Randomized controlled trial of melatonin for children with autistic spectrum disorders and sleep problems

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Abstract

Background Melatonin is often used for autistic children with sleep disorders, despite a lack of published evidence in this population.

Methods A randomized, placebo-controlled double-blind crossover trial of melatonin was undertaken in 11 children with autistic spectrum disorder (ASD).

Results Seven children completed the trial. Sleep latency was 2.6 h [95% confidence intervals (CI) 2.28–2.93] baseline, 1.91 h (95% CI 1.78–2.03) with placebo and 1.06 h (95% CI 0.98–1.13) with melatonin. Wakings per night were 0.35 (95% CI 0.18–0.53) baseline, 0.26 (95% CI 0.20–0.34) with placebo and 0.08 (95% CI 0.04–0.12) with melatonin. Total sleep duration was 8.05 h (95% CI 7.65–8.44) baseline, 8.75 h (95% CI 8.56–8.98) with placebo and 9.84 h (95% CI 9.68–9.99) with melatonin.

Conclusions Although the study was small owing to recruitment difficulties, it still provides evidence of effectiveness of melatonin in children with sleep difficulties and ASD, which we predict a larger study would confirm.

Keywords
autistic spectrum disorder, melatonin, sleep problem

Introduction

Our aim in undertaking this study was to establish whether melatonin is an effective treatment for children with autistic spectrum disorder (ASD) and sleep problems.

Melatonin is an endogenous neurohormone secreted by the pineal gland in response to decreasing levels of light. It causes drowsiness. Melatonin levels increase rapidly after nightfall, peak in the middle of the night then decrease towards dawn.

Melatonin is increasingly being used as a treatment for sleep disorders in children with developmental disorders particularly ASD. It is an unlicensed drug in the UK and randomized controlled trials have been difficult to implement in children owing to its 'over the counter' status in some countries (Sweis 2005).

Children with ASD have a high rate of sleep disorders. Sleep difficulties in up to 67% of autistic children have been reported (Wiggs & Stores 2004). Sleep problems occur in normal children but less commonly (Blader *et al.* 1997). Sleep disorders occur in autistic children irrespective of their level of intellectual functioning (Richdale 1999). Common problems are difficulties in settling the child at bedtime with delays in sleep onset (sleep latency) once settled, a short sleep duration and frequent and prolonged night wakings.

The cause of sleep problems in autistic children is unknown. The sleep–wake cycle is a circadian rhythm, but social cues may be important in addition to the light–dark cycle (Aschoff *et al.* 1971).

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Autistic children have difficulty in interpreting social cues so this may be a causal factor in their sleep problems. Perseveration of thoughts and anxieties at bedtime or during night awakenings may be important. There is some evidence that melatonin levels may be lower in autistic children (Tordjman *et al.* 2005).

Currently, there is no literature purely focusing on the use of melatonin in children with ASD. There are few controlled trials of melatonin for sleep disorders in children. Melatonin has been shown to be safe and effective, in normal children with chronic sleep onset insomnia (Smits *et al.* 2003). In children with developmental disorders and sleep problems, melatonin decreases sleep latency but has no effect on total sleep time (Dodge & Wilson 2001).

Our clinical experience was that children with ASD and sleep problems responded well to melatonin and we therefore designed a randomized trial of melatonin specifically for children in this group.

Subjects

These were children with a diagnosis of ASD aged between 4 and 16 years, with significant difficulties in sleeping at night.

The criteria for a diagnosis of ASD was: difficulties in verbal and non-verbal communication, difficulties with social interaction and a lack of imagination. All the subjects had been diagnosed with ASD by a Consultant Community Paediatrician or Consultant Child Psychiatrist previously.

Our definition of sleeping difficulties was: a sleep latency of at least 1 h after desired bedtime or night awakenings that required parental attention. The problem had to be present at least four nights a week during the last 6 months and be causing distress to the child or other family members. There also had to be a failure of behavioural management techniques.

Children were recruited via community paediatricians, special schools, the local autism-support service and the local parents-support group.

Children who had used melatonin previously were excluded from the trial to avoid bias. Children who had been using other sedative medication were not allowed trial entry until they had completed 4 weeks of medication.

Children with additional diagnoses such as learning difficulties, attention-deficit hyperactivity disorder (ADHD) and dyspraxia were included as this represents much of the population with ASD.

Methods

The study was a randomized crossover double-blind placebo-controlled trial of melatonin. The effect of the melatonin and placebo on the children's sleep patterns was quantified by the daily use of sleep charts, completed by the parents. All children had their baseline sleep pattern recorded, using the sleep chart, for 1 week prior to receiving the first treatment.

Children were randomized at trial entry regarding the sequence in which they received the two trial medications, melatonin 5 mg and placebo. Randomization was performed using random number tables, by the hospital pharmacy.

Children took each trial medication for a period of 4 weeks. There was a washout period of 1 week between each of the treatment periods.

A flow chart of the study is shown at Fig. 1.

The sleep charts recorded total sleep time, sleep latency, night awakenings and morning awakening. Parents were not expected to get up in the night to check if their child was asleep. It was assumed that unless the parents were disturbed in the night that the child was asleep.

All parents received a standard advice leaflet about establishing good sleep hygiene measures.

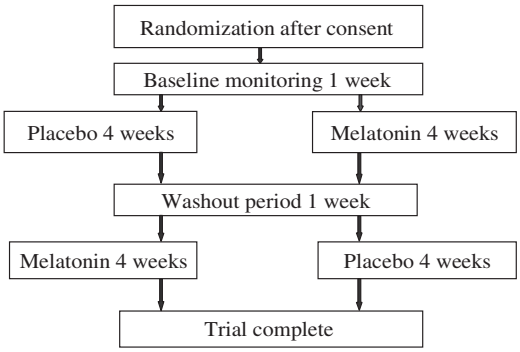

Figure 1. Flow chart of study.

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Ethical approval was obtained from the local ethics committee.

The trial started in January 2003 and finished in December 2004.

Results

Eleven children, of whom seven were boys, started the trial.

The demographics and additional diagnoses of the children are shown in Table 1. Most of the children did not have learning difficulties and attended mainstream school.

Table 1. Children's demographic details and additional diagnoses

Age of child (year)	Sex	Other diagnoses	School
7	F	Mild LD	Main stream
6	M	Dyspraxia	Main stream
6	F	Severe LD	Special
5	M		Main stream
12	M		Main stream
9	M	Dyspraxia	Main stream
15	F	Moderate LD	Special
10	F	Moderate LD	Special
8	M		Main stream
6	M	Mild LD	Main stream
11	M	Mild LD	Main stream

M, male; F, female; LD, learning difficulty.

Seven children, of whom six were boys, completed the trial. The trial had to be suspended when it was found that some of the placebo capsules were empty, necessitating a drugs recall. This forced two girls to drop out of the trial. Subsequently, one boy dropped out owing to a house move and one girl became involved in a child protection enquiry.

The data were analysed for the children who completed the trial as we did not have complete sleep data on those who dropped out.

The mean and 95% confidence intervals for sleep latency, number of wakings per night and total sleep time were calculated for the baseline period, placebo period and melatonin period. The results are shown in Table 2.

Melatonin significantly reduced sleep latency, number of night wakings and increased the total sleep time. This is illustrated in Figs 2–4.

Several parents commented that their children were easier to manage and less rigid in their behaviour while taking melatonin. The class teachers shared these views.

All children completing the trial continued on melatonin afterwards at the request of their

Table 2. Mean and 95% confidence intervals (CI) of treatment on sleep patterns

	Sleep latency (h)		Wakings per night		Total sleep (h)	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
Baseline	2.60	2.28–2.93	0.35	0.18–0.53	8.05	7.65–8.44
Placebo	1.91	1.78–2.03	0.26	0.20–0.34	8.75	8.56–8.98
Melatonin	1.06	0.98–1.13	0.08	0.04–0.12	9.84	9.68–9.99

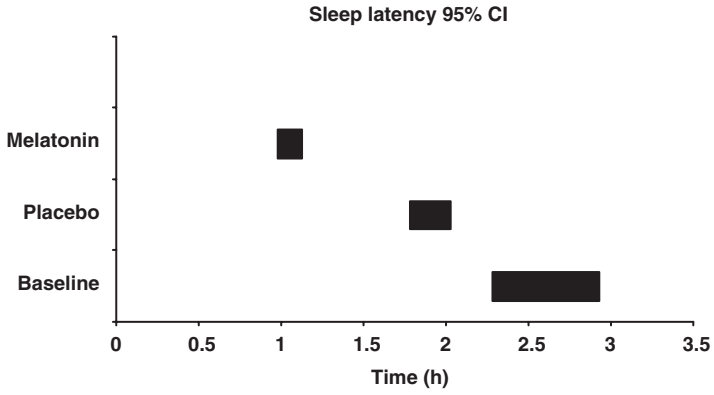

Figure 2. Graph of 95% confidence intervals (CI) for sleep latency.

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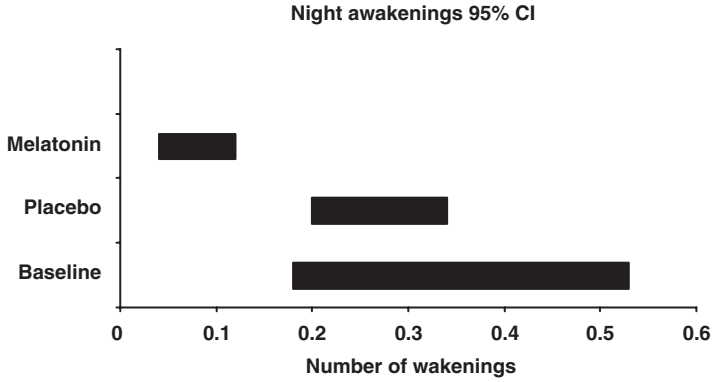

Figure 3. Graph of 95% confidence intervals (CI) for night awakenings.

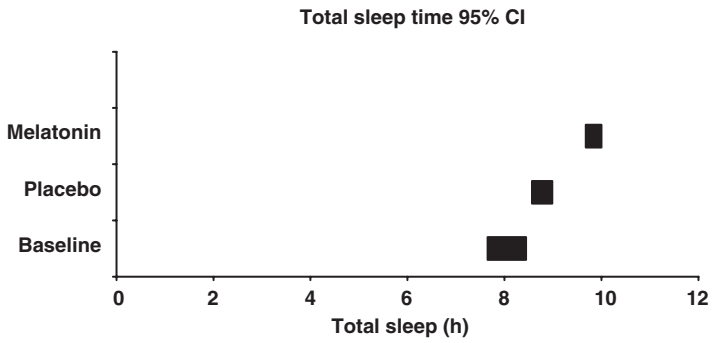

Figure 4. Graph of 95% confidence intervals (CI) for total sleep time.

parents. Three of the four children who dropped out were subsequently prescribed melatonin.

Discussion

Our study is unique in that it focuses purely on autistic children with sleep problems. Melatonin was beneficial but the study is small, so the results may not be generalizable.

Our sample size reflected huge difficulties in recruitment. The drug recall, mentioned previously, resulted in the trial having to be suspended for several months. Many local autistic children were already taking melatonin so were ineligible for the trial. Often parents of suitable children were unwilling to take part in the trial. There were many reasons for this. Some parents did not want to attend extra clinic appointments. Frequently, a request for melatonin was triggered by a crisis in addition to long-standing sleep problems leading to parents wanting treatment immediately.

Children should receive safe and effective drugs prescribed on the basis of best available evidence (Department of Health 2003). The European Union is proposing legislation to encourage and enforce more research into children's medicines. This is greatly needed.

A larger study is needed to confirm these results. Although ASD is a common condition, it is likely that other centres would experience similar recruitment difficulties and we recommend that a multicentre approach is used should this be studied in the future.

Acknowledgements

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