Nesiritide: A recombinant human BNP as a therapy for decompensated heart failure

The rationale for the treatment with various pharmacologic agents administered in the management of both chronic and acute decompensated heart failure (ADHF) are based on our understanding of underlying pathophysiology of the patient’s diseases. Recently, the management of HF has shifted from traditional drugs that are administered to ameliorate the gross hemodynamic manifestations of volume overload and hypoperfusion to the agents that modulate the neurohormonal derangements associated with the failing heart. This has marked a paradigmatic shift from thinking of HF in the hemodynamic model to understanding the syndrome in terms of neurohormonal activation.

Clinicians have offered treatment modalities aimed at addressing the overt hemodynamic imbalance of decompensated HF, namely positive ionotropic agents and parenteral diuretics. Elucidation of the neurohormonal contribution to HF pathophysiology has been a seminal development in understanding the natural history of the syndrome and targeting drug therapy to reduce morbidity and mortality.[1] Neurohormonal stimulation, initially a compensatory mechanism, ultimately leads to cardiac dysfunction. Baroreceptor sensitivity is often down-regulated in HF, even when normal arterial pressures are restored and the sympathetic stimulation is maintained. The major hormones known to be elevated and likely to have the detrimental effects in chronic HF include angiotensin II, aldosterone, norepinephrine, arginine, vasopressin, and endothelin.[2] The natriuretic peptide is a major homeostatic force that counterbalances the vasoconstriction and retentive effects of sustained neurohormonal secretion.[3] Brain natriuretic peptide (BNP) is one of the three natriuretic peptides that are important in maintaining hemodynamic and neurohormonal equilibrium in normal human physiology. The other two (atrial natriuretic peptide – ANP and C-type natriuretic peptide) have coordinated actions with BNP that help maintain adequate vascular volume and pressure in response to volume overload. The BNP is synthesized and released by cardiac myocytes in response to ventricular stretch and volume overload. The correlation of plasma BNP with the severity of HF suggested its use as a biomarker in HF.[4] Although, neurohormonal blockade is becoming a recognized principle in the treatment of chronic HF, this is not routinely implicated in the management of acute heart failure (HF).

Nesiritide, a synthetic natriuretic peptide, is the first approved vasoactive agent for management of ADHF. It is a recombinant form of human BNP that is structurally and biochemically identical to endogenously produced BNP (Fig. 1). The BNP is important in hemodynamic and neurohormonal equilibrium. It helps to maintain adequate vascular volume and pressure in response to volume overload. Nesiritide mimics the biologic effects of BNP by binding to guanylate cyclase receptors (natriuretic peptide receptors) in the heart, vasculature, kidneys, and other organ systems to increase intracellular levels of cyclic guanosine monophosphate. Nesiritide has been shown to significantly improve dyspnea and rapidly reduce pulmonary capillary wedge pressure (PCWP) in patients with decompensated HF. Nesiritide has also been shown to increase diuresis and natriuresis while maintaining renal blood flow.[5] Animal and in vitro studies suggest that nesiritide may reduce ventricular remodeling by exerting an antifibrotic effect on cardiac fibroblasts, reducing deposition of collagen and fibronectin in extracellular matrix, and reducing production of inflammatory mediators. In addition, experimental studies demonstrated that BNP might reduce aldosterone activation in response to furosemide.[6]

As such, nesiritide is indicated for intravenous administration, however, it should not be the primary vasoactive agent for patients in cardiogenic shock or with systolic blood pressure less than 90 mm Hg. The HF patients with low cardiac filling pressures are not considered to be suitable for nesiritide due to its ability to reduce preload. Despite different dosing strategies used in clinical trials with nesiritide, the approved regimen is an intravenous bolus of 2 µg/kg followed by a continuous infusion of 0.01 µg/kg/min. Its elimination appears to be biphasic, with an initial elimination phase of 2 min and a terminal half-life of approximately 18 min. However, its pharmacodynamic effects actually may be longer than anticipated by this pharmacokinetic half-life. The mean volume of distribution of nesiritide at steady state is relatively small, 0.19 l/kg. Nesiritide is cleared through three elimination pathways: direct binding to the natriuretic peptide clearance surface receptor proteolytic cleavage by neutral endopeptidase and renal filtration. The mean clearance of nesiritide is 9.2 ml/min/kg.

In general, the ability of nesiritide to lower PCWP and systolic blood pressure is seen in the first 15 min of the infusion, with maximal effects occurring within 1–3 h. Symptomatic improvement may not be evident until several hours after the infusion and may not occur in all in some patients. It is expected that at the approved dosage of nesiritide, patients will have an approximate 3-fold increase in BNP concentrations from baseline.[7] A relative common side effect is hypotension, which results largely from the ability of nesiritide to reduce preload. It lacks arrhythmogenic properties as compared to the other standard therapies like dobutamine. Although BNP and nesiritide are eliminated
partially through glomerular filtration, dosing regimens need not be adjusted in patients with renal insufficiency. Patients receiving nesiritide whose creatinine levels are greater than 2.0 mg/dl may have similar reductions in PCWP and blood pressure as those with creatinine 2.0 mg/dl or less.

Various clinical trials like VMAC, PRECEDENT, PRESERVD-HF, PROACTION have investigated the safety and efficacy of nesiritide in comparison to the standard therapies in various clinical settings. The vasodilatation in the management of acute heart failure (VMAC) trial demonstrated hemodynamic superiority of nesiritide over nitroglycerin to a modest degree, other effects being similar to those of nitroglycerin. The prospective randomized evaluation of cardiac ectopy with dobutamine or natrecor therapy (PRECEDENT) study compared the proarrhythmic effects of nesiritide and dobutamine in a head-to-head fashion. It was observed that patients randomized to nesiritide had fewer episodes of sustained and nonsustained ventricular tachycardia than those randomized to dobutamine. The pilot randomized study of nesiritide versus dobutamine in heart failure (PRESERVD-HF) compared the effects of nesiritide vs dobutamine on myocardial necrosis as measured by troponins I and T release. The prospective randomized outcomes study of acutely decompensated congestive HF-treated initially in outpatients with HF using nesiritide (PROACTION) trial showed a trend towards decreased admissions and readmission rates with nesiritide.

The latest open-label, standard care controlled, 12-week FUSION I pilot trial studied the safety and tolerability of nesiritide in the outpatient setting. Serial infusions of either 0.005 or 0.01 µg/kg/min of nesiritide were given in addition to the usual long-term cardiac medications, excluding intravenous ionotropes. A total of 1645 infusions of nesiritide were given during the trial, of which, fewer than 1% were stopped due to safety concerns. Data trends in FUSION I also suggest that nesiritide may improve clinical outcomes (reduced hospitalizations and mortality) in end-stage HF. Although the study was not powered as an efficacy trial, these data support a blinded, placebo-controlled study of nesiritide in this setting. FUSION II; phase IIb study is being conducted to further confirm the findings of FUSION I in a blinded, placebo-controlled study, with the goal to demonstrating a reduction in all-cause mortality and/or hospitalization for cardiovascular and/or renal causes with serial infusions of nesiritide. Nesiritide will be administered as a bolus of 2 µg/kg followed by an IV infusion of 0.01 µg/kg/min for 4–6 h.

Based on its mechanism of action of mimicking the beneficial effects of endogenous BNP, being relatively safe as compared to other agents and its favorable tolerability profile, nesiritide appears to be a useful new agent for administration in patients with acute decompensated or advanced HF. Nesiritide is approved for marketing in the United States, Israel and Switzerland, and it is indicated for the intravenous treatment of patients with acutely decompensated congestive HF who have dyspnea at rest or with minimal activity.

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References