

Melatonin for the Treatment of Handicapped Children With Severe Sleep Disorders

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Sleep disorders are common in children with mental retardation and neurologic disorders. Melatonin, a recently developed natural compound, has been used successfully in sleep disorders. I report my experience with melatonin in an open, prospective trial to treat circadian rhythm sleep disorder in handicapped children. The sleep disorder had been present for at least 6 months and had not responded to at least one hypnotic drug. The therapeutic response was recorded according to the average number of hours asleep per 24 hours, average number of awakening per night, average number of nights with delayed sleep onset, and average number of nights with early morning arousals. Ten consecutive children (four males, six females; age range = 1-11 years, mean 5.4) were included. Nine children had documented mental retardation that was severe in six (67%). Most had epilepsy and visual impairment (70%). All children were monitored for 4-12 months (mean 7.5 months) after the initiation of 3-mg bedtime melatonin. Most (80%) had a dramatic response to melatonin. No side effects were reported. Melatonin is a well-tolerated, safe, relatively inexpensive, and effective drug, with minimal side effects, for the treatment of severe circadian rhythm sleep disorder in handicapped children. Wider use of this drug is recommended. © 2000 by Elsevier Science Inc. All rights reserved.

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Introduction

Sleep disorders are common in children with mental retardation and neurologic and developmental disorders [1,2]. These children often have disturbed sleep patterns,

with fragmented sleep and frequent nocturnal awakenings [2]. This disturbed circadian rhythm pattern is highly disruptive to the parents, and limited solutions are available. The sleepless nights may be more disturbing to the parents than the child's physical demands [3]. The lack of an adequate night's sleep will affect the daytime productivity of the parents. Therapeutic options to this difficult problem are few. Hypnotics are generally effective initially but lose their effect within few days because of tolerance. Also, they have a short duration of action and therefore may be effective only for the initial night hours.

Melatonin is a recently developed natural compound for treating disturbed sleep rhythms available over the counter in pharmacies and health food stores [1,4-6]. The biology and pharmacology of melatonin have been well described [7]. Melatonin is not a sedative-hypnotic agent; its effect on sleep is that of phase setting [4]. It is the hormone of darkness, because the detection of darkness by the visual receptors activates the hypothalamus to stimulate the pineal gland by way of the sympathetic pathways to increase melatonin secretion [5]. Visual impairment diminishes the ability of the child to perceive and interpret the multitude of cues for synchronizing sleep with the environment [1], making these children susceptible to circadian sleep-wake cycle disturbances.

Melatonin has been successfully used in visually impaired children with circadian sleep-wake disturbances [8]. An evening dose dramatically improved the sleep-wake cycle in all children [8]. Other investigators with larger experience found it effective in 80% of mentally handicapped children with sleep-wake cycle disturbances [1]. Subsequently, it has been implicated in sleep disorders associated with various other central nervous system disorders, including Rett syndrome [9], tuberous sclerosis [10], autism [11], Asperger syndrome [11], and pineal tumor [12].

Although melatonin appears to be a safe, inexpensive,

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Table 1. Clinical characteristics and overall response to melatonin (n = 10)

Pt. No.	Sex	Age (yr)	Diagnosis	Visual Impairment	Mental Retardation	Epilepsy	Response
1	F	9.5	Static encephalopathy	No	Severe	Yes	Yes
2	F	4.5	Cerebral palsy	Yes	Severe	No	Yes
3	F	5	Static encephalopathy	No	Severe	Yes	Yes
4	F	2.5	HIE	Yes	Moderate	Yes	Yes
5	F	11	HIE	Yes	Moderate	Yes	Yes
6	F	8	Deafness, behavioral disorder	No	Moderate	No	No
7	M	7.5	Migration disorder	Yes	Severe	Yes	Yes
8	M	1	Migration disorder	Yes	Not tested	No	No
9	M	2	HIE	Yes	Severe	Yes	Yes
10	M	3	HIE	Yes	Severe	Yes	Yes

Abbreviations:

F = Female

HIE = Hypoxic ischemic encephalopathy

M = Male

Pt. No. = Patient number

and effective treatment of sleep-wake cycle disorders, it has yet to gain wide use among pediatricians (personal experience). I report my experience with melatonin. On the basis of data from available published reports, I hypothesized that melatonin is quite effective in treating severe circadian rhythm sleep disorder in handicapped children.

Method

An open trial of melatonin in a group of handicapped children with severe sleep disorders was prospectively conducted. Children were identified through referrals and consultations to the pediatric neurology service at King Abdulaziz University Hospital from August 1, 1998 to July 31, 1999. My institution is a multispecialty adult and pediatric hospital providing primary care to the Jeddah area and secondary and tertiary care to a regional population of western Saudi Arabia. It is the main teaching center of western Saudi Arabia and is linked to the King Abdulaziz University Medical School.

Patient and disease-related data were collected during initial visits. The sleep disorder was defined according to the Diagnostic and Statistical Manual of Mental Disorders (DSM), 4th edition (IV) criteria (307.45) as the circadian rhythm sleep disorder [13]. It involved persistent or recurrent sleep disruption leading to frequent nocturnal arousals, delayed onset of sleep, or early morning awakening frequent enough to cause clear social or functional disruption to the child or parents [13]. The inclusion criteria included the presence of this pattern for at least 6 months, use of instructions in behavioral approaches to nocturnal awakening, and use of at least one sedative-hypnotic drug without success. Children with this sleep pattern occurring in the course of another sleep disorder (obstructive sleep apnea) or other mental disorder were excluded. Children were also excluded if the sleep disturbance was related to the direct physiologic effects of medication (e.g., benzodiazepines or phenobarbital).

After obtaining verbal consent, melatonin was prescribed as a single 3-mg dose 1-2 hours before the target bedtime each night. The same target bedtime was maintained in each child, depending on the parents' sleep pattern. The parents monitored the child's sleep and one pediatric neurologist monitored all children to document the therapeutic response and occurrence of side effects. The therapeutic response was recorded according to the following four factors [14]: (1) average number of hours asleep per 24 hours, (2) average number of awakening per night, (3) average number of nights with delayed sleep onset, and (4) average number of nights with early morning arousals before 7 AM.

Results

Ten children (four males and six females; age range = 1-11 years, mean 5.4 years) with severe sleep disorder and neurologic abnormalities were included. Their sleep disorder fulfilled the DSM-IV criteria (307.45) for circadian rhythm sleep disorder (sleep-wake schedule disorder) [13]. All parents complained repeatedly that their child had severe problems with fragmented sleep. The children had been examined by several physicians and had been administered a number of sleep drugs without response. Table 1 presents a summary of their clinical data and underlying diagnoses. Nine children had documented mental retardation, which was severe in six (67%). Most had epilepsy and visual impairment (70%). The causes of the visual impairment included severe refractive error with amblyopia (Patient 2), cortical blindness (Patients 4, 5, 9, and 10), and optic atrophy (Patients 7 and 8).

All children were monitored for 4-12 months (mean 7.5 months) after the initiation of melatonin. Most children (80%) had a dramatic response to melatonin (Table 1). Their sleep patterns before and after melatonin are summarized in Table 2. The average number of hours asleep

Table 2. Therapeutic responses as measured using the four sleep factors in the eight children with a favorable response

Sleep Factor	Before Melatonin	With Melatonin
Average number of hours asleep per 24 hours	6-9 (mean 6.8)	7-9 (mean 7.9)
Average number of awakening per night	1-5 (mean 3)	0-2 (mean 0.5)
Average number of nights with delayed sleep onset per week	6-7 (mean 6.8)	0-2 (mean 0.4)
Average number of nights with early morning arousals per week	6-7 (mean 6.8)	0-1 (mean 0.3)

per 24 hours marginally improved, from a mean of 6.8 hours before melatonin to 7.9 hours while the child was taking it. However, the average number of awakenings per night, average number of nights with delayed sleep onset, and average number of nights with early morning arousals remarkably decreased after initiation of melatonin therapy (Table 2). The benefit was observed after the initial few nights and persisted in all responders. These parents were very happy and amazed with the response (many mentioned that it was like magic) and reported less disturbance and more productivity in their daytime activities.

Two children had no response to melatonin (Patients 6 and 8). Patient 6 was a female with congenital sensorineural deafness, severe behavioral problems, and moderate mental retardation. Patient 8 was an infant with severe migration disorder. No changes in their sleep patterns were observed despite continued use of melatonin for 1 month. None of the children had side effects. One child (Patient 1) had a history of persistent nocturnal enuresis, which completely disappeared after initiating melatonin therapy. The parents of another child (Patient 3) observed improvements in her behavior and decreased hyperactivity. Drug administration was missed unintentionally in two children (Patients 9 and 10). The mother of Patient 9 reported that the child remained awake all night after missing the dose. Severe restlessness and irritability persisted for 3 days in Patient 10 after missing the dose.

Discussion

The study results confirm that melatonin is very effective in regulating sleep in handicapped children. All children had severe sleep disorder with fragmented sleep, delayed onset of sleep, and early arousals. All parents complained repeatedly to many physicians that their child had severe problems with fragmented sleep. All had disrupted lives and most had house helpers to take care of their children when awake at night. Instructions in behavioral approaches to nocturnal awakening and sedative-hypnotic drugs were unsuccessful. Most children (80%) had a remarkable response to melatonin, with decreases in the average number of awakenings per night, average number of nights with delayed sleep onset, and average number of nights with early morning arousals. This result is impressive when one considers the severity of the children's sleep disorders. The benefit was quick and long lasting. These parents were happy and amazed with the response, and many reported less disturbance and more productivity in their daytime activities.

The therapeutic response observed in our study was similar to that reported by Jan and O'Donnell [1]. However, other investigators determined that melatonin was ineffective or only marginally effective [14]. This finding was likely the result of the small doses used (0.5-1 mg daily) compared with our 3-mg dose. Other investigators safely used higher doses (up to 10 mg daily) with remarkable efficacy [1,15,16]. It has been suggested that

melatonin has a dual effect on sleep, including acute sleep promotion that typically occurs within 1 hour of administration and the ability to alter the phase of the underlying circadian rhythm with repeated use [17]. A recent study found the hypnotic properties, sleep quality, and sleep latency with a 5-mg dose significantly greater than with a 0.5-mg dose [18]. This evidence suggests a better and longer lasting effect with higher doses.

No side effects were observed in our children, and the drug was well tolerated and relatively inexpensive. These findings are similar to the experience of other investigators who used higher doses [1], keeping in mind that most of the included children were mentally handicapped, which may interfere with the reporting of side effects. Of interest was a child with a history of persistent nocturnal enuresis, which completely disappeared after initiation of melatonin therapy. Many parents observed other nonspecific improvements in the overall daytime behaviors of these children, with less hyperactivity and more relaxed attitudes. We did not study this issue specifically; however, most parents were convinced that the behavioral improvements were attributable to melatonin. More likely, it was the result of their improved sleeping patterns.

In conclusion, melatonin is a well-tolerated, safe, and effective drug. It has minimal side effects and is relatively inexpensive. This study and many others provide evidence that melatonin provides a simple solution to a difficult problem. This evidence supports the recommendation that melatonin should be used more frequently and probably as a first-line therapy rather than as a last resort in the treatment of severe circadian rhythm sleep disorder, particularly in handicapped children.

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