Effects of Valsartan and Nebivolol Treatment on Blood Pressure Variability in Hypertensive Patients

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Abstract

Background
The exploration of Blood Pressure (BP) variability and of the influence of different antihypertensive drugs on BP variability may improve understanding of the mechanism involved in BP changes induced by drugs. We therefore evaluated the long-term effects of the angiotensin-receptor blocker Valsartan and of the ultraselective beta blocker Nebivolol.

Methods
A prospective study was conducted at the regional outpatient Diagnosis and Treatment Center from Cluj-Napoca, Romania. The study included newly diagnosed adult hypertensives of either sex. All patients underwent 24 hour ambulatory blood pressure monitoring (ABPM) and systolic and diastolic 24 hour blood pressure variability was measured. A total of 80 hypertensive patients were randomly assigned to receive 80 mg of Valsartan or 5 mg of Nebivolol. Patients were divided into two groups according to antihypertensive medication: group A included 42 hypertensive patients treated with Valsartan and group B included 38 hypertensive patients treated with Nebivolol.

Results
Both Valsartan and Nebivolol decreased 24h BP variability but long-term treatment with Valsartan proved to be more efficient in reducing SBP variability during the night time period. Valsartan reduces more the systolic BP variability during the night time period when compared to Nebivolol.

Conclusions:
Treatment with ARBs (Valsartan) and BBs (Nebivolol) efficiently reduced the BP variability during the day and night period of time as first line antihypertensive agents. Valsartan reduces more the systolic BP variability during the night time period when compared to Nebivolol. Antihypertensive treatment using long acting agents like an angiotensin receptor blocker or an ultraselective beta blocker could offer a better cardiovascular protection by reducing the BP variability.

Key Words
Hypertension, ABPM, blood pressure variability, Valsartan, Nebivolol

Background
Hypertension (HT) is the leading cause of cardiovascular disease worldwide [1] despite the development of many antihypertensive drugs. It is well known that blood pressure (BP) has a high variability within and between individuals and has been shown that BP variability increases with increasing blood pressure [2]. The exploration of BP variability and the influence of different antihypertensive drugs on BP variability may improve understanding of the mechanism involved in BP changes induced by drugs.

It is well known that antihypertensive drugs reduce cardiovascular risk, in different ways through different mechanism and to different extents but the exact impact of these drugs on BP variability remains unclear. The aim of the present study was to investigate the effects of the angiotensin receptor blocker (Valsartan) and of ultraselective beta blocker (Nebivolol) on BP variability after one year of treatment by using ABPM method.

Angiotensin receptor blockers (ARBs), through their unique blockade of the renin-angiotensin system, reduce morbidity and mortality which are associated with hypertension [3]. Their excellent tolerability, ability to reduce blood pressure rapidly and to control hypertension for 24-hours position them as an important choice in cardiovascular medications.

Beta-blockers represent a very heterogeneous class of antihypertensive drugs. The criticisms made to some atenolol-like beta-blockers may not necessarily apply to more recent compounds which are either more β1-
selective or exhibit some vasodilating activity like Nebivolol dose. Vasodilating beta-blockers exert a hemodynamic profile which is similar to that of ACE inhibitor and which diverges markedly from that of conventional beta-blockers [4]. Humoral factors like angiotensin, endothelin, nitric oxide may be responsible for BP fluctuations [5] and this is why this study tried to evaluate the effects of a widely used angiotensin receptor blocker (Valsartan) versus an ultraselective long-acting beta-blocker which acts in part via the endothelial L-arginine/nitric oxide pathway (Nebivolol) [6-10].

Methods

The present prospective clinical study was conducted at the regional outpatient Diagnosis and Treatment Center in Cluj-Napoca, Romania between January 2005 and August 2008. The study included consecutive eligible adult outpatients of either sex, newly diagnosed hypertensives with either office sitting systolic BP (SBP) of 140-179 mmHg or office diastolic blood pressure (DBP) of 90-109 mmHg. The hypertension status was defined according to the European 2007 ESC/ESH guidelines [1] and was measured by mercury sphygmomanometer in a sitting position in at least three separate casual measurements within the last month. All the patients with seated systolic blood pressure (SBP) >200 mmHg and known or suspected secondary hypertension and patients with clinical or laboratory evidence of cardiovascular, pulmonary, renal, hepatic disease, diabetic mellitus and those with intolerance to Valsartan or Nebivolol were excluded from the study.

Before taking part in the present study, all the patients gave their written informed consent. The study proposal was reviewed, approved and granted by the Research Ethics Review Boards of the Medicine and Pharmacy University from Cluj-Napoca, Romania.

A total of one hundred and five hypertensive patients completed the inclusion criteria and completed data on the doctor’s evaluation (clinical, laboratory and paraclinical evaluation) before the initiation of the antihypertensive treatment and after three, six and twelve months of treatment. All patients underwent 24 hour ambulatory blood pressure (ABPM) monitoring for systolic and diastolic blood pressure evaluation at the beginning of the study and during the follow up. Blood pressure variability (SDBP) has been assessed by calculation of the standard deviation of 24 hour systolic and diastolic arterial pressure. A blood pressure variability was considered increased if was ≥13/10mmHg for systolic BP/ diastolic BP over the day period and 11/9mmHg for systolic BP/ diastolic BP over the night period. Hypertensive patients were divided into two groups according to antihypertensive medication: group A included hypertensive patients treated with angiotensin receptor blocker- Valsartan and group B included hypertensive patients treated with ultraselective beta-blocker-Nebivolol. Single day doses of 80mg of Valsartan and 5mg of Nebivolol were initially used. For patients with uncontrolled BP values the doses were increased up to 160mg/day for Valsartan and 10mg/day for Nebivolol.

Statistical analysis

Descriptive statistics, including means, standard deviation (SD), ranges and percentages, were used to characterize the study subjects. Statistical differences between groups were assessed using the Student’s test on normally distributed independent samples and the Mann-Whitney U-test on non-normally distributed data. A p-value less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS 12.

Results

There were no statistically significant differences between the two groups of patients in demographic baseline characteristics. Baseline characteristics of the study population are reported in Table 1 bellow.

Table 1. Baseline Characteristics of the study population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A Valsartan (n=42)</th>
<th>Group B Nebivolol (n=38)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.76±14.2</td>
<td>56.65±13.45</td>
<td>ns.</td>
</tr>
<tr>
<td>Men/women (%)</td>
<td>47.6/52.4</td>
<td>47.4/52.6</td>
<td>ns.</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.5±4.6</td>
<td>30.3±3.6</td>
<td>ns.</td>
</tr>
<tr>
<td>Blood glucose level (mg/dl)</td>
<td>114±35.2</td>
<td>113±15.11</td>
<td>ns.</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>195±34</td>
<td>198±37</td>
<td>ns.</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>45±11</td>
<td>56±18</td>
<td>ns.</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>184±85</td>
<td>179±66</td>
<td>ns.</td>
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</tbody>
</table>
In both treatment groups after 12 months treatment of either Valsartan or Nebivolol, a statistically significant decrease of SBP variability during the day time was observed when compared to baseline values of SBP variability during the day in hypertensive patients. No statistically significant difference between groups of treatment in the decrease of the SBP variability during the day was observed (-12.59±2.24 mmHg group A vs. 11.71±1.73 mmHg group B, p=0.570).

After 12 months treatment SBP variability during the night time significantly decreased when compared to baseline values of SBP variability during the night time in hypertensive patients in both treatment groups. The decrease of the SBP variability during the night was higher in group A-treated with Valsartan when compared to group B-treated with Nebivolol (-10.35±3.01 mmHg vs. 6.27±4.26 mmHg, p=0.349).

<table>
<thead>
<tr>
<th></th>
<th>Group A-Valsartan</th>
<th>Group B-Nebivolol</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>After 12 months treatment</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ECG variability/day (mmHg)</td>
<td>172.76±12.7</td>
<td>173.58±14.23</td>
<td>ns</td>
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<tr>
<td></td>
<td>106.86±13.92</td>
<td>107.37±16.63</td>
<td>ns</td>
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<tr>
<td>ECG variability/night (mmHg)</td>
<td>26.17±8.61</td>
<td>26.13±7.48</td>
<td>ns</td>
</tr>
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<td></td>
<td>17.83±6.02</td>
<td>14.13±8.18</td>
<td>ns</td>
</tr>
<tr>
<td>ECG variability/day (mmHg)</td>
<td>20.05±7.37</td>
<td>18.52±5.20</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>14.21±5.58</td>
<td>16.31±3.83</td>
<td>ns</td>
</tr>
</tbody>
</table>

Figure 1. The evolution of the SBP variability/day after 12 months treatment

Figure 2. The evolution of the SBP variability/night after 12 months treatment

In both groups after 12 months of treatment with either Valsartan or Nebivolol, a statistically significant decrease of DBP variability during the day time was observed when compared to baseline values of DBP variability during the day at hypertensive patients. The decrease of DBP variability during the day was higher in group A-treated with Valsartan but without a statistically significant difference between groups of treatment (-10.73±2.91 mmHg in group A-treated with Valsartan vs. 7.97±2.15 mmHg, in group B treated with Nebivolol, p=0.555).

After 12 months of treatment, DBP variability during the night time showed a statistically significant decrease when compared to baseline values of hypertensive patients in both treatment groups. The decrease of DBP variability during the night wasn’t statistically significant different between group A-treated with Valsartan when compared to group B-treated with Nebivolol (-8.31±2.95 mmHg in group A-treated with Valsartan vs. 8.07±5.26 mmHg in group B – treated with Nebivolol, p=0.793).

Figure 3. The evolution of the DBP variability/day after 12 months treatment
Angiotensin receptor blockers (ARBs) and calcium channel blockers remain first choice in the treatment of primary hypertension [26] and optimal ARB monotherapy can achieve recommended BP goals in a significant proportion of hypertensive patients [27]. Also, beta blockers are among the classes of drugs recommended as first-line therapy for the treatment of hypertension by the US JNC 7 guidelines [28, 29] and also according to the European guidelines beta-blockers remain a first line choice for the treatment of hypertension [1].

In accordance with these recommendations in this study we tried to evaluate the effects of ARB vs. BB on BP variability by using the ABPM method in hypertensive patients. Both groups of hypertensive patients revealed a higher SBP and DBP variability during the night and day period at baseline. After 12 months of antihypertensive treatment with Valsartan or Nebivolol the systolic and diastolic BP variability during the day or night period, was significantly reduced from baseline values.

This study revealed a higher difference in the reduction of SBP variability during night between the Valsartan treatment group and Nebivolol treatment group of hypertensive patients. The 12 months treatment with Valsartan reduced more the SBP variability/night compared to Nebivolol treatment. A recent study [30] showed that SBP variability could be an independent predictor for cardiovascular events in untreated hypertensive patients. Considering this, Valsartan could offer better cardiovascular protection compared to Nebivolol.

Conclusion

Both treatment with ARBs (Valsartan) and BBs (Nebivolol) efficiently reduced the BP variability during the day and night period of time as first line antihypertensive agents. Ultraselective beta blocker–Nebivolol proved the efficacy in controlling the BP as a first line agent. Angiotensin receptor blocker -Valsartan reduces more the systolic BP variability during the night time period when compared to beta-blocker- Nebivolol. Antihypertensive treatment using long acting agents like an angiotensin receptor blocker or an ultraselective beta blocker could offer a better cardiovascular protection by reducing the BP variability.

References


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SN and LL were involved in the data collection as well as in its analysis. SB was involved in statistical analysis.

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CONFLICTS OF INTEREST
The authors declare that they have no competing interests