

# Melatonin and insomnia

C. M. ELLIS, G. LEMMENS and J. D. PARKES

University Department of Neurology, King's College School of Medicine and Dentistry and the Institute of Psychiatry

Accepted in revised form 18 August 1995; received 12 June 1994

**SUMMARY** The hypnotic action of melatonin 5 mg p.o. was explored in 15 subjects with psychophysiological insomnia in a double-blind controlled self-report questionnaire study. Melatonin or placebo was taken at 20.00 hours for a 1-week period in random order. Effects on sleep and wakefulness were monitored by visual analogue scale and structured interview. Bedtime, sleep onset time, estimated total sleep and wake time, as well as self-rated sleep quality, were not altered by melatonin, and estimates of next-day function did not change. The period of melatonin treatment was retrospectively correctly identified by 8 of 15 subjects. Despite unchanged ratings of night sleep quality on the last night of each treatment, 7 of 15 subjects reported that sleep had subjectively improved to a minor extent in the week of active treatment. Side-effects attributed to melatonin included headache and an odd taste in the mouth. These data indicate that melatonin is probably of no clinical value in the management of psychophysiological insomnia.

**KEYWORDS** melatonin, psychophysiological insomnia, therapeutic efficacy

## INTRODUCTION

There is an obvious relationship between the secretion of melatonin at night and sleep, and there has been considerable speculation about a physiological role for melatonin in normal sleep promotion since the discovery of this hormone (Barchas *et al.* 1967; Anton-Tay *et al.* 1971; Nakagawa *et al.* 1992). However, since nocturnal, as well as diurnal, animals secrete melatonin at night it cannot be directly related to sleep induction as a general rule (Arendt 1995). There is no definite association between melatonin profile and any sleep stage in humans but many studies have shown that melatonin, in addition to a phase-setting and entraining action in blind subjects, jet lag and the delayed sleep phase syndrome, has a definite sedative effect (Arendt *et al.* 1986; Sack *et al.* 1991; Dahlitz *et al.* 1991). During the initial development of melatonin Marczyński *et al.* (1964) showed that sleep could be induced by melatonin injection into the hypothalamus of unrestrained cats and Anton-Tay *et al.* (1971), Cramer *et al.* (1974) and Vollrath *et al.* (1981) showed that melatonin facilitates sleep onset or promotes sleepiness in humans. There is a complex relationship between body temperature, sleep and melatonin secretion with a reciprocal relationship between the low point

of temperature rhythm, which usually occurs during sleep at 02.00–04.00 hours, and peak plasma melatonin levels in humans (Cagnacci *et al.* 1992). Acute phase-shifting effects of melatonin have been linked to temperature reduction (Deacon *et al.* 1994) although it is still not clear if melatonin-associated lowering of temperature is associated with physiological sleep onset. Biological ageing is often associated with night sleep problems and daytime napping. Low plasma melatonin levels have been reported in elderly people, some of whom have been shown to have delayed onset and peak times of 6-sulphatoxy melatonin excretion (Iguchi *et al.* 1982; Haimov *et al.* 1994). Despite these observations, and a number of studies exploring the action of melatonin in both children with disturbed sleep and in insomniac adults (James *et al.* 1990; MacFarlane *et al.* 1991; Jan *et al.* 1994), the role of melatonin in the practical treatment of many different forms of insomnia, when this is not accompanied by any circadian disturbance, is uncertain.

Reported here is a study of short-term melatonin treatment in 15 subjects with severe psychophysiological insomnia, resistant to conventional medical or behavioural therapy.

## SUBJECTS AND METHODS

### Subjects

Fifteen subjects attending the Maudsley Hospital Sleep Disorders Clinic with the initial diagnosis of psychophysio-

*Correspondence:* Professor J. D. Parkes, Department of Neurology, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK. Fax: +44/(0)171 703 9989.

logical insomnia defined by ICSD criteria were investigated. Insomnia, combined with a complaint of decreased function during wakefulness had been present for 1–45 years (mean  $21.7 \pm 13$  y). This was combined with learned sleep-preventing associations. Nine subjects were male and 6 female, aged 32–67 y (mean  $46 \pm 11$  y). The mean estimated total sleep time (excluding periods of wakefulness) in these subjects was  $5.6 \pm 1.7$  h with a bed time of  $22.9 \pm 0.8$  h and wake-up time of  $5.6 \pm 1.8$  h. All these subjects had been previously treated with hypnotics and behavioural approaches to therapy but with the development of tolerance to benzodiazepines or zopiclone and, at the time of study, persisting severe insomnia. Patients taking benzodiazepines on a regular basis were excluded from the study. Four of 15 subjects on benzodiazepines and 4 on zopiclone on an occasional basis were withdrawn from all hypnotics a minimum of 14 days prior to the study.

All agreed to take part in a double-blind controlled short-term study of the action of melatonin vs. placebo. This study had the approval of the Maudsley Hospital/Institute of Psychiatry Ethics Research Committee.

### Medication

Melatonin capsules (oral 5 mg; Stockgrand Ltd, University of Surrey) and matched placebo capsules were taken at 20.00 hours, each for a consecutive 7-day period in random order.

### Assessment

This study was double-blind. A standard self-report questionnaire, using yes-no and visual analogue scales (VAS), was used to evaluate different aspects of sleep and wake behaviour over a 24-hour period. The following areas were evaluated:

- 1 Clock time of initial sleep preparation, bedtime, lights out time, initial sleep time, and duration of sleep and wake episodes whilst in bed.
- 2 Subjective assessments of sleep quality, pre-sleep and next-day mood, anxiety and sleepiness levels.
- 3 Check-list of subjective adverse effects including headache, fatigue, gastrointestinal discomfort.

Subjects were asked to complete the questionnaire at the start of the trial and on Days 8 and 15 of the trial, referring to the previous 24-h period (from Tuesday 20.00 hours to Wednesday 20.00 hours). This questionnaire was supplemented by a structured interview at the start and end of the trial. All subjects completed the Beck Depression Inventory (BDI) before commencing the trial.

The Wilcoxon paired rank test was used to analyse VAS scores between melatonin and placebo. VAS scores were also analysed using independent paired t-test and one way analysis of variance. Yes/no responses were expressed as a frequency and chi-squared tests were performed if the expected frequency in each cell was 4 or more. Pearson correlation coefficients were computed. Significant results were reported if  $P < 0.05$ .

### RESULTS

Results are shown in Table 1. Bedtime, sleep onset time, estimated total sleep and wake times as well as get-up times were similar in the pretreatment, melatonin and placebo period. Sleep quality, as estimated by rating scale, was poor in all three conditions and overall was not altered by melatonin or placebo treatment. Sleep environment as determined by quietness levels and security ratings did not change throughout this study. The mean number of recalled arousals throughout the sleep period in the pre-treatment period was  $2.3 \pm 1.8$ ; on melatonin  $2.1 \pm 2.1$  and on placebo  $1.92 \pm 1.5$  (NS all comparisons). Ratings of mental and physical fatigue, muscle stiffness and pain and anxiety level were similar in all study periods.

Eight of 15 subjects retrospectively correctly identified the melatonin period by the subjective occurrence of 'mental' as well as 'physical' fatigue in the 2–3-h period following the oral administration of melatonin. Of the remaining 7, 2 patients identified the placebo as the active drug and 5 subjects were not able to distinguish melatonin from placebo.

Of the 8 subjects who correctly identified the melatonin treatment period, 7 reported a subjective improvement in sleep. In response to the question 'how much has your present treatment altered your sleep?', mean ratings  $\pm$ SD (rating scale 0–100; worse–better) were, on melatonin  $68.6 \pm 7.7$ , and on placebo  $47.1 \pm 4.6$  ( $N=7$ ,  $P < 0.001$ ). One patient reported a deterioration on melatonin.

At the time of initial diagnosis of pathophysiological insomnia no patient was clinically depressed although depression of moderate severity, as determined by BDI rating scores, developed in 3 subjects prior to melatonin treatment. Of the 7 subjects who reported an improvement on melatonin, none had pre-treatment BDI scores suggestive of depression ( $< 5$  in all cases). Of the 7 patients who reported no effect or deterioration of sleep on melatonin, 3 were clinically depressed at the time of study with BDI scores of 12, 24 and 24, respectively.

Four subjects attributed possible adverse effects to melatonin. In all cases these were minor. Symptoms included mild headache on Day 1; slight headache; poor sleep quality; headache; odd taste in mouth; slight 'muzziness' 2 h after taking medication. One subject attributed extreme tiredness during the night with inability to sleep to placebo.

No correlation was found between any measured variable and age, sex, previous duration of insomnia or order of melatonin:placebo administration.

### DISCUSSION

Melatonin, given in a wide dose-range (0.1 mg–6 g daily), and administered by a number of routes (intranasal, intravenous and oral) has a mild and usually brief (2–4 h) sedative effect in normal subjects. Subjective fatigue, sleep promotion and performance decrement are usually minor as compared to the responses seen following conventional doses of benzodiazepines. In preliminary studies, melatonin given

**Table 1** Responses to melatonin and placebo

	Pre-treatment	Melatonin 5 mg	Placebo
<i>Sleep timings (clock times)</i>			
Initial bed preparation	22.50 ± 0.67	22.64 ± 0.60	22.60 ± 0.79
Bed time	22.86 ± 0.78	23.00 ± 0.56	23.02 ± 0.81
Lights out	23.16 ± 0.85	23.40 ± 0.51	23.41 ± 0.89
Sleep onset	24.06 ± 0.96	24.55 ± 1.68	24.39 ± 1.05
First wake	03.19 ± 2.80	03.60 ± 2.66	04.14 ± 2.39
Final wake	05.55 ± 1.82	05.63 ± 1.92	06.08 ± 1.30
Get up time	07.36 ± 0.89	07.21 ± 0.91	07.41 ± 0.91
Total sleep time (h)	05.60 ± 1.68	04.92 ± 1.63	05.28 ± 1.35
Total wake time in bed (h)	02.46 ± 1.45	02.71 ± 2.10	02.28 ± 1.60
Sleep efficiency	68%	63%	66%
<i>Sleep-wake ratings (0–100)</i>			
Sleep quality (poor–excellent)	47.9 ± 38.6	44.2 ± 34.9	46.2 ± 31.1
Subjective sleep duration (too short–too long)	28.5 ± 24.2	26.8 ± 16.5	29.6 ± 18.5
Excessive daytime sleepiness (none–great deal)	54.3 ± 31.0	41.8 ± 30.6	37.0 ± 24.0
Mood (depressed–happy)	58.0 ± 25.1	70.7 ± 15.4	60.5 ± 23.0
<i>Adverse effects</i>			
Mental fatigue (nil–great deal)	54.3 ± 31.8	53.0 ± 27.7	49.5 ± 25.9
Physical fatigue (nil–great deal)	47.2 ± 31.8	49.9 ± 29.9	46.2 ± 26.2
Muscle pain (nil–great deal)	15.5 ± 24.3	14.9 ± 17.4	14.7 ± 18.8
Subaltrtness (nil–great deal)	47.0 ± 31.8	44.8 ± 30.2	43.1 ± 24.4

Subjective responses in 15 subjects with severe insomnia given melatonin 5 mg p.o. or placebo at 20.00 hours, each for a 7-day period. Evaluation during last 24-h period on each treatment. No differences melatonin:placebo significant ( $P > 0.05$ ) Wilcoxon t-test.

intravenously in a dose of 0.25–1.75 mg kg<sup>-1</sup> body weight (Anton-Tay *et al.* 1971) or 50 mg (Cramer *et al.* 1974) reduced sleep latency or facilitated sleep onset in normal subjects. Vollrath *et al.* (1981) reported facilitated sleep onset with a sensation of well being after awakening following intranasal melatonin 1.7 mg given at 09.00–10.00 hours. During chronic (1 month) treatment, Arendt *et al.* (1985) showed that timed (17.00 hours) low-dose (2 mg daily) melatonin given to normal subjects consistently increased subsequent evening ratings of fatigue. Recently in a study of 20 healthy male volunteers, Dollins *et al.* (1994) have shown that melatonin 0.1–10 mg given at 11.45 hours causes sleepiness and fatigue as determined by self-report. There is also an increase in subsequent sleep duration with a decrease in sleep latency, oral temperature and the number of correct responses on the Wilkinson Auditory Vigilance Task. In all these studies the individual response to melatonin may depend to some extent on the exact experimental situation as well as the degree of monotony and levels of noise and illumination. An important observation from these studies, stressed by Tzischinsky and Lavie (1994) is that the effect of melatonin on sleep propensity is somewhat delayed.

A number of dose-ranging studies of the effect of melatonin have been done. Dollins *et al.* (1993, 1994) found a dose-related increase in sedation over the range melatonin 0.1, 0.3 and 1 mg with the 0.1 and 0.3 mg doses generating peak serum melatonin levels within the normal range of nocturnal melatonin in untreated people. Ingestion of 10 mg had approximately the same effect as 1 mg. Plasma concentrations of melatonin in

man following oral absorption of different preparations vary widely (Aldhous *et al.* 1985). Thus direct comparison between different individuals and different studies is difficult. However, using supraphysiological doses of melatonin (6 g daily orally for 1 month; 80 mg orally, single dose: Waldhauser *et al.* 1984, 1990) the observed sedative effect may not be much greater than that reported in different studies following lower dosages. Dollins *et al.* (1994) highlighted the finding that the pattern of physiological and performance responses after melatonin resembles that observed following drugs of the benzodiazepine family. However, in the present authors' experience melatonin is not an effective hypnotic drug in the treatment of insomnia. It may also lack the anxiolytic, muscle relaxant and anti-epileptic effects of benzodiazepines. The dose–response relationships of melatonin and benzodiazepines, as well as the nature and distribution of brain receptors, are different.

Melatonin, despite a minor sedative effect in both normal and insomniac subjects, may have little or no important clinical effects in the treatment of psychophysiological insomnia. Waldhauser *et al.* (1990), in a study of 20 young subjects, induced insomnia experimentally using traffic noise. In this situation a single pharmacological dose of melatonin reduced sleep latency and improved sleep maintenance as compared to placebo. In 10 adults with persistent insomnia, given melatonin 1 mg and 5 mg by James *et al.* (1990), there was a minor overall subjective improvement in sleep quality although no major change in electroencephalographically recorded sleep was found. Comparable subjective findings were reported by

MacFarlane *et al.* (1991) in a group of 13 insomniac subjects given higher melatonin dosages (75 mg) for 14 consecutive days at 22.00 hours. This caused a partial increase in the subjective assessment of total sleep time and daytime alertness. In a group of 15 children with brain damage accompanied by behavioural and sleep disorders, fragmented sleep patterns or delayed sleep onset Jan *et al.* (1994) found in an open study that melatonin 2–10 mg improved these problems. In contrast, in the present study of 15 adult subjects with psychophysiological insomnia, melatonin had no subjective effect on any measured aspect of sleep. These subjects had previously shown an initial hypnotic response to benzodiazepines or zopiclone despite the eventual development of tolerance, waking hangover or depression.

Melatonin has phase-shifting and entraining actions in human subjects. Many totally blind people have free-running melatonin rhythms although these are not necessarily associated with periodic insomnia or daytime sleepiness. Nakagawa *et al.* (1992) reported a 44-year-old totally blind man who maintained a conventional sleep schedule and did not complain of significant insomnia in his normal environment. When studied using an ultra-short sleep/wake schedule his sleep propensity free ran with melatonin, temperature and cortisol rhythms in keeping with the concept that melatonin has a physiological role in normal sleep induction. Sack *et al.* (1991) investigated 5 totally blind men with free-running endogenous melatonin rhythms and found that these were phase-advanced by exogenous melatonin, with, in 3 subjects, a phase-shift in cortisol rhythm. Light therapy, with phase-shifting of the melatonin rhythm, has been used as a treatment for sleeping problems in seasonal affective disorders (Weydahl 1994). In humans with the delayed sleep phase syndrome where sleep onset and wake times occur far later than normal, as well as in an animal model of this syndrome, melatonin causes a partial but not complete phase-advance of the major sleep period (Dahlitz *et al.* 1991; Armstrong *et al.* 1993). In the overall population the delayed sleep phase syndrome may be an important contributor to complaints of sleep onset insomnia. In 18 young adults, studied in an ultra-short 7/13 sleep/wake paradigm, after an overnight sleep deprivation, Tzischinsky and Lavie (1994) have made the important observation that pharmacological doses of melatonin (5 mg) had a definite hypnotic effect in a time-dependent manner across a 24-hour cycle. As well as subjective sleepiness, melatonin increased electroencephalographic measures of sleep propensity and there was a significant decrease in oral temperature. The latency from melatonin administration to maximum increase in sleep propensity varied from 1 h at 21.00 hours to 3 h 40 min at 12.00 hours. The time of melatonin administration in both circadian and sleep/wake studies is critical.

#### ACKNOWLEDGEMENTS

CE was supported by Kings Healthcare Neurology Research Fund. We gratefully acknowledge the assistance of Judy Grimshaw.

#### REFERENCES

- Aldhous, M., Franey, C., Wright, I. and Arendt, J. Plasma concentration of melatonin in man following oral absorption of different preparations. *Br. J. Clin. Pharmacol.*, 1985, 19: 517–521.
- Anton-Tay, F., Diaz, J. and Fernandez-Guardiola, B. On the effect of melatonin on human brain and its possible therapeutic implications. *Life Sci.*, 1971, 10: 841–850.
- Arendt, J., Bojkowski, C., Folkard, S., Franey, C., Marks, V., Minors, D., Waterhouse, J., Wever, R.A., Wildgruber, C. and Wright, J. Some effects of melatonin and the control of its secretion in humans. *Ciba Found. Symp.*, 1985, 117: 266–283.
- Arendt, J., Aldhous, M. and Marks, V. Alleviation of jet lag by melatonin: preliminary results of controlled double blind trial. *Br. Med. J.*, 1986, 292: 1170.
- Arendt, J. Association with sleep. In: *Melatonin and The Mammalian Pineal Gland*. Chapman & Hall, London, 1995: 212–213.
- Armstrong, S.M., McNulty, O.M., Guardiola-Lemaitre, B. and Redman, J.R. Successful use of S20090 and melatonin in an animal model of delayed sleep phase syndrome. *Pharmacol. Biochem. Behav.*, 1993, 46: 45–49.
- Barchas, J., De Costa, F. and Spector, S. Acute pharmacology of melatonin. *Nature*, 1967, 214: 919–920.
- Cagnacci, A., Elliott, J. and Yen, S. Melatonin: a major regulator of the circadian rhythm of core temperature in humans. *J. Clin. Endocrinol. Metab.*, 1992, 75: 447–452.
- Cramer, H., Rudolph, J., Consbraun, U. and Kendel, K. On the effects of melatonin on sleep and behaviour in men. *Adv. Biochem. Psychopharmacol.*, 1974, 11: 187–191.
- Dahlitz, M.J., Alvarez, B., Vignau, J., English, J., Arendt, J. and Parkes, J.D. Delayed sleep phase syndrome response to melatonin. *Lancet*, 1991, 337: 1121–1124.
- Deacon, S., English, J. and Arendt, J. Acute phase-shifting effects of melatonin associated with suppression of core body temperature in humans. *Neurosci. Lett.*, 1994, 178: 32–34.
- Dollins, A.B., Lynch, H.J., Wurtman, R.J., Deng, M.H., Kischka, K.U., Gleason, R.E. and Harris, H.R. Effect of pharmacological daytime doses of melatonin on human mood and performance. *Psychopharmacology*, 1993, 112: 490–496.
- Dollins, A.B., Zhdanova, I.V., Wurtman, J.R., Lynch, H.J. and Deng, M.H. Effect of inducing nocturnal serum melatonin concentrations in daytime on sleep, mood, body temperature, and performance. *Proc. Natl. Acad. Sci. USA*, 1994, 91: 1824–1828.
- Haimov, I., Laudon, M., Zisapel, N., Souroujon, M. Nof D., Schlitner, A., Herer, P., Tzischinsky, O. and Lavie, P. Sleep disorders and melatonin rhythms in elderly people. *Brit Med J.* 1994, 309: 167.
- Iguch, H., Kato, K. and Ibayashi, H. Age-dependent reduction in serum melatonin concentrations in healthy human subjects. *J. Clin. Endocrinol. Metab.*, 1982, 55: 27.
- James, S.P., Sack, D.A., Rosenthal, N.E. and Mendelson, W.B. Melatonin administration in insomnia. *Neuropharmacology*, 1990, 3: 19–34.
- Jan, J.E., Espezel, H. and Appleton, R.E. The treatment of sleep disorders with melatonin. *Dev. Med. Child Neurol.*, 1994, 36: 97–107.
- MacFarlane, J.G., Cleghorn, J.M., Brown, G.M. and Streiner, D.L. The effects of exogenous melatonin on the total sleep time and daytime alertness of chronic insomniacs: a preliminary study. *Biol. Psychiatry*, 1991, 30: 371–376.
- Marczynski, J.J., Yamaguchi, N., Ling, G.M. and Grodzinska, L. Sleep induced by the administration of melatonin to the hypothalamus of unrestrained cats. *Experientia*, 1964, 20: 436–437.
- Nakagawa, H., Sack, R.L. and Lewy, A.J. Sleep propensity free-runs with the temperature, melatonin and cortisol rhythm in a totally blind person. *Sleep*, 1992, 15: 330–336.

- Sack, R.L., Lewy, A.J.K., Blood, M.L., Stevenson, K. and Keith, L.D. Melatonin administration to blind people: phase advances and entrainment. *J. Biol. Rhythms*, 1991, 6: 249-261.
- Tzischinsky, O. and Lavie, P. Melatonin possesses time-dependent hypnotic effects. *Sleep*, 1994, 17: 638-645.
- Vollrath, L., Semm, P. and Gammel, G. Sleep induction by intranasal application of melatonin. *Bio Sciences*, 1981, 29: 327-329.
- Waldhauser, F., Lynch, H.S. and Wurtman, R.F. Melatonin in human body fluids; clinical significance In: L. Reiter RD (Ed.) *The Pineal Gland*. Raven Press, New York, 1984: 345-369.
- Waldhauser, F. Saletu, B. and Trinchar-Lugan, I. Sleep laboratory investigations on hypnotic properties of melatonin. *Psychopharmacol. Berl.*, 1990, 100: 222-226.
- Weydahl, A. Evening melatonin in January after changes to hour of habitual exercise during fall among youths living in the subarctic. *Arctic Med. Res.*, 1994, 53: 146-151.