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Normalization of the sleep–wake pattern and melatonin and 6-sulphatoxy-melatonin levels after a therapeutic trial with melatonin in children with severe epilepsy

Abstract: This study evaluated the sleep–wake pattern, plasma melatonin levels and the urinary excretion of its metabolite, 6-sulphatoxy-melatonin among children with severe epileptic disorders, before and after a therapeutic trial with melatonin. Ten paediatric patients, suffering from severe epileptic disorders, were selected and given a nightly dose of 3 mg of a placebo, for 1 wk; for the next 3 months, the placebo was replaced with a nightly dose of 3 mg of melatonin. At the end of each treatment period, the urinary excretion of 6-sulphatoxy-melatonin (for the intervals 09.00 – 21:00 hr or 21:00–09:00 hr) and plasma levels of melatonin (recorded at 01:00, 05:00, 09:00, 13:00, 17:00 and 21:00 hr) were recorded, over a period of 24 hr; an actigraph record was also kept. Sleep efficiency among patients who received melatonin was significantly higher than among those given the placebo, with fewer night-time awakenings. Periodic plasma melatonin levels were regained and a better control gained of convulsive episodes, in that the number of seizures decreased. We conclude that melatonin is a good regulator of the sleep–wake cycle for paediatric patients suffering from severe epilepsy, moreover, it to a better control of convulsive episodes.

J. Uberos[1], M. C. Augustin-Morales[1], A. Molina Carballo[1], J. Florido[2], E. Narbona[1] and A. Muñoz-Hoyos[1]

[1]UGC Pediatría, Hospital Clínico San Cecilio, Granada, Spain; [2]Servicio de Obstetricia y Ginecología, Hospital Clínico San Cecilio, Granada, Spain

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Address reprint requests to J. Uberos, c/Málaga 1, 18170 Alfacar, Granada, Spain.
E-mail: uberosfernandez@terra.es

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Introduction

Normal circadian rhythmicity is altered following convulsive episodes, and patients with epilepsy frequently present alterations in the sleep–wake rhythm [1] in association with changes in the normal sleep architecture, as documented by polysomnography [2]. Although the question of whether sleep modifies the course of epilepsy or whether epilepsy modifies sleep rhythms has been extensively investigated [3, 4], published reports to paediatric epileptic disorders are uncommon.

The aetiology of sleep disorders among children with epilepsy is multifactorial and includes factors derived from epilepsy per se and those related to medication prescribed to control convulsions. Drugs such as valproic acid, which is commonly used in such cases, may induce significant weight gain and increase the risk of the patient developing a sleep disorder related to the sleep apnoea syndrome. In these cases, adenoidectomy can alleviate sleep fragmentation and, secondarily, help control convulsions [5]. Various studies have concluded that sleep fragmentation disorders and excessive day time somnolence may provoke an increase in the frequency of convulsive attacks and hamper their control [6]. The reverse is also the case, such that the type of convulsion may also affect the development of sleep disorders, and patients with generalized convulsions may develop sleep disorders more frequently than do those with simple or complex partial convulsions [7].

Various studies [8] have related melatonin deficiency with disorders of the sleep–wake rhythm, while melatonin is often considered to be promoted as a sleep inducer [9, 10]. In this study, we evaluated the sleep–wake pattern, plasma melatonin levels and the urinary excretion of its metabolite, 6-sulphatoxy-melatonin, in children with severe epileptic disorders, before and after a therapeutic trial with melatonin.

Materials and methods

Patients and treatments

We studied 10 children with severe epileptic disorders (three with West syndrome, two with Lennox syndrome, two with progressive myoclonic epilepsy, two with epileptic encephalopathy secondary to hypoxic-ischaemic encephalopathy and one with epilepsy secondary to cytomegalovirus infection), aged from 4–10 yr (mean: 6.4; S.D. 2.1). Prior authorization for the study was obtained from the Hospital's Ethics Committee, as was the informed consent of the children's parents; 30 min. before bedtime, and for 1 wk, the children were given an oral placebo (3 mg of lactose, in a single dose). The urinary excretion of 6-sulphatoxy-melatonin was determined for periods of 09:00–21:00 hr, and 09:00–21:00 hr plasma levels of melatonin were recorded over 24 hr (at 01:00, 05:00, 09:00, 13:00, 17:00 and 21:00 hr). A 3-day actigraph record was taken.

Immediately following the placebo intervals, melatonin was administered 30 min. before bedtime, orally, at a dose of 3 mg, for a period of 3 months. At the conclusion of this period, we measured the urinary excretion of 6-sulphatoxy-melatonin and the plasma levels of melatonin, at the same time periods as above, and a 7-day actigraph record was taken.

Assays for melatonin and its urinary metabolite

The urinary metabolite of melatonin, 6-sulphatoxy-melatonin, was determined using a enzyme immunoassay technique (EIA), using a aMT6s-bovine serum albumin-horseradish peroxidase (aMT6s-BSA-HRP) conjugate as the enzyme label [11].

Actigraph measurements

The actigraph (Actiwatch® Activity Monitoring System; Cambridge Neurotechnology Ltd., Granada, Spain) was fitted to the patient's wrist, which enabled data (intensity and/or frequency of body movements) to be recorded by sampling the electrical signal provoked by the subject's movement, up to 10 times per second, with a duration ranging from 6 hr to 21 days. At the conclusion of the study period, these signals were discharged and analysed, using purpose-built software capable of transforming the movements registered by the accelerometer into activity (awake) or inactivity (asleep) signals. This transformation enabled us to study the following parameters: (i) Bedtime, the time during which the subject is lying in bed, intending to sleep, (ii) Sleep efficiency, the ratio between the time the signal indicates the subject is asleep and the time he/she is in bed and (iii) Number of arousals, the number of awakening episodes detected during the time he/she remains in bed. Levels of motor activity were evaluated in accordance with the periods of time noted in the subject's diary. The distribution of daily activity was analysed in three different ways: the night interval was arbitrarily established as the time the subject remained in bed with the intention of sleeping, while the day was the period during 24 continuous hours when the subject was not in bed. The spectral analysis of maximum entropy enabled us to detect the dominant frequency of activity (i.e. the most intense spike of activity in the spectrum) during the study period. The analysis performed provided the following information: (i) a graphical representation of each subject's actigram, (ii) a frequency analysis (Fourier transform) and (iii) a periodogram. In addition, the sleep analysis produced the following data: (i) bedtime, (ii) getting up time, (iii) time spent in bed, (iv) moment at which sleep begins, (v) moment at which sleep ends, (vi) subjective sleep time, (vii) real sleep time, (viii) subjective time as a percentage of real sleep time, (ix) real time awake in bed, (x) sleep efficiency and (xi) sleep latency.

Statistical analyses

The statistical analysis of the data consisted of an analysis of the variance, a paired data t-test and a cosinor analysis.

Results

The subjects were being treated with melatonin, less time was spent in bed by the group of patients with epilepsy given the placebo, and their real sleep time was also less (Table 1). Sleep efficiency was significantly higher when the patients were given melatonin.

The administration of 3 mg of melatonin daily, for a period of 3 months, produced circulating values that were clearly higher than those obtained in the same patients during administration of the placebo. Nevertheless, the aspect of greatest clinical interest is probably the concurrent clinical improvement observed. The latter could be due not just to the administration of melatonin, but also to the form of administration, which enabled us to obtain acrophases at appropriate times, and a circadian variation in accordance with the light–dark periods that are normal for humans. Figures 1 and 2 show that while the patients were taking the placebo, there was no rhythmic secretion of melatonin, while the urinary secretion of 6-sulphatoxy-melatonin was slightly greater during the 21:00- to 09:00-hr period, although the latter levels were 50% lower than those presented by nonepileptic paediatric subjects (unpublished data).

Treatment with 3 mg of melatonin, administered orally 30 min. before bedtime, produced a recovery of the circadian secretion of melatonin, with the maximum melatonin value being recorded at 01:00 hr. These observations are of particular significance for convulsive patients, because such patients not only present quantitative variations in melatonin secretion, but frequently suffer modifications in the level of melatonin production, thus affecting the acrophase. The following sleeping disorders were observed among the group of children with epilepsy : six of the ten children presented an irregular wake–sleep pattern, two suffered from advanced sleep phase syndrome and another two from delayed sleep phase syndrome.

Discussion

The paediatric patients with severe epilepsy examined in the present study presented alterations from normal sleep

Table 1. Actimetry, mean values (standard deviations) after placebo and melatonin treatment

	Placebo (n = 10)	aMT (n = 10)
Bedtime	20:43 (32′)	21:03 (42′)*
Getting up time	09:07 (30′)	09:35 (20′)*
Time in bed	11:56 (34′)	12:32 (43′)*
Onset of sleep	20:52 (34′)	21:05 (24′)*
Conclusion of sleep	08:32 (28′)	09:15 (20′)*
Theoretical sleep time	11:40 (26′)	12:10 (36′)*
Real sleep time (h)	10:48 (25′)	11:55 (21′)*
Real sleep time (%)	92.5 (1.6)	97.9 (4.6)*
Time awake	00:52 (23′)	00:15 (20′)*
Sleep efficiency	90.8 (1.2)	95.07 (2.2)*
Latency	00:11 (2.8)	00:6 (3.5)
Arousals	3.3 (1.5)	2.3 (2.5)

*$P < 0.001$. aMT, Melatonin.

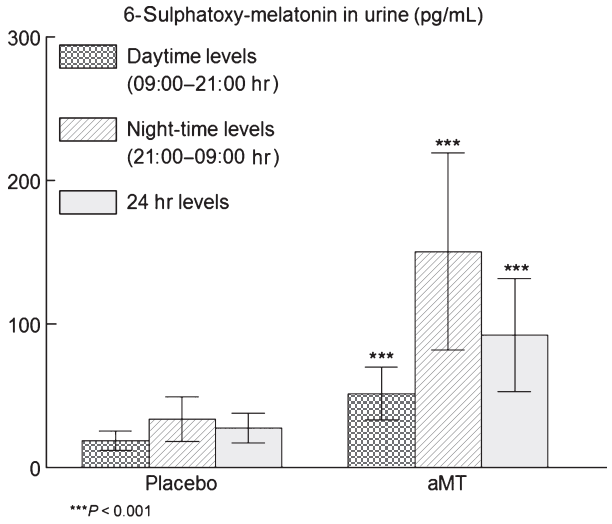

Fig. 1. Levels of 6-sulphatoxy-melatonin in urine. Mean values (S.D.) after placebo administration and melatonin treatment.

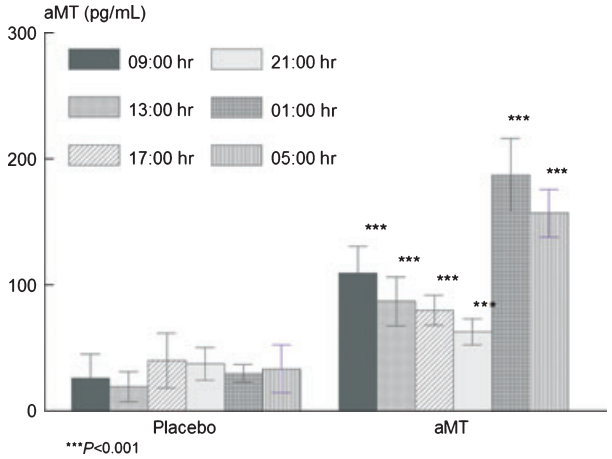

Fig. 2. Mean levels (S.D.) of melatonin in children with severe epilepsy after placebo and melatonin treatment.

architecture, and their melatonin secretion patterns were also affected. This was corrected following the therapeutic trial with melatonin. The patients with epilepsy who received a night-time dose of melatonin achieved a more efficient sleep than did those given only the placebo; they also exhibited a better objective control of the illness, in terms of a reduction in the number of epileptic seizures suffered.

Nunes et al. [12] carried out a polysomnographic study of 17 paediatric patients with refractory partial epilepsy and observed a reduction in the total time spent in bed and in total sleep time. They concluded that patients with this form of epilepsy present slight changes in sleep architecture, attributable either to the epilepsy per se or to the anti-convulsive medication prescribed. Kaleyias et al. [2] found no differences in sleep architecture between patients with partial or with generalized epilepsy. However, the refractoriness of the convulsions seems to be a factor that is closely related to sleep rhythm disorders, as a better control of such convulsions is achieved when the associated sleep disorders are corrected. These authors obtained a polysomnograph record showing that children with poor pharmacological control of convulsions have less efficient sleep, with a higher index of arousals and a higher percentage of rapid-eye-movement sleep. In the present trial, the patients who were given melatonin presented both improved sleep efficiency and a better control of their condition, with fewer seizures. It is difficult to compare the different clinical trials performed in this respect, because there is no consensus as to the dose of melatonin to be administered [13, 14], or the time for its administration [15] or the clinical indications for its administration [16].

Children with severe psychomotor retardation (which is frequently associated with epilepsy and/or blindness) often present an irregular sleep pattern and very low levels of urinary excretion of 6-sulphatoxy-melatonin, and an absence of circadian variation [17]. To some extent, these findings are corroborated in the present study. Some nonepileptic disorders, such as Down syndrome (DS), are associated with psychomotor retardation and alterations in the nocturnal secretion of melatonin. In DS, the pattern of elimination of tryptophan metabolites by the kynurenic acid pathway or by that of anthranilic acid, in patients with DS, is very different from that observed in healthy individuals. The lower levels reported among patients with DS of the enzyme 3-hydroxykynurenine transaminase would account for the decrease observed in the synthesis of xanthurenic acid [18]. So that the data we have cannot know whether the abnormal production of melatonin is associated with brain damage, with seizures or both.

Most studies considering this type of patient report that melatonin treatment produces an increase in the percentage of night-time sleep and greater sleep efficiency. Nevertheless, total sleep time, during a 24-hr period, remains unaltered because day time sleeping decreases [19], while no secondary effects are provoked [20]. In this respect, some studies have concluded that the administration of melatonin is only useful in cases of circadian rhythm sleep disorders, which are frequently caused by a visual disorder because of the elimination of the synchronizing effect of exposure to light [13]. The results we present, together with other, more recent observations (unpublished data), show that the therapeutic trial with melatonin is useful against intrinsic sleep disorders that produce alterations in the circadian rhythm, insufficient hormone production or phase lagging/leading.

The relation between sleep and epilepsy is so strong that changes in the sleep pattern affect the EEG reading, activating paroxysmal anomalies when these are present, and producing morphologic changes, both quantitative and qualitative, in the paroxysmal activity of a subject to epileptic seizures. For this reason, it has long been believed that sleep deprivation has a marked influence on epileptogenic activity. Studies have been performed, with human subjects, of the anti-convulsant potential of administering pharmacological doses of melatonin. Epileptic convulsions are distributed following a circadian rhythm, and the alteration of normal cycles as a result of sleep-pattern

alteration, or stress, alcohol, pregnancy, etc., may provoke an increase in convulsive frequency [21]. The first published mention of the anti-convulsive role of melatonin was made by Anton-Tay [22], who observed that melatonin doses exceeding 2 g/day reduced spike activity and convulsive frequency among patients with intractable epilepsy of the temporal lobe, although these patients continued to need other anti-convulsive drugs to control their illness. Spike activity was replaced with slow theta waves, in the hippocampal gyrus and in the temporal cortex.

Molina-Carballo et al. [23, 24] reported a reduction in the circadian rhythm of melatonin among children with epileptic convulsions, while this rhythm disappeared completely among another group of children affected by febrile convulsions. A linear correlation has been reported between serum levels of melatonin and the duration of the convulsive episode. These results are interpreted as an immediate pineal response to stop the convulsion, which would be indicative of a possible direct action of melatonin on neural excitability, acting as an inhibitory neurotransmitter, and therefore involved in the onset of the postictal refractory period. The same authors [25] began melatonin treatment for a child aged 1 yr, who had had progressive myoclonic epilepsy since the first month of life. Despite receiving multiple anti-convulsant treatments, the child suffered 15–20 seizures every day, and on several occasions these were convulsive. After treatment with melatonin, the frequency and intensity of the seizures decreased. After almost 3 yr' treatment, transaminase levels were observed to rise and the melatonin treatment was withdrawn, but the seizures then reappeared, in greater number and intensity.

Niles et al. [26] showed that the chronic administration of melatonin in rats induces a greater GABA affinity for its receptor, without reducing the number of receptors, which suggests that the psychopharmacologic effects of melatonin are related, at least in part, to its capacity to increase GABAergic transmission by modulating the activity of the GABA receptor. In the rat, eliminating circulating melatonin by pinealectomy reduces and alters the circadian rhythm of benzodiazepine receptors [27] and increases the number of GABA receptors, and at the same time it inverts their circadian rhythm [28]. The administration of melatonin reverses these changes and produces an increase in GABA levels and in seratonin levels in the hypothalamus [29].

Another action mechanism could be that of the catabolism of indoleamine to kynurenine produced in the CNS [30], which has been associated with the control of convulsive activity [31]. Kynurenine, administered by injection into the CNS, produces convulsions [32]. However, kynurenic acid delays the appearance of convulsions in rats [33] and inhibits audiogenic convulsions in mice [34]. The specific mechanism by which kynurenic acid acts remains unknown, although it is a nonselective antagonist of excitatory amino acid receptors [35].

We can conclude that melatonin is useful for normalizing the sleep–wake cycle in paediatric patients with refractory epilepsy. This favours more efficient sleep and contributes to the better control of convulsive episodes.

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