Prolonged Melatonin Administration Decreases Nocturnal Blood Pressure in Women

Angelo Cagnacci, Marianna Canoletta, Antonietta Renzi, Francesco Baldassari, Serenella Arangino, and Annibale Volpe

Background: The nocturnal decline of blood pressure (BP) is almost coincident with the elevation of melatonin, which may exert vasodilatating and hypotensive effects. In this study we investigated whether prolonged nocturnal administration of melatonin could influence the daily rhythm of BP in women.

Methods: In a randomized double-blind study, 18 women, 47 to 63 years of age and with normal BP (N = 9) or treated essential hypertension (N = 9), received a 3-week course of a slow-release melatonin pill (3 mg) or placebo 1 h before going to bed. They were then crossed over to the other treatment for another 3 weeks. In each woman ambulatory BP was recorded for 41 h at baseline at the end of each treatment period.

Results: In comparison with placebo, melatonin administration did not influence diurnal BP but did significantly decrease nocturnal systolic (−3.77 ± 1.7 mm Hg, P = .0423), diastolic (−3.63 ± 1.3 mm Hg, P = .0153), and mean (−3.71 ± 1.3 mm Hg, P = .013) BP without modifying heart rate. The effect was inversely related to the day–night difference in BP.

Conclusion: These data indicate that prolonged administration of melatonin may improve the day–night rhythm of BP, particularly in women with a blunted nocturnal decline. Am J Hypertens 2005;18:1614–1618 © 2005 American Journal of Hypertension, Ltd.

Key Words: Melatonin, blood pressure, circadian rhythm, human, hypertension.

All biological functions, including blood pressure (BP) regulation, show a circadian rhythm, which is dependent on the activity of the main body pacemaker localized in the suprachiasmatic nuclei (SCN) of the hypothalamus. As a consequence of this circadian rhythm, BP declines at night by about 20%. This decline, which allows the cardiovascular system to rest, represents an important mechanism for reducing cardiovascular disease. The nocturnal decrease in BP is temporally related to the rise of melatonin, the secretion of which, by the pineal gland, is almost entirely confined to the night. Melatonin exerts different effects. Among these, it contributes to the occurrence of the nocturnal modifications of several biological functions. Receptors for melatonin have been detected in animal and human arteries. In animals, melatonin modulates arterial response to norepinephrine. In human beings melatonin may decrease norepinephrine levels, increase nitric oxide production, and reduce great artery resistance to blood flow. Accordingly it is possible that melatonin contributes to reduce the activity of the cardiovascular system at night. Studies on the effect of melatonin on BP control in hypertensive individuals have yielded conflicting results. However, it was recently reported that prolonged administration of melatonin amplifies the nocturnal decline of BP in hypertensive men. In the present study we examined whether prolonged melatonin administration would amplify the nocturnal decline of BP in women. The study aimed to evaluate the effect of melatonin in a general population of middle-aged women with no selection on the basis of baseline BP values, although women using some specific antihypertensive therapies were excluded. The prolonged experimental setting was used to test the maintenance of the eventual hypotensive effect of melatonin, which has been inconsistently demonstrated in acute experiments.

Methods

The local ethics committee and Institutional Review Board previously approved the study.

Received March 7, 2005. First decision May 16, 2005. Accepted May 18, 2005.

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This study was partially supported by Nathura s.r.l., Montecchio Emila, Italy.

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0895-7061/05/$30.00

doi:10.1016/j.amjhyper.2005.05.008

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Study Population

A total of 22 healthy women, aged 47 to 63 years, gave their informed consent to participate in the study. At enrollment, women were required to be normotensive or to have essential hypertension controlled by diuretics or angiotensin converting enzyme (ACE) inhibitors or both. Treatments were kept constant throughout the study. Women who were receiving β-blockers or calcium antagonists were excluded from the study because of the possible interference on melatonin synthesis and action. Eventual sleep problems were not considered among the inclusion or exclusion criteria.

Experimental Design

According to a balanced, computer-generated list of randomization, each woman was assigned in a double-blind fashion to receive, 1 h before bedtime (21:30 to 24:00), a pill containing slow-release melatonin or placebo. The melatonin pill was formulated to release 1 mg of melatonin rapidly and 2 mg slowly (Armonia Retard, Nathura s.r.l., Montecchio Emilia RE, Italy). After 3 weeks of treatment each subject was crossed over to the alternate treatment (melatonin or placebo) for another 3 weeks. In the week preceding the study and for the entire study, each woman was requested to keep her daily activity and bedtime as constant as possible. The Greene climacteric scale was filled out by each woman both at baseline and after each treatment period. The scale evaluates a series of subjective climacteric symptoms, which include hot flushes, sleep, and psychologic disturbances. Blood pressure and heart rate values recorded at baseline were measured at baseline and at the end of each treatment period by an oscillometric BP monitoring device (ABP Monitor; SpaceLabs Medical, Redmond, WA). Starting at 17:00 BP was sampled consecutively every 30 min for 41 h. During the recording period patients were requested to limit their physical activity to avoid stressful events and to consume no more than 2000 kcal/day. Breakfast was allowed between 07:00 and 08:30, lunch between 12:30 and 14:30, and dinner between 19:00 and 20:30. During readings, subjects were requested to maintain the arm motionless and parallel to the trunk when the cuff was inflated. When the first try was unsuccessful, BP was checked again. Unsuccessful readings were recorded as event codes (subjects’ movements, heart arrhythmia, unreasonable BP, etc.). Reports were considered appropriate when successful readings exceeded 90%. To exclude the effect of first-night accommodation, valuable data were considered those from 08:00 to 08:00 of the next day.

Statistical Analysis

Readings were transferred to a computer, smoothed by a three-point moving average, then used at hourly intervals for rhythmometric evaluation by cosinor analysis. When cosinor analysis was significant, we calculated and recorded the nadir (time of minimal cosine function; that is, the time in the 24-h period when BP and heart rate were at their theoretical minimum). Rhythms were put in phase by considering the nadir as the circadian time 0. The 24-h, daytime, and night-time (3 h before and 3 h after the time of nadir) values were separately evaluated. Assuming that the difference induced by melatonin was equal to 1 standard deviation of the difference, and setting type I error at 0.05 and type II error at 0.20, eight subjects were sufficient to detect a statistically significant modification in any of the investigated indexes. After the assessment of the normal distribution of the differences we used the paired t-test to compare the data obtained during the administration of melatonin or placebo.

Simple regression analysis followed by multiple regression analysis was used to identify those parameters conditioning the eventual BP or heart rate response to melatonin. Percentages of subjects showing a response were compared by contingency tables and the χ²-test. All results are expressed as the mean ± SE.

Results

Of the 22 enrolled women, 20 completed the study. Two other women were excluded for insufficient 24-h readings. Accordingly, calculations were performed on 18 subjects. Blood pressure and heart rate values recorded at baseline in the 24-h period are reported in Table 1. Among the 18 subjects, nine were normotensive and nine had pharmacologically controlled essential hypertension. All hypertensive women were treated only with ACE inhibitors. In

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (Mean ± Standard Error)</th>
<th>Hypertensive (Mean ± Standard Error)</th>
<th>Normotensive (Mean ± Standard Error)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>53.1 ± 1.1</td>
<td>54.2 ± 1.7</td>
<td>52.8 ± 1.4</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>74.5 ± 2.8</td>
<td>75.6 ± 4.9</td>
<td>73.6 ± 3.0</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.60 ± 0.1</td>
<td>1.60 ± 0.2</td>
<td>1.59 ± 0.1</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.1 ± 1.1</td>
<td>29.2 ± 1.9</td>
<td>28.9 ± 1.2</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>120.7 ± 3.7</td>
<td>120.0 ± 5.0</td>
<td>121.4 ± 5.6</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>79.7 ± 2.5</td>
<td>77.5 ± 2.7</td>
<td>81.9 ± 4.2</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>107.0 ± 3.1</td>
<td>105.8 ± 4.1</td>
<td>108.2 ± 4.9</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>69.6 ± 2.9</td>
<td>67.2 ± 4.8</td>
<td>72.0 ± 3.2</td>
</tr>
</tbody>
</table>
BP analysis identified that the extent of the nocturnal BP decline was more pronounced during melatonin use than placebo use (83.3% vs. 38.9%; P = .0167). Multiple regression analysis identified that the extent of the nocturnal BP decline induced by melatonin was related to day–night difference of BP (0.706 ± 0.105; P < .0001) and normotension/hypertension (6.02 ± 1.46; P < .0001) but not to baseline BP values, as evaluated in the placebo night, age, weight, body mass index, or menopausal status. Linear regression of the melatonin effect on day–night BP decline was y = −8.57 + 0.886 x; r² = 0.7516; P = .0053 in hypertensive women and y = −12.88 + 0.67 x; r² = 0.7787; P = .0014 in normotensive women (Fig. 2). The score of the Greene climacteric scale was similar during placebo or melatonin administration (22.2 ± 2.5 vs 19.5 ± 2.6). In addition anxiety, depression, somatization, vaso-motor, and sexuality subscales were not significantly different during placebo or melatonin administration.

### Discussion

The present data show that, in women, potentiation of the melatonin signal by exogenous melatonin amplifies the nocturnal BP decline by about 4 mm Hg. This is similar to values recently obtained in hypertensive men.14 Only half of the women in our study had hypertension, which was controlled by ACE inhibitors alone.

Normotensive and treated hypertensive women had similar general characteristics. Both groups responded to the prolonged administration of melatonin, although the effect was slightly less pronounced in hypertensive women. Whether this attenuated response is dependent on hypertension per se or on medicines used to treat the disease is presently unknown. For example an attenuation of the nocturnal BP decline has been reported with the use of diuretics, which were not used by the women in our study.16

### Table 2. Mean (± standard error) blood pressure (BP, mm Hg) and heart rate (beats/min) values observed after 3 weeks of placebo or melatonin (3 mg) administration in 18 women

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Melatonin</th>
<th>Net</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic BP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-h</td>
<td>123.2 ± 3.5</td>
<td>122.9 ± 3.3</td>
<td>−0.26 ± 1.6</td>
<td>.8694</td>
</tr>
<tr>
<td>Day</td>
<td>126.3 ± 3.7</td>
<td>126.8 ± 3.5</td>
<td>0.54 ± 1.8</td>
<td>.7705</td>
</tr>
<tr>
<td>Night</td>
<td>115.4 ± 3.3</td>
<td>111.7 ± 3.0</td>
<td>−3.77 ± 1.7</td>
<td>.0432</td>
</tr>
<tr>
<td>Day-night difference</td>
<td>10.9 ± 2.2</td>
<td>15.2 ± 1.8</td>
<td>4.31 ± 1.8</td>
<td>.0354</td>
</tr>
<tr>
<td><strong>Diastolic BP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-h</td>
<td>76.9 ± 1.9</td>
<td>75.6 ± 1.8</td>
<td>−1.26 ± 1.0</td>
<td>.2112</td>
</tr>
<tr>
<td>Day</td>
<td>79.6 ± 2.0</td>
<td>79.2 ± 2.2</td>
<td>0.38 ± 1.1</td>
<td>.7550</td>
</tr>
<tr>
<td>Night</td>
<td>69.6 ± 1.9</td>
<td>65.9 ± 1.3</td>
<td>−3.63 ± 1.3</td>
<td>.0153</td>
</tr>
<tr>
<td>Day-night difference</td>
<td>9.9 ± 1.5</td>
<td>13.2 ± 1.6</td>
<td>3.26 ± 1.7</td>
<td>.0744</td>
</tr>
<tr>
<td><strong>Mean BP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-h</td>
<td>92.6 ± 2.3</td>
<td>91.2 ± 2.2</td>
<td>−1.33 ± 1.0</td>
<td>.2072</td>
</tr>
<tr>
<td>Day</td>
<td>95.1 ± 2.5</td>
<td>95.2 ± 2.5</td>
<td>0.22 ± 1.2</td>
<td>.9856</td>
</tr>
<tr>
<td>Night</td>
<td>84.9 ± 2.3</td>
<td>81.2 ± 1.7</td>
<td>−3.71 ± 1.3</td>
<td>.0130</td>
</tr>
<tr>
<td>Day-night difference</td>
<td>10.2 ± 1.7</td>
<td>13.9 ± 1.6</td>
<td>3.73 ± 1.5</td>
<td>.0286</td>
</tr>
<tr>
<td><strong>Heart rate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-h</td>
<td>69.5 ± 1.6</td>
<td>70.7 ± 2.0</td>
<td>1.22 ± 1.4</td>
<td>.4010</td>
</tr>
<tr>
<td>Day</td>
<td>72.1 ± 1.7</td>
<td>73.5 ± 2.3</td>
<td>1.37 ± 1.6</td>
<td>.4120</td>
</tr>
<tr>
<td>Night</td>
<td>62.4 ± 1.7</td>
<td>63.2 ± 1.6</td>
<td>0.86 ± 1.5</td>
<td>.5884</td>
</tr>
<tr>
<td>Day-night difference</td>
<td>9.7 ± 1.3</td>
<td>10.2 ± 1.3</td>
<td>0.51 ± 1.7</td>
<td>.7712</td>
</tr>
</tbody>
</table>
hot flashes, which may influence sleep.22,23 The Greene and some of the women in our study were experiencingations of SNC have been described.14 Although only half in hypertensive individuals in whom anatomical alter-
the phenomenon of regression toward the mean, the effect being observed in individuals with blunted nocturnal decline. Although this may partially be caused by the significantly greater prevalence of the amplified nocturnal BP decline during melatonin over placebo use suggests a genuine melatonin effect. The possibility that different levels of endogenous melatonin determine a different response to melatonin administration can not be disregarded. Indeed, it has been reported that nocturnal levels of melatonin are reduced in hypertensive individuals with blunted or absent nocturnal BP decline.17

A 10% nocturnal decline of BP over daytime values is considered appropriate to reduce the cardiovascular risk.2 During placebo use only 39% of the subjects reached this value, but this rate surged to 84% during melatonin administration.

Different mechanisms may mediate the effect of melatonin. Repeated intake of melatonin can control nocturnal BP by the amplification of the circadian output of SCN to the cardiovascular system, as reported in experimental animals.18 This mechanism of action has been suggested in hypertensive individuals in whom anatomical alterations of SNC have been described.14 Although only half of our subjects were hypertensive, this hypothesis may still hold, as our subjects were women in their 50s or 60s, in whom age-related decline of SCN activity19 and melatonin20,21 may yet have occurred.

Sleep problems are frequent among women of this age; and some of the women in our study were experiencing hot flashes, which may influence sleep.22,23 The Greene climacteric scale, which also evaluates sleep and hot flashes,15 was not modified by melatonin administration. We ac-

Interestingly, the major determinant of the response to melatonin was the extent of the day–night BP decline observed during placebo administration, the greatest effect being observed in individuals with blunted nocturnal decline. Although this may partially be caused by the phenomenon of regression toward the mean, the significantly greater prevalence of the amplified nocturnal BP decline during melatonin over placebo use suggests a genuine melatonin effect. The possibility that different levels of endogenous melatonin determine a different response to melatonin administration can not be disregarded. Indeed, it has been reported that nocturnal levels of melatonin are reduced in hypertensive individuals with blunted or absent nocturnal BP decline.17

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knowledge that this is not an appropriate method for correct evaluation of sleep. Melatonin has sleep-inducing and hypnotic effects,4 reduces time to fall asleep, improves sleep efficacy, and reduces awake time during the night.24 Because sleep deprivation can cause resetting of the arterial baroreflex on higher values and induce an increase BP,25 the effect of melatonin on sleep may be of relevance for the cardiovascular system. However, in the study previously performed in men, the ability of melatonin to decrease nocturnal BP was independent of sleep improvement, as indirectly evaluated by monitoring wrist movement.14 Similar conclusions were drawn in adolescent diabetic individuals.26

However, melatonin may exert cardiovascular effects that are independent of those on sleep. Melatonin may act directly at the arterial wall6 and may influence sympathetic activity8,27,28 and baroreflex set-point.29,30 Furthermore, in awake individuals, acute administration of melatonin produces vasodilation of arteries,9 –11 increases nitric oxide levels,10,11 reduces norepinephrine levels,9,10 and reduces BP values.9–11

In conclusion, the present data show that the prolonged administration of melatonin may improve the day–night rhythm of BP. Because a reduced day–night ratio is associated with left ventricular hypertrophy, progression of renal damage, and higher incidence of silent cerebrovascular disease and cardiovascular disease,2 amplification of the day–night ratio by melatonin may contribute to cardiovascular protection in women. The association of melatonin with other antihypertensive therapies (which were neither evaluated nor excluded from the present study) and longer clinical trials are necessary for a full exploration of the potential effects of melatonin.

References


