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Effect of zolpidem on sleep architecture and its next-morning residual effect in insomniac patients: A randomized crossover comparative study with brotizolam

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Abstract

This study was conducted to determine the effect of zolpidem (ZOL) 10 mg orally on the sleep architecture and the next-morning residual effect in patients with non-organic insomnia (ICD-10) as compared to the effect of brotizolam (BTM) 0.25 mg orally, a widely used short-acting benzodiazepine (BZD) hypnotic in Japan, in a randomized, crossover comparative study. Fourteen patients with non-organic insomnia (3 males and 11 females; mean age of 54.9±S.D. 8.9 years). First three nights with placebo, middle three nights with either ZOL 10 mg or BTM 0.25 mg, and last three nights again with placebo in each session (a total of two sessions). Primary endpoints were polysomnography findings of sleep stages, sleep parameters, and sleep latency (SL) in the morning to examine calculable sleepiness as a residual effect. Secondary endpoint was sleep quality assessed by self-assessment questionnaire. At 150 min after Tmax, both ZOL and BTM significantly increased stage 2 (S2), and ZOL showed significantly longer slow wave sleep (SWS; stage 3+4) as compared to BTM. Stage wake was significantly increased by ZOL at the first withdrawal night and by BTM at the second withdrawal night. ZOL did not affect SL after rising, whereas BTM showed significantly shorter SL. Both drugs reduced the number of nocturnal awakenings and improved subjective sleep quality. The common adverse drug reaction (ADR) was sleepiness (3 patients) in each treatment. All events were mild. No serious adverse events occurred. ZOL is as effective as BTM in improving subjective sleep quality in patients with psychophysiological insomnia (PPI). ZOL has advantages over BTM in having a unique profile of increasing SWS with less next-morning residual effect.

Keywords: Brotizolam; Crossover study; Insomnia; Polysomnography; Zolpidem

1. Introduction

Insomnia is usually associated with mental stress, psychiatric disorders, and physical disorders. A recent survey in Japan indicated that approximately 20% of Japanese people suffer from sleeping problems (Okuma, 1995). Zolpidem (ZOL) is a non-benzodiazepine (NBZD) ultra-short-acting imidazopyridine hypnotic. It has high affinity for the BZ1 subclass of the $GABA_A$ macro-

Abbreviations: ADR, adverse drug reaction; ANOVA, analysis of variance; BTM, brotizolam; BZD, benzodiazepine; ICSD, International Classification of Sleep Disorders; NBZD, non-benzodiazepine; PPI, psychophysiological insomnia; PSG, polysomnography; SL, sleep latency; SLT, sleep latency test; SR, stage REM; SWS, slow wave sleep; S1, stage 1; S2, stage 2; ZOL, zolpidem.

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molecular receptor in the central nervous system (Langtry and Benfield, 1990). With its hypnoselectivity, ZOL at therapeutic doses minimizes the myorelaxant effect which is a potential disadvantage of benzodiazepines (BZDs).

The clinical efficacy of ZOL has been well demonstrated in Japan (Kazamatsuri et al., 1993; Kudo et al., 1993; Tsutsui et al., 1993, 2000), as well as in Europe (Dujardin et al., 1998; Monti et al., 1994; Parrino and Terzano, 1996) and USA (Fry et al., 2000; Nowell et al., 1997). A series of previous clinical studies in Japan also showed that ZOL has enough efficacy and safety in insomniac patients. ZOL has been reported to decrease sleep latency (SL) and the number of nocturnal awakenings, and to increase sleep time and improve sleep quality without affecting stage REM (SR) in insomniac patients (Monti, 1989). In Japan, although the effect of ZOL on sleep architecture has been much studied in normal volunteers (Kanno et al., 1993: Nakagome et al., 1993; Nakajima et al., 2000a,b), few studies have been conducted in patients with insomniac patients.

Brotizolam (BTM), a short-acting BZD hypnotic most widely used in Japan, has been well demonstrated to be effective and safe in the treatment of patients with insomniac patients. It was reported that BTM reduced the time to fall asleep and the number of nocturnal awakenings without affecting sleep stages in normal volunteers (Ohgawa et al., 1984), and reduced the number of nocturnal awakenings in patients with insomnia (Kim et al., 1991).

However, the differences in the effects on sleep between ZOL and BZDs in insomniac patients have not been directly compared. The purpose of this study was to compare the effect of ZOL with BTM on sleep architecture and the next-morning residual effect polysomnographically, and also to assess the patient's subjective sleep quality every morning using a self-rating questionnaire given to patients with non-organic insomnia.

2. Subjects and methods

2.1. Patients

Fourteen patients with non-organic insomnia classified by ICD-10 Classification of Mental and Behavioural Disorders (WHO, 1992) (3 males, 11 females; age: 40–63 years, average 54.9 years, and S.D. 8.9 years) participated in the present study. They all gave written informed consents. All subjects had to have sleep induction disturbances and complain of insomnia for not less than 1 week consecutively. In addition, they had to fulfill the following criteria such as age ranged from 40 to 64 years of both sexes, and body weight ranged from 45 to 85 kg with BMI of 20–25 for males and 19–24 for females.

Subjects with alcohol abuse, physical disorders with pain or discomfort, history of ZOL or BTM allergy, serious hepatic disorder, severe myasthenia gravis, acute narrow-angle glaucoma, highly decreased respiratory functions, pregnancy or expected pregnancy, or breastfeeding, and patients who participated in other clinical trials within the past 6 months were excluded from this study.

The study was approved by the Institutional Review Board of the Kurume University and performed in accordance with Good Clinical Practice, and Ministerial Ordinance by Ministry of Health, Labour and Welfare in Japan.

Two subjects dropped out of the study because of protocol violation and agreement withdrawal.

2.2. Study design

The study had a randomized crossover design. Polysomnography (PSG) was performed on nine consecutive nights. The nine nights comprised one adaptation night and two control nights with placebo, followed by three drug nights with ZOL or BTM, and then three withdrawal nights with placebo. The two sessions were held with an interval of more than 3 days.

The subjects were then randomly assigned to receive either ZOL 10 mg/day or BTM 0.25 mg/day for 3 days in the first session, and then their drugs were exchanged to receive BTM 0.25 mg/day or ZOL 10 mg/day for another 3 days in the second session. These are normal clinical doses and may give maximal or close to maximal hypnotic effects (Kinoshita et al., 1992; Salva and Costa, 1995).

If the subjects had previously received psychotropic drugs, the treatment was preceded by a washout period of at least threefold the T1/2 of the drugs. The subjects were not permitted to have naps, perform excessive activity, or take any psychotropic drug, anti-histamine, alcohol, or irritant food or drinks throughout the study.

2.3. Procedure

During the study period, subjects were hospitalized from days 1 to 10 for nine nights in each session. The examinations, including the PSG and sleep latency test (SLT) in the morning, were performed at an air-conditioned, light-controlled sleep laboratory. The PSG was recorded from 11 p.m. to 7 a.m. for a total of 480 min of each night by an experienced rater. ZOL, BTM or placebo was orally given to the subjects at bedtime (11 p.m.), when the light was turned off. To keep the blindness of the study, the study drugs were given to the blindfolded subjects by two persons in charge of drug allocation and drug administration, who were independent of the investigator. The subjects were required to wake up at 7 a.m. and the recording of the PSG was stopped. When the subjects fully awoke before 7 a.m., the subjects were requested to stay in bed. A morning questionnaire was filled out before the SLT. SLT was performed at 8 a.m. every morning, according to Carskadon et al. (1986). Polysomnographic data were recorded on a microcomputer and kept on CD or DVD record. After the PSG records were coded blindly, the sleep stage was