

Melatonin in the treatment of chronic sleep disorders in adults with autism: a retrospective study

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Summary

Background: Melatonin may be used to treat sleep disorders in both children and adults with intellectual disability. The evidence for its efficacy, potential adverse effects and drug interactions are reviewed in the context of prescription of melatonin to patients with autism.

Methods: This study presents the use of melatonin to treat severe circadian sleep-wake disturbances in 6 adults with autism. Melatonin was initiated at a daily dose of 3 mg at nocturnal bedtime. If this proved ineffective, the melatonin dose was titrated over the following 4 weeks at increments of 3 mg/2 weeks up to a maximum of 9 mg, unless it was tolerated. Assessments included Clinical Global Impression-Severity (CGI-S) and CGI-Improvement (CGI-I).

Results: Melatonin administered in the evening dramatically improved the sleep-wake pattern in all patients. Melatonin appears to be ef-

fective in reducing sleep onset latency and is probably effective in improving nocturnal awakenings and total sleep time in adults with autism. Its effectiveness remained stable for the 6-month period of administration. Melatonin was well tolerated in all patients and no side effects were noted during the therapy.

Conclusions: Melatonin appears to be promising as an efficient and seemingly safe alternative for treatment of severe circadian sleep disturbances in adults with autism. There may be heterogeneity of response depending on the nature of the sleep problem and cause of the intellectual disability or associated disabilities. Further studies are necessary before firm conclusions can be drawn and guidelines for the use of melatonin in people with autism formulated.

Key words: melatonin; sleep disorders; autism; adult

Introduction

According to the diagnostic criteria of the International Classification of Diseases, 10th edition (ICD-10) [29], autism is classified as a pervasive developmental disorder. It is characterised by qualitative changes in reciprocal social interactions and modes of communication, as well as by a restricted inventory of interests and activities that are stereotyped and repetitive. These qualitative anomalies represent pervasive characteristics of the subject's functioning in any situation, and are accompanied by behavioural problems such as hyperactivity, poor concentration, impulsiveness, outbursts of anger, and self- and hetero-aggressive acts. Autism is diagnosed in the first years of life and is frequently associated with mental retardation [1-4].

Children with autism often suffer from sleep problems which are quite frequently described as severe [5-8b], with a prevalence ranging from 40-80% depending on the study [9-13]. These prob-

lems frequently persist into young adulthood in the form of a disordered sleep/wake pattern, lengthy nocturnal awakenings, early awakening and prolonged lack or absence of sleep. Few studies have been published on sleep disturbances in adults with pervasive developmental disorder; their prevalence is approx. 15% [14]. Several studies [9b, 15] emphasise the fact that sleep disturbances contribute to daytime behavioural problems, making it even more important to treat these sleep disturbances effectively.

At present several considerations seem to indicate that chronic sleep disorders in children with pervasive developmental disorder are associated with a disturbance in melatonin secretion [16, 17]. First, regulation of melatonin secretion appears to be abnormal in children with pervasive developmental disorder: elevated daytime levels, decreased amplitude and absence of nocturnal secretion have been observed [9, 17-21]. Alteration

in melatonin rhythm may be responsible for sleep-onset and maintenance difficulties in autism, and there has been speculation that those with sleep-onset problems may have a melatonin rhythm which peaks later in the night, while reduced rhythm amplitude may be related to night waking and early-morning waking [7, 9]. Second, several studies suggest that the use of melatonin is efficacious in the treatment of sleep disorders in children with neurological pathologies, developmental disorders and neuropsychiatric problems [22–25]. Indeed, melatonin, an endogenous signal of darkness, is an important component of the body's internal timekeeping system. As such it regulates major physiological processes including the sleep-wake cycle, pubertal development and seasonal adaptation. In addition to its relevant antioxidant activity, melatonin exerts many of its physiological actions by interacting with membrane MT1 and MT2 receptors and intracellular proteins such as quinone reductase 2, calmodulin, calreticulin and tubulin; moreover, large pharmacological doses of melatonin may exert seda-

tive/hypnotic affects by interacting with GABA-receptors in the central nervous system [33, 34].

Although the advantages of melatonin in sleep disorders in adults remain controversial [26, 27], a recent review [28] observes that melatonin primarily acts on the length of time needed to fall asleep and on the total length of sleep, and that it has many advantages compared to commonly used medications such as the benzodiazepines since it has no side effects when used for short periods and does not induce dependence or withdrawal syndromes.

All of these considerations led us to prescribe melatonin to adult patients with autism and sleep disorders. As mentioned above, several studies have documented the advantages of this substance in the treatment of sleep disorders in children and adolescents with pervasive developmental disorders, but, to the best of our knowledge, no studies have been published examining its use in adults with pervasive developmental disorders. For this reason our clinical experience was deemed worth reporting in the form of this retrospective study.

Method

Participants

This retrospective study was approved by our hospital's ethics committee. Six patients, one woman and five men, who are followed in a psychiatric unit specialising in patients with intellectual deficiencies, participated in the study. They presented autism associated with mental retardation ranging from moderate to severe according to the diagnostic criteria of the International Classification of Diseases, 10th edition (ICD-10) [29]. These patients presented the following accompanying behavioural problems: severe psychomotor agitation, auto-aggressive behaviour (including minor and severe automutilation) as well as violent behaviour directed towards objects and others. In this context they were under treatment with anxiolytic psychotropic medication, mood stabilisers and/or antipsychotic medication. Renal and hepatic function was normal for all participants.

All of the participants presented sleep disorders with moderate to severe difficulty in falling asleep, multiple nocturnal awakenings (with associated "nocturnal wandering") and early awakenings. All of these problems resulted in a significant reduction in the total amount of sleep.

When melatonin was prescribed, none of the patients were being treated with hypnosis, and other psychotropic treatments which may foster sleep were not modified for the month before and the 6 months following the introduction of melatonin.

All of the participants had been previously treated with traditional insomnia medication such as zolpidem, zopiclone, flurazepam or chloral hydrate. As the therapeutic response to these treatments had been only partial, completely absent, or accompanied by unwanted side effects (exacerbated psychomotor agitation, irritability, phases of confusion), these treatments had been stopped. The use of sedative antipsychotic medication (laevopromazine, clotiapine) had no effect on their insomnia.

Clinical evaluation

The clinical files of the patients contained information on the presence, severity and possible improvements in different aspects of their sleep disorders: resistance to going to bed, difficulty falling asleep, length of sleep with records of bedtime and waking time, nocturnal anxiety, nocturnal awakenings, daytime sleep, and severity of nocturnal and diurnal behavioural problems. These data are based on clinical observations and were not quantified. Global severity and global improvement of sleep disorders were evaluated before and after the 6-month period of treatment with melatonin. The response to treatment (6-month follow-up) was evaluated based on the data contained in patient files and using the Clinical Global Impression scale – severity (CGI-S) of illness (ranging from 1 = normal to 7 = extremely ill) and the Clinical Global Impression scale – improvement (CGI-I) of illness (ranging from 1 = very much improved to 7 = very much worse). Non-parametric statistics (Wilcoxon signed-rank test) were used to describe the statistical significance of CGI-S

Treatment

Melatonin treatment was initiated at 3 mg/d, administered 40–50 minutes before bedtime. If this dose did not prove efficacious and tolerance was good after 4 weeks, the dose was increased to 6 mg/d and, if necessary, to 9 mg/d after another 2 weeks. The melatonin used was prepared by our hospital's pharmacy.

Ethical considerations

The patients or their legal guardians had given informed consent at the time of the initial prescription, which was not related to a research project. Our institution's ethics committee approved the publication of the data as a retrospective study.

Results

Six patients, one woman and five men, presenting autism were included in the study. Their age, the melatonin doses, the psychotropic medications and the global clinical evaluation of their sleep disorder before and after 6 months of melatonin treatment are presented in table 1. Improvement was observed in all of the patients' sleep disorders, and for five of the six patients the improvements were major; improvement was statistically significant, with median score 5.5 before and 1.0 after treatment (Wilcoxon signed-rank test, $P = 0.031$). The improvements observed concerned length of sleep. For example, the number of hours of sleep increased from 2 hours per night to 6 hours per night for patient 6 and from 5

hours per night to 7 hours per night for patient 4, with normalisation of awakening at 7:00 a.m. and resolution of nocturnal awakening episodes and episodes of "nocturnal wandering". The same trend was observed in the other patients, with an increase in the amount of sleep from 1–3 hours/night, a decrease in the time needed to fall asleep, a decrease or even resolution of nocturnal awakening episodes with associated "nocturnal wandering", and episodes of early awakening.

No unwanted side effects linked to melatonin treatment were observed. The blood tests carried out during the treatment period revealed no anomalies.

Table 1

Patients	Sleep disorders	CGI-S before treatment	Melatonin	Associated psychotropic medication	CGI-S 6 months after treatment	CGI-I 6 months after treatment
Patient 1 52 years old	Disrupted sleep	6	6 mg/d	Olanzapine Clotiapine Clonazepam	2	2
Patient 2 34 years old	Nocturnal wandering, early awakening	6	6 mg/d	Zuclopenthixol Clonazepam	1	1
Patient 3 21 years old	Early awakening	4	6 mg/d	Haloperidol Huclopenthixol Clonazepam	1	1
Patient 4 19 years old	Nocturnal wandering, early awakening	4	6 mg/d	Zuclopenthixol Levopromazine Venlafaxine Clonazepam	1	1
Patient 5 48 years old	Disrupted sleep	5	6 mg/d	Zuclopenthixol venlafaxine valproate	1	1
Patient 6 38 years old	Disrupted sleep	6	6 mg/d	Risperidone Clotiapine Lithium Clonazepam	1	1

Sleep improvement was statistically significant with median score 5.5 before and 1.0 after treatment (Wilcoxon signed-rank test, $P = 0.031$)

Discussion

Melatonin appears to be a promising treatment for sleep disorders in adults with autism, to both induce and maintain sleep, and it may lead to improvements in behavioural problems. To the best of our knowledge this is the first publication to discuss adult patients, and it confirms the results of studies investigating melatonin in children and adolescents [22–26]. Nevertheless, this study is merely an open study carried out with a limited number of patients. Moreover, the study was retrospective and did not use an instrument specialised in sleep evaluation. However, it may be noted that special care was taken to ensure that the sleep improvement could not have been due to changes made in other psychotropic treatments for the associated psychiatric disorders. All the

same, these preliminary observations require confirmation by randomised, double-blind clinical studies, if possible with objective data collection (actimetry – polysomnography). By chance, our population was mainly composed of male subjects (even if a gender difference is not very likely). The group was also primarily composed of young adults, but a good therapeutic response was also observed in the 2 subjects who were aged over 45.

No unwanted side effects were observed in our patients, although several studies have reported unwanted effects linked to melatonin intake, such as cephalalgia, fatigue, dizziness, confusion, nausea and tachycardia [30, 31], though some authors have suggested that these effects were linked to impurities in the product [16, 18,

32]. The good tolerance we observed in our patients must be qualified by the fact that we did not use a systematic instrument to record side effects, as this measurement could prove difficult to carry out in our study population.

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