Efficacy and Tolerability of Losartan in Patients with Essential Hypertension: a Multicentre, Double-Blind Comparison of Losartan with Metoprolol

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J. Dobovšek, J. Špinar, J. Niegowska, M. Souček, V. Kanić, S. Rekč

A multicentre, randomised, double-blind, comparative study of antihypertensive efficacy and safety of losartan and metoprolol was carried out in 77 patients with mild to moderate essential hypertension. Normalisation of sitting diastolic blood pressure (SiSBP) and sitting systolic blood pressure (SiSBP) at the end of the study was considered as the primary criterion for evaluation. A decrease of SiDBP for at least 10% and that of SiSBP for at least 15% was considered as response to treatment. After 2 weeks of single placebo run-in period the patients were randomised to either losartan 50 to 100 mg od or metoprolol 50 to 100 mg bid. After 3 weeks of the treatment the initial dose of both drugs was doubled if target SiSBP was not achieved. After 6 weeks of monotherapy hydrochlorothiazide 12.5 mg was added for the last 3 weeks if necessary.

Losartan and metoprolol significantly reduced SiSBP and SiDBP versus baseline: −20.8/15.9 mmHg and −16.2/16.6 mmHg, respectively (all p < 0.001). There was no significant difference between the treatment regimens found during the study in regard to SiSBP and SiDBP decrease. In the losartan arm the primary criterion for efficacy was achieved in 72.3% for both SiSBP and SiDBP. In patients treated with metoprolol these results were 63.0% and 85.2%, respectively (n.s.). No significant differences between treatment regimens were observed in regard to complete normalisation of blood pressure (SiSBP < 140/90 mmHg in single patient) and overall blood pressure response. In both groups heart rate decreased significantly and similarly. Both treatments were well tolerated. Adverse events were reported by 16.3% of patients treated with losartan and 21.4% of patients treated with metoprolol (n.s.). There were no serious adverse events.

Conclusion: In this study in patients with mild to moderate essential hypertension, losartan in comparison with metoprolol exerted substantial and comparable antihypertensive efficacy, as well as a similar safety profile. J Clin Basic Cardiol 2005; 8: 43–6.

Key words: essential hypertension, losartan, metoprolol.
The aim of the treatment during this study was to reduce the siDBP < 90 mmHg and siSBP < 140 mmHg. Primary criterion of efficacy was the value of blood pressure at the end of the study. The final evaluation of efficacy was the value of blood pressure at the end of the study when compared with baseline. Statistically significant blood pressure reduction was observed already at week 3, i.e. after the initial dose of both drugs. There was no significant difference in blood pressure or heart rate between two treatment regimens found during the study: week 0: p < 0.85, week 3: p < 0.12, week 6: p < 0.21, week 9: p < 0.28.

### Results

#### Study Sample

A total of 77 patients were enrolled. 74 patients completed the study according to the protocol. Three patients left the study prematurely. Two of them, who discontinued the study after few days of active treatment were included form the statistical analysis. The data of one patient who left the study during the study was done by Chi square test and Cochran-Mantel-Haenszel test. Analysis of efficacy was per protocol. Safety analysis included all patients from the time of randomisation to the end of the study, or to the point at which the study drug was permanently stopped, whichever came first.

#### Blood Pressure and Heart Rate

The changes in siSBP and siDBP are presented in Table 2. Both treatment regimens significantly reduced siSBP, siDBP, and heart rate at the end of the study when compared with baseline. Statistically significant blood pressure reduction was observed already at week 3, i.e. after the initial dose of both drugs. There was no significant difference in blood pressure or heart rate between two treatment regimens found during the study: week 0: p < 0.85, week 3: p < 0.12, week 6: p < 0.21, week 9: p < 0.28.

<table>
<thead>
<tr>
<th>Table 2. Mean changes in siSBP and siDBP during the study (mmHg)</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline siSBP*(mmHg)</td>
<td>153.7</td>
<td>150.8</td>
</tr>
<tr>
<td>After 3 weeks (mmHg)</td>
<td>-14.6*</td>
<td>-12.5*</td>
</tr>
<tr>
<td>After 6 weeks (mmHg)</td>
<td>-17.0*</td>
<td>-16.0*</td>
</tr>
<tr>
<td>After 9 weeks (mmHg)</td>
<td>-20.9*</td>
<td>-16.8*</td>
</tr>
<tr>
<td>Baseline siDBP*(mmHg)</td>
<td>100.3</td>
<td>99.3</td>
</tr>
<tr>
<td>After 3 weeks (mmHg)</td>
<td>-10.6*</td>
<td>-11.1*</td>
</tr>
<tr>
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<td>-14.0*</td>
<td>-15.8*</td>
</tr>
<tr>
<td>After 9 weeks (mmHg)</td>
<td>-15.7*</td>
<td>-16.7*</td>
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</table>

* sitting systolic blood pressure, † sitting diastolic blood pressure, *p < 0.001

#### Table 1. Demographic characteristics of each treatment group

<table>
<thead>
<tr>
<th>Mean values</th>
<th>Group A (n = 49)</th>
<th>Group B (n = 28)</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>50.6</td>
<td>54.3</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172.4</td>
<td>170.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81.9</td>
<td>82.8</td>
</tr>
<tr>
<td>BMI** (kg/m²)</td>
<td>27.5</td>
<td>28.5</td>
</tr>
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</table>

* Body Mass Index

The study was approved by local ethics committees and authorities. The patients had to sign the written informed consent prior to inclusion.

All patients underwent basic cardiovascular examination, including routine ECG and laboratory examinations. At the visits after 3 and 6 weeks of active treatment serum concentration of creatinine and potassium and proteinuria were determined. At the final visit all examinations performed at the inclusion were repeated.

All patients underwent the controlled single-placebo run-in (wash-out) period of 14 days of duration. Patients were excluded from the study in the case of blood pressure (wash-out) period of 14 days of duration. Concomitant medication was reduced to the minimal dose possible, at least 2 weeks prior to inclusion. Ninety-two percent of patients in both groups took the placebo phase the eligible patients were randomised to either losartan (group A) or metoprolol (group B). Randomisation ratio losartan : metoprolol was 2 : 1. The initial dose of losartan was 50 mg once daily and that of metoprolol 50 mg twice daily. At the visit after 3 weeks of double-blind treatment with lower dose of both drugs, the patients in whom siDBP achieved normal values (< 90 mmHg) continued the initial treatment. In other patients the doses were doubled for the next 3 weeks. Then, the properly controlled patients (siDBP < 90 mmHg) continued to take initial or doubled doses. To the patients in whom siSBP exceeded 89 mmHg hydrochlorothiazide (HCTZ) 12.5 mg once daily was added for the last 3 weeks.

Blood pressure was measured according to the recommendations of the American Heart Association using mercury sphygmomanometer. After 15 minutes of rest 3 consecutive measurements were taken at 2-minute intervals. The average of the second and third measurement was then calculated and registered.

The study was conducted between September 2000 and May 2001.

By decision of the National Ethics Committee in Slovene centres only untreated patients at the time of inclusion were allowed to enter the study. Common exclusion criteria were in force for this study, among them women in childbearing period, secondary hypertension, malignant hypertension, bradycardia < 50 beats/min, all stages of atrioventricular block, stroke or transient cerebral ischaemia within the last 12 months, myocardial infarction within the last 6 months, heart failure, angina pectoris, diabetes mellitus (with the exception of stable type 2 controlled with peroral agents) etc.

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The aim of the treatment during this study was to reduce the siDBP < 90 mmHg and siSBP < 140 mmHg. Primary criterion of efficacy was the value of blood pressure at the end of the study. The final evaluation of efficacy was made by the investigators using the following criteria: normalisation of blood pressure (< 140/90 mmHg), response i.e. reduction of siSBP by at least 10 % and siSBP by at least 15 % but without normalisation, and no response i.e. reduction of siDBP by less than 10 % and siSBP by less than 15 %.

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<td>27.5</td>
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</tr>
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</table>

* Body Mass Index

A personal computer with SAS software was used for double data entry, data management, and statistical analysis. The quantitative variables are described by their mean and standard deviation values. For the quantitative variables the Student’s t-test taking into account the possible inequality of the variance and Wilcoxon rank test were performed. The comparison between the two groups for the qualitative variables was done by Chi square test and Cochran-Mantel-Haenszel test. Analysis of efficacy was per protocol. Safety analysis included all patients from the time of randomisation to the end of the study, or to the point at which the study drug was permanently stopped, whichever came first.
In 24 patients (50 %) in group A and in 10 patients (37 %) in group B the initial doses had to be doubled at week 3 (n.s.). A diuretic had to be added in 12 patients (25 %) in group A and in 5 patients (15 %) in group B at week 6 (n.s.).

At the end of the study the assessment of treatment efficacy was classified according to predefined classification (see above). No statistically significant differences could be established between two treatment regimens. This assessment is presented in Table 3.

The satisfactory blood pressure decrease (normalisation plus response) was achieved in 36 patients (76.6 %) treated with losartan (plus diuretic) compared with 22 patients (81.5 %) treated with metoprolol (plus diuretic). Target sDBP (< 90 mmHg) was achieved in 34 patients (72.3 %) in group A and in 23 patients (85.2 %) in group B. Target sSBP (< 140 mmHg) was achieved in 34 patients (72.3 %) in group A and in 17 patients (63.0 %) in group B. The complete normalisation of blood pressure (SBP and DBP < 140/90 mmHg) was observed in 55.3 % of patients treated with losartan (plus diuretic) compared with 66.7 % of those receiving metoprolol (plus diuretic) (n.s.).

Adverse Events
On the whole, 14 patients (18.2 %) [8 patients (16.3 %) in group A and 6 patients (21.4 %) in group B] reported at least one adverse event during the study (n.s.). The most frequent adverse events were vertigo (4 patients), headache (3 patients), dizziness (2 patients), and palpitations (2 patients). In 3 patients the treatment was interrupted owing to adverse events (see above). No serious adverse events were noted. Regarding absolute and/or cut off values no clinically important changes in laboratory parameters were observed.

Table 3. Assessment of treatment efficacy

<table>
<thead>
<tr>
<th>Group</th>
<th>Normalisation of BP* (n.s.)</th>
<th>Satisfactory BP* decrease (n.s.)†</th>
<th>No response (n.s.)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>A</td>
<td>26</td>
<td>55.3</td>
<td>36</td>
</tr>
<tr>
<td>B</td>
<td>18</td>
<td>66.7</td>
<td>22</td>
</tr>
</tbody>
</table>

*blood pressure, †no significance
In the 12 week-study of Dahlöf and co-authors the monotherapies with losartan 50–100 mg and atenolol 50–100 mg were compared [16]. In antihypertensive treatment, the daily dosage 50–100 mg of atenolol is thought to be equivalent to 100–200 mg of metoprolol. In this study no difference was found in the antihypertensive efficacy of both treatment regimens. The absolute reduction of blood pressure after 6 weeks in the presented study (losartan vs. metoprolol), when all patients were treated with monotherapy, was greater in both groups than in the losartan vs. atenolol study after 12 weeks: −17.2/14.2 mmHg (losartan) and 15.4/15.7 mmHg (metoprolol) compared with −12.2/8.3 mmHg (losartan) and 11.3/10.1 mmHg (metoprolol).

In a trial with patients with isolated systolic hypertension these were treated for 8 weeks with the lower dose of losartan or atenolol, 50 mg once daily of each [17]. Then HCTZ 12.5 mg was added in patients in whom systolic blood pressure remained ≥160 mmHg. In patients not titrated to HCTZ the mean systolic blood pressure reduction was 25.0 mmHg in the losartan group and 25.4 mmHg in the atenolol group. This effect seems to be greater than in our study but the studies are not completely comparable due to different inclusion criteria.

Usually, the dose of irbesartan 150–300 mg appears to be equivalent to 50–100 mg of losartan in the treatment of hypertension [18]. In a study of 24 weeks of duration [19] the normalisation of diastolic blood pressure was achieved in 72 % of patients treated with 75–150 mg of irbesartan daily and in 63 % of patients receiving atenolol 50–100 mg daily (n.s.). In another study of 48 weeks of duration systolic and diastolic blood pressure reductions were similar with 150 mg of irbesartan and with 50 mg of atenolol daily [18]. But the effect of irbesartan on left ventricular mass was significantly greater: a decrease of 47 % vs. 32 % [20]. In the LIFE study losartan lead to a significantly greater decrease of ECG-left ventricular hypertrophy than atenolol [9].

So, the antihypertensive efficacy of angiotensin II receptor antagonists appears not to be significantly different from that of beta-blockers, but the difference in favour of former treatments seems to exist in organ protection.

Knowing data arising from clinical studies with angiotensin II receptor antagonists in whom the placebo-like incidence of adverse events was reported, a low incidence of adverse events in patients treated with losartan in our study has been expected. No typical clinically significant adverse events were observed after metoprolol in our study and metoprolol demonstrated a similar safety profile than losartan. In other controlled clinical trials, losartan was better tolerated than other antihypertensive drugs as determined by the incidence of patients reporting any drug-related adverse experience [19]. The percentage of any drug-related adverse event in patients treated with losartan was 15.3 compared with 26.5 in patients treated with atenolol. In that was similar to safety of ACE inhibitors and felodipine ER and higher than the incidence of adverse events with HCTZ [15]. In our study the interruption due to adverse events in patients treated with losartan was 4.1 % compared with 2.3 % in meta-analysis of controlled clinical trials [19].

Conclusion

In this double-blind comparison, losartan 50–100 mg once daily exhibited substantial antihypertensive efficacy. It was comparable with metoprolol 50–100 mg twice daily. Both drugs were combined with low-dose HCTZ in patients in whom normal siDBP was not achieved after monotherapy. Both drugs showed similar safety profiles.

References:

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