

Hypnotic Efficacy of Zaleplon for Daytime Sleep in Rested Individuals

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Study Objectives: The primary objective of this study was to determine whether zaleplon (10 mg) effectively promoted sleep during the daytime in well-rested individuals when compared to placebo. A secondary objective was to see if, while not expected, the use of zaleplon impacted the performance of well-rested individuals upon awakening.

Design: Repeated measures with 2 within-subject factors: drug (placebo/zaleplon) and trial (hourly testing during waking hours). Polysomnographic variables were recorded during a 3.5-hour nap following drug administration. Performance measures and subjective reports were collected during every waking trial of each session.

Setting: The study was conducted at the Chronobiology and Sleep Laboratory located at Brooks Air Force Base.

Participants: Twelve participants, 6 men and 6 women.

Interventions: 10-mg zaleplon or placebo capsules, single afternoon dose. Drug administration was counterbalanced and double-blinded.

Measurements and Results: Zaleplon allowed participants to obtain significantly more slow-wave sleep than under placebo. There was also a trend for participants under zaleplon to accomplish a greater amount of sleep than under placebo. Performance was not adversely impacted following a 3.5-hour daytime sleep under zaleplon, nor were any undesirable symptoms induced.

Conclusions: Zaleplon improves sleep quality when used by rested individuals to accomplish daytime sleep.

Key Words: zaleplon, sleep, nap, daytime, performance

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INTRODUCTION

IN MANY INSTANCES (EG, ROTATING SCHEDULES), JOB PERFORMANCE MAY BE INCREASED IF WORKERS ARE ABLE TO ACQUIRE SLEEP DURING BRIEF (< 6 HOURS) DAYTIME BREAK PERIODS. It is difficult to accomplish daytime sleep in many circumstances due to factors such as noise or reduced sleep propensity. In such cases, an effective short-acting sleep aid may provide a substantial improvement in the ability to acquire daytime sleep. This study will examine whether zaleplon might be such a sleep aid.

Beer et al¹ found maximum plasma concentrations of zaleplon to occur at approximately 1 hour after the dose was given, with a half-life of about 1 hour. Zaleplon is commonly administered in 10-mg oral doses, but is also given in 20-mg doses to people more resistant to its effects, for the treatment of insomnia. Increases in subjective sleep quality and subjective total sleep time for nighttime sleep in elderly insomniacs have been demonstrated by Hedner et al.² This group also found a reduction in subjective sleep latency for subjects taking both 5- and 10-mg doses, as did Elie et al³ using a 10-mg dose in adult insomniacs. Walsh et al⁵ found a significant reduction in time to persistent sleep (subjective and polysomnographic data) with a 10-mg dose, while total sleep length was not significantly increased, and there were minimal changes in sleep architecture.

Studies have been conducted to determine the effect of zaleplon upon performance, both with and without sleep. In a review of this literature, 2 studies were found to have significant nega-

tive effects, which persisted for 3 to 5 hours after a single 10-mg dose was given.^{5,6} The remainder found negative effects to abate by 3 hours or to not be present at all. Thus, there is little to no evidence that counters the idea of using zaleplon for accomplishing short daytime sleep.

Previous studies do not answer the question of whether there are benefits to the use of zaleplon in normal rested individuals attempting daytime sleep. The primary goal of this study was to examine the ability of zaleplon to improve both the quantity and quality of daytime sleep in a normal, non-sleep-deprived, adult population. Secondary goals were to study the impact of the drug on postawakening performance and subjective symptoms.

METHODS

Participants

Twelve participants, 6 men and 6 women, volunteered to participate in this study. The mean age of the group was 28.1 years (range 19-43 years). The mean weight for males was 78.7 kg (range, 63.5-89.4 kg), and the mean weight for females was 58.3 kg (range, 44.5-70.3 kg). Based upon a telephone interview and a sleep-history survey, participants were non-shift workers, with no record of sleep disorders, and were not heavy caffeine users. Participants were screened medically (blood chemistry and liver function) prior to their first experimental session. Participants were paid for their participation and signed a voluntary consent document prior to participation. The research protocol for this experiment was reviewed by the Brooks Air Force Base Institutional Review Board, approved by the Air Force Surgeon General (#F-BR-2002-0030-H), and funded by the Air Force Research Laboratory (contract #F41624-97-D-6004).

Design and Procedures

The study was conducted at the Chronobiology and Sleep Laboratory located at Brooks Air Force Base, Tex. The zaleplon doses used in this study were 10-mg zaleplon capsules, individually repackaged inside gelatin capsules. Placebos were capsules

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of identical appearance but containing granular fiber. All capsules were prepared by the Wilford Hall Pharmacy, Lackland AFB, Tex.

A repeated-measures design was employed in which each subject received zaleplon and placebo on separate test weeks. Drug administration was counterbalanced and double-blinded. Participants were told to get a normal night's sleep and to not consume alcohol the night before an experimental session. Participants were limited to 1 caffeinated beverage on the morning of a session. Training on the performance tests was accomplished the week prior to the first experimental session. Participants experienced 1 experimental session per week (10 hours duration) for 2 successive weeks. Participants arrived at 10:30 AM and completed 1 set of warm-up performance trials, followed by lunch. Electroencephalogram (EEG) electrodes were then applied, and data recording began. Participants completed their baseline testing trial at noon. Drug administration occurred at 1:00 PM, and participants then attempted to sleep from 1:00 to 4:30 PM. Participants, if not already awake, were awakened at 4:30 PM (3.5 hours after the dose) and immediately began testing. Testing was performed again at 5:00, 6:00, 7:00, and 8:00 PM.

Tests and Measures

Sleep Measures

SleepWatch-L model actigraphs (Ambulatory Monitoring, Inc., Ardsley, NY) and activity logs were issued to each participant to record sleep-wake information 3 days prior to each experimental session. During the experimental sessions an EEG Technology ambulatory recorder (model #34-24R8B20, Leveroy, Netherlands) was used to collect EEG signals from the O4, C2, A1, and A2 scalp leads of the International 10-20 system⁷ and electrooculogram signals to support sleep scoring by a polysomnographic technologist. A total of 11 electrodes were used (4 scalp, 2 mastoid, 2 outer canthi, 2 chin, 1 forehead). The EEG signal was digitized at 128 samples per second. Records were analyzed with software developed by Stellate Systems (Montreal, Canada). Sleep latency, total sleep time, time spent in each stage of sleep, and stage of sleep upon awakening were assessed.

Performance Measures

Seven cognitive-performance tests (Code Substitution [Learning, Immediate, & Delayed], Simple Reaction Time, Mathematical Processing, Matching to Sample, and Symbolic Logical Reasoning) from the Automated Neuropsychological Assessment Metrics battery and the Psychomotor Vigilance Test were administered at each of the 6 test times of each experimental session. Grip strength and balance were assessed hourly throughout the session as well. A word memory test was given 30 minutes and 3.5 hours after awakening.

Affect and Symptom Measures

The Profile of Mood States, a modified Stanford Sleepiness Scale, and a sleep-aid symptom survey (containing 17 items relevant to this study) were administered at all trials.

Statistical Procedures

EEG sleep variables were analyzed using Student 2-tailed paired *t* tests to compare the effects of zaleplon with placebo. For the remaining variables, repeated-measures analyses of variance were used for interval data, and Wilcoxon signed-rank tests were used for ordinal data to test for significant drug effects. Prior to analysis, the change from baseline was calculated at each post-sleep time point for all outcome variables except word memory and the sleep variables (which did not have baselines) to counter any potential week-to-week differences in individuals' responses. Based on a power analysis for the tests performed on the sleep variables (the primary tests of interest) we determined that, when testing at the 2-tailed .05 α level, a sample of 12 participants would provide a 90% chance of detecting a standardized effect size equal to 1.0.

RESULTS

One of the 12 participants was dropped from the study due to the development of a medical concern unrelated to the study. An additional participant was removed from the polysomnographic analysis due to data loss in one experimental session.

Sleep

Based on data collected with the activity logs and actigraphs, there was no significant difference between the average sleep attained for the three nights preceding the zaleplon and placebo sessions (zaleplon, 7.4 hours \pm 1.2 SD; placebo, 7.8 hours \pm 1.6 SD). Over the 2 sessions, the mean sleep start time for sleep the night before the study was 11:54 PM. Napping in our participants was minimal, in general, with naps occurring on 5 out of 60 recorded days.

Descriptive statistics and results for the sleep variables are shown in Table 1. Mean total sleep time and, consequently, sleep efficiency were marginally better under zaleplon than under placebo. Total slow-wave sleep (stage 3 + stage 4) was significantly greater for the zaleplon condition. We observed a 60% gain in stage 3 sleep under zaleplon and a 37% gain in stage 4 sleep under zaleplon when we split the slow-wave sleep into stages.

Performance

Of the 11 performance tests, drug main effects were observed for Code Substitution Learning ($F_{1,10} = 5.90$, $P = .036$, $MSE = 95.5$) and Match to Sample ($F_{1,10} = 12.99$, $P = .005$, $MSE = 96.7$), and a drug effect was also detected for word memory at the 7-hour postdose trial (Wilcoxon, $z = 2.22$, $P = .026$). In each case, zaleplon performance was better than placebo performance.

Affect and Symptom

No significant differences were found between the placebo and zaleplon conditions with respect to subjective sleepiness, the Profile of Mood States, or any item in the Symptoms Questionnaire. Sleepiness and Profile of Mood States scores changed very little from baseline. Subjective symptoms were rarely and equally recorded under both drug conditions. Following awakening in the second experimental session, only

half of the participants accurately guessed the drug condition they were under.

DISCUSSION

Overall, zaleplon significantly improved the quality of sleep (ie, amount of slow-wave sleep) and marginally increased the total sleep time for the group, relative to placebo. In a posthoc inspection of the individual participant outcomes, we found that every participant experienced at least a 15% improvement under zaleplon in 1 of the 2 measures with no marked decrease in the other.

The participants of this study were non-shift-working individuals who were attempting to sleep during a period when they would normally be awake. The sleep-initiation start time was also a time when the propensity to remain asleep was low relative to nighttime levels in unrested individuals.⁸ Participants received what they would consider a normal night's sleep, not quite 7 hours, the night prior to the experimental sessions. Given that optimal rest involves 8 or more hours of sleep a night, these participants had a sleep debt likely equivalent to that of the population at large. In addition, the ambient and physical conditions were ideal for sleep: participants slept in slightly cool (21.1°) light- and sound-attenuated private rooms, were completely prone and resting on a comfortable bed with a desired level of sheets and blankets, and were precluded from performing any activities other than sleeping or reading in bed. It is not surprising then that, even under placebo, participants were able to sleep for a substantial duration, 2.72 hours. Thus, that zaleplon even marginally extended sleep duration to 3.03 hours supports its hypnotic efficacy. A more-controlled sleep environment prior to each session would probably result in reduced sleep debts for the participants and would be a fairer test of zaleplon, since it would reduce the floor effect for sleep. Additionally, participants in this study were restricted to 3.5 hours of daytime sleep, which may have produced a ceiling effect. A study with unrestricted daytime sleep might increase the difference seen between placebo and zaleplon as well.

There was no drug-condition difference observed for sleep latency. Under both conditions, participants fell asleep quickly (< 14 minutes). Given this short placebo sleep latency, it is unlikely that significant levels of zaleplon were in the participants' system, since the digestion time of the zaleplon capsule within a gel cap should be approximately that duration or longer. This is in

agreement with Multiple Sleep Latency Test results, in which participants have been found to have a mean latency to sleep onset of approximately 12 minutes at 1:30 PM.⁹

No deleterious cognition, memory, balance, or muscular performance effects were observed under zaleplon when compared to the placebo condition. To the contrary, cognitive performance, as measured by our battery of tests, was significantly improved in 3 tests for the zaleplon condition relative to placebo. Across all trials, zaleplon performance was never worse than placebo performance for these 3 tests (including the first test point, which captured sleep inertia effects). To attempt to determine if there was some facet of sleep that led to improved performance in this study, we examined the relationship between in-study sleep (total sleep time and total slow-wave sleep) and the performance variables that exhibited the greatest improvement under zaleplon relative to placebo (eg, matching to sample throughput) using Pearson correlation analysis. No significant correlation between performance and either sleep variable was observed. Thus, sleep differences do not seem to account for the possibly beneficial performance results of zaleplon.

Participants were unable to accurately determine whether they had received zaleplon or placebo. Additionally, no significant differences between drug conditions were observed for any of the symptom data. Nor were there any anecdotal reports of discomfort or unease following awakening from zaleplon-induced sleep. Thus, participants awakened from a restful sleep not knowing whether or not they had received a sleep aid. This bodes well for postawakening performance and supports the use of zaleplon in situations when only short periods are available for sleep.

This research shows zaleplon to be efficacious at promoting sleep in normal individuals during the day. It also shows that zaleplon increases the amount of slow-wave sleep. 'Negative' changes in sleep architecture were not expected from zaleplon, while 'positive' changes seemed unlikely, given the study by Walsh et al.⁴ However the general lack of polysomnographic evidence in the zaleplon literature left the issue somewhat open. The ability of zaleplon to promote 'deep' sleep during daytime rest periods may be particularly useful in demanding environments. As mentioned earlier, these results were observed in a physical environment ideal for sleep. Further research should investigate the robustness of the hypnotic efficacy of zaleplon by requiring individuals to sleep in less-ideal environments. In a study designed specifically to examine the sleep-promoting effects of zaleplon in 1 type of nonconductive sleeping environment (noise-

Table 1—Polysomnography: Descriptive Statistics and *t* Test Results

Variable	Mean		SD (diff)	<i>t</i> (9 df)	<i>P</i> (2-tailed)
	Placebo	Zaleplon			
Stage 1, min	14.6	15.1	17.1	0.09	.928
Stage 2, min	90.1	91.6	34.9	0.14	.892
Stage 3, min	11.8	18.9	10.8	2.09	.066
Stage 4, min	25.6	35.1	16.7	1.80	.106
Total slow wave sleep, min	37.4	54.0	18.0	2.92	.034*
Rapid eye movement, min	20.8	21.3	16.1	0.10	.924
Sleep latency, min	12.6	13.5	10.8	0.26	.792
Sleep efficiency, %	76.4	86.6	15.1	2.13	.062
Total sleep time, min	162.8	182.0	30.2	2.02	.074

* Significant difference between placebo and zaleplon ($P < .05$).

induced sleep-maintenance insomnia model), Stone¹⁰ found zaleplon to reduce the time to persistent sleep over placebo (10 mg and 20 mg). Stone found no other changes in sleep under the 10-mg condition.

In summary, the use of zaleplon allowed participants to accomplish a greater amount of sleep and to sleep 'more deeply' than under placebo. Furthermore, performance was not adversely impacted following a 3.5-hour daytime sleep under zaleplon, nor were any undesirable symptoms induced. Thus, zaleplon has shown significant benefits for individuals attempting to accomplish uninterrupted sleep during a nonoptimal rest period.

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