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Case report

Dose response to melatonin treatment for disordered sleep rhythm in a blind child

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Abstract

We assessed the effectiveness and safety of melatonin in normalizing sleep in a 7-year-old blind child with a longstanding sleep/wake cycle disorder, using a double-masked, randomized treatment trial of placebo, a physiological dose (0.14 mg) and a supraphysiological dose (2.2 mg) of melatonin. Sleep onset and sleep offset were erratic and inappropriately early with placebo and low dose melatonin, but improved significantly on high dose melatonin. This report confirms that melatonin may be effective in treatment of disordered sleep rhythm in blind children, and illustrates a protocol that enables dose adjustment for optimal treatment response.

Keywords: Blindness; Child; Melatonin treatment; Sleep

1. Introduction

Blindness is often accompanied by disrupted circadian rhythms and sleep problems [1]. Melatonin treatment has been successful in restoring a normal sleep pattern in some blind adults and children [2,3]. We describe results of a placebo-controlled masked study of two doses of melatonin in a blind child.

2. Case report

The patient is a 7-year-old boy with blindness, static encephalopathy and long standing sleep disorder. He suffered birth asphyxia and has septo-optic dysplasia with lack of light perception, absent pupillary light reflexes and hypopituitarism that is well controlled by growth hormone, thyroxine and cortisol. His sleep pattern is disruptive, he falls asleep between 16:00 and 18:00 h or earlier and gets up between 01:00 and 04:00 h. The family history did not disclose any sleep disorder or other significant medical problems. The parents experience chronic fatigue related to the nightly sleep interruptions. Several behavioral approaches failed to alter the sleep/wake pattern.

3. Methods

The Institutional Review Board approved the protocol and the parents gave written consent. The study consisted of three consecutive 8-week treatment phases of melatonin or placebo using a randomized double-masked design that followed an initial phase of 4 weeks of adaptation to the protocol. Placebo, low dose melatonin (7 μg/kg) and high dose melatonin (110 μg/kg) were assigned in random order by the investigational drug pharmacist. Investigators and parents remained blinded to the dose used in each phase until completion of the study.

Melatonin of high purity (Regis Technologies Inc., IL, USA) was used (IND #42,901). Identically appearing gelatin capsules of melatonin or placebo with lactose filler were given at the desired bedtime, about 21:00 h. The low dose (0.14 mg) was equivalent to the physiologic adult dose of 0.3 mg [4]. The high dose (2.2 mg) was equivalent to adult dose of 5 mg for disordered circadian rhythm in blind people [2]. The dose was adjusted from these respective adult doses based on: (1) body weight; (2) faster metabolism

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in children [5] and (3) higher nocturnal melatonin peak in children [6] than in adults [7].

Daily sleep logs and wrist actigraphy (Mini Motionlogger Actigraph, Ambulatory Monitoring Inc., Ardsley, NY, USA) recorded sleep. The actigraphy-specific software Action-W used the Cole and Kripke algorithm [8] for automatic sleep scoring of actigraphy data. Safety monitors included a daily side effects log, medical examinations, complete blood counts and renal and liver profiles.

4. Results

The order of treatment was phase 1-placebo, phase 2-low dose melatonin and phase 3-high dose melatonin. During the 4 weeks of adaptation and the 8 weeks of phase 1 the child cooperated with continuous use of the actigraph. The sleep logs and actigraphy demonstrated erratic sleep, particularly irregular sleep onset time often in the mid-afternoon – 15:30 or 16:00 h. In addition, waking times were inappropriately early, 01:00–04:00 h. The observation noted in the sleep diary that the child would not return to sleep after the early morning awakening was confirmed by actigraphy (Fig. 1). The sleep efficiency calculated from actigraphy as % sleep time of the total time in bed [8] was ≥90% in these phases. Subsequently, during phases 2 and 3 he refused to keep the actigraph on his wrist while awake. Limited actigraphy recording continued daily for the night period, as the parents placed the instrument on the child's wrist shortly after sleep onset. However, soon after awaking, the child routinely removed the instrument. To maintain consistency, the final data analysis used sleep onset time recorded by sleep log and sleep offset time by actigraphy.

Once asleep, the child did not have wakenings until sleep offset. Naps were rare. The duration of sleep was not significantly different: 9:09 ± 1:46 h, 9:17 ± 2:04 h and 8:50 ± 1:39 h in phases 1, 2 and 3, respectively (P = NS). In contrast, sleep onset time was significantly different in the three treatment phases: 18:40 ± 1:32 h, 19:26 ± 1:49 h and 22:02 ± 1:36 h for phases 1, 2 and 3, respectively ($P < 0.05$). Also, sleep offset time was significantly different in phase 3 (06:49 ± 1:45 h) from phases 1 (04:53 ± 3:38 h) and 2 (05:14 ± 3:02 h) ($P < 0.05$). Moreover, the frequency of inappropriately early sleep onset – defined as % days in each phase with sleep onset earlier than 19:00 h – was 61, 50 and 16% in phases 1, 2 and 3, respectively ($x^2(2) = 25.0$, $P < 0.05$). Likewise, the frequency of inappropriately early sleep offset – defined as % days in each phase with sleep offset earlier than 06:00 h – was 90, 80 and 23% in phases 1, 2 and 3, respectively ($x^2(2) = 65.4$, $P < 0.05$). The child did not have any side effects and there were no significant changes in the blood count or the renal and liver profiles.

Melatonin treatment was discontinued at the end of the study protocol. Over the ensuing 3 weeks the child's sleep pattern gradually shifted toward the pre-treatment pattern of early morning awakening. Reintroduction of the higher melatonin dose normalized the sleep pattern again. Although there is no rigorous follow up of the child who is now 11 years old, the parents report that about once a month his sleep pattern begins to drift and they give him melatonin (2 mg) for a few consecutive days.

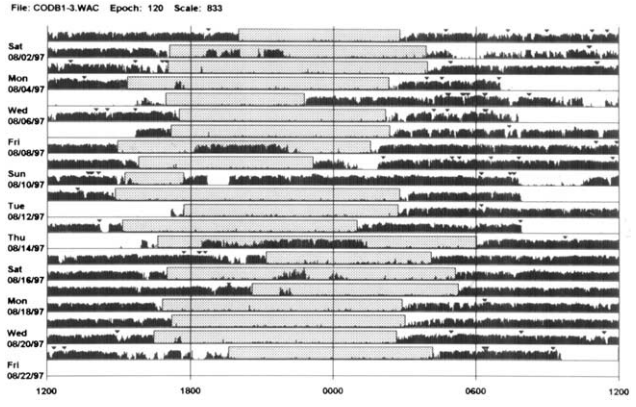

Fig. 1. Actigraphy during the first 3 weeks of baseline observation of sleep/activity patterns in a 7-year-old blind child. The dark vertical lines are wrist activity data compressed to 1-min epochs. The shaded areas indicate time in bed determined by sleep diary. The periods with low amplitude wrist activity in these shaded areas indicate sleep. The periods without any tracing were related to physical activities with the instrument off, e.g. swimming or field trips. The vertical arrows indicate activation of the event button, which normally permits correlation with events reported in the sleep diary. In this case, these event markings were spurious activation of the button by this child's rather uncontrolled motions and should be ignored in the interpretation of the tracings.

5. Discussion

An impact of birth asphyxia on the child's sleep problem cannot be excluded, although children with static encephalopathy without blindness typically present multiple nocturnal awakenings rather than an abnormal sleep rhythm. This child's sleep problem may be classified as advanced sleep phase syndrome, as described in some adults with blindness [9]. Alternatively, because of the anatomic abnormality of the anterior visual pathways, we surmise that this child had disrupted circadian rhythm regulation as described in adults with blindness secondary to disorders of the anterior visual pathways [1]. In all likelihood, the free-running circadian rhythms were partly masked by environmental and social factors. The child's lack of understanding and limited cooperation precluded more invasive procedures that are necessary to assess circadian rhythm regulation, e.g. deep body temperature or melatonin secretion.

The results show minimal response to the physiologic dose of melatonin and remarkable improvement in sleep schedule with the high, supraphysiologic dose. The putative mechanism of action of melatonin on sleep in blind patients is through high affinity melatonin receptors in the supra-

chiasmatic nuclei, the site of the circadian clock [10]. The lack of response to the physiologic dose in this case does not argue against the presumptive diagnosis of circadian rhythm disorder. In fact, erratic absorption and kinetics of the substance may explain the need for a higher dose, equivalent to that described as successful in adults [2].

Disordered sleep rhythm associated with blindness is one of the few accepted clinical indications for melatonin treatment in adults in Europe, where melatonin is a prescribed drug. Despite being widely available in the USA without prescription, there are general concerns about indications and long-term safety of melatonin [11]. In prepubertal children one should also consider the potential effects of melatonin on the reproductive axis. Indeed, delayed puberty was noted in one of six children on long-term melatonin treatment [12]. Hence, melatonin should be used judiciously in children. This case report suggests one medical indication for use of melatonin in children, that is treatment of severe sleep disorder associated with blindness, where the potential benefit may outweigh the potential risks. Until more information is available, therapeutic trials should begin with low doses of melatonin.

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