Improvement of sleep quality in elderly people by controlled-release melatonin

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Summary

Melatonin, produced by the pineal gland at night, has a role in regulation of the sleep-wake cycle. Among elderly people, even those who are healthy, the frequency of sleep disorders is high and there is an association with impairment of melatonin production. We investigated the effect of a controlled-release formulation of melatonin on sleep quality in 12 elderly subjects (aged 76 [SD 8] years) who were receiving various medications for chronic illnesses and who complained of insomnia.

In all 12 subjects the peak excretion of the main melatonin metabolite 6-sulphatoxymelatonin during the night was lower than normal and/or delayed in comparison with non-insomniac elderly people. In a randomised, double-blind, crossover study the subjects were treated for 3 weeks with 2 mg per night of controlled-release melatonin and for 3 weeks with placebo, with a week's washout period. Sleep quality was objectively monitored by wrist actigraphy. Sleep efficiency was significantly greater after melatonin than after placebo (83 [SE 4] *vs* 75 [3]%, $p<0.001$) and wake time after sleep onset was significantly shorter (49 [14] *vs* 73 [13] min, $p<0.001$). Sleep latency decreased, but not significantly (19 [5] *vs* 33 [7] min, $p=0.088$). Total sleep time was not affected. The only adverse effects reported were two cases of pruritus, one during melatonin and one during placebo treatment; both resolved spontaneously.

Melatonin deficiency may have an important role in the high frequency of insomnia among elderly people. Controlled-release melatonin replacement therapy effectively improves sleep quality in this population.

Lancet 1995; **346:** 541–44

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Introduction

Sleep disturbances become more common with age. The high frequency of sleep complaints in elderly people may result from primary endogenous, age-related sleep disorders and the increased likelihood of disease and the use of drugs, which can cause secondary sleep disorders.[1]

Several studies have shown an age-related deterioration in the circadian time-keeping system; consequently, the amplitudes of core body temperature and endocrine rhythms are reduced in old age.[2] Melatonin (N-acetyl-5-methoxytryptamine), which is produced by the pineal gland at night,[3] can reset sleep onset through its synchronising effect on the internal biological clock.[3,4] Melatonin is rapidly metabolised by the liver and more than 85% is excreted in urine as 6-sulphatoxymelatonin (6-SMT). Urinary excretion of 6-SMT can therefore serve as a reliable measure of the serum melatonin profile.[5]

Serum melatonin concentrations decrease in old age.[6] We found that urinary 6-SMT excretion was significantly lower and the onset of excretion and peak time were delayed in healthy elderly people who had insomnia compared with age-matched controls who had no sleep disorders.[7] The impairment in melatonin production may contribute to the increased frequency of sleep disorders in the elderly. On the other hand, completely unrelated factors may lead to disturbed sleep in this age group. For example, the age-related increase in chronic diseases, particularly those causing pain, shortness of breath, urinary frequency, and gastrointestinal discomfort, and the side-effects of drugs (eg, nausea, sweating, itching, or urinary frequency) may also cause repeated awakenings and impaired sleep. Apart from the non-specific adverse effects of drugs on the quality of sleep, some drugs may specifically impair sleep by inhibiting or distorting the melatonin rhythm. Benzodiazepines, the most commonly used drugs in the treatment of insomnia, can potentiate inhibition of melatonin synthesis and secretion induced by γ-aminobutyric acid.[8] Beta-blockers, widely used for treatment of hypertension and heart disorders, may be associated with impairment of sleep; they inhibit melatonin production by binding to pineal beta-adrenoreceptors.[5]

Oral, intranasal, or intravenous administration of exogenous melatonin enhances daytime sleep, with normal or enhanced rapid eye movement (REM) electroencephalographic patterns, but the effects on nocturnal sleep are equivocal.[4] Melatonin is short-lived with a half-life in serum of only 40–50 min; serum concentrations reach a peak within 20 min of oral administration and then fall rapidly.[3] Thus, to maintain effective serum concentrations of melatonin throughout the night sleep, high-dose or repeated low-dose

administration is required. We have investigated a controlled-release formulation of melatonin (2 mg), which was designed to maintain effective concentrations of the hormone throughout the night.

We found previously that in healthy elderly people with reduced melatonin production, one week of treatment with controlled-release melatonin increased sleep maintenance, whereas treatment with the normal fast-release preparation of melatonin improved sleep initiation only.[9,10] The main objectives of this investigation were to measure 6-SMT excretion in unhealthy elderly insomniac patients who were receiving various drugs, and to assess the effect of controlled-release melatonin replacement therapy on the quality of their sleep.

Subjects and methods

The study population was recruited after a lecture on sleep disorders in a residential centre for senior citizens. Of the first 15 volunteers, three were excluded after the initial assessments because of dementia or poor compliance. 12 independently living elderly subjects took part (seven male, five female; mean age 76 [range 68–93; SD 8]). They all complained of long-term insomnia. Six participants had hypertension, five ischaemic heart disease, four spondyloarthrosis, three Parkinson's disease, and two diabetes mellitus. None had liver or renal disorders (serum creatinine below 133 μmol/L). All subjects were taking between one and six different drugs (mostly nitrates, calcium-channel blockers, diuretics, aspirin, beta-blockers, and analgesics) and also used at least one kind of sleep medication.

The study protocol was approved by the local ethics committee and health authorities. The aims, methods, expected benefits, and potential side-effects of the replacement therapy were explained to the participants in non-technical terms. Throughout the study period subjects had free access to the physician, and they have been interviewed and checked at least once a week. Before the study started, the subjects were woken every 3 h during one night (1800–0600 h), with the aid of a trained technician. Urine was collected, the volume was measured, and 1 mL samples from each collection were frozen until measurement of urinary 6-SMT in duplicate by radioimmunoassay (Stockgrand Ltd, Surrey, UK).[5]

Several days later, the quality of sleep was objectively assessed in each subject by wrist actigraphy for 3 consecutive nights. Actigraphy is an established method, based on wrist movements, that can automatically discriminate sleep-wake patterns.[11] Actigraphic estimates of sleep variables show high correlation with corresponding variables scored by polysomnography (0·82–0·90, $p<0·0001$).[11] Furthermore, the method was sufficiently sensitive to detect the effects of insomnia treatment in elderly subjects.[12] Actigraphy enables monitoring of the natural circumstances of sleep with negligible distortion, while subjects are sleeping at home in their own beds, and it is most suitable for long-term studies. The actigraph (Somnitor, Neurim Pharmaceuticals, Tel-Aviv, Israel) is a small computerised device attached to the wrist; it continuously records wrist movements over several consecutive nights. Motion recordings were analysed by an automatic scoring algorithm to determine sleep variables:[11] latency (time between bedtime and sleep onset), efficiency (total time asleep as a percentage of total time in bed), total sleep time (time spent asleep after sleep onset), and wake after sleep onset (WASO; accumulated time awake after sleep onset).

In a randomised, double-blind, crossover design, the subjects were given tablets of 2 mg controlled-release melatonin (Circadin, Neurim Pharmaceuticals) or a placebo identical in appearance, which contained the inactive ingredients but not melatonin. The tablets were taken 2 h before desired bedtime every night for 3 weeks. After a washout period of a week the subjects received 3 weeks' treatment with the other preparation. During the treatment periods, patients, investigators, and co-workers were unaware of which drug had been given. The randomisation code was known to the pharmacist who prepared the tablets in containers. Treatment codes were broken after all study results had been obtained.

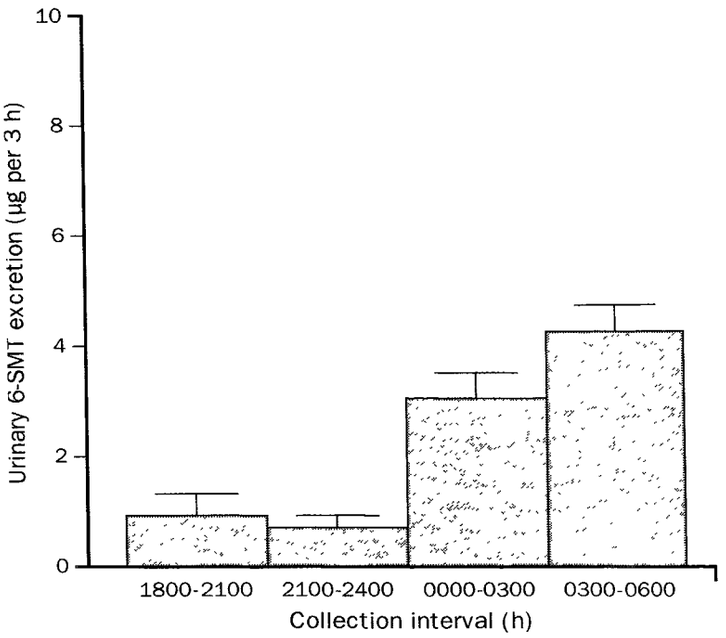

Figure: **6-SMT excretion in urine samples collected every 3 h during the night**
Data are mean (SE) of 3-night averages for each subject.

Sleep quality was monitored at the end of each 3-week treatment period for 3 consecutive nights. For each variable, the average of the 3 nights was calculated for all subjects. Two-tailed *t* tests for dependent samples were used for comparisons of the two treatments. All the subjects completed the study and no data were missing.

Results

The mean amount of 6-SMT excreted in urine per hour was higher between 0300 and 0600 h than during the other collection periods (figure). In comparison with elderly people without insomnia in our previous study[7] the peak excretion of 6-SMT was delayed in all 12 participants in this study; the peak began at 0300 h rather than midnight. In the urine collection encompassing 0200 h, the normal peak time, the absolute values were low (mean 0·93 μg/h [range 0·03–2·1]) compared with values in young adults (5·3 μg/h) and age-matched healthy individuals without sleep disturbances (3·7 μg/h).[7]

Sleep variables after the placebo period did not differ significantly from pretreatment values, although a trend towards longer latency was noted with the placebo (table). However, the melatonin and placebo periods differed significantly in sleep efficiency and WASO ($p<0·001$, table). A trend towards lower sleep latency was noted with melatonin ($p=0·088$). Total sleep time was not significantly affected by melatonin treatment.

Variable	Mean (SE; range) of 3-night average for each subject			
	Pretreatment	After 3 weeks of placebo	After 3 weeks of melatonin	p*
Sleep efficiency (%)	75 (3; 52–92)	75 (3; 53–89)	83 (4; 56–96)	<0·001
Latency (min)	27 (3; 19–53)	33 (7; 10–102)	19 (5; 3–49)	0·088
WASO (min)	82 (18; 12–209)	73 (13; 10–179)	49 (14; 6–194)	<0·001
Total sleep time (min)	352 (19; 251–462)	365 (20; 249–535)	360 (21; 212–508)	0·49

*For difference between melatonin and placebo by two-tailed *t* test for dependent samples.

Table: **Sleep variables obtained by actigraphy**

The treatment was well tolerated. No definite adverse effects of melatonin were reported. One subject complained of pruritus during melatonin treatment and another reported pruritus during placebo treatment. In both cases, the itching resolved spontaneously.

Discussion

This study shows that despite the presence of chronic diseases and the use of drugs, controlled-release melatonin has an overall beneficial effect on sleep quality in melatonin-deficient elderly people. The therapeutic effects of melatonin on circadian-based sleep disorders in blind people, travellers with jet-lag, and patients with delayed-sleep-phase syndrome are well established.[4] In people with chronic insomnia[13] and in healthy adults with artificially induced insomnia,[14] however, melatonin in doses of 1–75 mg given for up to a week failed to show consistent hypnotic effects, though there was some improvement of sleep.

Before treatment the sleep variables in our 12 subjects were similar to those previously reported for insomniac elderly people.[15] These findings objectively confirmed our subjects' complaints of poor sleep quality. After 3 weeks' treatment with controlled-release melatonin, values for both sleep efficiency and WASO were similar to actigraphic and polysomnographic values reported for healthy elderly people without insomnia.[7,15] There are several possible explanations of why a significant improvement of sleep quality by melatonin was found in this study but not in previous investigations. First, all our subjects had documented melatonin deficiency, whereas in other studies the subjects may not have had distorted melatonin rhythms. The decline in 6-SMT excretion in the elderly parallels a similar decrease in plasma melatonin.[16] We have shown that 6-SMT excretion in elderly people without insomnia does not differ significantly from that of young adults.[7] Thus, urinary 6-SMT excretion may be regarded as a valid measure of melatonin rhythm in the elderly. None of our subjects had impaired liver or renal function, so the low 6-SMT excretion probably reflects impaired melatonin production. Second, the use of a controlled-release melatonin formulation enables maintenance of effective melatonin concentrations throughout the night with a single low dose of melatonin. High doses of fast-release melatonin may also be used to achieve effective concentrations throughout the night with no toxic effects.[3] However, in rats melatonin negatively regulates its receptors.[17] Although no such effects have been shown in human beings, it is possible that high melatonin concentrations may desensitise the brain to the hormone. Third, the longer duration of treatment we used might have caused the difference; in a previous study of a regular melatonin formulation for only 1 week, a similar beneficial effect was found but the results did not reach statistical significance.[9] We have observed that treatment for 2 months with controlled-release melatonin in healthy elderly subjects gave much better results than 1 week of treatment.[9,10]

Why is a long duration of treatment necessary to establish beneficial effects of melatonin replacement therapy? Upregulation of melatonin receptors may be needed. In aged rats, the density and diurnal rhythm of melatonin binding sites at specific brain areas is reduced,[18,19] and melatonin administered in drinking water for 30 days augmented the density of melatonin binding sites in some of these areas.[20] If such mechanisms occur in human beings, melatonin-deficient, insomniac elderly people may have reduced amounts of melatonin receptors; they would therefore require long-term melatonin exposure to restore specific sensitivity to this hormone. Another possible explanation is that synchronising effects of melatonin on the biological clock are involved. These synchronising effects are manifested only at specific times of the day.[21] As a result of deterioration of the biological clock in the elderly, the synchronising effects of melatonin on the brain might phase out of the day/night cycles. Hence, exogenous melatonin given at night may not coincide with the peak responsiveness to this hormone and several days of treatment may be needed to align the sleep/wake cycle with day/night cycles.

We believe that melatonin-deficiency-related insomnia is common, whether caused by ageing, drug treatment, or both. The rational therapeutic approach to insomnia should start with an attempt to identify diseases and drugs that may secondarily impair normal sleep. Such diseases should be treated or offending drugs withdrawn or their dosage reduced. The next step would be the evaluation of nocturnal melatonin profile by measurement of 6-SMT in urine. Whenever melatonin deficiency is found, melatonin replacement therapy (preferably with a controlled-release preparation) can be tried for at least 3 weeks. If a beneficial effect on sleep is achieved, gradual reduction of doses of sleep medications should be attempted during melatonin replacement therapy. This approach has been successfully accomplished in some of the subjects reported here after only 2–3 months of replacement therapy with controlled-release melatonin.

We thank Dr J Atsmon for fruitful discussions and Ms A Karasic and Ms S Dudai for excellent technical assistance.

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Linkage to *BRCA2* region in hereditary male breast cancer

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Breast cancer is rare in men, and family history of the disease is a risk factor. The recently discovered *BRCA2* gene on chromosome 13q is thought to account for some families with increased risk of breast cancer, including male breast cancer. We descibe a family with multiple cases of male breast cancer but, interestingly, no increase in female breast cancer. Linkage to the *BRCA2* region is demonstrated and all the affected men share the same haplotype for the *BCRA2* markers and loss of the other alleles in their tumours.

Lancet 1995; **346:** 544–45

Carcinoma of the breast is about a hundredfold less common in men than in women and accounts for about 1% of all male cancers. The risk of female breast cancer in relatives of men with the disease may be increased and male relatives of female patients are also at increased risk of breast cancer.[1,2] Endocrine factors have a role in the development of some male breast cancers, and mutations in the androgen receptor gene have been found in at least two families with familial male breast cancer.[3,4]

Familial susceptibility to early-onset breast and ovarian cancer in women has been linked to the *BRCA1* gene on chromosome 17q, but male breast cancer is rare in families with *BRCA1* mutation.[5] Linkage to the more recently identified *BRCA2* locus on chromosome 13q has been found in pedigrees with a high frequency of female breast cancer and there also appears to be increased risk of breast cancer in men in some of the families.[6] The *BRCA2* gene itself has not been isolated. Germline mutations in the *TP53* gene have mainly been found in families with the Li-Fraumeni syndrome and are thought to be responsible only for a very small proportion of familial breast cancer.[7]

We have examined a family with four male breast-cancer patients, three brothers and a cousin. An abridged version of the pedigree shows how the patients are related (figure). The proband in this family was a 67-year-old woman diagnosed with breast cancer in 1922. The expanded pedigree includes 252 men and 229 women with three female and four male cases of breast cancer, and 32 cases with 41 malignant tumours (7 breast, 5 thyroid, 5 stomach, 4 prostate, 3 urinary bladder, 3 sarcomas, 3 tumours of the uterine corpus, and 1 each of cancer of the ovary, oesophagus, colon, pancreas, lung, kidney, peritoneum, and unknown origin). The cancers in this family do not fit any obvious syndrome patterns. In generation II, cancers occurred in five of seven sibs; in generation III, 13 of 34 family members have been diagnosed with cancer. Four of the breast cancer patients are first-degree relatives (three brothers and their sister). The age at diagnosis for the breast cancer cases was 46, 60, and 67 for the women and 46, 63, 72, and 79 for the men. The breast cancer cases in the family are not different from sporadic breast cancer in clinical behaviour and survival.

The androgen receptor gene is on the X chromosome and can therefore be excluded as a cancer predisposition gene in this pedigree on the basis of male to male transmission. Serum levels of oestrogen, testosterone, luteinising hormone, and prolactin were normal in affected and non-affected family members. All affected men in this family are fertile and have children. Mutations in exons 5–8 of the *TP53* gene were not found in tumour samples from affected men. Linkage to the *BRCA1* gene has been excluded in this family.[5]

Polymorphic microsatellite-repeat markers that flanked the *BRCA2* locus were used for linkage analysis. Samples from 24 individuals in three generations were analysed.

DNA was extracted from lymphocytes, fresh tissue, and/or paraffin sections. DNA was amplified by PCR with one primer labelled on the end with [γ^{32}P]-ATP with T4 polynucleotide kinase. The PCR product was subjected to electrophoresis on 6% denaturing polyacrylamide gels and made visible by autoradiography. Seven markers in the *BRCA2* chromosome region were used to examine haplotype sharing in affected individuals (figure). Allele frequencies were estimated from a random sample of 95 unrelated individuals from the same population.

Two-point lod (logarithm of the odds of linkage) scores were computed for each of the markers 13S260 and 13S267 with the LINKAGE program.[8] Cancers besides breast cancer were ignored. We used the liability classes and their "penetrance" probabilities from Easton et al.[9] Male breast-cancer cases were assigned to the same liability class as female cases under the age of 30 on the assumption that this rare disease in men is likely to result from genetic predisposition.

The lod score for marker 13S260 in this family was 0·51. That for 13S267 was 0·30. The same haplotype was found in all the male breast-cancer cases and one female case (figure). Surprisingly the youngest affected woman (aged 46) did not share this haplotype. No sample was available from one breast-cancer case (proband, diagnosed in 1922). The youngest affected man (aged 46)