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Brain & Development 26 (2004) 373–376

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Melatonin in wake–sleep disorders in children, adolescents and young adults with mental retardation with or without epilepsy: a double-blind, cross-over, placebo-controlled trial

Giangennaro Coppola, Giusi Iervolino, Marina Mastrosimone, Graziella La Torre, Francesca Ruiu, Antonio Pascotto*

Clinic of Child and Adolescent Neuropsychiatry, CIRN, Second University of Naples, Via Pansini 5 80131, Naples, Italy

Received 9 December 2002; received in revised form 17 September 2003; accepted 23 September 2003

Abstract

The aim of the present study was to verify the clinical efficacy of melatonin (MLT) in children, adolescents and young adults with wake–sleep disorder and mental retardation, most of them on chronic anticonvulsant therapy for epileptic seizures, by means of a randomized, double-blind, placebo-controlled cross-over trial. Twenty-five patients (16 males, nine females), aged from 3.6 to 26 years (mean 10.5 years), all affected with mental retardation mostly with epileptic seizures, were randomized to oral synthetic fast-release MLT or placebo. Melatonin was initiated at the daily dose of 3 mg, at nocturnal bedtime. In case of inefficacy, MLT dose could be titrated up to 9 mg the following 2 weeks at increments of 3 mg/week, unless the patient was unable to tolerate it. The analysis of all the sleep logs disclosed a significant treatment effect of melatonin on sleep latency ($P = 0.019$). Melatonin was well tolerated in all patients and no side effects were reported. In conclusion, our study supports the efficacy of MLT in young patients with mental disabilities and epileptic seizures in improving the wake–sleep disorders such as time to fall asleep. Overall, MLT appeared to influence the seizure frequency poorly, though there may be occasional seizure worsening or improving. Such a dual effect requires further studies in young epileptic patients.

Keywords: Melatonin; Sleep disorders; Mental retardation; Epilepsy

1. Introduction

Sleep disorders, mainly including increased latency to sleep onset, an increased number and duration of awakenings after sleep onset, reduced sleep efficiency (total sleep time/total sleep time plus waking time after sleep onset), are common in children and adolescents with mental impairment and motor handicap [1,2]. Such disorders are more frequent when associated with both crypto-symptomatic [3,4] or idiopathic [5] generalized and partial seizures, that disrupt night-time sleep. Moreover, sleep disturbances were seen with and without the occurrence of seizures during the course of the polygraphic recordings and may not be attributed to recent seizure events. A wake–sleep disorder, on the other hand, contributes significantly per se to worsen both seizure frequency and cognitive-behavioral pattern in these patients.

Among the pharmacologic armamentarium for sleep problems in children, melatonin (MLT), which is a substance naturally produced in the human pineal gland that helps to regulate our sleep–wake cycle through its action on the suprachiasmatic nucleus in the hypothalamus, has raised much interest in recent years. Mostly uncontrolled data are reported in the literature on its efficacy in children without [6,7] or with developmental disabilities [8–12] and, to a lesser extent, with epilepsy [13].

The aim of the present study was to verify the clinical efficacy of MLT in children, adolescents and young adults with wake–sleep disorder and mental retardation, most of them on chronic anticonvulsant therapy for epileptic seizures, by means of a randomized, double-blind placebo-controlled trial.

* Corresponding author. Tel.: +39-81-5666692; fax: +39-81-5666694.

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doi:10.1016/S0387-7604(03)00197-9

2. Materials and methods

Patients were enrolled into the study based on the following criteria: (i) mental retardation with/without epileptic seizures; (ii) age more than 12 months, in order to avoid difficulty with calculating infant dosages; (iii) diagnosis of sleep disorder, defined according to the Diagnostic and Statistical Manual of Mental Disorders (DSM), 4th edition (IV) criteria (307,45) as the circadian rhythm sleep disorder [14] including delayed onset of sleep, multiple night awakenings, and short duration of night sleep through a baseline period of 6 months; (iv) exclusion of medical issues such as gastroesophageal reflux, pain or epileptic seizures mimicking sleep disorders; (v) persisting sleep disturbances despite maintaining appropriate sleep hygiene; (vi) informed consent by parents and/or caregivers. Patients were excluded from the trial if there were: (i) progressive neurological and/or systemic diseases; (ii) age <12 months; (iii) poor compliance from parents/caregivers with the study requirements before trial entry.

Participants were recruited from institutions providing health care to children with neurodevelopmental disabilities and from our epilepsy service of the Clinic of Child Neuropsychiatry. The medical staff administered parents and/or caregivers a sleep-questionnaire to screen the main characteristics of the sleep–wake cycle of each patient. Questions were about five sleep features: (1) average time to fall asleep; (2) average number of night awakenings; (3) average total time of nocturnal sleep; (4) average total time of diurnal sleep; and (5) presence of early morning arousals. Based on the analysis of the sleep questionnaire, filled in on an estimate basis, including the persistence of the sleep disorder for at least 6 months, patients were recruited for the study. Parents were given a sleep diary and instructed to stay up all night with the subject to fill in the sleep logs, concomitantly to the sleep disorder. Data were collected in all days throughout the study and then averaged by the medical staff every 4 weeks. Relative to the night awakenings, parents were asked if the interruption of the night sleep added to epileptic seizures or other causes. Polygraphic sleep-video-EEG monitoring was only performed in those patients in which epileptic seizures or pseudoseizures mimicking sleep disorders were suspected. Seizure frequency, type and duration before and during the trial were also recorded in an epilepsy diary by parents and caregivers both at home and at school.

Each patient enrolled into the study was randomized to oral synthetic fast-release melatonin or placebo, and then entered phase 1 (melatonin or placebo) that lasted 4 weeks. After a cross-over period of 1 week, each patient entered phase 2 that also lasted 4 weeks. Melatonin was initiated at the daily dose of 3 mg (Melatonin AFOM-Medical, 3-mg tablet), at nocturnal bedtime. In case of inefficacy, melatonin dose could be titrated up to 9 mg the following 2 weeks in increments of 3 mg/week, unless the patient was unable to tolerate it. EEG, side effects and blood levels of concomitant AED were monitored in all patients at baseline and at the end of each melatonin or placebo 1-month phase of the study. The dose of pre-existing medication was maintained unaltered throughout the trial. At the end of the second phase, responders to MLT entered an open-label phase of 2 months.

The data were not completely normally distributed; therefore, statistical analysis was performed using the Student's *t*-test (two-tailed), the chi-square test and the Fisher's exact test for independent samples.

3. Results

Patients enrolled in the study were 32, of whom 25 completed both MLT and placebo phases. The main characteristics of these patients were: 16 males, nine females, aged from 3.6 to 26 years (mean age 10.5 years), all affected by mental retardation with or without epilepsy. Mental delay was mild in 3 (12%) patients, moderate in 8 (32%), and severe in 14 (56%). Epileptic seizures were present in 18/25 patients (72%); they were complex partial (8), with secondary generalization (5), tonic–clonic (4), tonic (3), drop-attacks (2), atypical absences (1), myoclonic seizures (2). Type of epilepsy was the following: partial epilepsy (9); generalized symptomatic (5) or cryptogenic (1) epilepsy; multifocal epileptic encephalopathy (3). A genetic syndrome was diagnosed in five cases (20%); they were the following: Angelman syndrome; Saethre–Chotzen syndrome; 11p13 microdeletion; Leber amaurosis; CHARGE syndrome. CT/MRI scans showed the following findings: normal, 11 (44%); brain malformation (1), brain atrophy (9), white matter hypodensity (2), arachnoid cyst (2). Congenital visual impairment (Leber syndrome, congenital glaucoma, severe posthypoxic syndrome, CHARGE syndrome) was present in four patients (16%), cerebral palsy in eight (32%) (Table 1).

Before starting melatonin treatment, epileptic patients were on AED monotherapy (11), bitherapy (2;), and tritherapy (5). Seizure frequency was the following: seizure-free (7); sporadic (3); 1–3/month (3); >1/week (2); >1/day (3). In a given patient polygraphic sleep-video-EEG monitoring was performed to rule out epileptic seizures mimicking sleep disorders.

Seven patients (28%) were lost to the study because of the following reasons: change of mind about participation in two; intercurrent illness in other two; family lost to follow-up due to poor results in three patients while assuming first phase placebo. Results are summarized in Table 2. The analysis of all the sleep logs disclosed a significant treatment effect on sleep latency (χ^2; $P = 0.019$); in fact, the resulting sleep latency decreased on melatonin compared to the baseline and placebo phase in all subjects but one. Melatonin effective doses (24/25 patients) were the following: 3 mg/day in seven patients (29.2 %), 6 mg/day in 11 (45.8%), 9 mg in five (20.8%), and 12 mg in one (4.2%).

Table 1
Study population ($N = 25$)

Age at enrolment	3.6–26 years (mean 10.5 years)
Mental retardation	25 (100%)
Epileptic seizures	18 (72%)
Genetic syndrome	5 (20%)
Cerebral palsy	8 (32%)
Congenital visual impairment	4 (16%)

In one patient, melatonin was ineffective at the daily dose up to 12 mg.

Melatonin treatment did not significantly modify the number of nocturnal awakenings (χ^2; $P = 0.768$) and the total time of diurnal sleep (χ^2; $P = 1$); furthermore, the overall data show that the total time of resulting nocturnal sleep increased both on melatonin and on placebo versus baseline (7.9, 7 and 4.4 h, respectively; $P =<$;10-6 and $<$ 2.20-5 at the Student' *t*-test). It must be underlined that total time of nocturnal sleep overlapped in both phases when melatonin was administered first (7.8 and 7.2 hours, respectively; $P = 0.104$ at Student' *t*-test, two-tailed). The number of early arousals, though not significant ($P = 0.123$, Fisher' exact test), appeared to be somewhat influenced by melatonin treatment as well.

Melatonin was well tolerated in all patients and no side effects were reported. About half the parents/caregivers referred to improved behavior and alertness in their children who appeared more quiet and better disposed to rehabilitation treatment. In addition, the overall familial environment improved concomitantly, relative to a better quality of night time.

Out of the 11 seizure-free patients before starting the study, nine remained unchanged on melatonin; in the other two, seizures reappeared after 1 month (one Lennox–Gastaut syndrome; one partial seizures). Soon after discontinuing melatonin, seizures stopped in both these patients. Among the seven uncontrolled patients during the baseline phase, one became seizure-free (one secondarily generalized partial seizure), two partially improved (one partial seizure; one myoclonic seizure), and the other two were unchanged; the remaining two showed a seizure worsening 1 month after starting MLT phase (one cryptogenic generalized seizure; one secondary generalized partial seizure). In the latter patients, seizures decreased soon after MLT withdrawal.

The analysis of the 2-month MLT open phase (19 patients) shows a persistent effect with further improvement of sleep latency (mean 0.2 h), duration of night sleep (mean 8.4 h) and early arousal (mean 2.0).

4. Discussion

In the present randomized controlled study, melatonin was effective in decreasing the time to fall asleep in children with mental disabilities, most of them on antiepileptic drugs for epileptic seizures. This result is very much in keeping with other series relative to young patients affected with developmental disabilities [9,15]. Similar to other series in which a short-acting preparation of melatonin was employed, in our patients the number of night awakenings did not appear to be significantly modified. Interestingly, the duration of nocturnal sleep increased significantly on both melatonin and placebo compared to baseline period. Such a result is particularly due to the subgroup of patients who were started first on melatonin. According to the modulating action of melatonin because it is able to phase shift and reset the endogenous rhythm-generating system [6], in these patients a beneficial effect of melatonin on duration of night sleep, at least throughout the first days of the following placebo phase, can be hypothesized (night sleep total time of 6.5 and 7.2 h during the placebo phases before and after melatonin phase, respectively; $P = 0.305$). According with two recent studies using melatonin in specialized populations, tuberous sclerosis [16] and Rett syndrome [17], there is also some evidence in our series of an increase in total sleep time as a primary effect of short-acting melatonin administration.

According to Zhdanova et al. [18], our patient with Angelman syndrome improved consistently on melatonin, though at high doses (about 9 mg/day). Wake–sleep cycle worsened in this child soon after discontinuing melatonin treatment and it promptly recovered when melatonin was restored in the open label phase.

Table 2
Effect of melatonin on sleep

	Baseline			Placebo			Melatonin		
	n	Mean	S.D.	*n*	Mean	S.D.	*n*	Mean	S.D.
Sleep latency (h)	25	1.6	1.6	25	0.7	1.0	25	0.3	0.92
Night sleep total time (h)	25	4.4	1.7	25	7	2.2	25	7.9	1.43
Diurnal sleep time (h)	25	1	1.5	25	0.7	1.7	25	0.6	0.91
Night awakenings	25	2.2	1.5	25	1.5	2.1	25	0.9	1.0
Early arousal	25	13[a]	0.50	25	6[a]	0.43	25	2[a]	0.27

[a] Number of patients in which this condition is present.

Together with other series [9,13], MLT dose in the range of 5–6 mg is necessary to affect sleep in this population and up to 9 mg/bedtime is required in some patients. As reported in another double-blind, placebo-controlled trial [19], MLT doses of 0.5–1 mg seem to be definitely misleading, especially in children on antiepileptic drug co-therapy.

As to seizure frequency, we found no overall significant change on melatonin, except for a few patients in whom either a seizure recurrence or worsening (22.2%) or a seizure control (5.5%) manifested 1 month after the onset of MLT therapy. These contrasting results are very much in keeping with what is reported on the potential role of MLT either as anticonvulsant or as proconvulsant in neurologically disabled children [20–24]. It must be underlined that the antiepileptic drug co-therapy was not modified during the trial and no significant change of AED blood level was found along with melatonin therapy.

The following 2-month open label phase in responders appeared to confirm the sustained efficacy of MLT on sleep improvement; in addition, wake–sleep disorder reappeared in some patients soon after discontinuing melatonin.

In conclusion, our study supports the efficacy of melatonin in young patients with mental disabilities and epileptic seizures in improving the wake–sleep disorders such as time to fall asleep; duration of nocturnal total sleep and early arousal seem to be favorably affected as well. Melatonin appears to influence seizure frequency poorly, though there may be random seizure worsening or improvement; such a dual effect seems to require further studies in epileptic young patients.

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