

Effect of bedtime dosing of barnidipine hydrochloride in non-dipper hypertensive patients with obstructive sleep apnoea not treated with continuous positive airway pressure

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Abstract. – **OBJECTIVE:** Obstructive sleep apnoea (OSA) is considered a cause of secondary hypertension. About 50% of patients with OSA show elevated blood pressure levels. Non-dipper pattern (blunted or absent nocturnal decrease of blood pressure) is frequently observed in patients with OSA and is associated with increased cerebral, cardiovascular and renal events. The aim of this study was to observe the effect of barnidipine calcium channel blocker on these patients.

PATIENTS AND METHODS: Forty-one patients (mean age 69 ± 17 years, 18 females) with previously diagnosed OSA (by reduced channel home-based polysomnography) who were not being treated with continuous positive airway pressure (CPAP) because of contraindications or because of patient intolerance or rejection were evaluated. Non-dipper status was defined as the presence of a nighttime fall in systolic blood pressure (BP) which was $< 10\%$ that of daytime systolic BP as observed in a previous ambulatory blood pressure (ABP) monitoring. OSA was defined according to the presence of 5 or more episodes per hour of apnoea, hypopnoea or arousal due to respiratory effort.

The reproducibility of non-dipping status was confirmed through a second 24-h ABP monitoring performed at baseline. On top of the previous stable treatment regimen (which excluded calcium-channel blockers), a 10 mg dosing of barnidipine hydrochloride at bedtime was added to all subjects during a 12-week period.

RESULTS: Among the 41 non-dipper patients, 32 (78%) showed complete normalization of circadian rhythm. Add-on treatment with barnidipine was generally well tolerated.

CONCLUSIONS: Bedtime dosing of the calcium-channel blocker (CCB) barnidipine significantly reduced mean nighttime systolic and diastolic ABP in hypertensive patients presenting with non-dipper pattern and OSA – not on CPAP treatment. Moreover, it restored the previously altered circadian rhythm in the majority of them.

Key Words:

Barnidipine hydrochloride, Non-dipper pattern, Obstructive sleep apnoea, ABP monitoring.

Abbreviations

OSA = obstructive sleep apnoea; CPAP = continuous positive airway pressure; ABP = Ambulatory blood pressure; CCB = calcium channel blocker.

Introduction

Obstructive sleep apnoea (OSA) syndrome is a common condition affecting around 5% of the general population. It is consistently more prevalent in males with a male to female ratio of up to 8:1¹⁻².

The association between OSA and hypertension is well documented. Scientific data and clinical awareness regarding the interaction between OSA and hypertension are continuously increasing³. Approximately 50% of patients with OSA are hypertensive, and an estimated 40% of hypertensive patients have OSA⁴⁻⁶.

The prevalence of hypertension in OSA syndrome appears to be influenced by the severity of the breathing disorder. In patients with OSA an augmented sympathetic activity at rest, which persists not only during the apneas, has been observed. The increased sympathetic tone affects vascular resistance, cardiac output, and renin-angiotensin-aldosterone system activity. These changes play an essential role in the genesis of the organism's acute and chronic responses, and partly explain the pathophysiological mechanisms behind the chronic cardiovascular consequences related to OSAS, and in particular hypertension⁷⁻¹¹.

One of the characteristics of hypertensive patients with OSA is the blunted nocturnal decline in blood pressure (non-dipper pattern)^{3,12-14}. The specific relationship between non-dipper status and the risk of cerebral, cardiovascular and renal events is well established¹⁵⁻¹⁸. Therefore, the normalization of the circadian BP rhythm should be

considered an important goal of antihypertensive treatment.

A better lifestyle and dietary intervention should always be considered as the first step in the treatment of patients with OSA.

Overweight/obesity and a sedentary lifestyle are very common in such patients, as well as alcohol and tobacco consumption. Thus, body weight reduction, increased physical activity, smoking cessation and alcohol intake reduction should be suggested to all apnoeic subjects, independently of the presence of hypertension or other cardiovascular risk factors.

Other measures such as avoiding the supine position (lying on one's back) during sleep in the event of positional OSA, the use of mandibular advancement prosthesis (oral appliance) or, more rarely, surgery, have shown some positive effects in the management of OSA syndrome. However, in terms of specific therapies, continuous positive airway pressure (CPAP) remains the reference treatment for OSA.

Prospective cohort studies in patients with OSA syndrome have shown that treatment with CPAP significantly reduces the risk of cardiovascular events in patients with severe OSA¹⁹⁻²².

The effects of CPAP on BP have also been investigated, but the results of these studies are sometimes divergent and not conclusive. Some studies show a beneficial effect with significant systolic and diastolic BP reduction, while others show only a minor and non-significant reduction in BP²³⁻²⁹.

Only a few studies have analyzed the variations in dipper/non-dipper profiles with CPAP treatment and their results are not homogeneous²⁴⁻²⁷.

One of the concerns regarding CPAP treatment is adherence to the therapy. When adherence is defined as the use of CPAP for more than 4 hours per night, 46 to 83% of apnoeic patients have been reported as being non-adherent to treatment^{30,31}. Furthermore, it is a common clinical observation that the proposal of CPAP treatment is often rejected by many patients.

Regarding antihypertensive therapy, there is no obvious antihypertensive drug class that has repeatedly demonstrated superior efficacy in OSA patients with hypertension³².

However, the altered circadian rhythm that may characterise apnoeic hypertensive individuals, suggests that, the increased antihypertensive efficacy during nighttime could, at least theoretically, reverse the non-dipper pattern.

The aim of our study was to evaluate the effect of an add-on bedtime dosing of barnidipine on the circadian rhythm of BP in non-dipper hypertensive patients with OSA, who were not being treated with CPAP because of contraindications or patient intolerance or rejection.

Barnidipine hydrochloride is a safe, effective and well tolerated dihydropyridine calcium channel blocker, available in a modified-release formulation, which has a gradual onset of action and a sustained effect. Its antihypertensive action is mainly related to the reduction of peripheral vascular resistance³³⁻³⁶.

Patients and Methods

In a post-hoc analysis of a larger observational study³⁷⁻³⁸, in which we evaluated the response to the add-on treatment with barnidipine in non-dipper hypertensive patients, we have analyzed the effect of this calcium-channel blocker in a subset of patients with OSA. We considered 41 pharmacologically treated non-dipper hypertensive patients (18 females, mean age 69 ± 17 years) with OSA and who were not being treated with CPAP.

The evaluation of respiratory disorder was carried out by using a reduced channel home-based device (Embletta X 100, Broomfield, CO, USA). Overnight Polysmnography was evaluated by an experienced pulmonologist.

OSA was defined as the detection of 5 or more symptomatic events per hour (apnoea, hypopnoea or arousal due to breathing effort) or 15 or more events per hour in the absence of reported symptoms. Patients with a central apnoea index above 5 were excluded.

Non-dipper pattern was defined as the presence of a nighttime fall in ambulatory systolic blood pressure which constituted less than 10 % of daytime systolic blood pressure at baseline. Patients with symptomatic hypotension during the entire ABPM recording were excluded.

ABP monitoring was performed by using a non-invasive, portable validated recorder (SpaceLabs Inc. model 90207-30). Patients wore the device for 24 hours on all days except holidays and the recorder was set to take readings every 15 minutes during daytime (7 am to 11 pm) and every 30 minutes during nighttime (11 pm to 7 am).

The analysis of ABP monitorings, the evaluation of daytime nighttime and circadian rhythm and the night-to-day BP ratio were performed according to the 2013 ESH-ESC guidelines³⁹.

ABP recording was considered complete when 80% or more of the scheduled readings were available, with at least 2 valid readings per hour.

Antihypertensive treatment included angiotensin-converting-enzyme inhibitors, early-distal-tubule diuretics, angiotensin-receptor blockers and beta-adrenergic blockers, while patients being treated with calcium-channel blockers of any kind were excluded from the study. Before enrollment, all patients had been receiving stable antihypertensive treatment during the previous 2 months at least, without changes in dosage or type of drug.

All patients received a 10 mg dosing of barnidipine hydrochloride, to be taken at bedtime (10-11 pm), in addition to their previous treatment regimen.

A 24-hour ABP monitoring was repeated after 12 weeks of treatment.

The Ethical Committee approved the study, and all participants gave their informed written consent.

Statistical Analysis

The primary outcome variable was the change in nighttime mean systolic and diastolic ABP. The secondary outcome variable was the normalization of the non-dipper pattern.

Statistical software (SPSS version 18.0 for Windows; Chicago, IL, USA) was used for data processing and statistical analysis. Continuous variables are expressed as a mean $\pm$ SD, and qualitative variables are expressed as a percentage.

Changes in ABP systolic and diastolic values (mean 24-h BP, daytime BP and nighttime BP) after intervention were compared to baseline values by using the Student's *t*-test for paired samples (two-sided, alpha level $p < 0.05$). To compare two qualitative variables with repeated measures, the non-parametric test of Wilcoxon for paired samples was used.

The sample size was calculated to detect a change of 4 mm Hg in nighttime systolic ABP compared to baseline.

Results

The study was completed in forty-one individuals⁴¹ with moderate-to-severe OSA, as well as hypertension with confirmed non-dipper pattern.

All patients had mean daytime ABP values above 135/85 mmHg and mean nighttime ABP values above 120/70 mmHg. In all patients, the nocturnal systolic mean ABP fall resulted in less than 10% with respect to daytime mean values (night-day BP ratio > 0.9).

Among the 41 patients, 9 of them showed a riser pattern, with BP increasing rather than dipping during the night.

At baseline, diurnal and nocturnal ABP averaged $139.1 \pm 9.6/87.4 \pm 7.7$ and $135.8 \pm 9.9/85.1 \pm 8.1$ mmHg, respectively.

After an add-on treatment with barnidipine at bedtime, a BP decrease was observed in both periods.

The mean ABP was $129.8 \pm 8.9/82.1 \pm 7.1$ mmHg for daytime and $118.2 \pm 7.9/76.6 \pm 6.9$ mmHg for nighttime after the second 24-hour monitoring. Diurnal and nocturnal, systolic and diastolic differences reached statistical significance ($p < 0.05$ for daytime mean systolic and diastolic values and $p < 0.025$ for nighttime mean systolic and diastolic values).

The main results are depicted in the Table I.

The mean differences between daytime and nighttime BP were $3.3 \pm 5.6/2.3 \pm 4.9$ mmHg at baseline. The corresponding differences at the second ABPM after the add-on treatment were $11.6 \pm 10.6/5.5 \pm 7.1$ mmHg for systolic and diastolic ABP respectively ($p < 0.05$).

Among the 41 non-dipper patients, 32 (78%) showed complete normalization of circadian rhythm ($p < 0.05$).

The hourly mean ABP before and after intervention are depicted in the Figure 1.

The circadian pattern after barnidipine bedtime add-on treatment was clearly and significantly modified with a more pronounced shift during nighttime (11 pm-7 am).

Table I. Average ambulatory blood pressure (ABP) values before and after bedtime administration of barnidipine 10 mg. The data are expressed as mean values $\pm$ SD. Student's *t*-test for paired samples (two-sided, alpha level $p < 0.05$).

	Before barnidipine dosing	After barnidipine dosing	<i>p</i>
Daytime Systolic ABP	139.1 ± 9.6	129.8 ± 8.9	< 0.05
Daytime Diastolic ABP	87.4 ± 7.7	82.1 ± 7.1	< 0.05
Nighttime Systolic ABP	135.8 ± 9.9	118.2 ± 7.9	< 0.025
Nighttime Diastolic ABP	85.1 ± 8.1	76.6 ± 6.9	< 0.025

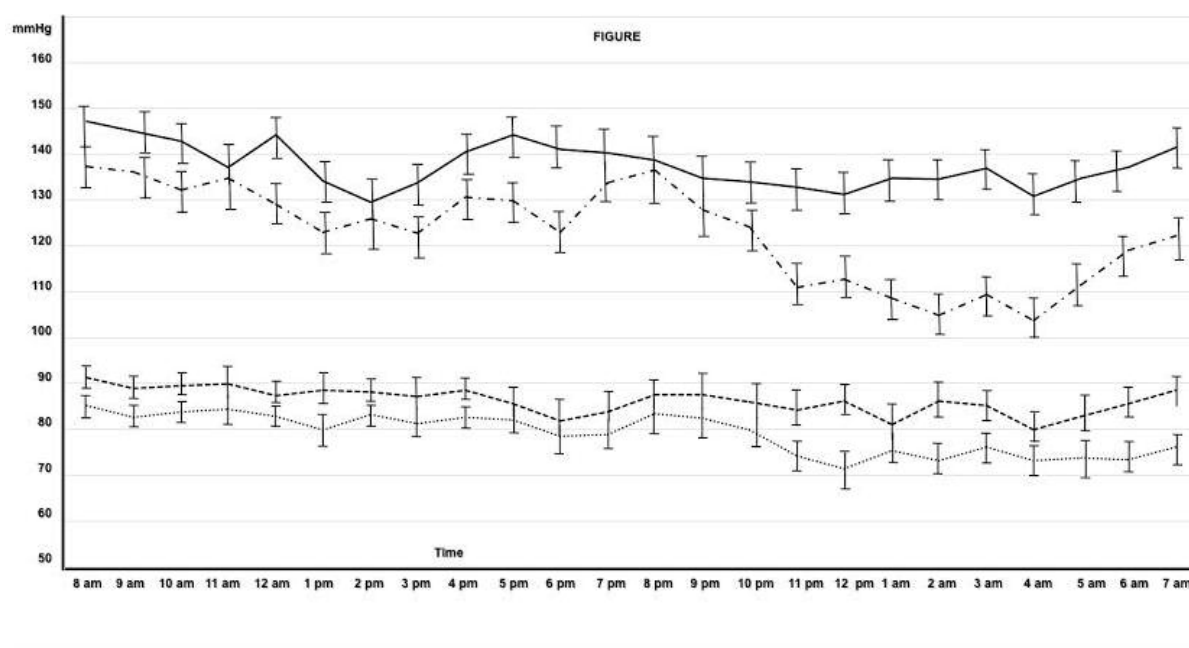


Figure 1. Hourly mean ABP obtained before and after bedtime administration of barnidipine 10 mg in 41 patients.

Add-on treatment with barnidipine normalized the previously altered circadian rhythm in 78% of the patients who concluded the study ($p < 0.05$, test of Wilcoxon for paired samples).

Add-on treatment with barnidipine was generally well tolerated.

Three patients developed mild symptomatic diurnal hypotension and 6 showed mild-to-moderate leg oedema. Both side effects did not require treatment withdrawal.

Discussion

A bedtime dosing of the calcium-channel blocker barnidipine (added to a previous, stable antihypertensive treatment) significantly reduced systolic and diastolic ABP in non-dipper hypertensive patients with OSA syndrome, who were not being treated with CPAP.

Bedtime administration of barnidipine 10 mg was more effective on nighttime ABP than on daytime ABP.

Add-on treatment with barnidipine normalized the previously altered circadian rhythm in the great majority (78 %) of the patients who concluded the study.

Barnidipine was generally well tolerated and no patients were withdrawn from the study due to adverse events.

OSA constitutes a relevant cardiovascular risk factor, particularly when associated with hypertension and a non-dipper BP pattern.

CPAP treatment is still performed in a minority of patients, and even in those with more serious forms of OSA.

The relevant proportion of normalization of circadian BP rhythm obtained in this particular group of patients (not treated for OSA and non-dipper hypertension) seems very promising. In fact, considering the high cardiovascular risk profile of patients with OSA and the well-established correlations between nocturnal BP levels and cardiovascular morbidity and mortality, the reversal of the altered BP circadian rhythm should be considered an extremely important goal.

A potential limitation with regards to this study is the lack of a placebo-control group, since it was designed to be observational, interventional and prospective. However, the antihypertensive effect of barnidipine has been properly demonstrated in randomized, double-blind, placebo-controlled studies and our results may be considered complementary to those previous studies^{34,40}.

The choice of carrying out a study with observational design was determined by the particular characteristics of the participating patients and the strict inclusion criteria (OSA not being treat-

ed with CPAP, BP values not on target, non-dipper/riser ABP patterns, stable treatment excluding CCB). A randomized, placebo-control design would have greatly limited the number of observations and increased the expenditures required to cover insurance.

Conclusions

The bedtime dosing of barnidipine, in hypertensive patients with non-dipper pattern and OSA, not being treated with CPAP, significantly reduced mean nighttime systolic and diastolic ABP and, in the majority of these patients, restored the previously altered circadian rhythm.

These findings may be of particular interest since CPAP treatment is not feasible for many hypertensive patients with a non-dipper pattern associated with OSA.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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