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THE EFFECTS OF MODAFINIL, D-AMPHETAMINE, AND PLACEBO ON PHYSIOLOGICAL AND PSYCHOLOGICAL STRESS DURING SLEEP DEPRIVATION

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The effects of modafinil, d-amphetamine, and placebo on physiological and psychological stress during sleep deprivation

Yvonne Shek and Ross Pigeau

Defence and Civil Institute of Environmental Medicine, North York, Ontario, Canada

Two methods were used to measure the effects of two drugs for alleviating stress due to sleep loss. The two drugs were: modafinil and d-amphetamine (vs. placebo). The first method was the NASA Task Load Index (TLX), a subjective measure of workload. The second was a physiological measure of salivary cortisol levels. The NASA TLX was found insensitive to drug conditions and showed no signficant variation over time. Subjects who were given d-amphetamine had significantly higher salivary cortisol levels than subjects who were given placebo or modafinil. Salivary cortisol levels varied with the circadian cycle, peaking at 0730 hours for each of the sleep loss days. There was no correlation between the TLX scores and salivary cortisol levels ($r = -.05$).

INTRODUCTION

Sleep loss is one of many stressors that concerns the soldier because of its psycho-physiological cost which often manifests itself in deteriorated cognitive performance and mood (Angus & Heslegrave, 1985; Haslam, 1982; Singleton, 1971; Parrot, 1971). It is unrealistic to expect to alleviate the soldier from all stressors, including sleep loss, but there is a critical point where the "stress source" (Singleton,1971) may be beyond the coping capability of the individual (Karasek and Theorell, 1990; Lazarus and Folkman, 1984) and alternative (external) coping strategies need to be considered. One such strategy is the use of pharmacological aids to overcome fatigue due to sleep loss, a solution that is becoming more common among military organizations— e.g., during the Falklands campaign (Nicholson, 1984), the Libyan Air Strike in 1986 (Senechal, 1988) and Desert Storm (Atkinson, 1993).

In this paper we report the effects of two drugs, modafinil and d-amphetamine (vs. placebo) on their ability to alleviate psychological and physiological stress resulting from pairing sleep loss with continuous cognitive work.

Psychological stress (Singleton,1971) was measured using the NASA Task Load Index (TLX; Hart & Staveland, 1988; Hart & Wickens, 1990). NASA TLX is a subjective estimate of workload that combines workload estimates on six subscales: mental workload, physical workload, performance (how well subject thought he/she performed), time pressure, effort, and frustration level. Insofar as workload reflects psychological stress — i.e., greater workload implies greater stress — do subjective estimates of workload increase with increasing fatigue? Also, since Pigeau *et al.* (in press) found that the use of amphetamine and modafinil alleviated performance decrements due to sleep loss, will subjective estimates of workload be similarly affected by such substances?

One view of physiological stress is that it is a function of arousal. The degree of arousal in an individual is governed partly by cortisone, a hormone that is released from the adrenal cortex when stimulated by adrenocorticotropic hormone (ACTH) from the anterior pituitary gland (Carlson, 1986). Cortisol is a reduction product of cortisone (Motohashi, 1992; Cumming et al., 1983; Robertson et al., 1981). Cortisol levels vary as a function of the circadian cycle (Motohashi, 1992; Riad-Fahmy et al, 1982; Umeda et al, 1981). To estimate the degree of physiological stress individuals experienced as a result of fatigue due to sleep loss, saliva samples were collected and analyzed to determine cortisol levels. Salivary cortisol is easy to acquire (compared to serum cortisol), involves uninvasive procedures for the sleep deprived soldier and is reliable as a measure of free cortisol (Motohashi, 1992; Hiramatsu, 1981; Umeda et al, 1981). We investigated whether the circadian response that is associated with

cortisol is affected by the ingestion of amphetamine and modafinil.

The final question investigated in this paper is: to what extent is psychological stress, as measured by the TLX workload index, correlated with physiological stress as measured by cortisol?

METHOD

For a detailed description of the experiment see Pigeau et al. (1995).

Subjects. Saliva samples from only 17 Canadian Forces personnel were analyzed because the collection facilities were not available in time for the first three runs of the experiment. Also, one female subject, who had been in the amphetamine group, did not complete the experiment because she developed flu symptoms. Therefore, there were only 5 subjects in the amphetamine group.

Procedure. The TLX and saliva samples were collected at the same times throughout the sleep deprivation portion of the experiment for all three drug conditions. For each group of subjects, the first TLX and saliva samples were taken during the baseline day (Monday at 1730) before the sleep deprivation portion of the experiment. The last samples were taken at the same time during the recovery day (Friday at 1730) after ≈ 13 hours of recovery sleep . During the 64 hour sleep deprivation portion of the experiment ten samples were taken at 6 hour intervals. Thus, a total of 12 samples for each of NASA TLX and saliva cortisol were collected.

NASA TLX ratings. For the NASA TLX task, the subjects were asked to rate themselves on their perceived workload based only on the previous 2-hours of work — i.e., within that particular work session — not since the previous TLX estimate which was six hours before. The TLX questionnaire was presented on a VT100 computer monitor and the subjects were asked to rate themselves on a scale of 1 to 100 on each of the six TLX subscales that make up the TLX workload estimate. The six subscales include: mental workload, physical workload, performance (how well subject thought he/she performed), time pressure, effort, and frustration level. After the six subscales were scored, the subjects were asked to pick one subscale (that was more salient) over the other, for a total of 15 paired comparisons. The number of times each subscale was chosen was multiplied by the original rating number for that subscale, producing a subscale score (between 0 and 500). The overall NASA TLX score is the sum of all the subscale scores divided by 15. The cognitive tasks on which the subjects rated themselves included: serial reaction time; logical reasoning; addition and subtraction; tracking; perceptual comparison with and without subjective performance ratings; encoding-decoding; short-term memory; planning; SYNWORK (a short term memory multitasking environment); physiological baseline (e.g., heart rate, blood pressure, core temperature); subjective questionnaires; and time of day and elapsed time estimates.

Saliva samples for cortisol analysis. Immediately after completing the TLX ratings, the subjects were asked to provide a one-millilitre sample of their saliva in a plastic test tube. The test tubes were then frozen at -70°C for subsequent analysis. Salivary cortisol levels were analyzed by Coat-A-Count Cortisol RIA kits (Diagnostic Products Corporation, LA, CA) using the following procedure. Samples were centrifuged by a Sorvall RC-5B Refrigerated Superspeed Centrifuge at 11,000 rpm, at 10° C, for 10 to 15 minutes. The supernatant was then separated for analysis. After the ^{125}I cortisol was added to each tube and incubated for 3 hours, the tubes were decanted and counted for 1 minute in a Canberra Packard gamma counter. Salivary cortisol values were determined from a logit-log representation of the calibration curve, using the calibrator values listed in a special "determination in saliva" package provided by Diagnostic Products Corporation. The

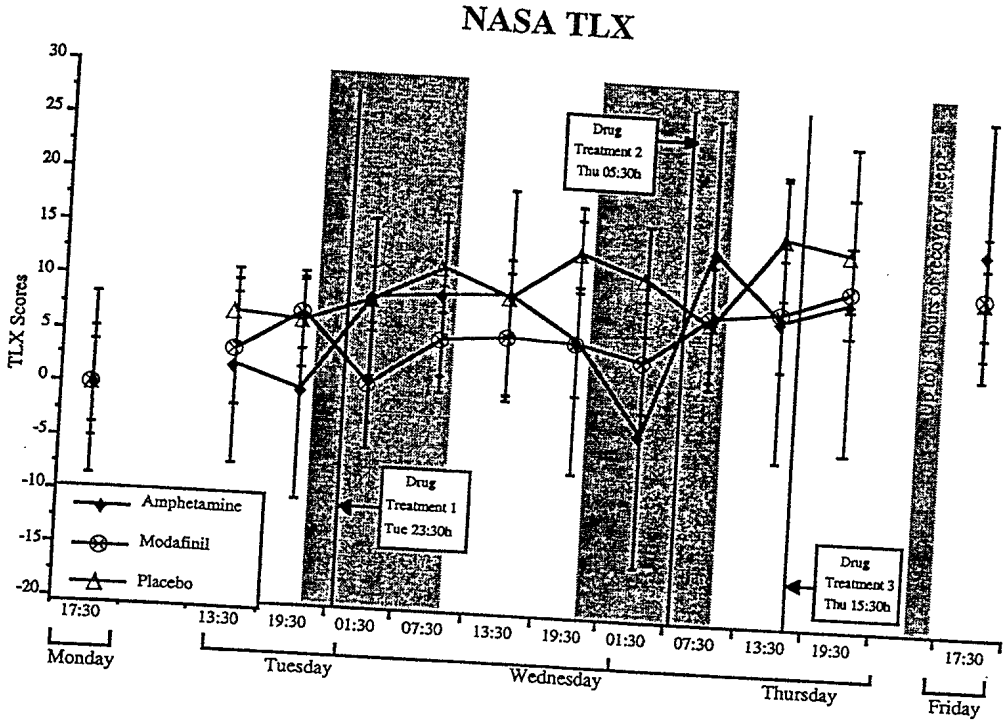

Figure 1. Normalized mean NASA TLX results for three drug conditions across all sampling periods.

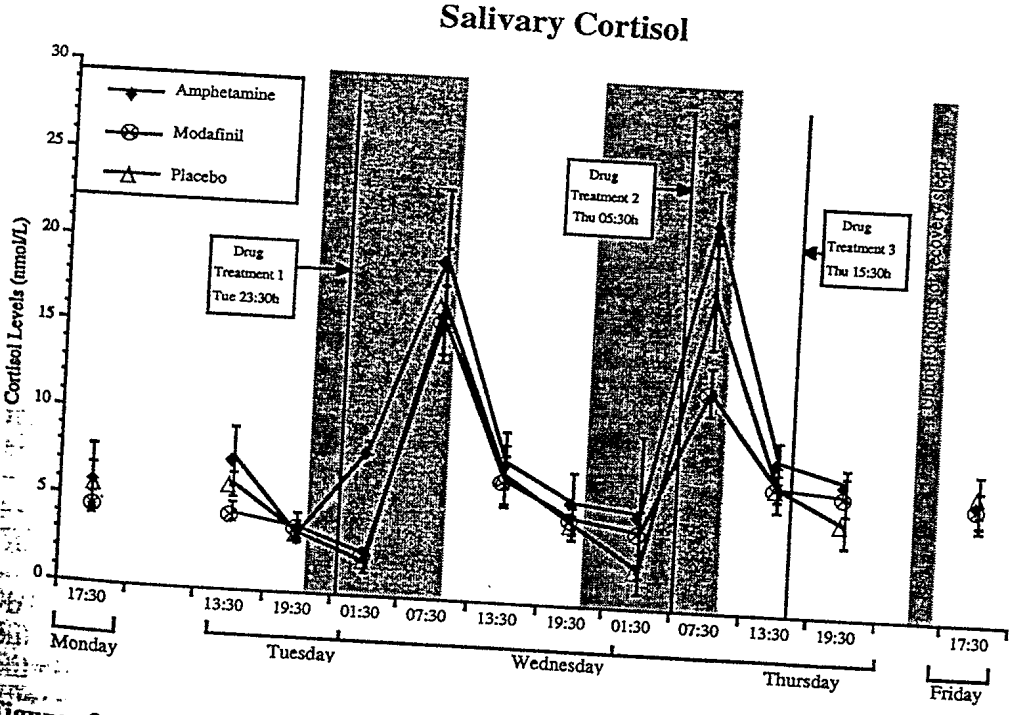

Figure 2. Mean salivary cortisol results for three drug conditions across all sampling periods. Note circadian effects and some differences between drug treatments (not significant in post hoc t-tests) at post-drug trials.

salivary cortisol levels for each sample were printed by a gamma counter printer.

RESULTS

The TLX data were z-score nomalized and submitted to a 3-between x 12-within mixed analysis of variance (ANOVA). Though Figure 1 suggests a trend towards increasing TLX scores over time for all three drug conditions, there were no statistically significant main effects for drug condition, no main effects for time during sleep deprivation and no interactions.

A similar ANOVA was performed on the salivary cortisol data. A significant main effect for drug was obtained ($F(2,163) = 8.23$, $p<.0004$) where the amphetamine group had significantly higher mean salivary cortisol levels (9.61±1.04 nmol/L) than either the placebo (7.21±.73 nmol/L) or modafinil (6.76±.53 nmol/L) groups. There were no significant differences between modafinil and placebo. Salivary cortisol levels changed significantly according to time-of-day throughout the sleep loss portion of the experiment for all three drug conditions ($F(11,163) = 20.45$, $p<.0001$ see Figure 2). The interaction between drug and test time approached but did not reach statistical significance ($F(22,163) = 1.5$, $p=.08$). Although the amphetamine group appeared to show increased levels of cortisol after drug treatments 1 and 2— which likely contributed to the overall main effect — post hoc t-tests on these means (Wed, 0130 and Thu 0730) were not significant ($t_{Am,Pl(8)} = 1.32$, $p < .25$ and $t_{Am,Mo(8)} = .76$, $p < .25$ respectively), probably due to the small sample size.

Given the unchanging values of the NASA TLX, it is not surprisingly that there was no correlation between the TLX scores and salivary cortisol levels ($r_{TLXxCort} = -.05$ and $r_{Log10(TLX)xLog10(Cort)} = -.04$).

DISCUSSION

The NASA TLX results for all three drug conditions did not vary with the circadian cycle or with increasing fatigue (see Pigeau et al., in press). Gaillard (1993) and Hockey et al. (1986) have stated that subjective feelings of workload may involve processes different from those of arousal. Gaillard's model (1993) predicts that subjective ratings of fatigue, mood, etc. will be positively correlated with declining cognitive performance, a result supported by the findings of the Pigeau et al. (in press). Subjective estimates of workload, however, did not change — even though there was a slight upward trend in TLX scores for all three drug conditions over the duration of the week. There are at least two possible explanations for these results. First, the NASA TLX is not sensitive to the stressor of sleep loss. Second, the workload perceived by the subject during the experiment did not vary because actual cognitive workload did not change. Recall that the data were collected every six hours. It so happens that the entire set of cognitive questionnaires and tasks used throughout the experiment was also repeated every six hours. If, despite increasing fatigue due to sleep loss, subjects were able to maintain their *meta* -cognitive ability to monitor the level of work demanded of them, subjective estimates of workload would remain constant because the amount of work they had completed in the intervening period was the same. This interpretation is consistent with Baranski (1995) who found that the *meta* -cognitive ability to monitor one's own accuracy during task performance remains stable throughout the sleep loss period. If this interpretation is correct then it is interesting to note that the TLX workload estimates were also resistent to the alerting influences of amphetamine and modafinil.

The main effect of drug condition on salivary cortisol level suggested that amphetamine was more arousal-inducing than modafinil or placebo. (The failure of the post hoc t-tests to reach statistical significance is unfortunate and may have been due to the small sample size.) The elevation of cortisol in amphetamine compared to placebo and modafinil may have been due to different pharmacological pathways used by d-amphetamine and modafinil. Cortisone in the adrenal cortex and norepinephrine (NE) in the adrenal medulla have similar functions with respect to metabolism and response to stress (Carlson, 1986). In respect of biochemical mechanism associated with amphetamine, there is evidence that the direct amphetamine-

dopamine pathway (Groves et al, 1975) results in greater unbound NE and cortisol (Kebabian et al, 1972; Ungerstedt, 1974a). By contrast, the modafinil involves the modafinil-apha-1-adrenergic pathway (Warot et al., 1993; Lyons & French, 1991; Rambert et al., 1990; Saletu et al., 1990) which is a negative feedback system (Axelrod, 1974a), resulting in suppressed levels of NE and cortisol. In future studies, NE should also be measured along with cortisol.

Salivary cortisol showed a strong circadian effect with distinct peaks occurring at 0730h on the first and second days of sleep deprivation. Althought the interaction between the drug condition and test time only approached statistical significance, the trends in the data are consistent with the postulated physiological mechanisms for amphetamine and modafinil described above. Recall that cortisol levels exhibited by the placebo group changed very little between the first and the second circadian cycle. The amphetamine group, however, had elevated cortisol levels after the second drug treatment while the modafinil group had reduced levels — indeed, below that even of the placebo group.

The lack of a correlation between the NASA TLX and cortisol levels attests to the different interpretations of the concept of 'stress' embodied by each measure. If cortisol is indicative of general physiological arousal, and any physiological system that is aroused is therefore being stressed, then circadian fluctuations in cortisol levels should also reflect circadian levels of stress. Although workload can similarly be considered stressful, its perception (i.e., subjective estimate) may be independent of general levels of physiological arousal. Perhaps other subjective estimates are more appropriate for estimating psychological stress. For example, Gaillard (1993) suggests that some psychological estimates of stress (e.g., mood or fatigue scales) can be distinguished from subjective perceptions of workload (NASA TLX) — the former being more related to both psychological and physiological stress. The measurement of arousal using subjective scales (Pigeau et al., in press; Warot et al., 1993) and performance measures (Angus & Heslegrave, 1985; Haslam, 1982) seem to correlate better with biochemical changes (Cumming et al., 1983; Riad-Fahmy et al., 1982; Robertson et al., 1981), and circadian changes (Motohashi, 1992; Zurbrügg, 1976) of arousal.

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