Correspondence

Combined treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARB): ‘Beating a dead horse’ or meaningful mechanism-guided therapy?

I read with great interest the recent editorial, by Gautam and Aditya, and the ‘Letters to the Editor’, by Tandon and Sharma, et al. dealing with the pros and cons of combining ACE inhibitors with ARBs.[1-3]

The involvement of the renin-angiotensin-system (RAS) in various pathologies is well recognised. The inhibition of either production of angiotensin-II via ACE inhibition or blockage of the deleterious angiotensin-II effects using ARB are well established therapeutic approaches. The therapy of hypertension is, in the majority of cases, a combination therapy and almost every possible drug combination has been employed. Azizi et al., in France, Bisognano and Horwitz in the US and Meyer in Germany were among the first to look at the possibility of combination therapy with ACE inhibitors and ARB.[4-6]

The mechanistic arguments put forth for adding an ARB to full dose ACE inhibition are the existence of non-ACE-dependent angiotensin-II production (thus insensitive to ACE inhibition) and the importance of bradykinin-related effects of ACE inhibitors. While this line of thinking is certainly valid, the arguments are not particularly strong. One might be tempted to see, in the combination of ACE inhibitors with ARB, a perfect example for a pharmacodynamic pleonasm. Finnegan and Gleason recently reviewed data concerning combined ACE inhibitor and ARB therapy for hypertension and concluded that while studies have shown statistically significant blood pressure reductions with the ACE inhibitors-ARB combination therapy, clinical significance is lacking.[7] This view is not universally accepted. Kuriyama states that the majority of pilot studies, investigating the renoprotective effect of ACE inhibitors plus ARB, revealed a better antiproteinuric effect of this combination than either of the monotherapies for patients with either diabetic or non-diabetic renal diseases.[8]

These results are in line with the results of the COOPERATE Study (combination treatment of angiotensin-II receptor blocker and angiotensin-converting enzyme inhibitor in non-diabetic renal disease) which concluded that “combination treatment safely retards progression of non-diabetic renal disease compared with monotherapy”.[9]

Recently, evidence has emerged that not all sartans (ARB) are equal. Several reviews have pointed out that, at clinically relevant dosage, telmisartan (but not other sartans) acts as a partial gamma-PPAR agonist.[10-12] Losartan metabolites (and possibly metabolites of other sartans) are also active at the same receptor.[13]

The constellation of obesity, dyslipidaemia, hypertension and insulin resistance is very common and has been baptised metabolic syndrome. Hypertension is a major determinant of cardiovascular events in these patients and strict blood pressure control is a must. For the high-risk hypertensive patient, ACE inhibitors, in addition to lowering blood pressure, increase insulin sensitivity and confer renal and vascular protection.[14-15] Different theories have been put forth to explain the ACE inhibitor mediated protection. However, none of them is entirely convincing.[16]

The clinical effects of ACE inhibitors have similarities with those of both fibrates and glitazones, known activators of the peroxisome proliferator activator receptor (PPAR) alpha- and gamma-, respectively. We hypothesised that the long-term advantages of ACE inhibitor use, beyond mere BP lowering, might be due to a PPAR mediated effect.

Recently, we have been able to show that captopril and moexipril can induce catalase activity in rat liver.[17,18] To the extent to which catalase activation is a surrogate marker for PPAR activation, the results lend support to the assumption that ACE inhibitors are upregulating PPAR. Our results complement those reported by da Cunha et al that enalapril upregulated the expression of alpha- and gamma-PPAR mRNA in mice.[19]

Due to the well-known species differences (i.e. sensitivity to peroxisome proliferation in rodents versus relative refractoriness in humans), extrapolation of results obtained in rodents to humans is difficult and therefore, as always, the caveat that further work is required, is necessary.[20] Also, further studies will have to elucidate the question whether the described phenomenon is a class effect (all ACE inhibitors) or not and, if yes, to quantify and compare the ability of the different ACE inhibitors to upregulate this class of receptors.

The finding, however, that at least some ACE inhibitors upregulate PPAR expression provides a possible mechanistic rationale for combining ACE inhibitors (prils) with sartans acting as partial PPAR agonist at these receptors. Mixing (some) sartans with (some) prils might make sense, after all.
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References