Vasopeptidase inhibition: A new treatment approach for endothelial dysfunction

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Vasopeptidase inhibition: A new treatment approach for endothelial dysfunction. Angiotensin-converting enzyme (ACE) inhibition is a well-established principle in the treatment of endothelial dysfunction. Numerous preclinical and clinical studies have clearly demonstrated the beneficial effects of inhibiting the renin-angiotensin-aldosterone system (RAS) in states of impaired endothelial function. The successful use of ACE inhibitors encouraged attempts to inhibit other key enzymes in the regulation of vascular tone, such as the neutral endopeptidase (NEP). Similar to ACE, NEP is an endothelial cell surface metalloproteinase that is involved in the degradation of several regulatory peptides, including the natriuretic peptides, and, thus, NEP inhibition augments vasodilatation and natriuresis through increased levels of atrial natriuretic peptide (ANP). By inhibiting the RAS and potentiating the natriuretic peptide system at the same time, combined NEP/ACE inhibitors, the so-called vasopeptidase inhibitors, reduce vasoconstriction and enhance vasodilatation, thereby decreasing peripheral vascular resistance and blood pressure. Within the vessel wall this may lead to a reduction of vasoconstrictor and proliferative mediators, such as angiotensin II and endothelin-1, and may increase local levels of bradykinin as well as natriuretic peptides. Even though first results of both preclinical and clinical studies indicate that combined inhibition of ACE and NEP by vasopeptidase inhibitors represents a promising strategy in the treatment of hypertension and heart failure, angioedema occurs more frequently on vasopeptidase inhibition as compared to ACE inhibition. To establish vasopeptidase inhibition as a novel option in the treatment of cardiovascular disease, further validation of efficacy and safety of this promising therapeutic principle is mandatory.

The importance of the renin-angiotensin-aldosterone system (RAS) in the pathophysiology of endothelial dysfunction, which represents an early stage of cardiovascular damage, is illustrated by numerous trials which demonstrate improvement of endothelial function [1], and even reduction of clinical end points, using agents that interrupt this system. The RAS plays a crucial role in cardiovascular regulation both as a circulating and paracrine local vascular system. The endothelium is a source of potent paracrine mediators such as nitric oxide (NO), angiotensin II, and endothelin-1 (Fig. 1). The different circulating and local systems show important synergisms and interactions. They may either have synergistic effects or may be the functional counterpart of another system in a subtle multivariate balance. As such, atrial natriuretic peptides (ANP) counteract the effects of angiotensin II. Since effects of endothelium-derived substances are not limited to vasoconstriction or vasodilatation, but may also include regulation of mitogenesis, endothelial dysfunction not only affects the function of the cardiovascular system, but also its structure. In fact, some endothelial substances stimulate the production of cytokines and growth factors, leading to vascular smooth muscle cell proliferation. Thus, the balance of vasoactive peptides warrants an appropriate adaptation of vascular tone and regulates oxidative, proliferative, and inflammatory processes (Fig. 1). Therefore, the maintenance of the subtle endothelial balance is crucial for the prevention and treatment of cardiovascular disease.

ACE INHIBITION AND NEP INHIBITION: THE COMPONENTS OF VASOPEPTIDASE INHIBITION

The beneficial effect of ACE inhibition has been documented in many large randomized trials for the treatment of hypertension [2], after myocardial infarction, and in heart failure. The Heart Outcomes Prevention Evaluation (HOPE) study confirmed that ACE inhibitors are vasoprotective, independent of their effects on blood pressure and remodeling [3]. In addition, in patients with coronary artery disease, improvement of endothelial function by ACE inhibition could be demonstrated angiographically in the Trial on Reversing Endothelial Dysfunction (TREND), particularly in patients with high serum cholesterol who are prone to severe endothelial dysfunction [1]. The mechanisms involved may be related to inhibitory effects on angiotensin formation and/or on activation of bradykinin-related effects. ACE inhibitors not only prevent the formation of a potent
vasoconstrictor with proliferative properties, but also increase the local concentration of bradykinin. In turn, the production of NO and prostacyclin, which may contribute to the vascular protective effects of ACE inhibitors by vasopeptidase inhibition, by improving local blood flow, and preventing platelet activation. As a principle of vasopeptidase inhibition, beneficial effects of ACE inhibition are combined with the additional inhibition of the neutral endopeptidase (NEP).

Selective NEP inhibition prevents the degradation of vasoactive peptides such as ANP, BNP, CNP, substance P, and bradykinin, and increases their biologic activity. This implicates that simultaneous inhibition of ACE and NEP may exceed the effects of inhibiting either system alone. Therefore, compounds with the capability of inhibiting ACE and NEP at the same time may offer the possibility to inhibit the RAS and to potentiate the natriuretic peptide system by the use of one single molecule, and, thus, may simultaneously reduce vasoconstriction and enhance vasodilatation. Correspondingly, a number of substances with affinities for both ACE and NEP are currently under development. Among those so-called “vasopeptidase inhibitors,” omapatrilat is the compound for which most preclinical and clinical data are presently available.

VASOPEPTIDASE INHIBITORS IN EXPERIMENTAL HYPERTENSION

Vasopeptidase inhibition has been shown to lower blood pressure under various experimental conditions, including renovascular hypertension, spontaneous hypertension [4, 5], deoxycorticosterone acetate-induced hypertension [5], as well as salt-sensitive hypertension [6, 7]. In spontaneously hypertensive rats, vasopeptidase inhibition significantly lowered blood pressure, even when combined with experimental diabetes [4]. Since antihypertensive effects of combined ACE/NEP inhibition exceeded those of ACE inhibition alone, and resulted in additional improvement of endothelial function to a greater extent than attributable to lowering of blood pressure [6, 8], vasopeptidase inhibition may advance as a promising novel option for the treatment of various forms of hypertension.

In salt-sensitive Dahl rats omapatrilat, as compared with equipotent doses of the ACE inhibitor captopril, restored the impaired NO system by increasing protein levels of endothelial NO synthase and vascular nitrate levels, and normalized endothelium-dependent relaxations [6]. Since endothelial dysfunction is not only the result, but also initiator as well as promoter of cardiovascular disease, vasopeptidase inhibition may be beneficial in interrupting the vicious cycle of altered endothelial function.

VASOPEPTIDASE INHIBITORS IN THE TREATMENT OF HYPERTENSION

Vasopeptidase inhibitors have been shown to be well-tolerated and effective in clinical trials on hypertensive patients under several conditions. In 63 patients with
salt-sensitive hypertension, 40 mg/day of omapatrilat revealed a greater reduction in systolic, diastolic, and in mean arterial pressure as compared to 20 mg/day of lisinopril [9]. In a study on 690 patients with mild to moderate hypertension, omapatrilat (5 to 40 mg/day) lowered systolic blood pressure (sBP) a much greater extent than lisinopril (20 to 40 mg/day). However, compared with studies of other antihypertensive drugs, such as ACE inhibitors, the number of patients treated with vasopeptidase inhibitors at present is rather small. Therefore, a large-scale clinical trial with 12,600 patients, Omapatrilat in Persons with Enhanced Risk of Atherosclerosis (OPERA), was initiated to evaluate the impact of vasopeptidase inhibition in isolated systolic hypertension [10]. Patients older than 65 years with S-BP between 140 and 160 mm Hg will be randomized in 900 centers to receive either 40 mg/day of omapatrilat or placebo, and cardiovascular morbidity and mortality will be followed up for 3 to 5 years. Another clinical trial with 25,267 hypertensive patients, the Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril (OCTAVE) trial, to assess the efficacy and safety of low doses (10 mg/day) of omapatrilat versus 5 mg/day of enalapril has recently been completed and preliminary results were presented in March 2002. These data indicate that in all subgroups, omapatrilat was capable of lowering sBP and dBP after 8 and 24 weeks of treatment, respectively, to a greater extent when compared to enalapril.

VASOPEPTIDASE INHIBITORS AND THE KIDNEY

Because inhibition of ANP degradation seems to be one of the most important features of vasopeptidase inhibitors, and elevation of plasma ANP levels by vasopeptidase inhibition has been demonstrated in several preclinical [6] and clinical studies, there is a strong link to renal involvement in the regulatory processes induced by vasopeptidase inhibition. Since renal protection, such as in diabetic nephropathy, is one of the favorable effects of ACE inhibitors, the influence of vasopeptidase inhibitors on renal function is of major interest. In experimental diabetes, vasopeptidase inhibition reduced albuminuria and led to improvement of renal function [4]. In 89 patients with impaired renal function (creatinine clearance <60 mL/min), 12 weeks treatment with omapatrilat reduced proteinuria by about 20% and increased serum creatinine by about 15%, thus indicating improvement of renal function by vasopeptidase inhibition. Meanwhile, vasopeptidase inhibition has been proven to slow the progression of renal injury in subtotally nephrectomized rats [11, 12]. Since renal impairment is a frequent condition among patients with advanced cardiovascular disease, safety of pharmacotherapy in these patients is an important issue. The plasma concentrations of omapatrilat administered to 29 patients with moderate to severe renal impairment, and even in patients on hemodialysis treatment, did not differ between the control and those patients with normal renal function [13]. Therefore, no dose adjustment of omapatrilat is required in patients with renal impairment, independent of its severity. In addition, even in patients with impaired renal function, omapatrilat increased urinary ANP excretion [14, 15], indicating the presence of its beneficial properties irrespective of the degree of renal impairment.

SAFETY OF VASOPEPTIDASE INHIBITORS

Vasopeptidase inhibitors have been used over a broad range of dosages, but the number of patients treated and documented at present is still rather low. In clinical studies, side effects were comparable to those of ACE inhibitors. Cough and flush in 573 patients in the Inhibition of Metalloproteinase in a Randomized Exercise and Symptoms Study in Heart Failure (IMPRESS) trial were reported to occur equally often with ACE inhibitor treatment [16]. Similarity of adverse effects of ACE inhibition and vasopeptidase inhibition were recently confirmed in 5770 patients in the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVER-TURE) trial [17]. Nevertheless, in data submitted for the new drug application of omapatrilat to the US Food and Drug Administration (FDA), 44 instances of angioedema were reported among more than 6600 patients [18]. Therefore, the incidence of angioedema reported in the Heart Outcomes Prevention Evaluation (HOPE) study [3] was about twice as high (0.7%) as on treatment with ramipril. Since patients in the IMPRESS and OVERTURE trial were pretreated with ACE inhibitors, elevated incidence of angioedema after the onset of vasopeptidase inhibition requires even more careful evaluation in large scale, randomized, double-blind clinical trials. The OCTAVE study was especially designed to evaluate the risk of adverse effects on omapatrilat treatment in low doses. Preliminary data of the OCTAVE study released in March 2002 indicate that in the treatment of hypertension, omapatrilat is indeed efficient and safe. Although all other adverse effects occurred with comparable frequency, angioedema presented with a threefold higher incidence in patients treated with a vasopeptidase inhibitor as compared to patients on ACE inhibitors (2.17% vs. 0.68%, respectively). Thus, an increased incidence of angioedema appears to be associated with simultaneous inhibition of NEP and ACE, and it may be speculated that its occurrence is linked to the decreased degradation of bradykinin. Since patients were treated for 24 weeks only in the OCTAVE study, safety of vasopeptidase inhibitors remains a matter of
REFERENCES


CONCLUSION

In all preclinical and clinical trials completed so far, vasopeptidase inhibition has proven highly effective in treatment of endothelial dysfunction, hypertension, and heart failure. To replace or extend traditional treatment concepts, novel cardiovascular drugs will have to provide an excellent profile of beneficial effects and/or minimized side effects. Vasopeptidase inhibition has been demonstrated to be beneficial in diabetes and renal failure, which are common conditions among cardiovascular patients. The encouraging experimental and clinical results obtained with this broad spectrum and potent cardiovascular active agent warrant further clinical investigation. Since clinical trials on vasopeptidase inhibition in hypertension have demonstrated efficient blood pressure lowering by this novel therapeutic principle, but suggested a higher incidence of angioedema as compared to ACE inhibitor treatment, the relation of efficacy and safety will have to be evaluated carefully in large-scale clinical studies. Their future results will help to better assess the place of vasopeptidase inhibition in the treatment of cardiovascular disease.

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