A Double-blind, Randomized, Comparative Study to Evaluate the Efficacy and Safety of Zaleplon versus Zolpidem in Shortening Sleep Latency in Primary Insomnia

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Background: Benzodiazepines cause a high proportion of adverse effects while non-benzodiazepine compounds have demonstrated high efficacy and less adverse effects in patients with insomnia. The objective of this study was to compare the effectiveness and safety of non-BZ zaleplon and zolpidem in primary insomnia.

Methods: This was a randomized, double-blind, active-controlled, double-dummy, comparative study. A total of 48 patients were enrolled, of which 45 patients completed the study. Patients who entered the study were required to take the study drug orally once daily at bedtime for two weeks. Each patient kept a sleep diary and answered a questionnaire. We used these documents to measure and evaluate changes from baseline to Week 2 in sleep latency, duration and quality of sleep, the number of awakenings and incidence of rebound insomnia.

Results: The data revealed a significant decrease in sleep latency from baseline to Week 2 for patients receiving zaleplon 10 mg and zolpidem 10 mg. Patients receiving zaleplon exhibited a marginally greater, but not statistically significant, reduction in sleep latency than those who received zolpidem. There was no significant difference in the frequency of adverse effects between the zaleplon and zolpidem groups; however, during this clinical trial there was one lethal event caused by a traffic accident in the zaleplon group.

Conclusion: There was no significant difference between zaleplon and zolpidem in the efficacy of reducing sleep latency or adverse effects. A large pharmacovigilance study is needed before concluding that either zolpidem or zaleplon is free from next-day residual effects.

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Key words: hypnotics, non-benzodiazepine, insomnia, sleep latency

The American Academy of Sleep Medicine defines insomnia as unsatisfactory sleep that impacts daytime functioning.(1) Daytime repercussions of poor sleep include fatigue, sleepiness, impaired functioning, and impaired ability to concentrate, as well as depression, anxiety, and other

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mood changes. Early treatment for insomnia can improve sleep quantity and quality, improve daytime function, and cause minimal adverse drug effects. The two most commonly used diagnostic systems, the International Classification of Diseases, 10th Revision and The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, categorize insomnia as primary or one of several subtypes of secondary insomnia.[2,3]

Over the last 30 years, benzodiazepines have been the cornerstone drugs for the treatment of insomnia. However, the use of benzodiazepines results in a variety of problems, such as alteration of sleep structure, tolerance of the hypnosedative effects, pharmacological dependence, rebound insomnia and withdrawal reactions at discontinuation, anterograde amnesia, cognitive and psychomotor impairment, abuse potential and respiratory depression. Newer, more selective non-benzodiazepine compounds, such as zopiclone, zolpidem and zaleplon, have been developed in an attempt to overcome some of the adverse effects of benzodiazepines, and represent new tools in the pharmacological treatment of insomnia.[4] A previous study demonstrated that 10 mg of zaleplon is an effective dose in reducing the time to sleep-onset in non-elderly adults and this result was comparable with 10 mg of zolpidem.[5] Pharmacokinetic data indicate that zaleplon is rapidly absorbed, with a time to peak concentration and a terminal phase elimination half-life of approximately one hour, while zolpidem has a time to peak concentration and a terminal phase elimination half-life of 2.2 hours and 1.5-3.2 hours, respectively.[6] How do these newer compounds compare in effectiveness in reducing sleep latency in a different ethnic population? The objectives of this trial were to compare the efficacy and safety of zaleplon with that of zolpidem and to prove the primary hypothesis of non-inferiority of zaleplon to zolpidem in Taiwanese patients with primary insomnia.

METHODS

Subjects

This was a randomized, double-blind, active-controlled, double-dummy, comparative study. Patients were recruited from Chang Gung Memorial Hospital and Mackay Memorial Hospital in Taiwan according to the inclusion and exclusion criteria listed below. This study received approval from the facilities' institutional review boards. This study was conducted in accordance with the Declaration of Helsinki. Informed consent was signed by each participant before entry into the study. A sample size of 20 per group would be required in order to detect an effect size of 0.9 with 80% power at a 5% level of statistical significance. Assuming a 20% drop-out rate, we planned to randomize a total of 50 patients in this study to target a minimum of 40 evaluable patients. Patients were considered eligible to be enrolled in the study only when all of the following inclusion criteria were met: (1) male or female between 20 and 65 years old; (2) met the DSM-IV Diagnostic Criteria for primary insomnia and had the following symptoms present at least one week prior to randomization: typical or modal time to sleep onset of 30 minutes or more in four out of seven nights, insomnia-associated daytime complaints (fatigue, irritability, difficulty concentrating), a mean total sleep duration of ≦ 6.5 hours per night or prolonged (≧ 30 minutes) or frequent (three or more per night) nocturnal awakenings with difficulty falling back to sleep; (3) women could not be pregnant/breastfeeding and had to be using adequate contraception; and (4) signed an informed consent form. Patients were excluded from the study if they had any of the following: (1) transient or situational insomnia, e.g. insomnia due to time-zone shifts, shift-work schedules, acute stress, drugs or alcohol; (2) a history or current manifestations of sleep apnea, restless leg syndrome, or a history of routine daytime napping; (3) a current or past history of seizure disorder, clinically significant head injury, or a major psychiatric disorder that would likely affect the study; (4) concurrent hormonal therapy or a clinically significant, acute, recurrent or chronic unstable illness or disorder (e.g., severe migraine or hyperthyroidism) that was likely to affect the study, as judged by the investigator; or (5) clinically significant liver dysfunction (aspartate transaminase, alanine transaminase ≥ 2 x upper limit of normal and/or renal dysfunction (creatinine > 2 mg/dl)).

Interventions

The study period for all eligible patients was approximately 28 days, during which time the patient underwent a placebo washout for 7 days, treatment period for 14 days and a follow-up period for 7 days.

The patients were randomized in balanced blocks of 12 with an equal probability of receiving either a zaleplon 10 mg capsule or zolpidem 10 mg capsule (encapsulated tablet). Eligible patients were instructed to take the study drug (either zaleplon or zolpidem) at bedtime. The overall treatment compliance was measured by tablet counts at all visits during the study.

Outcome measurements

The primary efficacy endpoint was to evaluate the change in sleep latency from baseline to Week 2. Secondary efficacy endpoints, i.e. sleep duration, number of awakenings, sleep quality rated by patients and incidence of rebound insomnia, were measured using patient questionnaires. Physical examination, vital signs, laboratory evaluation (with pregnancy test) and 12-lead ECG were performed at baseline, day 7 and day 14. Patients were asked to complete a sleep diary each day upon awakening during the placebo washout period, treatment period, and the first three days of the post-treatment period (placebo run-out period). Entries addressed sleep latency, sleep duration, and number of awakenings. Sleep quality was rated according to the following scale: 1 = excellent; 2 = very good; 3 = good; 4 = fair; 5 = poor; 6 = very poor; 7 = extremely poor.

Statistical analysis

Continuous variables were compared between the two study groups using the t-test. If the t-test assumption was violated, the Wilcoxon Rank Sum test was used for the non-parametric method. The chi-square test and Fisher's exact test were used to compare categorical variables between the two treatment groups. For ordinal variable comparison, the Cochran-Mantel-Haenszel test was adopted. Data analyses and summaries of efficacy and safety assessment were performed for the intention-to-treat (ITT) population and safety population. For patients who took a prohibited medication before the termination of the study, only the efficacy data prior to the use of the prohibited medication were included in the efficacy analysis. If the patient was lost to follow-up, a Last Observation Carried Forward (LOCF) method was applied. If data were unavailable at the analysis time point, the last available measurement prior to that visit was used to fill in the missing value.

RESULTS

Sample description

Forty-eight patients were enrolled in the study with 24 in each group. Thirty-three (69%) of the patients were women, and fifteen (31%) were men. The mean age was 42.4 $\pm$ 10.9 years in the zaleplon group and 37.4 $\pm$ 11.7 years in the zolpidem group. The baseline characteristics (age, sex, height, weight, body mass index and sleep latency) were comparable between the zaleplon and zolpidem group with no statistically significant difference. The mean sleep latency at baseline was 63.0 $\pm$ 34.5 minutes in the zaleplon group and 61.9 $\pm$ 44.7 minutes in the zolpidem group; there were thus no differences between these two groups. In terms of drug compliance throughout the study, 22 patients (91.7%) in the zaleplon group and 22 patients (91.7%) in the zolpidem group took more than 80% of the study drugs. Two patients (8.3%) from the zaleplon group and two patients (8.3%) from the zolpidem group took less than 80% of the study drugs. No significant difference was observed in drug compliance between these two groups. The subjective sleep latencies at baseline, day 7 and day 14 in the ITT population were also measured.

Sleep outcome measurements

Comparisons of sleep measurements between the zaleplon and zolpidem groups are presented in Table 1. A significant reduction in subjective sleep latency was observed in the zaleplon group (reduced from 63.0 $\pm$ 34.5 minutes at baseline to 31.6 $\pm$ 20.5 minutes; $p < 0.05$) and zolpidem group (reduced from 61.9 $\pm$ 44.7 minutes at baseline to 30.0 $\pm$ 31.1 minutes; $p < 0.05$) as early as seven days after treatment. No statistically significant difference was observed between the zaleplon group and zolpidem group in sleep latency ($p = 0.084$, at day 14). After seven days of therapy, sleep duration improved markedly and the number of awakenings was significantly reduced.

The zaleplon group evidently showed a comparable improvement in subjective sleep duration and a reduction in the number of awakenings compared to the zolpidem group in all subsequent visits. No statistically significant difference was observed between the zaleplon group and the zolpidem group

Table 1. Mean Changes in Sleep Measures from Baseline

Sleep measures	Day 7			Day 14		
	Zaleplon (N = 24)	Zolpidem (N = 24)	*p* value	Zaleplon (N = 24)	Zolpidem (N = 24)	*p* value
Sleep latency, minutes	–31.4 (24.8)	–32.0 (24.7)	0.492	–33.7 (23.9)	–25.3 (28.2)	0.084
Sleep duration, minutes	67.7 (48.5)	70.84 (36.0)	0.801	68.3 (57.2)	70.9 (47.5)	0.868
Number of awakenings	–0.7 (1.2)	–0.6 (0.7)	0.868	–0.7 (1.0)	–0.6 (0.8)	0.637
Sleep quality	–0.8 (1.2)	–1.2 (0.7)	0.266	–0.9 (1.1)	–1.0 (0.8)	0.648

Data are presented as mean (SD).

in sleep duration and number of awakenings. A significant improvement in the sleep quality score was observed in both the zaleplon and the zolpidem groups at days 7 and 14, but there was no statistically significant difference between these two groups.

Safety and withdrawal symptoms

Table 2 shows the commonly reported adverse events (defined as those occurring > 5% of subjects in either group). Among the 48 patients included in the safety analysis, the mean duration of study drug exposure was 13.8 ± 2.4 days for the zaleplon group and 14.9 ± 3.7 days for the zolpidem group (p = 0.239). None of the patients in either group showed rebound insomnia. Throughout the treatment period, 24 patients were reported to have experienced 43 adverse events. Among these events, 23 adverse events were reported by 13 patients in the zaleplon group (13/24; 54.2%), and 20 adverse events were reported by 11 patients in the zolpidem group (11/24; 45.8%). The most frequently reported adverse effects were headache, dizziness, anxiety and urinary tract infection. There was no significant difference in the frequency of each adverse effect between the zaleplon and zolpidem groups. All adverse events were reported to be "mild" or "moderate," with one exception in the zaleplon group. A 30-year-old man was involved in a traffic accident which resulted in death in the treatment phase of this study. The motor accident occurred in the afternoon. Upon arrival at the emergency unit at 5:30 PM, the patient was found to have no vital signs, and had a hemothorax, intracranial hemorrhage and left knee fracture. Information was not sufficient to rule out a relationship between this lethal event and the study drug. In addition, five patients in the zaleplon group (5/24; 20.8%) were reported to have experienced "possible" or "probable" treatment-related adverse events, while two patients in the zolpidem group (2/24; 8.3%) were reported to have experienced "possible" treatment-related adverse events. A total of three patients (two patients in the zaleplon group and one in the zolpidem group) prematurely exited from the study. One of these three patients was the victim of the fatal traffic accident, and the other two withdrew from the study because of ineffectiveness and an adverse event.

Table 2. Treatment-emergent Adverse Events (reported by > 5% of subjects in either group)

Adverse event	Zaleplon (N = 13)	Zolpidem (N = 11)	*p* value (N = 24)
Headache	1 (4.2%)	2 (8.3%)	1.000
Dizziness	3 (12.5%)	2 (8.3%)	1.000
Anxiety	0 (0.0%)	3 (12.5%)	0.234
Urinary tract infection	2 (8.3%)	0 (0.0%)	0.489

DISCUSSION

This study used a small sample size evaluating the efficacy and safety of zaleplon and zolpidem. When interpreting these results, some limitations of this study have to be considered, such as the small sample size and the population and behavior of the patients. Moreover, there were no objective sleep tests such as polysomnography and actigraphy. The results of this study indicate that zaleplon 10 mg and zolpidem 10 mg both reduce the time to fall asleep in

patients diagnosed with primary insomnia. Although the clinical benefits of zaleplon and zolpidem have been previously reported,[7,8] this is the first study providing direct comparison of these two active compounds in Taiwan.

Evidence has shown that patients who received zaleplon experience shorter sleep latency at Week 1 than at baseline.[5,9] In this study, patients receiving zaleplon 10 mg experienced a median sleep latency which was on average 23.9 minutes shorter at Week 1 than at baseline; in the zolpidem group, the sleep latency at Week 1 was shorter by an average of 22.6 minutes. Our data showed that the reduction in sleep latency for zaleplon is consistent with previous findings. However, direct comparisons of the sleep latencies of zaleplon and zolpidem have led to inconsistent results.[10,11] Ancoli-Israel et al. demonstrated significantly reduced sleep latency in the zaleplon group,[11] whereas Allain et al. presented results in favor of the zolpidem group.[9,10] The different results may be due to small sample sizes and the lack of an objective sleep test. In our study, the direct comparison of primary efficacy, measuring change from baseline to the end of the treatment period, showed that the difference between these two groups nearly reached a significant *p*-value ($p = 0.084$). A possible explanation could be attributed to the limited number of patients enrolled in each group.

The secondary subjective efficacy measurements, sleep duration, number of awakenings and sleep quality, were evidently consistent with the findings of primary efficacy measurements. Patients who received either zaleplon 10 mg or zolpidem 10 mg had significant numerical improvement in the scores for sleep duration, number of awakenings, and sleep quality in all visits. The extent of reduction from baseline in the subjective number of awakenings was comparable in these two groups in all subsequent visits until the end of treatment, and no statistically significant difference was observed between groups. A plausible explanation for this observation could be the subjective nature of the rating system employed in the study and the limited number of patients enrolled in each group.

Rebound insomnia refers to the worsening of insomnia symptoms beyond baseline levels. This symptom is evident especially after the withdrawal of short-term treatment.[12,13] Fry et al. reported that a significantly higher number of patients taking zaleplon 10 mg experienced awakenings the first night after cessation of a 28-day treatment compared to baseline (10%).[14] In another study, however, Elie et al. reported the proportion of patients taking zaleplon 10 mg experienced rebound insomnia, but no significant difference was observed.[5] In the present study, none of the patients showed rebound insomnia within the week following abrupt discontinuation.

The plausible reasons for the different rates of rebound insomnia from previous studies could be the subjective nature of the rating system employed in the study or the limited number of patients enrolled in each group. While the clinical efficacy of benzodiazepine as a hypnotic has been well established,[15,16] the use of many of these compounds is associated with a number of side effects, such as rebound insomnia, withdrawal effects and residual sedation.[15,17]

In the present study, both drugs were generally well-tolerated. There was no significant difference in the frequency of adverse effects between the zaleplon and zolpidem groups. There was, however, one lethal event caused by a traffic accident during this clinical trial in the zaleplon group. Information was not sufficient to rule out a relationship between this lethal event and the study drug. Residual sleepiness during the day may affect performance of daily activities such as driving a car. Pandi-Perumal et al. suggested that the non-benzodiazepine hypnotics zolpidem and zaleplon have no significant next-day residual effects when taken as recommended,[18] while benzodiazepine hypnotics and zopiclone have residual effects the following day including sleepiness and reduced alertness. Nevertheless, a large pharmacovigilance study is needed before making a confident conclusion that zolpidem and zaleplon are really free from next-day residual effects.

In summary, the results of this trial are consistent with findings from other clinical studies with direct comparisons of zaleplon and zolpidem.[5,19] There was no significant difference between zaleplon and zolpidem in efficacy of reducing sleep latency or other sleep measurements. Both drugs were well-tolerated during the two weeks of treatment.

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以雙盲隨機臨床試驗評估 Zaleplon 及 Zolpidem 在原發性嗜睡病人之減少睡眠延遲的效用及安全性

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背 景： 失眠患者的藥物治療上，苯二氮平有著很高比例的副作用，非苯二氮平的藥物則表現出了高的效用和較少的副作用。本研究目的是比較 zaleplon 及 zolpidem 這兩種非苯二氮平藥物治療原發性失眠的效用及安全性。

方 法： 本研究採用隨機雙盲及控制組的研究方式。總共有 48 名患者納入研究，其中有 45 名患者完成了完整的研究追蹤。納入研究的患者必須每天睡前口服一次研究的藥物，並持續兩週。我們在治療後的第二週和基準測量值比較其前後變化，評估項目包含睡眠潛伏期、睡眠時間、醒來次數、睡眠品質，藥物停止後的失眠反彈現象等，我們是利用睡眠日誌和睡眠問卷量表做以上評估。

結 果： 統計結果服用 10 mg zaleplon 或 10 mg zolpidem 的患者與基準測量值相比在睡眠潛伏期皆有顯著的下降，而服用 zaleplon 的患者比服用 zolpidem 的患者睡眠潛伏期有略爲較好的改善，不過這部份未達統計上顯著。經過兩週的治療再完全停藥後，沒有任何一個患者有藥物停止後失眠反彈的現象。此外在副作用的頻率比較方面，zaleplon 和 zolpidem 兩組並無顯著的不同。然而 zaleplon 組中有一例車禍致死事件。

結 論： 在減少睡眠潛伏期的效用及副作用比較上，zaleplon 和 zolpidem 並沒有顯著的不同，但要確定 zaleplon 及 zolpidem 無第二日殘餘作用仍需更大規模的藥物安全研究。
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關鍵詞： 助眠劑，非苯二氮平，失眠，睡眠潛伏期

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