Nesiritide – A New Agent For Acute Decompensated Heart Failure

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Introduction

Acute decompensation is the most common reason for hospitalization of patients with congestive heart failure due to left ventricular systolic dysfunction [1]. Such patients are treated with intravenous diuretics, vasodilators such as nitroglycerin and nitroprusside, inotropes such as dobutamine and inodilators like milrinone. All these are associated with limitations like arrhythmias with milrinone, electrolyte disturbances with diuretics, hypotension with nitroprusside and tolerance with nitrates [2,3].

Nesiritide, a synthetic recombinant human B-type natriuretic peptide, has recently been introduced as short-term infusion in patients with congestive heart failure to improve volume overload and cardiac decompensation. This therapy represents a novel approach to 'physiologic' management of heart failure, enhancing naturally occurring protective mechanisms [4].

Natriuretic peptides

The atria and other tissues of mammals contain a family of peptides known as atrial natriuretic peptides (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) with natriuretic, diuretic and vasorelaxant properties. Atrial cells release a 28-amino acid peptide which is now known as ANP. ANP has got powerful effect on kidney and vascular system. BNP, like ANP is primarily synthesized in the heart. BNP exhibits natriuretic, diuretic and hypotensive activity similar to ANP. Nesiritide is the first of a new class drugs. Human B-type natriuretic peptide (hBNP) manufactured from E.coli using DNA recombinant technology has the same 32 amino acid sequence as the endogenous peptide and mimics the biologic effects of BNP.

Pharmacological properties of Nesiritide

Brain natriuretic peptide exerts its action by binding

to the type A natriuretic peptide receptor (NPR-A) which is present in large numbers in large vessels, kidneys and adrenals. Activation of the NPR-A receptor raises intracellular cGMP leading to biological effects such as vasodilation, natriuresis, diuresis and inhibition of the renin-angiotensin-aldosterone and adrenergic systems. Nesiritide has actions identical to that of BNP [5].

The elevated level of endogenous BNP in systolic and diastolic dysfunction forms the theoretical basis for its use as a drug for the treatment of heart failure [5]. Increased production of these peptides by the stretching of the atrial and ventricular walls results in vasodilatation especially in the capacitance vessels. Increased vascular permeability, enhanced sodium excretion and overall hemodynamic and neurohumoral effects opposite to that of angiotensin II are noted, making it rational in the management of decompensated heart failure. Nesiritide produces dose-dependent reduction in pulmonary capillary wedge pressure (PCWP) and systemic arterial pressure.

Pharmacokinetics of Nesiritide

Being a peptide, nesiritide is administered by intravenous infusion and it undergoes biphasic elimination. The initial mean elimination phase is 2 minutes and terminal elimination time is 18 minutes. However, pharmacodynamic half life of nesiritide is longer than its pharmacokinetic half-life. This drug is cleared from the body by lysosomal degradation on internalization, proteolytic cleavage by neutral endopeptidases and renal filtration.

Dosage and Administration

Nesiritide is recommended to be administered as an IV bolus of 2 mcg/kg over 60 seconds followed by continuous fixed dose infusion of 0.01 mcg/kg/min. The reconstituted drug must be used within 24 hours. There is limited data on the infusion of Nesiritide beyond 48

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hours.

Clinical Use

Nesiritide was approved for clinical use by the US FDA in Aug 2001. It is indicated for the treatment of acutely decompensated heart failure with dyspnoea at rest or with minimal activity [6].

Adverse Effects

In the recommended dose, nesiritide is well tolerated. Hypotension (incidence 11% compared to 12% with Nitroglycerine) is a common side effect and is dose dependent. Hypotension can be managed by discontinuing nesiritide till blood pressure rises to the previous value and then restarting it at 50-75% of the previous dose. Ventricular tachycardias (incidence 3% compared to 5% with Nitroglycerine), headache, abdominal and back pain, insomnia, anxiety, dizziness, nausea and vomiting are the other adverse effects [7].

Contraindications and Special Precautions

Hypersensitivity to any of the components of the formulation is a contraindication to its use. Nesiritide should not be used as primary therapy for cardiogenic shock or when systolic blood is less than 90 mm Hg.

Parenteral use may cause allergic/anaphylactic reactions. Blood urea levels may rise in patients with compromised renal function due to severe heart failure [7]. Caution is recommended in pregnancy, lactation and patients dependent on preload for maintenance of cardiac output [8].

Drug Interactions

No major or significant interactions have been noticed with other drugs used for CCF. In some instances an increase in hypotension in patients receiving oral ACE inhibitors has been observed [7].

Physical and Chemical Interactions

Nesiritide is incompatible with the preservative sodium metabisulfite and drugs containing it should not be administered in the same infusion line as Nesiritide. Heparin, insulin, furosemide and hydralazine should not be coadministered as infusion with Nesiritide.

Current Recommendations and Comparative Efficacy

The drug has been evaluated in a number of trials including two major randomized controlled clinical trials known as VMAC (Vasodilation in the Management of Acute Congestive Heart Failure) and PRECEDENT (Prospective Randomised Evaluation of Cardiac Ectopy with Dobutamine and Nesiritide) and both have reported

improved hemodynamics and less arrhythmogenicity with nesiritide [9,10]. Nesiritide has a role in treatment of patients with congestive heart failure who are hospitalized with severe fluid and sodium retention and have failed to improve after a single IV bolus of loop diuretic. Nesiritide is easier to administer in efficacious doses than nitroglycerine [11].

Conclusion

The development of human BNP (nesiritide) from *Escherichia coli* using recombinant technology represents a new approach. Since the drug lacks many of the adverse effects of earlier drugs, it is likely to evolve as a valuable agent for the management of these patients.

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