SCIENTIFIC LETTER

Effects of combined treatment with enalapril and losartan on myocardial function in heart failure

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Recently published studies have shown that angiotensin converting enzyme inhibitors can be combined with angiotensin II antagonists and are highly effective in reducing mortality and improving the quality of life of patients with heart failure.^{1–3} There is little information about the effects of this combination on the myocardial function of patients with severe myocardial dysfunction. Thus, in 21 patients with stable heart failure of ischaemic aetiology, with New York Heart Association functional class III–IV and a resting left ventricular ejection fraction (EF) of $\leq 40\%$, who were treated with diuretics, β blockers, and/or digoxin (given at unchanged dosage), we studied the effects on myocardial dysfunction induced by adding either enalapril as a monotherapy, or the combination of enalapril and losartan.

PATIENTS AND METHODS

Patients were aged 50–75 years and gave their consent. The ethical committee approved the protocol. All patients underwent clinical routine examinations encompassing routine laboratory tests, ECGs, and colour Doppler transthoracic echocardiograms. The study was double blind, and double dummy and randomised (three parallel groups). Seven patients were treated with placebo (placebo + placebo), seven patients with enalapril, and seven patients with a combination of enalapril + losartan. In the placebo group the initial dosage were two tablets (“doses” 1) and it was escalated successively at weekly intervals at “doses” 2, 3, and 4. In the enalapril group the initial dose of 5 mg enalapril (+ “dose” 1 of placebo) was increased at weekly intervals, successively to 10 mg (+ “dose” 2 of placebo), 20 mg (+ “dose” 3 of placebo), and 40 mg (+ “dose” 4 of placebo). In the enalapril + losartan group the dosage started with 2.5 mg enalapril and 25 mg losartan, and it was increased to 5/50 mg, 10/75 mg, and 20/100 mg, respectively. Each dose was maintained for one week, followed by the upward titration. The highest dose was chosen according to safety, tolerance, and cardiac symptoms, and it was maintained for six weeks.

Results were analysed by using one way analysis of variance (ANOVA), Wilcoxon signed rank test, and Mann-Whitney U test; in addition, adjusted mean changes were calculated by analysis of covariance (ANCOVA). EF and regional wall ventricular motility were assessed by echocardiography (Teicholz formula and modified Simpson's rule) at rest and after dipyridamole stress, at baseline, and again at the end of the treatment. The wall motion score index, at rest and after the stress test, was measured with a 16 segment model of the left ventricle.⁴ A wall motility score index was obtained by dividing the sum of the individual segment scores by the total number of visualised segments.⁵

RESULTS

Both regimens were well tolerated, but the enalapril + losartan combination improved the cardiac function more than

Figure 1 Left ventricular ejection fraction, at rest and after dipyridamole stress, baseline, and after treatment with placebo (PBO), enalapril (EN) or enalapril + losartan (EN + LOS). B, baseline, EF, global ejection fraction; r, at rest; s, after dipyridamole stress; T, after treatment. EF at rest (EF r): the effect of EN + LOS was significant ($p < 0.009$) and superior to EN ($p < 0.03$). Stress EF (EF s): the effect of EN + LOS was significant ($p < 0.003$) and superior to EN ($p < 0.01$).

enalapril alone. At baseline resting EF (%) was inferior in the enalapril + losartan group (mean (SD) 31.0 (4.5)) compared to the placebo (33.3 (3.6)) and the enalapril groups (33.9 (2.6)), but the difference was not significant ($p = 0.03$). After treatment EF increased in all groups: placebo 34.4 (4.7), enalapril 36.6 (4.9), and enalapril + losartan 34.9 (6.5). The increase was small and non-significant with placebo and enalapril. On the other hand, with enalapril + losartan, EF increased in all patients and the change was significant ($p < 0.009$). Intergroup comparisons revealed a superior effect of enalapril + losartan versus placebo and versus enalapril alone ($p < 0.03$).

Stress EF

At baseline EF was inferior in the enalapril + losartan group (32.3 (1.42)) compared to the placebo (34.7 (0.16)) and the enalapril (35.22 (0.26)) groups, but the difference was not significant ($p = 0.1$). After treatment, stress EF increased in all groups, but the change was not significant with placebo (35.8 (0.18)) and with enalapril (37 (0.27)). With enalapril + losartan stress EF improved in all patients, and again the change was significant ($p < 0.003$). Intergroup comparisons

revealed a superior effect of enalapril + losartan versus placebo and versus enalapril alone ($p < 0.01$). Results are shown in fig 1. The combination had exactly the same effect on the wall motility score index (data not presented but are available on request, together with full data about blood pressure, heart rate etc).

DISCUSSION

Our data show that the combination of enalapril + losartan is more effective than enalapril alone in improving myocardial function both at rest and after stress. The effect is detectable after six weeks of treatment. We believe that the positive effect of the combination is attributable to a more effective anti-ischaemic effect, perhaps by reducing the escape phenomenon observed with monotherapy with angiotensin converting enzyme inhibitors. However, the superior efficacy could be partially caused by a greater afterload reduction. Our findings support the use of combination treatment in selected patients with severe myocardial dysfunction.

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IMAGES IN CARDIOLOGY

Preoperative treatment with phenoxybenzamine restores ECG to normal in a woman with pheochromocytoma

A 52 year old woman with a 10 year history of arterial hypertension was referred to the outpatient hypertensive clinic because of episodes of palpitations and high blood pressure. These episodes had deteriorated during the last few months (systolic blood pressure up to 240 mm Hg), although she was receiving antihypertensive treatment (angiotensin converting enzyme inhibitor, β blocker, diuretic). The ECG revealed significant diffuse repolarisation abnormalities (below left, upper panel), suggestive of severe ischaemia or hypertrophic cardiomyopathy. Chest x ray, echocardiogram, and biochemistry tests, including urine VMA and metanephrines, were normal. An adrenal mass of 5.6 cm diameter was visualised by renal ultrasound and computed tomography. An MIBG scan established the diagnosis of left adrenal pheochromocytoma (below right). The patient was treated with oral phenoxybenzamine (10 mg three times a day) and a β blocker during the preoperative management and her ECG became normal (below left lower panel). The latter event is uncommon and proves the effect catecholamines have on myocardial repolarisation.

Adrenergic hormone effects are responsible for a functional coronary insufficiency with an imbalance of supply and demand of oxygen, which may cause myocardial damage. Also, acute heart failure and transient low voltage in the ECG after massive catecholamine release from a pheochromocytoma have been previously described. Blockade with phenoxybenzamine in pheochromocytoma, apart from its well defined effects on vagal activity and the occurrence of ventricular arrhythmias, also contributes to an improvement in myocardial repolarisation. The patient underwent an operation where the tumour was excised and histological examination revealed it to be a left adrenal pheochromocytoma. The patient's blood pressure returned to normal without any further medical treatment.

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