Original Article

Clinical Considerations Derived From the Administration of Melatonin to Children With Sleep Disorders

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ABSTRACT

BACKGROUND AND OBJECTIVES: Despite the numerous investigations carried out in relation to melatonin, there is a lack of knowledge about the specific melatonin secretion patterns in the diverse primary sleep disturbances. The objective of this study was to analyze the plasma melatonin concentrations in children with primary sleep disorders and the effects of melatonin therapy on their serum levels and their actigraphic sleep parameters. **METHODS:** Fourteen participants (nine girls; seven to 14 years old) diagnosed with diverse primary sleep disorders were recruited. Four different melatonin secretion patterns were identified: low plasma melatonin levels, absence of a circadian rhythm, advanced acrophase, and delayed acrophase. A placebo (one week) was administered followed by three months of melatonin therapy (3 mg/night). Urinary 6-sulfatoxymelatonin levels, 24-hour plasma melatonin concentrations, and a seven-day actigraphic record were collected after both treatments. **RESULTS:** After melatonin therapy, a significant increase ($P < 0.001$) of urinary 6-sulfatoxymelatonin excretion with a clear circadian variation was observed. Plasma melatonin concentrations were also significantly higher with a recovery in the circadian rhythm. Actual sleep time was significantly longer, with a substantial reduction in the sleep onset latency and night awakenings. No severe side effects were reported. **CONCLUSIONS:** The main clinical implication of this study is to demonstrate the efficacy of melatonin in three main circumstances: an insufficient hormone production, a disturbed circadian rhythm, and an advanced or delayed acrophase. As ongoing work, we are exploring the effect of different doses of melatonin on the regulation of its concentrations and of its secretion rhythm.

Keywords: melatonin, 6-sulfatoxymelatonin, circadian rhythm, sleep disorders, children

Introduction

Sleep problems are common among children. Indeed the prevalence rates of sleep difficulties are estimated to reach between 30%[1] and 40%[2] of the pediatric population. Short-term sleep loss is known to have negative effects on health, interpersonal relations, psychological functioning, daily activities,[3,4] and school performance.[5,6] Moreover, chronic sleep difficulties may cause neuronal damage and impaired brain development,[7] leading to the appearance of cognitive, behavioral, and emotional disorders.[5,8,9] To prevent all of these consequences, an early optimal treatment is essential.

The pineal hormone melatonin is the cornerstone in the synchronization of the sleep-wake rhythm. Its secretion increases at night and is inhibited throughout the day.[10] Well-timed and well-dosed exogenous melatonin has been proved to be effective in advancing sleep onset and increasing the total sleep duration in children with chronic sleep onset insomnia.[11-13] Additionally, the hormone seems to have positive effects on health, behavior problems, and parenting stress.[14] Furthermore, melatonin has been reported to show an adequate safety profile without severe side effects in children.[15]

Despite the numerous investigations carried out in relation to melatonin,[16-19] several important questions still remain to be solved in the context of pediatric sleep disturbances. Among them, we highlight the particular alteration of melatonin secretion in some primary sleep disturbances or in those related to several neurodevelopmental disorders[20]; the specific sleep disorder in which melatonin demonstrates better results; the most appropriated dosage[21]; or the treatment duration.[14]

Regarding possible alterations of melatonin production in the context of different sleep disorders, chronic sleep onset insomnia in children has been associated with a delayed time at which endogenous melatonin concentration starts to increase in dim light (dim light melatonin onset). This fact suggests that the biological clock rhythm in these patients is fixed at a later clock time than desired.[22] A low excretion of the metabolite 6-sulfatoxymelatonin (aMT6s) in urine with an absence of circadian variation has often been reported in pediatric patients with severe psychomotor delay (frequently associated with epilepsy or blindness).[23] On the other hand, in children with autism spectrum disorders and insomnia responsive to exogenous melatonin treatment, normal endogenous melatonin profiles have been demonstrated.[24] However, there are no studies that have reported specific melatonin secretion patterns in children with different primary sleep disturbances.

Our initial hypothesis was that recognizing the particular alteration of melatonin production in the diverse sleep disorders might help us to identify those that would benefit from melatonin therapy. In a previous study carried out on children diagnosed with diverse primary sleep disorders,[25] we obtained four different melatonin production patterns based on the urinary excretion of aMT6s. Involving those patients who presented a low melatonin production pattern or the absence of a circadian rhythm, we conducted a placebo-controlled clinical trial with the aim of analyzing their plasma melatonin concentrations and their actigraphic sleep parameters, as well as the possible effects derived from exogenous melatonin administration.

Materials and Methods

Study population

Participants came from the Health Area of Granada (Spain) and were recruited from patients at the General Pediatric Unit and the Neuropediatric, Neuropsychology and Early Intervention Unit of San Cecilio University Hospital (Granada).

The initial group of children with primary sleep disorders included 124 patients, 65 boys (52.42%) and 59 girls (47.60%), aged four to 14 years old (9.33 ± 3 years old). All of them were selected after being diagnosed with one of the sleep disorders recognized by the third edition of the International Classification of Sleep Disorders.[26] These sleep problems were not justified by the presence of neurological, metabolic, or endocrine disturbances. After measuring the aMT6s concentrations in diurnal and nocturnal urine collections, as well as in 24-hour urine samples, we identified four different melatonin production patterns. On the one hand, 76 patients showed a *standard melatonin production pattern* and 18 children exhibited a *melatonin hyperproduction pattern*. On the other hand, 12 patients showed a *low melatonin production pattern* and the remaining 18 children presented *a melatonin production pattern with an absence of circadian variation*. The latter 30 patients met the inclusion criteria to participate in the current clinical trial.

Study protocol

Evaluation of urinary and plasma melatonin concentrations

aMT6s is the major metabolite of melatonin in the urine[27] and its presence allows the evaluation of the global melatonin production rate. To measure urinary aMT6s levels and its circadian variation, urine samples were collected over a period of 24 hours. We obtained isolated diurnal (from 09:00 to 21:00) and nocturnal (from 21:00 to 09:00 of next day) urine samples, as well 24-hour urine from their mixture. Plasma levels of melatonin were recorded over 24 hours (at 09:00, 13:00, 17:00, 21:00, 01:00, 05:00) and allowed us to assess the pattern of melatonin secretion. To minimize venous punctures, a catheter was placed in the forearm. Radioimmunoassay was carried out to determine melatonin and aMT6s concentrations.

Sleep assessment

Actigraphy was the method used to evaluate the sleep characteristics of our patients. Actigraphs (Actiwatch AW7, Cambridge Neurotechnology Ltd, Cambridge, UK) were worn on the non-dominant wrist 24 hours a day, for seven consecutive days. Recordings of the amount of movement were made at one minute (60 second)-epoch and at the higher threshold value of sensitivity (threshold value for each sensitivity setting: low sensitivity = 80, medium sensitivity = 40, high sensitivity = 20). The activity score for each epoch was then compared with the threshold to determine if the epoch was scored as wake or sleep.[28] Particularly, this device model incorporated a light sensor to record the luminous intensity of white light and compare this information with that one provided by sleep diaries in relation to bedtime (or lights out) and get-up time. The data extraction and summary analysis were computed by using a software (Actiwatch Activity & Sleep Analysis version 7.27, Cambrige Neurotechnology Ltd, Cambridge, UK) that employed a validated sleep estimation algorithm.[29] Before data analysis, the devices were properly inspected to reject possible inconsistencies (e.g., when the actigraph was not worn). The following sleep parameters were analyzed: (1) *sleep start*, which was considered as the start of a period of at least 10 minutes (ten epochs for a 60-second epoch) of consecutively recorded immobile data following lights out; (2) *sleep end* was considered as the period of five minutes (five epochs for a 60-second epoch) of consecutively recorded immobile data before the get-up time; (3) *time in bed*, the total elapsed time between lights out and the get-up times; (4) *total sleep duration*, considered as the duration from *sleep start* until *sleep end*; (5) the actual amount of sleep (*actual sleep time*), calculated as the *total sleep duration* minus estimated time awake in the period from *sleep start* until *sleep end*; (6) *actual sleep percentage*, the *actual sleep time* expressed as a percentage of the *total sleep duration*; (7) *sleep onset latency*, the time period between lights out and *sleep start*; (8) *sleep efficiency*, the ratio between the *actual sleep time* and the time the subject was in bed; (9) *night awakenings*, the number of contiguous sections categorized as wake in the epoch-by-epoch wake/sleep categorization; (10) *actual wake time*, the total time spent in wake according to the epoch-by-epoch wake/sleep categorization; (11) *actual wake percentage*, *actual wake time* expressed as a percentage of the *total sleep duration*.[28]

Therapeutic intervention

After measuring urinary aMT6s concentrations and plasma melatonin levels, an oral placebo containing 3 mg of lactose was administered in one single dose 30 minutes before bedtime and for one week. Urinary samples and a seven-day actigraphic record were collected afterward. Immediately following the placebo intervals, melatonin was administered at a dose of 3 mg, 30 minutes before bedtime, for three months. At the conclusion of this period, urinary and plasma melatonin levels were measured again, and a one-week actigraphic record was carried out.

Ethical aspects

The study protocol was approved by the local Ethical Committee of Biomedical Research of Granada (Spain). All procedures were carried out in accordance with the Helsinki Declaration as revised in 2013.[30] Written informed consent signed by parents or legal guardians was required both to participate in the study and to publish the results, as well as the assent of school-aged children to their involvement in the research. Written informed consent was also required from participants over age 12 years who were sufficiently mature in relation to their developmental age.

Statistical analysis

Analyses were conducted using Statgraphics Centurion version XVII (Statpoint Technologies, Inc, Warrenton, VA). Descriptive data were presented as mean ± standard deviation (SD). The Kolmogorov-Smirnov test was applied to verify data normality. The two-tailed Student *t* test for paired samples was performed to compare means of melatonin/aMT6s concentrations and actigraphic parameters before and after treatment with exogenous melatonin. The level of significance was set at the usual alpha = 5%.

Results

Study population

As previously mentioned, 30 children were found eligible to participate in this clinical trial. Due to several reasons (logistical problems due to the shortage of actigraphs, social activities, attending high school and family circumstances), 12 patients were excluded before the beginning of the study.

After measuring the 24-hour plasma melatonin concentrations in the remaining 18 children (Supplementary Table S1), four patients were discarded from the study (participants number 1, 9, 12, and 16) as they showed a "standard" melatonin secretion profile. Normal melatonin concentrations in relation to age,[31] with an acrophase (time of maximum melatonin concentrations) occurring between 02:00 and 04:00, were detected in these four patients.

Our final study sample was then composed of the remaining 14 patients, nine girls (64.30%) and five boys (35.71%), aged seven to 14 years old (11.31 ± 2.44 years old). According to the major sleep disorders considered by the third edition of the International Classification of Sleep Disorders, the majority of them were diagnosed with circadian rhythm sleep-wake disorders (n = 6; 42.86%), followed by different types of parasomnias (n = 3; 21.43%). Sleep-related breathing disorders and insomnia disorders each represented 14.30% (n = 2) of the total. Finally, central disorders of hypersomnolence accounted for 7.14% (n = 1) of patients. The demographic and clinical characteristics of our participants are shown in Table 1.

Four different melatonin secretion profiles were then identified among our 14 patients:

TABLE 1.
Demographic and Clinical Characteristics of Participants Included in This Clinical Trial

Parameter	Participants
Sex, n (%)	
Male	5 (35.71)
Female	9 (64.30)
Age (years), mean ± SD	11.31 ± 2.44
Sleep disorders*, n (%)	
Circadian rhythm sleep-wake disorders	6 (42.86)
Delayed sleep-wake phase disorder	3 (21.43)
Circadian sleep-wake disorder not otherwise specified	3 (21.43)
Parasomnias	3 (21.43)
Nightmare disorder	1 (7.14)
Sleepwalking	1 (7.14)
Sleeptalking	1 (7.14)
Sleep-related breathing disorder (OSA pediatric)	2 (14.28)
Insomnia	2 (14.28)
Chronic insomnia disorder	1 (7.14)
Other insomnia disorders	1 (7.14)
Central disorders of hypersomnolence (idiopathic hypersomnia)	1 (7.14)

Abbreviations:
% = Percentage of participants
n = Number of participants
OSA = Obstructive sleep apnea
SD = Standard deviation
* Sleep disorders recognized by the third edition of the International Classification of Sleep Disorders.

(1) A melatonin secretion profile characterized by low plasma melatonin levels and an absence of circadian variation was found in four children (Supplementary Fig S1).
(2) A second group was composed of four patients who showed an advanced melatonin acrophase, between 17:00 and 21:00 (Supplementary Fig S2).
(3) Another melatonin secretion pattern was characterized by a delayed acrophase (between 05:00 and 09:00), and it was detected in two participants (Supplementary Fig S3).
(4) The remaining four patients exhibited adequate plasma melatonin concentrations in relation to their age, but without the presence of any circadian rhythm (Supplementary Fig S4).

Once the disturbance of the global melatonin production rate or its secretion rhythm was confirmed in our 14 participants, they were treated with placebo and exogenous melatonin. Along with both treatments, parents and children were advised to carry out appropriate sleep hygiene practices (age-appropriate bedtimes, schedules and routines, independence when falling asleep, avoiding possible triggers, etc.) in accordance with the Spanish Clinical Practice Guideline on Sleep Disorders in Childhood and Adolescence.[32]

An overview of the scheme is provided in Fig 1 which shows the study protocol and the patient selection process.

Urinary and plasma melatonin concentrations

The urinary aMT6s levels obtained in our 14 patients after the administration of placebo (one week) and after treatment with melatonin (three months) are shown in Table 2.

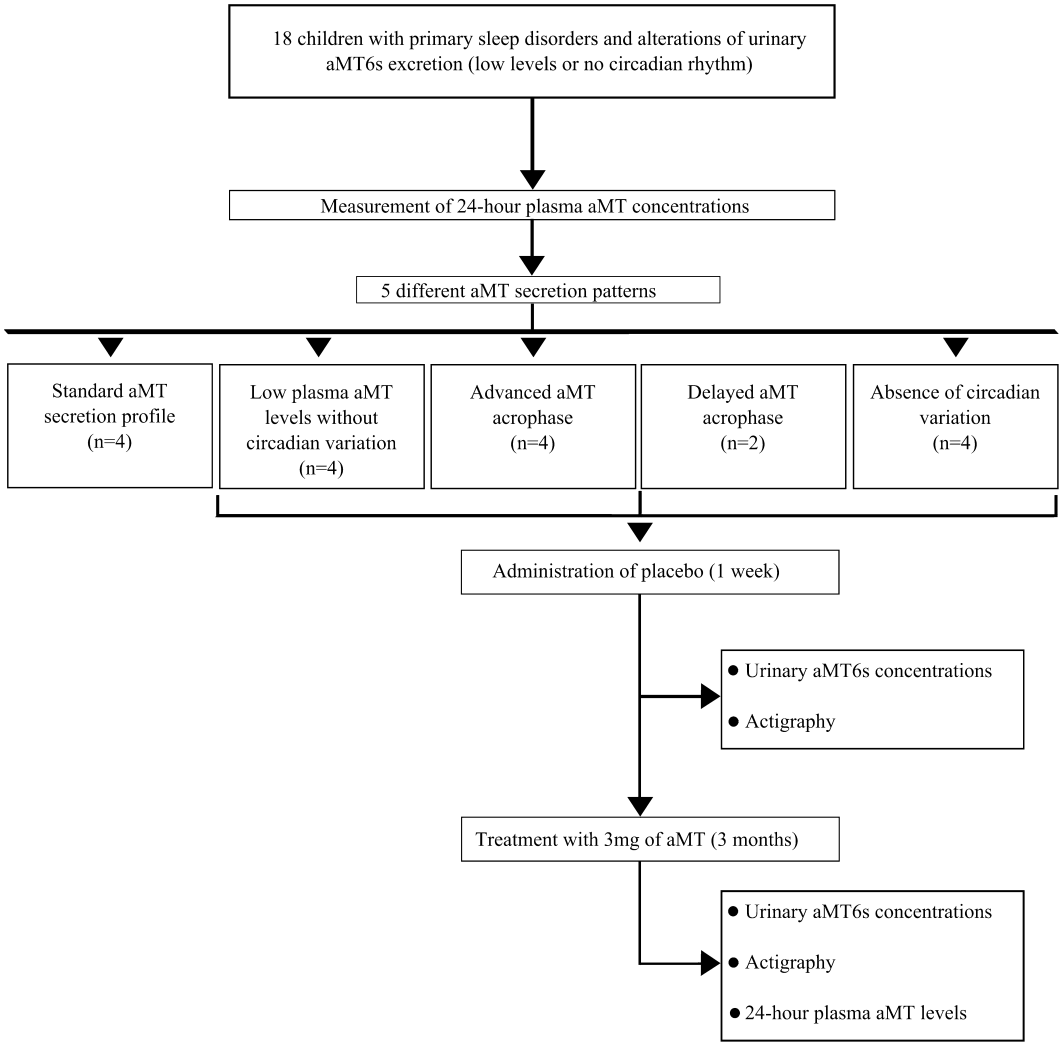

FIGURE 1.
Flow chart describing the study protocol and the patient selection process. aMT6s, 6-sulfatoxymelatonin; aMT, melatonin.

TABLE 2.
Comparative Analysis of Urinary 6-Sulfatoxymelatonin (pg/mL) Levels After Administration of Placebo (One Week) and After Three Months of Treatment With Melatonin

Urine Samples	Melatonin Concentrations (pg/mL)		
	After Placebo (Mean ± SD)	After Melatonin (Mean ± SD)	*t* Score/ *P* Value*
Diurnal urine	21.60 ± 7.10	70.10 ± 13.10	16.09/†
Nocturnal urine	38.40 ± 17.60	228.60 ± 59.40	23.58/†
24-Hour urine	29.80 ± 11.80	128.20 ± 52.40	14.70/†

Abbreviation:
SD = Standard deviation
* *t* Score is derived from the application of Student *t* test. Every *t* score has an associated *P* value (statistical significance).
† $P < 0.001$.

A significant increase of urinary aMT6s excretion ($P < 0.001$) with a clear circadian variation were observed after melatonin administration, in the 12-hour as well as in the 24-hour urine samples.

In relation to melatonin secretion, the 24-hour plasma melatonin concentrations after three months of treatment with this hormone are provided in Supplementary Table S2. Overall, the administration of melatonin produced circulating values that were significantly higher ($P < 0.001$) at four different moments (09:00, 13:00, 01:00, and 05:00) than those obtained in the same patients before treatment (Table 3). In addition, a recovery of the circadian secretion of melatonin was achieved after melatonin therapy, with an acrophase detected at 01:00 (171.50 ± 45.53 pg/mL) (Fig 2).

TABLE 3.
Comparative Analysis of Plasma Melatonin Concentrations (Expressed as pg/mL) Before Receiving Treatment and After Three Months of Exogenous Melatonin Administration

Hours	Plasma Melatonin Concentrations (pg/mL)		
	Before Treatment (Mean ± SD)	After Melatonin Therapy (Mean ± SD)	*t* Score/ *P* Value*
09:00 Hour (pg/mL)	30.80 ± 18.15	114.07 ± 30.05	9.95/†
13:00 Hour (pg/mL)	28.0 ± 10.70	91.0 ± 24.0	9.47/†
17:00 Hour (pg/mL)	44.64 ± 25.13	60.64 ± 14.80	1.91/ns
21:00 Hour (pg/mL)	41.21 ± 19.93	48.14 ± 7.07	1.20/ns
01:00 Hour (pg/mL)	36.57 ± 14.94	171.50 ± 45.53	10.72/†
05:00 Hour (pg/mL)	31.21 ± 14.19	142.14 ± 35.98	13.14/†

Abbreviations:
ns = Not statistically significant ($P > 0.05$)
SD = Standard deviation
* *t* Score is derived from the application of Student *t* test. Every *t* score has an associated *P* value (statistical significance).
† $P < 0.001$.

We also provided a comparative analysis of individual 24-hour serum melatonin concentrations before and after melatonin administration (Supplementary Table S3). The increase of mean plasma melatonin concentrations after melatonin therapy was not statistically significant ($P > 0.05$) in the case of three patients (21.43%). Two of them were respectively diagnosed with nightmare disorder and other insomnia disorders (participants number 10 and 17), and were characterized by an advanced acrophase (Supplementary Fig S2). The third patient was diagnosed with a circadian sleep-wake disorder not otherwise specified (participant number 11) and showed adequate plasma melatonin concentrations with an absence of circadian variation (Supplementary Fig S4).

Sleep assessment

The changes observed in the urinary and plasma melatonin levels were accompanied by a clinical improvement reported by parents and demonstrated by the actigraphic results.

Results from the comparative analysis between the actigraphic sleep parameters after treatment with placebo and after taking melatonin are shown in Table 4. After melatonin administration, the *total sleep duration* and *actual sleep time* were found to be significantly longer, as well as the *sleep efficiency* which was significantly higher ($P < 0.001$). A

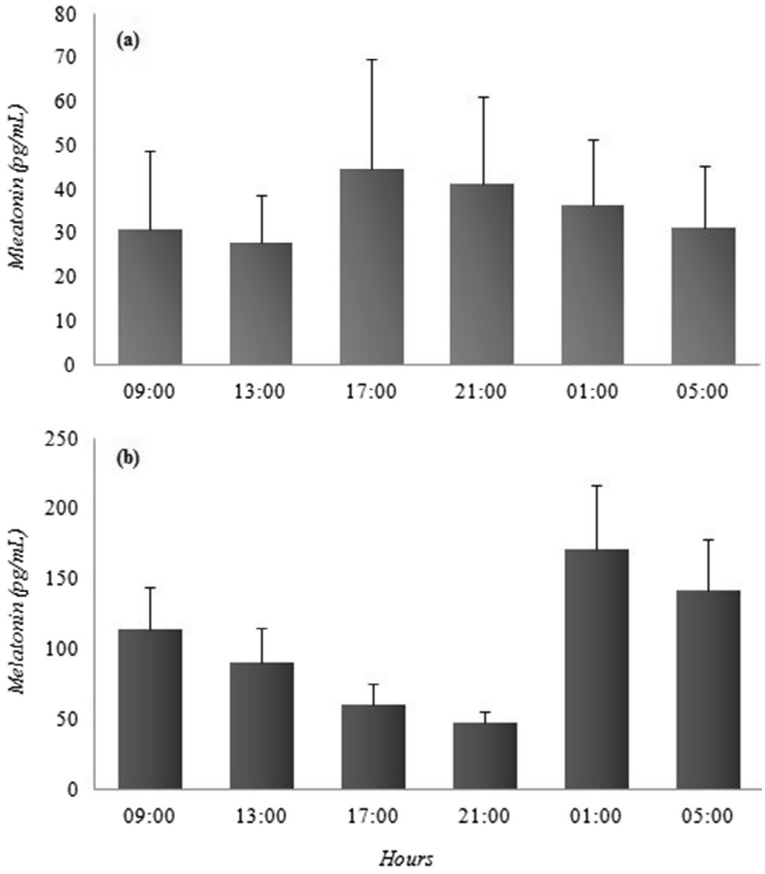

FIGURE 2.
Twenty-four-hour plasma melatonin concentrations (expressed as mean ± standard deviation) before (A) and after three months of melatonin administration (B). Note the increase of plasma melatonin levels with a recovery of circadian variation after three months of treatment with exogenous melatonin.

TABLE 4.
Comparative Analysis of Sleep Parameters (Expressed as Mean ± Standard Deviation) Measured by Actigraphy After Taking Placebo (One Week) and After 3 Months of Treatment With Melatonin

Sleep Parameters	After Placebo (mean ± SD)	After Melatonin (Mean ± SD)	*t* Score/*P* Value*
Time in bed (HH:MM)	08:27 ± 00:36	09:38 ± 00:24	28.62/†
Total sleep duration (HH:MM)	07:48 ± 00:29	09:22 ± 00:20	37.89/†
Actual sleep time (HH:MM)	06:53 ± 00:21	09:10 ± 00:21	55.22/†
Actual sleep time (%)	88.20 ± 2.80	97.20 ± 4.80	18.14/†
Actual wake time (HH:MM)	00:55 ± 00:12	00:12 ± 00:10	17.33/†
Actual wake time (%)	11.70 ± 15.0	2.70 ± 2.50	5.18/†
Sleep efficiency (%)	81.40 ± 1.90	95.50 ± 2.90	12.63/†
Sleep onset latency (HH:MM:SS)	00:18:00 ± 00:02:30	00:05:36 ± 00:03:30	9.21/†
Awakenings	6.20 ± 2.30	2.20 ± 2.40	8.06/†

Abbreviations:
% = Percentage
HH:MM = Hours:Minutes
HH:MM:SS = Hours:Minutes:Seconds
SD = Standard deviation
* *t* Score is derived from the application of Student *t* test. Every *t* score has an associated *P* value (statistical significance).
† $P < 0.001$.

significant reduction in the *sleep onset latency* and number of *awakenings* ($P < 0.001$) was also observed.

We highlight that all of our participants (100%) complied with melatonin treatment. However, only nine of them (64.30%) admitted following the recommended sleep hygiene practices initially proposed.

Tolerability and adverse effects

No severe side effects were reported after three months of melatonin treatment. The tolerability was adequate in all participants.

Discussion

This is the first study describing specific alterations of the melatonin production pattern in a group of children with different primary sleep disorders and the effect derived from exogenous melatonin administration. After three months of treatment with melatonin (3 mg), an overall significant increase of plasma melatonin concentrations and urinary aMT6s levels were observed. Together with an improvement of the global melatonin production, a recovery of the circadian secretion rhythm was also reached, obtaining acrophases at appropriate times and a circadian variation in accordance with the light-dark periods that are normal for humans. We assume that the latter could be due not just to the intake of melatonin, but also to the way it was administered. In addition, all these changes were reflected in the actigraphic results.

Melatonin is a pineal hormone that regulates the circadian rhythm. Sleep induction is the most recognized property of melatonin,[21] which appears to be effective in reducing time to sleep. However, its efficacy in decreasing nighttime awakenings and other aspects of sleep disturbances is reported to be variable.[33] In this context, apart from a significant reduction of the sleep onset latency, significant increases in the actual sleep time and sleep efficiency with a reduced number of night awakenings were also observed in our clinical trial after melatonin administration. In contrast, in a recent double-blind placebo-controlled clinical trial conducted on children with chronic sleep onset insomnia and late melatonin onset, an increase in night awakenings was reported after melatonin administration in comparison with placebo and bright light therapy. Whereas the sleep onset latency decreased by 15 minutes, the total sleep duration increased by only five minutes.[34] However, this trial differed from ours with respect to the patient selection, study period, and time of melatonin administration. On the other hand, more remarkable changes in sleep times were obtained in previous studies with similar treatment duration.[12,13] It seems that increased night awakenings may disappear when the melatonin dose is reduced, according to current clinical experience at the Dutch Centre of Sleep-Wake Disorders and Chronobiology (MG Smits, personal communication, April 26, 2016). When the dose is too high, the response to melatonin treatment may be lost, due to CYP1A2 polymorphisms which might lead to a slower melatonin metabolism.[35,36] Consequently, the currently recommended initial dose of melatonin in healthy children is lower (1 mg),[21] which differs from the dose we used and the quantity administered by van Maanen et al.[34] Nevertheless, we observed a significant reduction in the number of night awakenings after melatonin administration. Thus we defend that new studies are needed to investigate the possible association between the number of night awakenings and the dose of melatonin.

Some studies conclude that the administration of melatonin is only useful when a circadian rhythm sleep disorder exists,[37] which is frequently caused by a visual impairment because of the elimination of the synchronizing effect of exposure to light.[38] However, the results we present demonstrate that melatonin seems to be effective in three main circumstances: (1) a disturbed circadian rhythm, (2) an insufficient hormone production, and (3) an acrophase lagging/leading. Our observations are in line with the results of a previous placebo-controlled trial of melatonin supplementation conducted by our research group.[39] In fact, a recent Task Force commissioned by the American Academy of Sleep Medicine recommends the use of exogenous melatonin for children and adolescents suffering from delayed sleep-wake phase disorder and those diagnosed with neurological disorders and an irregular sleep-wake rhythm disorder.[40] For the time being, the strength of these recommendations is

still weak.[40] Nevertheless, the development of future investigations focused on intrinsic circadian rhythm sleep-wake disorders are expected to provide more evidence in relation to the role of melatonin in these sleep disturbances.

Three of our participants did not show a significant increase in their serum melatonin concentrations after three months of melatonin therapy. This result might be related to the fact that melatonin may be more effective in improving certain sleep disorders than others. During the follow-up that we are currently carrying out, our aim is to investigate the correspondence between specific melatonin secretion profiles and a particular sleep disorder. To achieve this objective, more patients with diverse sleep disturbances will have to be recruited. We can already advance that certain sleep disorders, such as the delayed sleep-wake phase disorder and chronic sleep onset insomnia, are more likely to improve after melatonin administration. However, in the case of other sleep disturbances, the sample size will have to be increased and other factors that might influence the results and the conclusions about the effectiveness of melatonin in these sleep disorders will have to be discarded.

According to previous studies conducted on adults[41,42] and children,[11,15] no severe side effects were reported in our study after melatonin treatment. The wide therapeutic window[42-44] and few side effects exhibited by melatonin allow administrating it in children with diverse diseases,[45,46] including neurological and neurodevelopmental disorders,[39,47-51] especially attention deficit or hyperactivity disorder,[52,53] and autism spectrum disorders.[54] Despite this evidence, several animal research studies showed that exogenous melatonin affects seasonal reproduction capacity[55] and might cause an inhibitory effect on hypothalamic-pituitary-gonadal function in humans.[56] However, this assumption has not been supported by a subsequent long-term questionnaire-based study conducted on children and adolescents.[57] Therefore further investigations regarding the safety of melatonin in pediatric populations are recommended by current literature reviews.[58,59]

The potential limitations of this study need to be highlighted. Firstly, the number of participants was small due to logistical problems such as the availability of actigraph devices, and this could have contributed to the significant results. Secondly, differences of melatonin concentrations related to age, sex, and season were not considered. Thirdly, the chronobiological effect of melatonin could have been even more noticeable if the hormone had been administered two or three hours before the dim light melatonin onset.[21] The reason why melatonin was administered 30 minutes before bedtime in our study was mainly to achieve a sleep induction.[21] However, with the intake of 3 mg of melatonin at this time, we were able to demonstrate not only an enhanced melatonin production, but also a recovery of circadian rhythm secretion. Fourthly, it is reasonable to consider that sleep hygiene practices could have influenced the sleep actigraphic results.[32,60] However, less than 65% of participants complied with these recommendations.

The main strength of our study was to demonstrate the positive effect of melatonin on diverse specific alterations of its production and of its secretion rhythm in children with different primary sleep disorders. Consequently, this investigation suggests other possible indications for the administration of this hormone and highlights the importance of exploring particular disturbances of melatonin secretion in each sleep disorder before starting treatment. In addition, this work initiates a line to encourage and promote new investigations about the benefits of melatonin (administered at different doses and at different times of day) in diverse types of sleep disorders.

Conclusions and Future Lines of Research

Melatonin seems to be effective under three main conditions: an insufficient hormone production, a disturbed circadian rhythm, and an advanced or delayed acrophase. Nevertheless, it would be convenient to explore the particular melatonin production pattern in each primary sleep disorder before starting treatment. Additionally, no severe side effects were reported in our trial after melatonin administration.

We have identified as ongoing work exploring the effect of different doses of melatonin on the regulation of its concentrations and of its secretion rhythm. This will assist us in finding the lowest effective dose of this hormone in each sleep disorder and minimize the probability of adverse effects, as we have mentioned above. Additionally, it would be interesting to conduct long-term clinical trials to investigate the risk of recurrence of sleep problems depending on the dosage and time of administration and on the type of primary sleep disorder.

Author Contributions

AMH conceived and developed the study. AMH analyzed and interpreted data together with AMC. ACR contributed to the data interpretation, drafted the manuscript, and designed tables. AMG contributed to the statistical analysis. MAMG collaborated with the patient recruitment and data analysis. SNG, AJC, and MCAM contributed to data acquisition. All authors critically revised the manuscript, gave their final approval, and agreed to be accountable for all aspects of work, ensuring integrity and accuracy.

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Supplementary data

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