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Scientific Update™

New and Different Angiotensin II-Receptor Blockers

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Angiotensin II (AII) is capable of producing functional and structural alterations in coronary arteries and myocardium. Studies of its activation and inhibition of synthesis through ACE inhibition have contributed significantly to our understanding of the pathophysiology and treatment of CHF. Stimulation of angiotensin type I receptor (AT_1) by AII mediates many of the pathophysiologic changes; therefore, the recent development of AT_1 inhibitors may add significantly to our armamentarium of CHF treatments. The potential benefits of AII-receptor blockers in CHF and renal disease as well as LV hypertrophy are discussed.

Clinical Overview Comparing Valsartan with other Antihypertensive Therapies

Michael Weber, MD

Clinical Issues in Hypertension

Although there has been much progress over the course of the last several decades in the identification and treatment of hypertension, much remains to be done. According to the recent NHANES III survey,[1] 69% of hypertensive patients in the USA are aware of their diagnosis and 53% of these are being treated. However, of these, only 24% meet accepted criteria for adequate blood pressure control. Thus, even today, there is considerable room for improvement of antihypertensive therapy. A recent meta-analysis of the impact of antihypertensive therapy on cerebro- and cardiovascular complications suggested that, while we are observing reductions of upwards of 60% in the incidence of stroke, there is only a less than 10% decline in coronary heart disease. Among the many reasons for this disappointing performance is the effectiveness and tolerability of the current armamentarium of antihypertensive therapy.

It has been known for many years that patients with high plasma renin activity (PRA) are at particularly high risk for complications of hypertension, including left ventricular (LV) hypertrophy, strokes, and myocardial infarction.[2] More recently, the importance of the renin-angiotensin system (RAS) was underscored by the observation that high PRA conferred high risk of myocardial infarction, independent of other major risk factors, such as reduced glucose tolerance or elevated cholesterol.[3]

Renin-Angiotensin System and its Modulation

The link between activation of the RAS and the development of cardiovascular complications of hypertension has become better understood in recent years. Angiotensin II (AII) has two major ways of acting. In the short term, the circulating RAS mediates vasoconstriction; this has been traditionally thought to be a major mechanism of increased systemic vascular resistance in many patients with hypertension as well as a contributing factor to renal glomerular

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hypertension by causing efferent arteriolar constriction and mesangial cell contraction. However, AII is also an important trophic factor, and long-term activation of tissue RAS is now thought to contribute importantly to LV hypertrophy and vascular remodelling in hypertension. More recently, the question of a potential role for the RAS in the pathophysiology of atherosclerosis and its complications has been raised. Recent clinical data from large multicenter trials seem to confirm an important role for the RAS in atherosclerosis. For example, in the SOLVD trial, there was a significant reduction in the incidence of fatal and nonfatal myocardial infarction in patients receiving an angiotensin-converting enzyme inhibitor (ACEI).

However, these effects of ACEI may not be solely due to reduced AII production. Inhibition of the angiotensin-converting enzyme also reduces the degradation of bradykinin, an important endogenous stimulator of endothelial nitric oxide (NO) production. NO in turn may have a variety of beneficial actions on the vessel wall, including vasodilation, antithrombotic effects, and inhibition of smooth muscle proliferation and vascular hypertrophy. The extent to which the clinically important beneficial effects of ACEI may be due to mechanisms independent of AII generation are at present unclear. Moreover, it is now known that there are mechanisms of AII generation that are independent of the angiotensin-converting enzyme. Other enzymes that are present in human vascular and ventricular tissues, such as chymase and cathepsin G, are capable of activating angiotensin I to AII.

Regardless of the pathway of synthesis, AII, once formed, will interact with specific AII receptors, of which 4 to 5 different forms have been identified. The most relevant for the cardiovascular effects of AII are the AT_1 and AT_2 receptors. In particular, the AT_1 receptor mediates the vasoconstrictor and trophic effects of AII, whereas recent evidence indicates that the AT_2 receptor opposes these effects of AII (Fig. 1). The AT_1 is constitutively expressed, although its expression may be exaggerated in atherosclerosis, where it may contribute to smooth muscle cell proliferation, matrix synthesis, and endothelial dysfunction. The AT_2 receptor is developmentally regulated and is normally markedly down-regulated immediately after birth. However, the expression of this receptor can be reinduced by vascular injury, i.e., following PTCA or in hypertension, where it may mediate vasodilation and have antiproliferative effects, perhaps in part by increasing endothelial NO release.

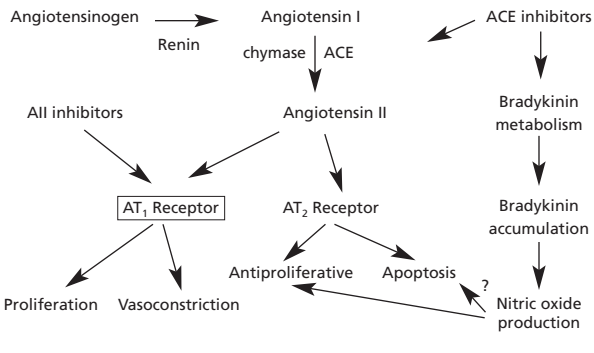
Angiotensin II-receptor Antagonists

Specific antagonists have been developed for the AT_1 receptor, including losartan, valsartan, and irbesartan. These agents may have a therapeutic role, since they effectively block the vasoconstrictor and growth-promoting actions of AII regardless of the mechanism of production (e.g., ACE or chymase). Moreover, they do not interfere with the AT_2 receptor, which may have beneficial effects on vascular structure and function in hypertension.

Losartan is the first agent in this class to be released and is already being used extensively in the treatment of hypertension. In comparison to other antihypertensive agents, losartan shows similar efficacy; however, full antihypertensive effects are often delayed for up to 12 weeks. These late effects may be due to a delayed inhibition of smooth cell growth and beneficial vascular remodelling during prolonged therapy with the AII-receptor blocker. As well, this agent does not appear to demonstrate a true dose-response relationship, and higher doses do not necessarily provide additional therapeutic benefit.

Valsartan and ibersartan are newer compounds that may offer advantages over losartan, while sharing the highly favourable side-effect profile characteristic of this class of antihypertensive agents. Valsartan exhibits a dose-effect relationship between 20 and 320 mg/day. The usual starting dose is 80 mg, which produces sustained reductions in blood pressure during 24-hour ambulatory monitoring and results in approximately 40 to 50% success in the treatment of hypertension. In comparison with ACEI, Valsartan showed similar efficacy but was much better tolerated. In particular, this class of drugs does not induce cough, a side effect which occurs all too frequently with ACEI and often limits the usefulness of these agents.

Figure 1: Angiotensin II-receptor Blockers



Potential Benefits of Angiotensin II-receptor Blockers in Heart Failure

J.N. Cohn, MD

In an experimental model of LV remodelling induced by repeated electric countershocks, it was found that the ACE inhibitor ramipril retarded the process of LV remodelling when compared to placebo. However, when ramipril was combined with HOE-140, an antagonist of bradykinin, this beneficial effect of remodelling was attenuated. These findings indicate that, in this model, the remodelling process may involve not only AII but also bradykinin.

While these observations may be model-specific, they might form the theoretical bases for the claim that angiotensin-receptor blockers may not be used interchangeably with ACE inhibitors. The inhibition of bradykinin metabolism by ACEI which leads to augmentation of NO levels does not occur with the use of AII antagonists. Results of the ELITE study presented at this meeting revealed a greater reduction in mortality in a small number of patients with CHF and NYHA III symptoms treated with an AII antagonist (losartan) vs. an ACE inhibitor (captopril). These results should be considered preliminary at this stage. As shown in Figure 1, the classical pathway of AII generation involves the enzyme ACE, but it is known that there are alternative pathways, such as chymase, which will also generate AII. As well, blocking the AT_1 receptor in the absence of ACE inhibition, will lead to unopposed enhanced stimulation of AT_2 receptors through the reduced negative feedback on angiotensin I. The consequences of AT_2-receptor stimulation or blockade as well as the potential of combination therapy requires further study.

In a recent study, 83 patients with left heart failure from the Veterans Administration Hospital were randomized to receive a specific AII-receptor blocker (valsartan) or placebo on top of therapy of ACE inhibitors, diuretics, and digoxin. Invasive hemodynamics were obtained for 12 hours after the administration of study medications. Compared to placebo, valsartan produced a dose-dependent decline in systolic blood pressure as well as pulmonary artery diastolic blood pressure. The study medications were then administered for 28 days, e.g., valsartan 80 mg twice a day or 160 mg twice a day or matching placebo, and the hemodynamic study was repeated. Once again, compared to placebo, there was a dose-dependent decrease in both systolic blood pressure and pulmonary artery diastolic pressure. Furthermore, there was also a significant decrease in plasma aldosterone with a trend for a decline in plasma norepinephrine. This preliminary study indicated that a specific angiotensin-receptor blocker, administered in addition to an ACE inhibitor, produced favourable hemodynamic and neurohormonal effects.

AII promotes vasoconstriction, tissue growth, further neurohormonal stimulation, oxidative stress, and arrhythmias. Given the above considerations as well as compelling data of favourable effects on survival provided by ACE inhibitors, Dr. Cohn believes that future trials of the use of angiotensin-receptor blockers should involve the concomitant use or direct comparison to ACE inhibitors. The possibility that the AII-receptor blockers may improve survival in patients already treated with conventional therapy, including ACE inhibitors, is being addressed by a new international study using valsartan. In this study, valsartan 160 mg twice a day will be compared with a placebo in patients who are on background therapy of ACE inhibitors.

The Latest on Angiotensin II-receptor Blockers in Left Ventricular Hypertrophy

Franz H. Messerli, MD

The Framingham data indicate that patients with LV hypertrophy are at higher risk of myocardial infarction, sudden cardiac death, congestive heart failure, and stroke than those without LV hypertrophy, even when patients have similar blood pressures. There is evidence to suggest that AII is mitogenic and promotes cardiac hypertrophy. AII can stimulate myocardial hypertrophy, independent of its blood-pressure effect. Accordingly, ACE inhibitors can reduce LV hypertrophy independent of the blood pressure-lowering effect and may potentially be a novel class of agents for regression of LV hypertrophy. Furthermore, AII may directly and indirectly accelerate the development of coronary artery disease by influencing at least four pathways: (1) vasoconstriction, (2) proliferation, (3) oxidative stress, (4) vascular permeability. The last three pathways will lead to foam cell formation and vascular smooth muscle proliferation thereby contributing to coronary artery disease. Therefore, AII receptor blockers may have a role in the regression therapy of atherosclerotic lesions as well. Studies are underway to test these exciting possibilities.

Angiotensin II-receptor Blockers in Renal Disease: Potential Benefits

George L. Bakris, MD

Data to date suggest that ACE inhibitors confer a unique protection against the progression of renal disease in diabetic patients. Furthermore, these renoprotective effects appear to be independent of blood-pressure reduction. The progression of renal disease in diabetic nephropathy is mediated by three mechanisms, namely (1) mesangial expansion, (2) increased glomerular pressure, (3) increased glomerular permeability. The first two mechanisms are responsible for microalbuminuria, whereas AII may affect the last two mechanisms. It has been found that lowering blood pressure without reducing proteinuria does not reduce the progression of renal disease.

Recent studies in animal models of renal failure in hypertension have suggested that the angiotensin-receptor blockers have a profile very similar to that of ACE inhibitors. Both class of agents increase salt excretion and reduce intraglomerular pressure via dilatation of the efferent arteriole as well as reducing proteinuria. On the other hand, there may be subtle differences. The AII blocker does not reduce afferent arteriolar tone as much as the ACE inhibitors. Potassium excretion may be less with the angiotensin-receptor blockers. Fundamentally, angiotensin-receptor blockers do not increase bradykinin and therefore are associated with a very small incidence of cough, compared to ACE inhibitors.

The importance of blood-pressure reduction in controlling the progression of renal disease is widely recognized. However, to date, there are no long-term clinical data to suggest the use of angiotensin-receptor blockers for the prevention of progression of renal disease. There are three ongoing, large, international, placebo-controlled trials which will evaluate the effects of different angiotensin-receptor blockers on progression to end-stage renal disease. Until these data are available, AII-receptor blockers should not be considered as first-line agents for the prevention of renal disease.

Summary

AII receptor blockers provide a targeted approach to treatment of heart failure and may offer unique opportunities in combating functional and structural alterations that result from neurohormonal activation.

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