The Effects of Eprosartan Mesylate and Lercanidipine on Reducing Microalbuminuria in Patients with Nephropathy due to Type 2 Diabetes

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Abstract

In total, 57 patients (31 males and 26 females) with diabetic nephropathy were studied on a comparative basis to observe the renoprotective effectiveness of eprosartan mesylate and lercanidipine. Eprosartan mesylate revealed a higher nephroprotective effect compared with lercanidipine at comparable antihypertensive effects of equivalent doses of both these preparations.

Keywords: diabetic nephropathy, eprosartan mesylate, lercanidipine.

Introduction

Diabetic nephropathy (DN) is the most common cause of end-stage renal disease (ESRD) in the United States, Japan and Europe [1]. The treatments currently employed may slow down, although usually not arrest, progression toward ESRD [2]. As a result, all therapeutic strategies that assist in slowing down the progression towards advanced chronic kidney disease (ACKD) and the appearance of cardiovascular complications are very welcome.

As established by the current nephrology guidelines [3-4], the approach to diabetic patients with chronic kidney disease (CKD) must be multifactorial, with well-established objectives aimed at effectively reducing blood pressure (BP) and proteinuria, while controlling the other associated vascular risk factors, and pharmacologically blocking the renin-angiotensin system (RAS). Such a multifactorial approach enabled us to significantly reduce the macro/microangiopathic complications in diabetes [5].

Considering the vital role played by the intra-renal activation of the RAS in the pathophysiology of DN, identification of an effective method for blocking this pathway becomes very important to slow down the progression of the disease to advanced or terminal CKD [6].

Several therapeutic alternatives based on the pharmacological blockade of the RAS are used in the primary, secondary, and tertiary prevention of DN [7]. These alternatives include the use of angiotensin II receptor (AT1) blockers (ARB) [8-9].

Although these studies demonstrated the renoprotective benefits of this drug compared with placebos and other medicines such as amlodipine, this treatment poses a persistently high residual risk of renal function deterioration in these patients, and approximately 30% of patients under treatment experience a midterm progression towards ACKD [10].

Aggressive BP control to prevent the onset of nephropathy or its progression, if already present, is emphasized in the current guidelines [11]. As many classes of antihypertensive agents are available, utilizing them will control the drop in the glomerular filtration rate (GFR) and the subsequent development of ESRD [12].

The DEMAND study included 32,280 patients from 33 countries with previously diagnosed diabetes type II. Among them 39% of patients had microalbuminuria, whose prevalence was found to increase with age, duration of diabetes and the presence of hypertension [13].

Certainly, one of the key mechanisms of diabetic kidney disease is hypertension, frequently observed in diabetes mellitus type II patients, leading to the more rapid development of vascular complications [14]. Particularly, the MRFIT and PROCAM studies established that in type II diabetes the risk of cardiovascular disease is two times higher than in the general population [15].

As hypertension and microalbuminuria raised the degree of the initially increased risk of cardiovascular complications in diabetic patients, a proper control of blood pressure and albuminuria in these patients becomes crucial to improve the prognosis [16].

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the heart and kidneys is not yet fully understood.

Therefore, the aim of our study was to evaluate the hypotensive and renoprotective efficiency of eprosartan and lercanidipine in patients with diabetic nephropathy.

**Material and Methods**

Our study included a total of 57 patients (31 males and 26 females), including patients fulfilling the clinical criteria for diagnoses of DN. The mean age was 53.6 ± 6.1 years. The selection criteria for patients included the presence of hypertension [11]. We excluded patients with non-diabetic CKD, severe infectious or neoplastic disease before or during the study, chronic liver disease, pregnant women, estimated survival of less than 3 years, or patient refusal to participate. The study was 12 weeks in duration.

All patients were informed of the study objectives and provided informed consent for participation. After inclusion in the study, patients were started on a multifactorial treatment regimen designed to achieve the therapeutic targets proposed by the ADA [3].

All the patients received conventional therapy including correction of metabolic disorders, acid-base balance and antianemic drugs.

Patients treated with antihypertensive drugs regularly, for 5-7 days prior to treatment stopped taking them (during the “washout”). Before starting treatment, patients were randomized into two comparable groups. Group 1 patients (n=28) were allocated to the angiotensin receptor blocker II – eprosartan mesylate (Teveten) at a dose of 600 mg/day. Group 2 patients (n=29) received the calcium antagonist - lercanidipine (Lerkamen) at a dose of 10 mg/day. The control group consisted of 20 healthy volunteers, comparable with the major groups in age and sex.

Renal functions were estimated using sCr (in μmol using the modified Jaffe method) and the glomerular filtration rate (GFR) employing the abbreviated MDRD formula [186.3 x sCr\(^{-1.14}\) x age\(^{-0.20}\) x (0.742 for women) x (1.21 for African Americans)] [17]. In addition, the patients had urinary albumin level determined daily. For each patient the albumin/creatinine ratio (ACR) was determined in the morning urine sample as an index, with the high sensitivity and specificity reflecting the daily urinary albumin excretion [18].

At baseline and after 12 weeks, the patients underwent blood pressure monitoring (BPM) using the “Kardiotechnika-4000AD” (Inkart, St. Petersburg) device by the oscillometric method. Measurements were recorded every 15 minutes during the day and every 30 minutes at night. Estimates of the average systolic blood pressure (SBP), diastolic blood pressure (DBP), mean hemodynamic blood pressure (MBP) and degree of the night reduction of MBP were recorded [19].

We also measured kalemia (mEq/L), baseline glycaemia(mg/dL), glycosylated hemoglobin (HbA1c, %), haemogram, lipid profile, C-reactive protein (CRP), and uric acid (mg/dL). Characteristics of the patients are shown in Table 1.

Statistical data processing was performed using the software package Statistica 6 for Windows and the Excel package of Microsoft Excel 2007. Student’s unpaired and paired t-tests were used to compare two groups for data with normal distribution. The Wilcoxon signed-rank test was used to compare the differences between the two dependent groups (for non-parametric data). The value of p less than 0.05 was considered significant.

**Table 1.**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>1st group (n = 28)</th>
<th>2nd group (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>16/12</td>
<td>15/14</td>
</tr>
<tr>
<td>Age</td>
<td>54.8 ± 6.5</td>
<td>52.4 ± 5.6</td>
</tr>
<tr>
<td>Duration of diabetes, years</td>
<td>15.2±3.3</td>
<td>14.5±5.3</td>
</tr>
<tr>
<td>Duration of hypertension, years</td>
<td>12.1±4.4</td>
<td>11.6±3.7</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>10.2 ± 4.2</td>
<td>9.8 ± 4.7</td>
</tr>
<tr>
<td>Creatinine, mcg/L</td>
<td>161.3 ± 28.4</td>
<td>169.2 ± 27.6</td>
</tr>
<tr>
<td>GFR ml/min/1.73m²</td>
<td>44.7 ± 8.2</td>
<td>41.1 ± 9.4</td>
</tr>
<tr>
<td>Albuminuria, mg/g</td>
<td>382.3±32.4</td>
<td>389.6±35.6</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>32.4±5.8</td>
<td>31.9±6.3</td>
</tr>
<tr>
<td>Serum potassium, mEq/L</td>
<td>4.9 ± 0.8</td>
<td>4.6 ± 0.9</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>6.4±1.2</td>
<td>6.7±1.4</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>165.4±8.1</td>
<td>167.2±7.5</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>95.2±4.7</td>
<td>97.5±5.2</td>
</tr>
</tbody>
</table>

**Results and Discussion**

According to our study, eprosartan mesylate pronounced a significant hypotensive effect in patients with DN and stage I - II degree AH, to a greater degree than by the application of equivalent doses of lercanidipine. Thus, based on BP, in Group 1 patients after 12 weeks of treatment with eprosartan mesylate, the mean 24-hour SBP decreased by an average of 19.3 ± 1.6 mmHg (the mean SBP in the first group after 12 weeks of therapy was 144.5 ± 5.3 mmHg) (p<0.05); the reduction in the mean 24-hour DBP at 12 weeks was 8.5 ± 0.6 mmHg (the mean DBP – 87.6 ± 4.5) (p<0.05). In Group 2 patients treated with lercanidipine, the SBP decreased by 17.1 ± 1.4 mmHg (the mean SBP in the second group after 12 weeks of therapy was 148.7 ± 6.1 mmHg) (P <0.05); the reduction in the mean 24-hour DBP at 12 weeks was 7.6 ± 0.4 mmHg (the mean DBP – 89.8 ± 4.9) (p<0.05).

Thus, a significant decrease in the blood pressure was noted in both groups, with some more positive dynamics being observed in the group of patients treated with eprosartan compared with the treatment with equivalent doses of lercanidipine.

Based on the results of the quantitative determination of microalbuminuria (MAU) in the morning urine sample, we compared the renal protection efficacy of eprosartan and lercanidipine. At baseline, no statistically significant differences were recorded between the groups for urinary albumin excretion levels. After the 12-week prescribed eprosartan mesylate treatment in Group 1 patients, microalbuminuria was significantly reduced by 28.4% (the mean MAU in the first group after 12 weeks of therapy was 271.6 ± 21.5 mg/g). In Group 2 patients, after 12 weeks of treatment with lercanidipine the microalbuminuria level dropped by 15.2% (the mean MAU in the second group after 12 weeks of therapy was 323.3 ± 25.8 mg/g) (p < 0.05) (Table 2).
Table 2

The dynamics of BP and MAU during treatment

<table>
<thead>
<tr>
<th>Parameters</th>
<th>1st group (n = 28)</th>
<th>P</th>
<th>2nd group (n = 29)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>before</td>
<td>after</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>165.4 ± 8.1</td>
<td>144.5 ± 5.3</td>
<td>&lt;0.05</td>
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</tr>
<tr>
<td></td>
<td>167.2 ± 7.5</td>
<td>148.7 ± 6.1</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>95.2 ±4.7</td>
<td>87.6 ± 4.5</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>97.5 ± 5.2</td>
<td>89.8 ± 4.9</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>MAU, mg/g</td>
<td>382.3 ± 32.4</td>
<td>271.6 ±21.5</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>389.6 ± 35.6</td>
<td>323.3 ± 25.8</td>
<td>&lt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

Note: P – with initial data.

The study demonstrated no significant differences in the antihypertensive effectiveness of the drugs from the group of angiotensin II receptor blockers (eprosartan mesylate) and calcium antagonists (lercanidipine) in equivalent doses, although the renoprotective effects of eprosartan mesylate, according to our results were more obvious than that of lercanidipine.

The renoprotective effects of angiotensin II AT1 receptor blockade (ARB) in patients with DN appear to be primarily based on blocking the angiotensin II activity in the renal tissue, because this enzyme is very active in the renal cortex of diabetic patients, where we can detect the upregulation of the expression of renin and AT1 receptors [20].

Besides all the changes in intraglomerular hemodynamics (decrease in intraglomerular pressure), the anti-proteinuria effects of ARB appear to be mediated by the structural changes in the interstitial/mesangial and glomerular capillaries. The angiotensin II blockade improves the selectivity of the charge and size of the glomerular membrane pores, which in part is associated with the loss of nephrin in the podocytes of the glomerular capillaries, which in turn plays a leading role in the functioning of the glomerular filtration barrier [21]. Additionally, ARB appears to block the other effects mediated by angiotensin II, such as endothelial dysfunction, oxidative stress, inflammation and collagen production [22], which seems to be related to their anti-proteinuric effects. The benefits derived from blocking these pathophysiological mechanisms are also corroborated by the indicators of regression of renal damage that have been obtained in experimental animal studies using high ARB doses [23].

Conclusion

1. During the follow up period in our study, eprosartan mesylate showed a significant hypotensive effect in patients with DN and stage I-II degree of AH when compared with the baseline data, to a better degree to the results from the application of equivalent doses of lercanidipine.

2. In both patient groups, there was a significant reduction in the microalbuminuria; however, the renal protection effect was more obvious in the eprosartan group, although the differences in the dynamics of SBP and DBP in these groups were less expressed. This indicates a better expressed effect on renal protection by the eprosartan mesylate versus lercanidipine at comparable antihypertensive effects of equivalent doses of both these preparations.

References


18. www.kidney.org/professionals/KDOQI/guidelines_ckd/p5_lab_g5.htm


