

Review article

The therapeutics of melatonin: a paediatric perspective

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Abstract

The production of melatonin by the pineal gland and its functions are considered, and then its possible uses in the treatment of children. Institutionalized children, and those with severe learning disorders, often have irregular sleep–wake patterns, and there is evidence that melatonin can result in improvement to the benefit of both the child and the carers. The affected children can become less irritable, calmer, happier, and content. Also they may socialize better and become more attentive, with an improvement in their cognitive abilities. Another group of children who are likely to suffer from disturbed sleep are those who are visually handicapped. Melatonin given in the evening can improve their sleep patterns, and often their performance. No important side-effects have been reported. It is generally accepted that if a child is liable to epileptic seizures sleep deprivation may well exacerbate them. There is some evidence from clinical trials that in that event melatonin can be helpful. There are many other problems in which it is claimed that treatment with melatonin is justifiable. These are mentioned, but further confirmatory studies are needed in most of them. There is no doubt that melatonin can effect the circadian system, and shift the sleep–wake cycle; and that there are situations in which this can be desirable. © 2000 Published by Elsevier Science B.V. All rights reserved.

Keywords: Melatonin; Sleep–wake cycle; Paediatric disorders; Effects of treatment

1. Introduction

The discovery of a neurohormone, melatonin, excreted mainly by the pineal gland has raised a number of therapeutic possibilities. It is produced during darkness and has been implicated in the regulation of the mammalian circadian system, especially in sleep and reproductive rhythms. It is also claimed that when the sleep pattern of children improved on treatment with melatonin they become less irritable, calmer, happier, more playful, content and affectionate, with fewer temper tantrums. Also, the children were able to socialize better and were gentler with their siblings and pets. They became more attentive, and their cognitive abilities and mobility improved [1]. In addition there is experimental evidence of a role in immunological reactions [2], and possibly reproductive functions [3]. Related to this may be an anti-cancer effect although this is more likely to be due to antimitotic activity [4]. The link between the pineal gland, and its influence on the thymus, does raise the possibility of using melatonin in the treatment of primary and secondary immunodeficiencies [5].

The pineal gland consists of two types of cells; pinealocytes which produce indolamines, mostly melatonin, and

peptides; and neuroglial cells. In the production of melatonin tryptophan is converted to serotonin, and then to *N*-acetylserotonin, and finally to melatonin. Newborn infants produce little or no melatonin until about 3 months of age, and then the levels increase for the next 9 or 10 months and remain stable until the levels decline just before puberty. Circadian rhythms are an adaptation to the solar changes of light and dark, and it is the suprachiasmatic nucleus of the anterior hypothalamus which is responsible for this function. This nucleus, and the anterior hypothalamic area, the paraventricular nucleus, and the lateral hypothalamic area are influenced by light transmitted to the retina; and melatonin levels rise in darkness. There is also a correlation between this rise and the onset of sleep [6], and it is suggested that when melatonin is given in high doses it may promote sleep by causing relative hypothermia [4]. Nocturnal sleep onset correlates well with the onset of melatonin secretion, and the timed administration of medicinal melatonin can result in the earlier onset of endogenous night-time secretion, thus resetting the endogenous circadian pacemaker.

There are a number of conditions which are said to be improved by treatment with melatonin, but which need further study, such as tinnitus [7], facilitating the termination of benzodiazepine treatment while maintaining good

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sleep quality [8], and as already mentioned in the treatment of cancer [9]. It is also suggested that melatonin can help in the diagnosis of neoplastic disease, in the control of gastric ulcers and of colitis, and even in the treatment of migraine [10], and of tension headaches in patients who suffered from delayed sleep onset [11]. It is also possible that melatonin can be used in the prophylaxis of cluster headaches. The cause of these are unknown, but if melatonin plays a part in the regulation of core body temperature, and if concentrations of melatonin rise as body temperature falls, the link may be the finding of lower concentrations of this hormone among sufferers; as there is a suggestion that body heat can be a precipitating factor [12]. It is claimed that melatonin can improve the sleep disorders associated with severe depression, among adults anyhow [13]. Animal experiments may indicate that melatonin can have a protective effect when damage occurs in focal ischaemia [14], and in toxic damage to the dopaminergic system [15]; and this finding may warrant further study. Also chronic sleep disorders can adversely affect the child's development, as sleep plays a major role in the early maturational process in the brain [6]. There is still not universal agreement over the dose of melatonin, and this can vary from 0.3 to 25 mg of fast release synthetic melatonin. Infants are usually started on 2.5 mg and older children on 5 mg [1]. Plasma levels usually peak after about 1 h, and show a biphasic elimination pattern with half-lives of 3 and 45 min [16]. Also the content of melatonin products may vary.

2. Irregular sleep–wake patterns among institutionalized children, and those with severe learning disorders

Sleep disturbances are relatively common. Many elderly people complain of sleeping badly, although this may have to be confirmed by observation. However, there is evidence that during the night serum melatonin levels among the elderly who suffer from insomnia are low compared with age matched controls. They are even lower in such patients living in institutions rather than in the community, which may be linked to lack of exposure to bright light, insufficient physical exercise, or to some form of cerebral disorder [17]. Pillar et al. [2] studied an institutionalized 13 year old girl with psychomotor retardation who suffered from an irregular sleep–wake pattern. Urinary concentrations of sulphatoxy–melatonin were abnormally low, and there was no significant difference between day and night measurements. After administration of melatonin in the evening there was increased urinary excretion of sulphatoxy–melatonin and nocturnal sleep increased; findings which suggest that such disabled children may be helped in this way.

Treatment with melatonin has been tried on children with severe learning disorders and abnormal sleep patterns, living at home. When this occurs it may cause very considerable stress to the parents and other carers. For example Zhdanova et al. [18] studied 13 children, aged 2–10 years of

age, with Angelman syndrome who suffered from insomnia. Motor activity was constantly monitored in their home environment for seven days prior to melatonin treatment, and for five days during which a 0.3 mg dose of melatonin was given daily for 6 days, 30 min to 1 h before their usual bedtime. Blood samples were withdrawn at hourly intervals over two 21-h periods to measure individual endogenous serum melatonin levels and the levels induced by melatonin treatment. The recordings of motor activity showed a significant improvement in the children's sleep patterns as a result of the treatment, with both a decrease in motor activity and an increase in the duration of the total sleep period.

Another group of children who have been studied for the effects of treatment with melatonin are girls with Rett syndrome. McArthur and Budden [19] monitored nine such girls 24 h a day over a period of 10 weeks, and baseline sleep–wake patterns were assessed for 1 week. Then they were treated for 4 weeks with melatonin in doses ranging from 2.5 to 7.5 mg in a double-blind placebo controlled crossover protocol, with a one week washout between treatments. Among the affected children the quality of sleep was poor, and this was significantly improved while on treatment although the response was variable. It is hypothesized that melatonin may advance the suprachiasmatic nuclei clock. There were no adverse side effects.

In another investigation two patients with Rett syndrome and severe sleep disorders the circadian rhythm of serum melatonin levels were measured before and during melatonin treatment, 5 mg orally before bedtime. This dramatically improved the sleep–wake cycle in the first patient, and in the second it showed a hypnotic effect but early morning awakening still sometimes occurred, which may be due to rapid absorption and metabolism. When the melatonin was stopped the sleep disorders recurred [20].

Children with autism frequently suffer from severe sleep difficulties, often of unknown origin. Richdale [21] has stressed that behavioural intervention may well be effective; as may methods of influencing the circadian sleep–wake cycle, especially the giving of melatonin. Also light therapy can be used, when bright light in the morning can advance sleep–wake rhythms, and chronotherapy in which the sleep–wake cycle is successively delayed until the desired bedtime is reached.

3. Irregular sleep–wake patterns among visually impaired children

Children who may be especially liable to suffer from disturbed sleep patterns are those with impaired vision. In a discussion of sleep disorders in visually impaired children, Stores and Ramchandani [22] stress the importance of early recognition and treatment of sleep disorders in visually impaired children, otherwise their development and behaviour may be adversely affected. Among a wide range of therapeutic possibilities they include the use of melatonin;

but emphasise that its effectiveness has still to be definitely proven, particularly in the long term. In their study Espezel et al. [23] treated 70 children, aged 1–20 years old, with melatonin because of chronic sleep disorders. The latter were correlated with the children's visual diagnoses, visual loss, age, associated disabilities, level of independence, and type of placement. Melatonin, given orally (2.5–10 mg) at bedtime quickly improved sleep patterns without side effects, and their moods were better, they became more alert and sociable and showed developmental gains with great benefit to the children and their carers. Palm et al. [24] used oral melatonin therapy to treat eight functionally blind children and young adults with severe circadian sleep–wake disturbances. Six of them had defects in the anterior visual pathways, and had severe learning disorders. Their carers kept sleep diaries, and diurnal variations in serum and urinary melatonin levels were checked. Melatonin secretion peak times were delayed in seven patients and body temperature variation was out of phase relative to sleep and melatonin levels in five; confirming signs of internal desynchronization. Melatonin given in the evening improved the sleep–wake pattern in all the patients, and the effect was maintained for between 1 and 6 years in six patients, with benefit to the patients and their families from a reduction of night waking and daytime drowsiness. No side effects were noted. It is suggested that the cause of the sleep–wake disturbance is that these children did not perceive the light–dark alterations which synchronize the chronological and physiological day. Among those with defects in the anterior visual pathways information on alterations between light and darkness is not conveyed correctly to the pineal gland. The other two had disorders of cortical visual function which presumably may have had a similar effect. Normal puberty does not seem to change melatonin levels, but high levels have been noted among boys with delayed puberty, and low levels in cases of precocious puberty [25].

Sleep–wake disorders in children and adolescents, including those with visual impairment, have been reviewed by Jan et al. [6]. They confirm the usefulness of melatonin in a number of sleep disorders, but warn that it is not a blanket treatment for them all. They recommend that it is given 20–30 min before the desired bedtime; and sleep induction occurs within 30 min. They also stress that the sleep environment must be well structured. Improvement can occur within days but may take weeks; and personal experience and a review of the literature confirmed that if normal sleep patterns can be established children will tend to become less irritable, calmer, happier, more playful, and more affectionate. Also learning, memory and behaviour are likely to improve.

This had been confirmed by earlier work of Jan and his collaborators [26]. They studied 15 children, most of whom were multiply handicapped, and nine had ocular or cortical visual impairment. They had severe persistent sleep disorders; nine with fragmented sleep patterns, three with

delayed sleep onset, and three had non-specific sleep disturbances of unknown cause. All had failed to respond to conventional management, and they were given 2–10 mg of oral melatonin at bedtime. Sleep patterns improved, and associated with this there were health, behavioural and social benefits, which helped the whole family; and the absence of side effects was confirmed.

Kunz and Bes [27] treated six adults with melatonin who had sleep behaviour disorders associated with vivid dreams and REM sleep without muscle atonia; and there was a dramatic improvement in five of them. On this treatment there was a significant tendency for REM sleep to become normal, and it is suggested that the improvement was due to a restoration of the integrity of the circadian timing system.

4. The benefits of melatonin in children with epilepsy

It is generally accepted that deprivation of sleep in a child suffering from epilepsy can result in an exacerbation of seizures, and melatonin can lead to an improved quality of sleep. A parental questionnaire was used to assess sleep problems by Cortesi et al. [28]. Eighty-nine children with idiopathic epilepsy were studied for comparison with 49 siblings and 321 healthy control children equally distributed for age and sex. The sleep problems included parasomnias, sleep fragmentation, daytime drowsiness, and bedtime difficulties; and daytime behaviour and psychological adjustment were assessed by a child behaviour checklist. The children with epilepsy showed more sleep problems than the controls, and more behaviour problems and maladjustment. Age, paroxysmal activity density, duration of the illness, seizure frequency, and behavioural problems were significantly associated with sleep disorders in the epileptic group. These results confirm the links between the sleep problems and behaviour in this selected group of children with a benign form of epilepsy, and this may well be due to difficulties of adaptation; and if the former can be improved by treatment benefits may ensue.

Ross et al. [29] treated 45 children with melatonin, and the response could be assessed in 43 of them. All of them suffered from sleep–wake cycle disorders and 24 of them from epilepsy. A fast-release preparation of melatonin was used in a dose of 2.5–7.5 mg for children under the age of two and 2.5–10 mg for older children. Their epilepsy tended to be difficult to treat, and they also had learning and behaviour difficulties. Twenty of them showed a good response in terms of their sleep problems, and seizure control improved in some of them. Certainly their families were very pleased with the results. Also Molina-Carballo et al. [30] have suggested that melatonin may be a useful addition to other anti-epileptic therapy, and that this may be related to its neuroprotective role, or more likely to its inhibitory action on glutamate receptors and its potentiation of the GABA-benzodiazepine receptors.

Melatonin has been tried in the treatment of non-epileptic

myoclonus [31] Three children suffered from markedly delayed sleep onset due to recurring myoclonus, and low doses of melatonin were given, 3–5 mg, which unexpectedly stopped the myoclonus and allowed them to sleep. This may be due to the enhancement of GABAergic systems; and certain similarities between melatonin and benzodiazepines, resulting in inhibition of neurones in those areas of the CNS involved in the generation of the myoclonus.

5. Conclusions

Children with severe learning and behaviour disorders are particularly liable to sleep problems [32], and from these various studies there seems to be no doubt that for certain children treatment with melatonin, with its dual effect as a hypnotic and as a means of altering the circadian pacemaker which controls the time of sleeping and waking [33], will improve their sleep patterns; and as a result many aspects of their behaviour. This will not only be of benefit to the child but also be a relief to their carers. For example, Okawa et al. [34] observed the sleep disorders of adolescents which are relatively common. Most affected patients had difficulty in adjusting to school life, poor class attendance, or refusal to go to school. Treatment included the reordering of their life at school and at home, bright light exposure, and the use of drugs, one of which was melatonin; and over half of them improved. It does not always act as both asleep inducer and a phase setter, but may only be effective for one or the other [35].

The aim of treatment will be to establish healthy sleep patterns, whatever the cause of the disorder. This will involve retraining, with melatonin used as an adjuvant in as low a dose as possible, but maybe up to 5 or 10 mg; and in view of its short half life within 1 h of bedtime [36]. Once improvement has occurred it may well be possible to withdraw it, but this has to be on a trial and error basis as this is sometimes not possible [37]. Short-term side effects, such as headaches, drowsiness, confusion, nausea, tachycardia, and pruritis are few and it is difficult to know if these are really due to melatonin [6], but the safety of long-term treatment with melatonin has still to be established [38]. If such treatment is successful the patient will acquire an acceptable sleep–wake cycle [39]. There are still many unanswered questions, and many more well constructed clinical trials will be needed before melatonin can be widely recommend [16]. The indications for treatment must be better defined and assurances given that there are no significant adverse effects.

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