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Comparative Efficacy of Zolpidem and Eszopiclone in Primary Insomnia

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ABSTRACT

Primary insomnia is sleeplessness or the perception of poor quality sleep that cannot be attributed to a medical, psychiatric, or environmental cause (such as drug abuse or medications. Zolpidem and eszopiclone are hypnotic agents with demonstrated efficacy. Each has been shown to alleviate insomnia. The primary objective of this study was to compare hypnotic efficacy of zolpidem 10 mg to that of eszopiclone 2 mg in a double blind, parallel group, placebo-controlled study. Subjects were assessed to assure that they were in good mental and physical health, with no evidence of significant cardiovascular, pulmonary, renal, hepatic, gastrointestinal, physical or CNS disease. They were also excluded if a physical examination revealed a significant medical abnormality; if they had a medical condition in which treatment with hypnotics would be contraindicated; if abnormal laboratory test findings necessitated treatment; or if their sleep schedulehad varied regularly by at least 6 h within the last 6 months. The digit symbol substitution test (DSST) (Stone, 1984) and symbol copying test (SCT) (Lucki et al., 1986), standard performance measures frequently utilized to assess levels of alertness or sedation, were administered. The comparison between zolpidem and Eszopiclne was made at a nominal significance level of 0.05. All other pairwise significant differences between treatment group means were assessed using the Tukey±Kramer multiple comparisons procedure. Hypnotic efficacy was evaluated using PSG values and subjective estimates of the interval from lights out to initiation of persistent sleep, perceived duration of wakefulness prior to initiation of sleep, and PSG measurements and subjective estimates of ease of entry into sleep and of the capacity to maintain sleep over the night. With respect to the PSG measures of sleep latency and sleep efficiency, no significant differences were observed between zolpidem and ezopiclone. With regard to sleep architecture, zolpidem and placebo groups spent a similar percentage of time in the various sleep stages, while the eszopiclone group had significantly less Stage 3/4 sleep than the zolpidem group and significantly more Stage 2 sleep than the zolpidem or placebo groups.

KEYWORDS Sleep Latency ; Insomnia ; Hypnotics

INTRODUCTION

Primary insomnia is characterized by an increased sleep latency (the interval from lights out to sleep onset) and by decreased total sleep time in a previously normal sleeper (International Classification of Sleep Disorders Diagnostic and Coding Manual, 1990). Primary insomnia is sleeplessness or the perception of poor quality sleep that cannot be attributed to a medical, psychiatric, or environmental cause (such as drug abuse or medications). Common causes of primary insomnia include environmental disturbances, time zone changes and acute stress. Management recommendations generally suggest that efforts should be made to define and treat underlying causes, with hypnotic medication used as an adjunct (National Institutes of Health Consensus Development Conference Statement, 1991). Other acute changes in mental set and physical setting can also precipitate insomnia. Shift workers who must sleep during daytime hours frequently experience a similar pattern of sleep disturbances (Akerstedt, 1988). Zolpidem is a imidazopyridine hypnotic agents whereas Eszopiclone a cyclopyrrolone hypnotic agent.Both are Non-Benzodiazepine Hypnotic agents. Zolpidem studies in various insomniac populations have demonstrated a low incidence of next-day disturbances of psychomotor performance (Scharf et al., 1994; Roth and Vogel, 1995; Fair-weather et al., 1992) and maintenance of normal sleep architecture (Merlotti et al., 1989). Eszopiclone also has been shown to be effcacious in the treatment of primary insomnia in various models including phase delay (French et al., 1990). Eszolipclone and zolpidem are known to modify normal sleep architecture), with a tendency to decrease Stages 3 and 4 of non-REM sleep (Sachais et al., 1990) and to increase Stage 2 sleep (Roehrs et al., 1990). The clinical significance of these effects, if any, are uncertain. Administration of eszopiclone 2 mg does not appear to cause impaired next-day performance (Donaldson and Kennaway 1991; Roth et al., 1985), whereas higher doses lead to psychomotor and memory impairment (Fraschini and Stankov, 1993). In the present study, the effects of treatment with zolpidem, eszopiclone and placebo were compared in a sleep laboratory study of primary insomnia. The primary objective of this study was to compare hypnotic efficacy of zolpidem 10 mg to that of eszopiclone 2 mg in a double blind, parallel group, placebo-controlled study. The two doses used in this study were the manufacturers' recommended doses for adult use at the time of study initiation, and at the time that the study was initiated it was felt that these were equipotent doses.

METHODS

Subjects

Subjects were required to maintain a sleep diary for the 5 days preceding the study night, and met thefollowing criteria to qualify for randomization: a bedtime each night between 9:30 and 11:30 PM, and reported sleep each night of between 7 and 8 h. Subjects were excluded for any of the following reasons: a past history or current evidence of any serious medical or psychiatric disorder, regular use of medication with known central nervous system (CNS) effects, alcoholism or drug abuse (within 1 year), history of hypersensitivity to benzodiazepines or other CNS depressants, seizures or serious head injuries, previous sleep experience in a sleep laboratory, and sleep apnea or nocturnal myoclonus. Subjects were assessed to assure that they were in good mental and physical health, with no evidence of significant cardiovascular, pulmonary, renal, hepatic, gastrointestinal, physical or CNS disease. They were also excluded if a physical examination revealed a significant medical abnormality; if they had a medical condition in which treatment with hypnotics would be contraindicated; if abnormal laboratory test findings necessitated treatment; or if their sleep schedulehad varied regularly by at least 6 h within the

last 6 months. Volunteers were required to be within 25% of their ideal body weight as defined by the Metropolitan Life Insurance Company Statistical Bulletin. All volunteers provided written, informed consent and received payment for their participation. A total of 768 healthy volunteers were enrolled into the study, 634 of whom were randomized. Among the 134 subjects dropped from the study prior to randomization, reasons for exclusion included failure to meet entry criteria (103), failure to comply with study schedules (16), and use of prohibited medication (5). A total of 631 completed the trial; two subjects left the sleep lab during the night of study after receiving study medications, and one was determined to have not been using acceptable birth control after having received treatment. Subjects were normal sleepers as defined by the following criteria: a customary total sleep time of 7± 8 h with a usual bedtime between 9:30 and 11:30 PM, a reported typical sleep latency of 30 min or less, and no complaints of insomnia or decreased daytime functioning associated with sleep loss.

Procedure

At study entry, within 1 week prior to the study night, subjects provided a medical history and received a physical examination. Screening laboratory blood and urine tests were performed, including a urine drug toxicology screen. The digit symbol substitution test (DSST) (Stone, 1984) and symbol copying test (SCT) (Lucki et al., 1986), standard performance measures frequently utilized to assess levels of alertness or sedation, were administered. All subjects agreed to abide by the following restrictions in order to be accepted as participants in the study: no caffeinated beverages after 3:00 PM on any of the 5 days preceding the study or on the day of the study night, no food within 2 h of arrival in the laboratory, no alcohol or CNS medications during the day preceding the study night, and no use of medications within 2 weeks of the study night without the knowledge and approval of the investigator. Nicotine use was allowed. Subjects were randomly assigned to one of the three treatment groups: zolpidem 10 mg; Eszopiclone 2 mg; or placebo. The ratio between groups was 3:3:1, respectively, based on a statistical analysis which demonstrated that this ratio provided a proper balance of subjects for the zolpidem and Eszopiclone groups, within which primary comparisons would be made, with a requirement for fewer subjects in the placebo condition. pon arrival at the sleep laboratory for the study night, a urine sample was collected for drug screening, vital signs were taken and a pre-sleep questionnaire assessing the level of subjective sleepiness was completed. Medication was dispensed in a double- blind fashion 15 min before `lights-out', defined for each subject as 2 h earlier than the `mean usual bedtime' for that subject. The mean usual bedtime was determined by averaging the bedtime recorded in each subject's sleep diary for the five nights immediately prior to randomization. Drug was administered 15 min prior to bedtime due to the rapid onset of action of Zolpidem. A standard polysomnographic (PSG) tracing was recorded for 7.5 h after `lights-out.' Subjects were then awakened and vital signs were taken; after toilet, dressing and a light breakfast, subjects completed the DSST and SCT, a 10-item Morning Questionnaire, and a 7-item Drug Effects Questionnaire. An assessment of heel-to-toe gait as a measure of intoxication was performed. If the subject desired to return to bed in order to obtain additional sleep or demonstrated possible intoxication, as suggested by abnormalities in the heel-to-toe gait test, additional time in bed was allowed. PSG recordings were scored using standard Rechtschaffen and Kales scoring criteria (Rechtschaffen and Kales, 1968). Subjective assessments of sleep were obtained using the Morning Questionnaire and the Drug Effects Questionnaire. The ability to concentrate in the morning and severity of morning sleepiness complaints were rated by the subjects using a visual analog scale. Severity of morning sedation was assessed by the DSST and SCT. Information regarding adverse events was obtained from spontaneous patient reports, the assessment of vital signs and the Morning Questionnaire.

Statistical analysis

The Intent-to-treat Data Set included all data from all 634 randomized patients. Following completion of the study, minor protocol violations, such as use of prohibited medications on the day of the study or variance from the required sleep schedule in the days prior to the sleep laboratory night, were determined to have been made by 76 patients. The group of 558 patients with no such protocol violations comprised the Evaluable Data Set. All outcome measures which were analyzed for the Intent-to-treat Data Set were repeated using results from the Evaluable Data Set.Results of data analysis for the Evaluable Data set did not differ from data analysis of the Intent-to-treat Data Set; therefore, only results from the Intent-totreat Data Set are presented. Comparison of treatments was performed using an analysis of variance (ANOVA) for each efficacy measure. The comparison between zolpidem and Eszopiclne was made at a nominal significance level of 0.05. All other pairwise significant differences between treatment group means were assessed using the Tukey±Kramer multiple comparisons procedure. In this study, as in other zolpidem studies, to reduce heterogeneity among the treatment variances the values of latency to persistent sleep were transformed by the logarithm of the value and the values of sleep efficiency were transformed by the logit of the value where the logit of a number p, $0<p<1$, is defined as log (p/1-p). The overall ANOVAs were performed on these transformed values. Performance measures were analyzed using ANOVAs.

Results

Demography

No significant demographic differences were found among the three treatment groups, including the 631 subjects who completed the trial. Similarly, no significant between-group differences were found in any aspects of sleep history, including assessment of usual sleep quality, sleep latency, sleep time, wake time during sleep, depth of sleep, number of awakenings, daytime sleepiness, and daytime ability to function. The results suggested that all subjects were healthy, normal sleepers with no complaints regarding sleep initiation or sleep maintenance.

Hypnotic efficacy

Hypnotic efficacy was evaluated using PSG values and subjective estimates of the interval from lights out to initiation of persistent sleep, perceived duration of wakefulness prior to initiation of sleep, and PSG measurements and subjective estimates of ease of entry into sleep and of the capacity to maintain sleep over the night. Latency to persistent sleep and sleep efficiency, measured polysomnographically, were the primary outcome measures in these categories. Treatment effects on sleep initiation and sleep efficiency are summarized in Table 1. There was no significant difference among zolpidem, Eszopiclone and placebo with regard to latency to persistent sleep as measured by PSG. Subjective latency to persistent sleep, however, was significantly longer ($p<0.003$) for placebo than for either the zolpidem or Eszopiclon treated groups. There was no significant difference between the two active treatment groups. Treatment comparisons of the subjective ratings of ease of falling asleep showed that the subjects on zolpidem reported greater ease in falling asleep than those on Eszopiclon or on placebo. Subjects who received Eszopiclon found it significantly easier to fall asleep than those that received placebo. For PSG sleep efficiency, a primary outcome measure, a significant difference was detected among treatments. The placebo group generated a sleep efficiency of 86.6%, significantly lower (p.0.004) than that seen with both zolpidem (90.3%) and Eszopiclon (89.5%), with no significant difference observed between the two active drugs. The effects of zolpidem and Eszopiclon on several parameters of sleep maintenance and sleep quality are presented in Table 2. PSG wake time during sleep was significantly different (p.0.007) between zolpidem (19.2 min) and placebo (28.6 min), with no significant difference observed between eszopiclone (21.6 min) and placebo or between zolpidem and eszopiclone.

Table-1. The Effect of Zolpidem , Eszopiclone or Placebo on parameters of sleep initiation and sleep efficiency (minutes ± SE)

	Placebo,N = 89	Zolpidem 10mg ,N=269	Eszopiclone 2mg,N=272
PSG latency to Persistent Sleep	29.3 ± 3.0	24.0 ± 1.2	26.2 ± 1.3
Sunjective latency to Persistent sleep #	35.0 ± 3.9	23.0 ± 1.3 *	23.9 ± 1.2 *
Subjective Ease of falling asleep	56.7 ± 2.69	42.4 ± 1.55 * ^	47.7 ± 1.53 *
PSG sleep efficiency(%± SE)	86.6 ± 1.14	90.3 ± 0.53 *	89.5 ± 0.45 *

Scale : 0 = very easy ; 100 = not easy

* Significantly different from placebo (< 0.01)

^ Significantly different from temazepam (p < 0.003)

Table-2 : The effect of Zolpidem , Eszopiclone or Placebo on Parameters of Sleep Maintenance and Sleep Quality

	Placebo,N=89	Zolpidem 10mg,N=269	Eszopiclone 2mg,N=272
PSG wake time during sleep (minutes ± SE)	28.6 ± 3.32	19.3 ± 1.56*	21.6 ± 1.32
PSG number of awakenings (mean ± SE)	5.2 ± 0.37	4.1 ± 0.22*^	4.7 ± 0.18
Subjective total sleep time (minutes ± SE)	398.2 ± 7.77	423.5 ± 2.55*^	414.1 ± 3.06*
Subjective wake time after sleep (mean ± SE)	27.0 ± 4.69	10.5 ± 1.40*^	15.8 ± 1.65*
Subjective number of awakenings (mean ± SE)	3.0 ± 0.29	1.3 ± 0.084*^	2.0 ± 0.11*
Subjective quality of sleep #	2.8 ± 0.08	2.1 ± 0.04*^	2.3 ± 0.05*

Scale;1=excellent ;2=good ;3=fair ;4=poor

* Significantly different from placebo (p< 0.01)

^ Significantly different from Eszopiclone (p<0.01)

In contrast, subjective wake time after sleep was rated differently among the three treatment groups. Both zolpidem (10.5 min) and eszopiclone (15.8 min) were significantly (p<0.001) different from placebo (27.0 min) and from each other, with zolpidem subjects reporting significantly (p<0.05) less wake time compared to the ezopiclone group. Analysis of data for number of awakenings yielded comparable results for PSG and subjective criteria. PSG evaluation revealed that the zolpidem group (4.1 awakenings) had significantly fewer awakenings (p.0.008) than either the eszopiclone (4.7 awakenings) or the placebo (5.2 awakenings) groups; the eszopiclone group was not significantly different from placebo. Using subjective criteria for number of awakenings, both zolpidem (1.3 awakenings) and eszopiclone (2.0 awakenings) were significantly different from (p<0.001) and superior to placebo (3.0 awakenings); the zolpidem group reported significantly (p<0.001) fewer awakenings than did the eszopiclone group. Thus, all three treatments were significantly different from each other, with subjects in the zolpidem group reporting and experiencing the least number of awakenings. The results of the subjective total sleep time, as assessed by the Morning Questionnaire, generally reflect the objective data obtained by PSG. Both the zolpidem (423.5 min) and the eszopiclone (414.1 min) reported significantly (p<0.001) longer sleep times than the placebo group (398.2 min). In addition, there was a significant(p<0.05) difference (favoring zolpidem) between the zolpidem and eszopiclone groups. Subjects also evaluated their overall sleep quality, using a rating scale where 1is excellent and 4is poor. A significant overall treatment difference was found, with subjects on zolpidem (2.1) reporting significantly (p<0.001) better quality sleep than subjects on either placebo (2.8) or eszopiclone (2.3).

Sleep stages

The percent of sleep time spent in the various stages of sleep (Stages 1, 2, 3/4, REM) is presented in Table 3. For the single night of treatment, subjects in the eszopiclone group (59.3%) had a significantly (p<0.001) higher percent of Stage 2 sleep time than did subjects in the zolpidem (56.5%) and placebo (56.7%) groups. Subjects in the eszopiclone group (17.0%) had significantly (p<0.001) less Stage ¾ sleep than did subjects in the zolpidem group (21.1%); the placebo group (19.1%) did not differ from either the zolpidem or eszopiclone groups. The percent of time spent in REM sleep was similar forall treatment groups.

Table 3. Mean percent of sleep time spent in each sleep stage (mean ± SE)

	Placebo, N =89		Zolpidem 10 mg, N =269		Temazepam 15 mg, N =272	
Stage 1	7.8	± 0.59	6.8	± 0.28	7.3	± 0.28
Stage 2	56.7	± 1.03	56.5	± 0.54	59.3	± 0.51 *^
Stage 3/4	19.1	± 0.86	21.1	± 0.55	17.0	± 0.45^
REM	16.5	± 0.55	15.6	± 0.29	16.4	± 0.30

* Significantly different from placebo (p < 0.001).

^ Significantly different from zolpidem (p < 0.001).

DISCUSSION

The relationship between subjective and objective measures of sleep has been examined in several studies (Carskadon et al., 1976; Kryger et al., 1991; Lewis, 1969), in which there is general agreement on a significant correlation between subjective and objective measures of total sleep time and sleep latency. Lewis (1969) reported that normal sleepers underestimated total sleep time, but overestimated sleep latency. In the present study, we found a good agreement between objective and subjective measures of sleep, with close numerical correlation between them. This study thus provides the opportunity to compare the hypnotic efficacy of zolpidem to that of eszopiclone, using both objective and subjective sleep parameters. Analysis of the effects of the two hypnotics on sleep initiation and sleep maintenance demonstrated that neither zolpidem nor eszopiclone objectively facilitated initiation of sleep. Subjectively, both drugs reduced sleep latency and facilitated falling asleep, with zolpidem subjects experiencing a significantly greater ease of falling asleep than did ezopiclone subjects. Subjective and objective sleep latencies were numerically and qualitatively comparable. With regard to sleep maintenance, both drugs induced measurably longer total sleep times. The limited time in bed of 7.5 h used in this study may have contributed to the high levels of sleep efficiency seen. Zolpidem subjects reported greater improvement in other parameters of sleep maintenance both objective (wake time during sleep and number of awakenings) and subjective (number of awakenings and quality of sleep) than did eszopiclone subjects. Overall, zolpidem 10 mg generated a larger number of objective and subjective effects on hypnotic efficacy outcome measures than did eszopiclone 2mg

Table-4 : Summary of sleep outcome measures comparing Zolpidem and Eszopiclone

Outcome Measure	Zolpidem	Eszopiclone	Z:E** (p<0.05)
Objective			
Sleep Latency*	-	-	-
Sleep Efficiency*	↑	↑	-
Number of Awakenings	↓	-	-

Wake time during sleep	↓	-	-
Subjective			
Sleep Latency	↓	↓	-
Total Sleep Time	↑	↑	Z > E
Nu. Of Awakenings	↓	↓	Z < E
Ease of Falling Asleep	↑	↑	Z > E
Wake time after Sleep	↓	↓	Z < E
Quality of Sleep	↑	↑	Z > E

* Primary Outcome Measure

[↑: Significantly greater than Placebo (p<0.01); ↓: Significantly smaller than placebo (p<0.01)

** Significant Difference between Zolpidem and Eszopiclone (p <0.05)

(Table 4). Three PSG outcome measures (efficiency, wake time during sleep and number of awakenings) were significantly improved with zolpidem compared to only one with eszopiclone (efficiency). Of the six subjective outcome measures, five were rated significantly better for zolpidem compared to eszopiclone (total sleep time, number of awakenings, ease of falling asleep, wake time after sleep and quality of sleep). The sleep architecture (percent of time spent in different sleep stages) seen in subjects who received zolpidem was essentially identical to that of subjects who received placebo. This finding confirms numerous previous observations in which zolpidem was found to preserve normal sleep architecture, and contrasts with changes in sleep architecture induced by eszopiclone, which produced a significant increase in sleep spent in Stage 2. In summary, in this double-blind, placebo-controlled trial, zolpidem 10 mg provided greater subjective hypnotic efficacy than eszopiclone 2 mg in the tested model of primary insomnia. With respect to the PSG measures of sleep latency and sleep efficiency, no significant differences were observed between zolpidem and ezopiclone. For two sleep maintenance variables, wake time during sleep and\ number of awakenings, zolpidem produced significantly better results than placebo while eszopiclone did not. With regard to sleep architecture, zolpidem and placebo groups spent a similar percentage of time in the various sleep stages, while the eszopiclone group had significantly less Stage 3/4 sleep than the zolpidem group and significantly more Stage 2 sleep than the zolpidem or placebo groups. Zolpidem significantly improved sleep compared to eszopiclone for many subjective measures (total sleep time, number of awakenings, ease of falling asleep, wake time after sleep onset, and sleep quality. Treatment emergent adverse event incidence rates were small and similar in the three treatment groups.

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