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Original Article

Evaluation of subjective efficacy and safety of ramelteon in Japanese subjects with chronic insomnia

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ABSTRACT

Objective: To assess patient-reported efficacy and safety of ramelteon in Japanese patients with chronic insomnia.
Methods: Randomized, double-blind, placebo-controlled, multicenter trial. After a placebo lead-in period, 987 adults with chronic insomnia received ramelteon 8 mg or placebo once daily for 2 weeks, followed by a placebo run-out period to monitor rebound insomnia. Patient-reported sleep data were collected using sleep diaries.
Results: Ramelteon significantly reduced mean patient-reported sleep latency (primary endpoint) compared with placebo during week 1 (−4.54 min; $p = 0.001$). Ramelteon maintained greater efficacy in sleep latency than placebo at week 2, but the difference did not achieve statistical significance. In a subset of patients who adhered to treatment and completed their diaries as instructed, a statistically significant reduction in subjective sleep latency was sustained through week 2. Compared with placebo, ramelteon also significantly improved mean total sleep time and mean sleep quality during week 1, the number of awakenings during week 2, and overall patient global impression scores. There was no evidence of rebound insomnia. Adverse events were generally mild and transient.
Conclusions: In Japanese adults with chronic insomnia, ramelteon 8 mg significantly reduced patient-reported sleep latency, increased total sleep time and improved sleep quality after 1 week of treatment. Ramelteon was generally well tolerated with no rebound insomnia.

1. Introduction

Insomnia is a common sleep disorder that can have a negative effect on daily activities, productivity, and quality of life [1,2]. In the Japanese general population the prevalence of insomnia was calculated to be about 20%, increasing to approximately 30% in individuals aged 60 years and over [3,4]. Values reported in population studies involving people from various countries estimated that approximately one-third of the population is affected by insomnia, with 10–15% experiencing chronic insomnia [1,2].

Pharmacotherapy is generally indicated when non-pharmacological measures such as educational and behavioural therapies do not have an adequate effect [5]. Among widely used drugs, benzodiazepine receptor agonists ('benzodiazepines') exert their hypnotic effects through binding to gamma-aminobutyric acid-A receptor complexes (including associated benzodiazepine receptor binding sites) in the brain [5]. However, this mechanism of action of the benzodiazepines can lead to impairments in cognitive and psychomotor functions and increases the potential for dependence and withdrawal symptoms, including rebound insomnia [5]. Non-benzodiazepine hypnotics such as zolpidem and zopiclone differ structurally from benzodiazepines, but in terms of mechanism of action they also appear to act via benzodiazepine receptors. Nevertheless, while these "newer" agents have similar efficacy as benzodiazepines, they may be associated with less next-day sedation and have a lower risk of dependence [5,6].

Melatonin is a neurohormone secreted by the pineal gland that is involved in regulating the sleep–wake cycle and circadian rhythms [7]. Its secretion is regulated by the suprachiasmatic nucleus, and the melatonin MT_1 and MT_2 receptors located there play a pivotal role in this process [7]. MT_1 receptors appear to be involved in sleep onset, while MT_2 receptors mediate the phase-shifting effect of melatonin on circadian rhythm. Another melatonin receptor, MT_3 (located predominantly outside of the central nervous system), is not thought to be involved with sleep/circadian rhythms [7]. Overall, results from clinical studies of exogenous melatonin in the treatment of insomnia have been inconclusive, which may in part relate to

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its short half-life and lack of specificity for particular melatonin receptors [7].

Ramelteon, a synthetic melatonin analog, is a selective MT_1/MT_2 agonist which has a 3- to 5-fold greater affinity for these receptors than melatonin, while having very weak affinity for the MT_3 receptor [8]. Ramelteon has no significant affinity for benzodiazepine, dopamine, or opiate receptors, sites which can be associated with adverse effects on cognitive function and potential for abuse [8]. In clinical trials, mostly performed in the USA, ramelteon has been shown to reduce sleep latency, with no evidence of adverse psychomotor or cognitive effects, rebound insomnia, or potential for abuse [9]. Placebo-controlled clinical trials with ramelteon in Japanese patients have not been previously reported, and the current study was designed to evaluate the effects of ramelteon 8 mg on sleep latency in Japanese patients with chronic primary insomnia.

2. Methods

2.1. Patients

One thousand six hundred and five male or female outpatients aged 20–85 years with primary insomnia were enrolled in 59 centers across Japan between October 2006 and August 2007. Entry criteria included patients with primary insomnia (as defined in DSM-IV), a daytime complaint associated with disturbed sleep that had persisted for at least 3 months, a habitual subjective sleep latency of at least 60 min, a habitual subjective total sleep time of 6.5 h or less, and a usual bedtime between 9:00 PM and 1:00 AM. Patients had to have a body mass index greater or equal to 17 and less than 34 kg/m^2. To avoid including patients with depression, subjects with a Self-rating Depression Scale (SDS) score of 53 points or more, measured using a validated Japanese version of the SDS scale, were excluded. Also excluded were patients with a significant psychiatric illness, a history of sleep apnea, epilepsy, chronic obstructive pulmonary disease, or other significant medical disorder. In addition, patients were not permitted to have taken any medication that might have affected the central nervous system (CNS) or sleep–wake function within 7 days prior to study start, and they were not allowed to make any substantial changes to daily habits that could affect sleep–wake function (e.g., shift work, exercise regimens, weight-loss programs) during the study period.

Enrolled patients underwent a 7-day placebo lead-in period during which they had to meet the following secondary criteria in order to enter the randomized phase of the study: earliest and latest bedtimes within 2 h and a sleep latency of at least 45 min for at least 3 nights, stable sleep latency (a difference of less than ±30 min between the first and last 3 days of the placebo lead-in period), adherence to sleep hygiene instructions, and fully completed sleep diary entries.

2.2. Study design

This randomized, double-blind, placebo-controlled, parallel-group, multicenter trial assessed the efficacy and safety of ramelteon 8 mg in Japanese patients with chronic insomnia. It was conducted in accordance with the World Medical Association Declaration of Helsinki and the International Conference on Harmonization Harmonized Tripartite Guidelines on Good Clinical Practice. The institutional review board for each site approved the protocol and patients were required to provide written informed consent.

The trial consisted of a 7-day single-blind placebo lead-in period (to assess baseline sleep latency), a 14-day double-blind treatment period, and a 7-day single-blind placebo run-out period (to assess rebound insomnia). At the end of the placebo lead-in period, patients who met the secondary eligibility criteria were randomly assigned to treatment with ramelteon 8 mg or placebo. Patients took a single tablet with water once daily 30 min prior to their usual bedtime. Placebo tablets were identical in appearance to the ramelteon tablets.

Randomization used a dynamic allocation method to achieve balance across the following factors: sex, age, disease duration, smoking history, and fluctuation of sleep latency during the lead-in period. The investigators, all personnel involved in the study (other than the allocation manager), and patients were all blinded to treatment allocation, and the prescribed study medication was allocated to patients based upon a drug number supplied by the independent allocation manager.

Concomitant use of any medication that could affect the CNS or sleep–wake function was not allowed during the study. Patients were given sleep hygiene instructions, with an emphasis on avoiding alcohol- and caffeine-containing beverages for 3 h prior to study drug administration until bedtime; to refrain from smoking within 1 h of bedtime and during awakenings at night; to go to bed at the same time weekdays and weekends; to sleep with the lights off; and to avoid reading books, watching TV, etc., during bedtime.

2.3. Assessments

During the screening period, patients underwent a physical examination and provided a medical history, including a sleep history (usual bedtime, waking time, sleep latency and total sleep time). Patients completed a sleep diary on a daily basis throughout the study, including details of bedtime, sleep latency, total hours of sleep, number of awakenings, sleep quality (rated on a 7 point categorical scale from 1 = excellent to 7 = extremely poor), and time of rising. The diary was completed at a regular time each day by the patient, and time-recorder stamps were employed to verify the date and time of each entry. Compliance was estimated from information obtained from each subject's sleep diary, as well as from an evaluation of the time-recorder stamps to assess patient compliance with the procedures. In addition, patients completed a global impression questionnaire (evaluating time to fall asleep, total sleep time, sleep quality, daytime distress, and usefulness of treatment, using a 3-point scale: 1 = improved, 2 = unchanged and 3 = worsened) and underwent a physical examination on a weekly basis. Adverse events were monitored throughout the study.

The primary efficacy variable was the mean patient-reported sleep latency during week 1 of treatment (day 1 to day 7), based on sleep diary entries. Secondary variables included the mean sleep latency for week 2 of treatment (day 8 to day 14) and the mean patient-reported total sleep time for week 1 and for week 2. In addition, each patient's global impression of treatment was recorded on day 8 and day 15. Safety variables included adverse events, clinical laboratory parameters and vital signs. Rebound insomnia was also evaluated.

2.4. Statistical methods

Based upon findings from previous studies the following were assumed: a difference of 6 min in sleep latency, a common standard deviation of 37 min, and a common correlation coefficient with the covariate of 0.7 in the primary endpoint. Employing these assumptions it was calculated that 306 patients per group would enable a difference in the mean sleep latency for week 1 to be detected between the ramelteon and placebo groups, with an 80% power at a significance level of 5% (two-sided) using analysis of covariance (ANCOVA), with the mean sleep latency in the placebo lead-in period as a covariate. Allowing for a dropout rate of 7%, it was planned to enrol 330 patients per group. But the rate of screen failures in the lead-in period was smaller than expected suggesting that the number of screened patients originally planned would make it possible to achieve a number of randomized patients in