Is enalapril and losartan combination irrational?

I read with great interest the editorial by C.S. Gautam and S. Aditya, which appeared in the Indian Journal of Pharmacology in June 2006 (vol. 38(3):167-70). A very important topic was addressed in the editorial, and I compliment the authors on this. On the other hand, I felt confused when I found Enalapril + Losartan in the list of irrational fixed dose combinations, I agree with the authors that combining the two drugs affecting the same pathway is irrational as it does not add to its efficacy, but I am not sure whether this combination should be categorised as irrational or as rational. The results of ongoing research may answer this question in future.

Apparently this combination may appear irrational, but actually rationality does exist for combining these two drugs.

- From a physiological point of view, the general mechanism of action of both angiotensin-converting enzyme inhibitor and AT₁ receptor antagonist is the same, i.e., inhibition of the rennin-angiotensin system. Their sites of action are, however, different and, therefore, differences exist in their intrinsic mechanisms of action. Angiotensin converting enzyme inhibitor acts by blocking conversion of angiotensin I to angiotensin II, while angiotensin receptor blockers act at terminal receptor level.

- It has been shown that even maximum doses of angiotensin converting enzyme inhibitors do not completely suppress angiotensin II generation because it is known that there are several alternative pathways to generate this peptide from angiotensin I. The conversion of angiotensin I into angiotensin II is catalysed not only by angiotensin-converting enzyme, but also by other peptidases, such as, chymase, tonin, and cathepsin G. This fact might explain the loss of antihypertensive and antihypertrophic effects during long-term use of angiotensin-converting enzyme inhibitors in hypertensive patients. The addition of an angiotensin II type 1 receptor blocking agent to an ACE inhibitor would theoretically block ACE as well as non-ACE-dependent angiotensin II formation and will achieve a more complete inhibition of the renin-angiotensin.

- ARBs also simulate rennin release. With ARBs, however, this translates into a several fold increase in circulating levels of angiotensinogen II. As AT₁ receptors are not blocked by clinically available ARBs, ARBs indirectly stimulate AT₂ receptors by increasing angiotensin II levels. Therefore, in the presence of ACE inhibitors, it will block conversion of angiotensin I to angiotensin II and will prevent this indirect stimulation of AT₂ receptors. The clinical significance of this action, however, remains to be defined.

- Enalapril and losartan do exert dose-dependent and, when combined, additive effects in terms of blood pressure fall and cardiac hypertrophy limitation and synergistic effects in terms of plasma active renin stimulation and blockade of exogenous angiotensin I pressor effects. Therefore, the enalapril-losartan combinations are more potent at achieving these goals than any of their constituents individually.

- Similarly synergistic efficacy of enalapril and losartan in combination on exercise performance and oxygen consumption at peak exercise in congestive heart failure has been suggested.

- The combination of an angiotensin-converting enzyme inhibitor and an angiotensin II receptor antagonist (AT₁ receptor antagonist) in patients can significantly enhance reduction in left ventricular hypertrophy. This can provide greater protection to the heart against the overload caused by persistent hypertension. Furthermore, the combination of these drugs did not increase the incidence of adverse effects. On the contrary, the possibility of using a lower dose of angiotensin converting enzyme inhibitor, combined with an AT1 receptor antagonist, might in fact reduce the chance of persistent cough, the main factor limiting the use of angiotensin-converting enzyme inhibitor in hypertension.

- Similarly, the beneficial effect of combination therapy with an angiotensin II receptor antagonist and angiotensin-converting enzyme inhibitor on overt proteinuria in a patient with type I diabetic nephropathy is very encouraging.

- A combination of a full-dose ACE-inhibitor and an ARB may be a rational choice in selected patients. Further trials are, however, needed to evaluate long-term safety, efficacy, quality of life, and survival before the combination can be recommended for routine use.

Therefore, I would like the authors to address this issue and contemplate whether it is right to categorise this combination as irrational just because it is not in the approved list of WHO. I especially recommend this because the answer about its rationality is awaited from the ongoing research in this field.

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References