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Original Article

A randomized placebo-controlled polysomnographic study of eszopiclone in Japanese patients with primary insomnia ☆

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ABSTRACT

Objectives: To evaluate the efficacy and dose–response effect of eszopiclone on sleep latency and sleep maintenance in Japanese patients with primary insomnia.
Methods: In this randomized, double-blind, five-way crossover study, 72 patients received placebo, eszopiclone 1 mg, 2 mg, and 3 mg, and zolpidem 10 mg in random order for two consecutive nights with a washout period between treatments. Objective sleep measures from polysomnography (PSG) and subjective patient reports were collected.
Results: All active treatments produced significant improvement in objective and subjective sleep latency compared with placebo ($P < 0.05$ for all comparisons); linear dose–response relationships were observed for eszopiclone. PSG-determined wake time after sleep onset (WASO), sleep efficiency, and number of awakenings (NA), and patient-reported measures of WASO, NA, sleep quality, sleep depth, and daytime functioning significantly improved following treatment with eszopiclone 2 mg and 3 mg and zolpidem 10 mg versus placebo ($P < 0.05$). Eszopiclone at all doses increased total sleep time and stage 2 sleep time ($P < 0.001$ for both comparisons), but did not alter REM or slow-wave sleep. Eszopiclone was generally well tolerated; the most frequently reported adverse event was mild dysgeusia.
Conclusions: In Japanese patients with primary insomnia, eszopiclone 2 mg and 3 mg significantly improved PSG-determined and patient-reported sleep latency and sleep maintenance relative to placebo.

1. Introduction

Nationwide epidemiology studies in Japan have estimated the prevalence of insomnia among adults to be between 17% and 22% [1]. In the US, a general consensus has emerged from population-based studies that 30% of adults have one or more symptoms of insomnia (difficulty initiating sleep, difficulty maintaining sleep, waking up too early, or poor quality of sleep) and 10% also have daytime symptoms associated with a diagnosis of insomnia [2,3]. A recent nationwide survey based on health care claims, with confirmatory evaluations by clinical sleep medicine experts, estimated the prevalence of insomnia among American adults to be 23% [4], remarkably similar to the prevalence in Japan. Insomnia has a substantial negative impact on work absenteeism, work productivity and performance, health care utilization and costs, and quality of life [4–8] and is also associated with medical and psychiatric comorbidities [3,7]. Relatively limited published research is available regarding the effects of insomnia in Japanese populations [8], but studies have shown an association between sleep disturbances and absenteeism, work performance, physical and psychological health, and quality of life [8–10]. High prevalence rates in combination with the associated personal and socioeconomic burdens make insomnia a significant public health issue.

Eszopiclone is an S-isomer of racemic zopiclone; it is a nonbenzodiazepine cyclopyrrolone agent indicated for the treatment of insomnia in the US [11,12]. In studies of nonelderly adults with chronic primary insomnia, both short-term (6 weeks) and long-term (6–12 months) nightly treatment with 2–3 mg eszopiclone produced significant improvement in sleep latency, sleep maintenance, and daytime functioning compared with placebo [13–15].

☆ *Clinical Trial Information:* A phase II/III study of SEP-190 (eszopiclone) in patients with primary insomnia; Registration #NCT00770510; http://www.clinicaltrials.gov/ct2/show/NCT00770510.

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Similar benefits were observed in studies conducted in elderly patients with primary insomnia [11,16] and nonelderly patients with comorbid insomnia [17–19]. No signal for tolerance has been observed; rebound insomnia was rare, and when it did occur, was limited to the first night after discontinuation of medication [11,13,14].

A placebo-controlled, crossover study conducted in a US patient population with primary insomnia evaluated four doses of eszopiclone from 1 mg to 3 mg [20]. All doses were superior to placebo regarding measures of sleep latency and sleep efficiency. Treatment with 3 mg eszopiclone also provided greater improvement in sleep maintenance compared with placebo [20]. There are otherwise no previously published reports of eszopiclone in the treatment of Japanese patients with primary insomnia. In general, drug responses may vary depending on different ethnic groups [21–23]. We therefore, designed this study to evaluate the efficacy and safety in Japanese patients with primary insomnia.

The current study evaluated the efficacy and safety of incremental doses of eszopiclone (1–3 mg) in a placebo-controlled crossover study of nonelderly Japanese patients with primary insomnia. Insomnia is a subjective complaint and is typically diagnosed and treated based on patient-reported symptoms; therefore, it is clinically relevant to include in a study not only polysomnography (PSG)-based objective assessments, but also patient-reported subjective assessments of sleep disturbance. The co-primary endpoints required that statistically significant changes in objective latency to persistent sleep (LPS) were also associated with significant improvement in the patients' subjective estimate. The recommended dose for clinical use of eszopiclone in nonelderly patients in the US is 2–3 mg [12]; therefore, the primary objectives were to assess the dose–response relationship of eszopiclone and to evaluate the superiority of treatment with eszopiclone 2 mg and 3 mg compared with placebo for sleep latency based on both PSG-determined and subjective evaluations. The secondary objective of the present study were to evaluate the effects of eszopiclone on other PSG-determined sleep measures and patient-reported measures of sleep and daytime functioning.

2. Methods

2.1. Study design

This was a randomized, double-blind, placebo-controlled, dose–response, five-way crossover study conducted at 21 sites in Japan between September 2008 and May 2010. The study consisted of a 2-week screening period, a treatment period that included five intervals of two consecutive nights, each of which was separated by a washout of approximately 5 days, and a follow-up period of 6 days. Placebo, eszopiclone 1 mg, 2 mg, and 3 mg, and zolpidem 10 mg were administered in random order. Zolpidem was included as an active reference to allow qualitative comparisons of eszopiclone. A third-party patient enrollment center generated the randomization table, enrolled patients in the study, and assigned each patient to one of 10 prespecified treatment sequence patterns using block randomization (18 blocks, each containing all 10 sequence patterns). A third-party drug randomization manager assigned study medication codes to drug boxes, confirmed the indistinguishable appearance of the study medication formulations at the time of allocation, and maintained sealed study medication codes until study completion, ensuring that patients and all other study personnel were blinded to the treatment sequence. PSG recordings and subjective sleep evaluations were conducted during the screening and treatment periods. The protocol and written patient information were approved by the Institutional Review Board at each site, patients provided written informed consent prior to enrollment, and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Japan Good Clinical Practice guidelines.

2.2. Patients

Japanese patients ages 21–64 years with a diagnosis of primary insomnia based on *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision* (DSM-IV-TR; Japanese version) criteria were eligible for the study [24]. Additional key inclusion criteria were history of at least 4 weeks duration of sleep latency $\geqslant$30 min for at least 3 days per week and total sleep time $\leqslant$390 min for at least 3 days per week. Eligible participants entered a screening period during which they were administered placebo 30 min prior to PSG recording on two consecutive nights in a single-blind manner. An LPS of $\geqslant$20 min for two consecutive nights based on PSG, and either objective total sleep time (TST) $\leqslant$420 min or objective wake time after sleep onset (WASO) $\geqslant$20 min for two consecutive nights based on PSG were required for study entry. Exclusion criteria included comorbid primary sleep disorder other than primary insomnia (e.g., circadian rhythm disorder, restless leg syndrome, periodic limb movement disorder, sleep apnea), apnea–hypopnea index $\geqslant$15 for two consecutive nights during screening, periodic limb movement index $\geqslant$10 for two consecutive nights during screening, presence of DSM-IV-TR Axis I or Axis II psychiatric illness or personality disorder, and history of drug abuse or alcohol dependence.

2.3. Study medication

Study medication was provided in identical blister cards containing eight tablets (four tablets per day for 2 days of treatment). During each treatment term, one tablet per day contained active medication (eszopiclone 1 mg, 2 mg, or 3 mg or zolpidem 10 mg depending on the randomly assigned treatment sequence) and the other tablets contained matching placebo; during treatment with placebo, no tablets contained active medication. In this manner, study medications for the five different treatments were indistinguishable to patients and study personnel. Each night, study personnel removed four tablets from the blister card and gave them to the patient for administration 30 min prior to starting PSG recording. During screening, treatment, and follow-up, the concomitant administration of sedative hypnotics, anxiolytics, antineurologic disease drugs, anticonvulsants, Parkinson's disease medications, antihistamines, corticosteroids, melatonin, oriental medicines indicated for insomnia, or other medications that could influence sleep was prohibited. Medications known to be potent inhibitors or inducers of cytochrome P450 isoenzyme 3A4 were also prohibited.

2.4. Assessments

The primary efficacy assessments were LPS based on PSG and sleep latency (SL) based on subjective evaluation. During the screening period, patients were provided a diary in which they recorded the time of lights out before bedtime for 1 week prior to PSG evaluations. PSG recording was performed according to a manual for overnight PSG. The start time for PSG recording was individualized and scheduled within ±30 min of the patient's median bedtime as recorded in the sleep diary. PSG recording duration for scoring was 8 h.

Assessments obtained from PSG during the screening and treatment periods were LPS, TST, and WASO. Sleep efficiency (SE; the ratio of total sleep time to the total time in bed of 8 h $\times$100, expressed as a percent), objective number of awakenings (NA) during sleep, and sleep stages were also measured during the treatment