MIDAZOLAM AND SLEEP IN INSOMNIAC PATIENTS

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- 1 The effects of midazolam (15 and 30 mg p.o.) on the sleep of insomniac patients were assessed by means of polysomnographic recordings.
- 2 As compared with placebo, 15 mg midazolam significantly increased non-REM sleep while other objective measures of insomnia were only slightly modified.
- 3 At the 30 mg dose, midazolam significantly decreased total wake time and wake time after sleep onset. On the other hand, total sleep and non-REM sleep time were increased.
- 4 No development of tolerance was observed following 2 weeks of drug use.

Introduction

Midazolam is a novel imidazobenzodiazepine which shares the characteristic effects of benzodiazepines in experimental animals. In addition the derivative has a remarkably short duration of action. Its half-life of elimination in man amounts to 1.3–2.2 h. In the present study the effects of 15 and 30 mg midazolam in patients with moderate insomnia were evaluated in the sleep laboratory.

Methods

A total of nine insomniac patients (three males and six females), 29–60 years of age, were selected to participate in this study. They had a subjective insomnia defined by a sleep latency of usually 45 min and always greater than 30 min; an average of less than 6 h of total sleep time and more than 3 nightly awakenings. In eight patients, insomnia was associated with symptom and personality disorders (non-affective and non-psychotic) and in one patient with a relatively mild neurotic depression.

A 21-night schedule run single-blind was used as follows: on the first night, patients were adapted to the sleep laboratory. During nights 2, 3 and 4 baseline measurements were obtained. Placebo was administered on each of these 4 nights. Patients were given midazolam by oral route during nights 5 to 18 but only slept in the laboratory on nights 5, 6 and 7 (initial and short-term effectiveness), 16, 17 and 18 (intermediate-term effectiveness). Three subjects were studied at the 15 mg dose and six subjects at the 30 mg

dose. On nights 8 to 15 they were given the corresponding doses of midazolam but were sleeping at home. Nights 19 to 21 were placebo nights in the sleep laboratory to allow for measurement of withdrawal effects. On laboratory nights continuous EEG, EOG and EMG recordings were made for 8 h. All medication was discontinued at least 7 days before the baseline period. During the recording nights the placebo or midazolam was given just before lights-out in identically matched tablets. The recordings were classified according to the standards of Rechtschaffen & Kales (1968). Baseline placebo nights were averaged and compared with the drug and the placebo post-drug nights for NREM (non-rapid eye movement) sleep latency, wake time after sleep onset, total wake time, number of awakenings, total sleep time, NREM sleep time, NREM sleep stages, REM sleep time and latency for the first REM period.

Mean values of the different variables corresponding to short-term drug, intermediate-term drug and withdrawal nights were tested by analysis of variance for dependent samples followed by comparisons with baseline using the Scheffé test (Winer, 1962).

Results

During midazolam (15–30 mg) administration, the EEG revealed an increase of β activity through wakefulness, NREM and REM sleep. A reduction in the frequency of occurrence of waves in the alpha range was apparent during the wake state. NREM sleep was

characterized by a marked increase in the number and duration of sleep spindles, while delta wave activity was almost abolished.

As compared with placebo, nights on 15 mg midazolam did not show any significant reductions in NREM sleep latency, total wake time, wake time after sleep onset and the number of awakenings. Total sleep time showed only a moderate increment. In contrast, NREM sleep time was increased. This effect was associated with larger amounts of stage 2 sleep. REM sleep latency and percentage of total sleep time were modified only slightly.

At the 30 mg dose, short and intermediate-term midazolam administration significantly decreased total wake time and wake time after sleep onset while total sleep and NREM sleep values were increased. NREM sleep latency and number of awakenings were not significantly reduced ($P < 0.1$). On withdrawal nights wake time was increased over baseline. The highest values corresponded always to the first recovery night. The mean values for stage 2 sleep were increased but those corresponding to stage 3 were reduced. Stage 4 was abolished by the drug. With short and intermediate-term drug administration REM sleep was slightly diminished. No rebound was observed on withdrawal nights. The latency for the first REM period was increased during the whole drug administration period and this effect was still evident during withdrawal nights.

References

- MONTI, J.M., DEBELLIS, J., GRATADOUX, E., ALTERWAIN, P., ALTIER, H. & D'ANGELO, L. (1982). Sleep laboratory study of the effects of midazolam in insomniac patients. *Eur. J. clin. Pharmac.*, **21**, 479-484.
- RECHTSCHAFFEN, A. & KALES, A. (1968). *A Manual of Standardized Terminology, Techniques and Scoring*

Discussion

Fifteen milligrams of midazolam significantly increased NREM sleep time, but other objective measures of insomnia including NREM sleep latency, total wake time and the number of awakenings were modified only slightly. Thirty milligrams rated higher than the 15 mg dose on most sleep induction and maintenance parameters measured. Accordingly, total wake time and wake time after sleep onset were reduced, while total sleep and NREM sleep time were augmented. Of particular importance was the fact that no development of tolerance was observed following 2 weeks' use of 30 mg midazolam. Withdrawal of midazolam was followed by a worsening of sleep as compared with baseline. The rebound insomnia was more marked on the first withdrawal night when sleep latency, total wake time and wake time after sleep onset were increased above baseline. With regard to its effects on sleep stages, 30 mg midazolam markedly decreased stage 3 and abolished stage 4. In contrast, stage 2 was increased significantly. REM percentage was only slightly reduced while REM latency was significantly longer than that of baseline nights.

Part of the data reported here has already been published elsewhere in Monti *et al.* (1982).

- System for Sleep Stages in Human Subjects*. National Institutes of Health, Publ. No. 204. US Government Printing Office, Washington DC.
- WINER, B. (1962). *Statistical Principles in Experimental Design*. New York: McGraw-Hill.