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

Dobovisek J, Kanic V, Niegowska J, Rekic S, Soucek M, Spinar J

Homepage:
www.kup.at/jcbbc

Online Data Base Search for Authors and Keywords
Efficacy and Tolerability of Losartan in Patients with Essential Hypertension: a Multicentre, Double-Blind Comparison of Losartan with Metoprolol

J. Dobovišek1, J. Špinar2, J. Niegowska3, M. Souček4, V. Kanić5, S. Rekš6

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 (siDBP) 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 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 siDBP 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 (< 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.

Key words: essential hypertension, losartan, metoprolol.

A rtial hypertension is widely recognised as the most common cardiovascular disease in countries with western life-style. Hypertension is a potent risk factor for all major cardiovascular events, but the most for cerebrovascular accidents particularly in the elderly [1]. Cardiovascular morbidity and mortality may be reduced by the control of blood pressure but the extent of reduction depends on the magnitude of blood pressure lowering [2]. Blood pressure reduction achieved with beta-blockers and diuretics was the best-recorded intervention to date for prevention of cardiovascular morbidity and death in patients with hypertension. A significant reduction of the incidence of stroke (38 %), coronary artery disease (16 %), and cardiovascular mortality (21 %) was achieved with blood pressure lowering of average 9–10/5–6 mmHg over 5 years by use of diuretics and beta-blockers [3]. Later, comparable but not better results were obtained in trials with calcium antagonists and/or angiotensin-converting enzyme (ACE) inhibitors [2, 4–8].

In numerous comparative studies the recently introduced class of antihypertensive agents, angiotensin II receptor antagonists, has proven a comparable antihypertensive efficacy with other classes of antihypertensive drugs but much better cardiovascular and safety profile. Until now, in patients with high risk only losartan demonstrated better efficacy in reducing the composite cardiovascular endpoints and stroke [9]. So, LIFE study was the first comparative trial in which a newer antihypertensive drug exerted significantly better protection against overall cardiovascular morbidity and stroke than an older drug [9]. Earlier some studies with losartan [10, 11], valsartan [12], and irbesartan [13, 14] already suggested that in this respect angiotensin II receptor antagonists will not differ from proven drug classes. In hypertension, they have been compared more often with atenolol than with other beta-blockers. Angiotensin II receptor antagonists exerted similar antihypertensive efficacy but the incidence of adverse events was much lower than with atenolol [15–19].

The aim of this study was first to prove the antihypertensive efficacy of losartan in a double-blind study, and secondly, to compare the efficacy and safety of losartan with the cardio-selective beta-blocker metoprolol that has not been extensively compared with angiotensin II receptor antagonists in patients with non-complicated mild to moderate essential hypertension.

Methods

It was a multicentre, prospective, randomised, double-blind, parallel-group, clinical study, carried out at four medical centres in the Czech Republic (one), Poland (one), and Slovenia (two). 77 outpatients, male and female in the age of 18 to 75 years with essential hypertension were eligible. The main inclusion criteria were a sitting diastolic blood pressure (siDBP) of 95–114 mmHg and a sitting systolic blood pressure (siSBP) < 180 mmHg. The patients had to be angiotensin II receptor antagonist- or beta-blocker-naive. In patients who were already treated with other antihypertensive drugs in monotherapy, the control of blood pressure had to be under satisfactory. These drugs were withdrawn at the in-
Table 1. Demographic characteristics of each treatment group

<table>
<thead>
<tr>
<th>Mean values</th>
<th>A (n = 49)</th>
<th>B (n = 28)</th>
</tr>
</thead>
<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>
</tbody>
</table>

Table 2. Mean changes in siSBP and siDBP during the study (mmHg)

<table>
<thead>
<tr>
<th>Group</th>
<th>siSBP</th>
<th>siDBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 excluded from the statistical analysis. The data of one patient who left the study up to the time of withdrawal was 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 < 0.05, week 3: p < 0.12, week 6: p < 0.21, week 9: p < 0.28.

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.

### Discussion

For many years the treatment of hypertension has been hampered by frequent and untoward side effects of antihypertensive medication. For years the medical community has called for new agents that would be effective given once a day and, perhaps more importantly, exhibit no side effects. Over the last 20 years we have come closer achieving this goal; cases in point are the ACE inhibitors and long acting calcium antagonists. With the development of the new class of angiotensin II receptor antagonists, and their high affinity for the AT-1 receptor subtype, we have come much closer to the realisation of this goal. This pharmacological group has been already appointed as the first choice by recent WHO/ISH guidelines, but the official indication has remained side effects with other drug classes, for example cough provoked by ACE inhibitors [20, 21]. Data comparing endpoints like cough provoked by ACE inhibitors or long acting calcium antagonists. With the development of the new class of angiotensin II receptor antagonists, and their high affinity for the AT-1 receptor subtype, we have come much closer to the realisation of this goal. This pharmacological group has been already appointed as the first choice by recent WHO/ISH guidelines, but the official indication has remained side effects with other drug classes, for example cough provoked by ACE inhibitors [20, 21].

### Table 3: Assessment of treatment efficacy

<table>
<thead>
<tr>
<th>Group</th>
<th>Normalisation of BP* (n.s.) 1</th>
<th>Satisfactory BP* decrease (n.s.) 1</th>
<th>No response (n.s.) 1</th>
</tr>
</thead>
<tbody>
<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 mono- thesises 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 in the atenolol group. These effects seem to be greater than in our study but the studies are not fully 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 % [28]. 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 metropol in our study and metropol 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 26.3 in patients treated with atenolol. 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 metropol 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:

Mitteilungen aus der Redaktion

Besuchen Sie unsere zeitschriftenübergreifende Datenbank

- Bilddatenbank
- Artikeldatenbank
- Fallberichte

e-Journal-Abo
Beziehen Sie die elektronischen Ausgaben dieser Zeitschrift hier.
Die Lieferung umfasst 4–5 Ausgaben pro Jahr zzgl. allfälliger Sonderhefte.
Unsere e-Journale stehen als PDF-Datei zur Verfügung und sind auf den meisten der marktüblichen e-Book-Readern, Tablets sowie auf iPad funktionsfähig.

Bestellung e-Journal-Abo

Haftungsausschluss

Bitte beachten Sie auch diese Seiten:

* Impressum
* Disclaimers & Copyright
* Datenschutzerklärung