Therapeutic potential of the natriuretic peptide system

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Abstract

Neurohormonal activation has a central role in the pathophysiology of various cardiovascular disorders. Despite recent therapeutic advances, potential exists to further manipulate these activated systems. The natriuretic peptide family consists of at least four structurally related peptides, with varying degrees of biological similarity. In the context of cardiovascular disease, the vast majority of data relates to atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP).

Key words: atrial natriuretic peptide, brain natriuretic peptide, heart failure, vasopeptidase inhibitor.

Introduction

ANP, first discovered in 1981, is primarily secreted from the cardiac atria in response to atrial stretch.[1] Although BNP was first isolated from porcine brain, it is found at higher concentrations in ventricular myocardium.[2]

Natriuretic peptide receptors and metabolism

The biological effects of the natriuretic peptides are generated from specific interactions with transmembrane natriuretic peptide receptors (NPR) and the subsequent formation of intracellular cyclic guanosine monophosphate (cGMP).[3] Several NPR exist and NPR-A has greater affinity for ANP and BNP, whilst NPR-B is more specific for C-type natriuretic peptide (CNP).[4] These receptors are well distributed, but are notably found in vascular smooth muscle cells, the kidney and the heart.

In contrast, NPR-C acts as a clearance receptor.[5] Following binding of a natriuretic peptide, the NPR-C-ligand complex undergoes endocytosis and degradation. The second route of natriuretic peptide metabolism involves cleavage by neutral endopeptidase.[6] This enzyme has a fairly ubiquitous location, although notably it is found at high levels in the vascular endothelium and kidney. Inhibition of this enzyme is an important therapeutic target.

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Biological properties

ANP and BNP share vasodilatory properties in addition to many other important biological actions.[7,8] They both enhance natriuresis and diuresis as a consequence of increasing glomerular filtration rate and decreasing sodium reabsorption in the collecting duct. In addition to their direct effects, ANP and BNP inhibit the production of renin (and, therefore, the subsequent generation of angiotensin II) and aldosterone.[9,10]

In light of these biological properties, interest in therapeutic manipulation of the natriuretic peptide system has developed for a variety of cardiovascular disorders. Although in this article we will focus on the treatment of heart failure, we will also discuss possible therapies for patients with hypertension and ischaemic heart disease.

Heart failure (table 1)

Therapy guided by plasma natriuretic peptide levels

Plasma BNP concentration provides a reflection of ventricular filling pressures and wall stress.[11] It has, therefore, been suggested that titration of vasodilator therapy guided by plasma BNP levels would prove to be superior to standard clinical assessment. Troughton *et al.*[12] compared conventional drug therapy intensified to reduce plasma BNP levels to within normal range against therapy directed by standard clinical assessment in 69 patients with symptomatic chronic heart failure (CHF). After a minimum of six months follow-up, there were fewer total cardiovascular events (death, hospital admission or heart failure decompensation) in the BNP-guided therapy group when compared to the clinical group (19 *vs.* 54, p=0.02). Intensification of therapy in this study followed a strict and relatively complicated protocol and resulted in the BNP group receiving slightly higher doses of angiotensin-converting enzyme (ACE) inhibitors and diuretics (including spironolactone). Larger studies are required to evaluate the applicability of this approach in the routine management of CHF patients.

Initial BNP assays were somewhat complicated, limiting use in clinical practice. However, greater potential now exists with the recent introduction of 'bed-side' BNP testing kits.[13] If appropriately validated, these would certainly lend themselves to busy clinical practice, including specialist nurse-led heart failure clinics.

Therapeutic manipulation of the natriuretic peptide system

Favourable manipulation of the natriuretic peptide system in heart failure has been attempted by two distinct routes – inhibition of neutral endopeptidase, the enzyme involved in natriuret-

Table 1. Summary of several recent clinical studies involving therapeutic manipulation of the natriuretic peptide system

Study	Design	Intervention	Results/outcomes
Troughton *et al.*[12]	69 subjects, LVEF < 40% Double-blind randomisation Median follow-up 9.5 months Primary end point – total cardiovascular events	Treatment guided by plasma BNP or by standard clinical assessment	Fewer cardiovascular events (death, admission, CHF decompensation) in BNP group (19 *vs.* 54, p=0.02)
Northridge *et al.*[15]	60 heart failure patients, NYHA class I-III Double-blind, placebo controlled study Exercise duration assessed after 12 weeks	Candoxatril 200 mg b.d. (n=22), captopril 25-50 mg b.d. (n=23) or placebo (n=15)	Placebo-adjusted increase in exercise duration was 56 sec (95% CI, -26 to +137 sec; p=0.12) with candoxatril and 37 sec (-43 to +117 sec; p=0.29) with captopril
McClean *et al.*[16]	48 subjects, LVEF < 40% Dose-ranging pilot study over 12 weeks Primary objective - effect of treatment on clinical status, LV function, neurohormones and blood volume	Omapatrilat 2.5 mg to 40 mg	Improvement in clinical status at 12 weeks Dose-dependent improvement in LVEF, together with reduction in systolic blood pressure and blood volume (p<0.001, p<0.05 and p<0.05 *vs.* baseline, respectively)
IMPRESS[17]	573 subjects, LVEF < 40% Prospective, randomised, double-blind for 24 weeks Primary end point – improvement in maximum exercise treadmill test at week 12	Omapatrilat at target dose 40 mg or lisinopril at target dose 20 mg	No difference in primary end point Fewer cardiovascular system serious adverse events in omapatrilat group (20 *vs.* 34, p=0.04)
Colucci *et al.*[28]	Subjects hospitalised with symptomatic congestive heart failure a. efficacy study (127 subjects) b. comparative study (305 subjects)	a. Randomised, double-blind to nesiritide or placebo b. Randomised, open-label nesiritide or standard i.v. therapy for up to 7 days	a. Significant reduction in pulmonary-capillary wedge pressure and improved clinical status with nesiritide b. Similar symptomatic improvements but nesiritide associated with decrease in diuretic use
Burger *et al.*[31]	Randomised efficacy and safety study (305 subjects) Symptomatic acute CHF requiring intravenous vasoactive therapy	Nesiritide (either 0.015 or 0.03 µg/kg/min) or standard therapy (e.g. i.v. nitroglycerin, dobutamine)	Decreased incidence of life-threatening arrhythmias (1% *vs.* 12%) and non-sustained VT (11% *vs.* 17%) with nesiritide *vs.* dobutamine No adverse effects of higher nesiritide dose

Key: BNP = brain natriuretic peptide; CHF = chronic heart failure; LVEF = left ventricular ejection fraction; LV = left ventricular; NYHA = New York Heart Association; sec = seconds; VT = ventricular tachycardia

ic peptide metabolism and the exogenous intravenous infusion of synthetic ANP and BNP.

1. Neutral endopeptidase and vasopeptidase inhibition

Initial studies with neutral endopeptidase (NEP) inhibitors revealed limitations as a consequence of opposing biological actions of the activated renin-angiotensin-aldosterone system.[14] Northridge *et al.*[15] performed a placebo-controlled study evaluating the effects of candoxatril, an orally active NEP inhibitor, and captopril on exercise tolerance in patients with CHF. Both candoxatril and captopril were well tolerated and appeared to increase treadmill exercise duration, although this failed to reach significance.

In CHF it would be desirable to have a drug combining the established benefits of ACE inhibition with the potential benefits of enhancing the natriuretic peptide system. Vasopeptidase inhibitors – molecules simultaneously inhibiting NEP and ACE – have now been developed. In human heart failure, the majority of available data relates to omapatrilat, a highly selective inhibitor of both NEP and ACE.

McClean *et al.*[16] evaluated the efficacy of omapatrilat in human CHF. Following 12 weeks of treatment they were able to demonstrate improvements in functional status and left ventricular performance, together with a reduction in blood pressure. Omapatrilat also resulted in enhanced natriuresis and a reduction in total blood volume. A subsequent prospective, randomised, double-blind trial compared the effects of omapatrilat with lisinopril in 573 patients followed-up for 24 weeks (IMPRESS study).[17] The primary end point was improvement in exercise testing at week 12, whilst secondary end points included death and co-morbid events indicative of worsening heart failure. Whilst there were no significant differences in the principal end points, there were fewer cardiovascular system adverse events (combined data) in the omapatrilat group. Although individual cardiovascular end points relating to worsening heart failure did not reach significance, the results favoured omapatrilat in each case. In addition, rises in serum creatinine were three times less common with omapatrilat than lisinopril, which may reflect beneficial changes in renal haemodynamics.

Despite this promising data, doubts remain over the side

effect profile of omapatrilat and, in particular, the association with angioedema.[18] The 0.7% rate found with omapatrilat is in excess of the 0.34% previously documented with ramipril.[19] It has been suggested that this might be a reflection of the population group studied since the omapatrilat trial programme included significant numbers of black participants, a group known to have a higher rate of angioedema associated with ACE inhibitors as compared with Caucasians.[20] ACE inhibitors reduce the breakdown of bradykinin and this is thought to be the prime mediator involved in the subsequent development of angioedema.[21] However, NEP is also involved in the metabolism of bradykinin. Blais *et al.*[22] have confirmed that vasopeptidase inhibitors result in more complete inhibition of bradykinin metabolism than ACE inhibition alone; conceivably this could contribute to the development of more adverse side effects. In contrast, it has also been suggested that enhanced levels of bradykinin (with subsequent increased formation of nitric oxide, cGMP and prostaglandins) contributes significantly to the beneficial effects of conventional ACE inhibition.[23]

Further clinical studies, with larger numbers of patients, are required to determine the role of vasopeptidase inhibitors in current clinical practice. In this respect, formal presentation of safety data from the OCTAVE (Omapatrilat Cardiovascular Treatment Assessment versus Enalapril) study, designed to assess both the efficacy and safety of omapatrilat in the treatment of hypertension and recruiting approximately 25,000 subjects, are currently awaited.

Preliminary results from the OVERTURE (Omapatrilat Versus Enalapril Randomised Trial of Utility in Reducing Events) were recently presented at the 51st Annual Scientific Session of the American College of Cardiology (March 2002, Atlanta, USA). At the doses and regimes utilised in this study, combined ACE and NEP inhibition with omapatrilat produced a benefit in reducing mortality and morbidity in patients with CHF that was equivalent but not significantly better than ACE inhibition alone.

2. Exogenous ANP and BNP

Studies with intravenous infusions of ANP and BNP have produced variable results. Whilst infused ANP resulted in the expected natriuresis and diuresis in control subjects, it had little effect in patients with CHF.[24] Despite this apparent renal resistance, an improvement in haemodynamics and inhibition of neurohormonal activation still occurred. Whether this results from down-regulation of renal NPR, similar to that found on platelets of patients with CHF, remains to be seen.[25]

In contrast, incremental infusions of human BNP were associated with favourable haemodynamic and natriuretic effects when assessed in 20 patients with severe CHF.[26] A recent study has confirmed that infused BNP resulted in beneficial haemodynamic responses in decompensated CHF.[27] Despite a fall in mean arterial pressure, there were no significant changes in glomerular filtration rate or renal blood flow. This beneficial preservation of renal haemodynamics may relate to the documented renal vasodilating properties of the natriuretic peptides.

In a double-blind efficacy study infused nesiritide, a recombinant human BNP, improved haemodynamic function and clinical status as compared with placebo in patients hospitalised with decompensated CHF.[28] Indeed, nesiritide infusion resulted in a dose-related decrease in pulmonary capillary wedge pressure, associated with a decrease in systemic vascular resistance and increase in cardiac index. This improvement in haemodynamics occurred without an associated reflex tachycardia. Nesiritide has also been compared with standard intravenous agents such as dobutamine and nitrates.[28] Improvements in clinical status were similar between groups, leading to the suggestion that nesiritide may be helpful in the short-term management of decompensated patients with heart failure. The fact that nesiritide avoids the tachycardia associated with dobutamine therapy is particularly appealing and may relate to suppression of the sympathetic nervous system or interactions with baroreceptor control of the circulation.[29,30] In addition, the administration of nesiritide is associated with a lower incidence of serious ventricular arrhythmias as compared with dobutamine.[31]

A novel therapeutic approach using repeated short-term administration of subcutaneous BNP has recently been studied in a canine model of CHF.[32] This method still resulted in an improvement in cardiovascular haemodynamics. If confirmed in humans, this has potential for an exciting new route for the chronic administration of BNP in CHF.

Why do studies with BNP appear more promising than those with ANP? One reason may be in study design. In early studies with ANP shorter analogues and not the full human peptide chain were used.[33] It is feasible that this may have resulted in reduced biological effect. In addition, infusions were given over relatively short time periods, which may not have been adequate to achieve steady-state plasma levels. In contrast, human BNP has a significantly prolonged plasma half-life when compared with ANP. Another possible explanation stems from the fact that the majority of patients in the ANP studies were not taking ACE inhibitors. Angiotensin II enhances cGMP degradation and, therefore, ACE inhibitors or angiotensin receptor blockers may actually enhance the biological effects of natriuretic peptides.[34]

Ischaemic heart disease

Infused ANP results in vasodilatation of both epicardial and smaller resistance coronary arteries.[35] ANP has also been shown to increase regional coronary blood flow in ischaemic myocardium of dogs with coronary stenoses.[36] Since ANP also reduces venous return without a significant reflex tachycardia it has been suggested that ANP may improve myocardial perfusion without increasing oxygen consumption, making it an attractive therapeutic option for patients with ischaemic heart disease. Lai *et al.*[37] confirmed that intravenous administration of ANP attenuated exercise-induced myocardial ischaemia, assessed by thallium myocardial scintigraphy, in patients with stable angina (confirmed by angiography). A more realistic use of intravenous natriuretic peptide infusion is in the treatment of unstable angina, where conventional therapy with nitrates is often limited by the

Key messages

- Natriuretic peptides are powerful vasodilators with important natriuretic and diuretic properties
- Therapeutic manipulation of the natriuretic peptide system has significant potential in the management of patients with CHF, hypertension and ischaemic heart disease
- Vasopeptidase inhibitors (combining ACE and NEP inhibition) are particularly appealing, but further safety data are required
- Intravenous BNP may represent a novel strategy in the management of decompensated heart failure

development of tolerance or reflex tachycardia. Whether or not vasopeptidase inhibitors have similar benefits that could be cultivated in the out-patient setting remains to be seen.

Hypertension

Despite the fact that many different classes of blood pressure-lowering agents are available, the management of hypertensive patients remains far from ideal.[38] Hypertension is a major risk factor for the development of heart failure and renal dysfunction and thus any agent able to prevent or reduce end-organ damage is especially appealing. Although ACE inhibitors are of proven benefit in the treatment of hypertension, the magnitude of blood pressure reduction is limited in certain subjects, including those with lower plasma renin activity.[39] Whilst selective inhibition of NEP has limited effects on systemic blood pressure,[14] vasopeptidase inhibitors have held more promise. Omapatrilat appears to be an effective antihypertensive agent in animal models, irrespective of plasma renin activity.[40] Early human trials have confirmed its blood pressure-lowering capabilities.[41] This class of agent may prove to be particularly useful in patients resistant to conventional ACE inhibition and in the prevention and/or treatment of hypertensive heart failure.

Conclusion

Greater understanding of the biological properties of the natriuretic peptide family has established their importance in the pathophysiology of various cardiovascular disorders. Therapeutic manipulation of this system is now a real and exciting prospect. Trials with intravenous BNP are continuing and this treatment avenue may be of major use in patients with decompensated CHF. Vasopeptidase inhibitors, simultaneously blocking ACE and NEP, represent a novel therapeutic strategy for patients with CHF, hypertension and ischaemic heart disease. Whilst studies with omapatrilat have shown early promise, more data regarding its clinical safety and mortality and morbidity benefits (assessed as primary end points) when compared to conventional therapy are eagerly awaited from ongoing studies.

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