Nebivolol Reduces Symptoms of Cardiac Arrhythmias in Patients with Arterial Hypertension: An Observational Pilot Study

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Betablockers are widely recommended in the treatment of arterial hypertension. Many clinical trials have investigated these drugs under various aspects of anti-hypertensive action and outcome. Despite their pharmacology being well-understood, the exact mechanism by which their anti-hypertensive action is unfolded remains an open question.

Nebivolol is a rather new third-generation betablocker with very pronounced cardioselectivity and additional features such as NO-dependent vasodilation. It has been used successfully in the treatment of patients with arterial hypertension and congestive heart failure. Betablockers, in fact, have long been regarded as effective agents for supra-ventricular and ventricular arrhythmias. Betablockers as a class show multiple anti-arrhythmic mechanisms such as various membrane-stabilising effects and they limit spontaneous depolarisation. Nebivolol, too, exhibits a remarkable anti-arrhythmic potential. However, there have been few attempts to explore and use it therapeutically. In this observational pilot study, we assess the anti-hypertensive effect of nebivolol in patients treated for arterial hypertension.

In 62 subjects, we found that after $67 \pm 4$ (± SEM) days of treatment, systolic blood pressure was reduced from $154 \pm 3$ mmHg to $140 \pm 3$ mmHg and diastolic pressure was reduced from $86 \pm 2$ mmHg to $79 \pm 2$ mmHg. Besides, we studied the effect of nebivolol upon arrhythmia-related symptoms in hypertensive patients and found that palpitations present in 81% of all patients at the beginning of the study were seen in only 13% of all participants after 67 days of treatment. Similar findings were made concerning symptoms of tachyarrhythmias: 47% at the beginning, 3% of all patients at the last visit. Despite the limitations of this study being non-randomised and observational, we conclude that nebivolol exerts a satisfactory anti-hypertensive effect and helps to reduce symptoms usually related to arrhythmias. This special feature of nebivolol may render the drug particularly helpful in patients with arterial hypertension complaining about symptoms related to arrhythmias. 

Key words: nebivolol, arrhythmia, hypertension

Material and Methods

This is an observational pilot study in patients who received nebivolol as an anti-hypertensive treatment. Sixty-three patients were prospectively included between January and September 2006. The patients had mild to moderate hypertension at the time of admission. Nebivolol treatment started at a dose of 2.5, 5 or 7.5 mg/day either as a single dose or divided into two doses. Possible contraindications for betablocker treatment were carefully assessed and patients with such contraindications were excluded from the study. Drug-related adverse events and clinical symptoms were recorded at each visit for all patients. The observation followed a simple protocol. The reasons for the decision to treat with nebivolol were recorded (e.g., ineffectiveness of another medication, side effects encountered with other drugs, first-line therapy according to guidelines and others). The demographic data of the patients studied can be taken from Table 1.

At the first visit, in all patients ECG, blood pressure and heart rate were taken, optionally a 24-h-ECG. Patients were
Table 1. Baseline data of patients studied.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (m/f)</td>
<td>25/37</td>
<td>40/60</td>
</tr>
<tr>
<td>Age (years)</td>
<td>66.7 ± 1.6</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77.0 ± 1.8</td>
<td></td>
</tr>
<tr>
<td>Size (cm)</td>
<td>168.9 ± 1.1</td>
<td></td>
</tr>
<tr>
<td>Hypertension (years)</td>
<td>6.7 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>11</td>
<td>18%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>39</td>
<td>63%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14</td>
<td>23%</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>32</td>
<td>52%</td>
</tr>
<tr>
<td>CHF</td>
<td>10</td>
<td>16%</td>
</tr>
<tr>
<td>Pretreated hypertension</td>
<td>49</td>
<td>79%</td>
</tr>
</tbody>
</table>

Table 2. Cardiovascular risk factors and comorbidities in 62 patients participating in the study.

<table>
<thead>
<tr>
<th>Risk factors and comorbidities</th>
<th>n = 62</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker</td>
<td>11</td>
<td>18%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>39</td>
<td>63%</td>
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</tr>
<tr>
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<td>32</td>
<td>52%</td>
</tr>
<tr>
<td>CHF</td>
<td>10</td>
<td>16%</td>
</tr>
</tbody>
</table>

Results

Baseline data: sixty-three patients were included (one dropout) and 62 patients completed the study (25 males, 37 females). The mean age of the patients was 66.7 ± 1.6 years and their mean weight amounted to 77.0 ± 1.8 kg. The patients’ mean starting dose was 4.4 ± 0.2 (± SEM) mg/day nebivolol, and was increased to 4.7 ± 0.3 mg/day at the third visit. Table 2 shows cardiovascular risk factors and comorbidities.

Discussion

This observational study on patients with arterial hypertension who received nebivolol as an anti-hypertensive drug was intended to investigate the anti-hypertensive efficacy of nebivolol as well as the drug’s safety. Furthermore, it was
designed as a pilot observation investigating a possible anti-arrhythmic potential of nebivolol. Arrhythmias of all kinds are commonly seen in patients with arterial hypertension and patients regularly complain about their symptoms, in particular in long-lasting arterial hypertension. Late stages of hypertension often lead to atrial fibrillation, harbouring the danger of embolic complications. Arrhythmias are usually confined to supra-ventricular and ventricular ectopies and occur irregularly. Mostly, during the short time frame of an ECG, no arrhythmias can be detected and 24-h-ECG offers another, somewhat longer time frame. Both do ultimately not suffice in properly assessing arrhythmias qualitatively as well as quantitatively. Hence, symptomatic exploration is generally more helpful than ECG in judging the success of anti-arrhythmic treatment.

Betablockers are widely recommended in the treatment of arterial hypertension [1-3]. Many clinical trials have investigated these drugs under various aspects of antihypertensive action and outcome [4-9]. Despite their pharmacology being well understood, the exact mechanism by which their anti-hypertensive action is unfolded remains an open question [15]. However, decreased cardiac output and a delayed reduction in peripheral vascular resistance constitute key mechanisms in this context. Some betablockers show additional properties alpha1-blocking effects [16] or features NO-dependent vasodilation [17-20].

Betablockers are effectively used in the treatment of supra-ventricular and ventricular arrhythmias. Treatment of the latter by metoprolol has been shown effective as an electrophysiologically guided anti-arrhythmic therapy [22] and the CAST study showed that betablockade reduces all-cause mortality and arrhythmia-related deaths [23]. Anti-arrhythmic actions such as various membrane-stabilising effects and the limitation of spontaneous depolarisation are typical class-associated effects of these drugs. A class-III-effect prolonging action potential duration is seen in sotalol only. Nebivolol, too, exhibits a remarkable anti-arrhythmic potential [24-27].

In this observational pilot study, we assessed the anti-hypertensive effect of nebivolol in patients treated for arterial hypertension. We found at the first visit that in patients with arterial hypertension, nebivolol was a highly effective anti-hypertensive drug, regardless of whether used as a first-line therapy or as an add-on-therapy. We also found a mild decrease in heart rates between the first and the second as well as the third visits, however, bradycardia was not observed. These results are in accordance with earlier studies on the effect of betablockers on arterial hypertension. Besides, we looked at the effect of nebivolol on symptoms of arrhythmias in hypertensive patients before and after receiving nebivolol. Palpitations, in particular, drastically improved and so did all other symptoms that generally can be related to arrhythmias. It is, however, difficult to judge whether the reduction of palpitations is a plain anti-arrhythmic effect directly exerted by the drug or if the reduction of arterial blood pressure per se also leads to a reduction of these symptoms: this could, on one hand, result from reduced pressure alone and be due to a decrease in the reduced pulse pressure of each pulse wave resulting itself from increased post-extrasystolic filling time despite the persistence of arrhythmias. On the other hand, pro-arrhythmogenic mechanisms directly related to arterial hypertension (e.g., shear stress etc.) are of course reduced once arterial blood pressure is reduced.

Furthermore, we have to regard the limitations of the study: this was a non-randomised, prospective observational study entailing the known disadvantages resulting from the lack of a randomised control group. However, it was intended to investigate whether or not further well-designed and hence more costly studies on the anti-arrhythmic effects of nebivolol could be useful, in particular, since there is currently no such indication for this drug despite anti-arrhythmic effects being class effects of betablockers. The superior affinity to cardiac betareceptors over all other betablockers would also argue for this drug being an interesting anti-arrhythmic agent. Randomisation to placebo would, in principle, be possible in order to address the above questions in hypertensives since hypertension in the studied subjects was mild and the observational period short. Furthermore, arrhythmias were not malignant. Alternatively, a two-armed
randomisation study using another, less cardio-selective beta-blocker in patients with arrhythmias would be easy to perform since we deal with a class effect of well-established drugs. Such a study would certainly provide evidence for nebivolol being an antiarrhythmic drug superior or equal to others.

In conclusion, the present study showed that nebivolol is able to effectively reduce arterial blood pressure in patients with mild to moderate arterial hypertension. Furthermore, it has provided evidence that symptoms usually related to arrhythmias can be successfully improved with nebivolol. Further studies are, however, needed in order to provide sufficient evidence for the antiarrhythmic effects of nebivolol. The present study, however, is suggestive of such an antiarrhythmic action and supports the idea that further investigational work on the subject may provide important data.

References:

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