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Krause & Pachernegg GmbH · VERLAG für MEDIZIN und WIRTSCHAFT · A-3003 Gablitz/Austria

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

S. Gasser, K. Gaugl, E. Kraigher-Krainer, S. Zunko, R. Gasser

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 ± 4 (± SEM) days of treatment, systolic blood pressure was reduced from 154 ± 3 mmHg to 140 ± 3 mmHg and diastolic pressure was reduced from 86 ± 2 mmHg to 79 ± 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 antihypertensive 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. ***J Clin Basic Cardiol 2006; 9 (online): 27–30.***

Key words: *nebivolol, arrhythmia, hypertension*

Betablockers are first-line treatment of arterial hypertension along with diuretics according to the Joint National Committee [1] and the British Hypertension Society [2], and are regarded by the WHO/ISH [3] as a first-line alternative with various antihypertensives. Physicians have now more than four decades of experience with antihypertensive treatment using betablockers [4]. There is a multitude of clinical trials which have investigated these drugs under various aspects of antihypertensive action and outcome [4–9]. Despite being commonly used drugs, the exact mechanism by which their antihypertensive action is unfolded remains an open question [10–15]. However, decreased cardiac output and a delayed reduction in peripheral vascular resistance constitute key mechanisms in this context. Some betablockers, like carvedilol, entail an additional alpha$_1$-blocking effect and hence are very potent antihypertensives [16]. Nebivolol is a rather new third-generation betablocker with very pronounced cardioselectivity and additional features such as NO-dependent vasodilation [17–20]. It has been used successfully in the treatment of patients with arterial hypertension and congestive heart failure [21] and is registered in Austria for this purpose.

Many patients with arterial hypertension suffer from (mostly) supraventricular arrhythmias, and in later stages of arterial hypertension, atrial fibrillation is not uncommon. While supraventricular arrhythmias in general are harmless, in most cases there is no need to treat them. However, many patients feel disturbed by the classical symptoms of arrhythmias such as palpitations or dizziness and ask for specific treatment. Using betablockers in these patients is generally successful in controlling both arterial hypertension and symptoms of arrhythmias.

Betablockers, in fact, have long been regarded as effective agents for supraventricular and, for more than a decade, for ventricular arrhythmias. Treatment of the latter by metoprolol has been shown effective as an electrophysiologically guided antiarrhythmic therapy [22] and the CAST study showed that betablockade reduces all-cause mortality and arrhythmia-related deaths [23]. Betablockers as a class show multiple antiarrhythmic mechanisms such as various membrane-stabilising effects and they limit spontaneous depolarisation. A class-III-effect prolonging action potential duration is seen in sotalol only. Nebivolol, too, exhibits a remarkable antiarrhythmic potential. However, there have been few attempts to explore and use it therapeutically as an antiarrhythmic agent [24–27]. In this observational pilot study, we assess the antihypertensive effect of nebivolol in patients treated for arterial hypertension. Besides, we look at the incidence of arrhythmia symptoms in hypertensive patients before and after receiving nebivolol as an antihypertensive drug.

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

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From the Department of Cardiology, University Dept. of Internal Medicine, Medical University of Graz, Austria.
Correspondence to: Prof. Robert Gasser, MD PhD, Dept. of Cardiology, University Department of Internal Medicine, Auenbruggerplatz 15, A-8036 Graz, Austria; e-mail: robert.gasser@meduni-graz.at

Table 1. Baseline data of patients studied.

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

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

Risk factors and comorbidities	n = 62	100%
Smoker	11	18 %
Hyperlipidemia	39	63 %
Diabetes	14	23 %
Smoker	11	18 %
CHD	32	52 %
CHF	10	16 %

asked about symptoms of arrhythmias such as palpitations, dizziness or syncope. Furthermore, their cardiovascular risk profiles were carefully assessed and general questions concerning cardiovascular disease were asked, such as cold feeling in the limbs, shortness of breath, decreased quality of life. Arrhythmias, when evident in ECG or 24-h-ECG, were classified using the LOWN classification. The second visit followed approximately a week later, again arterial blood pressure as well as heart rate were assessed and the dose of nebivolol was adjusted, if necessary. Patients were asked about symptoms of arrhythmias as well as about their general well-being. At a third visit after approximately 3 months, both blood pressure as well as heart rate were studied and patients again were asked about symptoms of arrhythmias. Furthermore, ECG and an optional 24-h-ECG were carried out and arrhythmias were again classified according to the LOWN classification, if possible. Furthermore, general questions concerning cardiovascular disease were asked, such as cold feeling in the limbs, shortness of breath or decreased quality of life. Arrhythmias, when evident in ECG or 24-h-ECG, were classified using the LOWN classification. At the end of each observation, the physician was asked about his personal impression of the anti-hypertensive and anti-arrhythmic properties of the drug and whether or not treatment was discontinued and if so, detailed reasons had to be given. We also monitored the smoker status of the patients throughout the study and any changes.

Statistics: continuous variables in each group were expressed as mean values ± standard error of mean. The differences in blood pressure between the values at each visit were tested using the paired student T test, a difference considered significant if $p < 0.5$.

Results

Baseline data: sixty-three patients were included (one drop-out) 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'

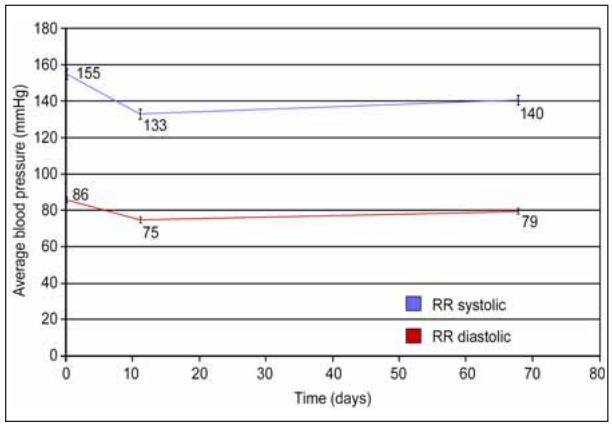

Figure 1. Arterial blood pressure over time in patients treated with nebivolol for arterial hypertension (n = 62; ± SEM)

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. Treatment was given as an add-on therapy in 50 patients (84 %) or as a monotherapy (16 %).

From the first visit, arterial blood pressure decreased from initially 154.7 ± 2.8 mmHg to 132.6 ± 2.8 mmHg (± SEM; $p < 7.02$; E-13) after 11.7 ± 1.7 days, and stabilised at the third visit at 140.4 ± 2.5 mmHg after 67.1 ± 4.0 days. Compared to initial measurements, the reduction was statistically significant (± SEM; $p < 1.1$; E-5). Diastolic blood pressure was elevated at the first visit at 85.7 ± 1.6 mmHg, decreased at the second visit to 74.7 ± 1.6 mmHg (± SEM; $p < 5.9$; E-12) and remained stable at the third visit at 79.2 ± 1.6 mmHg (± SEM; $p < 0.00015$) when compared to initial values. Figure 1 shows a graphic display of arterial blood pressure in patients treated with nebivolol for hypertension.

Compliance of all patients was good and the antihypertensive action of nebivolol was marked with 2.2 ± 0.1 by the physicians involved (scale from 1 [= best] to 5). The mean heart rate of patients at the first visit was 77.4 ± 1.8 bpm, at the second visit 67.5 ± 1.3 bpm and 69.4 ± 1.5 bpm at the third visit, there was a significant fall in heart rate between the first and the second visit ($p < 8.4$; E-9), however, between the second and the third visit the heart rate did not change significantly anymore ($p < 0.14$). Values can also be taken from Table 3 and Figure 2.

Nebivolol reduced symptoms of arrhythmia in hypertensive patients (Tab. 4; Fig. 3): at the first visit, 50 (81 %) of all patients showed palpitations, at the second visit 12 (19 %) showed palpitations and at the third visit 8 (13 %) reported palpitations. Symptoms of tachycardia were reported in 29 (47 %) of the patients at the first visit, 2 (3 %) had symptoms of tachycardia at the second visit and 2 (3 %) at the third. Similarly, dizziness was seen in 35 (56 %) of the patients at the first visit, in 15 (24 %) at the second visit and in 10 (16 %) at the third. History of syncope was seen in the recent history of 6 (10 %) patients and re-occurred in 2 (3 %) of those, four remained without syncope after the administration of nebivolol.

Adverse effects were minimal during the observation period. No noteworthy adverse effects were seen.

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

Table 3. Effect of nebivolol on blood pressure, heart rate and atrial fibrillation

	Visit 1	Visit 2	Visit 3
Days	0	11.2 ± 1.7	67.9 ± 4.1
RR syst	154.7 ± 2.8	132.6 ± 2.8	140.4 ± 2.5
RR diast	85.7 ± 1.6	74.7 ± 1.6	79.2 ± 1.6
Heart Rate bpm	77.4 ± 1.8	67.5 ± 1.3	69.4 ± 1.5
Atrial fibrillation	15 (24 %)	6 (10 %)	5 (8 %)
Nebivolol mg/d	4.4 ± 0.2	4.5 ± 0.3	4.7 ± 0.3

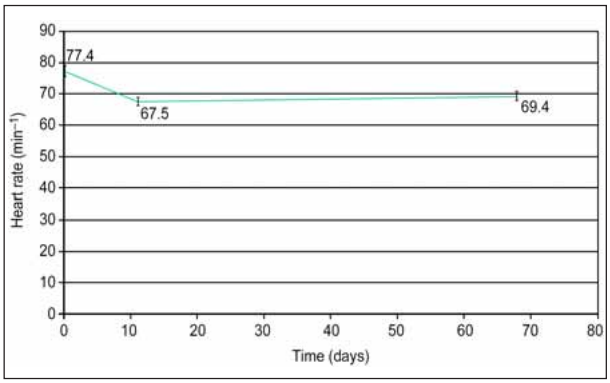

Figure 2. Development of heart rate during treatment with nebivolol in patients with arrterial hypertension

Table 4. Effect of nebivolol upon symptoms of cardiac arrhythmias in patients with hypertension

	Visit 1	Visit 2	Visit 3
Palpitations	50 (81 %)	12 (19 %)	8 (13 %)
Tachycardia	29 (47 %)	2 (3 %)	2 (3 %)
Dizzyness	35 (56 %)	15 (24 %)	10 (16 %)
Syncope	6 (10 %)	2 (3 %)	2 (3 %)

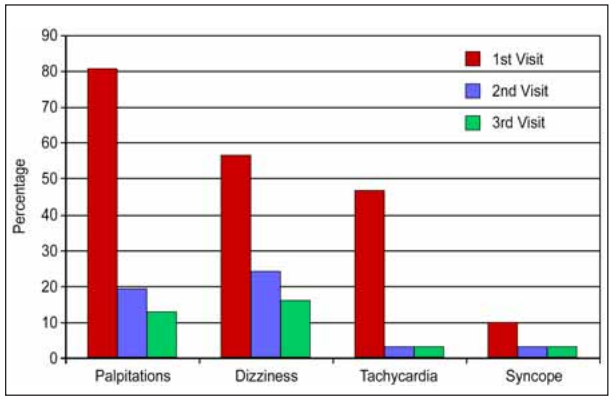

Figure 3. Typical symptoms occurring with cardiac arrhythmias such as palpitations, dizziness, tachycardia and syncope improved under treatment with nebivolol

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 antihypertensive 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 as additional properties alpha$_1$-blocking effects [16] or features such as 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 betablocker 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.

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