Does the addition of losartan improve the beneficial effects of ACE inhibitors in patients with anterior myocardial infarction? A pilot study

P Di Pasquale, V Bucca, S Scalzo, S Cannizzaro, A Giubilato, S Paterna

Abstract

Objective—To verify the efficacy of the combination of captopril (75 mg/day) and losartan (25 mg/day) in early postinfarction phases of reperfused anterior acute myocardial infarction.

Design and patients—99 patients, hospitalised for suspected anterior acute myocardial infarction within four hours from the onset of symptoms, were randomised into two groups: group A included 50 patients who received captopril 75 mg/day and placebo; group B included 49 patients who received captopril 75 mg/day within three days of admission plus losartan 12.5 mg, as a first dose, and 25 mg/day successively. An additional 23 patients with anterior acute myocardial infarction received losartan 25 mg alone and acted as controls (group C) to check the effects of losartan on plasma angiotensin II (AII) concentrations. Noradrenaline (norepinephrine) (NA) and AII plasma concentrations were measured on the third and 10th day after admission in 93 patients (35 from group A, 35 from group B, and 23 from group C). 90 days after admission patients underwent echocardiography to determine end systolic volume (ESV) and ejection fraction (EF).

Results—Patients in groups A and B were similar with regard to age, sex, creatine kinase peak, EF, ESV, and risk factors. Group B (captopril plus losartan) patients showed a significant reduction in mean (SD) systolic blood pressure within the group (basal 128 (10) mm Hg; 10 days after admission 105 (9) mm Hg, p < 0.001), and in comparison with group A (captopril) patients (basal 127 (11) mm Hg; 10 days after admission 116 (10) mm Hg, p < 0.001). Diastolic blood pressure was also lower in group B patients versus group A (66 (11) v 77 (11) mm Hg). Group C (losartan) patients also showed a significant reduction in systolic blood pressure (131 (13) mm Hg down to 121 (12) mm Hg, p < 0.001). Neither NA nor AII plasma concentrations in groups A and B differed significantly in basal samples (NA 673 (138) v 675 (141) pg/ml; AII 12.77 (4.79) v 12.65 (4.71) pg/ml) or 10 days after admission (NA 283 (93) v 277 (98) pg/ml; AII 5.31 (2.25) v 6.09 (3.31) pg/ml). However, patients in group C had higher plasma concentrations of AII (14.79 (5.7) pg/ml on the third day and 7.98 (4.92) pg/ml on the 10th day) than patients in either group A or B (p = 0.006). After 90 days following treatment, group B (captopril plus losartan) patients had a smaller ESV than patients in group A (captopril) and group C (losartan).

Conclusion—The data suggest that the combination of captopril plus losartan is feasible in the early treatment of acute myocardial infarction patients, and it appears that this combination has more effect on ESV than captopril alone in the short term.

Keywords: acute myocardial infarction; angiotensin converting enzyme inhibitors; captopril; losartan
of captopril plus losartan, and to verify if this combination is able to avoid the increase of AII found with losartan treatment alone.\textsuperscript{11} A randomised single blind study involving patients with anterior acute MI in the early postinfarction phase was carried out.

**Patients and methods**

**PATIENT POPULATION AND ELIGIBILITY CRITERIA**

From January 1996 to February 1998, 574 patients were admitted consecutively to hospital with suspected acute MI. To be eligible to enter the trial, patients had to have a first episode of anterior acute MI, Killip class I–II, an acceptable echocardiographic window, and to be admitted to hospital and thrombolysed within 4 hours of the onset of symptoms (pain). On ECG there had to be an ST elevation of >1 mm in the peripheral leads and/or 2 mm in precordial leads, involving more than one lead, with concomitant alterations of the segmentary kinetics in the echocardiogram performed at entry. The basal creatine kinase (CK, CK-MB isoenzyme before thrombolysis) had to be within the normal range. All patients admitted into the study had to have successful reperfusion and had to receive the target dose of captopril (75 mg/day) three days after admission. The end systolic volume (ESV) was measured at the end of the T wave. The modified Simpson four chamber and two chamber view was used. The end systolic volume (ESV) was measured at the end of the T wave. The modified Simpson dynamic investigation (7–10 days after admission). Angiographic findings and left ventricular function. Patients enrolled in the study continued treatment after discharge. They were regularly followed up as outpatients.

**STUDY PROTOCOL**

Patients suitable for thrombolysis received captopril 6.25 mg orally, as first dose, 2–4 hours after starting thrombolysis. Blood pressure (first 6 hours), heart rate, and ECG were monitored continuously, recorded on tape (first 2 hours), and then analysed to check any rhythm disturbance, focusing attention on the time of pain cessation and regression of ST segment alteration. Ventricular tachycardia and ventricular fibrillation were recorded. Blood CK concentrations were measured every 3 hours during the first 24 hours and then every 6 hours until they returned to normal, to determine the enzymatic peak (12 hours). Providing blood pressure was >100 mm Hg, captopril doses were increased up to 25 mg every 8 hours (first three days). All the patients had to receive, at three days after admission, 75 mg captopril per day. Randomisation (single blind) was carried out by sequentially numbered boxes and was decided on the third day. Figure 1 shows the outcome of the study. Patients receiving captopril 25 mg every 8 hours after three days and with blood pressure >120 mm Hg were randomised (single blind) into two groups, followed by echocardiography: group A (50 patients) received captopril (75 mg/day) and placebo; group B (49 patients) received captopril (75 mg/day) plus losartan 12.5 mg as a first dose, and then after 24 hours the dose was increased up to 25 mg/day according to the patient’s blood pressure (lower limit 110 mm Hg). Blood pressure was controlled continuously for 6 hours after losartan administration. In addition, 23 patients received losartan only, 12.5 mg as first dose 2–6 hours after starting thrombolysis, the dose subsequently being increased up to 25 mg/day. This losartan only group (group C) was used as a control to monitor the effects of losartan on plasma AII concentrations. After 10 days, when the second sampling of NA and AII was performed, the dose of losartan was increased to 50 mg/day. Before discharge, patients underwent 24 hour Holter monitoring to evaluate late ventricular arrhythmias, taking into account only those in Lown’s class >2, as well as a symptom limiting exercise test. All patients entered into the study underwent a haemodynamic investigation (7–10 days after admission). Percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) were performed according to angiographic findings and left ventricular function. Patients enrolled in the study continued treatment after discharge. They were regularly followed up as outpatients.

**FOLLOW UP**

Echocardiography was carried out according to a standard procedure on day 3 (just after randomisation) and day 90 after admission. Patients lay in the left lateral position during the examination; echocardiographic recordings were obtained at the end of the expiratory phase during normal breathing, and an apical four chamber and two chamber view was used. The end systolic volume (ESV) was measured at the end of the T wave. The modified Simp-
son’s rule, which uses two cross section views (four and two chamber apical views) was followed. All members of the study team had completed at least five years of internal cardiology residency and training in two dimensional echocardiography. Two observers blinded to the clinical and ECG data evaluated the two dimensional echocardiographic images. In case of discrepancy, the two dimensional echocardiographic images were again reviewed, and a decision was made by consensus. The mean of three measurements was used. The interobserver and intraobserver coefficients of variation were 4% and 3%, respectively.

NEUROHORMONAL ASSESSMENT
Blood was obtained for measurement of NA and AII concentrations on the third day, when all the patients were given the target dose of captopril (75 mg/day), and on the 10th day after admission (seven days after losartan administration); the same sampling procedure was followed in patients treated with losartan alone. Plasma was obtained and frozen immediately. AII concentrations were determined by radioimmunoassay (reproducibility 10%), after initial high performance liquid chromatography (HPLC) separation of AII and AIII, and NA concentrations were assessed by HPLC as previously reported. Neurohormonal assay was performed by a pharmacologist who was blinded to treatment, as were the physicians who performed the haemodynamic study to obtain ESV and ejection fraction (EF).

STATISTICAL ANALYSIS
Results are expressed as mean (SD). Data were analysed by the two tailed t test to identify differences between the groups and analysis of variance (ANOVA) for repeated measures with Bonferroni correction for intragroup data. Nominal data were analysed by χ² test; p < 0.05 was considered to be significant.

Results
Ninety nine patients met the entry criteria and continued the study in accordance with the study protocol. In addition 23 patients were given losartan alone. The patients who had proved reperfused anterior acute MI and late coronary angiography had an infarct related artery patency corresponding to the classification of reperfusion based on non-invasive diagnosis. Five patients in group B and seven patients in group A initially entered into the study did not show subsequent patency of the infarct related artery and were excluded. NA and AII levels in these patients were similar to those of patients enrolled into the study (group A—basal NA 706 (198) pg/ml, on 10th day 375 (152) pg/ml, basal AII 13.35 (6.5) pg/ml, on 10th day 6.2 (3.8) pg/ml; group B—basal NA 726 (212) pg/ml, on 10th day 387 (189) pg/ml, basal AII 13.45 (7.1) pg/ml, on 10th day 6.15 (4.52) pg/ml). In addition, they showed clinical signs of heart failure (EF < 40%). The groups were similar in regard to age, sex, diabetes, smoking habits, hypertension, CK enzymatic peak, adjuvant therapy, EF, ESV, and incidence of CABG/PTCA. Table 1 shows the clinical data of patients with proved reperfused anterior acute MI and the results obtained from each group.

NEUROHORMONAL AND BLOOD PRESSURE DATA
In 93 patients (35 from group A, 35 from group B, and 23 from group C) mean NA and AII concentrations (in those patients with proved reperfused anterior acute MI) were reduced on the 10th day (table 2). AII values in samples drawn at later times tended to be lower in the captopril treated patients (group A) versus the captopril plus losartan treated patients (group B), even if the difference was not significant. The patients receiving losartan alone (group C) showed higher AII plasma concentrations in comparison with the other two groups, but the difference was significant only when compared with the captopril treated patients (group A) (p = 0.006). Patients in group B (captopril plus losartan) showed a significant reduction in systolic and diastolic blood pressure in comparison with patients in group C.
Captopril plus losartan in acute MI

Discussion

Specific receptor antagonism has obvious theoretical advantages. ACE cleaves not only AI to form AII, but also cleaves bradykinin, encephalin, and substance P.21 Some important side effects of ACE inhibition (cough and angioedema) are most likely caused by these non-specific actions.22 In addition, some non-converting enzyme dependent conversion from AI to AII occurs locally within cardiac and arterial wall tissues.13 ACE inhibitor treatment appears to enhance this pathway and, thus, the blockade of the potentially detrimental effects of AII by ACE inhibitor may remain incomplete.14 23 Blocking the actions of AII at the receptor level represents an attractive alternative approach to treatment. A favourable vasodilator and neurohumoral response in patients with heart failure has been documented for losartan.7–11 Recent reports suggest that losartan and ACE inhibitors (enalapril and captopril) are of comparable efficacy and tolerability in the short term treatment of moderate or severe congestive heart failure, whereas one long term study showed losartan reduced mortality when compared with captopril.11 24 On the other hand, the randomised evaluation of strategies of left ventricular dysfunction

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Neurohormonal data</th>
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<tbody>
<tr>
<td>Noradrenaline</td>
<td>Angiotensin II</td>
</tr>
<tr>
<td></td>
<td>Group A (captopril)</td>
</tr>
<tr>
<td>Day 3</td>
<td>673 (138)‡</td>
</tr>
<tr>
<td>p Value</td>
<td>0.001</td>
</tr>
<tr>
<td>Day 10</td>
<td>283 (93)§</td>
</tr>
<tr>
<td>p Value</td>
<td>0.001</td>
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</tbody>
</table>

Values are mean (SD) in pg/ml. *p < 0.006.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Changes in systolic and diastolic blood pressure</th>
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<tr>
<td>Systolic blood pressure</td>
<td>Diastolic blood pressure</td>
</tr>
<tr>
<td></td>
<td>Group A (captopril)</td>
</tr>
<tr>
<td>Day 3</td>
<td>127 (11)</td>
</tr>
<tr>
<td>p Value</td>
<td>0.001</td>
</tr>
<tr>
<td>Day 10</td>
<td>116 (10)†‡</td>
</tr>
<tr>
<td>p Value</td>
<td>0.001</td>
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Systolic blood pressure: *p < 0.001; †p < 0.01. Diastolic blood pressure: **p < 0.001; ‡p < 0.001.

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<tr>
<th>Table 4</th>
<th>Changes in end systolic volume and ejection fraction 90 days after treatment</th>
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<tbody>
<tr>
<td>End systolic volume (ml/m²)</td>
<td>Ejection fraction (%)</td>
</tr>
<tr>
<td></td>
<td>Group A (captopril)</td>
</tr>
<tr>
<td>3 days</td>
<td>46.2 (14)</td>
</tr>
<tr>
<td>7–10 days</td>
<td>45.5 (9.5)</td>
</tr>
<tr>
<td>90 days</td>
<td>48.8 (9)‡</td>
</tr>
<tr>
<td>p Value</td>
<td>NS</td>
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End systolic volume tP = 0.023; †p = 0.016. Ejection fraction †P = 0.054.

group A (captopril) (p < 0.001) (table 3). Group C (losartan) patients also showed a significant reduction in blood pressure by the 10th day (p < 0.001). EF values were higher, though not significantly so, in group B patients (captopril plus losartan) than in group A patients (captopril) and group C patients (losartan). Serum creatinine, serum potassium, and blood urea did not show any significant differences between groups A and B. The first dose of losartan (12.5 mg) did not produce significant changes in blood pressure.

HAEMODYNAMIC DATA

In the follow up from January 1996 to May 1998 (range 3–29 months; minimum period of observation three months from May 1998), two patients in each group died as a result of reinfarction and heart failure. Ninety five patients completed the study period of 90 days (48 from group A and 47 from group B) and underwent echocardiographic examination. The same procedure was also performed in the 23 patients in group C. ESV values at 90 days were compared, the values for group B (captopril plus losartan) differed from those for group A (captopril) (p = 0.016) and group C (losartan) (p = 0.023). There was no significant difference between the ESV values in group A and group C. The EF values were higher in patients in group B than in groups A and C 90 days after admission, although the differences were not significant (p = 0.054) (table 4). Four ischaemic events were observed during the follow up period (one episode of reinfarction and one episode of unstable angina each in groups A and B). In group C one episode of unstable angina and one of heart failure were recorded.

Discussion

Specific receptor antagonism has obvious theoretical advantages. ACE cleaves not only AI to form AII, but also cleaves bradykinin, encephalin, and substance P.21 Some important side effects of ACE inhibition (cough and angioedema) are most likely caused by these non-specific actions.22 In addition, some non-converting enzyme dependent conversion from AI to AII occurs locally within cardiac and arterial wall tissues.13 ACE inhibitor treatment appears to enhance this pathway and, thus, the blockade of the potentially detrimental effects of AII by ACE inhibitor may remain incomplete.14 23 Blocking the actions of AII at the receptor level represents an attractive alternative approach to treatment. A favourable vasodilator and neurohumoral response in patients with heart failure has been documented for losartan.7–11 Recent reports suggest that losartan and ACE inhibitors (enalapril and captopril) are of comparable efficacy and tolerability in the short term treatment of moderate or severe congestive heart failure, whereas one long term study showed losartan reduced mortality when compared with captopril.11 24
mediated effects to achieve the bradykinin/nitric oxide vascular and myocardial tissues, and ACE inhibitors to prevent the effects of AII on vascular and myocardial tissues, and ACE inhibitors to achieve the bradykinin/nitric oxide mediated effect.\(^{27}\) With this scenario in mind, we considered it would be of interest to test the association between captopril and losartan in the early phases of postacute MI in a selected group of patients. Our data showed that using a combination of these drugs blocked the RAS more completely than ACE inhibition or losartan alone.\(^{22}\) Patients treated with captopril plus losartan (group B) showed a significant reduction in blood pressure compared with captopril alone (group A). No important side effects were observed. Furthermore, there was no significant difference in AII concentrations between the two groups seven days after treatment.

We thought that the low dose of losartan used may have caused an incomplete inhibition of AT\(_1\) receptors on the myocytes. The captopril plus losartan combination may be able to block the detrimental effects of the AII chymase dependent system with persisting concentrations of AII after ACE inhibitor treatment. It is possible that an increase in AII was not found because the conversion of AI to AII was blocked by ACE inhibition. In this way, we hoped to obtain the goal of reducing the detrimental effects of AII by losartan and probably reducing the effects of AII produced by the chymase system. The dose of losartan used was low, which perhaps lessened the major effects on the blood pressure. It would be interesting to use a lower dose of captopril and a higher dose of losartan, to determine if it is more important to block the effects of the alternative system (chymase) or the ACE system. We preferred to use enough ACE inhibitor to maintain the effects on kinins (bradykinin, prostaglandin, endothelin, etc.),\(^{27,28}\) and to determine the additive effects of losartan on AII plasma concentrations.

The reduction in AII plasma concentrations from day 3 to day 10 after acute MI in both groups is caused probably by two mechanisms: a reduction of RAS activation, observed during the acute phase of acute MI; and the effects of captopril. The lack of an increase in AII with the association of losartan was probably caused by the concomitant action of the ACE inhibitor, which did not allow an increase in AII plasma concentrations, but to prove this hypothesis it was necessary to treat patients with losartan alone. The value of the AII concentrations measured at day 10 may be questioned in view of the short observation period. For this reason we treated a third group with losartan alone (group C), to act as a control to verify the effects of losartan on plasma AII concentrations. After 10 days, when the second sampling of NA and AII was performed, the dose of losartan was increased to 50 mg/day. The patients receiving losartan alone (group C) showed higher AII plasma concentrations in comparison with the other two groups, but the difference was significant only when compared with the captopril group (group A) (\(p = 0.006\)). In addition, patients in group C (losartan) showed a significant reduction in blood pressure and no difference in ESV and EF.

It is difficult to reach a conclusion about the value of the lack of increase in AII observed in patients treated with captopril plus losartan and/or of the increase in AII observed in the patients treated with losartan alone. On the other hand, our data are in agreement with recent papers showing a significant increase of AII concentrations during short term AII receptor antagonism.\(^{8-10}\) The most striking results of this study were the safety and tolerability of the losartan plus captopril combination and the significant reduction of ESV three months after treatment. In addition, our data are in agreement with recent experimental reports showing that dual treatment with ACE inhibitors and AII receptor antagonists may provide further beneficial effects and enhance myocyte contractile performance in heart failure.\(^{29}\) This result must be interpreted with caution because of the selection of patients (low risk, thrombolysed, and reperfused). In the follow up, as the sample size was small, only large differences could be detected; no significant differences in the fatal and non-fatal event rates were observed between two groups. The reduction in ESV 90 days after admission could be interpreted as an effect of the captopril plus losartan combination on remodelling. These are very preliminary data which suggest further investigations are required.

**LIMITS OF THE STUDY**

The major limitations of the study were the small number of patients and the single blind randomisation. Because of the small number of patients we could not show possible beneficial effects on morbidity and mortality. The beneficial effects reported on early remodelling must be interpreted with caution because both groups received ACE inhibitor treatment, and were thrombolysed and reperfused. However, the patients were strictly selected in order to test, for the first time, the effects of combination treatment with losartan plus an ACE inhibitor in acute MI. For the same reason the patients were given single blind treatment.

We are indebted to Miss Valeria Anna Cuccia and Antonio Di Paola for their assistance.
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