



## Improvement of sleep quality by controlled-release melatonin in benzodiazepine-treated elderly insomniacs

D. Garfinkel<sup>a</sup>, M. Laudon<sup>b</sup>, N. Zisapel<sup>c,\*</sup>

<sup>a</sup>*Aging Research, Day Care Unit, The E. Wolfson Medical Center, Holon 58100 and Meonot Maccabi, 7 Hanna Senech St., Bat-Yam 59303, Israel*

<sup>b</sup>*Neurim Pharmaceuticals Ltd., 8 Hanachoshet St., Tel-Aviv 69710, Israel*

<sup>c</sup>*Department of Neurobiochemistry, Faculty of Life Sciences, Tel-Aviv University, Tel-Aviv 69978, Israel*

Received 18 June 1996; revised 18 July 1996; accepted 19 July 1996

---

### Abstract

Benzodiazepines are widely used in the elderly population for the initiation of sleep. However, very frequently, complaints about poor sleep maintenance persist despite benzodiazepine treatment. Melatonin, a hormone produced by the pineal gland at night, is involved in the regulation of the sleep/wake cycle. Melatonin production decreases with age and can also be inhibited by benzodiazepines. We have recently reported on the association between insomnia and impaired melatonin output in the elderly. In the present study we have investigated the efficacy of melatonin replacement therapy in improving sleep in 21 elderly subjects who have been taking benzodiazepines and had low melatonin output. In a randomized, double-blind, crossover designed study the subjects were treated for three weeks with 2 mg per night of controlled-release melatonin and for 3 weeks with placebo, 2 h before desired bedtime with a 1-week washout period between treatment periods. Subjects' sleep was assessed by wrist actigraphy. Melatonin treatment significantly increased sleep efficiency and total sleep time and decreased wake after sleep onset, sleep latency, number of awakenings and fragmental index, as compared to placebo. The results of our study indicate that melatonin replacement therapy can improve sleep quality in the elderly and that the beneficial effects are augmented in the presence of benzodiazepines. Copyright © 1997 Elsevier Science Ireland Ltd.

---

\* Corresponding author.

**Keywords:** Melatonin; Benzodiazepines; Insomnia; Elderly

---

## 1. Introduction

The incidence of sleep disturbances increases with age; in comparison to younger adults, healthy older individuals take a longer time to fall asleep, awaken frequently during night, have less slow-wave sleep and decreased total sleep time. The high frequency of sleep complaints reported in the aged may result from a primary endogenous, age-related sleep disorder, or from the increased incidence of diseases, which may cause secondary sleep disorders. The latter include chronic diseases and particularly those associated with pain, dyspnea, nocturia and gastrointestinal discomfort as well as side effects of drugs. Several studies indicate an age related deterioration of the circadian time-keeping system in man; consequently, the amplitudes of core body temperature and endocrine rhythms are reduced in old age (Arendt, 1988). Melatonin (*N*-acetyl-5-methoxy-tryptamine), a hormone produced by the pineal gland at night, can reset sleep onset in humans through its synchronising effect on the internal biological clock (Arendt et al., 1985; Dawson and Encel, 1993). Melatonin is rapidly metabolized by the liver (Kveder and McIssac, 1961) and over 85% is eliminated in the urine as 6-sulphatoxy-melatonin (6-S-MT) (Kopin et al., 1961; Waldhauser et al., 1984). Therefore, the urinary excretion of 6-S-MT can serve as a reliable measure of serum melatonin profile (Arendt et al., 1985). Serum melatonin concentrations decrease in old age (Sharma et al., 1989). We reported that in healthy elderly people suffering from insomnia, urinary 6-S-MT was significantly lower and its onset and peak time delayed, in comparison to age-matched controls with no sleep disorders (Haimov et al., 1994). Similarly, in elderly females, 6-sulphatoxy melatonin levels were found to be significantly lower in poor compared to good sleepers (Lushington et al., 1995).

These findings suggest that primary impairment in melatonin production may contribute to the increased incidence of sleep disorders in the aged, apart from the secondary factors. There is an age related increase in drug consumption due to the increase in age-related diseases, and this too may interfere with normal sleep. Indeed, the incidence of drug-related sleep disorders also increases with age and is found in 7% of the elderly but only in 0.1% of young adults.

Intriguing in particular is the relationship between melatonin and benzodiazepines, the most commonly used drugs in the treatment of insomnia. Benzodiazepines can potentiate gamma-amino-butyric acid (GABA) –induced inhibition of melatonin synthesis and secretion in some species including man. They suppress the nocturnal rise in plasma melatonin and shift its day–night rhythmicity (McIntyre et al., 1988).

The effects of exogenous melatonin on sleep have been recently reviewed (Dawson and Encel, 1993). Oral, intranasal and intravenous administration of melatonin has been reported to enhance daytime sleep in various species including man, but its effect on nocturnal sleep is equivocal. Melatonin is short-lived and its half life is

only 40–50 min; peak serum concentrations are reached within 20 min of oral administration and then decay rapidly. Hence, in order to maintain effective serum concentrations of melatonin for several hours, high doses or repeated administration of low doses are required. We therefore decided to use a controlled-release formulation of melatonin which was designed to maintain effective levels of the hormone throughout the night. We found previously that in elderly people with reduced melatonin production, treatment with controlled-release melatonin increased sleep maintenance (Garfinkel et al., 1995), sleep latency improved but not significantly. On the other hand treatment with the normal fast-release preparation of melatonin improved sleep initiation only (Haimov et al., 1995). The main objectives of this investigation were to measure 6-S-MT excretion in unhealthy elderly insomniac patients who were receiving benzodiazepines, and to assess the effect of controlled-release melatonin replacement therapy on the quality of their sleep.

## 2. Materials and methods

The study population was recruited following a lecture on sleep disorders in a residential center for senior citizens. Twenty-one independently living elderly subjects (13 men, eight women; mean age 79 (range, 68–93) years (S.D. = 5.2)) participated. They all complained of long-term insomnia. The participants suffered from a variety of chronic diseases: hypertension was present in six, ischemic heart disease in 10, spondyloarthritis in four, Parkinson's disease in three and diabetes mellitus in two. None had liver or renal problems (serum creatinine less than 1.5 mg/dl). All subjects used at least one kind of benzodiazepine-containing medication. The study protocol was approved by the local ethics committee and health authorities.

Before entering the study, subjects were awoken at 3-h intervals overnight (18:00–06:00 h), with the aid of an expert technician. Urine was collected, volume was measured and urine samples (1 ml) from each collection period were then frozen until assayed. Urinary 6-S-MT was assayed in duplicate by RIA (Stockgrand Ltd., Surrey, UK). Several days afterwards, the quality of sleep was objectively assessed in each subject by wrist-actigraphy for three consecutive nights. Actigraphy is an established method, based on wrist movements, which can automatically discriminate sleep–wake patterns. Actigraphic estimates of sleep parameters show high correlations with corresponding parameters scored by polysomnography (0.82–0.90,  $P < 0.0001$ ; Cole et al., 1992). Furthermore, the actigraph was found to be sufficiently sensitive to detect the effects of hypnotic treatment in elderly subjects (Brooks et al., 1993). Actigraphy enables monitoring of the natural circumstances of sleep with minimal distortions, while subjects are sleeping at home in their own beds, and it is most suitable for long-term studies.

The actigraph used by us (Somnitor™, Neurim Pharmaceuticals, Tel-Aviv, Israel), is a small computerized device attached to the wrist that continuously records wrist movements over several consecutive nights. Motion recordings are

analyzed using an automatic scoring algorithm to determine sleep parameters. Latency (time between bedtime and sleep onset), Efficiency (percent of total time asleep out of total time in bed), total sleep time (TST, time spent asleep after sleep onset), wake after sleep onset (WASO, mid-sleep arousal time after sleep onset), fragmental index (percentage of number of quiet episodes which are shorter than 1 min from the total quiet episodes) and the number of awakenings (the total number of awakenings during sleep).

On a randomized, double-blind crossover basis, the subjects were given tablets of either 2 mg of controlled-release melatonin (Circadin™, Neurim Pharmaceuticals, Tel-Aviv, Israel) or a placebo identical in appearance, which contained the inactive ingredients but not melatonin. The tablets were taken 2 h before desired bedtime, for a period of 3 weeks. This treatment period was followed by a wash-out period of 1 week and then by another 3-week period of treatment with the other preparation (melatonin or placebo). During the treatment periods, patients, investigators and co-workers were blinded to the drug given. Access to the randomization code was given to the pharmacist who prepared the tablets in containers. Treatment codes were opened after all study results were recruited and analyzed. Patients' sleep data were analyzed by means of six *t*-tests for paired samples (one for every parameter: fragmental index, sleep efficiency, sleep latency, waso, TST, and number of awakenings), comparisons were made between placebo and melatonin treatments. In addition, in order to check if the timing of the treatment (the first treatment administered: placebo or melatonin) had any effect by itself or interacted with the difference between placebo and melatonin, an analysis of variance for repeated measurements was performed for every index, while the repeated measurements were the index outcomes under placebo and melatonin, and with a between subjects factor of first treatment administered (placebo or melatonin).

### 3. Results

The mean amount of urinary 6-S-MT was higher at 06:00 h (1.26  $\mu\text{g/h}$ ; range, 0.03–2.2  $\mu\text{g/h}$ ) than at the other collection periods (Fig. 1). In all of these subjects, the peak excretion of 6-S-MT was delayed, (beginning at 03:00 h instead of midnight in age-matched individuals without insomnia). The absolute 6-S-MT levels were low (mean 0.93  $\mu\text{g/h}$ , range 0.03–2.1  $\mu\text{g/h}$ ) at 02:00 h, which is the normal peak time, in comparison to 5.3  $\mu\text{g/h}$  in young adults and 3.7  $\mu\text{g/h}$  in age-matched healthy individuals without sleep disturbances (Haimov et al., 1994). Sleep quality of the subjects was monitored at the end of each 3-week treatment period, with either melatonin or placebo, for three consecutive nights each. For each parameter, the average of three nights was calculated for all subjects. Sleep parameters, were subjected to *t*-tests for paired samples ( $n = 21$ ). All 21 subjects completed the study and no data were missing. The means (S.D.) of the different sleep parameters obtained after the placebo and melatonin treatment periods are presented in Table 1. In addition, the percent improvement was calculated for each parameter and is depicted in Fig. 2.

Table 1  
 Sleep parameters obtained by actigraphy (mean (SD), three-night average for each subject)

	Efficiency (%)	Latency (min)	Fragmental index (%)	Total sleep time (min)	Number of awakenings	WASO (min)
Placebo	75.23 (2.2)	29.24 (6.2)	43.97 (2.3)	351.02 (14.9)	16.17 (1.45)	76.80 (12.5)
Melatonin	85.44 (2.4)	11.75 (2.0)	35.50 (3.0)	384.06 (14.6)	11.41 (1.4)	39.58 (7.6)

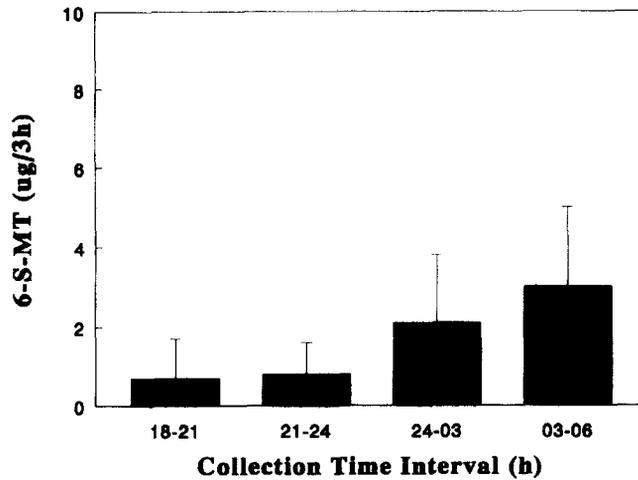


Fig. 1. Nightly 6-sulphatoxy-melatonin excretion in urine samples collected every 3 h over 12 h. Data is shown as  $\mu\text{g}$  6-S-MT excreted per 3-h interval (mean  $\pm$  S.D.).

Sleep efficiency was significantly higher for the melatonin treatment as compared to placebo ( $t(20) = -5.60$ ,  $P < 0.001$ ). The order of treatment administration had no main effect ( $F(1,19) = 0.40$ ,  $P = 0.53$ ), and the difference between placebo and melatonin was similar for those who received placebo and those who received melatonin first (no interaction,  $F(1,19) = 0.23$ ,  $P = 0.638$ ). A significant treatment effect was found (repeated measurements  $F(1,16) = 30.37$ ,  $P < 0.001$ ).

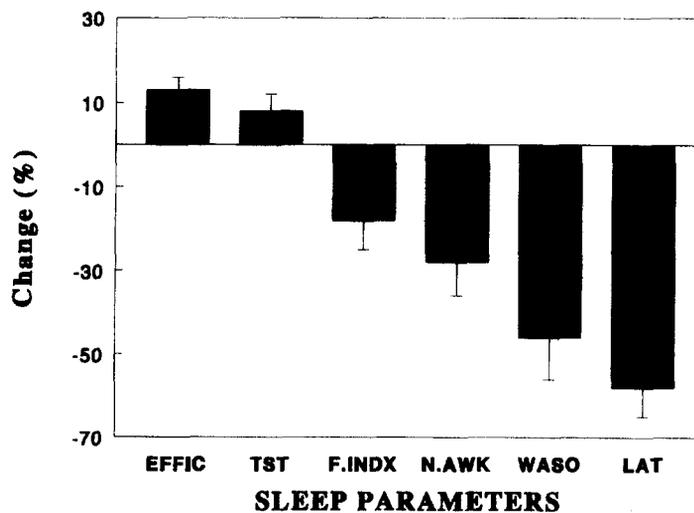


Fig. 2. Sleep parameters in elderly insomniacs at the end of three weeks of either placebo or melatonin treatment as obtained from actigraph recordings of 3-night average for each subject. Data are shown as percentage of difference between melatonin treatment and placebo (mean  $\pm$  S.D.).

Sleep latency was significantly shorter for the melatonin treatment as compared to placebo ( $t(20) = 2.99$ ,  $P = 0.007$ ). The order of treatment administration had no main effect ( $F(1,19) = 0.28$ ,  $P = 0.603$ ), and the difference between placebo and melatonin was similar for those who received placebo and those who received melatonin first (no interaction,  $F(1,19) = 0.34$ ,  $P = 0.566$ ). A significant treatment effect was found (repeated measurements  $F(1,16) = 8.49$ ,  $P = 0.009$ ).

Wake after sleep onset was significantly shorter for the melatonin treatment as compared to placebo ( $t(20) = 4.51$ ,  $P < 0.001$ ). The order of treatment administration had no main effect ( $F(1,19) = 0.92$ ,  $P = 0.350$ ), and the difference between placebo and melatonin was similar for those who received placebo and those who received melatonin first (no interaction,  $F(1,19) = 0.52$ ,  $P = 0.482$ ). A significant treatment effect was found (repeated measurements  $F(1,16) = 19.50$ ,  $P < 0.001$ ).

Total sleep time was significantly longer for the melatonin treatment as compared to placebo ( $t(20) = 2.39$ ,  $P = 0.027$ ). The order of treatment administration had no main effect ( $F(1,19) = 0.06$ ,  $P = 0.803$ ), and the difference between placebo and melatonin was similar for those who received placebo and those who received melatonin first (no interaction,  $F(1,19) = 0.01$ ,  $P = 0.907$ ). A significant treatment effect was found (repeated measurements  $F(1,16) = 5.38$ ,  $P = 0.032$ ).

Fragmental index was significantly lower for the melatonin treatment as compared to placebo ( $t(20) = 2.67$ ,  $P = 0.015$ ). The order of treatment administration had no main effect ( $F(1,19) = 0.61$ ,  $P = 0.444$ ), and the difference between placebo and melatonin was similar for those who received placebo and those who received melatonin first (no interaction,  $F(1,19) = 1.05$ ,  $P = 0.317$ ). A significant treatment effect was found (repeated measurements  $F(1,16) = 7.38$ ,  $P = 0.014$ ).

The number of awakenings was significantly lower for the melatonin the placebo ( $t(20) = 3.28$ ,  $P = 0.004$ ). The order of treatment administration had no main effect ( $F(1,19) = 1.07$ ,  $P = 0.313$ ), and the difference between placebo and melatonin was similar for those who received placebo and those who received melatonin first (no interaction,  $F(1,19) = 1.17$ ,  $P = 0.293$ ). A significant treatment effect was found (repeated measurements  $F(1,16) = 10.49$ ,  $P = 0.004$ ). No definite adverse effects of melatonin was reported.

#### 4. Discussion

The present study shows that controlled-release melatonin has a beneficial effect on sleep efficiency and WASO in melatonin-deficient elderly benzodiazepine-users which is similar to its effects on elderly insomniacs who are not taking benzodiazepines. However, there was also a significant shortening of sleep latency and an increase in total sleep time, parameters which were not significantly improved by controlled-release melatonin in our previous studies (Garfinkel et al., 1995; Haimov et al., 1995).

This stronger effect of melatonin on benzodiazepine-using elderly insomniacs may be explained by two mechanisms:

(a) The potentiation of benzodiazepine and melatonin binding to their receptors. In rats, melatonin augments GABA and benzodiazepine binding to the brain membranes (Gomar et al., 1993). In addition, pinealectomy results in a significant decrease while melatonin restores benzodiazepine receptor density in the cerebral cortex of the rat (Acuna-Castroviejo and Cardinali, 1986; Cardinali et al., 1986). Furthermore, we have recently found that in the rat brain benzodiazepines suppress melatonin binding and that this effect can be abrogated by melatonin supplementation (Atsmon et al., 1996).

(b) Replacement of endogenous melatonin which may be inhibited by both benzodiazepines and aging. Due to the adverse influence of benzodiazepines on melatonin secretion, the beneficial effect of melatonin replacement therapy may be more apparent in patients who are taking benzodiazepines than in those who are not. Additional studies will be required to substantiate a beneficial role for melatonin in alleviating symptoms of tolerance and/or addiction which are known to occur in chronic benzodiazepine users.

## References

- Acuna-Castroviejo, D. and Cardinali, D.P. (1986): Diurnal variation of benzodiazepine binding in rat cerebral cortex: disruption by pinealectomy. *J. Pineal Res.*, 3, 101–102.
- Arendt, J. (1988): Melatonin. *Clin. Endocrinol.*, 29, 205–229.
- Arendt, J., Bojkowski, C., Franey, C., Wright J. and Marks, V. (1985): Immunoassay of 6-hydroxymelatonin sulphate in human plasma and urine. Abolition of the urinary 24-h rhythm with atenolol. *J. Clin. Endocrinol. Metab.*, 60, 1166–1173.
- Atsmon, J., Okanin, S., Laudon, M., Laschiner, S., Gavish, M., Dagan, Y. and Zisapel, N. (1996): Reciprocal effects of chronic diazepam and melatonin on brain melatonin and benzodiazepine binding sites. *J. Pineal Res.*, 20, 65–71.
- Brooks, J.O., Friedman, L., Bliwise, D.L. and Yesavage, J.A. (1993): Use of wrist actigraph to study insomnia in older adults. *Sleep*, 16, 151–155.
- Cardinali, D.P., Lowenstein, P.R. and Rosenstein, R.E. (1986): Functional links between benzodiazepine and GABA receptors and pineal activity. *Adv. Biochem. Psychopharmacol.*, 42, 155–164.
- Cole, R.J., Kripke, D.F., Gruen, W., Mullaney, D.J. and Gillin, J.C. (1992): Automatic sleep/wake identification from wrist activity. *Sleep*, 15, 461–469.
- Dawson, D. and Encel, N. (1993): Melatonin and sleep in humans. *J. Pineal Res.*, 15, 1–12.
- Garfinkel, D., Laudon, M., Nof, D. and Zisapel, N. (1995): Improvement of sleep quality in elderly people by controlled-release melatonin. *Lancet*, 346, 541–544.
- Gomar, M.D., Castillo, J.L., Del Argulo, C.M., Fernandez, B. and Acuna-Castroviejo, D. (1993): Intracerebroventricular injection of naloxone blocks melatonin-dependent brain <sup>3</sup>H-flunitrazepam binding. *Neuroendocrinology*, 4, 987–990.
- Haimov, I., Laudon, M., Zisapel, N., Souroujon, M., Nof, D., Shlitner, A., Herer, P., Tzischinsky, O. and Lavie, P. (1994): Sleep disorders and melatonin rhythms in elderly people. *Br. Med. J.*, 309, 167.
- Haimov, I., Lavie, P., Laudon, M., Herer, P., Vigdor, C. and Zisapel, N. (1995): Melatonin replacement therapy of elderly insomniacs. *Sleep*, 18, 598–603.
- Kopin, I.J., Pare, C.M.B., Axelrod, J. and Weissbach, H. (1961): The fate of melatonin in animals. *J. Biol. Chem.*, 236, 3072–3078.
- Kveder, S. and McIssac, W.M. (1961): The metabolism of melatonin (*N*-acetyl-5-methoxytryptamine) and 5-methoxytryptamine. *J. Biol. Chem.*, 236, 3214–3220.
- Lushington, K., Lack, L. and Dawson, D. (1995): Melatonin production in good and poor elderly sleepers. *Sleep Res.*, 24A, 168.

- McIntyre, I.M., Burrows, G.D. and Norman, T.R. (1988) Suppression of plasma melatonin by a single dose of the benzodiazepine alprazolam in humans. *Biol. Psychiatry*, 24, 105–108.
- Sharma, M., Palacios-Bois, J., Schwartz, G., Iskandar, H., Thakur, M., Quirion, R. and Nair, N.P.V. (1989): Circadian rhythms of melatonin and cortisol in aging. *Biol. Psychiatry*, 25, 305–319.
- Waldhauser, F., Waldhauser, M., Liberman, H.R., Deng, M.H., Lynch, H.J. and Wurtman, R.J. (1984): Bioavailability of oral melatonin in humans. *Neuroendocrinology*, 39, 307–313.