

Efficacy of Modafinil and Caffeine to Counteract Hypnotic Induced Sleepiness during Sustained Operations

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ABSTRACT

Introduction: During sustained operations, a combined use of a hypnotic to induce sleep under difficult circumstances and a psychostimulant to improve performance and alertness during night-shift work or after sleep deprivation may be necessary. This study was conducted to evaluate the effect of modafinil and caffeine as countermeasures to hypnotic induced sleepiness.

Methods: 18 healthy subjects (moderate coffee consumers) participated in a randomized placebo-controlled double-blind crossover study. Sleepiness was induced by limited sleep deprivation combined with the administration of 20 mg temazepam (rapidly absorbed formulation). 200 mg modafinil or 400 mg caffeine or placebo were administered in a cross-over design, one hour after administration of temazepam. Subjects completed performance and alertness tests before administration of temazepam (baseline), once after administration of temazepam and at regular intervals during the night until eight hours after administration of modafinil, caffeine or placebo. Vigilance, alertness, complex information processing and subjective sleepiness were assessed.

Results: After temazepam intake, performance and alertness were significantly impaired. Compared with placebo, both caffeine and modafinil significantly counteracted the performance and alertness impairment caused by temazepam. The greatest impact of the psychostimulants was seen in performance on the vigilance task. The onset of beneficial action was shortest with caffeine (1½ hr), modafinil showed a significant counteraction to temazepam starting 4½ hours after administration. Both stimulants showed a beneficial effect in the vigilance task as long as eight hours after administration. No significant adverse effects were observed.

Conclusion: Both caffeine and modafinil are useful to counteract the sedative effects of temazepam. The onset of caffeine is earlier than the onset of modafinil. Therefore, in this study the mean performance enhancing effects of 400 mg caffeine were better in counteracting the hypnotic induced sleepiness of temazepam than the effects of 200 mg modafinil.

1.0 INTRODUCTION

Military round the clock operations are characterized by circadian disruptions, rapid work shift changes, prolonged duty overnight, 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. Inadequate sleep facilities and mission stress further contribute to serious sleep deprivation (French et al.

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1993, Nicholson & Stone, 1999), which is known to be an important cause of impaired performance of aircrew (Simons & Valk 1997, Perelli 1980, Simons & Valk, 1998). Therefore, sleep and alertness management is a major issue of attention for the medical support of military round the clock operations.

During sustained operations, both use of a hypnotic to induce sleep under difficult circumstances and a psychostimulant to improve performance in sustained and /or nightly operations might be considered. The situation could arise where a hypnotic has been given to ensure sleep and an emergency situation occurs. In this study, the effect was evaluated of two pharmacologically alertness enhancers as countermeasures to sleepiness. Sleepiness was induced by limited sleep deprivation combined with the administration of a hypnotic (temazepam). Temazepam has been the recommended hypnotic for air crew, in those cases where preservation of sleep is crucial (Nicholson & Stone 1983, Valk & Simons 1994). Modafinil and caffeine are alertness enhancers and have been demonstrated to be effective countermeasures to the detrimental effects of sleep loss. Comparisons between 600 mg caffeine and modafinil (in various doses) in counteracting sleepiness after sleep deprivation of 54.5 hours have been described by Wesensten et al. (2002). They concluded that modafinil did not appear to offer advantages over 600 mg caffeine for improving performance during sleep loss.

Knowledge on the effects of stimulants for alertness management shortly after usage of hypnotics is lacking. Benzodiazepines and caffeine in general produce antagonistic effects through functionally opposing mechanisms, however, the observed effects of drug combinations are dependent on the specific doses being tested and the tasks being examined. (Mattila et al. 1998, Rush et al. 1994). To our knowledge modafinil has not yet been used to counteract sedation induced by benzodiazepines.

The primary objective of this study was to assess the efficacy of modafinil (200 mg) and caffeine (400 mg) to counteract hypnotic induced sleepiness during nightly missions. The results of the tests obtained with this medication were compared to those observed with placebo.

In addition, adverse effects were recorded and the effect of modafinil or caffeine on the overestimation of actual cognitive performance was investigated by comparing self perceived effort for performing the tasks with the objective results of the tasks.

2.0 METHODS

The study was designed as a randomized, double blind, crossover trial, employing caffeine, modafinil and placebo. See table 1. On each of the three test days, subjects swallowed 1 capsule temazepam 20 mg (rapidly absorbed formulation), followed 1 hour later by ingestion of either 200 mg modafinil, or 400 mg caffeine or matching placebo with 200 ml water. The washout period between the test days was 7 days.

Table 1

Time	Action taken
21:00	Arrival-medical evaluation
21:30	Session 0 (practice)
22:30	Session 1 (reference)
23:00	Intake temazepam
23:30	Session 2
00:00	Intake modafinil / caffeine / placebo
00:30	Session 3
01:30	Session 4
02:30	Session 5
03:30	Session 6
04:30	Session 7
05:00	Breakfast
06:00	Session 8
07:00	Session 9
08:00	Session 10
08:30	Medical evaluation

Table 1: Schedule of assessments on a test day

At regular intervals during the night until eight hours after administration of modafinil, caffeine or placebo performance, alertness and subjective sleepiness was evaluated (see table 1). Piloting modern aircraft requires complex psychomotor co-ordination, high rates of information processing, and high-speed decision making. On the other hand, during prolonged operations, pilots have to sustain attention and to maintain vigilance under relatively monotonous conditions. During the last 10 years, tools have been evaluated and developed to assess pilot's performance during operational duties. The Vigilance and Tracking task (VigTrack; Valk 2004) and the Multi-Attribute Task battery developed by NASA (Comstock & Arnegard, 1992), were identified as the two tasks tapping both sides of the pilot workload spectrum. The combination of both tasks fulfils the demands as formulated by both the Civil Aviation Authority and the Royal Netherlands Air Force Working Group on Medication (RTO, 2001). Subjective sleepiness was evaluated by the Stanford Sleepiness Scale (SSS) (Hoddes et al. 1973).

Adverse events were recorded during the three test days and the wash-out periods. The subjects scored their perceived effort for performing the MAT task and Vigtrack task shortly after they had completed these tasks. A scale from 1 to 7 was used, ranging from very easy to very hard to perform the task. Coffee consumption was limited to a maximum of 4 cups per day on non-test days. Coffee and tea and other caffeine-containing beverages were not allowed at test days after 12.00. Alcohol consumption during the study period was limited to a maximum of 2 glasses per day. No alcohol was allowed 24 hours before the start of the measurements.

18 Healthy subjects (12 male and 6 female) entered the study after they had been fully informed about the objectives, procedures and risks of study participation and after signing a written informed consent form. The study was approved by an independent Ethics Committee. Subject characteristics are presented in table 2.

	Mean (\pm SD)
Age (years)	23 (\pm 2.6)
Weight (kg)	73.5 (\pm 10.5)
Height (cm)	178.8 (\pm 11.2)
Habitual caffeine intake (mg)	193 (\pm 83), range: 17- 374

Table 2: Subject characteristics

All primary VigTrack and MAT variables and SSS scores that were repeatedly measured on the three test days are tested in separate applications of repeated measures analysis of variance (treatment, group, trial day, treatment x trial, full factorial design). Comparisons between scores within treatment conditions are performed by Tukey's HMD. All statistical tests were performed at a significance level of $\alpha = 0.05$. The effect of temazepam was tested by comparing the results of session 1 of all subjects with the results of session 2 for each task.

3.0 RESULTS

3.1 Vigtrack tracking task

The data distribution of the VigTrack Root Mean Square tracking error was skewed and the results were log transformed to ensure a better reliability of the statistical tests. The results are shown in figure 1. After intake of temazepam the root mean square tracking error increased ($p < 0.01$).

1½ to 8 Hours after intake, the VigTrack RMS subjects' results in the caffeine condition were better compared to the placebo ($p < 0.01$) condition. 4½ to 8 Hours (from session 7 onwards) after intake, subjects in the modafinil condition showed better results for the VigTrack RMS compared to the placebo condition ($p < 0.05$).

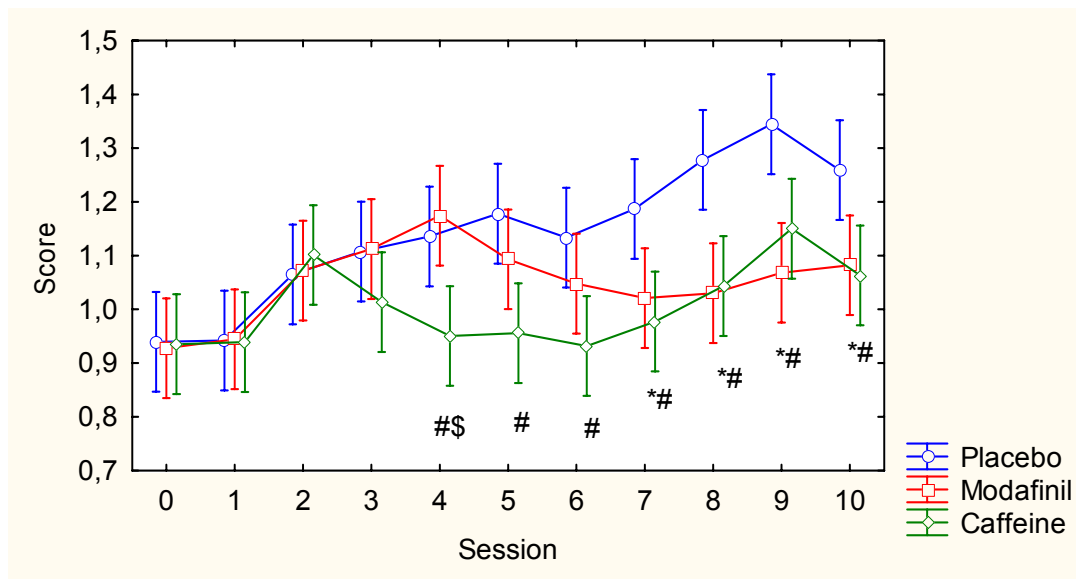


Figure 1 Log transformed root mean square results of the VigTrack tracking task in time for three study conditions. Vertical bars denote 0.95 confidence intervals. * significant effect modafinil versus placebo, \$ significant effect caffeine versus modafinil, # significant effect caffeine versus placebo

3.2 Resource management performance

Resource management performance is scored as the mean absolute deviation of fuel tanks A and B from the target of 2500 units. This is an example of a complex information processing task. Due to skewness of the data distribution the results were log transformed to ensure a better reliability of the statistical tests. Results are shown in figure 2. The mean absolute deviation from target did not increase significantly after intake of temazepam. 7 hours (session 9) after intake, subject had a better resource management performance in the modafinil condition compared to the placebo condition ($p < 0.05$). 7 And 8 hours (sessions 9 and 10) after intake, subject had better scores in the caffeine condition compared to the placebo condition ($p < 0.05$).

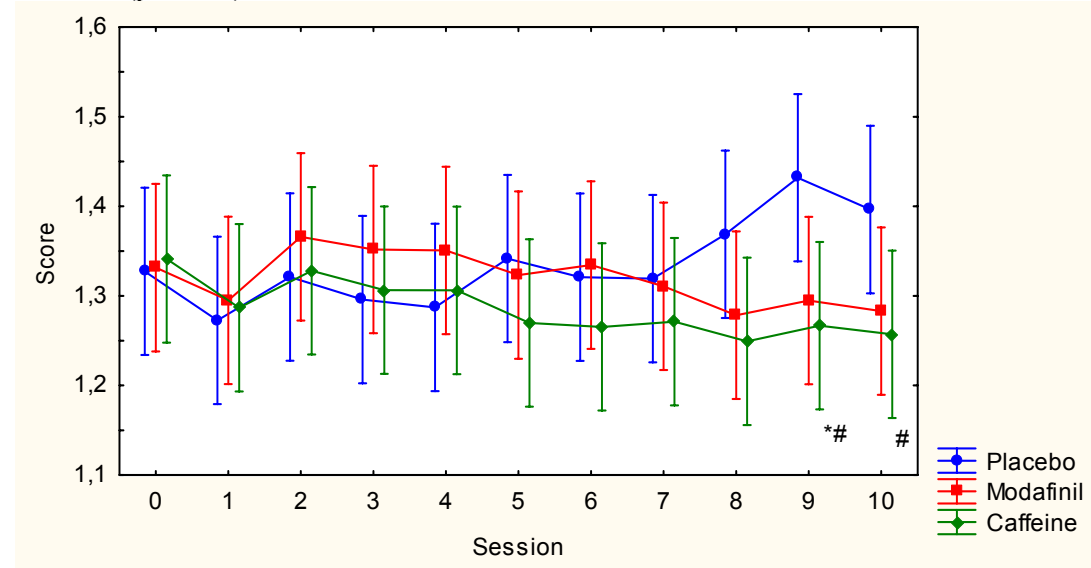


Figure 2: Multi Attribute Task battery resource management (log transformed), deviation from target in time per study condition. Vertical bars denote 0.95 confidence intervals. * significant effect modafinil versus placebo, # significant effect caffeine versus placebo

3.3 Other tasks

Results from the Vigtrack tracking task, resource management task and other tasks are summarized in table 3.

	Time points of improvement after ingestion of modafinil compared to placebo	Time points of improvement after ingestion of caffeine compared to placebo
VigTrack Tracking task	4½ to 8 h	1½ to 8 h
VigTrack Vigilance task	7 h	4½ and 8 h
MAT Reaction time	6 and 7 h	6 h
MAT Tracking task	6 to 8 h	6 to 8 h
MAT Resource management	7 h	7 and 8 h
Stanford Sleepiness Scale	7 h	4½ h

Table 3 Summarizing table of the results at the separate time points after ingestion of the study substances

Overconfidence after modafinil administration has been evaluated before by Baranski et al. (1997 and 2002) by asking the subjects a single question with a quantitative index, before and after a task, that asked the subjects to estimate the percentage of responses they answered correctly. In this way their estimation of overconfidence did not differ much from the method we used in the current study. The Perceived Effort Rating Scale (PERS) scores tracked the objectively registered results of the tasks, therefore in this study there was no indication overconfidence occurred. However, this PERS scale was developed by the investigators especially for this study only and has not been validated.

4.0 CONCLUSION

Based on the results of this study, we conclude that the performance enhancing effects of caffeine were better in counteracting the hypnotic induced sleepiness of temazepam than modafinil. Reported adverse symptoms were not serious or debilitating and not different between modafinil and caffeine. Based on the facts that caffeine is more socially accepted as a stimulant, that it is more widely available and that it is less expensive than modafinil, we recommend caffeine to be the “drug of choice” to improve performance and alertness after hypnotic induced sleepiness.

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