USEFULNESS OF TEMAZEPAM AND ZALEPLON TO INDUCE AFTERNOON-SLEEP

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INTRODUCTION

Military round the clock operations are characterized by circadian disruption, rapid work shift changes, prolonged duty, non-optimal 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\textsuperscript{1,2}. Sleep deprivation is an important cause of impaired performance of crew\textsuperscript{2,3}. Rapid changes from day to night shift may require crew to sleep prior to their duty\textsuperscript{4}. Because in the afternoon the body clock dictates wakefulness, it is anticipated that efficiency and quality of sleep in the afternoon will be low\textsuperscript{5}. Poor pre-duty sleep may lead to impaired alertness and performance during a night shift\textsuperscript{3}. To optimize daytime sleep, hypnotics may be required and temazepam 10-20 mg has been recommended for aircrew, in cases where preservation of sleep is crucial\textsuperscript{6,7}. The recently developed non-benzodiazepine 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 is unclear\textsuperscript{8}. Zaleplon had no negative effects on performance following a 3.5-hr daytime sleep\textsuperscript{9}. This study was conducted to assess the usefulness of temazepam (20 mg) and zaleplon (10 mg) to improve a 4.5 hr sleep in the afternoon in order to optimize performance and alertness during subsequent night shift work.

METHODS

Subjects

Twelve healthy male volunteers, mean age 23.0 yrs (range 19-35), participated in the study. Subjects had no history of insomnia, were non-smokers and drug free from 3 months prior to the study. The medical ethical committee of the Central Military Hospital of The Netherlands granted approval of the study.

Assessment methods

Quality of sleep on the trial day was assessed by a version of the Groningen Sleep Quality Scale\textsuperscript{10} that was adjusted for a sleep period shorter than 5 hours (AGSQS). The result of the AGSQS is a quality score ranging from 0 (very good) to 13 (very poor). Subjects also estimated their total sleep time. An actigraph device (Actiwatch Plus, Cambridge Neurotechnology) was used to record objective total sleep time, sleep efficiency (total sleep time/time in bed x 100%), and fragmentation index during the sleep period after drug intake\textsuperscript{11,12}. The Stanford Sleepiness Scale\textsuperscript{13} (SSS) was used to assess subjective sleepiness at baseline and during the night shift.
Each cognitive performance test session included a vigilance and tracking task (VigTrack) and the Multi-Attribute Task battery (MAT). The VigTrack task is a dual-task performed on a handheld computer measuring vigilance performance under the continuous load of a compensatory tracking task. The MAT battery includes a system monitoring task, tracking task, communication task, and a resource management task, which have to be performed simultaneously. This complex information-processing task is performed on a Personal Computer.

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

**Design and treatments**

Using the double-dummy technique, single doses of temazepam 20 mg (rapidly absorbed formulation), zaleplon 10 mg, and placebo were randomly employed 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 pm until 07:00 am. Each test session included the SSS, VigTrack (10 min), MAT battery (10 min), and isometric power testing of the underarm. On trial days, subjects performed a baseline test session prior to the sleep period and rated the subjective characteristics of their sleep at home (quality, total sleep time, bedtime, wake up time). After the baseline session they were in bed in a darkened room from 5:30 pm till 10 pm, wearing the Actiwatch on their non-dominant wrist. After waking up at 10 pm, subjects rated their sleep (quality, total sleep time, latency, number of awakenings). After 10 pm, subjects were kept awake and another 6 test sessions were performed at regular intervals from 10:15 pm until 07:00 am.

**Data analysis**

For performance measures, delta scores were computed, based on the difference between the results of the baseline session and the 6 post-sleep sessions. All repeatedly measured variables were tested in separate applications of repeated measures analysis of variance (ANOVA). Subjective ratings and actigraphy scores were compared by computing 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 headache before the start of the trial. Mean subjective total sleep time of sleep before the trial days was 7:58 hr (SD. 1:39). Mean quality score was 1.4 (SD. 1.8) indicating good sleep quality. No significant differences between treatment conditions were observed.

**Total sleep time and quality of the afternoon sleep**

Mean scores on subjective sleep quality, subjective total sleep time (TST), objective TST, and fragmentation index are summarized in table 1. Compared with zaleplon and placebo, sleep with temazepam showed the best subjective quality (with zaleplon: p<.05; with placebo: p<.01) and a lower fragmentation index than with zaleplon (p<0.01), or placebo (p<.05). Fragmentation index showed no significant differences between placebo and...
zaleplon. Subjective and objective TST were significantly longer with temazepam than with zaleplon (p<.05 and p<.01 respectively). Consequently, temazepam also showed a higher sleep efficiency than zaleplon (subjective: p<.05; objective: p<.01). 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.

Table 1. Results of subjective and objective measurements of afternoon sleep with Standard Deviation (SD). Lower AGSQS scores signify better quality. Significant difference with other study medication is presented by asterisks (**= p<.01 *p<.05). Max. time in bed was 270 min

<table>
<thead>
<tr>
<th>variable</th>
<th>temazepam</th>
<th>zaleplon</th>
<th>placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGSQS: sleep quality score</td>
<td>2.9*</td>
<td>5.3</td>
<td>5.4</td>
</tr>
<tr>
<td>(±SD)</td>
<td>(3.1)</td>
<td>(3.0)</td>
<td>(2.9)</td>
</tr>
<tr>
<td>subjective total sleep time (min)</td>
<td>220*</td>
<td>175</td>
<td>163</td>
</tr>
<tr>
<td>(±SD)</td>
<td>(52)</td>
<td>(54)</td>
<td>(73)</td>
</tr>
<tr>
<td>actigraphy: total sleep time (min)</td>
<td>240**</td>
<td>219</td>
<td>229</td>
</tr>
<tr>
<td>(±SD)</td>
<td>(13)</td>
<td>(28)</td>
<td>(20)</td>
</tr>
<tr>
<td>actigraphy: fragmentation index</td>
<td>28.7**</td>
<td>42.1</td>
<td>38.6</td>
</tr>
<tr>
<td>(±SD)</td>
<td>(14.0)</td>
<td>(15.5)</td>
<td>(13.7)</td>
</tr>
</tbody>
</table>

Mean subjective TST was 20-66 min shorter than TST measured with actigraphy (table 1) and a moderate correlation between these variables was found (r=.60; p<.0001). The longer the TST, the better sleep quality was (indicated by lower scores on the AGSQS; r=-.68, p<.0001). Subjective sleep quality and objective fragmentation index showed a moderate correlation (r=.50, p<.01). Objective TST and fragmentation index were highly correlated (r=-.87, p<.0001), indicating that the longer total sleep time, the less fragmented sleep was.

Subjective Sleepiness (SSS)
Sleepiness scores increased significantly during the night shift (F(6,231)=14,93; p<.001). No significant differences in sleepiness were found between temazepam, zaleplon, or placebo. Sleepiness scores prior to the sleep period did not differ significantly from scores 15 min after awakening. Subjective sleepiness showed a moderate correlation with quality of the afternoon sleep (r=.48, p<.01) and its subjective total sleep time (r=-.45, p<.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 (RMS tracking error) and vigilance (% omissions and number of false reactions) showed no significant changes during the night. There were no significant differences in performance during the night between temazepam, zaleplon, or placebo. No significant correlations were found between afternoon sleep variables and performance on the vigilance and tracking task.

Complex information processing (MAT)
Performance on tracking, resource management, system monitoring, and communication tasks showed no significant differences between temazepam, zaleplon, and placebo.
treatments. No significant correlations were found between afternoon sleep variables and performance on the MAT battery.

Maximal isometric muscle power of the underarm

Maximal power of the underarm muscles decreased significantly during the night shift in all treatment conditions (F(6,231)=9.77; p<.001). No significant differences were found between temazepam, zaleplon, and placebo and no significant correlations were found between afternoon sleep variables and isometric muscle power of the underarm.

DISCUSSION

Temazepam 20 mg induced the best afternoon sleep in terms of quality, total sleep time, efficiency, and fragmentation. This is in agreement with other studies in which temazepam was used to improve daytime sleep5,17,18. Zaleplon showed no significant advantage over placebo. This is in line with results of Drake et al.8, who found no increase of total sleep time with 10 mg zaleplon, but contrasted by the results of Whitmore et al.9, 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 sleep19.

In contrast to the non-benzodiazepine 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 shift, and subjects on temazepam did not perform better nor were less sleepy than those on zaleplon or placebo. It appears that although temazepam was beneficial for pre-duty sleep, this did not result in better performance during the night. This finding is in agreement with results from Porcù et al.20. 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.

CONCLUSION

Temazepam appears to be more useful to improve a brief daytime sleep than zaleplon or placebo. However, sleepiness and muscle fatigue increased during the night shift, irrespective of hypnotic treatment.

Grant Support

This study was conducted under Program V039 granted by the Department of Scientific Support of the Ministry of Defence of The Netherlands.

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