

Use of melatonin to treat sleep disorders in tuberous sclerosis

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The results of a therapeutic trial of the use of melatonin in patients with tuberous sclerosis complex who also have severe sleep problems are reported. We used a randomized double-blind placebo-controlled crossover design. Seven patients with confirmed diagnoses of tuberous sclerosis and significant sleep disorder were recruited. We employed three outcome measures: total sleep time, time to sleep onset, and number of awakenings. Patients treated with melatonin had a small but clinically significant improvement in total sleep time (mean improvement 0.55 hours, $P < 0.05$). They also tended to have an improvement in sleep-onset time but this did not reach statistical significance. Melatonin, in this trial, had no discernible effect on sleep fragmentation. We conclude that melatonin does have a beneficial effect in prolonging the total sleep time of patients with tuberous sclerosis and sleep disorder and that further trials are necessary to investigate the issues of optimal dosage, tolerance, and possible interactions with other medications.

Tuberous sclerosis complex (TSC) is a dominantly inherited genetic disorder, best known for its association with severe learning difficulties, epilepsy, and behavioural problems. Children with TSC often have severe difficulties with sleeping. In one postal survey of 300 people with TSC, carers reported problems with settling in 60% and night waking in 62% (Hunt 1993). Sleep problems in TSC are associated with general behavioural problems, epilepsy, parental stress, and family problems (Hunt and Stores 1994). The aetiology of sleep disorder in TSC is uncertain, but whatever the cause, the disorder is difficult to treat. Patients with TSC with a sleep disorder do not often respond to night-time sedatives or behavioural techniques.

Recently, some work has examined the use of melatonin in the treatment of children with neurological disabilities who have sleep problems. Melatonin is a hormone produced by the pineal gland. It plays an important role in organizing human circadian rhythms. It is thought that it helps to synchronize human sleep-wake patterns with the light-dark cycle of the normal day. Melatonin is synthesized in pinealocytes from tryptophan. The synthetic process begins at the retina where changes in light intensity are detected and a signal is sent via the retinohypothalamic pathway to the hypothalamus and from there to the pineal gland. Melatonin levels are high in darkness and low during daytime. Exogenous melatonin has been used successfully in regulating the sleep of shift-workers (Weitzman et al. 1981), individuals suffering from jet lag (Arendt et al. 1987), and blind individuals with abnormal circadian rhythms (Sack et al. 1991). Jan et al. (1994) appear to have had some success in using melatonin to treat the sleep disorders of children with multiple disabilities both with and without visual impairment. The success reported in treating neurologically disabled children without visual impairment led us to assess its use in patients with tuberous sclerosis with severe sleep problems.

Method

We recruited patients with a confirmed diagnosis of tuberous sclerosis and severe sleep problems. Patients were identified either through the Tuberous Sclerosis Association of Great Britain or through a specialist tuberous sclerosis clinic based at the Royal United Hospital, Bath. The presence of significant sleep difficulties was confirmed before the recruitment by a sleep diary, completed by the patients' main carer over a 1 week period, which confirmed both delayed sleep onset and sleep fragmentation, and a Quine sleep-index score of greater than 6 out of 8 (Quine 1991). The sleep index focuses on four areas of difficulty: problems settling the child to sleep, night-time waking, parental sleep loss, and frequency with which parents/carers have to attend to their child during the night. The sleep index sums the three point scores (zero to two) for each of the four areas and gives a final score which can range from zero (no problems) to eight (severe problems in all four areas).

The trial design was a randomized double-blind placebo-controlled crossover trial. The dose of melatonin used was 5mg. Melatonin was supplied by Penn Pharmaceuticals Ltd. Melatonin and placebo were administered in identical capsules. Therapy was given 20 minutes before each patient's usual bed time. The initial treatment period of 2 weeks was followed by a 1-week wash-out period before patients were

crossed over to the alternate therapy for a further 2 weeks. Throughout the total 5-week period of the trial, the individual patient's response was monitored by a sleep diary completed by the main carer. Outcome measures determined before the study were total sleep time, sleep-onset time (i.e. time taken to fall asleep) and number of awakenings during the night. Results were analysed using paired *t* tests.

Results

Seven patients (three males and four females) who satisfied the inclusion criteria were recruited. The age range was 2 to 28 years (median age 11 years). All patients had delayed sleep onset and fragmented sleep patterns. All patients had epilepsy and learning difficulties. Mean total sleep time, mean number of awakenings, and mean time to sleep onset were calculated for each subject while receiving melatonin and placebo. These results are shown graphically in Figures 1 to 3. Figure 1 shows that mean total sleep time improved in six patients whilst receiving melatonin. The mean improvement in total sleep time for the group was 0.55 hours (95% CI, 0.088 to 1.01) which, using a two-tailed *t* test, reached conventional levels of statistical significance ($P=0.027$). Figure 2 shows that the mean sleep-onset time when treated with melatonin improved (i.e. decreased) in four patients, deteriorated in two, and stayed the same in one. The mean improvement for the whole group was 0.39 hours (95% CI, -0.085 to 0.873) and this did not quite reach conventional levels of statistical significance ($P=0.079$). Figure 3 shows there was no obvious trend in this group towards improvement in the mean number of awakenings per night while on melatonin: three patients showed improvement receiving melatonin, three deteriorated, and one patient was apparently unaffected.

Discussion

This treatment trial suggests that melatonin is effective in prolonging total sleep time in patients with TSC who have difficulties in sleeping. The treatment effect was small (i.e. 0.55 hours) but significant. Sleep-onset latency also improved with melatonin therapy but this did not quite reach statistical significance. Melatonin did not have any discernible effect on sleep fragmentation. It is likely, therefore, given our results, that the significant improvement in total sleep time results from an improvement in sleep onset rather than a reduction in the total number of awakenings per night.

The results of this trial should be interpreted with caution, however. Firstly, the trial is small because of the rarity of the condition, and therefore it is possible that we did not see significant effects of therapy because of inadequate numbers of patients. Secondly, the data on patients' sleep parameters were collected by sleep diaries which are inferior to polysomnography as an objective measure of sleep patterns. Nevertheless, sleep diaries have the advantage of being cheap and unobtrusive, they are commonly used in sleep research, and they have been shown to correlate well with polysomnography (Rogers et al. 1993). The sleep diaries used were very similar to those used by Jan et al. (1994). Despite these reservations, we have seen a positive result. It is unlikely that this trial was undermined by the problems of period or treatment effects which can afflict many crossover trials. Sleep disorder in TSC is relatively stable over time and is unlikely to improve significantly over a period of 5 weeks, and melatonin has a half-life of less than 1 hour (Bojkowski 1988) which means that lingering treatment effects are unlikely. Two of seven patients in this trial were randomized to receive melatonin in the initial treatment period. The wash-out data in these two patients show that their sleep parameters worsened upon cessation of melatonin therapy. We hesitate to draw conclusions on the basis of two patients, but this data does suggest that melatonin does not have continuing effects after treatment has ended.

This was a pragmatic trial examining the effectiveness of using melatonin in the clinical setting. All the patients in this study were receiving a variety of anticonvulsant medications at the time of the trial. We did not alter their existing anticonvulsant regimes during the trial and we cannot rule out the possibility that melatonin may have interacted in some way with one or more of the antiepileptics these patients were receiving either to improve or to worsen their sleep profile. If drug interactions did occur then it would be difficult to identify them. The possibility of interactions does not detract from the result that in these patients with both TSC and epilepsy, total sleep time was improved when melatonin was added into their therapeutic regimen.

No one has previously reported their experience of using melatonin in patients with TSC. Some work has been published investigating the use of melatonin in individuals with learning difficulties and sleep problems. The results are mixed. Jan et al. (1994, 1996) report positive experiences in

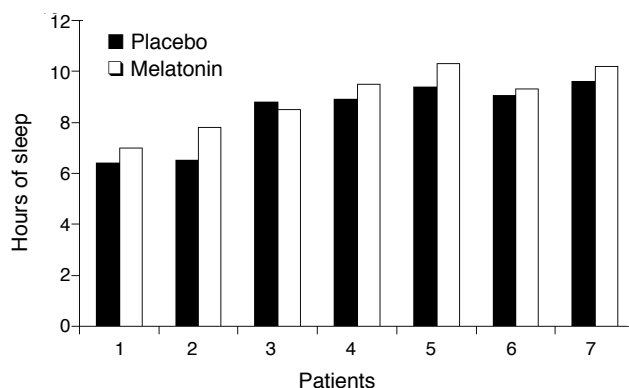


Figure 1: Mean total sleep time.

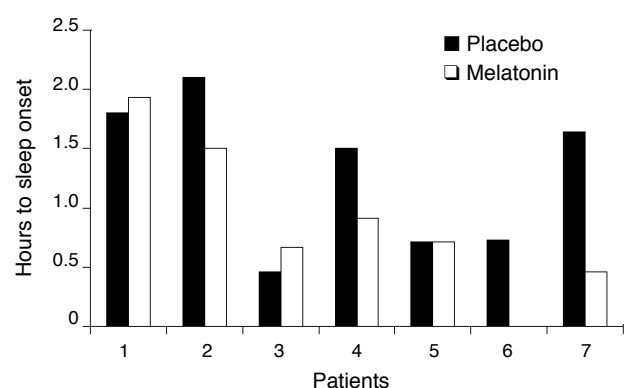


Figure 2: Mean sleep-onset time.

their group of neurologically disabled children using doses between 2.5mg and 10mg of melatonin given at bedtime. Camfield et al. (1995) report less impressive results in a group of six children given a dose of between 0.5mg and 1.0mg of melatonin at 18.00 hours. In both trials there was a mixture of children with normal and impaired vision. Recently McArthur and Budden (1998) have reported improvements in sleep-onset latency, total sleep time, and sleep efficiency in nine patients with Rett syndrome who were treated with between 2.5mg and 7.5mg of melatonin. Our results, like those of Jan et al. and McArthur and Budden, suggest a positive benefit of using melatonin even in those individuals who have no visual impairment.

The sleep disorder in TSC has a complex aetiology. Epilepsy probably has a central role. Stores (1992) has shown that epilepsy can disrupt sleep physiology in a variety of ways. Hunt and Stores (1994) also showed that the sleep disorder in TSC was strongly associated with epilepsy. However, behavioural problems (autism and hyperkinesia) and antiepileptic medication may also contribute to disrupted sleep patterns. It is not clear, therefore, why melatonin should work in patients with TSC. There has been some suggestion that epileptic patients may have abnormal patterns of melatonin secretion, with peak plasma concentrations occurring earlier in the night than in non-epileptic individuals. Moreover plasma concentrations of melatonin are significantly higher in children with epilepsy compared with children without (Molina-Carballo et al. 1994). It has long been known that huge doses of melatonin (i.e. >200 mg/kg) are effective in abolishing convulsions in epileptic mice (Sugden 1983) and there is some limited evidence that melatonin may reduce seizure activity in humans with temporal-lobe epilepsy (Fariello et al. 1977). It is possible that melatonin may work in patients with TSC because it modifies their epilepsy or moderates the sleep disruption caused by the epilepsy. However, a recent report suggested that melatonin, while improving sleep-wake disturbances in a group of six children with neurological disabilities, was associated with an increase in seizure activity in four of them (Sheldon 1998).

Another explanation of the improved total sleep time is that melatonin may simply have a sedative effect. The most consistent effect of very large doses of melatonin seen in healthy volunteers was that it induced sleep. Even in smaller, but still supraphysiological, doses (1 to 80mg) it has been noted to cause transitory sleepiness (Arendt 1995). The clinical effect seen in our study may be no more than the transitory sleepiness, previously seen in these studies, which would explain the reduction in sleep-onset time and improvement in total sleep time.

It could be hypothesized that exogenous melatonin is effective in our patients with TSC because, for some reason, they may have abnormally low or disordered melatonin secretion. Melatonin secretion is controlled not only by the light-dark cycle but also by behavioural zeitgebers (e.g. bedtime routines) which can be powerful enough in the absence of the light-dark cycle (e.g. as in the Antarctic winter) to entrain melatonin secretion patterns to the 24-hour day (Arendt 1995). It is possible that patients with TSC with learning difficulties may not be receptive to these social zeitgebers and, therefore, may have disordered or free-running patterns of melatonin secretion which are not synchronized with the

24-hour day and which thus result in sleep disruption. However, we feel that this is unlikely. As yet unpublished data on the excretion of 6-hydroxymelatonin sulphate (the major urinary metabolite of melatonin) in patients with TSC suggests that they have a normal pattern of melatonin secretion.

We gave our patients a dose of 5mg of melatonin. This will have resulted in the younger patients receiving a greater dose per weight than the adults. Interestingly, we did not see any evidence of an age effect in the response of our patients despite the different dose per kilogram they were receiving. The optimal dose in this situation is unclear but even 1mg will result in markedly supraphysiological plasma levels of melatonin in an adult. Jan et al. (1994, 1996) used a dose of between 2.5mg and 10mg in their study, whereas Camfield et al. (1995) used a lower dose of 0.5mg to 1mg. It is possible that the less encouraging results seen by Camfield's group resulted from the use of smaller doses. If melatonin is working in this situation because of its mild sedative effect, then it is possible that larger doses will be more effective. Moreover, it makes sense to give the dose close to the bedtime of the patient. Camfield et al. (1995) who gave the melatonin at 18.00 hours may have been giving the dose too early.

As in all but one previously published trials, the melatonin therapy had no adverse side effects in any of our patients (Sheldon 1998). There is good experimental evidence for very low toxicity of melatonin. For example, Sugden (1983) was unable to find a LD50 for melatonin given to rats. It has also not been found to be mutagenic in standard in vitro tests. Clinical trials certificates have been issued to cover the long-term administration of up to 300 mg per day (Voordouw et al. 1992). It is likely that use of melatonin in the doses used in this trial is extremely safe, although more information on long-term use, the potential for the development of tolerance, possible drug interactions, and the effect on seizure activity is needed.

In conclusion, this study has demonstrated a small but significant improvement in total sleep time in patients with TSC with sleep problems who were treated with melatonin. The mechanism by which melatonin improves sleep in these patients is unclear and there remain unanswered questions about optimum dosage and whether tolerance to treatment may occur. Further trials are clearly indicated. However, the therapy, which is easy to administer and probably very safe,

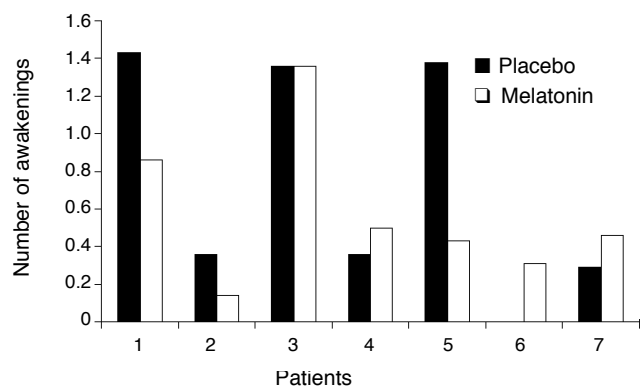


Figure 3: Mean number of awakenings

does show promise in this particularly difficult clinical situation where other therapies have proven ineffective and where any improvement in sleep pattern is valuable to highly stressed families.

Accepted for publication 7th August 1998.

Acknowledgements

Thanks to the Tuberous Sclerosis Association of Great Britain for their help in locating suitable patients for this study. Dr F J K O'Callaghan is a Wellcome Research Training Fellow in Clinical Epidemiology. Dr A A Clarke was supported by a grant from the Wessex Regional Health authority. Dr E Hancock is funded by a grant from the Tuberous Sclerosis Association of Great Britain and Cow and Gate. We acknowledge the continued support of the Bath Unit for Research in Paediatrics.

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