Facilitation of Benzodiazepine Discontinuation by Melatonin

A New Clinical Approach

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Background: Benzodiazepines are the most frequently used drug for the treatment of insomnia. Prolonged use of benzodiazepine therapy is not recommended. However, many patients, particularly older patients, have difficulties discontinuing therapy. Melatonin, a hormone that is produced at night by the pineal gland, promotes normal sleep in humans and augments sleep induction by benzodiazepine therapy.

Objective: To assess whether the administration of melatonin could facilitate the discontinuation of benzodiazepine therapy in patients with insomnia.

Methods: Thirty-four subjects receiving benzodiazepine therapy were enrolled in the 2-period study. In period 1, patients received (double-blinded) melatonin (2 mg in a controlled-release formulation) or a placebo nightly for 6 weeks. They 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. In period 2, melatonin was administered (single-blinded) for 6 weeks to all subjects and attempts to discontinue benzodiazepine therapy were resumed. Benzodiazepine consumption and subjective sleep-quality scores were reported daily by all patients. All subjects were then allowed to continue melatonin therapy and follow-up reassessments were performed 6 months later.

Results: By the end of period 1, 14 of 18 subjects who had received melatonin therapy, but only 4 of 16 in the placebo group, discontinued benzodiazepine therapy ($P = .006$). Sleep-quality scores were significantly higher in the melatonin therapy group ($P = .04$). Six additional subjects in the placebo group discontinued benzodiazepine therapy when given melatonin in period 2. The 6-month follow-up assessments revealed that of the 24 patients who discontinued benzodiazepine and received melatonin therapy, 19 maintained good sleep quality.

Conclusion: Controlled-release melatonin may effectively facilitate discontinuation of benzodiazepine therapy while maintaining good sleep quality.

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INSOMNIA IS a common complaint that is particularly troublesome in the elderly. Treatment with benzodiazepines, the most commonly used drug in the treatment of insomnia, is considered safe.[1] Nevertheless, the consensus guidelines for benzodiazepine therapy recommend prescription for the short-term therapy of insomnia, limited use for periods not exceeding 2 weeks, or intermittent courses.[2] However, some patients continue benzodiazepine therapy for prolonged periods and this, particularly in elderly people, may be associated with impaired functional status.[3] At least 50% of those receiving benzodiazepines have been reported to be willing to stop its use.[4] However, development of physical and/or psychological dependencies and rebound insomnia seem to interrupt most attempts at discontinuation.[4,5]

Melatonin (*N*-acetyl-5-methoxytryptamine), a hormone produced and secreted by the pineal gland into the blood circulation at night, plays a major role in the induction and regulation of sleep.[6] Benzodiazepine therapy has been found to suppress the nocturnal rise in plasma melatonin and shift its day-night rhythmicity[7]; this suppression may interfere with normal sleep-wake rhythmicity.

For editorial comment see page 2393

Melatonin therapy has been found to significantly improve sleep quality in elderly insomniacs (>55 years)[8-11] and in elderly insomniacs who had been undergoing benzodiazepine therapy for a prolonged period.[12] In younger populations of in-

SUBJECTS AND METHODS

The clinical study was performed in accordance with the guidelines set by the World Medical Assembly (ie, the latest version of the Declaration of Helsinki). Thirty-four patients who were living independently expressed willingness to discontinue benzodiazepine therapy, gave signed informed consent, and were enrolled in the study (9 men, 25 women; mean ± SD age, 68 ± 13 years; range, 40-90 years). None of these patients had cognitive impairment or liver or renal disorders (serum creatinine levels <133 µmol/L [1.5 mg/dL]). All subjects reported undergoing at least 1 type of benzodiazepine therapy daily for over 6 months; 27 received a single type of benzodiazepine therapy for sleep and 7 received a combination of 2 types (oxazepam [n = 13], brotizolam [n = 11], flunitrazepam [n = 5], lorazepam [n = 5], alprazolam [n = 4], nitrazepam [n = 2], and triazolam [n = 1]). All subjects received 0.5 to 2 benzodiazepine tablets per day.

Before entering the study, subjects were asked to collect all urine excreted between 10 AM and 10 PM and between 10 PM and 10 AM. Urine was collected, the volume was measured, and 1-mL samples from each collection were frozen for future measurement of levels of urinary 6-sulfatoxymelatonin (6-SMT), the main melatonin metabolite, in duplicate by radioimmunoassay (Stockgrand Ltd, Guilford, Surrey, England).

Patients received a controlled-release formulation of melatonin (CRM) that overcomes the fast clearance of melatonin (serum half-life of about 40 minutes)[16] and has been found to improve the nocturnal sleep of insomniacs.[8,9,12,15] A gradual benzodiazepine-tapering protocol was employed in an attempt to alleviate possible psychological dependence and enhance compliance.

The study included 2 periods. In period 1, subjects were randomized (double-blinded) to receive either 2 mg of CRM therapy (Circadin; Neurim Pharmaceuticals Ltd, Tel Aviv) or a placebo that was identical in appearance, 2 hours before bedtime (9-11 PM) for 6 weeks. During this period, patients were encouraged to reduce their usual benzodiazepine therapy dosage 50% during week 2, 75% during weeks 3 and 4, and then to discontinue benzodiazepine completely during weeks 5 and 6. In period 2, CRM therapy was administered (single-blinded) to patients of both the CRM therapy and placebo groups for another 6 weeks (weeks 7-12 of the study). Subjects who did not succeed in stopping benzodiazepine therapy during period 1 were encouraged to further reduce benzodiazepine dosage 50%, 75%, and 100% during weeks 8, 9 and 10, and 11 and 12, respectively. Subjects were informed that they were receiving at least 1 period of active treatment during the study, but they were unaware of whether they were receiving CRM therapy or placebo during each of these periods.

Throughout periods 1 and 2, benzodiazepine consumption and subjective sleep-quality scores were reported every morning by all subjects using a simple questionnaire. In this questionnaire, benzodiazepine consumption was reported as the number of tablets, and subjective assessment of sleep quality was reported as numerical ratings from 1 to 10 (1, poorest quality of sleep; 10, excellent sleep quality). Sleep-quality scores were averaged for each of the 12 weeks of the study. Collection and entry of all data were completed before revealing the randomization codes of the study. Only those subjects who had absolute 0 consumption over week 6 of the double-blind or single-blind periods were considered to have successfully discontinued benzodiazepine therapy.

Following the study, subjects who wished to continue treatment were given the same dosage of CRM every evening. Reassessments of subjective sleep quality and benzodiazepine and CRM consumption were performed after 6 months.

somnia patients (mean age, 33.4 and 46 years, respectively) the effects of melatonin therapy on sleep were equivocal.[13,14] We have recently reported that the administration of melatonin enabled rapid discontinuation of benzodiazepine therapy in a 43-year-old woman who was "benzodiazepine addicted."[15] Our main objective in this placebo-controlled trial was to assess whether melatonin therapy could facilitate the discontinuation of benzodiazepine therapy in long-term users.

RESULTS

COMPARABILITY AT BASELINE

The placebo (n = 16) and CRM therapy (n = 18) groups were comparable with regard to the female-male ratio (11:5 vs 14:4, respectively; mean ± SD age, 68 ± 16 vs 69 ± 11 years; range, 40-87 vs 52-90 years, respectively), daily prestudy benzodiazepine consumption (1.23 ± 0.61 vs 1.08 ± 0.38 tablets, respectively; range, 0.5-2.0 tablets), the types of benzodiazepine therapy administered, and the mean ± SD sleep-quality scores (6.13 ± 2.71 vs 6.82 ± 1.56; range, 2-10 vs 5-10, respectively).

Only 13 (8 women, 5 men) of the 34 patients complied with urine collection. The mean ± SD level of excretion of 6-SMT in 24 hours was 121 ± 173 (median, 57 µg/24 h; range, 12-617 µg/24 h). Ten of the 13 subjects manifested a paradoxical melatonin cycle; their mean ± SD daytime level of 6-SMT excretion (92 ± 126 µg/12 h; range, 6-435 g/12 h) exceeded their mean ± SD nighttime excretion level (56 ± 69 µg/12 h; range, 2-196 µg/12 h).

PERIOD 1

Detailed descriptions of the tapering patterns for benzodiazepine therapy in patients who succeeded and failed in the CRM therapy and placebo groups are presented in **Figure 1**. An overall tapering of benzodiazepine dosage with time was evident in both groups, as indicated by a significant time effect on benzodiazepine consumption ($F_{5,150} = 54.07$; $P<.001$). By the end of period 1, the benzodiazepine therapy discon-
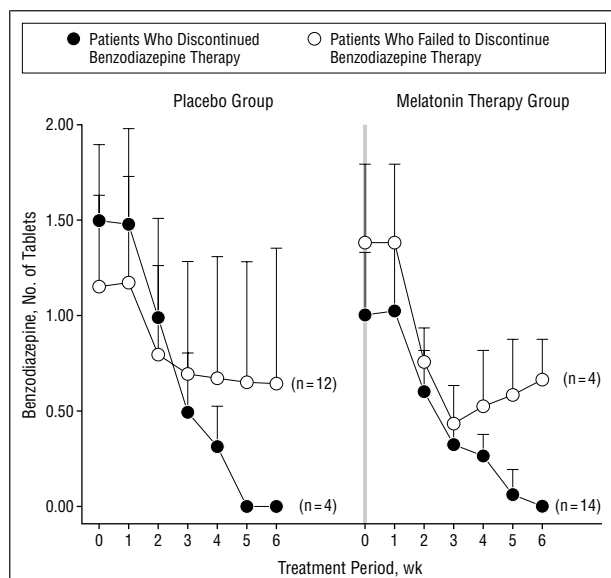
Figure 1. *Benzodiazepine tablet consumption for patients receiving long-term benzodiazepine therapy who were treated with placebo or controlled-release melatonin and successfully discontinued or failed to discontinue benzodiazepine therapy by week 6 of treatment.*

Figure 2. *Mean sleep-quality scores for patients receiving long-term benzodiazepine therapy at baseline and during the benzodiazepine therapy discontinuation study periods. Patients were treated with controlled-release melatonin during periods 1 and 2 or with placebo during period 1 and controlled-release melatonin during period 2. Values presented are mean ± SD for 34 patients for period 1 (weeks 1-6) and mean ± SD for 30 patients for period 2 (weeks 6-12). The range for sleep-quality score is 1 to 10 (1, poorest quality of sleep; 10, excellent quality of sleep).*

tinuation rate in the group receiving CRM therapy significantly exceeded that of the placebo group (11 of 18 vs 4 of 16, respectively [$\chi^2_1 = 3.86$; $P = .05$ for week 5] and 14 of 18 vs 4 of 16, respectively [$\chi^2_1 = 9.47$; $P = .002$ for week 6]).

The mean sleep-quality scores in the CRM therapy and placebo groups during period 1 are shown in **Figure 2**. Despite a higher rate of benzodiazepine discontinuation in the CRM therapy group, the sleep-quality scores in this group did not decrease. This is indicated by the lack of treatment and time effects ($F_{1,29} = 1.97$, $P = .17$ and $F_{5,145} = 0.45$; $P = .82$, respectively) and by the lack of interaction between treatment and time ($F_{5,145} = 2.04$; $P = .08$). Moreover, sleep scores computed for week 6 were significantly higher for the CRM therapy group than the placebo group (*t* test, $P = .04$).

PERIOD 2

Of the 34 enrolled patients, 30 (15 of 18 of the CRM therapy patients and 15 of 16 of the placebo patients) were willing to participate in period 2. Following 1 week of CRM treatment (on week 7), 6 additional subjects from the placebo group discontinued benzodiazepine therapy. Altogether, the number of patients who discontinued benzodiazepine therapy during periods 1 and 2 was 10 of 16 in the placebo group compared with 14 of 18 in the CRM therapy group.

The mean sleep-quality scores during period 2 (weeks 6-12) are shown in Figure 2. Just as in period 1, sleep quality was maintained in period 2 despite benzodiazepine discontinuation; this was indicated by the lack of time and treatment effects ($F_{5,145} = 0.45$; $P = .82$; and $F_{1,29} = 1.97$; $P = .17$, respectively) and the lack of interaction between treatment and time ($F_{5,145} = 2.04$; $P = .08$).
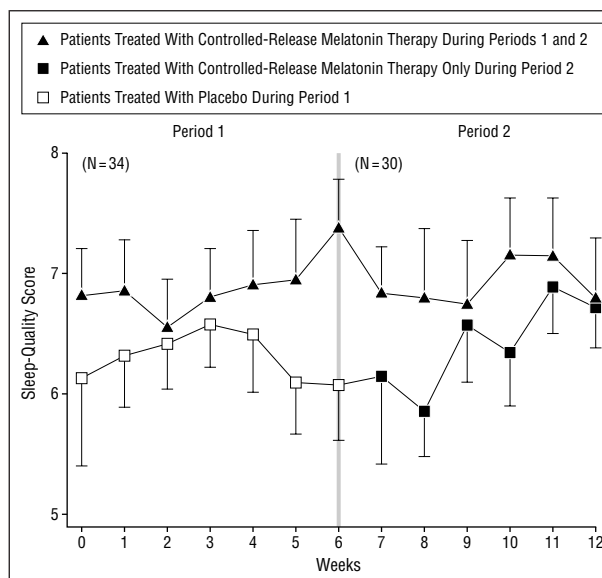
FOLLOW-UP

All 30 subjects who completed period 2 chose to continue CRM therapy; 24 of these subjects discontinued benzodiazepine therapy during period 1 or 2, and 6 failed to do so. After 6 months of CRM therapy, 19 (79%) of 24 patients who discontinued benzodiazepine therapy during the study still received melatonin therapy and remained free of benzodiazepine usage, while only 5 of the 24 who had discontinued benzodiazepine therapy during the study later resumed benzodiazepine treatment. The 6 patients who failed to discontinue benzodiazepine therapy during the study continued both CRM and benzodiazepine therapy. After 6 months of CRM therapy, the mean ± SD subjective sleep-quality score for the 19 subjects who discontinued benzodiazepine therapy was significantly higher than their mean ± SD prestudy score (8.05 ± 1.0 vs 6.26 ± 2.36, respectively; $P = .002$).

There was no apparent association between successful benzodiazepine therapy discontinuation and the specific type of benzodiazepine treatment used. The discontinuation rate was 8 of 13 for oxazepam, 8 of 11 for brotizolam, 2 of 5 for lorazepam, 1 of 2 for nitrazepam, 1 of 4 for alprazolam, and 1 of 5 for flunitrazepam therapy.

SAFETY AND ADVERSE EFFECTS

Overall safety and tolerability were good and identical for both groups. The most commonly reported adverse symptom in the CRM therapy and placebo groups was headache (2 vs 1 subject, respectively). No subjects withdrew from the study because of adverse effects.

COMMENT

Our results indicate that CRM therapy significantly facilitates the discontinuation of benzodiazepine therapy for long-term users compared with placebo. Despite the high rate of benzodiazepine therapy discontinuation in the CRM therapy group, sleep quality did not diminish. Moreover, by the end of period 1, sleep quality was significantly better in the CRM therapy group (in which 14 of 18 patients discontinued benzodiazepine therapy) compared with the placebo group (in which 12 of 16 patients still received benzodiazepine). The rate of benzodiazepine therapy discontinuation found in our placebo group (25%) is somewhat higher than that of spontaneous discontinuation (16%) reported in the United Kingdom in an 8-month follow-up study of 3234 patients receiving benzodiazepine,[17] possibly because of our tapering protocol.

The higher benzodiazepine therapy discontinuation rate in the CRM therapy compared with the placebo group cannot be attributed to differences in benzodiazepine therapy starting dosages or to subject compliance, since when given CRM therapy (in period 2), patients who had initially received placebo achieved benzodiazepine therapy discontinuation rates and sleep-quality scores comparable with those of the CRM therapy group. Moreover, the mean tablet consumption rate of the patients in the placebo group who succeeded to discontinue benzodiazepine therapy was slightly higher than that for those who failed benzodiazepine therapy discontinuation; the opposite was true for the melatonin therapy group. The significant time effect also indicates that attempts to reduce benzodiazepine consumption during the study were similar in the 2 groups.

Some patients who could not stop benzodiazepine therapy completely did reduce their dosages while receiving CRM. Many of those patients insisted on taking "a quarter" of the benzodiazepine tablet they had been using for years, probably owing to psychological dependence. However, as our study goal was to achieve complete discontinuation of benzodiazepine therapy, we categorized those patients as treatment failures.

The facilitation of benzodiazepine therapy discontinuation by CRM therapy was achieved with each of the different benzodiazepine preparations used by our patients, including those with a short half-life, which are considered to be more difficult to discontinue.[18] However, a larger group of patients should be studied to clarify whether CRM therapy would be equally effective for discontinuation of benzodiazepine therapy with different pharmacokinetics.

There are several possible explanations for maintaining the same or even better sleep quality despite discontinuation of benzodiazepine therapy. First of all, subjects may have developed a tolerance to benzodiazepine before entering the study.[19] Their sleep quality may have already been reduced and therefore not significantly affected by discontinuation of benzodiazepine therapy. Second, melatonin therapy has been shown to shorten sleep latency in healthy young individuals as well as in elderly insomniacs.[8-11] Hence, the success of CRM therapy in facilitating benzodiazepine therapy discontinuation may be attributed, at least in part, to beneficial effects on sleep induction. This hypothesis is further strengthened in light of a recent report showing that the depth of sleep (decreased stage 1 sleep and increased stages 3-4 sleep) and sleep latency were the best predictors of subjective sleep satisfaction in older adults with insomnia.[20]

Notably, a majority of those subjects who complied with urine collection produced normal amounts of melatonin (6-SMT, >50 µg/24 h) but with a paradoxical greater excretion during daytime. This is compatible with a previous report[7] and hints at the possibility that the efficacy of melatonin in benzodiazepine therapy discontinuation is possible in patients producing sufficient amount of endogenous melatonin but in whom circadian rhythmicity is impaired.

Not uncommonly, a person may initiate benzodiazepine therapy for any indication (eg, anxiety or insomnia) and for some reason continue to take it for several weeks or months. Long-term benzodiazepine therapy may impair the endogenous melatonin rhythm, which may in turn induce or aggravate sleep disturbances. Administration of CRM may break this vicious cycle by normalizing the night peak of melatonin and reinstating a robust nocturnal melatonin signal that results in improved night sleep. Such improvement may enable discontinuation of benzodiazepine therapy, which in many cases is already ineffective, counterproductive, and perhaps even unnecessary.

One may doubt the clinical benefit of benzodiazepine therapy discontinuation, arguing that we are merely substituting 1 type of drug (CRM) for another (benzodiazepines). A number of studies in elderly insomniacs, children, and patients with delayed sleep-phase syndrome as well as 2 case reports of a blind man and a sighted woman[8,21-23] reported that patients receiving melatonin therapy did not develop tolerance to the hormone during prolonged periods of use[8,21-23] and experienced no withdrawal effects upon discontinuation.[23]

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