Pharmaceutical, chronobiological and clinical aspects of melatonin
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Part 4

CLINICAL ASPECTS OF MELATONIN

- Melatonin improves quality of life in patients with Delayed Sleep Phase Syndrome
- Melatonin responsive headache in Delayed Sleep Phase Syndrome
- Traumatic brain injury-associated Delayed Sleep Phase Syndrome: successful treatment with melatonin.
4.1 EFFECTS OF MELATONIN ON THE QUALITY OF LIFE IN PATIENTS WITH DELAYED SLEEP PHASE SYNDROME

Abstract

Objective: The purpose of this study was to compare health related quality of life of Delayed Sleep Phase Syndrome (DSPS) patients with a random Dutch sample and four samples of patients with other chronic conditions. We also investigated the effectiveness of treatment with 5 mg of melatonin on the quality of life of DSPS patients.

Methods: Forty-three DSPS patients completed a quality-of-life questionnaire (Medical Outcome Study Short Form-36 (MOS SF-36) Health Survey) just before and 2-9 months after participation in a clinical trial involving the administration of melatonin. Scores were compared with responses to the same survey by a random Dutch sample and by patients with sleep apnea, clinical depression, migraine and osteoarthritis.

Results: MOS SF-36 scales scores were significantly lower in DSPS patients relative to age- and gender-adjusted norms for the Dutch sample. Some health dimensions were more affected and, others less affected, by DSPS compared to the other chronic conditions. Melatonin treatment improved all scales except the scale 'role due to emotional problems'.

Conclusion: DSPS has a unique-significant-quality of life burden that seems to be improved by treatment with melatonin.

Introduction

Delayed Sleep Phase Syndrome (DSPS) is an infrequently reported cause of severe insomnia [1], which results from a dysregulation of the circadian sleep-wake rhythm. DSPS is associated with major depression and severely disrupted work or social functioning. It is more resistant to treatment than other sleep disorders [1,2]. The extent to which health status is impaired in DSPS patients is unknown, nor its change after treatment. In a review article published in 1995, Regestein concluded that treatment is difficult and often multiple and varied treatments are required [3].

Recently, in addition to earlier clinical experiments [4,5], we have demonstrated that in DSPS the endogenous melatonin rhythm is delayed and that 5 mg of exogenous melatonin, administered 5 h before endogenous melatonin starts to increase in dim light (Dim Light Melatonin Onset, or DLMO [6,7]) advances both the endogenous melatonin rhythm and the sleep-wake rhythm. Previously, we concluded that melatonin appears to be promising treatment for DSPS patients [8]. To determine health status in DSPS patients, and to identify clinically meaningful changes after melatonin treatment, we have studied health status dimensions measured by a quality of life questionnaire, the Medical Outcome Study Short Form-36 (MOS SF-36).

The aim of our study in DSPS patients was to establish quality of life and to compare it with a random Dutch sample (n=1063)[9] and groups of patients with other chronic diseases of which it is already known that the quality of life is affected, including sleep apnea (n=95), clinical depression (n=262), migraine (n=546) and osteoarthritis (n=194) [10,11].

Second, we investigated whether melatonin treatment is effective in improving the quality of life of DSPS patients. Finally, we correlated the endogenous melatonin concentration with the different scales of quality of life.
Methods

Patients

Included in this open trial study were 43 patients (15 men, 28 women) with a mean age (±SD) of 34.1 ± 13.9 years. All suffered from DSPS as diagnosed by a neurologist specializing in sleep disorders according to the International Classification of Sleep Disorders (ICSD) criteria [12]. The mean sleep onset time [±SD] as stated by patients at their first visit to the Sleep Center was 02:04 hours ± 44 min. Sleep offset was not stated precisely, because this measure differed greatly per day per patient, depending on work, duties and social circumstances.

In selecting the patients, the following exclusion criteria were used: age under 12 years, any prior use of melatonin; liver diseases [13,14]; renal failure [15]; psychosis; severe neurological disorders [16,17] and pregnancy or a wish to become pregnant within the study period. The study was approved by the local Medical Ethics Committee. Prior to inclusion, informed consent was obtained from all patients.

Study protocol

The study covered a period of 2-9 consecutive months, depending on the time of inclusion. After inclusion, patients completed the MOS SF36 questionnaire. Within 1 week after completing the questionnaire, patients were required to stay in a hospital unit where 24 h measurement of melatonin was done. Two weeks later, melatonin treatment was started 5 hours before the time that the endogenous melatonin started to increase. On a fixed end-date all patients were asked to fill up the questionnaire again.

Twenty-four hour melatonin curves

Twenty-four-hour curves of endogenous melatonin production were assessed under semi-constant routine conditions [18], 2 weeks before the start of administration of melatonin. In the first group of 20 patients, melatonin production was hourly measured in serum, whereas in the latter 23 patients, melatonin was hourly measured in saliva. When the saliva sampling method became available and was validated by us [19], the medical ethics
committee ordered to switch from serum to saliva sampling, because this is less invasive. The conditions during sample taking and the methods of analysis have been described elsewhere [19, 20]. The time of administration of melatonin was based on this endogenous 24-hour profile. Lewy et al [6,7] showed that the time of the endogenous melatonin production could be advanced maximally if melatonin was administered 5 hours before the time of the individual Dim Light Melatonin Onset (DLMO). The DLMO was calculated as the time at which the melatonin concentration reached a level of 10 pg/ml in serum [7] and has been validated by us to be 4 pg/ml in saliva for DSPS patients [19].
Two weeks after assessment of the 24-hour melatonin curves the patients began taking orally a 5- mg dose of melatonin (Helsinn Chemicals SA, Biasca, Switzerland), mixed with microcrystalline cellulose in a gelatin capsule, every evening 5 hours before the calculated individual DLMO.

*MOS SF-36 questionnaire*

The questionnaire used for measuring physical, functional, mental and social health was the Dutch version of the Medical Outcomes Study Short Form-36 (MOS SF-36)[21-23]. The MOS SF-36 questionnaire contains 36 items, comprising eight scales and a one-item measure of the change in health. The scale include: physical functioning; social functioning; role disability due to physical problems; role disability due to emotional problems; mental health; vitality; bodily pain and general health perceptions [21]. The Dutch version of the MOS SF-36 has a high validity and reliability compared with the Nottingham Health Profile and can discriminate between healthy controls and subjects who suffer from mild health problems [23].

Patients were sent a questionnaire immediately after inclusion in the study, which had to be returned before the admission to the hospital for assessment of the melatonin curve. All patients again completed the MOS SF-36 again after melatonin treatment period that varied from 2 to 9 months, because the endpoint was based on a predetermined end date. Therefore, patients who came in the study 'early' were given longer-term treatment than patients who started later. The scores of the DSPS patients were compared with the Dutch population (a random sample of n=3000 taken from the Register of Population of which the response was n=1063, consisting of 35% men, 65% women, between 18 and 89 years (mean 44.1 years) [9] and to scores of patients with sleep apnea (n=95) [11], clinical
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Depression (n=262) [10], migraine (n=546) [10] and osteoarthritis (n=194) [10] (See Table 9 and).
The item scores of the MOS SF-36 questionnaire were summed to form scale scores and transformed to a 100-point scale. A higher score denotes a higher quality of health. The scores before melatonin treatment were compared with the scores of the same patients after treatment.

Results

**Twenty-four-hour curves**

DLMO (±SD) before treatment occurred at 23:22h (±110 min).

**MOS SF-36 questionnaire**

DSPS patients versus the Dutch sample

A t-test for independent variables was used to test whether there were differences between the MOS scores in a random Dutch sample and the DSPS patients before treatment with melatonin.

Table 9 shows that the scores of the MOS SF-36 were significantly lower in DSPS patients relative to the Dutch sample on all scales. Health change was also significantly worse. Item-scale correlation ranged from 0.38 to 0.76 indicating a high degree of internal consistency for each scale.
Table 9: Mean SF-36 health survey scores (±SD) and effect sizes for DSPS before and after treatment and comparison with the random Dutch sample.

* p<0.01  
** p<0.05

<table>
<thead>
<tr>
<th>Scale</th>
<th>Random Dutch sample (n=1063) [9]</th>
<th>DSPS patients before treatment (n=43)/after treatment (n=43)</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>81.9 ± 23.2*</td>
<td>71.4 ± 24.7</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80.6 ± 20.3*</td>
<td></td>
</tr>
<tr>
<td>Social functioning</td>
<td>86.9 ± 20.5*</td>
<td>54.9 ± 26.2</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td></td>
<td>67.2 ± 19.9*</td>
<td></td>
</tr>
<tr>
<td>Role-physical</td>
<td>79.4 ± 35.5*</td>
<td>27.3 ± 40.8</td>
<td>0.60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>51.7 ± 42.4*</td>
<td></td>
</tr>
<tr>
<td>Role-emotional</td>
<td>84.1 ± 32.3*</td>
<td>65.1 ± 43.6</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>79.1 ± 34.1</td>
<td></td>
</tr>
<tr>
<td>Mental health</td>
<td>76.8 ± 18.4*</td>
<td>62.4 ± 19.2</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td></td>
<td>69.8 ± 16.9**</td>
<td></td>
</tr>
<tr>
<td>Vitality</td>
<td>67.4 ± 19.9*</td>
<td>38.1 ± 17.7</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td></td>
<td>51.5 ± 18.9*</td>
<td></td>
</tr>
<tr>
<td>Bodily pain</td>
<td>79.5 ± 25.6*</td>
<td>67.0 ± 30.8</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>77.7 ± 24.6**</td>
<td></td>
</tr>
<tr>
<td>General health</td>
<td>72.7 ± 22.7*</td>
<td>55.6 ± 20.4</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td></td>
<td>62.6 ± 18.1**</td>
<td></td>
</tr>
<tr>
<td>Health change</td>
<td>52.4 ± 19.4*</td>
<td>37.8 ± 22.7</td>
<td>1.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>66.9 ± 24.2*</td>
<td></td>
</tr>
</tbody>
</table>
**Table 10: Comparison of mean SF-36 health survey scores (±SD) of DSPS patients with those of other groups of patients.**

* * p<0.01
**p<0.05

<table>
<thead>
<tr>
<th>Scale</th>
<th>DSPS patients (n=43)</th>
<th>Migraine (n=546) [10]</th>
<th>Depression (n=262) [10]</th>
<th>Sleep apnoea (n=95) [11]</th>
<th>Osteo-arthritis (n=194) [10]</th>
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<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>71.4 ± 24.7</td>
<td>83.2 ± 18.7</td>
<td>81.8 ± 35.6</td>
<td>75.6 ± 23.1</td>
<td>81.9 ± 45.9</td>
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<tr>
<td>Social Functioning</td>
<td>54.9 ± 26.2</td>
<td>71.1 ± 23.3</td>
<td>68.5 ± 38.9**</td>
<td>71.6 ± 25.2</td>
<td>90.1 ± 40.4*</td>
</tr>
<tr>
<td>Role-Physical</td>
<td>27.3 ± 40.8</td>
<td>54.0 ± 44.4</td>
<td>62.8 ± 35.6*</td>
<td>59.0 ± 36.6*</td>
<td>66.5 ± 71.0*</td>
</tr>
<tr>
<td>Role-emotional</td>
<td>65.1 ± 43.6</td>
<td>66.5 ± 44.4</td>
<td>47.8 ± 61.5</td>
<td>62.1 ± 41.2</td>
<td>85.5 ± 71.0</td>
</tr>
<tr>
<td>Mental health</td>
<td>62.4 ± 19.2</td>
<td>66.4 ± 18.7</td>
<td>53.8 ± 32.4*</td>
<td>68.8 ± 16.8</td>
<td>76.5 ± 32.0*</td>
</tr>
<tr>
<td>Vitality</td>
<td>38.1 ± 17.7</td>
<td>50.9 ± 21.0</td>
<td>49.0 ± 32.4**</td>
<td>40.2 ± 20.9</td>
<td>57.0 ± 41.8*</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>67.0 ± 30.8</td>
<td>51.3 ± 23.4</td>
<td>73.6 ± 37.2</td>
<td>75.6 ± 23.5</td>
<td>69.7 ± 46.0</td>
</tr>
<tr>
<td>General health</td>
<td>55.6 ± 20.4</td>
<td>70.1 ± 21.0</td>
<td>63.6 ± 29.1</td>
<td>61.1 ± 21.7</td>
<td>70.4 ± 33.4*</td>
</tr>
<tr>
<td>Health Change</td>
<td>37.8 ± 22.7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**DSPS patients versus patients with other chronic diseases**

A t-test for independent variables was used to test whether there were differences between the MOS scores in the DSPS patients before treatment with melatonin and the different groups of patients with a chronic disease.

From Table 10 it can be seen that the MOS SF-36 scale scores of DSPS patients before treatment with melatonin were significantly worse than the scores of patients suffering...
from sleep apnea, clinical depression, migraine and osteoarthritis on two scales (social functioning, role disability due to physical problems). The scores for vitality were equal in sleep apnea and DSPS and significantly better for the other diseases.

Effect of treatment with melatonin on DSPS

Multivariate Analysis of Variance (MANOVA) was used to test the overall effect of melatonin on the eight scales and the one-item measure of the change in health of the MOS SF-36 questionnaire. A repeated-measures MANOVA was applied, with treatment period as the between-subjects factor and pre-treatment versus post-treatment as the within-subjects factor. A paired student t-test was used to test whether there was a statistical difference between the MOS SF-36 scores in DSPS patients before and after melatonin treatment.

A treatment period varying from 2 - 9 months between patients could be used, because the MANOVA results showed no effect of the duration of the treatment period ($F_{1,40}=2.77; p=0.10$), and no interaction between period duration and pre-treatment versus post-treatment ($F_{1,40}=0.07; p=0.80$). Melatonin treatment had a highly significant effect ($F_{1,40}=7.66; p=0.009$).

The effect of melatonin treatment showed significant improvements for physical functioning ($p=0.001$), role disability due to physical problems ($p=0.004$), bodily pain ($p=0.012$), mental health ($p=0.011$), social functioning ($p=0.003$), vitality ($p=0.001$), general health perceptions ($p=0.033$) and health change ($p<0.001$). No statistical improvement was seen on role disability due to emotional problems ($p=0.060$). To detect clinically meaningful differences of the quality-of-life measures before and after treatment with melatonin the effect sizes were calculated using the method recommended by Kazis et al [24], taking the mean change in a variable and dividing it by the baseline standard deviation of the variable. An effect size of 1.00 is equivalent to a change of one standard deviation in the sample.

As a benchmark for assessing the relative magnitude of a change, Cohen [25] identified an effect size of 0.2 as small, 0.5-0.8 as moderate and > 0.8 as large. The effect sizes ranged from 0.32 for role due to emotional problems to 1.28 for health change.
Quality-of-life scores and biochemical markers

Pearson's correlation was calculated between the individual DLMO values and differences in scores between before and after melatonin treatment ('treatment effects'). The individual DLMO values before treatment did not correlate significantly with the MOS scores before treatment (r varied from -0.156 to 0.126; p>0.05) for the different scales. Correlations could not be found between DLMO before treatment nor between MOS score differences before or after treatment (r varied from -0.072 to 0.289; p>0.05).

Discussion

With respect to the control sample, in DSPS patients, all quality-of-life dimensions were evidently impaired. The most affected dimensions involved interference of physical health with usual daily activities ('role-physical scale') and of normal social activities ('social functioning') with the level of fatigue or energy ('vitality'). With respect to other chronic diseases quality of life was impaired mostly in DSPS. Only in depression, general mood ('mental health') and the extent to which emotional problems interfere with usual daily activities ('role-emotional') were affected more, whereas, with regard to migraine, 'bodily pain' was impaired more. Consequently, DSPS could be considered a disorder that severely impairs quality of life. Treatment with melatonin improved all quality-of-life dimensions. This improvement was significant for all, except for 'role emotional'. The moderate-to-large effect sizes of the melatonin treatment show that the improvements of the quality-of-life dimensions are of real clinical importance [24]. Melatonin especially improved the dimensions of 'role-physical', 'vitality' and 'health change' scales.

This study was not performed in a double-blind setting and therefore it cannot be excluded that factors as extra attention and attendance, as well as recognition of the syndrome, played a confounding role. However, the long period between starting treatment and completing the MOS SF-36 [26], the size effect of the treatment, and the specific pattern of responses across the different health dimensions make it very unlikely that the effects of melatonin were caused by placebo treatment [11]. From this study it is not clear if the improvement could be attributed to melatonin directly or to one or more of the mediators of which the concentration may be altered after administration of melatonin [20].
The main complaints of DSPS patients are insomnia and tiredness. The main complaint of sleep apnea is daytime somnolence. Tiredness and daytime somnolence can be associated with the quality-of-life dimensions 'vitality' and 'social functioning' [27]. The similarity between DSPS and sleep apnea concerning tiredness and daytime somnolence may explain why we found no difference between these diseases on the 'vitality' scale. 'Social functioning', however, was significantly worse in DSPS patients. We suppose that this can be explained by the social impact of insomnia. Insomnia patients have a higher rate of physical illness and a multitude of psychosocial difficulties [28]. Furthermore, insomnia increases mortality rate due to ischemic heart disease, cancer and stroke 1.6-1.7-fold [29,30].

It can be questioned if the quality-of-life pattern found in our patients could be explained fully by insomnia and tiredness. Some scales, like 'mental health' (a scale that is typical for depressive and nervous feelings) 'physical functioning' and 'general health', show low scores compared to the other chronic diseases, although they do not seem to be as directly related to insomnia and somnolence as the scales 'vitality' and 'social functioning'. Therefore, we suspect that the quality-of-life profile, as found in these patients, is not a simple summation of insomnia and somnolence influences, but may be specifically characteristic of DSPS patients [8].

'Bodily pain' in DSPS patients did not differ from patients suffering from sleep apnea, depression and, surprisingly, osteoarthritis. As expected patients with migraine score lower on this scale. Despite the fact that DSPS is not associated with pain, the scale 'bodily pain' improved significantly by treatment with melatonin, although the effect size is relatively small. On the basis of the chemical similarities between the Non Steroidal Anti-inflammatory Drug (NSAID) indomethacin and melatonin [31,32] we hypothesise that melatonin may be an endogenous non-steroidal anti-inflammatory peptide in a manner similar to endorphins, which are endogenous opioid peptides [33].

The conditions that were selected to compare the quality-of-life profile are useful comparisons because the clinical presentation of each is quite different; that is, some patients with DSPS complain about migraine [34], whereas, in other patients, DSPS coincides with depression [35]. In an earlier study of DSPS patients [3], 75% had previous or present severe depression and 45% were taking antidepressants when they first visited the clinic. This compares with 16% of non-DSPS chronic insomnia patients and 2% of
sleep apnea patients [3]. Experimentally, a delay of sleep has been shown to have a negative effect upon mood [36,37], whereas an advancement of the sleep phase may have a positive effect [38]. On the other hand, depression sometimes coincides with a dissociation between circadian rhythms [39-41]. Thus, although a close relationship between insomnia and depression has been suggested by several studies using psychiatric evaluation, the direction of this relationship remains unclear. Does chronic insomnia lead to development of depression or does insomnia occur secondary to a depressive illness [42,43]?

Several recent studies on melatonin have presented it as a well-established, effective, well-tolerated drug in the treatment of DSPS, whereas conventional treatments with benzodiazepines, antidepressants, vitamin B12 and alcohol have been ineffective [5]. Several investigators have concluded that melatonin decreases the latency of the sleep onset, advances sleep without affecting sleep architecture, and shifts the endogenous melatonin curve to an earlier timepoint [4,5,8]. Patients have been shown to feel more refreshed in the morning during treatment with melatonin [44].

Although we expected that a later DLMO could be improved by melatonin, and therefore should result in a larger improvement in quality of life, we did not find such a correlation. Thus, it is not possible to predict the effect of melatonin treatment by the use of DLMO. The divergent pattern of the MOS SF-36 scores in the DSPS patients and the differing effect of melatonin treatment at the scales suggest that the impairment of quality of life in DSPS cannot be explained merely by insomnia and somnolence. As with DSPS, the endogenous melatonin rhythm is disturbed, probably not only in regard to sleep-wake rhythm, but other physiological diurnal rhythms are also desynchronized.

A double-blind, placebo-controlled trial with a broad selection of physiological markers must be performed to obtain more detailed answers regarding the poor quality of life in DSPS patients and the chronopharmacological mechanism for improvement with 5-mg melatonin treatment administered 5 hours before DLMO.

Literature


44. Smits MG, Nagtegaal JE, Kerkhof GA. Melatonin in delayed sleep phase syndrome. *Chronobiol Int* 1997; 14 (Suppl 1): 159
4.2 MELATONIN-RESPONSIVE HEADACHE IN DELAYED SLEEP PHASE SYNDROME: PRELIMINARY OBSERVATIONS

Summary.

The occurrence of headache and its change after treatment with melatonin 5 mg were studied in 30 patients with Delayed Sleep Phase Syndrome. The medication was taken 5 hours before the endogenous nocturnal plasma melatonin concentration had reached 10 pg/ml.

Three women (14, 14 and 23 years) suffered from chronic tension-type headache. Their headache disappeared within 2 weeks after the start of treatment with melatonin. One 54-year-old man suffered from disabling migraine attacks without aura, twice a week. After starting melatonin treatment, only three migraine attacks were reported in 12 months. Ever since his forties a 60-year-old man complained of cluster headache episodes lasting about 2 months, twice a year. In the year since starting melatonin treatment, only one 5 day-cluster episode occurred. Nocturnal melatonin secretion in the patients with Delayed Sleep Phase Syndrome and headache did not differ significantly from that in the patients with the sleep disorder but without headache.

Melatonin may be helpful in patients with headache who are suffering from Delayed Sleep Phase Syndrome. Its effectiveness may be due to modification of vascular and nociceptive systems or to its chronobiological action which adjusts the patient's biological clock to his/her lifestyle.

Introduction.

Many different sleep disorders, including circadian rhythm disorders, are associated with headache [1]. The most frequent circadian disorder is the Delayed Sleep Phase Syndrome (DSPS) characterized by a persistent inability to fall asleep at conventional times. Once achieved, sleep is continuous and its length is normal when the patient is not obliged to

1JE Nagtegaal, MG Smits, ACW Swart, GA Kerkhof, YG van der Meer This chapter is reprinted from Headache 1998; 38:303-307.
maintain a strict schedule [2]. Melatonin advances the sleep-wake rhythm in patients with DSPS [3,4]. The effect on headache in these patients has not been described previously.

We studied the effects of melatonin 5 mg in 30 consecutive patients with DSPS [5]. All of these patients were asked for the presence and type of headache. In this report, we describe the patients with DSPS who suffered from headache. Possible influences of melatonin on pathophysiological mechanisms involving headache will be discussed.

Subjects and methods

All patients participated in a randomized, double-blind, placebo-controlled, cross-over study investigating the effect of melatonin in circadian rhythm disorders [5]. The study was approved by the local Medical Ethics Committee. All patients gave written informed consent.

Before treatment, the patients were questioned about the occurrence and type of headache. Diagnoses were made according to IHS criteria [6]. Endogenous plasma melatonin was measured every hour for 24 hours under dim light conditions (<100 lux) [7].

Each patient received 5 mg of melatonin or placebo for the first 14 days; they received the opposite preparation for the next 14 days. After the initial 28 days, all patients received melatonin for a period of at least three months. The medication was taken 5 hours before the time when the endogenous melatonin concentration reached 10 pg/ml. (Dim Light Melatonin Onset; DLMO). At that time, exogenous melatonin maximally advances circadian rhythms [8]. Sleep-wake rhythm was assessed by means of a diary, actography [9,10], and ambulatory cassette EEG [11,12]. Six weeks after the start of the study, a control 24-hour melatonin curve was performed under the same conditions as the first time. During that day the subjects did not take melatonin. Two weeks, 3, 6, 9 and 12 months later, the patients were questioned again about their headache.

Results

Headache was reported by five patients.

Patient 1 is a 54-year-old male engineer who had migraine without aura since childhood. The frequency of the attacks had increased to two attacks per week in the last five years. At least one day a week, he was not able to work. He took 4 g of paracetamol and 200 mg sumatriptan a week. During the day he felt tired. Besides these complaints, his medical
history was unremarkable. He went to bed at midnight and fell asleep at about 3 a.m. He needed three alarm clocks to wake up at 7:30 a.m. In the weekends, he slept until noon and felt less tired than on workingdays. He stated that he needed the weekends 'to fill his batteries' for the next week. To his great annoyance his 'batteries were often empty' before the start of the next weekend. For that reason he often reported sick. His neurological and biochemical examinations were normal. We recorded hypnograms during a weeknight and during a weekend night. Both hypnograms showed a normal sleep architecture from sleep onset to sleep end time. During the week, the patient slept only about 4 hours per night. On the weekends, he slept about 9 hours per night, however.

The patient was given information about the influence of sleep on daily functioning. In order to decrease the migraine, the patient tried to adjust his life-style to his biological clock. Furthermore the patient's company physician asked for the patient's work schedule to be adjusted to suit his biological clock. Thus the patient was allowed to start work at 1 p.m. and could work a few hours after dinner.

Three months later, the frequency of the migraine attacks had decreased to about one attack a month. The patient did not need his headache medication anymore.

A few months later, however, the frequency of the attacks gradually had increased to four per month. Also, his absenteeism increased to 3 days a month. The patient's explanation for the worsening was that he could not miss work in the morning because all important work meetings took place then. He had to attend these meetings in order to work properly. He had to choose between looking for other work or adjusting his biological clock to the demands of his work. He preferred the latter. Therefore, we included him in our study. He received melatonin during the first two weeks. From the second day after the start of the melatonin treatment, he fell asleep much earlier; he still went to bed at midnight, but fell asleep 30 minutes later. Spontaneously, he woke up at 7:30 a.m., feeling refreshed. At the weekend, he awoke at 9:30 a.m.. Migraine did not occur. Two days after the start of the placebo treatment phase, he had trouble falling asleep and awaking again. During this placebo treatment period, three migraine attacks occurred. When he was again treated with melatonin, his sleep pattern reverted to the same as during the first melatonin treatment period. His mood became slightly euphoric. Six weeks after the start of the study, i.e., 2 weeks after the start of melatonin treatment, the 24-hour melatonin curve was repeated,
showing an advance of 2 hours (Figure 18). Since he started melatonin treatment, only three migraine attacks have occurred.

Figure 18: Patient 1

![Graph showing melatonin levels before and after treatment]

Patient 2 was a 60-year-old man who, for the last 20 years, had suffered episodes of cluster headache lasting about 2 months, twice a year. From aged 40 to aged 45 he had to travel all over the world for business. Since that time, he had trouble falling asleep at conventional times. It was practically impossible to wake up in the morning. During the last few years, he fell asleep at 5 a.m. and had to awake at 8 a.m. From 1 p.m. he was exhausted. For a year, the cluster headache attacks were successfully treated with oxygen at 8 liters per minute for 10 minutes at the beginning of the pain. He used oxygen at home. Every time when he thought a headache attack had begun, he breathed some oxygen. For the last few months, he took oxygen nearly every day. His neurological and biochemical examinations were normal. His hypnogram showed a normal sleep architecture between sleep onset (5 a.m.) end sleep end (1 p.m.). His DLMO was at 4:23 a.m.

He was included in the study and received melatonin for the first 2 weeks. Once he started melatonin (at 11:30 p.m.), he fell asleep at 1 a.m. and awoke at 9 a.m. During the second week of the study, he did not need his oxygen. During the 2 weeks of placebo treatment, the old sleep pattern returned and he needed oxygen again. When the melatonin was restarted after this placebo treatment period, the headache disappeared and he returned his oxygen cylinder to the supplier. Two months later, trouble falling asleep started again and
a 5-day cluster headache episode occurred. He was advised to take the melatonin 2 hours earlier in order to advance his endogenous melatonin profile. From that time, he had no trouble falling asleep. Nine months later, sleep is still normal and headache has not returned. Because he lived too far from our hospital 'control' melatonin curves have not been performed.

Patient 3 was a 14 year-old schoolgirl who visited our outpatient clinic because of chronic tension-type headache present for 1 year. Her performance at school had diminished during the previous 6 months. From age of 12, she had trouble falling asleep. She went to bed at 10 p.m. and fell asleep between 1 and 3 a.m. Her parents had to 'pull' her from bed every morning. Neurological and biochemical examinations were normal. Her hypnogram showed normal sleep architecture between sleep onset (2 a.m.) and sleep end (11 a.m.). Dim Light Melatonin Onset was at 10:43 p.m. She was included in the study. With melatonin treatment, she fell asleep at 8 p.m. and awoke spontaneously at 7 a.m., feeling refreshed. The control melatonin curve showed that DLMO was advanced by 46 minutes. The headache disappeared completely within 2 weeks after beginning melatonin treatment and has not returned one year later. One night she forgot to take melatonin and had trouble falling asleep and awakening the next morning. Because the patient felt sleepy at 7 p.m. we determined if the time of administration could be later. Therefore, for two weeks she took melatonin at 7 p.m. and a placebo at 9 p.m., followed by the opposite schedule in a double-blind double-dummy study. It was shown that both sleep onset and sleep end times were delayed when melatonin was taken at 9 p.m. Headache did not reoccur.
Table 11: Summary of five Patients With Headache and Delayed Sleep Phase Syndrome. DLMO: Time at which nocturnal serum Melatonin concentration reached 10 pg/ml.

<table>
<thead>
<tr>
<th>Patient</th>
<th>AGE / SEX</th>
<th>DLMO time before treatment</th>
<th>DLMO advancement after treatment [min]</th>
<th>Type of headache</th>
<th>Severity of headache during treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54 / M</td>
<td>00:07</td>
<td>120</td>
<td>Migraine without aura</td>
<td>decreased</td>
</tr>
<tr>
<td>2</td>
<td>61 / M</td>
<td>04:23</td>
<td></td>
<td>Cluster Headache</td>
<td>disappeared</td>
</tr>
<tr>
<td>3</td>
<td>14 / F</td>
<td>20:40</td>
<td>46</td>
<td>Chronic Tension-type Headache</td>
<td>disappeared</td>
</tr>
<tr>
<td>4</td>
<td>14 / F</td>
<td>22:34</td>
<td>56</td>
<td>Chronic Tension-type Headache</td>
<td>disappeared</td>
</tr>
<tr>
<td>5</td>
<td>23 / F</td>
<td>22:18</td>
<td>60</td>
<td>Chronic Tension-type Headache</td>
<td>disappeared</td>
</tr>
</tbody>
</table>

The clinical findings of patients 4 and 5 are summarized in Table 11. Like patient 3, they received in the first 2 weeks of the study, placebo treatment. During that period the headaches remained unchanged.

In all five patients, DLMO (Table) was evidently delayed. In healthy adults, DLMO occurs before 9:30 p.m. [8]. The mean ± SD nocturnal melatonin secretion (404.6± 153.1 pg/ml) of the patients with headache did not differ from that of the 25 patients with DSPS without headache (393.8 ± 263.3 pg/ml).

Diary records and actography of the five patients showed a significant advance of sleep-wake rhythm during melatonin treatment compared with placebo treatment. The sleep architecture remained normal.

Comments

Our patients suffered from severe DSPS, as expressed by the late sleep onset times and DLMO. In all five patients, headache decreased dramatically after administration of melatonin. Therefore, a causative relationship with melatonin treatment is likely. As our patients had different kinds of headache, i.e., migraine without aura, cluster headache and
chronic tension-type headache, melatonin seems to influence basic pathophysiological mechanisms involved in headache.

Lowered urinary melatonin levels have been reported in patients with cluster headache [13,14] and in patients suffering from migraine without aura [15]. A double-blind placebo-controlled pilot study showed that melatonin is effective in the prophylaxis of cluster headache [16]. Several mechanisms have been suggested to explain the results [16]. Melatonin increases the activation threshold of GABAergic pain circuits that are reduced in cluster headache [17]. It also potentiates the inhibitory action of GABA [18]. Another possibility is that melatonin influences vasoconstriction [19] by modulation of 5HT₂ receptors [20] and melatonin receptors in cerebral arteries [21]. Melatonin is also known to inhibit the synthesis of prostaglandin E₂ [22], which activates sterile perivascular inflammation in the trigeminovascular system [23].

In our patients, nocturnal melatonin levels were normal; the marked interindividual variation taken into account [24, 25]. They also did not differ from those of the patients with DSPS who did not suffer from headache. This suggests that melatonin deficiency does not explain the occurrence of headache in our patients.

In all our patients, the sleep-wake rhythm was advanced after melatonin treatment. This chronobiotic action [26] synchronized the patients' biological clock to their lifestyle. This may have resulted in less psychological stress, consequently inducing a decrease of headache. Initially, we tried to adopt the life-style to the biological clock in the first patient. This induced the same dramatic decrease of headache. This suggests that reaching congruency of life-style and biological clock seems to be important in the treatment of headache patients with a disturbed circadian rhythm.

Biological clock dysfunctions may be expressed as circadian rhythm disorders. The most frequent is DSPS, first described in 1981 [2]. The prevalence in middle-aged adults was found to be between 0.10 % and 0.28%, with the mean age of onset 15.4 years and mean duration 19.2 years [27]. A survey of adolescents suggested a prevalence of greater than 7% [28]. Delayed Sleep Phase Syndrome might be viewed as the extreme end of a continuum of sleep timing changes that affect most adolescents [29]. In adults, DSPS has developed following Epstein-Barr viral infection and prolonged labour [30]. In our second patient, DSPS developed following a period in which he frequently crossed many time
zones in short time. This suggests that frequent interferences to the biological clock also may induce DSPS.

The original method of treating DSPS is chronotherapy: every consecutive day the patient goes to bed and have to wake up 3 hours later until the sleep schedule is realigned with the social schedule [31]. This must be followed by a strict adherence to the new schedule. Another method is the use of bright light (2500 lux) from 7 a.m. to 9 a.m. [31,32]. The third and promising treatment is by the administration of exogenous melatonin.

The human biological clock is situated in the suprachiasmatic nucleus [33,34]. This organ stimulates the pineal gland to synthesize melatonin. Bright light inhibits the production of melatonin [35]. Endogenous melatonin secretion is probably the strongest marker of the circadian rhythm [8]. The onset of nocturnal melatonin secretion is correlated with the opening of the nocturnal "sleep gate", an important condition to be able to fall asleep [36]. Exogenous melatonin seems to be promising in the treatment of DSPS. Dahlitz et al reported that melatonin was successful in 50% - 75% of patients, when taken 2 hours before desired bed time [3], but Lewy and colleagues had found that exogenous melatonin maximally advances circadian rhythms when given 5 hours before endogenous melatonin onset [8]. We hoped to increase this percentage by the administration of melatonin according to their findings. The decrease of the effectiveness of melatonin in the third patient when melatonin was administered 2 hours later, suggests that the time at which melatonin is taken, is clinically important in the treatment of DSPS patients. This is supported by the experience in the second patient. Melatonin, taken at 11 p.m., probably advanced the endogenous melatonin production and particularly DLMO so much in this patient, that the exogenous melatonin was probably not taken 5 hours before the DLMO.

The case histories described, suggest that it may be worthwhile to ask patients with headache about their sleep-wake rhythm. When there is a combination of complaints of insomnia and trouble awaking at conventional times, DSPS should be suspected. In case it is impossible to adapt the life-style to the biological clock, it is worthwhile to try to adapt the biological clock to the life-style of the patient. Thereafter, chronotherapy, light-therapy, or treatment with melatonin can be considered. When melatonin is to be given, we recommend a 24-hour melatonin profile which can now be easily measured in saliva with commercially available radio-immuno-assay methods. This establishes the optimal time of melatonin administration and avoids disturbances of the sleep-wake rhythms [37].
Prospective studies on the effects of melatonin in patients with headache with and without circadian rhythm disorders, may reveal if melatonin is effective by modifying vascular and nociceptive systems or by resetting the biological clock.

Literature


4.3 TRAUMATIC BRAIN INJURY-ASSOCIATED DELAYED SLEEP PHASE SYNDROME

Abstract

A 15-year-old girl developed a prominent delayed sleep phase syndrome (DSPS) following traumatic brain injury. Several physiological markers of the sleep-wake rhythm: plasma melatonin, body temperature, wrist activity and sleep architecture (EEG) were delayed almost half a day, returning to normal after treatment with 5 mg melatonin.

This report suggests an association between traumatic brain injury and DSPS. Awareness of this phenomenon may result in better possibilities for treatment of patients with brain injury.

Introduction

Delayed sleep phase syndrome (DSPS) is a disorder in which the major sleep episode is delayed in relation to the desired clock time. This results in symptoms of sleep onset insomnia, difficulty in awakening at desired time and dysfunctioning during the day [1].

Endogenous melatonin, a hormone produced by the pineal gland, plays a major role in the synchronisation of circadian rhythms. Small doses of exogenous melatonin bring forward the sleep-wake rhythm in DSPS patients [2].

In most DSPS patients the aetiology of their condition is unknown. Some DSPS patients reported that their difficulties began after alterations in the photoperiod such as after a period of late night studying or partying, or after working in the evening, or following a period of night shift [1].

We describe a patient who developed DSPS following a traumatic brain injury. After treatment of the DSPS the patient's condition improved remarkably.
Case report

Unexpectedly an iron tent pole fell on the back of the head of a 15-year-old girl scout. From that time, she suffered headache, neckpain, dizziness and frequent fainting and complained of loss of memory and concentration. Three days after the accident the girl saw coloured spots and became unconscious. She recovered consciousness spontaneously after several minutes, complaining about tension headache. At that time she became unable to fall asleep at night. She went to bed at 10 p.m. and fell asleep later and later. She then could not wake up in the morning, not even with two alarm clocks.

Six weeks after the accident the girl came to the outpatient clinic and medical examination showed that rotation and flexion of the neck were decreased. X-ray of skull and cervical vertebrae, cerebral CT scan, cerebral and cervical MRI, EEG, Hb, Ht, leukocytes and thyroid function were normal. The girl was tired and lacking in initiative but she was not depressed.

Two months after the accident, the girl was falling asleep at 7 am and waking at 4 p.m. Until the accident she had slept well. She used to go to bed at 10 pm and to wake up at 7 am.

She was admitted to hospital for observation. Several sleep markers were studied. A hypnogram showed a normal sleep architecture between sleep-onset (7.15 am) and sleep-end (2.05 p.m.). The sleep efficiency was 92.6% and sleep latency (time from light out until stage 1 sleep) was 48 min. Every hour plasma melatonin and every two minutes rectal body temperature (rectal probe from Yellow Spring YSI Series 400) were measured for 24 hours under semi-constant routine conditions.

The 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 [3]. A striking feature of the melatonin plasma curve was a 12-hour delay in its peak concentration. As shown in Figure 19 serum melatonin started to increase between 8 and 9 a.m. attained a peak value at 6 p.m. and returned to minimum concentrations between 7 and 8 p.m.
Figure 19: Figure 1: 24-hour melatonin concentration before and after treatment with melatonin at 3.30 a.m.

The temperature curve was fitted with a harmonic regression function with 24-hour and 12-hour components and is shown in Figure 20. The numerically calculated minimum of the fitted curve, which serves as phase estimate of the circadian body temperature rhythm, occurred at 5.30 p.m.
Figure 20 24-hour rectal temperature. A: Before treatment. Minimum: 5.30 p.m. B: After treatment with melatonin at 3.30 p.m. Minimum 9.59 a.m., which represents 7.5 h advance. C: After treatment with melatonin at midnight. Minimum: 6.50 a.m.
In order to quantify her sleep-wake behaviour, motor activity was recorded for 3 consecutive days by an activity monitor (Gaewiler Electronic), worn on the wrist of the nondominant hand. The monitor counts the occurrences of supra-threshold wrist activity per 30-second epoch. The 24-hour pattern indicates relatively little activity from about 5 a.m. to 2 p.m., corresponding with the subjectively estimated mean sleep period. The results are illustrated by Figure 21.

*Figure 21: Wrist activity monitoring. A: Before treatment. Sleep onset: 5.23 a.m. B: After treatment with melatonin at 3.30 a.m. Sleep onset: 4.25 a.m. C: After treatment with melatonin at midnight. Sleep onset: 1.29 a.m.*
In an attempt to bring forward her circadian rhythmicity, daily oral administration of melatonin 5 mg at 3.30 a.m. was started. The time of melatonin administration was determined as five hours before the time of the start of the endogenous melatonin production [4]. After daily use of melatonin for 4 weeks the patient felt much better. She fell asleep at around 5 a.m. and awoke at around noon.

Melatonin plasma concentration, wrist activity and rectal body temperature were measured a second time with no intake of melatonin on the day before and on the day of admission to hospital. These curves showed an advance compared with the first curves (Figures 19, 20, 21). Based on these curves we advised the patient to take melatonin at midnight, 5 hours before the 'new' start of endogenous melatonin production [4]. She fell asleep between 2 and 3 a.m. Wrist activity monitoring in this period, showed relatively little activity from about 1.30 am till 10 am. The 24-hour temperature measurement showed a comparable shift. The girl started to go to school in the afternoon. Three months after starting melatonin treatment, she is taking melatonin at 10 p.m. and feels refreshed every morning. Headache and neck pain have disappeared, concentration is better, and she attends school for the full day.

Discussion

Following traumatic brain injury our patient developed a marked delay in the circadian sleep-wake rhythm, the body temperature rhythm and the melatonin rhythm, consistent with DSPS.

As far as we know only one case is described where the occurrence of sleep-wake schedule disorder was linked to head injury [5]. Patten and Lauderdale describe a 13-year-old boy who developed a sleep-wake schedule disorder of the delayed type soon after suffering a head injury. However, our case shows that several sleep-related parameters support the diagnosis and while the chronotherapy used by Patten et al resulted in problems of non-compliance [5], melatonin treatment was immediately effective in our patient.

The pineal hormone melatonin plays a major role in synchronising circadian rhythms. The circadian pattern of serum melatonin is entrained by light and is controlled by the suprachiasmatic nuclei of the hypothalamus, which represents the endogenous circadian rhythm-generating system in the brain [6]. The suprachiasmatic nucleus receives direct visual input from the retina and gives rise to preganglionic fibres, which descend to the
intermediolateral column of the spinal cord. Finally, postganglionic fibres arising from the superior cervical ganglia reach the pineal gland [7]. Possibly the trauma had damaged these pathways, which may result in disruption of melatonin excretion [7]. The MRI did not show any damage but would only be expected to detect relatively gross lesions. Melatonin maximally advances circadian rhythms when taken 5 hours before the endogenous melatonin starts to increase [4]. Since melatonin delays circadian rhythms when taken at a wrong time it would appear necessary to evaluate endogenous melatonin secretion before treatment with melatonin [4,8]. In our patient circadian body temperature phase and time of peak melatonin concentration correspond closely. An ongoing study of DSPS patients [9,10] will reveal whether determination of the optimal time for treatment with melatonin based on a 24-hour temperature curve gives same results as optimal time for treatment based on a serum melatonin curve [9].

This case shows that DSPS may be associated with brain injury and that diagnosis may be based on analysis of the melatonin rhythm or temperature rhythm. To further our understanding of the association between DSPS and head injury we will start a study in a large group of patients with brain injury.

Literature


