Pharmaceutical, chronobiological and clinical aspects of melatonin
Nagtegaal, J.E.

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Part 3

CHRONOBIOLOGICAL ASPECTS OF MELATONIN

- Delayed sleep phase syndrome: a placebo controlled study on the effects of melatonin administered 5 hours before the individual dim light melatonin onset
- The effect of melatonin on sleep, daytime sleepiness and performance after a period of night work.
3.1 DELAYED SLEEP PHASE SYNDROME: A PLACEDO-CONTROLLED CROSS-OVER STUDY ON THE EFFECTS OF MELATONIN ADMINISTERED 5 HOURS BEFORE THE INDIVIDUAL DIM LIGHT MELATONIN ONSET

Summary

In a double-blind placebo-controlled cross-over study 30 patients with Delayed Sleep Phase Syndrome (DSPS) were included, of whom 25 finished the study. Melatonin 5 mg was administered during two weeks in a double-blind setting and two weeks in an open setting successively or interrupted by two weeks of placebo. Its impact was assessed by measurements of the 24 hour curves of endogenous melatonin production and rectal temperature (n=14), polysomnography (n=22), actigraphy (n=13), sleep log (n=22) and subjective sleep quality (n=25). Mean Dim Light Melatonin Onset (DLMO) (±SD) before treatment occurred at 23:17h (±138 min). Melatonin was administered 5 hours before the individual DLMO. After treatment, the onset of the nocturnal melatonin profile was significantly advanced by about 1.5 hour. Body temperature trough did not advance significantly. During melatonin use actigraphy showed a significant advance of sleep onset and polysomnography a significant decreased sleep latency. Sleep architecture was not influenced. During melatonin treatment patients felt significantly more refreshed in the morning. These results show that analysis of DLMO of patients suffering from DSPS is important both for diagnosis and therapy. These results are discussed in terms of the biochemistry of the pineal.

Introduction

Delayed Sleep Phase Syndrome (DSPS) is a circadian rhythm disorder characterised by an abnormally delayed sleep-wake rhythm. The major symptoms of DSPS are extreme difficulty to initiate sleep at a conventional hour of the night and great difficulty to wake up

1 JE Nagtegaal, GA Kerkhof, MG Smits, ACW Swart, YG van der Meer. This chapter is reprinted from the Journal of Sleep Research 1998; 7: 135-143.
on time in the morning for school or work [1]. The aetiology of DSPS is mostly unknown [2], although several developmental and environmental factors have been suggested [3] like e.g. long labour [3], infections [3] or shift work [4]. Once initiated, the sleep of DSPS patients is well consolidated with normal sleep architecture and total sleep time and no sleep pathology [2].

In adolescents a prevalence of greater than 7% is suggested [5,6], whereas in middle aged adults a prevalence of 0.7% is found [7].

Endogenous melatonin, a hormone produced by the pineal gland during the dark phase of the day-night cycle is thought to play a major role in the synchronisation of circadian rhythms. Its secretion is controlled by an endogenous oscillator that is entrained by light. The circadian rhythm of melatonin is highly reproducible and generally not easily altered [8].

From several studies [2,9,10,11] it has become clear that there are two methods to treat DSPS: with chronotherapy and with administration of melatonin. In 1991 Dahlitz [3] published the first study on the effects of melatonin administration in 8 patients with DSPS. Capsules with 5 milligrams melatonin were administered daily at 22:00h, 5 hours before the mean time of sleep onset. Sleep onset and time of waking up both shifted to an earlier time, on average respectively 1.3 and 2 hours. The patients returned to their previous, delayed pattern once the administration of the hormone was discontinued. In 1993 Tzischinsky et al [12] reported a study in 8 patients who were treated for 4-11 weeks with 5 mg of melatonin daily at 19:30 h. The authors described an advance of both sleep onset and time of waking up, each by a mean of about 2 hours.

In 1995 Regestein and Pavlova [5] suggested that melatonin might make more consistent therapeutic gains if doses were timed in relation to the evening rise or nocturnal peak in a patient's endogenous melatonin levels, or otherwise timed to some other circadian rhythm markers such as the daily body temperature minimum. Lewy et al [13] have shown that the response of the endogenous rhythm in the production of melatonin to the exogenous administration of melatonin in healthy subjects follows a phase response curve that mirrors the melatonin phase response curve for light. From several experiments in healthy volunteers, Lewy and co-workers generalised that exogenous melatonin advances circadian rhythms most effectively if administered 5 hours before the time that melatonin release starts to increase, the so-called Dim Light Melatonin Onset (DLMO) [13]. Thus, DLMO
seems a promising parameter for the evaluation of the treatment of DSPS patients, since Weitzman et al have hypothesised DSPS to be a disorder of the sleep-wake rhythm in which the advance portion of the phase response curve is absent or too small [1].

The goal of our study was to establish the effectiveness of melatonin, administered to DSPS patients 5 hours before their individual DLMO, in advancing the timing of sleep and the circadian rhythms of the endogenous melatonin release and body temperature. Furthermore, we were interested in the potential diagnostic value of DLMO and time of temperature trough as markers of circadian rhythmicity [14].

Our placebo-controlled study differs from earlier studies on the effects of melatonin in DSPS patients in that the time of administration is based on the patient's individual 24-h melatonin profile. Thus, we expected a better overall efficacy in advancing the circadian rhythms as compared with studies where melatonin was given at a fixed time in all patients.

Patients and Methods

Patients

Thirty patients (14 men, 16 women), aged 37.3 ± 15.3 years (Mean ± SD), and suffering from DSPS, were included in this study. Ten of the patients worked regularly by day, seven were scholars or students, twelve were unemployed and one shift-worked in the airforce. This man started to work regularly on daytime from two months before and during the study. DSPS was diagnosed according to the International Classification of Sleep Disorders (ICSD) criteria [4]. In selecting the patients, the following exclusion criteria were used: age under 12 years, any prior use of melatonin, liver diseases [15, 16], renal failure [17], severe neurological or psychiatric disorders [18, 19], pregnancy or a wish to become pregnant within the study period.

The study was approved by the local Medical Ethical Committee. Before the patients were included in the study, informed consent was obtained. Three patients (two men of respectively 31 and 41 years old and one woman of 50 years old) decided to withdraw before the study was completed. Two patients (a man of 19 years old and a woman of 45 years old) had to be excluded because of non-compliance.
Study protocol

The study covered a period of eight consecutive weeks. During the first day of the first week the patient stayed in a hospital unit where 24 h measurements of melatonin and rectal temperature were made. One week later, during two subsequent periods of two weeks each, the patient received either placebo followed by melatonin or melatonin followed by placebo, in a double-blind, cross-over design. In weeks 6 and 7 all subjects received melatonin in an 'open' condition, i.e. they were fully informed about the substance they received. Finally, in the morning following the last intake of melatonin, the patient was admitted to the hospital for a second 24 h recording of melatonin and rectal temperature. The design of the study is illustrated in Figure 10.

Figure 10: Design of the study

![Diagram of study design]

- 24-h melatonin
- 24-h temperature
- 2 weeks
- melatonin
- placebo
- melatonin
- placebo
- actigraphy
- polysomnography
- Sleeplog
Because of the practical limitation of only two 24 h recording sessions per patient, the open condition was added to the cross-over period (a cross-over condition by itself would necessitate three such recording sessions). In this way, the effect of melatonin administration upon these 24 h measurements could be compared with the baseline. However, it was preferred to measure the various sleep parameters during the double-blind, cross-over condition, and not following the open period. For, in the latter case, subjective influences might affect the sleep parameters.

Every evening all subjects took orally 5 mg melatonin (Helsinn Chemicals SA, Biasca, Switzerland), mixed with microcrystalline cellulose in a gelatin capsule, or a matched placebo, each for two weeks. It was decided not to include a wash-out procedure since melatonin has a short half-life of 35 minutes [20] and Dahlitz et al [3] had shown that the advancing effect of melatonin on the sleep-wake rhythm disappeared within 2 days after stopping the administration of melatonin. Twenty-four hour curves of endogenous melatonin production were assessed under semi-constant routine conditions, both 1-2 weeks before the start of the study and immediately after the 'open' melatonin period. During the 24-h semi-constant routine the patients stayed in bed, in a dimly lit room (from 8 a.m. till 6 p.m. the intensity of the ambient light was less than 100 lux, from 6 p.m. till 8 a.m. it was less than 20 lux). Room temperature varied between 19 and 21 degrees Celsius. Sleep was not prohibited. This protocol was followed in an attempt to prevent contamination of overt circadian rhythms by 'masking' influences caused by 24 hour variations in motor activity, ambient light and temperature [21]. Since a sampling interval of one hour was considered necessary for an accurate determination of the onset and the offset of the melatonin profile [22], 5 ml blood was collected hourly through a permanent forearm venous cannula into glass tubes. The time of administration of melatonin was calculated from the resulting endogenous 24 hour profile, according to Lewy et al [13, 23]. Lewy and co-workers showed that the time of the endogenous melatonin production maximally advanced when melatonin was administered five hours before the time of the individual Dim Light Melatonin Onset (DLMO).

The DLMO was defined as the time at which the melatonin concentration in serum reached a level of 10 pg/ml [13].
**Recordings and Analysis**

Blood samples were kept at four degrees Celsius until the experiment ended; then they were centrifuged (1000 * g, 10 min) and serum samples were stored at -20 degrees Celsius until assayed. Melatonin levels in serum were measured by a commercially available RIA kit (Bühlmann laboratories AG, Switzerland). The detection limit of the assay was 1 pg/ml sample.

During the semi-constant routines rectal temperature was recorded in 14 of the 30 patients (4 men, 10 women). Every two minutes rectal temperature (rectal probe from Yellow Spring YSI Series 400) was measured during 24 hours. The temperature curve was fitted with a harmonic regression function with 24 h and 12 h components [24]. The numerically calculated minimum of the fitted curve served as phase estimate of the circadian body temperature rhythm.

Twenty-two patients (8 men, 14 women) underwent ambulatory polysomnography in one of the three last nights of the placebo and of the 'blind' melatonin period. Sleep analysis used visual scoring performed on screen (combination of audio-visual scoring) according to standard criteria [25, 26]. The following parameters were derived from the hypnogram: sleep onset latency, time of sleep onset, REM latency, amount of REM sleep, number and duration of awakenings, actual sleep time and amount of slow wave sleep (stages 3 and 4).

REM episodes were defined as a series of consecutive sequences of epochs of REM sleep separated by less than 15 min of intervening NREM sleep or waking. Only REM episodes of longer than 1 min were included in the analysis. REM latency was calculated as the number of minutes from sleep onset to the first epoch of REM sleep.

Wrist activity was recorded in 13 patients during the last three days of the placebo and of the 'blind' melatonin period. Sleep onset as derived from the wrist activity records, was estimated according to the algorithm employed by Horne et al [27].

Diaries were completed by 22 patients during the four weeks of double-blind treatment. The following subjective estimates of several sleep-related parameters were daily quantified (scale: 0 (bad) - 5 (excellent)) by the patients: mood before going to bed, mood after getting up, the time of going to bed, sleep latency, number of awakenings after sleep onset (waso), duration of waso, the time of waking up, sleep duration, sleep efficiency and refreshed feeling after bed out. When the patients had finished the study, these results were averaged...
for each patient for the two periods of double-blind treatment and statistical analysis was performed.

Analysis

*Melatonin plasma curves*

The following parameters of each 24-h curve were calculated and are shown in Figure 11.

1. Dim Light Melatonin Onset (DLMO) (10 pg/ml) as defined by Lewy et al [13]. Since in some patients the diurnal baseline level was increased after treatment possibly due to a lower clearance of exogenous melatonin, a DLMO based on a fixed concentration of 10 pg/ml may cause misinterpretation of the results. Therefore we have also calculated alternative parameters, which were expected to give more information about any changes in the form of the curves. These parameters were:

2. Start time: the time after which the next two consecutive measurements exceeded a threshold, defined as twice the mean of the 10 lowest melatonin values over twenty-four hours.

3. Stop time: the offset of the nocturnal melatonin elevation; the time after which the following two consecutive measurements were less than 10 pg/ml, on the declining slope.

4. Peak time: the middle time of the three highest consecutive melatonin values.

5. Duration: the time during which the melatonin concentration is above 10 pg/ml.

These parameters were calculated from the individual curves before and after treatment.
Figure 11: Different parameters calculated from the 24h melatonin plasma curve

Statistics
To test for significant phase shifts t-tests for matched pairs were used. All parameters of the melatonin curves and temperature curves have been correlated by Pearson correlation. All parameters of the sleep log and polysomnography were tested by Wilcoxon signed rank test (2-tailed).
Results

*Melatonin and rectal temperature*

The mean plasma melatonin curves before and after treatment are shown in Figure 12 and the mean values of their respective parameters are shown in Table 5. The mean (±SD) advance shift of the DLMO value was 98 ± 69 minutes.

*Figure 12: Mean plasma curves from the DSPS patients (n=25) before and after treatment.*
Table 5: Mean ± SD (min) values of the parameters of the melatonin plasma curves of the patients before and after treatment (n=25). Parameters are explained in the text under ‘Analysis’.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>t-Value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLMO</td>
<td>23:17h ± 138</td>
<td>21:39h ± 94</td>
<td>7.00</td>
<td>0.001</td>
</tr>
<tr>
<td>Start time</td>
<td>22:21h ± 134</td>
<td>21:29h ± 92</td>
<td>3.55</td>
<td>0.002</td>
</tr>
<tr>
<td>Stop time</td>
<td>08:52h ± 163</td>
<td>08:13h ± 107</td>
<td>2.01</td>
<td>0.056</td>
</tr>
<tr>
<td>Peak time</td>
<td>03:48h ± 134</td>
<td>02:44h ± 121</td>
<td>2.13</td>
<td>0.044</td>
</tr>
<tr>
<td>Duration</td>
<td>9.65 h ± 0.45</td>
<td>10.56h ± 0.41</td>
<td>2.76</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Nearly all alternative phase markers showed a significant advance after melatonin treatment. The mean curves of Figure 12, however, strongly suggest that this advance only applies to the rising part of the curve. This is corroborated by the findings of a non-significant effect upon the offset and a significant increased duration of the curve after treatment.

The mean body temperature curves are shown in Figure 13. The mean time (± SD) of the minimum of the fitted temperature curve before treatment was 04:40h ± 36.1 min. After treatment this was 04:11h ± 62.4 min, which was not significantly earlier than the value before treatment ($t_{12} = 1.60, p=0.133$). Employing half an hour as the minimal value for the establishment of a phase shift, 6 patients showed an advance of their temperature curve, 3 patients a phase delay, and 5 patients no change.
Correlation matrices

In an attempt to test any differential effect of melatonin treatment upon the different features of the melatonin curve, correlations were calculated between the values before and after treatment, as shown in Table 6.
Table 6: Pearson correlations for the parameters of the melatonin curves, before (data in front of '/') and after (data behind '/') treatment. Parameters are explained in the text under 'analysis' (n=25).

* P < 0.05 (2-tailed)
** P < 0.01 (2-tailed)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DLMO</th>
<th>Start time</th>
<th>Stop time</th>
<th>Peak time</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLMO</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start time</td>
<td>.92'' / .81''</td>
<td>.53'' / .26</td>
<td>.68'' / .45'</td>
<td></td>
</tr>
<tr>
<td>Stop time</td>
<td>.53'' / .26</td>
<td>.68'' / .45'</td>
<td>.58'' / .67''</td>
<td></td>
</tr>
<tr>
<td>Peak time</td>
<td>.60'' / .28</td>
<td>.65'' / .41'</td>
<td>.58'' / .67''</td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>-.12'' / -.54''</td>
<td>.17 / -.23</td>
<td>.44'' / .67''</td>
<td>.25 / .37</td>
</tr>
</tbody>
</table>

For DLMO, start time, stop time and peak time the correlation between all parameters, except between stop time and peak time, decreased after treatment. This suggests an idiosyncratic effect of melatonin upon the different curve parameters. However, most correlations involving duration increased.

Correlation between DLMO and temperature minimum before treatment was 0.41 (P>0.05; n=13), after treatment with melatonin the correlation between these two parameters was decreased to 0.32 (P>0.05; n=13).

Hypnograms

The only hypnogram parameter which was significantly affected by the melatonin treatment was sleep onset latency. Its mean value decreased from 25.3 min ± 26.8 min during placebo to 15.3 min ± 16.2 min during melatonin (Wilcoxon z_{21}=3.04, p=0.002).

No significant influences could be found on the other sleep architecture parameters.

Even the sleep onset times were not significantly affected by melatonin (Wilcoxon z_{21}=1.62, p=0.10).


Actigraphy

The sleep onset times as estimated from the wrist activity records in the 'blind' melatonin period were 00:03 h ± 29.6 min (mean ± SD) and in the placebo period 00:41 h ± 31.5 min (mean ± SD), giving evidence of a significant advance of the sleep period ($t_{12}=3.78$, $p=0.003$).

Sleep log

Only one sleep log parameter turned out to have changed significantly by melatonin treatment. The patients felt significantly (Wilcoxon $z_{21}=2.62$, $p=0.01$) more refreshed during the period of melatonin than placebo.

Selection

Since the range of DLMO values before treatment of our patients was between 20:40h and 02:09h (one outlier of 08:01h) and DLMO in a 'normal population' is between 18:00h and 21:30h [23] we selected several parameters from the hypnograms and diaries of those patients that had an original DLMO later than 21:30h (13 women, 7 men). This selection resulted in one extra significant sleep log parameter and one extra significant hypnogram parameter in the group patients with an original DLMO later than 21:30h: mood after getting up was significantly better during melatonin (Wilcoxon $z_{10}=2.40$, $p=0.02$) and sleep onset was significantly earlier (Wilcoxon $z_{10}=2.28$, $p=0.03$) during the melatonin period (mean onset ± SD: 00:05h ± 16.6 min) than in the placebo period (mean onset ± SD: 00:37h ± 18.1 min).

Discussion

By treating DSPS patients with 5 mg of melatonin, administered 5 hours before their individual DLMO, the onset of their endogenous melatonin production could be advanced about 1.5 h. No significant phase advance was observed for offset of the melatonin curve, nor for the through of the body temperature curve, however. Actigraphy showed a significant advance of sleep onset during melatonin use. Polysomnographic registrations showed a significant decrease of sleep onset latency and a tendency to an earlier sleep onset during melatonin treatment, which reached statistical significance when only patients with
a DLMO later than 21:30h were selected. In agreement with Dahlitz et al [3], no influence of melatonin on sleep architecture was observed. During melatonin treatment patients felt significantly more refreshed in the morning.

In previous studies on the effects of melatonin in DSPS patients, melatonin was administered at fixed times, e.g. at 22:00h in [3] and at 19:30h in [12]. In these studies, melatonin administration caused a significant advance of sleep onset. In addition, in both studies an advance of the wake-up times was observed. A unique aspect of our study compared to these earlier studies concerns the individual assessment of the time of melatonin administration. In healthy volunteers Lewy et al showed that the advancing properties of melatonin are maximal if melatonin is administered 5 hours before the onset of the evening rise of the endogenous melatonin production, the so-called Dim Light Melatonin Onset (DLMO) [13]. In the present study we have based our treatment of DSPS patients on this outcome. As judged from our results however, it is not clear, if this individualized timing gives better clinical effects, compared to the results of experiments with melatonin administration at fixed times [3, 12]. In the latter studies sleep onset was advanced at least to the same or even to a larger extent as compared with the present study. Probably, a larger advance could have been accomplished through a successive advancement of the time of melatonin administration. For, Deacon and co-workers [28] have shown a shift of the endogenous body clock and therefore the phase response curve induced by a single oral dose of melatonin within one day. In another, single-case study of our group [29] this has been confirmed.

Lewy and Sack [23] pointed out that the use of DLMO for determining the phase position of the melatonin rhythm has several advantages over other points of the curve. Most importantly, markers which reflect later points of the nocturnal curve may be perturbed by processes causing subsensitivity of beta-adrenergic receptors in the pineal and depletion of melatonin precursors. Therefore DLMO seems to present the best estimate of the timing of the nocturnal melatonin curve. The present study shows that DLMO seems to be an appropriate marker to diagnose DSPS.

The baseline DLMO times of our DSPS patients varied from 20:40h - 02:00h. This range is larger and shifted to a later mean time as compared with the values published for healthy
subjects (18:00h-21:30h [30]) and for patients suffering from winter depression (19:30h-
23:30h [23, 31]).

It remains to be seen, however, if DLMO is the best parameter to use for the assessment of
the effect of melatonin treatment. For our results indicate that the different phase markers
of the melatonin curve may be differentially affected by melatonin treatment. Under the
influence of melatonin treatment, the shape of the melatonin curve changed, i.e. the rising
slope advanced while the falling slope did not, as was reported also by Deacon et al [32].
Similar changes of the shape of the curve have been found before and have led to the
hypothesis of the two-oscillator model with an oscillator for the onset of melatonin
('evening' oscillator) and for the offset of melatonin ('morning' oscillator) of melatonin
regulation [33, 34]. Alternatively, it is a matter of debate whether exogenous melatonin has
any effect at all upon the circadian timing of the endogenous melatonin production [35]. In
an attempt to formulate a more parsimonious explanation of the present results, we present
here two hypotheses, both in terms of the biochemistry of the pineal.
The first hypothesis is based on the assumption of enzymatic dysfunctioning in DSPS
patients. Maybe one of the enzymes involved in the melatonin synthesis is less active in
DSPS patients, causing a relatively late start of the melatonin production. Important
enzymes in the synthesis of melatonin from tryptophane are: N-acetyltransferase (NAT),
which is released by light- induced impulses from the Suprachiasmatic Nucleus (SCN)
regulating the rate of melatonin synthesis [36] and HydroxyIndole-O-Methyl Transferase
(HIOMT) [37]. Exogenous melatonin bypasses these enzymes and therefore may allow a
temporal recuperation of the enzymatic activity. Within this view, the administration of
exogenous melatonin constitutes a masking factor which selectively affects the onset of the
melatonin curve. Consequently, after a period of melatonin administration, this enzymatic
activity may have been sensitized. This would facilitate the triggering of the synthesis and
release of endogenous melatonin, and thus lead to an advance of its nocturnal rise. It
should be noted that this hypothesis only involves the rising slope of the melatonin curve,
and not its falling slope. In addition, the advance of the rising slope of the melatonin curve
may be due to an increased concentration of one or more precursors of melatonin, which
has been build up during treatment. This may lead to a temporarily faster and therefore
earlier time of melatonin synthesis when melatonin administration is stopped. In a similar
vein, Claustrat et al [38] explained the significantly lower endogenous melatonin concentrations in depressive patients by their lower serotonin precursor concentrations.

A second, more pharmacological explanation of the advance of the start of the nocturnal endogenous melatonin production might be given in terms of a supersensitivity of the $\alpha$ and $\beta$ receptors which are involved in the stimulation of the pinealis [36]. Supersensitivity of target organs or proliferation of receptors by pharmacologic agents is described for several receptors and organs [39]. When the administration of exogenous melatonin is stopped, less stimuli from the SCN may be necessary to start activation of the endogenous pathway for synthesis and release of melatonin.

No significant influences could be found on the sleep architecture parameters. Actigraphy showed an advance of sleep onset, and polysomnography a decrease of sleep onset latency. An advantage of actigraphy as compared with polysomnography for determining sleep onset is that actigraphy 1. is less intrusive; and 2. covered three days, and polysomnography only one day. Therefore actigraphy seems more representative of the habitual sleep-wake behaviour. Considering the absence of a significant advance of the 24 h curve of body temperature and offset of the melatonin curve, it seems unlikely that the advance of sleep onset is due to a shift of the circadian oscillator. Although a circadian mechanism cannot be fully excluded by our results, a 'soporific' effect of exogenous melatonin may be a better alternative [40]. Moreover, melatonin appears to improve the subjective sleep quality and the refreshed feelings in the morning.

In our patients the body temperature trough was not advanced significantly by exogenous melatonin. This is in contrast with the study by Kräuchi et al [41], who reported a phase advance of the body temperature rhythm of healthy volunteers after a single administration at 18:00h of 5 mg melatonin. In our patients neither the baseline measurements of melatonin and temperature nor the post-treatment measurements showed a correlation. A close relationship between the time of the temperature trough and the time of the peak of melatonin has been demonstrated by Cagnacci et al [14]. The lack of correspondence between the responses of the rhythm of melatonin and of body temperature in our patients may be due to the fact that some of the patients already showed a relatively early temperature minimum. However, even for a selection of patients with a baseline
temperature through later than 4:30h we did not find a significant advance of temperature minimum.

Ozaki et al [42] reported a mean temperature trough for their DSPS patients at 7:17 h, which is considerably later than the mean time of 04:40h observed in the present study. The mean time for the patients in the present study is comparable with the mean time of 04:56 h observed for the control group of the Ozaki study, and falls midway between the through times reported for ambulatory recordings of the body temperature rhythms of morning-type and evening-type individuals [43]. So, the temperature trough of our patients was of no value for diagnosing DSPS. The discrepancy between our results and the results of Ozaki et al. may be due to masking of temperature. Circadian phase markers such as body temperature or cortisol are easier influenced by masking effects than melatonin [44]. The finding that neither REM-sleep nor body temperature have been changed by the melatonin treatment of our study is in accordance with findings in free-running subjects by Czeisler et al [45]. These authors demonstrated that the occurrence of REM sleep is controlled, by an endogenous circadian oscillator which is coupled to the one generating the body temperature cycle. The question if there is a relationship between melatonin and body temperature remains unanswered by the results of our study. Minors et al [46] could not find a link between temperature and melatonin rhythmicity in isolation chamber experiments that imposed a 22.8 h day on their subjects. Sharp et al [47] were also unable to demonstrate a relationship between the shift in temperature rhythm seen in chronically sleep deprived surgical residents, and the rhythm of melatonin. Folkard et al [48] gave oral melatonin in pharmacological doses for a month and stabilized sleep onset in a blind man without changing the phase of his temperature rhythm. Strassman et al [49], however, concluded from their study that melatonin secretion contributes to the lowering of core body temperature seen in the early morning in humans, probably due to direct hypothermic effects of melatonin [50].

A final question is if it is possible to discontinue melatonin administration after a period of treatment without a loss of its clinical effects. In the patients of Duhlitz et al [3] the beneficial effects were lost when treatment was stopped. In three of our patients melatonin could be discontinued after 6-12 months without a relapse, i.e. a return of the original delayed phase. The difference in characteristics between patients with and those without a
relapse is not clear yet. It might be that melatonin suppletion can only be stopped if the temperature trough is advanced to the same extent as endogenous melatonin. This hypothesis will be worked out in future studies.

**Literature**


3.2 THE EFFECT OF MELATONIN ADMINISTRATION ON SLEEP, DAYTIME SLEEPINESS AND PERFORMANCE AFTER A PERIOD OF NIGHT WORK

Summary

Thirty shiftworkers complaining of after-effects in the period following night work were treated with melatonin in a double-blind placebo-controlled crossover study. Following two successive night shift periods, melatonin 5 mg or placebo was administered for three consecutive days, at 19:00 h, starting on the first evening after the last night shift. Twenty-four participants, 8 men and 16 women, completed the study. Eighteen subjects were employed in nursing, six had other occupations. The night shift started between 22:00h and 23:00h and ended 8 or 9 hours later between 06:00 and 08:00h.

The impact of treatment was assessed by the use of a sleep log, actigraphy, the measurement of rectal temperature and the measurement of reaction time and vigilance performance. The results showed that melatonin administration increased the duration of night sleep (sleep duration with melatonin ± SE: 472.3 min ± 17.1 versus placebo 425.9 min ± 17.6; p<0.05), subjective well-being upon awakening the following morning (3.03 ± 0.14 versus 2.90 ± 0.17; p<0.05), and subjective daytime sleepiness (2.77±0.13 versus 2.49±0.15; p<0.05). No effect was observed on the timing of sleep onset nor on the phase of the body temperature rhythm.

Performance measurements after three days of melatonin intake showed that the vigilance decrement (analysed as a function of four successive 7.5 min blocks) was prolonged ( F3,69 = 4.77; p<0.01, ε=0.333). In addition, the 10% slowest response times in a complex reaction task significantly increased (1274±61 ms versus 1157±63 ms; t23=2.27; p<0.05). It was concluded that the results of the present study indicate that the administration of melatonin may reinforce the recovery of sleep quality after a period of night work.

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6 JE Nagtegaal, GA Kerkhof, MG Smits, T van den Heuvel. This chapter is submitted to Chronobiology International. May 2001
Chapter 3.2

Introduction

Complaints of insomnia and/or excessive daytime sleepiness are prominent sequelae of shift work [1]. The Shift Maladaptation Syndrome (SMS) is characterised by (1) chronic sleep disturbance and waking fatigue; (2) gastrointestinal symptoms (e.g., dyspepsia, constipation, diarrhoea), (3) alcohol or drug misuse or abuse, (4) higher accident or near-miss rates; (5) depression, malaise or personality changes; and (6) problematic interpersonal relationships [2]. These symptoms may appear at any stage of shift work experience, i.e. soon after starting shift work or even after 20 years of well-tolerated shift work [3]. Between 5% and 20% of shift workers develop moderate to severe symptoms soon after starting shift work. Because of health complaints, 20% to 30% of the workers quit shift work within two to three years after having started shift work [4].

Some shift workers mainly complain of after-effects, i.e. problems in the period immediately following night work [5]. Meijman et al. [5] reported that the quality of the three night sleeps after a night shift period was significantly worse than that after a morning shift period. Therefore, recovery periods of two or three days might be too short to reach full recovery, resulting in the long-term accumulation of a sleep deficit and associated fatigue. The authors hypothesised that such an accumulation effect may play an important role in the pathogenesis of SMS.

Thus, one might say that in individuals suffering from SMS the adverse effects of night work have generalized in such a way that they never really recuperate. One of the measures to prevent the development of SMS may be to counteract the problems during the period of night work, e.g. by facilitating the adaptation to the shifted sleep period. The administration of bright light during the early part of the night has been shown to phase delay the circadian rhythmicity and thereby improve (day-) sleep and performance in subjects working a simulated night shift [6]. Similar though weaker - chronobiotic effects have been reported for exogenous melatonin, the analogue of the neurohormone which is produced by the pineal gland during the dark phase of the day-night cycle. When administered in the early evening, it reportedly causes a circadian phase advance, and when administered in the early morning, it may induce a phase advance. [7]. It remains to be seen, however, if adaptation should be pursued, especially in case of rapidly rotating
shift work. Adaptation to night work then would alternate with re-adaptation to a day-oriented lifestyle, leading to a more or less permanent state of flux of circadian rhythmicity. An alternative approach might be to reinforce the re-adaptation after a period of night work, rather than the adaptation during the period of night work. The counteraction of the after-effects then would facilitate the short-term recovery from night work, as well as prevent the long-term development of SMS. Melatonin might contribute significantly to this re-adaptation, especially because not only chronobiotic but also sleep inducing, soporific effects have been reported [8]. Melatonin has been shown to increase subjective sleepiness, independent of the time of administration [9 - 14]. When administered in the evenings of the after night work period, it may (1) have a phase advancing effect, sufficient to counteract the small phase delay which is likely to have occurred in the course of the night work period (chronobiotic effect); and (2) improve sleep by increasing evening sleepiness (soporific effect).

The goal of this study was to assess if melatonin administered in the early evening during the days after a period of night work may act as a countermeasure, by facilitating the recovery from the effects of night work. Effects on sleep parameters were measured during the days of melatonin intake, while body temperature [15] and daytime performance were measured after the last day of melatonin intake.

Methods

Subjects

Thirty subjects suffering from Shift Maladaptation Syndrome (SMS), were included in this study.

The following inclusion criteria were used:

I. A minimum of three of the following symptoms of SMS [2] for a period of at least 1 year during the transition from the night to day shift (the so-called 'after-effects'):

(1) chronic sleep disturbance resulting in sleepiness during the day;
(2) gastrointestinal symptoms (e.g., dyspepsia, constipation, diarrhoea);
(3) depression, malaise or personality changes;
(4) difficult interpersonal relationships;
II. Minimum age of 18 years;
III. A minimum of 2 periods of 3 successive night shifts within two months;
IV. No medication except for study medication.

The following exclusion criteria were used:
I. Sleep disorder unrelated to shift work;
II. Use of hypnotics and antidepressives in the month before the start of the study;
III. Alcohol use of more than 2 units a day
IV. Any prior use of melatonin;
V. Liver diseases [16,17];
VI. Renal failure [18];
VII. Severe neurological or psychiatric disorders [9,19];
VIII. Pregnancy or a wish to become pregnant within the study period.

The study was approved by the local Medical Ethical Committee. Before they were included in the study, informed consent was obtained from all 30 patients. All suspected adverse drug reactions were reported.

Six of the thirty patients who entered the study decided to stop before the end of the study, based on personal circumstances. Eight men and sixteen women finished the study. Several parameters of this group are summarised in Table 7.

Table 7: Parameters of the participants who finished the study (n = 24)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>39.8 ± 7.8</td>
<td>23 - 52</td>
</tr>
<tr>
<td>Years night shifts [years]</td>
<td>14.9 ± 8.5</td>
<td>1 - 32</td>
</tr>
<tr>
<td>Period between the night shifts [days]</td>
<td>26.8 ± 11.2</td>
<td>7 - 50</td>
</tr>
<tr>
<td>Number of nights in one period [nights]</td>
<td>4.8 ± 1.9</td>
<td>3 - 7</td>
</tr>
<tr>
<td>Period since start of complaints about ‘after-effects’ [years]</td>
<td>5.9 ± 4.1</td>
<td>1 - 15</td>
</tr>
<tr>
<td>Period of symptoms after one night shift [days]</td>
<td>4.5 ± 3.6</td>
<td>2 - 7</td>
</tr>
</tbody>
</table>
Eighteen of the subjects were employed as a nurse, six had other occupations (one policeman, four industrial process operators and one pump attendant). Seven participants, all nurses, worked in permanent night shifts (seven night shifts, seven days off), the others had shifts on rotation. Fourteen of the nurses worked 9 hours per night shift (from 22:45h - 7:45h), the other subjects worked 8 hours per night shift, starting between 22:00h and 23:00h and finishing between 6:00h and 7:00h. During both night shift periods the subjects attempted to fall asleep between 8:00 – 10:00 h. During both after-night shift periods the subjects attempted to fall asleep between 22:30h and 0:30h. Twelve of the twenty-four subjects received melatonin in the first test period and placebo in the second, while the other twelve received the opposite sequence. There was no significant difference in age or other subject parameters between the two groups.

Materials

Melatonin 5 mg (Helsinn Chemicals SA, Biasca, Switzerland) was mixed with microcrystalline cellulose in a gelatine capsule. The placebo consisted of pure microcrystalline cellulose and looked identical to the melatonin capsule.
Study protocol

The design of the study is illustrated in Figure 14.

*Figure 14: Design of the study*

<table>
<thead>
<tr>
<th>First Period</th>
<th>Second Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Night shift</td>
<td>Night shift</td>
</tr>
<tr>
<td>Interval</td>
<td>Interval</td>
</tr>
<tr>
<td>After-Night shift</td>
<td>After-Night shift</td>
</tr>
<tr>
<td>No shifts</td>
<td></td>
</tr>
</tbody>
</table>

- **Day 0**
  - Inclusion
  - Morning/Evening questionnaire

- **Day 3**
  - Reaction & cognition tests

- **Evening 4**
  - Sleep log
  - Actigraph
  - Smart reader

- **Ending at day 4, at 8:00 h**

- **Period 2 as period 1, medication cross over:**
  - Placebo or Melatonin

The study covered a period of 34.4 ± 10.7 days (Mean ± SD), with a range of 24 - 56 days. In this period two consecutive periods of night shift were studied. The 'after-night-shift period' is defined as: starting at 19:00h on the first evening (day 0) after the last night shift...
and ending after the fourth night on the morning of day 4, at 8:00 h. The intake of medication was started at the beginning of the 'after-night-shift period' at 19:00h (day 0) and repeated the following two evenings (day 1 and day 2). The study medication was administered in a double-blind, cross-over design. During the 'after-night-shift period', activity monitoring and sleep log recordings were made. Body temperature was recorded starting at 8:00 h of day 3 of the 'after-night-shift period' and ending 24 h later. On the afternoon of day 3 performance tests were administered between 14:00h and 16:00 h.

Recordings and Analyses

Morning-type and evening-type questionnaire
At inclusion, all subjects were asked to complete a morning-type / evening-type questionnaire [20].

Sleep log
During the 'after-night-shift' periods of both conditions the subjects daily recorded the following sleep-related variables: bed-in time, difficulty of falling asleep (5-points rating scale), estimated time of falling asleep, number of awakenings after sleep onset, time of final waking-up and subjective quality of sleep (5-points rating scale). During the waking part of the day, mood after getting-up (5-points scale), well-being upon awakening (5-points scale), subjective sleepiness (5-points scale) and napping behaviour were assessed. The 5 points scale was a linear scale: a score of 1 point was for the worst condition, a score of 5 points was for the best condition
Daytime sleepiness was rated every two hours. The ratings for 12,14,16,18,20 and 22 h were analysed, after linear interpolation of the missing values.

Actigraphy
During the melatonin and placebo conditions the sleep-wake behaviour was verified by actigraphy [21]. The method that was used was similar to the method described before [22]. Sleep onset was derived from the wrist activity records as estimated according to the algorithm employed by Horne et al [23] (start of the first period of 7 minutes with absolute
rest after bed in time). Using the concomitant sleep log data, additional sleep related parameters were calculated: sleep latency, total sleep time, motor activity during sleep (average number of counts as percentage of the maximum number per epoch) and sleep fragmentation (number of clusters of successive zero-count epochs divided by the total number of zero-count epochs).

**Body temperature**

During both conditions, on the morning of day 3 of the 'after-night-shift period' at 8:00 h ambulatory recording of rectal temperature was started. This recording lasted 24 hours and was performed with a Smart Reader Data Logger (ACR Systems Inc) and a probe (Yellow Springs, YSI 401 D), sampling one value every 2 minutes. Ambulatory recording of the rectal temperature rhythm is likely to be confounded by several masking effects associated with sleep and activity. Therefore, the temperature values (240 samples) were 'de-masked' using the actigraphy data, following a modification of the method described by Minors and Waterhouse [24].

The basic concept of this 'purification method' is that a measured rhythm consists of exogenous and endogenous components that act additionally. The shape and timing of the exogenous component depend upon several factors, including the individual's sleep and activity cycle, sleep lowering the body temperature and different types of activity raising it by different amounts. The endogenous component, whose phase is sought, is assumed to be described by a cosine curve.

The method requires a record of the motor activity in the previous half-hour. The method then 'purifies' the observed temperature data according to the following rules. Half-hour sums of raw activity data are categorised into 8 categories. The highest category has a lower limit, which is determined by visual inspection of the amplitude histogram of activity values. The limits for the other 7 categories were determined by dividing the remaining range of activity values by 7. Subsequently, the temperature data were fitted to a cosine curve, and residuals calculated. For each category separately, the mean residual 'error' was used to correct the corresponding temperature values. The process of fitting and correcting the temperature data was iterated until a pre-set criterion was reached. The maximum of the fitted curve served as phase estimate of the circadian body temperature rhythm.
Performance

On the afternoon of day 3 of the 'after-night-shift period' a vigilance test and two reaction time tests were performed between 14:00 and 16:00 h. The Mackworth clocktest [26] was used to measure the subjects' vigilance. In this test a clock is shown on a computer screen and a second-hand moves in discrete steps around the face. Each step occurs within a 1-second interval. During the 30 minutes test period, at long and irregular intervals, the hand travelled twice the usual distance in the same amount of time (i.e. in 'double jumps'). The double jumps were defined as targets: 112 in total. The subject was instructed to press a key within 1 second after the detection of a target. From the four different types of response proportions (hits, false alarms, misses, correct rejections) an index of perceptual sensitivity (d') and an index of response bias (log v) were calculated [26]. In addition, response latencies were recorded. In order to assess any time-on-task effects, response latencies and hit-proportions were analysed as a function of four successive 7.5 minutes blocks.

After the Mackworth Clocktest, two reaction time tests were administered. In both reaction time tests a dot was shown on the screen. To the left or to the right of the dot the word 'LEFT' or 'RIGHT' was shown. In the simple reaction time test (SRT) both the left and right shift key could be used to react. In the other reaction time test, also called the complex reaction test, the opposite (incompatible) shift key had to be used; so when the word 'LEFT' was shown one had to press the right shift key and vice versa. Both tests contained 40 trials and took 5 minutes to complete. Before the test started a short instruction followed by eight practice trials was given.

Analyses

Sleep log and actigraphic variables were analysed by Wilcoxon rank tests, while temperature, vigilance and reaction time data were analysed by t-tests and repeated measures analyses of variances (ANOVA's), with Medication (2) and Time on Task (4) as within-subjects factors (between brackets the number of levels). The sleepiness ratings were analysed in a repeated-measures ANOVA, with Medication (2), Day (3) and Time of Day (6) as within-subjects factors. Because of potential inhomogeneity of variances and covariance, the degrees of freedom were corrected by
using the Huynh-Feldt procedure. The original degrees of freedom and the correction factor $\epsilon$ are reported whenever applied.

Results

**Morning-type and evening-type questionnaire**

From the 24 patients who completed the study, 13 were characterised as ‘intermediate types’. Four of the 24 were definite evening-types, 1 was a moderate evening-type, 3 were definite morning-types and 3 were moderate morning-types.

**Sleep wake behaviour**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Method</th>
<th>Results placebo</th>
<th>Results melatonin</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST, night 3</td>
<td>Sleep log</td>
<td>422 ± 97</td>
<td>480 ± 85</td>
<td>$Z = -2.54$ $p = 0.011$</td>
</tr>
<tr>
<td>TST, nights 1-3</td>
<td>Actigraphy</td>
<td>426 ± 85</td>
<td>472 ± 82</td>
<td>$Z = -2.29$ $p = 0.022$</td>
</tr>
<tr>
<td>Mood at bedtime, nights 1-3</td>
<td>Sleep log</td>
<td>3.77 ± 0.45</td>
<td>3.47 ± 0.68</td>
<td>$Z = -2.05$ $p = 0.04$</td>
</tr>
<tr>
<td>Subjective sleep quality, nights 1-3</td>
<td>Sleep log</td>
<td>3.26 ± 0.54</td>
<td>3.59 ± 0.58</td>
<td>$Z = -1.95$ $p = 0.05$</td>
</tr>
</tbody>
</table>

As can be seen in Table 8 for the third night, total sleep time as derived from the sleep log was significantly longer for the melatonin than for the placebo condition ($p<0.05$). Actigraphy confirmed this effect of melatonin on total sleep time for the first three nights of the ‘after-night-shift period’ ($p<0.05$). No other actigraphy parameters were statistically significant. Two other sleep log parameters, however, differed significantly between the conditions: ‘mood before bed-in time’ was significantly better for the placebo than for the melatonin condition ($p<0.05$), while people felt significantly ‘better upon awakening the following morning’ during melatonin than during placebo treatment ($p<0.05$).
Sleepiness

All three main factors had a significant impact upon the sleepiness ratings. During the melatonin condition the subjects reported a higher level of sleepiness than during the placebo condition (mean ± SE) ratings for melatonin vs. placebo: 2.77 ± 0.13 vs. 2.49 ± 0.15; F_{1,14} = 6.53, p < 0.05, ε = 1.0). Gradually, in the course of the three days of the ‘after-night-shift period’, the overall level of sleepiness decreased significantly (F_{2,28} = 9.09, p < 0.01, ε = 0.997), following a linear trend (F_{1,14} = 22.85, p < 0.001). As suggested by Figure 15, sleepiness was also influenced by the time of day (F_{5,70} = 16.70, p < 0.001, ε = 0.946), with a trend which had significant linear (F_{1,14} = 71.50, p < 0.001) and quadratic components (F_{1,14} = 5.46, p < 0.05).

As evidenced by significant two-way interactions, these overall effects were not invariant with respect to medication and day of the ‘after-night-shift period’. The factor Medication interacted with both the factor Day (F_{2,28} = 7.77, p < 0.01, ε = 1.0) and the factor Time of Day (F_{5,70} = 6.80, p < 0.001, ε = 0.927). From Figure 15 it appears that, whereas melatonin gave an overall increase of sleepiness during day 1, its sleep inducing effect during the following two days narrowed down to the evening hours. The Day x Time of Day interaction (F_{10,140} = 4.25, p < 0.001, ε = 0.703), finally, corroborates the observation (cf. Figure 15) that sleepiness during the relatively early hours gradually diminished over the three days.
Figure 15: Course of sleepiness during day 0, 1, 2.
Square is melatonin condition, circle is placebo condition.
Error bar is SEM.

Performance

Neither the signal detection parameters d’ (perceptual sensitivity) and log v (response bias) nor the response latencies (overall and 10% slowest), calculated for the vigilance test, differed significantly between the two medication conditions. Analysed as a function of four successive 7.5 min blocks, the decrement of both the percentage of hits ($F_{3,69}=4.77$, $p<0.01, \varepsilon=0.333$) and response speed ($F_{3,69}=16.12$, $p<0.001, \varepsilon=0.850$) proved statistically significant. The percentage of hits decreased linearly ($F_{1,23}=8.43$, $p<0.01$), with a non-significant tendency of a larger decrement for the melatonin condition(cf. Figure 16).
While the response latencies for the placebo condition only increased from the first to the second block and levelled off thereafter, the response latencies for the melatonin condition appeared to show a sustained increment from the first to the fourth block (cf. Figure 17). This effect of melatonin on the duration of the speed decrement was suggested by a trend of a Medication x Time on Task interaction ($F_{3,69}=2.62$, $p<0.10$, $\epsilon=0.75$).
Figure 17: The response latencies vs. Time (in blocks of 7.5 min) during the MacWorth Clocktest during melatonin and placebo condition. Continuous line and square is melatonin condition, dshed line and circle is placebo condition. The error bars represent Standard Error of the Mean.

The results of the two reaction time tests did not show any significant effect, except for the slowest 10% values of the complex reaction time test, which were larger for the melatonin condition than for the placebo condition (mean ± SD for melatonin vs. placebo: 1274± 61 ms vs. 1157± 63 ms; t_{21}=2.27, p<0.05).

Body temperature

Melatonin had no significant effect on the phase of the 24 h body temperature curve, neither before nor after purification. Mean ± SE phase values of the cosine curves fitted to the raw data for the melatonin versus placebo conditions were 15.95± 0.40 h vs. 16.01± 0.44 h. After purification these values were: 16.05± 0.59 h vs. 16.32± 0.49 h.
Discussion

The present study shows that in shiftworkers complaining of after-effects in the period following night work, melatonin administration in the early evening of the three days following a period of night work increased subjective daytime sleepiness, the duration of night sleep and subjective sleep quality. No effect was observed on the timing of sleep onset nor on the phase of the body temperature rhythm. Vigilance performance and reaction speed, measured on the day following the last melatonin intake, appeared negatively affected by melatonin.

The results of the present study are in general agreement with those of previous studies [27,28], showing that melatonin induced sleepiness and reduced sleep latency. This is confirmed by a recent review [29], which concluded that melatonin, administered to insomniac patients, reduced sleep latency and/or increased total sleep time and sleep efficacy. Therefore, it appears that the primary complaint of shiftworkers suffering from after-effects can be counteracted successfully by the selective use of melatonin.

Sleepiness ratings showed that the subjects in our study felt significantly more sleepy during the day after their first intake of melatonin, an effect that narrowed down to the evenings of the following two days. The increased sleepiness during the first day may result from a reinforcing impact of melatonin on the effect of sleep deprivation accumulated during the previous days of nightwork. As for the evening rise in sleepiness during the following two days, this may only partly be attributed to higher plasma concentrations of melatonin during the evening, since the elimination half-life of melatonin is only about 30-45 minutes [30]. Additional mechanisms are likely to be involved, such as a neuromodulator effect as suggested by Slotten and Krekling [31]. These authors discuss several neuromodulator effects induced by exogenous melatonin, as e.g. on serotonin, on opioid peptides, on GABAergic transmission and on norepinephrine turnover [32]. It is still unknown, however, to what extent these neuromodulator effects represent either events downstream of central rhythm generating systems or a focus of action [32].

We have hypothesised earlier that the temporarily higher level of serotonin, which may result from melatonin intake, may play an important role in the shift of the endogenous
melatonin curve [22]. It would be interesting to measure endogenous serotonin levels and to see if they are related in some way to those of melatonin and subjective sleepiness.

To prevent confounding of the body temperature measurements by the acute temperature lowering effects of melatonin [15], body temperature was only measured the day after the last evening administration of melatonin. As compared to the placebo condition, the melatonin treatment appeared not to have had any effect on the phase of the body temperature rhythm. Thus, these results reinforce the scepticism concerning the existence of a circadian phase-resetting effect of melatonin [33].

Performance measurements after three days of melatonin intake showed that the vigilance decrement, which characterises the time course of performance in a sustained attention task, was prolonged. In addition, the 10% slowest response times (‘lapses of attention’, see [34]) in a complex reaction task significantly increased, also suggesting an impairment of attention. Thus, it appears that melatonin lowers the level of attention (arousal), in particular after some ‘time-on-task’. In the short run, immediately after the start of the task, extra effort can compensate for the decreased level of arousal. After some time, though, effort wanes which has the effects that performance becomes more dependent upon the basal level of arousal [35]. Similar indications of impaired performance as a result of melatonin intake have been reported previously. Dollins and coworkers [9] observed a reduction of the number of correct responses in a Wilkinson vigilance task following daytime administration of melatonin. Suhner et al. [36] assessed the impact of melatonin on driving performance. They found a significant effect on selective attention, measured 1 h after afternoon intake of melatonin. In addition, subjective sleepiness was increased, especially after a lengthy concentration task.

A remarkable aspect of the present results concerns the dissociation of subjective sleepiness and performance. At the time of performance testing, i.e. between 14:00 h and 16:00 h, no melatonin effect on sleepiness was apparent, which suggests that subjects were not aware of any attention deficit. This could mean that melatonin may have affected the ability to self-monitor sustained vigilance performance. A similar conclusion was formulated by Arnedt et al. [37], who compared the effects of prolonged wakefulness and alcohol on measures of subjective sleepiness, simulated driving performance and drivers' ability to
judge impairment. Their findings suggest that drivers have only a modest ability to appreciate the magnitude of performance decrements produced by alcohol.

The results of the present study indicate that the administration of melatonin may stimulate the recovery of sleep quality after a period of night work. Because SMS primarily involves disturbed sleep, melatonin may be used to reduce the symptoms of SMS. Furthermore, it may be speculated that melatonin, if taken systematically during a few days following each night shift period, may have a prophylactic effect and prevent the development of SMS. Such a study would require repeated intraindividual assessments of signs of SMS, in a blind, placebo-controlled design, applied to large groups of subjects.

Literature


