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Clinical trials of controlled-release melatonin in children with sleep–wake cycle disorders

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Abstract: This is the first study to examine effective doses of controlled-release (CR) melatonin in children with chronic sleep–wake cycle disorders. All 42 subjects had severe neurodevelopmental difficulties. Initially, a randomized double-blinded cross-over design was used in 16 children, comparing the effectiveness of fast-release (FR) and CR melatonin. In the remainder of the patients, the CR melatonin was studied on a clinical basis. The effectiveness of treatment was assessed by sleep charts and clinical follow-up. Emphasis was placed on the judgement of the parents, who had guidance from the physicians. The average final CR melatonin dose in the 42 patients was 5.7 mg (2–12 mg). The studies showed that the FR melatonin was most effective when there was only delayed sleep onset, but CR formulations were more useful for sleep maintenance. Children appeared to require higher doses than adults.

Introduction

In a review article on the therapeutic uses of melatonin, 24 pediatric studies from 1991–1998 were summarized [Jan et al., 1999b]. After that review was written, additional, related studies were published by O'Callaghan et al. [1999] and Miyamoto et al. [1999]. There is strong consensus among these researchers that exogenous melatonin is beneficial for treating chronic sleep–wake cycle disorders of children who have neurodevelopmental and neuropsychiatric difficulties. There is also increasing evidence in the literature that chronic sleep–wake cycle disorders are associated with disturbed melatonin secretion [Jan et al., 1999b; Miyamoto et al., 1999]. None of the authors noted significant adverse side-effects. In most instances, the oral dose ranged from 2 to 10 mg, given at nocturnal bedtime. A fast-release (FR) rather than a controlled-release (CR) form of melatonin was used in all studies and this is possibly because the CR melatonin only recently became available.

The melatonin in FR preparations is released quickly. Because of the short half-life of melatonin of less than 1 hr [Aldhous et al., 1985], FR preparations are most effective for sleep induction [Haimov et al., 1995; Jan et al., 1999b]. CR tablets release the agent in a more controlled manner. Thus, depending on the type of preparation, the latter can offer more physiological and sustained blood levels [Garfinkel et al., 1997]. In contrast to FR preparations, CR tablets must be swallowed whole in order to be effective. This can be a limiting factor in young or severely disabled children who have difficulties swallowing.

The melatonin treatment of sleep–wake cycle disorders is related to its chronobiotic [Deacon and Arendt, 1995], sedative [Cajochen et al., 1996], and hypothermic [Dawson et al., 1996] effects, but it is still unclear how much benefit is derived from each of these properties [Middleton et al., 1997]. It appears that melatonin induces sleep by inhibiting the 'wakefulness generating system' [Lavie et al., 1997; Sack et al., 1997]. This inhibitory effect in mice has recently been shown to be mediated by a common subtype of melatonin receptor, Mel 1a, while the phase shifting effect is mediated by a much rarer receptor, Mel 1b [Liu et al., 1997].

Several studies have found that CR melatonin treatment in adults is beneficial [Haimov et al., 1995; Garfinkel et al., 1995, 1997; Dolberg et al., 1998; Hoffmann et al., 1999], but no similar study has been reported in children. The purpose of the following clinical studies was to establish the most effective dose for CR melatonin in the treatment of chronic sleep–wake cycle disorders in multidisabled children and to investigate its potential advantage over FR melatonin. The effectiveness of treatment was assessed by the use of sleep charts and follow-up. Emphasis was placed on the judgement of the parents, who had guidance from the physicians.

Methods and results

For the initial CR dose-finding study, 16 multidisabled children with severe, chronic sleep–wake cycle disorders were selected. They had already been treated with FR melatonin for more than 3 months, but slept for less than 5–6 hr following its nighttime administration. The ages ranged from 4 to 21 years. While still on FR melatonin, sleep charting was done for 10 days by their caregivers. Then the 16 subjects were randomly prescribed CR or FR melatonin in a bubble pack, each for 11 days, following which the drugs were crossed over. Both investigators and caregivers were blinded as to the order of the medications. A wash-out period between the cross over was not used because the half-life of melatonin is so short that there is not believed to be a carry-over effect. In clinical practice, once the melatonin treatment is discontinued, most children with chronic sleep–wake cycle disorders begin experiencing sleep difficulties the same night. The FR dose of melatonin was the same as before the study. The CR melatonin was approximately 50% of the FR dose, since there was no previous information on the use of CR melatonin in children and in order to avoid possible adverse side-effects, especially excessive sedation, it was felt to be a safer approach.

After 22 days of treatment, the somnologs were analyzed for changes in the sleep pattern. Then the children were prescribed only the CR melatonin and, under supervision of the parents, were allowed to increase or decrease the dose in order to find the minimal most effective dose. After several weeks of further treatment, sleep charts were requested for another 10 days in order to reveal the final response to CR melatonin.

Table 1 summarizes the children's ages, the FR melatonin doses, and the initial and final doses of CR melatonin. The final, most effective minimal doses of CR melatonin were higher than the initial doses, but were slightly lower than the FR doses. The response to treatment was based on sleep onset, the number of awakenings, duration of sleep, and how the children behaved the following day. Unfortunately, it was not possible, as had been hoped, to quantify the improvement by a scoring system on the basis of prolonged sleep charting because of the frequent medical problems of our subjects. Thus, the response had to be assessed by a visual review of the sleep charts and by parental history. Improvements in the sleep patterns, to the satisfaction of the caregivers, were observed in 11 multidisabled children. The CR melatonin had no advantage over the FR prepara-

Table 1. A summary of the patients and the results of the initial dose-finding study

Case*	Age in years	Most effective FR dose (mg)	Initial CR dose (mg)	Most effective final CR dose (mg)	Melatonin response
1	10	5	2	4	Yes
2	8	10	4	6	Yes
3	12	7.5	3	6	Yes
4	4	10	4	8	Yes
5	13	5	2	4	Yes
6	7	15	6	8	Yes
7	7	5	2	8	Yes
8	21	15	6	8	Yes
9	8	10	4	4	Yes
10	6	10	4	4	Yes
11	14	25	10	8	Yes
12	16	15	6	6	No
13	5	10	4	0	No
14	4	5	2	0	No
15	10	10	4	0	No
16	16	10	4	0	No

* All subjects had multiple complex neurodevelopmental problems.

Table 2. Associated disabilities of patients

Disorders	Percentages in the 42 patients
Low intellect	74
Epilepsy	55
Blindness	48
Cerebral palsy	36
Brain injury	10
Autism	10
ADHD	7
Brain maldevelopment	7
Bipolar disorder	2
Depression	2
Brain tumor	2
No major disabilities	3
Miscellaneous	16

Most children had more than two chronic disabilities in addition to a variety of health problems. Low intellect: generally these patients were functioning at a very low level. Blindness: severe visual loss, only rarely total absence of sight. Brain injury: occurring later in life, often due to non-accidental injury. ADHD: attention deficit hyperactivity disorder.

tion in five children. The possible reasons for the lack of improvement were addiction to analgesics, uncontrolled epilepsy, poor nutrition, anxiety, and inability to swallow the CR tablets whole.

Following the initial dose-finding study, without the randomized double-blinded cross-over design, other patients on FR melatonin were allowed to change to the CR form when they continued to have sleep fragmentation and early morning awakenings. These multidisabled subjects were selected from a group of 144 children who started their FR melatonin treatment some time after 1991. The average age of these 144 patients was 8.6 years (0.5–21 years). The average duration of treatment was 2.2 years. The average initial FR melatonin dose was 4 mg (1.2–10 mg) and, after adjustments for the best effect, the final average FR dose was 7 mg (2–15 mg).

Table 3. Types of sleep–wake cycle disorders of patients

Sleep disturbance	Percentages in the 42 patients
Fragmentation	71
Delayed sleep onset	64
Early morning awakening	14
Free running rhythms	5
Other	5

Combinations of sleep disorders were common. Fragmentation: several prolonged interruptions of nocturnal sleep. Delayed sleep onset: usually several hours of delay in sleep onset. Early morning awakening: awakening 2 hr or more before the desired time. Free running rhythms: a daily shifting of sleep pattern, due to increasing delay of sleep onset.

The total number of children treated with CR melatonin was 42. There were 22 females and 20 males. Tables 2 and 3 show the associated disabilities and the types of sleep–wake cycle disorders. The FR preparation was replaced with CR formulation in 23 subjects. In 13 children, after adding CR melatonin, the parents continued to use a combination of FR and CR doses. CR melatonin was the first and only form of treatment in six patients. The average duration of CR melatonin therapy for the 42 subjects was 2.8 years. The average initial CR dose was 4.2 mg (1.5–12 mg) while the final average dose was 5.7 mg (2–12 mg). The younger children were started on lower doses, but they still received higher final CR doses per weight than the older patients. Out of the total group, 38 patients are still taking melatonin. Two children stopped their therapy because they apparently outgrew their predisposition to sleep difficulties and in the other two, the treatment was no longer necessary because a hidden source of pain was appropriately treated. In six instances, the parents eventually returned to FR melatonin therapy. The reason for returning to FR melatonin was most frequently associated with difficulty in swallowing the CR tablets.

Since beginning the use of FR and CR melatonin therapy in 1991, we have not encountered any significant adverse effects. The treatment had to be discontinued in only one subject because of excessive sedation. Epilepsy was diagnosed in 42.4% of the 144 children treated with melatonin and in 55% of the 42 subjects in the present study. None of our patients had significant exacerbation of seizure disorders requiring a discontinuation of melatonin therapy, but on occasions the anticonvulsant medications had to be adjusted after melatonin was added. Four children developed tolerance to the treatment, but this was difficult to prove because in patients with neurodevelopmental disorders other unrecognized causes of sleep disturbance can emerge, incorrectly suggesting tolerance.

Melatonin is an investigational drug in Canada and permission for its use was granted by the Health Protection Branch. For the first study, the FR melatonin was obtained from Sigma Company (St. Louis, MO) and was made into 5-mg tablets, and the CR form, Circadin™, came from Neurim Pharmaceuticals Ltd. (Tel Aviv, Israel) in 2-mg tablets. For the second study, the melatonin was obtained from Twin Laboratories Inc. (New York NY) (3-mg FR capsules and 2-mg CR tablets). The pharmacokinetics of CR formulations are not released by either company.

Discussion

This is the first pediatric study to examine an effective CR melatonin dose in the treatment of chronic sleep–wake cycle disorders. The subjects were all severely multidisabled and had a combination of mental retardation, cerebral palsy, epilepsy, blindness, deafness, and a number of other neurodevelopmental disorders, in addition to their sleep difficulties. It should be pointed out that randomized double-blinded cross-over designed studies in this patient population are extraordinarily difficult to do and more so than we anticipated at the beginning of our studies. They place an enormous demand on the caregivers and researchers alike. It is nearly impossible to control influencing factors, such as unexpected seizures, changes in anticonvulsant medications, occurrence of upper respiratory infections, hospital visits, unplanned minor surgical procedures and environmental variables, such as changes in daily living activities, new school staff and therapies, and the level of parental stress. This is why carefully designed scoring systems, which measure improvement in sleep, become too subjective and difficult to analyze. Nevertheless, it is important to study the sleep disorders of the disabled because they are common, they frequently tend to be unresponsive to therapeutic interventions and are very taxing on the families.

The studies confirm that the FR form is most effective when there is only delayed sleep onset and that the CR form is more useful for sleep maintenance. Using FR melatonin usually results in sleep onset after 30–40 min and taking the CR formulations used in this study produced a slightly later sleep onset. CR formulations can improve sleep fragmentation and early morning awakening in children with sleep–wake cycle disorders who did not fully benefit from FR melatonin. The FR formulations appear to have little or no effect after 5–6 hr following the bedtime dose [Jan et al., 1999b]. This is not an unexpected observation, since the half-life of melatonin is 30–53 min [Aldhous et al., 1985] and the above findings have already been shown in adult studies [Haimov et al., 1995; Garfinkel et al., 1995, 1997; Hoffmann et al., 1999]. Some patients with marked sleep onset delay and early morning awakening may benefit from the combination of CR and FR forms. In several children, this approach was found to produce the best sleep pattern.

The most effective average dose of CR melatonin (5.7 mg) is slightly lower than the FR dose (7 mg). It is surprising that children appear to require higher amounts of melatonin than do adults, as judged by the literature [Haimov et al., 1995; Garfinkel et al., 1997; Hoffmann et al., 1999] and supported by this study. Perhaps this is because endogenous melatonin levels are higher in children, who also metabolize this hormone faster before puberty [Waldhauser et al., 1988; Cavallo, 1993; Cavallo and Ritschel, 1996]. However, even with these doses, since beginning to use melatonin in 1991 we have noted no adverse effects, with the rare exception of daytime sedation.

Chronic sleep disturbance in multidisabled children has complex etiologies and children may have several simultaneous causes for their sleep difficulties. Those patients who are immobile must be regularly turned during the night and the mattresses on which they are lying must be soft, otherwise they repeatedly awaken, mimicking sleep fragmentation of sleep–wake cycle disorders. Esophageal reflux and orthopedic problems commonly cause nocturnal pain. Patients may have nocturnal seizures or may receive inadequate nutrition and medication, all of which can disturb their sleep. Some low-functioning children are easily over-stimulated in an uncontrolled environment, resulting in such high arousal levels that they are unable to settle down. Movement disorders (as in dyskinetic cerebral palsy), anxiety, and a number of psychiatric, neurologic, and health problems can also lead to poor sleep.

There is increasing evidence that chronic sleep–wake cycle disorders of children with neurodevelopmental disorders are associated with disturbed melatonin secretion [Palm et al., 1991; Petterborg et al., 1991; Tzinschinsky et al., 1991; Alvarez et al., 1992; Etzioni et al., 1996; Zhdanova et al., 1999; Lockley et al., 1997; Palm et al., 1997; Miyamoto et al., 1999]. These patients tend to have a great variety of neurological diagnoses involving different parts of the brain, but have diminished understanding of their environmental *Zeitgebers*. Indeed, melatonin is most likely to help when the sleep is disturbed due to lack of understanding the *Zeitgebers* [Jan and O'Donnell, 1996]. Normal individuals, who travel to different time zones, can readily adjust, but it appears that many severely disabled, even without travelling, in the same time zone are unable to synchronize their sleep–wake cycle generating system with the environment, resulting in abnormal melatonin secretion.

It is important to emphasize that epilepsy in our subjects was not a contraindication to mela-

tonin treatment. On the contrary, melatonin is known to have anticonvulsant properties [Muñoz-Hoyos et al., 1998] and children with epilepsy, especially when they experience sleep difficulties, may benefit from added melatonin therapy [Fauteck et al., 1999; Jan et al., 1999a].

Perhaps in the future, prior to melatonin treatment, all candidates will require proof of disturbed melatonin secretion. At the present time, this is difficult to achieve; therefore, the selection of patients must be done clinically. This process requires considerable experience, especially in multidisabled children. Researchers who study melatonin therapy and clinicians who prescribe this hormone must never assume that melatonin is the treatment of choice just because the child has neurodevelopmental difficulties. While this therapy is remarkably safe, this treatment should still be in the hands of skilled physicians who are also familiar with the problems of the disabled.

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