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.

NSOMNIA 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. 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. However, some patients continue benzodiazepine therapy for prolonged periods and this, particularly in elderly people, may be associated with impaired functional status. At least 50% of those receiving benzodiazepines have been reported to be willing to stop its use. However, development of physical and/or psychological dependencies and rebound insomnia seem to interrupt most attempts at discontinuation. 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. Benzodiazepine therapy has been found to suppress the nocturnal rise in plasma melatonin and shift its day-night rhythmicity; this suppression may interfere with normal sleep-wake rhythmicity.

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Melatonin therapy has been found to significantly improve sleep quality in elderly insomniacs (>55 years) and in elderly insomniacs who had been undergoing benzodiazepine therapy for a prolonged period. 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, Guildford, 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) and has been found to improve the nocturnal sleep of insomniacs. 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.” 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 (F1,150 = 54.07; P < .001). By the end of period 1, the benzodiazepine therapy discon-
followed by CRM therapy. During period 2, 15 of 18 patients receiving CRM therapy continued both CRM and benzodiazepine treatment. The 6 patients who failed to discontinue benzodiazepine therapy during period 2, and 6 who failed 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.
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, possibly because of our tapering protocol.

The higher benzodiazepine therapy discontinuation rate in the CRM therapy group 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. 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. 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. 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.

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 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.

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 reported that patients receiving melatonin therapy did not develop tolerance to the hormone during prolonged periods of use and experienced no withdrawal effects upon discontinuation.

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