The effect of treatment with melatonin for chronic sleep onset insomnia in children with attention deficit hyperactivity disorder: randomized placebo-controlled trial


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Introduction
Generally chronic sleep onset insomnia in children with attention deficit hyperactivity disorder (ADHD) does not respond well to pharmacological and non-pharmacological treatments (1). Melatonin advances sleep onset in adults with chronic sleep onset insomnia and delayed onset of endogenous melatonin (2). Children with delayed sleep onset and bedtime resistance, may also wake up later (3). This suggests that their sleep-wake rhythm is delayed. Early school times or early wake-up times of family members can prevent delayed wake up time. In ADHD children this lack of difficulty to arise in the morning probably is associated with the hyperarousal conditions of this disorder (4). Consequently a delayed sleep-wake rhythm can easily be masked.

Endogenous melatonin, a hormone produced by the pineal gland during the dark phase of the day-night cycle, plays a major role in the synchronisation of circadian rhythms (5). As early as the second half of the first year of life melatonin is involved in the evolution of the sleep-wake system (6). The circadian rhythm of melatonin is highly reproducible and generally not easily altered (7). The endogenous 24-h. melatonin profile is a reliable marker for circadian phase position. The time at which melatonin starts to rise in dim light, the Dim Light Melatonin Onset (DLMO), is shown to be particularly convenient, to assess circadian phase position, as it can usually be obtained before sleep (8). In adults with chronic sleep onset insomnia and a delayed sleep-wake rhythm, exogenous administered melatonin, 5 mg, advances both sleep onset and DLMO (9).
We hypothesized that administration of exogenous melatonin advances also sleep onset in children with ADHD and chronic sleep onset insomnia.

**Methods.**
This randomized placebo-controlled study evaluated the efficacy of oral melatonin, 5 mg day⁻¹, at 18:00 h. in primary school children with ADHD and chronic sleep onset insomnia. 40 children with chronic insomnia were randomly allocated to melatonin or placebo treatment. In 26 ADHD was diagnosed (DSM-IV criteria). 11 children were randomly assigned to melatonin and 14 to placebo treatment during 4 weeks (fig. 1.).

**Figure 1:** Trial profile. *: diary. **: actigraphy. DLMO: Dim Light Melatonin Onset. Numbers are numbers of patients involved.

In the week before the start of the treatment and during the fourth treatment week, sleep was assessed with diaries and actigraphy, severity of ADHD with the Connors Scale, and sustained attention with the Bourdon-Vos test by meas-
uring Rule Completion Time (RCT) (10). Salivary melatonin was collected hourly between 18:00 and 23:00 h. in dim light at the last night of the baseline week and at the last night of the fourth treatment week. The children did not take melatonin tablets at the last night of the fourth treatment week. After the trial all children received “open” melatonin. Treatment effects were analyzed with ANOVA repeated measures procedure with 2 factors, i.e. treatment (melatonin versus placebo) and measurement (baseline versus fourth treatment week). Significant treatment x measurement interactions, indicating a differential treatment effect across groups, were followed by post hoc comparisons of the baseline with treatment measurements, using paired T-Test; the between-group differences in the mean change from baseline to fourth treatment week were analysed using T-Test.

Results
Melatonin treatment advanced lights-off time, diary and actigraphic sleep onset, and melatonin onset, decreased sleep latency and increased total sleep time (table 1). Wake up time, Connor score and RCT did not change. One year after the trial all children still used melatonin. In 15 children behavior had improved remarkably. Adverse effects did not occur.

<table>
<thead>
<tr>
<th></th>
<th>baseline week melatonin</th>
<th>baseline week placebo</th>
<th>fourth treatment week melatonin</th>
<th>fourth treatment week placebo</th>
<th>treatment interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lights off time* (h:min)</td>
<td>21:21 (0:37)</td>
<td>20:56 (0:33)</td>
<td>20:51 (0:53)</td>
<td>20:57 (1:00)</td>
<td>6.12  0.022</td>
</tr>
<tr>
<td>Sleep onset* (h:min)</td>
<td>22:26 (0:45)</td>
<td>22:02 (0:28)</td>
<td>21:51 (1:10)</td>
<td>21:51 (0:34)</td>
<td>10.28  0.004</td>
</tr>
<tr>
<td>Sleep latency* (min)</td>
<td>63.3 (29.2)</td>
<td>65.4 (32.2)</td>
<td>25.5 (24.3)</td>
<td>55.5 (35.3)</td>
<td>7.19  0.014</td>
</tr>
<tr>
<td>Wake up time* (h:min)</td>
<td>7:30 (0:17)</td>
<td>7:19 (0:22)</td>
<td>7:13 (0:28)</td>
<td>7:01 (0:21)</td>
<td>0.13  n.s.</td>
</tr>
<tr>
<td>Total sleep time* (h:min)</td>
<td>9:02 (0:39)</td>
<td>9:22 (0:21)</td>
<td>9:56 (0:43)</td>
<td>9:10 (0:46)</td>
<td>21.04  0.001</td>
</tr>
<tr>
<td>Sleep onset** (h:min)</td>
<td>22:36 (1:32)</td>
<td>21:21 (0:43)</td>
<td>21:04 (0:54)</td>
<td>22:06 (1:53)</td>
<td>5.56  0.035</td>
</tr>
<tr>
<td>DLMO (h:min)</td>
<td>21:19 (2:00)</td>
<td>20:57 (0:42)</td>
<td>20:04 (2:01)</td>
<td>21:10 (1:06)</td>
<td>5.36  0.001</td>
</tr>
<tr>
<td>Mean RCT(s)</td>
<td>16.4 (3.9)</td>
<td>17.8 (4.8)</td>
<td>13.7 (2.8)</td>
<td>15.10 (3.9)</td>
<td>0.74  n.s.</td>
</tr>
<tr>
<td>Connors Scale</td>
<td>1.64 (0.27)</td>
<td>1.78 (0.15)</td>
<td>1.98 (0.37)</td>
<td>2.02 (0.44)</td>
<td>0.39  n.s.</td>
</tr>
</tbody>
</table>

Table 1: Mean (SD) sleep parameters, Dim Light Melatonin Onset (DLMO) and Mean Rule Completion Time (RCT) at baseline and fourth treatment week. *: Diary. **: Actigraphy. Treatment interaction determined by ANOVA with repeated measures statistics. F: F ratio. P: level of significance. N.S.: not significant (P >0.05)
Discussion
The present study showed that one month melatonin treatment advanced mean lights-off time, sleep onset, sleep latency and DLMO and increased sleep duration in the children with chronic sleep onset insomnia. Sustained attention and Connors score was not affected. Serious side effects did not occur. Seeing that normal values of DLMO in 6 – 12 years-old children have not been published, it is not known whether the mean baseline DLMO, which occurred in our group children around 21 p.m. is abnormal. However, Carskadon et al (11). found that mean DLMO occurs at 20:24h in 14-years old adolescents. One year later DLMO was delayed about 40 minutes. So the mean DLMO before treatment, which we found in our patients, probably is later than what might be expected. This late DLMO suggests that the endogenous circadian pacemaker might be delayed (8) in at least some ADHD children with chronic sleep onset insomnia. This can be due to dysfunction of clock genes (12, 13), enzymes involved in the melatonin synthesis (9) or neural connections between the retina and pineal gland (14). Melatonin, at least in the short term, seems to be an effective and safe treatment for chronic insomnia in children with ADHD. As long as toxicity and long term effects of melatonin not have been studied, we recommend prescribing melatonin only in well-performed trials.

Acknowledgement
This study was financially supported by the “Jan Dekker en dr. Ludgardine Bouwman” Foundation.

Reference List


Modelling the relation of body temperature and sleep: importance of the circadian rhythm in skin temperature

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A close relation between thermoregulatory and arousal related processes in basal forebrain and hypothalamic areas has been substantiated in many studies. It has been demonstrated especially - but not exclusively - in the preoptic area of the anterior hypothalamus (POAH), that a subpopulation of warm-sensitive neurons (WSNs) spontaneously increases firing rate at sleep onset, and that experimental local warming of the POAH induces a similar increase in firing rate and facilitates sleep onset. It has consequently been proposed that brain temperature may be involved in physiological regulation of sleep4. However, contrary to the experimental findings of increased sleep onset probability with a locally increased hypothalamic temperature, the likeliness of sleep onset in unmanipulated conditions is actually minimal at the time when the circadian rhythm in temperature reaches its peak. In fact, sleep onset probability increases on the falling limb of the circadian core temperature rhythm. How can this discrepancy of increased sleep with well-controlled experimental local POAH warming be reconciled with increased sleep with local cooling under natural conditions?

A suitable explanation has been put forward5: in modelling based on local warming experiments, it has generally been ignored that many of the locally thermosensitive neurons also respond, in a similar way, to changes in skin temperature. Thus, the very changes in cell membrane properties leading to sleep-related alterations in firing rate as induced by local warming in experimental conditions, may be induced by warming of the skin under natural conditions.

Several considerations support the importance of skin temperature. First, after warming of the skin, preoptic WSNs show a markedly increased firing rate to a level that can be reached only by extreme (non-physiological) local warming. Moreover, with elevated skin temperature, WSNs have a high firing rate irrespective of the local temperature, i.e. temperature input from the skin appears to dominate when competing signals are present1, 2. Second, sleep appetitive behavior like lying down, covering etc. is associated with a redistribution of warm blood to the extremities, thus increasing their temperature. Third, and