutamine (Table 3). During the study drug infusion, arrhythmic events that were classified by the investigator as life-threatening (sustained VT and cardiac arrest) occurred in 7 patients (12%) during treatment with dobutamine; in contrast, only 2 such events (1%) were reported in patients assigned to the nesiritide groups. Non-life-threatening ventricular arrhythmias (nonsustained VT) were also significantly more common in the dobutamine group (10 patients, 17%) compared with the nesiritide groups (23 patients, 11%) ($p = 0.029$). Three patients in the dobutamine group had cardiac arrest: 1 was secondary to electromechanical dissociation, whereas the other 2 were due to ventricular dysrhythmias. When the 2 nesiritide groups were analyzed separately, there was no significant effect of nesiritide

dose on the occurrence of ventricular arrhythmias. Finally, in this study population with a significant history of ventricular arrhythmias, dobutamine was associated with more arrhythmic events than nesiritide both in the acute phase of treatment (during the first 48 hours) as well as with prolonged drug exposure.

Adverse effects: Electrolyte abnormalities were uncommon among all study groups. Hypokalemia occurred in 3% of patients in each of the 3 study groups. Hypomagnesemia occurred in 3% of the group taking $0.015 \mu\text{g}/\text{kg}/\text{min}$ of nesiritide, 1% in the group taking $0.030 \mu\text{g}/\text{kg}/\text{min}$ of nesiritide, and none in the group taking dobutamine. Bradycardia tended to be more

TABLE 3 Arrhythmic Events by Initial Treatment Assignment

Characteristics	Dobutamine (n = 58)	Nesiritide ($\mu\text{g}/\text{kg}/\text{min}$)		Overall p Value*
		0.015 n = 103	0.030 n = 100	
During study drug				
Cardiac arrest	3 (5%)	0 (0%)	0 (0%)	0.011
VT	13 (22%)	17 (17%)	8 (8%)	0.032
Nonsustained	10 (17%)	17 (17%)	6 (6%)	0.029
Sustained	4 (7%)	0 (0%)	2 (2%)	0.014
During first 48 hours				
Cardiac arrest	2 (3%)	1 (1%)	1 (1%)	0.451
VT	8 (14%)	18 (17%)	5 (5%)	0.016
Nonsustained	5 (9%)	18 (17%)	5 (5%)	0.016
Sustained	3 (5%)	1 (1%)	0 (0%)	0.035

*Fisher's exact test.

common in the nesiritide groups (6% and 4% for the 2 respective nesiritide doses) than in the dobutamine group (2%), although this difference was not statistically significant ($p = 0.543$). The incidence of symptomatic hypotension was higher in the nesiritide than in the dobutamine group (12%, 18%, and 5%, respectively; $p = 0.061$). In terms of mortality, 5 (9%), 6 (6%), and 6 (6%) of patients in the dobutamine and the 2 respective nesiritide groups died within the 21-day study period.

DISCUSSION

In this analysis from a randomized controlled trial, we demonstrated that nesiritide use (both 0.015 and 0.030 $\mu\text{g}/\text{kg}/\text{min}$) was associated with significantly fewer serious ventricular arrhythmias than dobutamine in a hospitalized population with decompensated CHF. Life-threatening arrhythmias (sustained VT and cardiac arrest) were increased by approximately 12-fold, and nonsustained VT was increased by 1.5-fold in the dobutamine group compared with the nesiritide groups. The relative differences observed in this analysis may, in fact, have underestimated the true differences in arrhythmogenesis between nesiritide and dobutamine because patients taking nesiritide had a significantly higher frequency of prior sustained VT and ventricular fibrillation/sudden death. To our knowledge, this is the first large study of hospitalized patients with decompensated CHF in which patients with significant arrhythmias were not excluded from participation in the study. Furthermore, patients treated with nesiritide completed therapy significantly sooner (mean of -1.6 and -1.9 days for the 2 respective nesiritide doses relative to dobutamine).

CHF and its treatment represent a medical problem of significant and increasing importance. Despite a growing number of treatment choices for patients with CHF, there are approximately 50,000 to 200,000 patients for whom even the best conventional medical therapy cannot provide adequate relief of symptoms at rest.¹² These patients require inpatient care with parenterally administered agents to relieve symptoms, enhance a diuretic response, and allow readjustments of other medications.¹³ Although the clinical utility of

short-term intravenous positive inotropic therapy is well established in the management of acute heart failure, its benefits may be offset by the risk of new or worsened ventricular arrhythmias.^{12,14} Furthermore, there is no consensus regarding the relative merits of different intravenous vasoactive agents, as reflected by the wide variation in their use among heart failure centers.

A number of clinical investigations have demonstrated that inotropic agents such as dobutamine^{15,16} or milrinone^{15,17,18} may induce or aggravate arrhythmias. Ventricular arrhythmias attributed to dobutamine have been reported to occur in 3% to

10% of treated patients.¹⁴ Although these arrhythmias translate into life-threatening events in only a few patients during short-term infusions, dobutamine therapy is often withheld for fear of precipitating arrhythmia, or antiarrhythmic therapy is initiated. Although aggravation of complex arrhythmias may not be expected in patients with heart failure treated with vasodilators, vasodilators have not been shown to reduce ventricular arrhythmias in patients with CHF.¹⁹ Furthermore, a reduction in systemic arterial and central filling pressures by potent vasodilators such as nitroprusside may result in an increase in total body and cardiac norepinephrine spillover.²⁰

The results of the present study suggest that nesiritide infusion in the setting of decompensated CHF may be associated with a lower frequency of clinically significant ventricular arrhythmias than dobutamine. These results may be related to the direct proarrhythmic effects of dobutamine,^{14,21} as well as to the potentiation of proarrhythmic effects of hypokalemia and neurohumoral activation.²¹ Furthermore, the inhibitory effect of natriuretic peptides on sympathetic activity⁹⁻¹¹ may mitigate the proarrhythmic effects of sympathetic and neurohumoral activation in patients with decompensated CHF.

APPENDIX

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