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ORIGINAL ARTICLE

A Double Blind-placebo Controlled Study on Melatonin Efficacy to Reduce Anxiolytic Benzodiazepine Use in The Elderly

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Abstract

OBJECTIVE. The present double blind-placebo controlled study was carried out to assess whether melatonin (3 mg p.o., fast release form) could be useful to reduce benzodiazepine dosage in old patients with minor sleep disturbance. The possible correlation of urinary excretion of 6-sulphatoxymelatonin (aMT6s) before starting treatment and outcome of treatment was also examined.

METHODS. Forty-five patients (36 females, 70.5 ± 13.1 years old) regularly taking anxiolytic benzodiazepines in low doses were studied. Overall quality of morning freshness, daily alertness, sleep quality, and sleep onset and offset time were assessed from structured clinical interviews and from logs completed by the patients. Patients were randomized to receive either melatonin or placebo for 6 weeks. On day 14 of treatment, benzodiazepine dose was reduced by half and on day 28, it was halted. No significant modifications of sleep or wakefulness were detected after benzodiazepine withdrawal. As compared to basal, there was a general lack of changes in quality of wakefulness or sleep in patients taking melatonin or placebo. Sleep quality of patients taking melatonin during the first two weeks of treatment was significantly lower than that of placebo. Melatonin advanced sleep onset by 27.9 ± 11.9 min and decreased significantly the variability of sleep onset time ($p = 0.03$). The urinary concentration of aMT6s prior to the study did not correlate with any parameter examined.

CONCLUSION. The present study does not support melatonin efficacy to reduce the use of benzodiazepines in low doses. This contrasted with the demonstrable effectiveness of melatonin to reduce benzodiazepine consumption in insomniac patients when used in hypnotic amounts.

Introduction

Several studies have indicated that in aged patients with primary insomnia taking benzodiazepines, melatonin is effective to halt or reduce benzodiazepine consumption [1–6]. For example, we reported that 13 out of 20 insomniac patients taking benzodiazepines together with melatonin, benzodiazepine use could be stopped and in other 4 patients benzodiazepine dose could be decreased to 25–66 % of initial doses [6]. The data agreed with the efficacy of melatonin treatment to increase sleep efficiency and total sleep time and to decrease wake after sleep onset, sleep latency and number of awakenings in elderly subjects who have been taking benzodiazepines and had low melatonin output [5]. Moreover, a rapid reversal of tolerance to benzodiazepine hypnotics by treatment with oral melatonin has been observed [3].

In a study including 34 insomniacs kept on benzodiazepine therapy and who received melatonin (2 mg in a controlled-release formulation) or placebo for 6 weeks, the patients were encouraged to reduce their benzodiazepine dosage 50% during week 2, 75% during weeks 3 and 4, and to discontinue benzodiazepine therapy completely during weeks 5 and 6 [4]. Fourteen of 18 subjects who had received melatonin therapy, but only 4 of 16 in the placebo group, discontinued benzodiazepine therapy, sleep-quality scores being significantly higher in the melatonin therapy group.

Since many old patients with minor sleep disturbance received benzodiazepines in anxiolytic doses, we carried out the present study to assess whether melatonin could be useful to reduce low benzodiazepine dosage as it is in insomniac patients treated with hypnotic benzodiazepines. A double blind-placebo controlled study on the efficacy of a 3 mg-melatonin dose p.o. (fast release form) was carried out. A possible correlation of urinary excretion of 6-sulphatoxymelatonin (aMT6s) before starting treatment and outcome of treatment was also examined.

Methods

Forty-five patients (36 females) were included in the study. The participants gave written informed consent for the study. The study was monitored by an independent Ethics Committee. The mean ± S.D. age of patients was 70.5 ± 13.1 years. Most patients were taking low doses of anxiolytic benzodiazepines as follows: in the melatonin group, 34% of patients were taking lorazepam, 22% alprazolam, 22% bromazepam and 22% were taking other benzodiazepines. In the placebo group, 33% were taking alprazolam, 27% bromazepan, 15% lorazepam and 25% were taking other benzodiazepines. The mean doses of the anxiolytic benzodiazepines taken were: alprazolam, 0.66 ± 0.46 mg/day; lorazepam,1.62 ± 0.77mg/day and bromazepan, 3,0 ± 1.06 mg/day. The following exclusion criteria (assessed in structured interview) were used: presence of any kind of organic or psychiatric disorder, past history of neurological disorder, alcohol abuse or addiction to other drugs, or heavy smoking habits.

The experimental design of the study is outlined in Fig.1. Patients were initially interviewed by experienced physicians and a questionnaire [7] dealing with demographics and quality of wakefulness and sleep was distributed. All individuals in the study received placebo for 7 days and any patient exhibiting an improvement >30% of basal assessment was excluded from the study. In this way 66 out of 81 patients remained in the study and were randomized to receive gelatin capsules containing 3 mg of melatonin as immediate release form (Melatol^{R}, Elisium S.A., Buenos Aires) p.o. daily 30 min before expected sleeping time (as assessed from clinical interviews of the patients) or placebo for 6 weeks. Twenty-one patients were excluded from the final analysis because they failed to complete all stages of the study.

Table 1 summarizes the demographic data in the two groups of patients. No significant statistical differences were detected between groups, nor in the benzodiazepine dosage schedule receiving by the patients

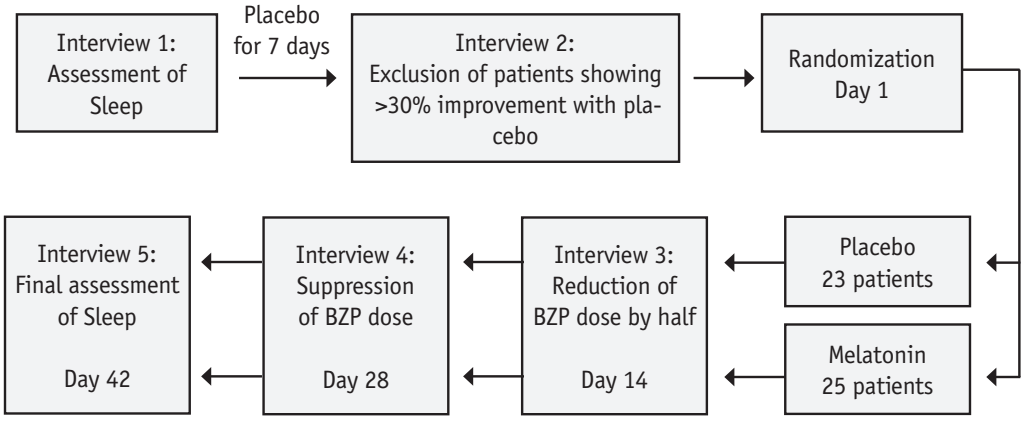

Figure 1. Experimental design of the study. All individuals received placebo for 7 days and any patient exhibiting an improvement >30% of basal assessment was excluded from the study. For details, see text.

Table 1. Demographic data of the patients included in the study

Mean±SD	Melatonin-treated	Placebo-treated
Number (female)	24 (19)	21 (17)
Age (years)	70.1±16.8	71.0±7.3
Body weight (kg)	67.3±23.6	65.5±22.4
Height (cm)	155.0±31.6	144.6±47.2
Urinary aMT6s (µg)	6.1±6.7	14.7±17.2

(data not shown). Likewise, urinary concentration of aMT6s prior to the study did not differ significantly between groups.

Besides the structured clinical interviews, daily logs completed by the patients on quality of morning freshness, daily alertness and sleep and daily sleep onset and offset times were used for assessment of the changes arising after treatment. The patients were asked to evaluate the quality of morning freshness, daily alertness and sleep (readiness to fall asleep and

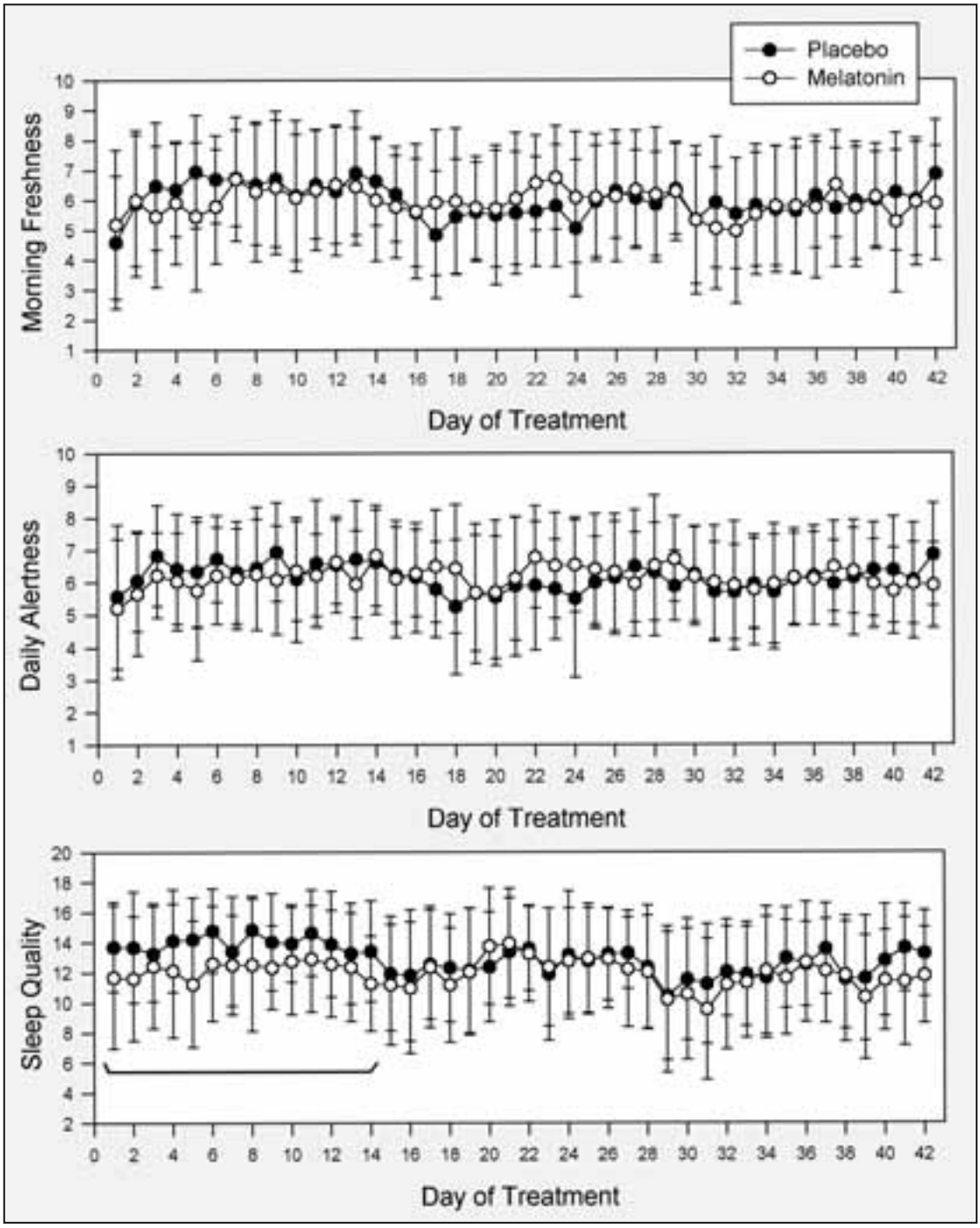

Figure 2. Effect of melatonin or placebo on subjective assessment of morning freshness, daily alertness and sleep quality, as derived from patient's log data. Shown are the means±SD of 24 patients (melatonin) and 21 patients (placebo). Sleep quality of patients taking melatonin during the first two weeks of treatment (line) was lower than that of placebo as shown by a factorial ANOVA (p= 0.027).

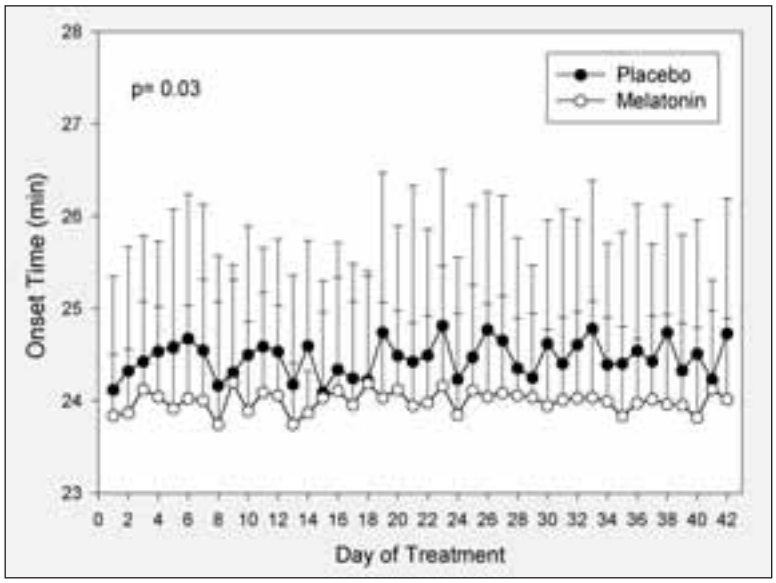

Figure 3. Effect of melatonin or placebo on sleep onset time. Shown are the means + SD of 24 patients (melatonin) and 21 patients (placebo). Melatonin advanced sleep onset (t= 15.19, p= 0.0001, one-sample *t-test*) and decreased significantly the variability of sleep onset time as compared to placebo (p= 0.03, Levene Test for homogeneity of variances).

quality of sleep) graphically in a scale rated from 0 to 10 (visual analogic scale). The sum of scores for readiness to fall asleep and quality of sleep was taken as an index of sleep quality.

On day 14 of treatment (clinical interview 3) benzodiazepine dose was reduced by half; on day 28 (clinical interview 4) all benzodiazepine treatment was halted (Fig.1). A final clinical assessment was made on day 42 of treatment.

For aMT6s measurement, urine was collected during 12 h (from 18:00 h to 06:00 h). aMT6s was measured by a specific RIA [8]; the intra- and interassay coefficients of variation were 6–8 %. Potential adverse effects were monitored throughout the study by an incumbent physician.

Results were statistically analyzed by a repeated-measures multivariate analysis of variance (ANOVA). A SPSS software version 10.1 (SPSS Inc., Chicago, ILL) was used.

Results

Figure 2 shows treatment efficacy, as derived from patient's log data. There was a general lack of significant changes in subjective assessment of morning freshness and daily alertness, as well as of sleep quality of patients taking melatonin or placebo. In addition, there was no significant modification of sleep quality, nor wakefulness, after benzodiazepine withdrawal (Fig.3).

Visual inspection of Fig.2 indicates that sleep quality of patients taking melatonin during the first two weeks of treatment was lower than that of placebo. This was statistically substantiated by a factorial ANOVA indicating a significant "treatment x time" interaction as far as sleep quality ($p < 0.02$). A segregated factorial ANOVA applied to the first two weeks of treatment indicated significantly less sleep quality in those patients taking melatonin ($p = 0.027$).

The effect of treatment on sleep onset time is depicted in Fig.3. Melatonin advanced sleep onset by 27.9 ± 11.9 min ($p = 0.0001$) and decreased significantly the variability of sleep onset time as compared to placebo ($p = 0.03$). No effect of treatment on sleep offset time was found (results not shown).

The urinary concentration of aMT6s prior to the study did not correlate significantly with any parameter examined (results not shown).

Discussion

In the elderly, sleep disturbance is complex and often difficult to relieve because the physiologic parameters of sleep normally change with age. Many times, old patients with minor sleep disturbance received, on a long-term basis, anxiolytic benzodiazepines or sedative-hypnotic benzodiazepines in low doses, for relief of a disturbance that has numerous, often concurrent etiologies, including medical conditions, medication or poor sleep hygiene [9]. Since any long-term use of benzodiazepines should be avoided, particularly in the elderly, appropriate strategies to decrease or to halt benzodiazepine use should be welcome.

Although melatonin was effective to reduce hypnotic benzodiazepine consumption in aged patients with established insomnia [1–6], there is no information on the possible melatonin efficacy to reduce benzodiazepines when they are employed in low, anxiolytic doses. That the patients included in the present study were taking benzodiazepines on reasons other than an established sleep disturbance was indicated by the lack of subjective changes in sleep quality after reduction to half (weeks 3 and 4) or the suppression of benzodiazepine dose (weeks 5 and 6).

Our results indicate that melatonin lacked to affect subjective assessment of wakefulness or sleep in this group of patients with minor sleep disturbance. This contrasted with the demonstrable sleep-promoting activity of melatonin in a wide variety of sleep disorders in the elderly [1,5,10–20]. Rather, during the first two weeks of the study (in which melatonin treatment co-existed with benzodiazepines), a decrease in subjective assessment of sleep quality was observed. Collectively, the present results do not sup-

port the use of melatonin to decrease benzodiazepines when these drugs are indicated mainly as anxiolytics.

Melatonin, however, was not devoid of activity in the group of patients examined. Melatonin advanced sleep onset and decreased significantly variability of sleep onset time as compared to placebo. While the use of melatonin as a circadian-active agent is supported by several studies [21–26], melatonin efficacy to reduce variability of the sleep onset time was first described in demented patients exhibiting sundowning [1,13,14] and is the basis for the indication of melatonin as an effective therapy of sundowning in Alzheimer's disease [27,28].

A last aspect of this study deserves comment. The urinary concentration of aMT6s prior to the study did not correlate significantly with any parameter of wakefulness or sleep examined. Circulating melatonin undergoes hepatic metabolism to 6-hydroxymelatonin, which is immediately conjugated to yield aMT6s and is excreted in urine as the main melatonin metabolite (accounting for more than 70% of the melatonin secreted). Although some results point out to a correlation of melatonin production with quality of sleep in the elderly [5] other observations do not support such a correlation [29–31]. Generally, the urinary excretion of aMT6s correlated negatively and significantly with age, but not with intensity of sleep disorder or outcome of treatment [6,32].

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