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To study the efficacy of zolpidem in inducing daytime sleep and maintaining mental alertness subsequent to awakening

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ABSTRACT

Introduction: In operational environment, naps in the daytime could help in maintaining alertness and hence performance. However, due to operational constraints and circadian effect, an aircrew may not get good quantity and quality sleep during the day, even though adequate sleep window is available. In such situations, zolpidem could be effectively utilized to induce sleep. This study intended to examine the beneficial effects of zolpidem 5 mg and 10 mg in inducing daytime sleep and maintaining mental alertness in the subsequent awake period.

Material and Methods: In a double-blind, placebo-controlled, repetitive measure design, 20 healthy male volunteers were longitudinally evaluated for their mental alertness and subjective perception of quality of sleep, sleepiness, and fatigue for a period of 12 h following zolpidem-induced daytime sleep. In addition, feedback was obtained on known untoward effects of zolpidem.

Results: Zolpidem, in doses of both 5 mg and 10 mg, could induce daytime sleep in all participants. Quality of sleep induced by zolpidem was similar to that of night sleep quality. With 5 mg zolpidem, the alertness was maintained soon after awake from daytime sleep, whereas participants perceived sleepiness for a period of 1–2 h with 10 mg zolpidem. Following awakening, there was a significant increase in the number of lapses with time in the placebo group, which was not found significant with administration of zolpidem. The occurrence of untoward effects with 10 mg zolpidem was more than 5 mg zolpidem.

Conclusion: Zolpidem 5 mg and 10 mg were found to be effective in inducing daytime sleep and maintaining performance subsequent to arousal. The sleepiness following arousal as well as adverse effects was found to be more for zolpidem 10 mg as compared to 5 mg. A mandatory ground observation of minimum of 8 h should be ensured following intake of zolpidem before undertaking any flying duties.

Keywords: Circadian effect, Zolpidem, Sleepiness, Fatigue, Performance

INTRODUCTION

Modern aviation operations because of multiple flight operation, long duty hours, early reporting times, restricted rest periods, suboptimal sleeping conditions, rotating work shifts, and jet lag, pose significant challenges for the aircrew.[1] Such operations, which involve insufficient recovery breaks, sleep deprivation, and circadian disruptions, expose the aircrew to a significant risk of developing fatigue. Fatigue is a complex internal state that affects physiological activity and mental state of aircrew and results in impaired judgment, difficulty in focusing, attentional lapses, and slower reaction

time with potential for performance decrement. Decreased performance related to sleep loss and circadian dysrhythmia has been implicated in some major aviation disasters.[2]

Many preventive strategies are being implemented to counteract the effects of fatigue in aviation duties; these include duty schedules, extended crew rest period, cockpit nap, use of bright lights during night shifts, alertness management education, and training.[3] However, these strategies cannot be always implemented due to operational constraints and hence not found to be much effective in mitigating fatigue in operational conditions. In such situations, it becomes difficult for an aircrew to get undisturbed sleep due to factors such as lack of sleep drive, uncomfortable sleep environment, and influence of social and other extrinsic factors. To overcome these sleep disturbances, in designated periods of rest dictated by operational requirements, use of drugs like hypnotics which aid in inducing and sustaining sleep, has been approved in military operations.[3]

Studies on use of hypnotics have shown that they can induce sleep in short time and maintain post-awake alertness.[3] Zolpidem is preferable among hypnotics because it helps in attaining sleep even in unconducive environment, does not have significant detrimental effects on psychomotor functions and overall sleep architecture. Assessment of attention and psychomotor skills has revealed that zolpidem has no residual effect on vigilance, concentration, and coordination performances on next day of zolpidem intake. Furthermore, no significant memory impairment has been observed 6 h after intake of zolpidem. Many studies have shown zolpidem to be relatively free from any adverse effect and do not cause tolerance or promote dependence.[4,5]

The present study was conducted to determine the efficiency of zolpidem on inducing sleep and maintenance of mental alertness for a period of 6 h subsequent to awakening (6 h after drug intake).

MATERIAL AND METHODS

A double-blind, placebo-controlled repeated measure design was employed on 20 healthy male participants. The exclusion criteria for the participants were; (a) history of any sleep disturbance or psychiatric disorders (b) inadequate sleep the previous night (c) subjects on any drugs or medications (d) smokers (e) females and (f) any disease or infirmity. The study was conducted at sleep laboratory in the Institute of Aerospace Medicine, Indian Air Force in three different sessions. Participants were administered either placebo/5 mg zolpidem/10 mg zolpidem in each session. During each session, the participants were evaluated subjectively and objectively to assess sleepiness, fatigue, and performance. Stanford Sleepiness Scale (SSS), Groningen Sleep Quality Scale (GSQS), and Chalder Fatigue Questionnaire (CFQ) were used for subjective assessment. Psychomotor vigilance task (PVT) monitor was used for objective assessment.

Each session was separated by at least 72 hr gap. Day before each session, participants were instructed not to do strenuous activities and have adequate sleep during the night. On the day of experimentation, each participant reported at 0730 h in the morning. The protocol for testing is given in Table 1. After 1st evaluation at 0800 h, participants were advised to do only routine duties not involving strenuous activities and to report back at 1200 h. They were instructed not to consume caffeine/alcohol during this period. After the 2nd evaluation at 1200 h, participants were advised to go for sleep in the sleep lab. The subjects were not disturbed till next evaluation which was conducted after 6 hours at 1800 h. The experimental protocol is shown in Table 1.

The data were evaluated for normality distribution using Shapiro–Wilk test to select an appropriate statistical test (parametric or non-parametric) for analysis. For analysis of sleep quality (GSQS), sleepiness/alertness (SSS), and fatigue (CFQ), non-parametric test (Friedman ANOVA) was employed, while for PVT data, repeated measures ANOVA was used. The two factors analysed were pharmacological intervention (placebo, zolpidem 5 mg and 10 mg) and time since wakefulness.

RESULTS

Analysis of subjective appreciation of sleep quality showed that 5 mg and 10 mg zolpidem could effectively induce sleep during daytime. Daytime sleep quality in zolpidem group was found to be similar to that of nighttime sleep quality [Table 2].

There was a significant increase in subjective sleepiness with continuous wakefulness in all the three groups;

Table 1: Study protocol.

Evaluation 1	800 h (Baseline)	• Sleep quality (GSGS) • Subjective sleepiness (SSS) • Subjective fatigue (CFQ) • 10 min PVT
Evaluation 2	1200 h Placebo/zolpidem 5 mg/zolpidem 10 mg	• Subjective sleepiness (SSS) • Subjective fatigue (CFQ) • 10 min PVT
SLEEP PERIOD (1200 - 1800 h)		**Tests during 3rd - 9th Evaluations**
Evaluation 3	1800 h	• Sleep quality (GSGS) @ 1800 h
Evaluation 4	1900 h	
Evaluation 5	2000 h	• Subjective sleepiness (SSS)
Evaluation 6	2100 h	• Subjective Fatigue (CFQ)
Evaluation 7	2200 h	• 10-min PVT
Evaluation 8	2300 h	• Assessment of side effects of zolpidem
Evaluation 9	2400 h	

placebo (F = 50.848, $P < 0.001$), zolpidem 5 mg (F = 31.093, $P < 0.001$), and zolpidem 10 mg (F = 52.466, $P < 0.001$). With 5 mg zolpidem, the alertness was maintained soon after waking from daytime sleep, whereas with 10 mg zolpidem, the subjects perceived sleepiness for about 1–2 h after waking vowing to sleep inertia and thereafter their alertness was maintained [Figure 1]. No significant differences in subjective fatigue was observed on analysis of CFQ scores.

The objective assessment by PVT revealed a significant main effect in number of lapses with placebo group (F = 16.761, $P = 0.033$). However, no significant effect was observed with zolpidem 5 mg (F = 3.716, $P = 0.882$) and zolpidem 10 mg (F = 13.725, $P = 0.089$). The same is depicted in Figure 2. The other PVT parameters of performance (mean reaction time, mean reciprocal reaction time, mean 10% fastest reaction time, and mean 10% slow reaction time) did not show any significant changes in any of the group. Analysis of adverse effects revealed that 10 mg zolpidem contributed nine reported side effects compared to two reported side effects with 5 mg zolpidem.

Table 2: Comparison of GSQS (sleep quality) – nighttime versus daytime.

	Placebo	5 mg zolpidem	10 mg zolpidem
800 h	1.35	1.50	1.60
1800 h	2.95	1.75	1.75
	P=0.013	*P*=0.564	*P*=0.366

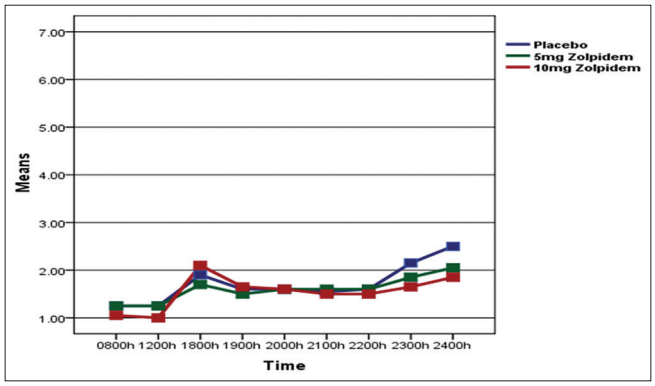

Figure 1: Subjective sleepiness (SSS) versus time.

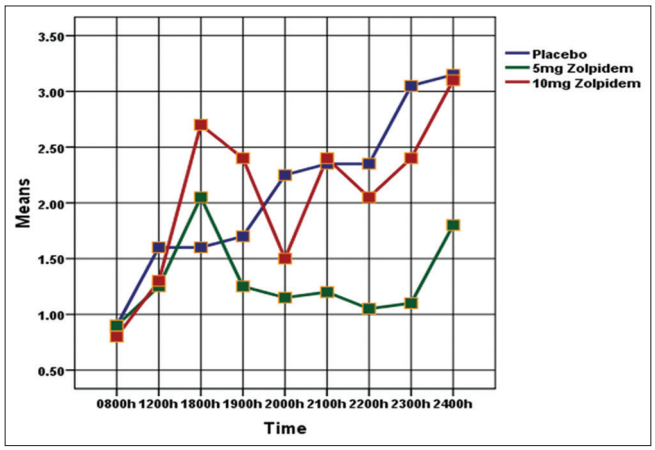

Figure 2: Lapses in Psychomotor Vigilance Task (PVT) with time.

DISCUSSION

The altered sleep quantity and quality are known to affect adversely the psychological and physiological well-being of an individual. Sleep deprivation interferes with the ability of the individuals to overcome the deleterious effects of sleepiness and results in performance deterioration.[6] The primary effect of sleep loss is on cognitive and sustained attention aspects of performance.[7,8] In operational environment, naps in the daytime could help in maintain alertness and hence performance. However, due to operational constraints and environment, and circadian effect, an aircrew may not get good quality and quality sleep during day, even though adequate sleep window is available. In such situations, zolpidem could be effectively utilized to induce sleep. The hypnotic effect of zolpidem has been clearly demonstrated in clinical trials (up to 1 year) in normal, elderly, and psychiatric patient populations with insomnia.[9] The present study intended to examine the efficacy of zolpidem 5 and 10 mg in inducing daytime sleep and effects on sleepiness subsequent to awakening.

The present study observed significant effect of drug intervention on sleep quality and mental alertness which was reflected in results. Zolpidem (5 mg and 10 mg) was found to be beneficial in inducing sleep at a time which was not conducive to sleep. Sleep quality induced by zolpidem was found comparable to routine nighttime sleep. Both 5 mg and 10 mg zolpidem attributed similarly in sleep quality perceived by participants as depicted by the subjective analysis using GSQS. Hence, its utility in inducing quality daytime sleep in an operational setting cannot be overemphasized.

The PVT parameter which showed a significant increase with wakefulness in the placebo group was lapses. However, there were no significant changes in the lapses in both zolpidem 5 mg and 10 mg groups. It has some important implications. Lapses have been documented as one of the important performances measure in sleep studies.[10,11] Lapse hypothesis explains about the effects of sleep loss on performance and it states that sleep loss produces lapses in performance which increase with increasing time duration since wakefulness.[12] Many studies have established the relationship between prior night sleep duration and performance on the psychomotor vigilance task and have observed that lapses were increased with sleep deprivation/sleepiness.[13,14] Hence, the effect on the PVT lapse parameters with wakefulness and changes in its effect due to zolpidem is considered an important observation in our study. Similar observations have also

been made in previous studies. In a study conducted among US Army personnel, zolpidem-induced prophylactic naps enhanced the alertness and performance of sleep-deprived pilots (relative to placebo) during the final 20 h of a 38 h period of continuous wakefulness without producing significant hangover effects.[15]

Following zolpidem-induced daytime sleep, the individuals were able to maintain alertness with minimal duration (1–2 h) of subjective feeling of sleepiness. With 5 mg zolpidem, alertness was maintained optimally soon after awakening from sleep when compared to 10 mg zolpidem as reflected in both SSS and PVT performance (lapse). It means that subjective appreciation of sleepiness following zolpidem-induced daytime sleep will persist for a longer period of time following 10 mg of Zolpidem compared to 5mg dosage. This was considered another important finding in the present study.

Literature shows that with zolpidem rebound insomnia, tolerance (treatment over 6–12 months), withdrawal symptoms, and drug interactions are absent, while dependence/abuse potential is low.[16,17] Overall, zolpidem appears to be a clinically safe and useful hypnotic drug which is devoid of the adverse side effects of the short-acting benzodiazepines.[18] In a study by Caldwell and Caldwell, naps induced with zolpidem offered greater protection from some of the effects of sleep deprivation than "natural" naps.[15] However, such an observation could not be deducted from the present study. Analysis of side effects profile in the present study revealed that study participants experienced side effects in the form of dizziness, headache, nausea, vomiting, and weakness. 10 mg zolpidem contributed nine reported side effects compared to two reported side effects with 5 mg zolpidem These findings further support the beneficial effect of zolpidem 5 mg compared to zolpidem 10 mg. The results of this study substantiate the FDA move of reducing the recommended dose of zolpidem from 10 mg to 5mg.[19]

Zolpidem 5 mg can be used both in civil and military scenario as a pharmacological countermeasure to induce quality daytime sleep before a night mission. However, before operational use of zolpidem, the safety of the drug, in terms of adverse effects, needs to be ascertained on ground for each aircrew. The results of the study indicate maximum 6 h of sleep following zolpidem intake and maximum 2 h of subjective sleepiness subsequent to arousal. Thus, a mandatory period of minimum 8 h of no flying (minimum 2 h of post-wake period) is recommended following intake of zolpidem before undertaking any flying mission.

CONCLUSION

Zolpidem 5 mg as well as 10 mg were found to be effective in inducing daytime sleep and maintaining performance subsequent to arousal. The sleepiness following awakening as well as adverse effects was found to be more for zolpidem 10 mg as compared to 5 mg. A mandatory ground observation of minimum of 8 h must be ensured following intake of zolpidem before undertaking any flying duties. This period must include a minimum 2 h of post-wake period following zolpidem-induced daytime sleep.

Declaration of patient consent

The authors certify that they have obtained all appropriate consent from the participants of the study.

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Conflicts of interest

There are no conflicts of interest. NK Tripathy is the editor of this journal. He does not have any competing interest.

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