Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in Combination: Theory and Practice

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Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are commonly used to treat hypertension and/or a range of progressive end-organ diseases. The success of each of these drug classes in disease-state management is without dispute, and has led to speculation that given together the observed response would improve upon that observed with a member of each drug class individually given. Few studies are available, however, which carefully address the effect(s) of the combination of an angiotensin-converting enzyme inhibitor and an angiotensin receptor blocker. Review of available studies would seem not to strongly support combination therapy with an angiotensin-converting enzyme inhibitor and an angiotensin receptor blocker as preferred therapy in the broad base of general hypertensive patients with or without end-organ disease. Additional clarifying studies are needed to determine if specific patient subsets exist that might benefit from such combination therapy. (J Clin Hypertens. 2001;3:383–387). ©*2001 Le Jacq Communications, Inc.*

Inhibition of the renin-angiotensin system (RAS) by administration of either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) reduces blood pressure (BP) similarly in hypertensive patients.[1] ACE inhibitors and ARBs also slow the progressive deterioration in renal function that reflects renal injury, particularly in patients with diabetic nephropathy,[2–4] perhaps as a function of these drugs' ability to reduce proteinuria.[5] Moreover, ACE inhibitors reduce cardiovascular mortality and morbidity in patients with increased cardiovascular risk,[6] left ventricular dysfunction, or congestive heart failure (CHF).[7] Similar data are now beginning to emerge with ARBs.[8,9] ACE inhibitors and ARBs might conceivably be effective as a combination because they act at different steps in the RAS cascade. Unfortunately, very few published studies have addressed the effects of combined ACE inhibitor and ARB therapy. Among the reported studies in patients with hypertension,[10–15] proteinuria,[16–24] or heart failure,[8,9,25–34] the results have been inconsistent. This review briefly summarizes the basis for combined use of ACE inhibitors and ARBs, and describes the results of clinical trials in which such a combination has been examined.

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THEORETIC BASIS FOR COMBINING ACE INHIBITORS AND ARBS

The pharmacologic actions of ACE inhibitors and ARBs are well characterized. The BP reduction and tissue protection derived from interrupting the RAS with either an ACE inhibitor or an ARB are in large measure an extension of their pharmacokinetic actions.[35,36] Numerous factors influence the BP and tissue responses to an ACE inhibitor or an ARB, including the point in the RAS where inhibition occurs, the compensatory changes in the RAS that occur after such blockade, and additional, unique effects of the drugs on non-RAS systems.[36]

Therapy with ACE inhibitors initially reduces both circulating and tissue concentrations of angiotensin II. This occurs through inhibition of the enzymatic con-

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version of angiotensin I to angiotensin II via ACE. Long-term treatment with ACE inhibitors leads to a gradual return of circulating angiotensin II concentrations to pretreatment values, a phenomenon termed "angiotensin II escape."[37,38] One proposed explanation for angiotensin II escape centers on the identification of enzymes in human tissues, such as chymase, cathepsin G, and chymostatin-sensitive angiotensin-generating enzyme, that can form angiotensin II from angiotensinogen and other peptide substrates.[39] Since this mode of angiotensin II generation is independent of ACE, it can proceed regardless of the presence of an ACE inhibitor.

The alternate pathways for production of angiotensin II appear to up-regulate with chronic ACE inhibition, although it is unclear precisely why this occurs.[40] In addition, ACE activity increases in diseased tissues, such as atheromatous lesions in vessel walls subjected to angioplasty. This traditional pathway for production of angiotensin II is difficult to completely suppress, even with high-dose ACE inhibitor therapy.[41,42] Despite strong evidence in support of the concept of angiotensin II escape in heart failure, escape from the BP-reducing effects of an ACE inhibitor has not been described to date.[36,43] If angiotensin II escape with ACE inhibitors is to prove relevant to clinical practice, it will not be on the basis of loss of BP control; rather, it will probably be a consequence of "suboptimal tissue protection."

ACE is also known as kininase II, which is largely in control of the proteolytic breakdown of bradykinin and similar small, vasoactive peptides. Accordingly, ACE inhibition suppresses the breakdown of bradykinin to biologically inactive products. The resultant increase in circulating bradykinin promotes release of the potent vasodilator nitric oxide via activation of the endothelial B_2 receptor. It is generally accepted that at least part of the reduction in BP that occurs with ACE inhibitor therapy is bradykinin-mediated, but the relative contribution of augmented nitric oxide release to reduction of the angiotensin II concentration is debated.[44] Blockade of the AT_1 receptor with an ARB does not immediately affect bradykinin, and this clearly differentiates ACE inhibitors and ARBs pharmacologically.

INTERPRETIVE ISSUES IN COMBINING ACE INHIBITORS AND ARBS

The goal of combining an ACE inhibitor with an ARB is to achieve a therapeutic outcome better than that achieved with either drug administered alone. The theoretic premise behind the combination of these two drug classes is plausible to a degree, but there are pitfalls that may be encountered if only superficial analyses are performed.

First, the 10 ACE inhibitors and six ARBs that are marketed in the United States have differing durations of action; thus, the combination of a short-acting ACE inhibitor, such as enalapril, with a long-acting ARB, such as telmisartan, can result in a more prolonged response. This may be mistaken for an additive response, when in reality it is little more than a mixing of drugs with differing half-lives for a sustained effect on BP.

Second, the time of day that drugs in these classes are administered should be considered in evaluating the response. Split dosing of these drug classes, with one given in the morning and the other in the evening, may be considered more effective than giving both drugs simultaneously. In reality, this approach may differ little from split dosing of a single agent.

Third, the sequence in which these medications are given may determine the final BP response. The fall in BP that occurs with an ACE inhibitor is related to both a reduction in angiotensin II levels and an increase in the bradykinin effect. If the latter is an important contributor to BP reduction, then the order in which the ARB is added may dictate the pattern of response. Theoretically, adding the ARB after the ACE inhibitor may have little effect on bradykinin levels, whereas adding the ARB before the ACE inhibitor may heighten the bradykinin effect of the latter.

Finally, the time course of response to the combination of an ACE inhibitor and an ARB is mechanistically relevant. For example, if the combination of these drugs results in a drop in BP within days of beginning such therapy, a direct pharmacokinetic/pharmacodynamic effect is likely. If a response occurs, but only after several weeks, the possibility exists that the combination facilitated vascular remodeling more than if either drug had been given alone (if they were individually administered). The most relevant question that remains when the combination of an ACE inhibitor with an ARB results in a positive BP response is whether the same phenomenon would have occurred with simple dose titration of one or the other of the medications. Thus, exploring the dose-response curve of each component is an important part of establishing the effects of the combination of an ACE inhibitor and an ARB.

CLINICAL TRIALS

Hypertension. The efficacy of both ACE inhibitors and ARBs as antihypertensive agents is well documented.[1,36] When compared head-to-head, ACE inhibitors and ARBs reduce BP comparably.[1] In contradistinction to the wealth of information on monotherapy with these drugs, there is strikingly little information about the efficacy of combined ACE inhibitor and ARB therapy.[10–14,26] Moreover, the re-

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sults of the trials published to date cannot be generalized, since in many instances they involved a small number of patients and employed study designs with inherent limitations. For example, in one clinical trial,[14] 20 patients received monotherapy with benazepril for 6 weeks. If average waking ambulatory diastolic BP remained at >85 mm Hg, subjects were randomized for 5 weeks to either valsartan 80 mg/day or matching placebo in a blinded manner, while continuing to receive background benazepril. The patients then crossed over to the alternative regimen for a second 5-week period. The combination of valsartan and benazepril reduced the average waking ambulatory BP by 6.5±12.6/4.5±8.0 mm Hg (systolic/diastolic) over placebo+benazepril. Nocturnal systolic and diastolic BPs were similarly reduced, by 7.1±9.4/5.6±6.5 mm Hg.

In a larger, 8-week, open-label trial,[13] the efficacy of the ARB candesartan cilexetil in a dose range of 16–32 mg/day was evaluated in 473 patients receiving ACE inhibitor monotherapy. The incremental reduction in BP with the addition of candesartan to an ACE inhibitor was 15.3/10.0 mm Hg. On the surface, this would appear to be a significant response. However, it is important to recognize that this study was neither blinded nor placebo-controlled. A placebo effect could have easily contributed to the observed incremental response, by virtue of "expectation bias." Furthermore, these studies employed a variety of ACE inhibitors with a wide range of doses. The nature of this study precluded identifying the background ACE inhibitors and their doses; thus, in these studies it is possible that background therapy with an ACE inhibitor was not maximized before the addition of candesartan. African Americans had a clinically important but somewhat reduced BP response when candesartan was added to an ACE inhibitor, although neither the exact number of African American patients nor their response was reported. Finally, the 127 patients with isolated systolic hypertension in this clinical trial experienced a 13.4/4.3-mm Hg drop in BP when candesartan was added to ongoing ACE inhibitor monotherapy.

There appears to be no basis for the routine use of an ACE inhibitor in combination with an ARB in stage 1 or 2 hypertension; most patients with BPs lower than 160/100 mm Hg are likely to achieve goal BP with either monotherapy or an RAS antagonist plus a diuretic. Existing studies also fail to resolve the question of whether ACE inhibitors and ARBs should be routinely combined in the management of complex hypertension.[15] Additional studies are needed to determine whether there are subgroups of hypertensive patients who are uniquely responsive to the combination of an ACE inhibitor and an ARB.

Congestive Heart Failure. The rationale for combination therapy with an ACE inhibitor and an ARB in CHF is stronger than that for their combined use in hypertension. CHF is characterized by significant activation of the RAS, particularly in the later stages of the disease. The principle of angiotensin II escape was originally developed to explain the changes in angiotensin II levels seen in CHF patients chronically treated with ACE inhibitors.[40,45] Consequently, high-dose ACE inhibitor therapy or combined ACE inhibitor and ARB therapy has been advocated, in part because of the necessity to reduce either the generation or the effects of angiotensin II escape as completely as possible.

Results of several short-term trials, all with small numbers of patients, most of whom had mild heart failure, have consistently shown that combined therapy with an ACE inhibitor and an ARB additively decreases BP, improves ventricular remodeling parameters, increases oxygen consumption during exercise, and reduces plasma aldosterone and norepinephrine concentrations.[9,25–34] These favorable effects on surrogate hemodynamic and neurohumoral parameters of CHF occur without apparent change in the tolerability of the drug regimen or increased adverse effects. Hemodynamic, neurohumoral, and clinical findings, however, do not necessarily confer long-term survival benefits.

Few data are currently available on the effect of combined therapy on heart failure-related mortality.[8] In the recently concluded Valsartan Heart Failure Trial (Val-HeFT),[8] valsartan was compared to placebo *on top of* background ACE inhibitor therapy in a cohort of 5010 CHF patients with New York Heart Association class II–IV heart failure (primarily classes II and III).[8] In both treatment arms, 93% of subjects were receiving ACE inhibitors. After randomization, valsartan was begun at a dose of 40 mg b.i.d. and titrated to 160 mg b.i.d. The two primary outcome measures were all-cause mortality or a combined end point (all-cause mortality, including sudden cardiac death with resuscitation, hospitalization for heart failure, and worsening heart failure requiring inotropic or vasodilating agents). Compared to placebo, valsartan reduced the combined mortality/morbidity end point by 13.3%, and hospitalization for heart failure by 27.5%, but all-cause mortality was *not* significantly reduced.[8]

Practice guidelines in CHF management have not yet been updated to outline when and in whom an ARB should be added to an ACE inhibitor. Such guidelines must ultimately consider the sequence of drugs to be added, given the expanding role of low-dose β blocker therapy in CHF management. Thus, because no significant improvement was seen in Val-

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HeFT when valsartan was given to patients taking both an ACE inhibitor and a β blocker, ARB therapy may become third-line therapy in CHF management unless a CHF patient is completely intolerant of ACE inhibitors, in which case an ARB can be substituted for the ACE inhibitor. If there is evidence of partial intolerance to an ACE inhibitor at the early stage of dose titration—such as a decline in renal function or an excessive drop in BP—the addition of an ARB to a reduced dose of the ACE inhibitor may succeed where ACE inhibitor dose titration has failed.

Renal Disease. The combination of an ACE inhibitor and an ARB has been occasionally used in progressive renal disease, particularly for an antiproteinuric effect beyond that obtained with a single agent.[16–23] For example, in an early study of normotensive patients with biopsy-documented immunoglobulin A nephropathy and non-nephrotic proteinuria,[19] the combination of losartan with an ACE inhibitor produced an average 73% greater reduction in proteinuria than either agent alone (ACE inhibitor 38% and losartan 30%). In this study, no further reduction in proteinuria was achieved by doubling the dose of either the ACE inhibitor or losartan. The observed changes could not be explained by either changes in systemic BP or the glomerular filtration rate. It is noteworthy that the additive antiproteinuric effect with an ACE inhibitor plus losartan was observed within 4 weeks of beginning the combination therapy.[19]

Recently, the randomized Candesartan and Lisinopril Microalbuminuria (CALM) study,[18] which evaluated the effect of combining the ARB candesartan and the ACE inhibitor lisinopril on microalbuminuria in 199 type 2 diabetic patients, yielded similar observations. Twelve weeks of combination therapy was begun after 12 weeks of monotherapy with either candesartan or lisinopril, each given at one half the usual maximal dose. In this study, the reduction in the urinary albumin:creatinine ratio with the combination of candesartan (16 mg/day) and lisinopril (20 mg/day) was significantly greater (50% decrease) than that observed with either agent alone (24% decrease with candesartan and 39% with lisinopril). As is often the case with combination therapy, BP values were lower than those attained with either agent individually, which makes interpretation of the findings difficult. After 24 weeks of therapy, diastolic BP was reduced to a greater degree with combination therapy (–16.3 mm Hg) than with either candesartan (–10.4 mm Hg) or lisinopril (–10.7 mm Hg) alone.

The importance of BP reduction as a confounder in terms of the additive antiproteinuric effects of combination therapy cannot be overemphasized.[16–18,20] The relationship between BP and the antiproteinuric effect of combination therapy may not be detected if only office-based readings are used, as these have a high degree of intrinsic variability. A recent study by Russo et al.[20] revealed no relationship between office measurements of trough BP and the antiproteinuric effect of combination therapy with enalapril and losartan. However, there was a significantly high correlation between mean ambulatory BPs and the degree to which urinary protein excretion fell.

Additional studies will be required to determine whether long-term cardiovascular and renal outcome measures are more favorably influenced by combination therapy. Moreover, the optimal dose relationship for combination therapy remains ill defined.

CONCLUSIONS

Both ACE inhibitors and ARBs have been proved effective and well tolerated antihypertensive agents when used separately. Moreover, these compounds now have an established record of effectiveness in the treatment of CHF, proteinuric states, and renal disease. Although inconclusive, the results of a limited number of studies support the notion that additive antihypertensive, cardioprotective, and antiproteinuric effects may be obtained with combined use of ACE inhibitors and ARBs in certain patient subsets. More studies are needed to confirm these preliminary observations, and to define more clearly the populations who might derive greatest benefit from this combination therapy approach. In particular, the question of whether maximal dose titration of either an ACE inhibitor or an ARB alone would duplicate the clinical findings obtained with combination of these drug classes needs to be resolved.

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