

EUROPEAN SOCIETY OF CARDIOLOGY: ANGIOTENSIN II ANTAGONISTS IN HYPERTENSION AND BEYOND

Angiotensin II Antagonists: Why Is There So Much Excitement?

Based on a presentation by Norman K. Hollenberg, MD

Presentation Summary

This presentation serves as an introduction to the mechanics involved in the workings of angiotensin II antagonists and reviews the historical research leading to the hypothesis that the angiotensin converting enzyme (ACE) pathway is not necessarily the dominant player in hypertension control. Several studies are cited that show that angiotensin II is produced by both ACE-dependent and ACE-independent cascades. These new drugs effectively prevent angiotensin II from binding to its receptor, thereby producing blood pressure control.

In addition, angiotensin II antagonists appear to be beneficial in other ways because they are metabolically

neutral and are very well tolerated because they do not cause the adverse events seen with other antihypertensive drugs. It is also suspected that the effects of these agents go beyond simple blood pressure lowering and extend to protecting organ systems known to be influenced by hypertension.

However, more safety data is needed for this class of agents, and comparisons between drugs of this class will be important to determine whether varying levels of tissue penetration and receptor affinity differences are important when choosing an agent for a specific patient. Meanwhile, whether angiotensin II antagonists can reduce mortality and cardiovascular risks among hypertensives and others deserves further study.

Angiotensin II antagonists might provide far more promise in hypertension management than originally thought. "As wonderful as the ACE inhibitor therapy story has been, in fact, it was an accident of toxicology, and there is the very real potential that we can do better by blocking other points within the renin-angiotensin system," noted Norman K. Hollenberg, MD, pro-

fessor, department of medicine, Harvard Medical School, and director of physiologic research, department of radiology. In the renin-angiotensin cascade, angiotensin II is created by both ACE- and non-ACE-dependent pathways to influence the angiotensin₁ (AT₁) receptor which in turn, controls vasoconstriction, cell growth, sodium and fluid retention, and sympathetic activation

which are all central in hypertension (Figure 1).

If a pharmacologist had originally been the one to address the renin-angiotensin cascade in order to develop a hypertension therapy, the least likely target site for blockage would have been the point at which ACE enters the pathway, he continued. "Far more attractive would have been the renin interaction with its substrate, or the AT₁ receptor itself," Dr. Hollenberg said.

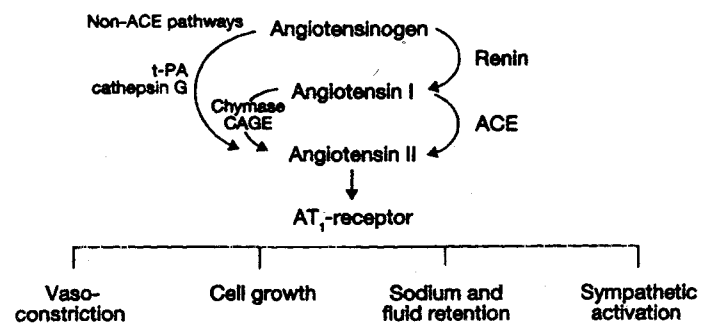
"There are 19 permutations and combinations of possible renal hemodynamic responses to blocking the renin-angiotensin system at the renin, ACE inhibitor, and AT₁ receptor. When research into the system began, the dominant hypothesis was that a good deal of the efficacy in terms of renal hemodynamic responses to blocking the system at the ACE level came from bradykinin and tachykinin metabolism changes, prostaglandin effects, and nitric oxide," Dr. Hollenberg said.

However, in order to test the hypothesis, the effect of renin inhibition on the angiotensin II-receptor relationship was used. If the ACE pathway was dominated by angiotensin II formation, then renin inhibition would produce the same effects as ACE inhibition. Graded doses of a renin inhibitor were administered to healthy men on a low-salt diet and plasma renin activity, immunoreactive plasma angiotensin II and aldosterone concentrations, inulin, and p-aminohippurate clearance were measured. There was a larger renal vascular response to a renin inhibitor than expected.¹ "This was not in keeping with our expectations which were based on the dominant ACE hypothesis," he said.

Comparative Tests

Further experiments compared the effects of a renin inhibitor, the ACE inhibitor captopril, and a placebo in a double-blind fashion on renal vascular response in both healthy and hypertensive men on a salt-restricted diet. The renin inhibitor produced a larger renal plasma flow in patients, Dr. Hollenberg

Figure 1. Renin-Angiotensin-Aldosterone System in the Development of High Blood Pressure



pointed out. The results of the experiments showed that the acute renal response to the ACE inhibitor largely reflected a reduction in angiotensin II formation, as did that seen with renin inhibition. "Even more remarkable was that despite identical diet and similar baseline angiotensin II levels, some patients were big responders to either drug and some were not. For those who were responders, the renin inhibitor induced a larger response. For those interested in genetics as they relate to hypertension, this creates an interesting possibility and challenge," he said.^{2,3}

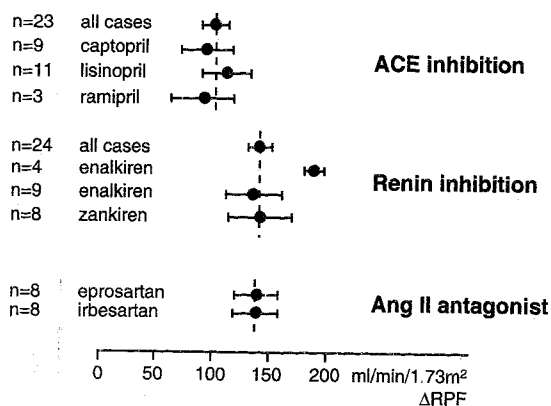
Additionally, a meta-analysis comparing three different ACE inhibitors with two renin inhibitors and two angiotensin II antagonists showed that the renin inhibitors produced a 50% larger renal hemodynamic response in patients than did the ACE inhibitors. "There is always the chance though, despite the fact that the renin molecule is so very specific, that there can be an unrestricted mechanism. In this context, the angiotensin II antagonist becomes a tie-breaker," noted Dr. Hollenberg. Indeed, when response to angiotensin II antagonists was analyzed, it was similar to that seen with the renin inhibitor (Figure 2).⁴

“Renin is clearly involved in this process, but these studies show that there is a very large, non-ACE-dependent generation of angiotensin II making

the AT₁ receptor blocker equal to the renin inhibitor. Whether this non-ACE mechanism is due to chymase or another enzyme remains to be seen,” Dr. Hollenberg said.

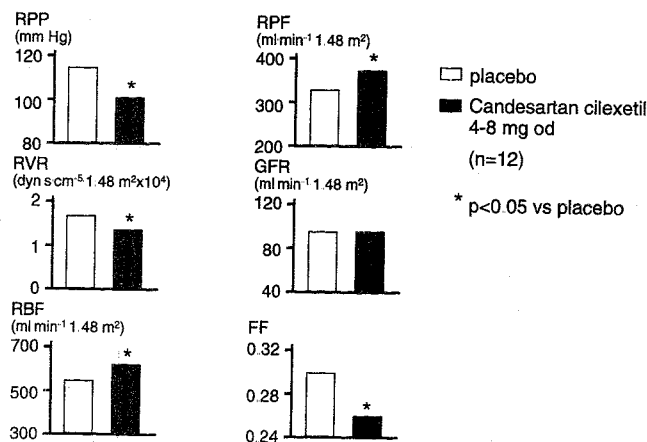
All of the previously mentioned trials were conducted primarily in non-hypertensive patients, and an important step was to test the effects of an angiotensin II antagonist in those with the disease. In one study, renal plasma flow response to the angiotensin II antagonist candesartan cilexetil was quite good despite the presumably high sodium intake of the Japanese patient population involved. Blood pressure was controlled with 4 mg of the drug in half the patients and 8 mg in the other half, and renal plasma flow in patients was similar to that expected of renin system blockade, according to Dr. Hollenberg (Figure 3).⁵

Figure 2. Meta-Analysis Comparing ACE Inhibitors, Renin Inhibitors, and Angiotensin II Antagonists



See reference 4.

Figure 3. Effects of Candesartan Cilexetil on Renal Haemodynamics in Hypertensive Patients (Measurements after 2 weeks of treatment)



See reference 5

Differentiation Criteria

When physicians are looking at therapeutic options, it can often be helpful for different classes of drugs for the same disease state to have different characteristics and in some cases, for agents within the same class to differ. Efficacy, tolerability, and safety are among the major criteria for differentiating between drugs.

“We know that angiotensin II antagonists compete directly with the effector molecule of the renin-angiotensin cascade-angiotensin II at its receptor. Therefore, these agents are highly specific and remarkably effective because they block the effects of angiotensin II produced by both the ACE and non-ACE pathways,” Dr. Hollenberg said. “However, I think there will be some battles over the efficacy of different angiotensin II antagonists.”

These agents are also well tolerated and do not interfere with bradykinin, substance P, or tachykinin metabolism which are responsible for the class-specific side effects associated with ACE inhibitors. “We do need much more information before we can have a final say about the safety of this class of drugs,” Dr. Hollenberg added.

The potency of different agents and cost may also be considered when differentiating between treatment options. "Cost is such a large factor now that having a more potent drug will be increasingly important. Among angiotensin II antagonists, the combination of tissue penetration and receptor binding profile of each particular drug may cause potency differences which could be quite important," according to Dr. Hollenberg.

Ultimately, the ideal antihypertensive agent should not only lower blood pressure but should provide 24-hour efficacy with few adverse events. It should also be metabolically neutral and able to provide organ protection. Hypertension adversely affects the heart through left ventricular hypertrophy and coronary heart disease; the kidneys through proteinuria and glomerulosclerosis; the vessels through neointima formation, endothelial dysfunction, and reduced vascular compliance; and the brain through stroke, Dr. Hollenberg explained.

Most important, antihypertensive treatment should reduce mortality. "It will be a few more years before we have mortality data for angiotensin II antagonists," Dr. Hollenberg concluded.

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