Onset and stability of melatonin treatment effect in childhood sleep onset insomnia

Início e estabilidade dos efeitos do tratamento com melatonina na insônia de início de sono infantil

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ABSTRACT

Backgroud and objective: To evaluate onset and stability of therapeutic effect of 4-week melatonin treatment for chronic sleep onset insomnia in elementary school-aged children. **Methods:** Retrospective analysis of unpublished data obtained from two previously published randomized, double-blind and placebo-controlled trials on melatonin treatment efficacy for childhood insomnia in children with chronic sleep onset insomnia, age 6-12 years (n=49). Intervention consisted of placebo (n=25) or melatonin 5 mg (n=24) administered at 6 (n=9) or 19h (n=40) during four weeks. Collected data were "light-out time", "sleep onset latency", "sleep onset", "total sleep time", "wake-up time", and subjective sleep measures recorded in a diary. **Results:** Melatonin treatment showed a phase-advance of lights out of 21h15 (1.05) to 20h28 (1.07); sleep onset advanced from 22h05 (0.93) to 20h45 (1.09) and sleep latency decreased from 53 (39) to 18 minutes (16). After the 4-week trial period, these values were 20h44 (1.27), 21h09 (1.33), 25 minutes (39). **Conclusions:** Melatonin advances sleep latency and sleep onset and increases total sleep time starting right from the first treatment night in children with chronic sleep onset insomnia. **Evidence is provided that the onset of melatonin treatment effect can be expected within a few days after commencement and, then, remains stable.**

Keywords: Sleep initiation and maintenance disorders/drug therapy; Melatonin/therapeutic use; Education, primary and secondary; Child

RESUMO

Objetivo: Avaliar o início dos efeitos e a estabilidade do tratamento para insônia de início do sono com melatonina por quatro semanas em crianças cursando escola primária. **Métodos:** Análise retrospectiva de dados inéditos obtidos de dois ensaios randomizados, duplo-cegos e controlados por placebo sobre a eficácia do tratamento da melatonina para insônia na infância em crianças com início de insônia crônica com idades entre 6 e 12 anos (n=49). A intervenção consistiu em placebo (n=25) ou melatonina 5 mg (n=24) ministrados às 18 (n=9) ou 19h (n=40) durante quatro semanas. Os dados coletados foram "horário em que as luzes foram apagadas", "latência até o início do sono", "início do sono", "tempo total de sono", "horário de despertar" e medidas subjetivas do sono registrados em um diário. **Resultados:** O tratamento com melatonina evidenciou fase adiantada quando as luzes estavam apagadas das 21h15 (1.05) às 20h28 (1.07); o início do sono avançou das 22h05 (0.93) às 20h45 (1.09) e latência ao sono diminuiu de 53 (39) para 18 minutos (16). Ao término das quatro semanas, esses valores passaram a ser 20h44 (1,27), 21h09 (1.33), 25 minutos (39). **Conclusões:** A melatonina adianta a latência ao sono e ao início do sono aumentando o tempo total de sono a partir da primeira noite em crianças que sofrem de insônia de início de sono crônica. As evidências demonstram que o efeito pelo tratamento de melatonina para o início do sono pode ser esperado dentro de alguns dias após o início do tratamento e, então, se mantém estável.

Descritores: Distúrbios do início e da manutenção do sono/quimioterapia; Melatonina/uso terapêutico; Ensino fundamental e médio; Criança

INTRODUCTION

Sleep onset insomnia is a highly prevalent disorder among school-age children. A chronic and severe presentation leading to long-term sleep deprivation can seriously affect a child's physical and mental development. We have previously shown in two randomized, double-blind and placebo-controlled studies in elementary school children with chronic sleep onset insomnia suggestive of delayed sleep phase disorder that melatonin (5 mg) advanced sleep-wake rhythm and lengthened total sleep duration [1,2]. However, the data

published merely included treatment measurements performed within the fourth week. We have further analyzed these findings by considering all data obtained from Day 1 to Week 4 in the treatment period, instead of focusing on endpoint data. Knowledge of the time-course and stability of the treatment effects during therapy initiation is clinically relevant for clinicians and researchers for this can prevent unnecessary long administration of melatonin, for example, when the appropriate dose of melatonin needs to be determined [3]. If, during the initiation phase, the dose effect is evaluable after days instead of weeks, the initiation phase of effective therapy can be shortened from weeks to days.

While long-term treatment efficacy has already been established by several research groups [4,5], and direct soporific effects of melatonin were recently described in the context of sedation for electroencephalogram (EEG) recording [6], this is the first study to report on the time-course and stability of melatonin treatment effects for insomnia treatment.

This study's aim was to evaluate the acute, wanted effects of melatonin administration to children with sleep onset insomnia. The long-term safety, especially addressing the influence on puberty onset, is a still to be sufficiently answered issue. For this population, long-term effects, including the adverse events, are described elsewhere [7].

METHODS

Subjects were elementary school children with chronic sleep onset insomnia, who participated in one of two randomized placebo-controlled studies published earlier [1,2]. They were aged 6 to 12 years and in otherwise good general health; their sleep problems were not related to any other pathology than attention deficit hyperactivity disorder (ADHD) and suggestive of delayed sleep phase disorder. Other sleep pathology was excluded by ambulatory polysomnography with 24-hour cassette electroencephalography at the child's home and parental report.

The institutional review board on human research approved both studies and informed consent was obtained from the parents of all participants. A 1-week baseline phase preceded a 4-week treatment phase. Melatonin immediate release tablets (5 mg) or identical-looking placebo were given at 18h (melatonin: n=19; placebo: n=19) daily in the first study [1] and at 19h (melatonin: n=35; placebo: n=36) in the second [2]. Sleep onset insomnia was defined as (a) complaints of sleep-onset problems expressed by parents and/or child; (b) occurrence on at least four days/week for longer than one year; (c) average sleep onset later than 20h30 for children at age 6 years and for older children 15 minutes later per year; and (d) average sleep onset latency exceeding 30 minutes. Exclusion criteria were disturbed sleep architecture as measured by ambulatory polysomnography, and sleep maintenance insomnia

(one awakening >30 minutes or two or more awakenings >5 minutes summing up to at least 40 minutes, occurring on one or more nights a week, for a period of at least 4 weeks preceding the start of the trial). Further exclusion criteria were mental handicap, severe learning disabilities, liver disease, renal failure, chronic pain, and severe neurological or psychiatric disorders. Finally, any prior use of melatonin, use of hypnotics, antidepressants, and neuroleptics was exclusion criterion. Allowed medications were methylphenidate and salbutamol by inhalation.

In the present paper, a sleep log was considered incomplete when it did not cover the entire four-week treatment period (which is the period of interest in the present study). This is in contrast to the previously published articles, when it was considered incomplete when there were no data of the fourth treatment week (which was the period of interest in the previous studies). This complete coverage of the four-week treatment was accomplished in 49% of the originally included participants. The 51% missing data during the first three treatment weeks is due to the fact that the decision to record sleep data over the entire four-week trial period (instead of during the fourth treatment week only) was made at a time when both trials were already in progress.

Parents were asked to complete the following parameters in sleep logs daily: light-out time (time when the light was turned off before sleeping), sleep onset time (estimated time when the child fell asleep, assessed by checking on the child through listening or watching every ten minutes, as noninvasive as possible), wake-up time (estimated time of waking up), get up time (time of getting out of bed). Means and standard deviations were calculated over the baseline week and each treatment week, resulting in five mean (SD) values per parameter. Intra, intergroup and interaction effects were tested using multivariate analyses of variance ($\alpha \leq 0.05$). Differences in means for four sleep parameters, i.e. sleep onset time, sleep onset latency, wake-up time and total sleep time were tested for each of the 34 pairs of consecutive days (1st and 2nd night... 34th and 35th night) using the Wilcoxon signed-rank test. To account for multiple comparisons the α-level was set at 0.00147 (0.05 was divided by the number of comparisons: 34). Besides the mean values above mentioned, we tried to rate therapy success with an individual parameter. We defined as criterion for successful therapy the number of patients with a decreased sleep onset latency of at least 25 minutes (being the standard deviation in sleep onset latency of both groups and even more important: a decrease expected to be experienced as a clinically relevant relief of sleep onset insomnia). We assessed this parameter for both groups (melatonin and placebo) after one, two, three and four weeks of therapy compared to baseline.

RESULTS

In the first study [1], there were 38 participants, of which 33 sleep logs were available on the fourth treatment week; however of those 33 only 9 sleep logs were completed during the entire four-week treatment period. In the other paper [2], there were 62 participants, of which 55 sleep logs were completed during fourth treatment week; however, only 40 sleep logs were completed during the entire four-treatment weeks – data are used for the present study.

Of the total sample included in the present study (n=49), 25 children (17 male and 8 female; 6 of trial [1] and 19 of trial [2]) were assigned to melatonin treatment and 24 children (19 male and 5 female; 3 of trial [1] and 21 of trial [2]) to placebo.

Figure 1 depicts the mean values for lights out and sleep onset time over the course of treatment. As can be seen, robust phase advances occur within the first week of melatonin treatment, after which the values remain stable except for a slight delay within the third treatment week. The convergent direction of the lights out and sleep onset lines indicate a decrease of sleep onset latency within the first treatment week.
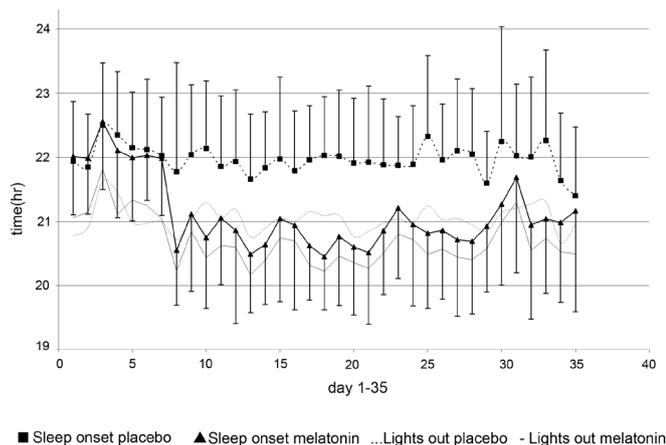

Figure 1: Mean light-out time and sleep onset time Day 1-7 (i.e. baseline) and Day 8-35 (i.e. intervention).

This sleep onset latency is of importance, since this parameter clearly demonstrates the trouble falling asleep for children sent to bed. Mean (± SD) sleep onset latency changed in the Treatment Group from baseline 53 (±39) to 18 minutes (±16) in treatment Week 1 to 16 minutes (±17) in Week 3, to 19 minutes (±21) in Week 4 and 25 minutes (±38) in Week 5.

On the contrary, lights out, sleep onset and therefore sleep onset latency did not significantly change in the Placebo Group, as illustrated by the white gap in Figure 1 (62 (±43), 55 (±48), 58 (±47), 60 (±51) and 49 (±52) minutes in the last treatment week) (Figure 2).
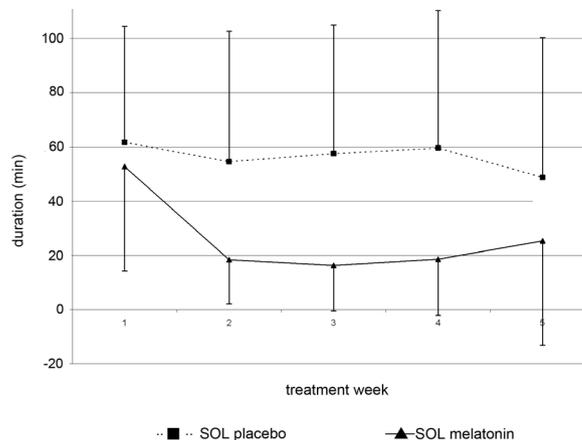

Figure 2: Mean sleep onset latency in Week 1 (i.e. baseline) and Week 2 to 5 (i.e. intervention).

Responders, defined as patients with a 25-minute decrease in sleep onset latency, were compared between weeks and groups, the group effect tested by type III between-subjects tests. During the 1st treatment week, in the melatonin group, 14 patients responded with a >25-minute decrease in mean sleep onset latency, while this was 4 in the Placebo Group (F=9.379; p=0.004). Responders in the 2nd week were 16 patients in Melatonin and 5 in Placebo Group (F=11.035; p=0.002); 13 in Melatonin and 4 in Placebo in the 3rd week (F=7.505; p=0.009), and 13 in Melatonin and 7 in Placebo in the 4th week (F=2.679; p=0.108). In the Melatonin Group, 11 patients met this criterion for success for each of the 4 weeks, against 1 in Placebo (F=10.177; p=0.003).

It is noteworthy that two patients in the Melatonin Group had any response and one patient in the Placebo Group had a consistent high response.

Figure 3 depicts wake-up time over the course of treatment, variation which shows an advanced phase that is most robust in the first treatment week and gradually stabilizes in the next treatment weeks. Values in placebo show a continuing irregular pattern.
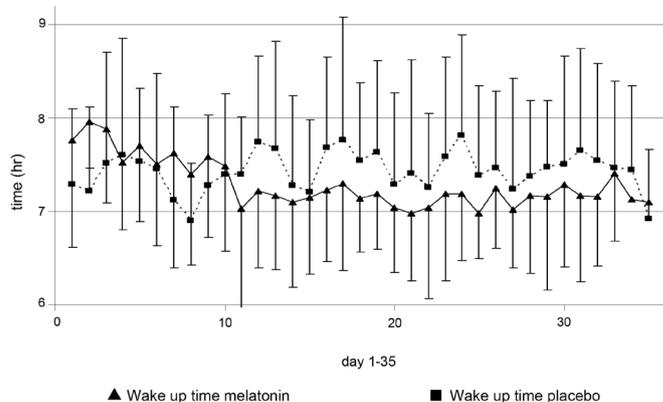

Figure 3: Mean wake-up time in Days 1 to 7 (i.e. baseline) and Days 8 to 35 (i.e. intervention).

Table 1: Results of multivariate analyses of variance for sleep parameters

Parameter/type	'Exposure' variable[a]	df1	df2	F	p-value	Form of the function
Sleep onset time						
Main	Week number	4	44	25.226	< 0.001	Advances
	Week number*treatment group	4	44	16.000	< 0.001	Advances
	Treatment group	1	47	16.511	< 0.001	Advances
Time contrasts	Week 1 *versus* later*treatment group	1	47	39.311	< 0.001	Advances
	Week 1 *versus* Week 2*treatment group	1	47	30.186	< 0.001	Advances
Sleep latency						
Main	Week number	4	44	9.011	< 0.001	Decreases
	Week number*treatment group	4	44	7.168	< 0.001	Decreases
	Treatment group	1	47	19.240	< 0.001	Decreases
Time contrasts	Week 1 *versus* later*treatment group	1	47	19.489	< 0.001	Decreases
	Week 1 *versus* Week 2*treatment group	1	47	18.344	< 0.001	Decreases
Total sleep time						
Main	Week number	4	44	11.203	< 0.001	Increases
	Week number*treatment group	4	44	2.523	0.054	
	Treatment group	1	47	16.284	< 0.001	Increases
Time contrasts	Week 1 *versus* later*treatment group	1	47	7.375	0.009	Increases
	Week 1 *versus* Week 2*treatment group	1	47	8.076	0.007	Increases
Difficulty falling asleep						
Main	Week number	4	44	20.095	< 0.001	Decreases
	Week number*treatment group	4	44	7.168	< 0.001	Decreases
	Treatment group	1	47	29.833	< 0.001	Decreases
Time contrasts	Week 1 *versus* later*treatment group	1	47	18.853	< 0.001	Decreases
	Week 1 *versus* Week 2*treatment group	1	47	18.348	< 0.001	Decreases
Feeling rested (morning)						
Main	Week number	4	44	4.925	0.002	Increases
	Week number*treatment group	4	44	3.226	0.021	Increases
	Treatment group	1	47	7.108	0.010	Increases
Time contrasts	Week 1 *versus* later*treatment group	1	47	0.849	0.362	
	Week 1 *versus* Week 2*treatment group	1	47	5.465	0.024	Increases

[a]: week number and week number*treatment group effects tested by Wilks' lambda; treatment group effect tested by type III between-subjects test.

Table 2: Results of the first treatment night in the melatonin treatment group

Sleep parameter	z	p-value
Sleep latency		
Difference in means of 7th night - 8th night	-3.92	0.00009
Sleep onset time		
Difference in means of 7th night - 8th night	-3.95	0.00008
Total sleep time		
Difference in means of 7th night - 8th night	-3.77	0.00016

Results of multivariate analyses of variance are summarized in Table 1. The results show that pretreatment to treatment changes of sleep onset, sleep latency, total sleep time light-out and wake-up time are significantly different whilst melatonin treatment as compared to placebo treatment (i.e. Week 1 *versus* later * treatment group). Further analysis shows that the difference in pretreatment to treatment changes of these sleep parameters are already significant after one week of treatment (i.e. Week 1 *versus* Week 2 * treatment group), except for get up time.

Main effects of week number and treatment group on total sleep time are significant when the interaction is not. This means that the Melatonin Group exceeds the Placebo Group on the average, but that the trend over the weeks does not differ between the two groups. Compared to placebo, melatonin resulted in a significantly larger decrease in children's perceived difficulties in falling asleep, from baseline to later weeks as well as from baseline to the second week. As compared to placebo, the Melatonin Group showed a significantly different change in feeling rested in the morning from baseline to the first treatment week. However, this effect did not sustain during the four-week treatment period. No significant effects were found for mood during the evening, mood at daytime and perceived sleep quality (not shown).

Finally, Table 2 shows the change in sleep latency, sleep onset time, and total sleep time from the final baseline night to the first treatment night within the Melatonin Treatment Group. The results reveal significant improvements in all three parameters during this first treatment night. The Wilcoxon signed-rank test revealed that for the 34 pairs of

consecutive daily means for sleep latency, sleep onset time and total sleep time the difference between consecutive pairs of nights was only statistically significant (α-level set at 0.00147) for the change over the final baseline night to the first treatment night in the Melatonin Treatment Group. Differences between consecutive night pairs of the four parameters within the Placebo Group were all statistically non-significant.

DISCUSSION

This paper is a further analysis of data from our two previous publications, and we have now found that effects of melatonin on sleep latency, sleep onset time and total sleep time occur from the first night of treatment. These effects were stable during a four-week intervention period. Melatonin initially also improved feeling rested in the morning, which however did not sustain during intervention.

Individual results for sleep onset latency and using this result as a criterion for successful therapy corroborate the mean study population results, since the variance of sleep measures (sleep onset and wake-up time in particular) is large in a population with varying sleep needs (age 6 to 12 years) and this variance is much smaller in the mean calculated measure sleep onset latency. What strikes in the responders results is that most responders in the Melatonin Group are consistent during the four treatment weeks [11], as in the Placebo Group this was only applicable for one patient.

In contrast to the Melatonin Group (which showed immediate decrease of sleep onset latency starting from Treatment Day 1), the Placebo Group showed decreasing sleep onset latency values from Week 1 to Week 4, although not statistically significant. One reason for this finding could be the conditioning effect of parents checking on the child every ten minutes. If children are anxious, knowing and having a parent come in and check on them in set intervals may have a curing effect on their insomnia. It is a common finding in randomized clinical trials studying treatment effect in insomniacs that placebo produces significant changes on self-reported sleep measures [8]. However, in our studies, sleep measures did not significantly change during placebo treatment, with one exception. This might be explained by the fact that the sleep measures were not assessed by the patients themselves.

There are several limitations of this study; one of which is that we did not assess sleep objectively by means of polysomnography or actigraphy. However, parents of sleep-disturbed infants have shown to be accurate reporters of actigraphically assessed sleep onset and sleep duration [9].

We used the data of two studies, with different timing of melatonin administration, although the two subsets show very similar characteristics of sleep-wake rhythm and endogenous melatonin onset. Moreover, the effect of melatonin on sleep parameters did not differ between the two studies [1-2]. Melatonin treatment for chronic insomnia in children has been criticized in the Netherlands. Jenni [10] stressed that cultural variation and developmental variation and biological variability of sleep behavior among normal healthy children should be taken into account. However, in our studies we did not include healthy children, but children with chronic complaints of insomnia who showed impaired general health and quality of life likely due to their insomnia problems [11].

To conclude, the results presented here provide proof that onset of melatonin treatment effect can be expected within a few days and this effect remains stable in the weeks after that, in addition to the earlier evidence [1,2,12] that melatonin is an effective treatment for sleep onset insomnia in children with late melatonin onset.

ACKNOWLEDGEMENTS

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