Nesiritide: The clinical experience

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Nesiritide is an effective therapy in decreasing symptoms and left ventricular filling pressure in patients with acute decompensated heart failure. Health Canada has recently approved this agent for the management of this patient population. The clinical trials to date using nesiritide for the management of decompensated heart failure have been summarized. The clinical experience including indications for use, contraindications, dosage and monitoring has been reviewed. The following should serve as a general guide for the clinical use of nesiritide.

Key Words: ADHF; Heart failure; Management; Nesiritide

Acute decompensated heart failure (ADHF) is characterized by the progression of signs and symptoms of venous congestion with reduced end-organ performance secondary to low cardiac output. Nesiritide has been shown to be an effective agent in decreasing symptoms of congestion as well as significantly improving hemodynamic measures of left ventricular filling pressure (1-4).

With the recent Health Canada approval of nesiritide (Natrecor, Janssen-Ortho Inc, Canada) for the treatment of ADHF, it is essential that the experience to date be reviewed to aid in the appropriate and effective use of this vasoactive agent. The clinical trials published to date using nesiritide for the inpatient treatment of ADHF are listed in Table 1. Trials with regard to the outpatient or perioperative use of nesiritide have not been included (5-7).

Initial feasibility and efficacy trials used varying bolus and infusion doses in an effort to optimize safety and effectiveness. Although there was a significant dose response in terms of improvement in hemodynamic measures, this was accompanied by an increase in asymptomatic and symptomatic hypotension. More recent and ongoing clinical trials examining the use of nesiritide for ADHF have used a lower infusion dose (0.01 µg/kg/min), maintaining an improvement in hemodynamics and symptoms.

COMPARISON WITH NITROGLYCERIN

Nesiritide and nitroglycerin, a commonly used agent for the treatment of ADHF, were compared in the Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial (3). The use of nesiritide resulted in a more rapid improvement in measures of left ventricular filling pressure (3 h decrease in pulmonary capillary wedge pressure [5.8 mmHg versus 3.8 mmHg, $P=0.03$]), which was sustained at 24 h (-8.2 mmHg versus -6.3 mmHg, $P<0.05$). Unlike nesiritide, the change in pulmonary capillary wedge pressure with nitroglycerin was not statistically different from placebo. Nesiritide and nitroglycerin improved symptoms by a similar degree at 3 h and 24 h. Both medications were well tolerated; however, fewer patients in the nesiritide group experienced headache or abdominal/catheter pain.

However, it must be noted there is a significant difference in the cost of these medications.

L'utilisation clinique du nésiritide

Le nésiritide est un traitement efficace pour soulager les symptômes de l'insuffisance cardiaque (IC) aiguë décompensée et diminuer la pression de remplissage du ventricule gauche. Santé Canada a approuvé dernièrement l'utilisation du médicament chez les patients touchés. Un résumé des essais cliniques du nésiritide, menés jusqu'à maintenant dans le traitement de l'IC aiguë décompensée sera présenté dans l'article. Nous avons examiné l'emploi clinique du médicament, plus particulièrement les indications, les contre-indications, la posologie et la surveillance. Le présent document devrait servir de guide général en vue de l'utilisation clinique du nésiritide.

META-ANALYSES

Meta-analyses have raised concern regarding a potential risk of worsening renal function and short-term mortality with the use of nesiritide. However, the inability of the meta-analyses to adjust for baseline characteristics makes conclusions with regard to these issues impossible. There have been several individual studies that have not supported worsening renal function using nesiritide, including Nesiritide Administered Peri-Anesthesia in Patients Undergoing Cardiac Surgery (NAPA) (5), B-Type Natriuretic Peptide in Cardio-Renal Decompensation Syndrome (BNP-CARDS) (8), and Follow-Up Serial Infusions of Nesiritide in Advanced Heart Failure (FUSION) I and II trials (6,9). The currently underway Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial will aim to answer these and other questions. This multicentre study will evaluate the use of nesiritide in the treatment of ADHF versus standard therapy in a double-blind design.

CLINICAL EXPERIENCE

The successful use of any medication requires careful patient selection. This is particularly true for vasoactive medications used in the treatment of ADHF. Nesiritide should be reserved for the use in patients with decompensated heart failure. This is defined as New York Heart Association functional class IV, dyspnea at rest or with minimal activity, with clinical evidence of fluid overload (Table 2).

Fluid overload may be assessed in terms of symptoms including orthopnea, paroxysmal nocturnal dyspnea or edema. Signs of volume overload include jugular venous distension, positive abdominal jugular reflux, ascites, hepatomegaly, edema or pulmonary rales. Eligible patients should have a systolic blood pressure (SBP) of greater than 90 mmHg and not have any signs of shock. Bedside evaluation of these patients should reveal a patient who is 'warm and wet' (10). Patients with significant aortic stenosis and hypertrophic cardiomyopathy should not receive nesiritide. Patients with low cardiac output in the setting of low left ventricular filling pressure ('dry and cold') should not receive this therapy. If there is any concern with regard to the ability to assess the volume and perfusion status of the patient, invasive hemodynamic monitoring should be considered.

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TABLE 1
Clinical trials evaluating nesiritide for heart failure (HF)

Study	Year	n	Bolus (mg/kg)	Infusion (µg/kg/min)	Duration (h)	Control	Blinded	Outcome	Oral medications
Mills et al (4)	1999	103	0.025 0.5 1.0	0.015 0.03 0.06	24	Placebo	Double-blind	Rapidly improved hemodynamics (PCWP, CI, SVR), dose dependent	Held ~48 h
Colucci et al (1)									
Efficacy	2000	127	0.3 0.6	0.015 0.03	6	Placebo	Double-blind	Improved hemodynamics (CI, SVR, PCWP) and symptoms	Held 4 h
Comparative	2000	305	0.3 0.6	0.015 0.03	Mean 30; up to 7 days	Std care (single vasoactive medication – dobutamine 57%)	Open label	Similar improvement in symptoms, less diuretic use in nesiritide group	Could be used
VMAC (3)	2002	498	2.0 2.0	0.01 0.01–0.03	Mean 24	Placebo or nitroglycerin	Double-blind	Improved hemodynamics, similar improvement in symptoms	Continued (beta-blocker often held)
PRECEDENT (9)	2002	255	0	0.015 0.03	Mean 24	Dobutamine	Open label	Less VT events in nesiritide group, similar improvement of symptoms	
ASCEND-HF (In progress) (8)		7000	2.0	0.01	>24	Std	Double-blind	HF readmission, mortality, symptoms	Continued

ASCEND-HF Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure; CI Cardiac index; PCWP Pulmonary capillary wedge pressure; PRECEDENT Prospective Randomized Evaluation of Cardiac Ectopy With Dobutamine or Natreacor Therapy; Std Standard; SVR systemic vascular resistance; VMAC Vasodilation in the Management of Acute Congestive Heart Failure; VT Ventricular tachycardia

TABLE 2
Indications and contraindications to nesiritide

Indications	Contraindications
• Decompensated HF (NYHA IV)	• Hypotension (SBP <90 mmHg)
• Evidence of volume overload	• Severe aortic stenosis
• Failure to respond to initial changes in management	• Hypertrophic cardiomyopathy
	• Low left ventricular filling pressure (PCWP ≤18 mmHg)

HF Heart failure; NYHA New York Heart Association; PCWP Pulmonary capillary wedge pressure; SBP Systolic blood pressure

DOSAGE

Appropriate patients should receive a 2 µg/kg intravenous bolus (over 1 min) followed by 0.01 µg/kg/min infusion. The infusion is generally continued until clinical improvement is evident (6 h to 36 h) or side effects that require discontinuation. Clinical improvement is ideally based on resolution of symptoms, diuresis and a clinically determined euvoletic status. In the VMAC trial (3), symptomatic hypotension occurred in 4% of patients. It is recommended to hold the infusion in patients with SBP less than 90 mmHg. It is reasonable to restart the infusion at half-dose once the SBP reaches 100 mmHg or greater. Patients who experience hypotension with nesiritide will likely remain hypotensive for longer than that seen with nitroglycerin. This is likely secondary to the longer half-life of the natriuretic peptide (18 min to 20 min). Nesiritide inactivation is not dependent on hepatic or renal function and therefore can be administered safely to patients with renal dysfunction (6,8,10).

MONITORING

Nesiritide does not require the use of invasive monitoring unless otherwise indicated (not responding, uncertain left ventricular filling pressure).

This is potentially a significant advantage over standard therapies. Nesiritide, unlike several other parenteral vasoactive drugs, does not increase the rate of significant dysrhythmias (11). This allows for its potential use in noncritical care environments.

It is suggested that patients have frequent blood pressure assessments (baseline, postbolus, every 30 min for first hour, every hour for subsequent 3 h and then every 4 h). Blood pressure and clinical status should be reassessed with the development of side effects or worsening symptoms of HF. In addition, serum electrolytes and creatinine levels should be monitored twice daily. Urine output and daily weights should be monitored as is suggested in the management of all patients with ADHF. A urine output of less than 50 mL over the first 4 h of nesiritide infusion should prompt physician reassessment.

CONCURRENT MEDICATIONS

Oral cardiac medications including beta-blockers, angiotensin-converting enzyme inhibitors and digoxin should be continued but may be held in patients with borderline low blood pressure. Careful attention to avoid overdiuresis should be made because the diuretic dose required once nesiritide has been started is often reduced. Nesiritide should be considered in patients in whom diuresis has been ineffective, insuring that the patient is volume overloaded.

SUMMARY

Nesiritide is the first new vasoactive therapy approved for ADHF in over a decade. This agent, used in the correct specific clinical setting, has the potential to improve symptoms and hemodynamics in patients with heart failure. More will be known about optimization of its use with the results of the ASCEND-HF trial.

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