Melatonin in Older People with Age-Related Sleep Maintenance Problems: 
A Comparison with Age Matched Normal Sleepers

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Study Objectives: To determine whether older people with age-related sleep maintenance problems have significantly lower melatonin levels than comparable normal sleepers.

Design: Case-control study.

Setting: A largely urban population, Auckland, New Zealand.

Participants: People over the age of 65 years, who either slept normally, or had age-related sleep maintenance problems. Participants were recruited through media advertising, and local interest groups. Initial screening was by mail (Pittsburgh Sleep Quality Index), followed by interviews at a hospital day clinic. Exclusions included those with depression, cognitive impairment, medical and/or environmental problems which might impair sleep.

Measurements and Results: A metabolite of plasma melatonin, 6-sulfoxyxymelatonin (aMT6s) was measured in the urine of 57 normal sleepers, and 53 people with age-related problems over 24 hours in three aliquots: 12:00-19:00h, 19:00-07:00h, 07:00-12:00h. There were clear differences in self reported quality of sleep but no difference in mean aMT6s 24 hour or total night excretory levels, or night/day ratios.

Conclusions: Older people with age-related sleep maintenance problems do not have lower melatonin levels than older people reporting normal sleep.

Key words: Melatonin; sleep; elderly; 6-sulfoxyxymelatonin

INTRODUCTION

MELATONIN (N-ACETYL-5-METHOXYTRYPTAMINE) IS A HORMONE PRODUCED DURING THE HOURS OF DARKNESS BY THE PINEAL GLAND. From very low daytime levels an increase in plasma melatonin occurs in the evening, peaking between 01:00-05:00h, and becoming barely detectable again by about 09:00-10:00h. Secretion in many animals is truly photoperiodic, that is it is influenced by the length of the day/night cycles during the year. In humans this photoperiodicity may be partially distorted by artificial lighting but can be sustained in subjects maintained for long periods in artificial short or long days.

Although plasma melatonin levels in older people are reported to be lower than younger people plasma levels vary widely in all ages. Some older people have relatively high levels of melatonin, others have significantly reduced levels, and a few have no evidence of melatonin secretion.

The effects of reduced melatonin levels are still uncertain, as is the potential of melatonin supplementation. Studies in younger participants have demonstrated the efficacy of melatonin as a mild sedative and sleep-promoting agent using various doses, especially if administered during daytime although administration may or may not alter normal sleep. Melatonin administered to older people with sleep problems has shown conflicting results. Improvement in sleep quality has been reported particularly with controlled release melatonin but others suggest that only sleep latency (from lights out to falling asleep) is reduced and sleep efficiency improved.

Age-related problems in sleeping are well described, and are more prevalent in women. For many, aging is associated with decreased total sleep time, increased sleep latency, and more awakenings particularly in the latter stages of the night (problems with sleep maintenance). Others have problems in sleeping for different reasons, for instance poor health, anxiety or depression, or less than optimal environment.

The object of this research was to investigate whether older people with age-related sleep problems do secrete significantly less melatonin than those who report normal sleep patterns. If this were the case, it would support the widespread but unproved belief that supplementary melatonin improves quality of sleep in this age group.

METHODOLOGY

Data were collected between May 1997 and October 1998, and are part of a larger study, the PROMISE (Possible Role of Melatonin In Sleep of Elders) study, designed to examine a number of possible relationships between melatonin and sleep in older people.

The study was approved by the Ethical Committee of North Health, the Northern Region of the Health Funding Authority of New Zealand.

Definitions

For the purposes of this study the following definitions were used:

Older people: People over 65 years of age.

Normal sleepers: Older people who perceived that they slept normally, and that sleep quality had not altered as they aged. Interview and screening instruments described below supported this perception.
Age-related sleep maintenance problems: Older people who reported bed-times normal for age (between 22:00 and 24:00h), normal or delayed sleep latency, and who reported significant problems in maintaining sleep after an initial sleep phase. This group perceived that sleep quality was reduced with advancing age. Participants reported normal sleep quality during young and middle age to at least age 50 years, with gradually deteriorating quality of sleep later in life. Screening instruments and interviews identified no other explanation for poor sleep.

Recruitment

Participants were recruited largely from the North Shore area of Auckland, New Zealand, which has a population of approximately 34,000 people over the age of 65 years. Requests for an expression of interest in participating in the study were made via the media (newspaper articles, advertisements, and talk-back radio); presentations to retirement villages and local interest groups such as 60's Plus, Grey Power, and bowling clubs; letters to family doctors; and through a promotional pamphlet advertising the study.

Screening

People interested in participating in the study made initial contact with the study co-ordinator identifying themselves either as normal, or problem sleepers. Some, mostly problem sleepers, were excluded after a brief discussion, usually because they were taking hypnotics, were younger than 65 years, or clearly had health problems interfering with sleep. The remainder were sent the Pittsburgh Sleep Quality Index (PSQI) questionnaire to be completed and returned by mail.24 The PSQI has been validated for older people25 and generates a global score after identifying seven components relating to sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medication, and daytime dysfunction. A PSQI score of over five indicates people with a sleep disorder, but not the reason or type of problem.

Exclusions

Exclusion criteria were: a) a score of below 26 (out of 30) points on the MMSE, as diminished cognitive function may result in difficulty in adhering to instructions when involved in the study, and because low melatonin levels have been reported in people with Alzheimer's type dementia;30,31,32 b) a score of greater than six on the GDS, indicating possible depression as depression is widely recognized as a cause of sleep disturbance; c) sleep problems which were not age-related or indicated another sleep disorder;33 d) where sleep hygiene was deemed to be the main problem (such as inappropriate bed-times, noisy or otherwise unsuitable environment); e) any medical condition which significantly interfered with sleep (minor or intermittent problems were not excluded), including any symptoms that might suggest sleep apnoea; f) any alterations in medication during the study; g) if any drug was taken as a hypnotic; h) creatinine clearance less than 0.41ml/sec, as sulphatoxymelatonin (aMT6s) excretion is validated as an accurate estimate of melatonin secretion for clearances above this value;9 or i) evidence of anemia, or positive hepatitis serology (a possible risk to staff).

Classification into Sleep Group

Classification as normal or age-related sleep maintenance problems (problem sleeper) was a clinical decision made at interview. Where the PSQI score was close to “borderline” and the sleep category generated seemed inconsistent with that reported at interview, the subject was allocated a sleep category based on a clinical decision. This decision was based on reported features of sleep patterns, for example sleep latency, numbers of awakenings, and deterioration in sleep quality after 50 years of age.

Estimation of Melatonin Secretory Profile

Melatonin secretion was estimated by measuring its principle metabolite, 6-sulphatoxymelatonin (aMT6s), in the urine of each subject. A 24 hour urine collection was arranged in three aliquots: 12:00-19:00h, 19:00-17:00h, 07:00-12:00h. Participants were issued with suitable instructions and receptacles for collection, in an insulated container containing ice packs. They were asked to maintain their usual routine during the collection period, including avoidance of a light at night for collection unless their usual habit included using a light when toiletting at night. If errors were made, the 24-hour collection was repeated.

In order to check for possible collection errors at home, including unreported exposure to light during the night, one third were randomly selected for closer supervision. This group started their supervision at 12:00H, and came into an outpatient section of the hospital at about 16:00h, and stayed overnight under close supervision until after 09:00h. Once participants had retired for the night light exposure was monitored with a highly sensitive illuminance meter (Minolta T-1) to ensure that light exposure was less than one lux. Some then elected to return home and return at 12:00h to complete the collect, and others.
stayed until completion. Each aliquot of urine was measured, and a 10ml sample taken from each. Then all three samples were combined, thoroughly mixed, the volume measured, and a further 10ml sample taken. Thus four samples from each volunteer were available: U1 (12:00-19:00h, 7 hours), U2 (19:00-17:00h 12 hours), U3 (07:00-12:00h, 5 hours), and UTotal (12:00-12:00h, 24 hours).

Urine samples were stored at -20 degrees centigrade, and transported frozen to Stockgrand Ltd., Guildford, United Kingdom for assay, unrevealed as to sleep quality. Sulphatoxymelatonin (aMT6s) was measured by radioimmunoassay.34

In reporting data, U4 was calculated by combining data of U1, U2, and U3, and these estimations were checked against the volumes and aMT6s estimations of the combined urine samples (UTotal). Urinary aMT6s estimations from each aliquot were reported as µg/collect. Night/day ratios were calculated from aMT6s estimations (µg/hour) for U2:(U1+U3), and U2:U1.

Table 1—Baseline characteristics of participants by sleep group.

<table>
<thead>
<tr>
<th></th>
<th>Normal Sleepers (n=57)</th>
<th>Sleep Maintenance Problems (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>40 (70.2)</td>
<td>35 (66.0)</td>
</tr>
<tr>
<td>Male</td>
<td>17 (29.8)</td>
<td>18 (34.0)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-69</td>
<td>18 (31.6)</td>
<td>17 (32.1)</td>
</tr>
<tr>
<td>70-74</td>
<td>21 (36.8)</td>
<td>24 (45.5)</td>
</tr>
<tr>
<td>75-79</td>
<td>13 (22.8)</td>
<td>10 (18.9)</td>
</tr>
<tr>
<td>80-84</td>
<td>5 (8.8)</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20</td>
<td>3 (5.3)</td>
<td>4 (7.5)</td>
</tr>
<tr>
<td>20-&lt;25</td>
<td>20 (35.1)</td>
<td>21 (39.6)</td>
</tr>
<tr>
<td>25-&lt;30</td>
<td>29 (50.9)</td>
<td>21 (39.6)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>5 (8.8)</td>
<td>7 (13.2)</td>
</tr>
<tr>
<td>Tea or coffee after 6pm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33 (57.9)</td>
<td>30 (56.6)</td>
</tr>
<tr>
<td>No</td>
<td>24 (42.1)</td>
<td>23 (43.4)</td>
</tr>
<tr>
<td>Alcohol (grams/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non/Occasional Drinker</td>
<td>20 (35.1)</td>
<td>17 (32.1)</td>
</tr>
<tr>
<td>1-10</td>
<td>20 (35.1)</td>
<td>20 (37.7)</td>
</tr>
<tr>
<td>11-20</td>
<td>12 (21.1)</td>
<td>12 (22.6)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>5 (8.8)</td>
<td>4 (7.5)</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blocker</td>
<td>10 (17.5)</td>
<td>5 (9.4)</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>2 (3.5)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Antiepileptic</td>
<td>1 (1.8)</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Antiparkinsonian</td>
<td>1 (1.8)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>0 (0.0)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Any combination of the above</td>
<td>13 (22.8)</td>
<td>9 (17.0)</td>
</tr>
</tbody>
</table>

No significant differences were found between any of the groups.

Power and Sample Size

Sample size calculations were estimated from an earlier pilot study. These calculations showed that in order to demonstrate a 70% difference in mean 24 hour aMT6s levels, a minimum of 50 participants would be required in each group (α = 0.05, β = 80%). We therefore aimed to recruit 60 participants in each group, to allow for up to 20% dropout after entry into the study.

Statistical Analysis

Data management and statistical analysis were conducted using SAS Version 6.12.35 Statistical comparisons of total aMT6s excreted per collect, estimated total excretion for 24 hours and night/day ratios were undertaken using t-tests of the log-transformed raw data since the distributions of all aMT6s variables

...
were positively skewed. The logged mean was then back-transformed and the geometric mean reported with 95% confidence intervals. Confirmatory analyses were undertaken using a repeated measures regression model using the logarithm of the mean hourly rate of melatonin excretion.

RESULTS

After an initial telephone discussion, a number of participants were excluded because they clearly did not meet the study criteria. In all 414 people volunteered for the study: 220 were excluded before completing the PSQI based on information given during direct contact, or by phone and/or post. A further 74 were excluded after completing the PSQI.

Sixty normal sleepers, and 60 age-related sleep maintenance problem participants, were entered into the study. In general the clinic interview-generated classification corresponded well with PSQI scores. However 11 of the 60 classified as normal sleepers had marginally high PSQI scores [6-7] even though they perceived themselves to be normal sleepers, the PSQI threshold for abnormal sleep being greater than five. Three of sixty with “poor” sleep scored below the threshold [4-5]. Fifty-seven normal sleepers completed the urine collects (one withdrawing because of ill health, and two due to protocol violations); and 53 problem sleepers completed urine collections (two withdrew due to ill health, two for personal reasons, two with protocol violations, and one urine sample was lost).

Table 1 shows that the demographic characteristics of the group were well matched at baseline for age, sex, medications, BMI, alcohol, and caffeine consumption. Details of sleep parameters recorded at the screening are given in Table 2, and demonstrate that the problem sleepers reported poorer sleep quality on several measures: one and a half hours shorter sleep time, 17 minutes longer spent in bed, 9 minutes longer sleep latency [time to sleep minus time to bed], 75% more awakenings (mean number 1.2 in normal sleepers, and 2.1 in problem sleepers), 32% lower sleep efficiency [time asleep over time in bed (lights out to final get up time)], and 32% lower sleep percentage [time asleep over time trying to sleep (lights out to final wake up)]. Mean PSQI scores were significantly higher for problem sleepers. Table 3 shows urinary aMT6s by sleep group and collection times. Total melatonin excreted over 24 hours was 6.82 µg (95% confidence interval 5.65, 8.22) in normal sleepers and 7.50 µg (6.97, 9.43) in people with sleep maintenance problems. Night:day excretory ratios were similarly indistinct, with U2:U1 3.72 (2.95, 4.69) and 4.77 (3.96, 5.75), and U2:(U1 +U2) 2.05 (1.69, 2.49) and 2.59 (2.17, 3.08) in normal and problem sleepers respectively. There was a wide variation in aMT6s 24-hour excretory rates and levels amongst participants in both sleep groups, and no significant differences between groups. Nor was there a difference between each group in total night-time excretion (U2), afternoon (U1), or morning (U3) excretory rates. When analyses were repeated including only those people not taking any medications (shown in Table 1), there were no meaningful changes to the results. Nor was there any difference in melatonin excretion when the categories of normal and abnormal sleep were classified solely by the PSQI.

There was no significant difference between data obtained from the urine collected by participants at home compared with those collected under supervised conditions, mainly within the hospital environment.

In the repeated measures analysis, no difference was seen between the two sleep quality groups, confirming the univariate analyses.

DISCUSSION

This study of sleep in older people found no relationship between age-related sleep maintenance problems and 6-sulphatoxymelatonin (aMT6s) levels, measured as an index of plasma melatonin secretion. There was no significant difference in melat-
Table 3—Urinary 6-sulphatoxymelatonin levels (aMT6s) (µg/aliquot) by sleep group

<table>
<thead>
<tr>
<th></th>
<th>Normal Sleepers (n=57)</th>
<th>Sleep Maintenance Problems (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean 95% CI</td>
<td>mean 95% CI</td>
</tr>
<tr>
<td><strong>aMT6S (µg/collect)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U1: 12pm-7pm</td>
<td>0.68 (0.58, 0.80)</td>
<td>0.63 (0.54, 0.74)</td>
</tr>
<tr>
<td>U2: 7pm-7am</td>
<td>4.32 (3.44, 5.43)</td>
<td>5.18 (4.03, 6.66)</td>
</tr>
<tr>
<td>U3: 7am-12pm</td>
<td>1.33 (1.08, 1.63)</td>
<td>1.26 (0.96, 1.64)</td>
</tr>
<tr>
<td>U4: 12pm-12pm</td>
<td>6.82 (5.65, 8.22)</td>
<td>7.50 (5.97, 9.43)</td>
</tr>
<tr>
<td><strong>Night/Day ratios</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U2/U1</td>
<td>3.72 (2.95, 4.69)</td>
<td>4.77 (3.96, 5.75)</td>
</tr>
<tr>
<td>U2/(U1+U3)</td>
<td>2.05 (1.69, 2.49)</td>
<td>2.59 (2.17, 3.08)</td>
</tr>
<tr>
<td><strong>Urine volume (ml)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U1: 12pm-7pm</td>
<td>529 (451, 606)</td>
<td>537 (475, 599)</td>
</tr>
<tr>
<td>U2: 7pm-7am</td>
<td>944 (842, 1045)</td>
<td>974 (876, 1072)</td>
</tr>
<tr>
<td>U3: 7am-12pm</td>
<td>402 (349, 455)</td>
<td>370 (322, 418)</td>
</tr>
<tr>
<td>U4: 12pm-12pm</td>
<td>1856 (1674, 2037)</td>
<td>1864 (1724, 2005)</td>
</tr>
</tbody>
</table>

CI = confidence interval

Melatonin and Sleep in Older People—Baskett et al
malities, which had not altered with age, they may have perceived that their sleep had always been and remained "normal."

A variety of physiological and degenerative changes, alone or in combination is thought to lead to reduced melatonin levels. There is a complex neural pathway between the retina and the pineal gland, which is likely to be susceptible to age-related degeneration and certain diseases. Nocturnal pineal secretion of melatonin is under control of the sympathetic nervous system. The neural pathway from the retina passes centrally via the suprachiasmatic nuclei and the paraventricular nucleus, then via the spinal cord superior cervical ganglia to the pineal gland to activate neurochemical transduction mechanisms.42 Degeneration of these pathways from retina to pineal gland, and/or reduction of pinealocyte β-adrenergic receptor functions may contribute to lower plasma melatonin levels. At autopsy fibrous tissue and calcium deposits largely replace the pineal gland of some older people and this could result in reduced melatonin levels. Availability of serotonin, the precursor of melatonin, poor illumination perception, and some medications are other possible causes of reduced production in older people.

The fact that older people in general have significantly lower melatonin levels than younger age groups poses important questions. Firstly, what is a "normal" melatonin secretory profile for an older person? Besides the total amount of melatonin secreted over a 24-hour period, or at night, other secretory parameters may change with age, for example time of onset, or the shape of the 24-hour secretory curve. None of these is yet well described.

Secondly, are there roles for melatonin in older people other than sleep? Some roles currently under investigation are related to many of the increased health problems of old age (e.g. immunocompetency, carcinoma, epilepsy, and pain).44 Will melatonin eventually prove to be of more importance in these areas than in sleep?

Thirdly, will supplementary melatonin improve sleep of older people, even in those who report "normal" sleep, and even if melatonin levels are relatively "high?" Work published to date suggests that when supplementary melatonin is given to older people with age-related insomnia only sleep latency is significantly improved,45 or that sleep efficiency as measured by actigraphy is improved.18 This question is addressed as part of our larger PROMISE study, and results will be reported separately. In summary, this study showed that older people with age-related sleep maintenance problems do not have lower melatonin secretory levels than age matched normal sleepers. More work is required to identify whether melatonin has any role in the quality of sleep in older people, either in those reporting normal sleep or those with age-related sleep maintenance problems.

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