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Research Article
Published: 13 Feb, 2018

SF Journal of Aviation and Aeronautical Science

Effect of Modafinil on Changes in Tolerance to +G_z Induced by Total Sleep Deprivation

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Abstract

Straining G level tolerance was measured of 45 healthy, males (20-22 years) in a baseline (non-sleep deprived) state and after 32 hours of Total Sleep Deprivation (TSD). Oral temperature (T_{Oral}), heart rate (HR) and mean arterial pressure (MAP) were also recorded. Stanford Sleepiness Scale (SSS) was used to score subjective perception of sleepiness/alertness. During TSD, the participants were randomised to receive two doses of Placebo (Group 'P'), Modafinil 100 mg (Group 'M1') or Modafinil 200mg (Group 'M2') at 2200h on D_0 and 0700h on D_{+1} (corresponding to ~16th and ~25th hours of TSD). Results were analysed using ANOVA/paired 't' test/χ^2 test. Modafinil (200 mg) significantly increased HR, MAP & T_{Oral}. Straining G level tolerance decreased significantly in TSD in Group 'P' (5.5±0.2 G in baseline versus 4.8±0.3G after TSD; t=2.51, p=0.026) and Group 'M1' (5.2±0.2G in baseline versus 4.3±0.3G after TSD; t=2.98, p=0.011). In Group 'M2', there was no significant change (5.1±0.2G in baseline vs 5.0±0.2G after TSD; t=0.56, p=0.583). Scores on SSS with a value of 4 or more (signifying somewhat foggy & let down state) were more in Group 'P' compared to those in Group 'M1' & Group 'M2' (χ^2 =25.56, p=2.81E-06). Modafinil (200mg) mitigated decrease in level G tolerance due to TSD. The mitigating effect of Modafinil on straining G level tolerance was not offset by an increase in T_{Oral} which exhibited a significant main effect of pharmacological manipulation (p<0.017).

Keywords: Total Sleep Deprivation; Modafinil; 'GO' pill; +Gz Tolerance

Introduction

Effect of total or partial sleep deprivation on orthostatic tolerance and exercise performance is rather intricate. Muenter et al [1] have reported that sleep restriction (4h sleep/ night for 4 consecutive nights) produced subtle changes in cardiovascular responses to orthostasis simulated in the form of lower body negative pressure (LBNP). However, these changes did not compromise orthostatic tolerance. Such a subtle effect of sleep deprivation on cardiovascular status and neuro-circulatory control has been reported by others, as well [2,3]. Notwithstanding this subtleness in physiological responses, perceived difficulty in performing anti-G straining maneuver (AGSM) certainly increases during sleep deprivation [4]. This is due to the effects of sleep deprivation on cardio-respiratory functions, mood and physical work capacity. Chen [5] reported altered cardio-respiratory functions at rest and the ability to perform maximal exercise after 30 hours of sleep loss. In a comprehensive study, Rodgers et al [6] demonstrated that total sleep deprivation (TSD) of 48 hours adversely affected cardio-respiratory functions, mood and physical work capacity (performance of physical work tasks requiring 30-45% VO_2max declined significantly). The above changes were without any effect on muscle contractile properties, measures of anaerobic power or resting blood glucose and lactate concentrations. Azboy & Kaygisiz [7] have reported a significant decrease in performance due to decreased exercise ventilation and time to exhaustion after sleep deprivation of one night. Anaerobic performance is reported to be impaired after 36 hours of sleep deprivation [8].

Modafinil [(±)-2-(benzhydrylsulfinyl) acetamide] is an analeptic drug known to have beneficial effects on measures of alertness and performance during sleep deprivation. For a review (especially in relation to its application to aviation environment), reference may be made to Caldwell et al [9]. However, beneficial effects of Modafinil are not limited to preservation of performance during sleep deprivation. It exerts a modest/ moderate sympatho-medullary activation [10] and, with a

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Received Date: 19 Dec 2017
Accepted Date: 06 Feb 2018
Published Date: 13 Feb 2018

Citation: Tripathi KK, Singh H, Baburaj VP, Chowdhary S. Effect of Modafinil on Changes in Tolerance to +G_z Induced by Total Sleep Deprivation. SF J Aviation Aeronaut Sci. 2018; 1(1): 1006.

ISSN 2643-8119

strong ergogenic effect, it is shown to significantly prolong 'time to exhaustion' (15.6±3.8 min with Placebo *versus* 18.3±3.5 min with Modafinil administered in a dose of 4 mg/kg three hours before exercise) and reduce 'perceived exertion' in volunteers exercising at 85% of their VO_2max [11]. These effects are likely to increase tolerance to $+G_z$. At the same time, Modafinil is known to induce a significant increase in core body temperature even in subjects who are maintained in a comfortable thermal ambience [12,13]. This increase in core body temperature may adversely affect tolerance to $+G_z$. Therefore, Modafinil is conceived to possess properties with potential for both an increase and decrease in tolerance to $+G_z$.

Modafinil has been approved as a 'GO' pill in the pharmacological strategy for sleep, alertness and fatigue management of fighter aircrew [9]. In view of the above usage of this molecule amongst fighter pilots for preservation of alertness and its physiological effects on core body temperature, mood and physical work capacity, the present study investigated effects of Modafinil on changes in tolerance to $+G_z$ induced by total sleep deprivation (TSD). The study made following scientific enquiries-

1. Does total sleep deprivation (of ~32 hours) reduce tolerance to $+G_z$?

2. Does such a reduction in tolerance to $+G_z$ get modulated if the participant is primed with Modafinil in a Dose of 100/200mg?

3. Whether an increase in body temperature (due to administration of Modafinil) offsets this modulation?

Methodology

Participants

45 healthy, male volunteers (20-22 years in age), served as participants. None were smokers. None had any exposure to flying training. They were ascertained to be healthy through a detailed history, clinical examination and resting ECG. A written consent was obtained after the experimental protocol was explained.

Experiment design

The study was a double blind, crossover, placebo controlled, mixed design (with both 'between the group' and 'within the group' evaluations).

Protocol & Experimentation

Present study was part of a large project (which was primarily to examine the effect of Modafinil on performance during extended wakefulness of 32 hours) with the protocol as summarized in Table 1.

The period of total sleep deprivation started from 0600h on the first day of the study (D_0) which extended till ~1400h the next day (D_{+1}). The entire period of study (of 32 hours) was divided into four Time Blocks.

Participants were divided into three Pools. Pool 'A' comprised of participant numbers 1-15, Pool 'B' comprised of participant numbers 16-30 and Pool 'C' comprised of participant numbers 31-45.

These well rested and slept (in the previous 3 night) participant were evaluated on three occasions, separated by a minimum of three days. The order of evaluation on three occasions was counterbalanced as shown in the Table 1 to obviate any 'carry over' effect. Evaluations in Time Blocks-III and IV were made in continuation (on the same occasion). Time Blocks-III and IV were designated as Sleep Deprivation (SD) Blocks.

Pools 'A' 'B' and 'C' were divided randomly into three groups (n=5 for each) which were examined with the administration of a Placebo, Modafinil (100 mg) or Modafinil (200 mg), during their evaluation in Time Blocks-III & IV. The two doses of Placebo/ Modafinil were administered at 2200 h on D_0 and 0700 h on D_{+1} corresponding to ~16th and ~25th hours of TSD. Thus, 15 participants could be studied, each in Placebo (P), Modafinil (100 mg) (M1) and Modafinil (200 mg) (M2) groups. Even though the participants in 'A', 'B' and 'C' Pools were divided into 'P', 'M1' and 'M2' groups, the division was only notional during Time Blocks-I & II. Put simply, it was without any drug intervention and merely for the sake of analysis ie, for 'within the group' comparison(s) with Time Blocks-III and IV.

Both Modafinil and Placebo were covered with capsules of the same size, shape and color.

Straining tolerance to $+G_z$ was assessed twice in human centrifuge using a gradual onset rate (GOR) profile. One evaluation was made in a non-sleep deprived state (Time Block- II) and the other after 32 hours of total sleep deprivation (Time Block-IV). These were deliberately planned in the same time of the day (~1400 hours) to avoid effect of any circadian variation.

Participants had breakfast, lunch and dinner at fixed times between 0700 h to 0800 h, 1300 h to 1400 h and 1900 h to 2000 h, respectively. Light refreshment was served between 0930 h to 1000 h and 1700 to 1730 h. After dinner, no intake of food/ beverages was allowed. They were not permitted to have any tea or coffee throughout the course of the study.

Assessment of straining tolerance

Participants practiced on 'ground' how to strain. It included tightening of muscles of trunk and limbs. They were then taken to gondola of the centrifuge, familiarised with the light bar and positioned in a seat with its back reclined to 17° from vertical. They were secured with a four point harness. The exposure to acceleration was without any Anti-G Straining Manoeuvre (AGSM) or G-suit. The gradual onset rate (GOR) exposure to $+G_z$ commenced at a rate of 0.1G/s and the acceleration was increased to +1.4Gz. Thereafter, the acceleration was increased till Peripheral Light Loss (PLL) of 56-52° occurred. The PLL was defined as the inability of the subject to see an array of light emitting diodes while focussing at the centre of the bar. At that point, the participants started straining. After the re-appearance of PLL, the subjects released a switch which brought the centrifuge to position of rest (+1Gz). The profile was 'open-loop' in the sense that the participants were not in control of the device but could stop the run at any time. Since the participants were ground personnel, unfamiliar to human centrifuge and without any previous exposure to acceleration, an evaluation of relaxed G level tolerance was considered to be impractical and not attempted, intentionally (in such subjects, what one measures as relaxed tolerance is, actually, something more than the actual relaxed tolerance and closer to straining tolerance).

Assessment of subjective perception of sleepiness

Stanford Sleepiness Scale (SSS) was used for the subjective appreciation of sleepiness (during the period of sleep deprivation). The SSS is a self-rating scale used to quantify the degree of sleepiness on a scale from 1 to 7. Initial validation of the scale was done by Dement & Barchas [14] who conceived it as a self-rating scale indicating levels of

Table 1: Study Protocol.

	No pharmacological intervention		Pharmacological intervention at 2200 h on D_0 & 0700 h on D_{+1} (corresponding to ~16th & ~25th hour of TSD) Placebo to A-P, B-P, C-P Modafinil (100 mg) to A-M1, B-M1, C-M1 Modafinil (200 mg) to A-M2, B-M2, C-M2	
	TIME BLOCK-I [0600 h – 1400 h]	TIME BLOCK-II [1400 h – 2200 h]	TIME BLOCK-III 2200 h – 0600 h $_{(D+1)}$	TIME BLOCK-IV 0600 h $_{(D+1)}$ – 1400 h $_{(D+1)}$
Occasion- 1	Pool A (n=15)	Pool B (n=15)	Pool C (n=15) C-P (n=5), C-M1 (n=5), C-M2 (n=5)	
Occasion- 2	Pool B (n=15)	Pool C (n=15)	Pool A (n=15) A-P (n=5), A-M1 (n=5), A-M2 (n=5)	
Occasion- 3	Pool C (n=15)	Pool A (n=15)	Pool B (n=15) B-P (n=5), B-M1 (n=5), B-M2 (n=5)	

Table 2: The scoring system of 'Owl and Lark' questionnaire.

Score	Type
70-86	Definitely Morning Type
59-69	Moderately Morning Type
42-58	Neither Type
31-41	Moderately Evening Type
16-30	Definitely Evening Type

Table 3: Physical attributes of participants.

	Group 'P' (Placebo)	Group 'M1' (Modafinil 100 mg)	Group 'M2' (Modafinil 200 mg)
Age (yr)	20.7±0.2	20.4±0.2	20.7±0.2
Height (cm)	172.7±1.6	172.9±1.6	171.6±1.6
Weight (kg)	64.1±1.1	62.1±1.1	61.0±1.1

Table 4: Distribution of participants with different scores.

Score	Type	Number in the Study Group		
		Placebo	Modafinil (100 mg)	Modafinil (200 mg)
42-58	Neither Type	7	3	6
59-69	Moderately Morning Type	8	11	9
70-86	Definitely Morning Type	Nil	1	Nil

sleepiness, sensitively and reliably. The SSS is especially useful in the context of the present study as it can be applied repetitively to assess the momentary subjective (introspective) sleepiness and can even be repeated at short intervals, for instance, to study circadian sleepiness [15]. In the present study, scores were obtained 12 times between midnight and 1400 hours on the next day (twice during the periods midnight to 0200 h, 0200 - 0400 h, 0400 - 0600 h, 0800 - 1000 h, 1000 - 1200 h and 1200 - 1400 h on D_{+1}).

Measurement of physiologic variables

Oral temperature, heart rate (HR) and mean arterial pressure (MAP) were measured once every two hours across the period of the study (starting from 0600h on D_0 to 1400h on D_{+1}) except between 0600 - 0800hs on D_{+1} during which the participants attended to their morning routines. However, the values presented and analysed (compared statistically) in Table 5 are those recorded between 1200 - 1400h on D_0 and D_{+1}.

Measurement of morningness/eveningness

Morningness/eveningness was determined with a self assessment 'Owl and Lark' questionnaire [16]. The scoring system for the questionnaire is reproduced in (Table 2).

Statistical analysis

Unless specified otherwise, the values are presented as Mean±SEM.

The data were examined, first, for normality of distribution using Shapiro Wilk's 'W' statistic to select an appropriate statistical test for analysis.

To examine significance of difference in the physical attributes (age, height, weight and morningness/ eveningness) across the three groups, one way analysis of variance (ANOVA) was employed.

For physiological variables (HR, MAP, core body temperature and tolerance to $+G_z$), two way ANOVA was used. The two factors were sleep deprivation and pharmacological intervention.

After a significant outcome from ANOVA (significant main effect of TSD), a paired't' test was used for individual comparisons to examine the significance of difference in straining G level tolerance between baseline and after TSD for the three drug interventions.

To compare the number of scores on SSS with a value of 4 or more, a χ^2 test was employed. It was also used to compare number of participants who could be labeled as 'Definitely Morning Type', 'Moderately Morning Type' and 'Neither Type'.

Significance level was set as $p<0.05$. The level of significance is reported in the results.

Results

Physical attributes of the participants in the three groups were statistically comparable (single factor ANOVA; F=0.82, p=0.447 for age; F=0.19, p=0.827 for height and F=2.19, p=0.124 for weight), Table 3 refers.

The scores in 'Owl & Lark' questionnaire were 59.3±1.4, 62.5±1.4 and 58.8±1.4 for the subjects in Placebo, Modafinil 100 mg and Modafinil 200mg groups, respectively. There was no variation across the three groups (single factor ANOVA; F=1.97, p=0.152). Scores in the data pooled across the three groups were 60.2±0.9. Distribution of participants with different scores is given in Table 4.

The distribution of scores in the Groups Placebo, Modafinil 100mg and Modafinil 200mg was not different (χ^2=4.13, p=0.39). These observations suggest that the participants were almost exclusively 'Neither/Moderately Morning Types', were distributed equally in the three groups and this attribute could not have confounded their $+G_z$ tolerance.

HR and MAP exhibited significant effects of both TSD and

Table 5: Straining G level tolerance & other physiological variables: Baseline (non sleep deprived) and after 32 hours of total sleep deprivation with the three drug interventions.

	Baseline				Sleep deprivation (32 hours)		
	Placebo	Modafinil 100 mg	Modafinil 200 mg		Placebo	Modafinil 100 mg	Modafinil 200 mg
HR (bpm)	63.6±1.9	68.3±1.8	65.2±1.8		69.4±1.7	76.9±1.6	75.1±1.6
MAP (mm Hg)	79.0±1.7	82.8±1.6	82.1±1.6		81.9±1.6	85.8±1.5	88.0±1.5
Oral Temperature (°C)	97.3±0.2	97.6±0.2	97.3±0.2		97.1±0.2	97.7±0.2	97.9±0.2
Straining G level tolerance	5.5±0.2	5.2±0.2	5.1±0.2		4.8±0.3	4.3±0.3	5.0±0.2

Table 6: Results of statistical analysis.

	Sleep deprivation	Pharmacological manipulation	Sleep deprivation x Pharmacological Manipulation
HR (bpm)	F=62.93, p=0.022	F=4.18, p=8.21E-10	F=1.32, p=0.279
MAP (mm Hg)	F=13.52, p=0.001	F=3.40, p=0.043	F=0.93, p=0.403
Oral Temperature (°C)	F=1.84, p=0.182	F=4.52, p=0.017	F=2.46, p=0.098
Straining G level tolerance	F=13.77, p=0.001	F=0.99, p=0.379	F=2.24, p=0.120

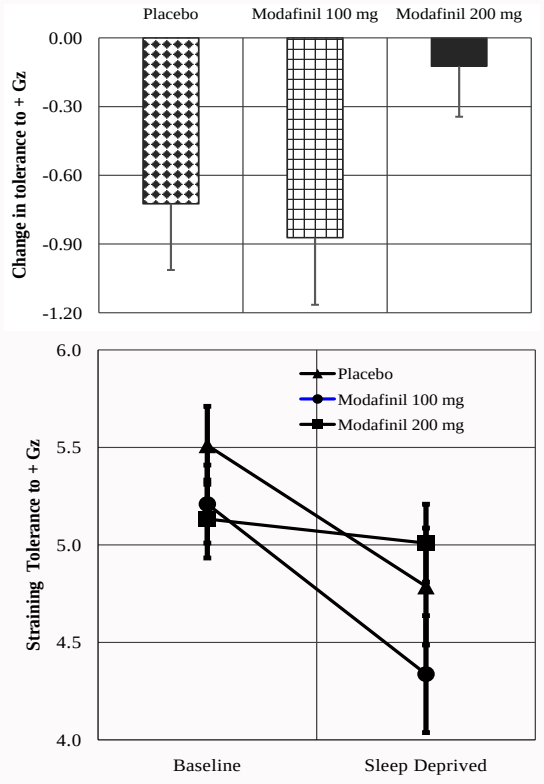

Figure 1: Effect of Modafinil on decrease in straining G level tolerance after 32 hours of Total Sleep Deprivation.

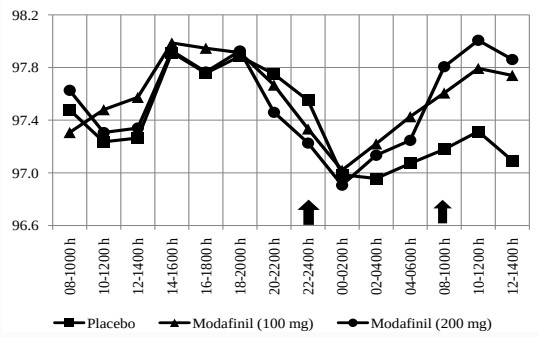

Figure 2: Effect of Modafinil on oral Temperature during 32 hours of total sleep deprivation. Modafinil/ Placebo was administered at 2200 h on D_0 and 0700 h on D_{+1} (marked with arrows).

pharmacological manipulation. T_{Oral} showed significant effect of pharmacological manipulation. Interaction between TSD and pharmacological manipulation was not significant for any of the above variables. Values of HR, MAP and T_{Oral} were significantly higher in groups 'M1' and 'M2' compared to group 'P'. These results are presented in Tables 5 & 6.

Straining G level tolerance exhibited a significant effect of only sleep deprivation. To further explore the significance of pharmacological manipulation, a paired 't' test was performed, individually, for the three groups. These comparisons revealed that in groups 'P' and 'M1' (Modafinil 100mg), there was a significant decrease in straining G level tolerance after TSD compared to baseline (t=2.51, p=0.026 for Placebo and t=2.98, p=0.011 for Modafinil 100mg). In group 'M2' (Modafinil 200), such a decrease in $+G_z$ tolerance was minimal and statistically insignificant (t=0.56, p=0.583). These results are presented in Tables 5, 6 and Figure 1.

The occurrence of scores on SSS with a value of 4 or more (representing somewhat foggy, let down state) was different across the three groups (χ^2=25.56, p=2.81E-06). These results are presented in the Table 7. For this analysis, all the responses with a particular drug intervention were pooled across the period of TSD. Thus, the total number of responses in any one drug intervention should have been 180. It is derived as follows- Number of subjects (15) x Number of evaluations made during sleep deprivation (6) x 2 (as the responses were collected twice). However, the actual total is less as the responses were not available from all the participants.

Discussion

Administration of Modafinil elicits a number of physiological effects which could contribute to an increase in level tolerance to $+G_z$. These include a modest sympatho-medullary activation [10] and a strong analeptic [9] & ergogenic [11] effect. Results of the present study support all the above mechanisms.

Evidence of sympatho-medullary activation was available in the form of a significant increase in HR and MAP in the groups 'M1' & 'M2'. A number of studies have shown an increase in HR and MAP after administration of Modafinil [10,13,17,18]. In a comprehensive

Table 7: Number of observations with different Stanford Sleepiness Scale ratings.

Score on SSS	Placebo	Modafinil 100 mg	Modafinil 200mg
1	16	14	16
2	24	48	50
3	62	77	72
4	41	25	18
4	17	2	6
6	2	0	4
7	0	0	0
Total	162	166	166
1-3	102 (63%)	139 (84%)	138 (83%)
4-7	60 (37%)	35 (16%)	38 (17%)
Total	162	166	166

evaluation, Taneja et al [10] have shown that Modafinil substantially perturbs autonomic cardiovascular regulation by increase in HR and BP. An analeptic & ergogenic effect was manifest in the form of maintenance of low scores (1-3) on SSS in the groups 'M1' & 'M2'. With the administration of Modafinil, the scores on SSS were 3 or less at about 83-84% occasions. In the placebo group, the corresponding figures were 63%. A score of 3 represents awake but relaxed; responsive but not fully alert state. Apropos, the scores with a value of 4 or more, signifying a 'let down' state were observed at only 16-17% of the occasions in the groups which were administered Modafinil. The corresponding figures in the Placebo group were 37%. Such an analeptic effect was observable with both 100mg and 200mg of dosage of Modafinil and is well established [9,19].

Additionally, the observed behaviour of these physiological variables (HR, MAP and T_{Oral}), as epiphenomena, endorsed that Modafinil was biologically available and effective.

As stated earlier, it is interesting to note that many of these effects achieved statistical significance even with 100mg of Modafinil (in group 'M1'). However, a dose of 100mg of Modafinil was not sufficient to completely overcome the detrimental effect of TSD on Gz tolerance (vide infra).

The principal observation of the present study is, however, a significant decrease in straining G level tolerance observed with TSD of 32 hours and its amelioration with the administration of Modafinil (two doses of 200mg each administered at 2200h on D_0 and 0700h on D_{+1} corresponding to ~16^{th} and ~25^{th} hours of TSD). Such a beneficial effect was not noticed with lower (100mg) dosage of Modafinil administered in the same time frame. The same was evident from the paired comparisons of G tolerance in the baseline (non-sleep deprived state) and that after 32 hours of TSD in the three pharmacological groups. Thus, straining G level tolerance declined significantly after TSD compared to baseline in groups 'P' (Placebo) and 'M1' (Modafinil 100mg). However, in group 'M2' (Modafinil 200), straining G level tolerance after TSD was comparable to that in the non-sleep deprived state.

Such a restoration of tolerance to $+G_z$, observed in the present study, is apparently not in consonance with the results of the two studies available in the peer reviewed literature on the subject. In one of these studies, Ramsey et al [20] examined 10 male subjects (mean age 32 yr), in a 'within-subject' (repeated measure) design, in five night conditions. Participants were administered Placebo, Dextroamphetamine (10mg), Modafinil (200mg), Methylphenidate (10mg) or Pemoline (37.5mg) at night at ~2230h. Thereafter, their tolerance to $+G_z$ was tested at an average of 17 hours of sustained wakefulness (and not 22 hours as reported in the abstract of the study). After the centrifuge runs, the participants were allowed a recovery sleep. Daytime centrifuge testing concluded by ~1000h on the next day. No difference in $+G_z$ tolerance, endurance and cognitive performance was observed. However, subjective perception of difficulty in performing anti-G straining maneuver (AGSM) was greater during the night placebo condition than during the daytime control, Methylphenidate and Modafinil night conditions reached statistical significance (p= 0.005, 0.012, 0.022, respectively).

In yet other study, Florence et al [21] evaluated 7 adult male rhesus monkeys for their tolerance to $+G_z$. Five were instrumented with ECoG and ECG wires and underwent two G tests (A and B). Each experiment consisted of five centrifuge runs. Before the runs, the monkeys received no drug (control) or were given either 7.5mg/kg Caffeine IM or 64 mg/kg Modafinil PO or the corresponding vehicles. The runs were performed up to +13Gz with an onset rate of 0.1 G/s (test A) or 3 G/s (test B). The run was ended when the electrical activity of one ECoG channel had disappeared (ie, G-LOC). In experiment A, drug administration had no significant effect. In experiment B, the injection of the caffeine-free solvent caused a delay in G-LOC compared with the control condition (no administration). It could be concluded that Caffeine and Modafinil administration had no significant effect on the G-tolerance of rhesus monkeys when compared with controls. However, the authors conceded that the result needs to be confirmed in humans.

Nonetheless, the two studies quoted above are essentially different from the present study. In the first study [20], the duration of TSD was only ~17 hours (from 0700h to ~2330h on the same day). Not much of fatigue and subsequent decrement in performance is expected in such a time frame. Additionally, the study suffers from a number of methodological inadequacies. To name a few are a small sample size and an inadequate recovery sleep after which basal 'day time' evaluation was done. Similarly, in the second study by Florence et al [21], the monkeys were neither sleep neither deprived nor fatigued. It is possible that Modafinil only prevents fatigue and decrease in tolerance to $+G_z$, it does not improve it beyond average tolerance in a non-sleep deprived state.

Another important observation of the present study is that the beneficial effects of Modafinil on tolerance to $+G_z$ were not offset by an increase in core body temperature which is shown to have a detrimental effect on level tolerance to $+G_z$ [22]. A number of studies have shown that Modafinil increases resting core temperature during periods of sustained wakefulness [12, 23,24,25,26]. The increase in body temperature (in resting subjects) is reported to be due to an increase in heat production during the first day of wakefulness followed by a lower evaporative heat loss during the second day [24]. In a state of TSD, fatigue may add to the effects of such an increase in core body temperature. In the present study, we did demonstrate a significant difference in T_{Oral} between the Modafinil and the Placebo groups. The comparison of T_{Oral} presented in Table 5 is restricted to its values recorded in the time frame corresponding with that for evaluation of tolerance to $+G_z$, Figure 2 presents T_{Oral} and its circadian rhythmicity for the entire duration of the study. It is possible that the detrimental effect of a small increase in body temperature is easily

overwhelmed by the sympatho-medullary activation and ergogenic effects of Modafinil. Or else, it may be possible that the core body temperature exerts a detrimental effect on tolerance to $+G_z$ only when it increases beyond normal circadian range. In the present study, the T_{Oral} did not exceed beyond the normal circadian range. As a matter of fact, we observed that, within the range of circadian normality, T_{Oral} correlated poorly and insignificantly with the tolerance to $+G_z$ (r=0.134 for non sleep deprived condition an r=0.000 for TSD). These results are not presented in the paper.

A pertinent question arises if the beneficial effects of Modafinil on tolerance to $+G_z$ will be observed even in a 'non-sleep deprived' state. In the past, there have been a number of unsuccessful efforts to exploit pharmacological manipulation to increase tolerance to positive acceleration in a 'non-sleep deprived' state. For a detailed review, reference may be made to Green [27] and Howard [28]. A stimulatory effect of Modafinil on sympatho-medullary activity supports such an effect. To explore such an effect, we conducted another study [29] to measure both relaxed & straining $+G_z$ level tolerance before and after pharmacological intervention with Modafinil (200mg)/Placebo (n=19 in each group) amongst fighter aircrew. Concomitant measurement of physiological variables (HR, MAP & T_{Oral}) and sympathetic responsiveness (in the form of cardiovascular responses to sustained Isometric Hand Grip) was also made. Subjective perception of fatigue was measured in the same time frame in a subset of subjects similarly randomised (n=15 in each group). Modafinil significantly increased HR, MAP & core body temperature. Response to sustained isometric hand grip, measured as increase in HR & MAP during Isometric Hand Grip from resting sitting values, was unaffected. Modafinil mitigated a significant decrease in Straining $+G_z$ tolerance and increase in perception of fatigue with repetition of exposure to acceleration. However, change in relaxed $+G_z$ tolerance was insignificant.

Therefore, it appears that Modafinil may be employed only to mitigate effects of fatigue associated with TSD or repeated exposures to $+G_z$. It may not be effective in improving relaxed tolerance to $+G_z$ in a non-sleep deprived and well rested individuals (at least in its traditional dosage of 200mg).

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