Usefulness of Temazepam and Zaleplon to Induce Afternoon Sleep

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Insufficient daytime sleep may result in reduction of effectiveness and safety during overnight military missions. The usefulness of temazepam and zaleplon to optimize afternoon sleep and their effects on performance and alertness during a subsequent night shift were studied. Method: In a randomized double-blind within-subjects design, 11 subjects took 20 mg of temazepam, 10 mg of zaleplon, or placebo before a 5:30–10:00 p.m. sleep period. Sleep length and quality were measured. Subjects were kept awake throughout the night while alertness, cognitive performance, and muscle power were repeatedly measured. Results: Temazepam provided significantly longer and qualitatively better sleep than zaleplon or placebo. During the night, sleepiness increased and muscle power was impaired in all conditions. Better sleep was correlated with less sleepiness during the night. Conclusion: Temazepam is useful to optimize a 4.5-hour afternoon sleep before overnight missions. Irrespective of hypnotic treatment, sleepiness and fatigue increased during the night shift.

Introduction

Military round-the-clock operations are characterized by circadian disruption, rapid work shift changes, prolonged duty, nonoptimal sleep facilities, sleep loss, and high stress levels. These factors may result in high levels of fatigue and sleepiness when on duty, with consequent reduction of operational effectiveness and safety.[1] Sleep deprivation is an important cause of impaired performance of crew.[2–5] Rapid changes from day-to-night shift may require crew to sleep before their duty.[6] Because in the afternoon the body clock dictates wakefulness, it is anticipated that efficiency and quality of sleep in the afternoon will be low.[7] Poor preduty sleep may lead to impaired alertness and performance during a night shift.[5] To optimize daytime sleep, hypnotics may be required and 10–20 mg of temazepam has been recommended for aircrew, in cases where preservation of sleep is crucial.[8,9] The recently developed nonbenzodiazepine zaleplon may also be considered for optimizing sleep in military crew. It has an elimination half-life of approximately 1 hour and appears to facilitate falling asleep but the effect on total sleep time (TST) is unclear.[10] Zaleplon had no negative effects on performance following a 3.5-hour daytime sleep.[11]

This study was conducted to assess the usefulness of temazepam (20 mg) and zaleplon (10 mg) to improve 4.5 hours of sleep in the afternoon to optimize performance and alertness during subsequent night shift work.

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Methods

Subjects

Twelve healthy male volunteers (mean age, 23.0 years; range, 19–35 years), participated in the study. Subjects had no history of insomnia, were nonsmokers, and were drug free from 3 months before the study. The medical ethical committee of the Central Military Hospital of The Netherlands granted approval of the study. Informed consent was obtained from all subjects after a full explanation of the nature of the study. Subjects were paid for their participation.

Assessment Methods

Quality of sleep on the trial day was assessed by a version of the Groningen Sleep Quality Scale (AGSQS) that was adjusted for a sleep period shorter than 5 hours[12]. The result of the AGSQS is a quality score ranging from 0 (very good) to 13 (very poor). Subjects also estimated their TST. An actigraph device (Actiwatch Plus, Cambridge Neurotechnology, Cambridge, United Kingdom) was used to record objective TST, sleep efficiency (TST/time in bed × 100%), and fragmentation index during the sleep period after drug intake.[13,14] The Stanford Sleepiness Scale (SSS; Ref. [15]) was used to assess subjective sleepiness at baseline and during the night shift. The result of the SSS is a score with increasing sleepiness from 1 to 7.

Each cognitive performance test session included a vigilance and tracking task (VigTrack) and the Multi-Attribute Task battery (MAT). The VigTrack task[16,17] is a dual task performed on a handheld computer measuring vigilance performance under the continuous load of a compensatory tracking task. The MAT battery[18,19] includes a system monitoring task, tracking task, communication task, and a resource management task, which has to be performed simultaneously. This complex information-processing task is performed on a personal computer.

Maximal isometric muscle power of the underarm[20] was measured during each test session. Subjects had to squeeze two vertically fixed grips with the preferred hand and exert full strength for 3 seconds. The best period of 2 seconds of the maximal force (N) delivery was taken as result.

Design and Treatments

Using the double-dummy technique, single doses of 20 mg of temazepam (rapidly absorbed formulation), 10 mg of zaleplon, and placebo were randomly used in a double-blind crossover design (sequentially balanced Latin square). Between the drug administrations, there was a wash-out period of 7 days.

Procedure

Volunteers were medically examined and trained on the performance tests. The night before each trial day, subjects slept at home from 11:00 p.m. until 7:00 a.m. Each test session included the SSS, VigTrack (10 minutes), MAT battery (10 min-

utes), and isometric power testing of the underarm. On trial days, subjects performed a baseline test session before the sleep period and rated the subjective characteristics of their sleep at home (quality, TST, bedtime, wake-up time). After the baseline session, they were in bed in a darkened room from 5:30 p.m. until 10:00 p.m., wearing the Actiwatch device on their nondominant wrist. After waking up at 10:00 p.m., subjects rated their sleep (quality, TST, latency, number of awakenings). After 10:00 p.m., subjects were kept awake and another six test sessions were performed at regular intervals from 10:15 p.m. until 7:00 a.m.

Data Analysis

For all performance measures, δ scores were computed, based on the difference between results of the baseline session and the results of the six postsleep sessions. All repeatedly measured variables were tested in separate applications of repeated measures analysis of variance. Subjective ratings and actigraphy scores were compared by computing the Student's t test for paired samples. For correlation analyses, Pearson's product moment correlation (r) was used under the null hypothesis that quantity and quality of sleep correlated with performance after the sleep.

Results

Eleven subjects completed the study. One subject was withdrawn due to a headache on arrival at the Institute on the first trial day. Mean subjective TST of sleep at home before the trial days was 7:58 hours (SD, 1:39). Mean quality score was 1.4 (SD, 1.8), indicating good sleep quality. No significant differences between treatment conditions were observed.

TST and Quality of the Afternoon Sleep

Mean scores on subjective sleep quality, subjective TST, objective TST, and fragmentation index are summarized in Table I. Compared with zaleplon and placebo, sleep with temazepam showed the best subjective quality (with zaleplon: $p < 0.05$; with placebo: $p < 0.01$) and a lower fragmentation index than with zaleplon ($p < 0.01$), or placebo ($p < 0.05$). The fragmentation index showed no significant differences between placebo and zaleplon. Subjective and objective TST were significantly longer

TABLE I

RESULTS OF SUBJECTIVE AND OBJECTIVE MEASUREMENTS OF AFTERNOON SLEEP WITH SD

Variable	Temazepam	Zaleplon	Placebo
Sleep quality score (±SD) AGSQS	2.9* (3.1)	5.3 (3.0)	5.4 (2.9)
Subjective total sleep time (min) (±SD)	220* (52)	175 (54)	163 (73)
Objective total sleep time (min) (±SD) actigraphy	240** (13)	219 (28)	229 (20)
Fragmentation index (±SD) actigraphy	28.7** (14.0)	42.1 (15.5)	38.6 (13.7)

Lower AGSQS scores signify better quality. Significant difference with other study medication is presented by asterisks (**, $p < 0.01$; *, $p < 0.05$). Maximum time in bed was 270 minutes.

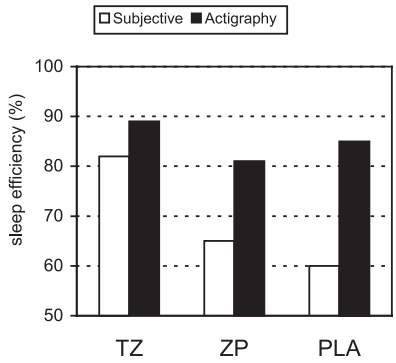

Fig. 1. Subjectively estimated sleep efficiency and objectively measured sleep efficiency (actigraphy) for the temazepam (TZ), zaleplon (ZP), and placebo (PLA) treatment condition.

with temazepam than with zaleplon ($p < 0.05$ and $p < 0.01$, respectively). Consequently, temazepam also showed a higher sleep efficiency than zaleplon (subjective: $p < 0.05$; objective: $p < 0.01$; Fig. 1). There were no significant differences in TST, sleep quality, and sleep efficiency between zaleplon and placebo. Sleep latency and frequency of awakenings showed no significant differences between the study medications.

Mean subjective TST was 20 to 66 minutes shorter than TST measured with actigraphy (Table I) and a moderate correlation between these variables was found ($r = 0.60$; $p < 0.0001$). The longer the TST, the better sleep quality was (indicated by lower scores on the AGSQS; $r = -0.68$, $p < 0.0001$). Subjective sleep quality and objective fragmentation index showed a moderate correlation ($r = 0.50$, $p < 0.01$). Objective TST and fragmentation index were highly correlated ($r = -0.87$, $p < 0.0001$), indicating that the longer TST, the less fragmented sleep was.

Subjective Sleepiness (SSS)

Sleepiness scores increased significantly during the night shift ($F_{(6,231)} = 14{,}93$; $p < 0.001$; Fig. 2). No significant differences in sleepiness were found among temazepam, zaleplon, or placebo. Sleepiness scores before the sleep period did not differ

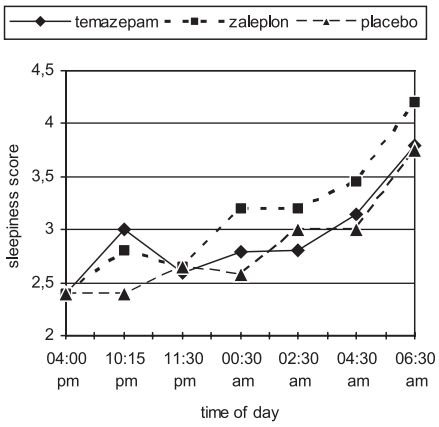

Fig. 2. Mean sleepiness scores (SSS) before sleep and during the night shift after awakening at 10:00 p.m. for the treatment conditions temazepam, zaleplon, and placebo.

significantly from scores 15 minutes after awakening. Subjective sleepiness showed a moderate correlation with quality of the afternoon sleep ($r = 0.48$, $p < 0.01$) and its subjective TST ($r = -0.45$, $p < 0.01$), indicating that poorer quality and shorter duration of afternoon sleep corresponds with higher levels of sleepiness during the night shift.

Vigilance and Tracking (VigTrack)

In all treatment conditions, tracking (root mean square tracking error) and vigilance (percentage of omissions and number of false reactions) showed no significant changes during the night. There were no significant differences in performance during the night among temazepam, zaleplon, or placebo. No significant correlations were found between afternoon sleep variables and performance on the VigTrack.

Complex Information Processing (MAT)

Performance on tracking, resource management, system monitoring, and communication tasks showed no significant differences among temazepam, zaleplon, and placebo treatments. Reaction time on the system monitoring task was significantly longer after awakening compared to the baseline session ($p < 0.05$). All treatment conditions showed a decrease in response time until the fourth session at 00:30 a.m., followed by an increase until the last session at 6:30 a.m. No significant correlations were found between afternoon sleep variables and performance on the MAT battery.

Maximal Isometric Muscle Power of the Underarm

As Figure 3 shows, maximal power of the underarm muscles decreased significantly during the night shift in all treatment conditions ($F_{(6.231)} = 9.77$; $p < 0.001$). No significant differences were found among temazepam, zaleplon, and placebo and no significant correlations were found between afternoon sleep variables and isometric muscle power of the underarm.

Discussion

Twenty milligrams of temazepam induced the best afternoon sleep in terms of quality, TST, and fragmentation. This is in agreement with other studies in which temazepam was used to improve daytime sleep.[7,21,22] Use of zaleplon showed no significant advantage over placebo. This is in line with results of Drake et al.,[10] who found no increase of TST with 10 mg of zaleplon, but contrasted by the results of Whitmore et al.,[11] who found a trend for a greater amount of daytime sleep with zaleplon. Sleep was significantly less fragmented with temazepam. This may be important, because fragmentation reduces the recuperative effects of sleep.[23]

Mean subjective TST was shorter than the objective TST. This is in agreement with findings in earlier studies.[5,24] It has been evidenced by polysomnographic studies that subjects often estimate their sleep duration to be shorter than in reality.[25]

In contrast to the nonbenzodiazepine zaleplon, temazepam might potentially cause muscle weakness. However, we found no evidence that temazepam induced more muscle weakness in the underarm than zaleplon or placebo.

Muscle power gradually degraded and sleepiness increased during the night, and subjects on temazepam did not perform better nor were they less sleepy than those on zaleplon or placebo. It appears that although temazepam was beneficial for preduty sleep, this did not result in better performance during the night. This finding is in agreement with results from Porcù et al.[26] However, the significant correlation of quality and quantity of the afternoon sleep with sleepiness levels during the night indicates that poorer quality and shorter duration of afternoon sleep is associated with higher levels of sleepiness during the night shift.

When subjects have to take action immediately after awakening from sleep, their performance may be impaired due to sleep inertia. In all treatment conditions, reaction time on the system-monitoring task (MAT) showed an increase during the session 15 minutes after awakening, but as none of all other variables showed significant effects, we were unable to find consistent evidence for sleep inertia in either of the three treatment conditions. However, our results do not convincingly rule out the occurrence of sleep inertia in individual cases. Therefore, we recommend to take sleep inertia into consideration when planning missions and to allow crew sufficient time to prepare for duty after awakening from a nap.

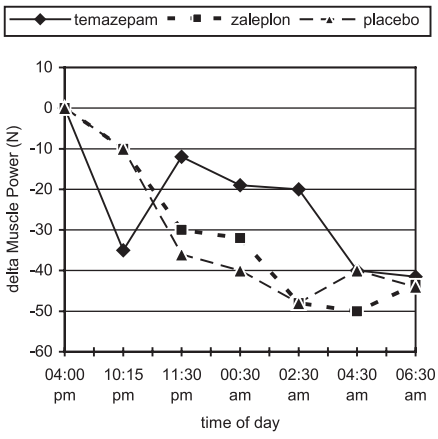

Fig. 3. Mean differences in muscle power of underarm (N) before sleep and during the night shift after awakening at 10:00 p.m. for the treatment conditions temazepam, zaleplon, and placebo.

Conclusion

When sleep problems are anticipated during military missions, temazepam appears to be more useful to improve daytime sleep than zaleplon or placebo. However, sleepiness and muscle fatigue increased during the night shift, irrespective of hypnotic treatment.

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References

1. French J, Neville KJ, Storm WF, Bisson RU, Boll P: Determinants of subjective fatigue for C-141 crews during operation Desert Storm, pp 17/1–12. NATO-

AGARD-CP 547, Recent Advances in Long Endurance Operation of Aircraft. NATO-AGARD, Neuilly-sur-Seine, France, 1993;
2. Perelli LP: Fatigue stressors in simulated long-duration flight. Technical report 80–49. Brooks AFB, TX, USAF School of Aerospace Medicine, 1980.
3. Penetar DM, Belenky G, Garrigan JJ, Redmond DP: Triazolam impairs learning and fails to improve sleep in a long range aerial deployment. Aviat Space Environ Med 1989; 60: 594–8.
4. Caldwell JA: Fatigue in the aviation environment: an overview of the causes and effects as well as recommended countermeasures. Aviat Space Environ Med 1997; 68: 932–8.
5. Simons M, Valk PJL: Early starts: effects on sleep, alertness and vigilance, pp 6/1–5. AGARD-CP-599; Neuilly-sur-Seine, France, NATO-AGARD, 1998.
6. Dinges DF, Whitehouse WG, Orne EC, Orne MT,: The benefits of a nap during prolonged work and wakefulness. Work Stress 1988; 2: 139–52.
7. Nicholson AN, Stone BM,: Sustained air operations: prolonged duty overnight, pp 1/1–14. AGARD-CP-599. Neuilly-sur-Seine, France, NATO-AGARD, 1998.
8. Nicholson AN, Stone BM: Hypnotics and stimulants in operational settings, pp K1–1/K1–8. RTO-MP-31. Individual Differences in the Adaptability to Irregular Rest-Work Rhythms/Status of the Use of Drugs in Sleep-Wakefulness Management. Neuilly-sur-Seine, France, NATO-RTO, 2000.
9. Simons M, Valk PJL: Sleep and alertness management during military operations: questions to be answered, pp 8–1/8–8. RTO-MP-31. Individual Differences in the Adaptability to Irregular Rest-Work Rhythms/Status of the Use of Drugs in Sleep-Wakefulness Management. Neuilly-sur-Seine, France, NATO-RTO, 2000.
10. Drake CL, Roehrs TA, Mangano RM, Roth T: Dose-response effects of zaleplon as compared with triazolam (0.25 mg) and placebo in chronic primary insomnia. Hum Psychopharmacol 2000; 15: 595–604.
11. Whitmore JN, Fischer JR, Jr, Storm WF: Hypnotic efficacy of zaleplon for daytime sleep in rested individuals. Sleep 2004; 27: 895–8.
12. Meijman TF, De Vries GM, De Vries-Griever AHG, Kampman R: The evaluation of the Groningen Sleep Quality Scale. Department for Experimental and Occupational Psychology, Biological Centre, University of Groningen, Groningen, The Netherlands, 1987.
13. Sadeh A, Alster J, Urbach D, Lavie P: Actigraphically based automatic bedtime sleep-wake scoring: validity and clinical applications. J Ambul Monit 1989; 2: 209–16.
14. Ancoli-Israel S, Cole R, Alessi C, Chambers M, Moorcroft M, Pollak CP: The role of actigraphy in the study of sleep and circadian rhythms. Sleep 2003; 26: 342–92.
15. Hoddes E, Zarcone V, Smythe H, Philips R, Dement WC: Quantification of sleepiness: a new approach. Psychophysiology 1973; 10: 431–6.
16. Valk PJL, Simons M, Struyvenberg PAA, Kruit J, Van Berge Henegouwen M: Effects of a single dose of loratadine on flying ability under conditions of simulated cabin pressure. Am J Rhinol 1997; 11: 27–33.
17. Valk PJL, vanRoon DB, Simons RM, Rikken G: Desloratadine shows no effect on performance during 6 h at 8000 ft simulated cabin altitude. Aviat Space Environ Med 2004; 75: 433–8.
18. Arnegard RJ: Operator strategies under varying conditions of workload. NASA CR-4385. Hampton, VA, Langley Research Center, National Aeronautics and Space Administration, 1991.
19. Comstock JR, Arnegard RJ: The Multi-Attribute Task battery for human operator workload and strategic behavior research. NASA TM-104174. Hampton, VA, Langley Research Center, National Aeronautics and Space Administration, 1992.
20. Vos JA: Static and dynamic power measurements. University of Ghent, PhD Thesis, Ghent, Belgium, 1976.
21. Caldwell JL, Prazinko BF, Rowe T, Norman D, Hall KK, Caldwell JA: Improving daytime sleep with temazepam as a countermeasure for shift lag. Aviat Space Environ Med 2003; 74: 153–63.
22. Wesnes K, Warburton DM: Effects of temazepam on sleep quality and subsequent mental efficiency under normal sleeping conditions and following delayed sleep onset. Neuropsychobiology 1986; 15: 187–91.
23. Levine B, Roehrs T, Stepanski E, Zorick F, Roth T: Fragmenting sleep diminishes its recuperative value. Sleep 1987; 10: 590–9.
24. Simons M, De Ree JJD, Valk PJL, Veldhuijzen van Zanten OBA, D'Huyvetter K: Quantity and quality of onboard and layover sleep: effects on crew performance and alertness. Technical Memorandum RD-31–94. Soesterberg, The Netherlands, Netherlands Aerospace Medical Centre, 1994.
25. Aritake S, Uchiyama M, Tagaya H, et al: Time estimation during nocturnal sleep in human subjects. Neurosci Res 2004; 49: 387–93.
26. Porcù S, Bellatreccia A, Ferrara M, Casagrande M: Performance, ability to stay awake, and tendency to fall asleep during the night after a diurnal sleep with temazepam or placebo. Sleep 1997; 20: 535–41.