Equilibrium and Vestibular Safety of Modafinil in Healthy Volunteers

Fengzhou Liu; Min Zhang; Tao Chen; Lihong Zhai; Zuoming Zhang; Junhui Xue

BACKGROUND: Modafinil, as a wake-promoting agent, is commonly used to relieve fatigue during military operations. However, there is a lack of clarity regarding the effects of modafinil on the equilibrium and vestibular organs, especially when prescribing this drug to flight crewmembers. The objective of this study was to evaluate the equilibrium- and vestibular-related safety effects of modafinil.

METHODS: In a randomized, double-blind, placebo-controlled, crossover study, 10 healthy male volunteers received a single 200-mg oral dose of modafinil or placebo. Equilibrium and vestibular functions were assessed 2 h after oral administration by the sensory organization test (SOT), adaptation test (ADT), and video head impulse test (v-HIT).

RESULTS: There was no change in the equilibrium scores of the six SOT conditions or the composite scores between the modafinil and placebo groups. Statistically significant differences were not observed for the sway energy score (SES) in the toe-down test. In the toe-up test, the SES decreased by 16.7% in the modafinil group relative to the placebo group in trial 2, while the differences in other trials were not statistically significant. In the v-HIT, there was no significant difference in the gain of each semicircular canal between the two groups.

DISCUSSION: A single 200-mg dose of modafinil did not cause any impairment to vestibular function, equilibrium ability, or adaptive balance response; in fact, modafinil might have a positive effect on adaptation function in healthy volunteers. These findings preliminarily suggest that there is no hidden risk of vestibular dysfunction among aviation employees using modafinil.

KEYWORDS: modafinil, equilibrium, vestibular, aviation safety.

Liu F, Zhang M, Chen T, Zhai L, Zhang Z, Xue J. *Equilibrium and vestibular safety of modafinil in healthy volunteers*. Aerosp Med Hum Perform. 2022; 93(6):487–492.

Modafinil, a drug developed for promoting wakefulness, overcoming fatigue, and enhancing cognition,[10] has been widely prescribed in military medicine, especially to individuals under intensive cognitive pressure, such as fighter pilots, helicopter pilots, and astronauts. Previous studies have shown that modafinil can significantly ameliorate the decreased alertness and cognitive dysfunction caused by fatigue during long flights and improve the work efficiency of the crew.[15]

For flight surgeons, it is important to evaluate the adverse effects of drugs on flight safety and work performance. Regarding modafinil, previous studies on drug safety have indicated mild adverse reactions, including headache, nausea, mental tension, anxiety, and insomnia,[11] which were not regarded as potential threats to flight safety. However, the potential adverse effects of modafinil on equilibrium and vestibular functions, which are important for the work efficiency of flight crew and astronauts, have not been systematically evaluated in previous studies.

In pharmacological studies, the wake-promoting effect of modafinil is related to the activation of the α1-adrenergic receptor, the promotion of dopamine, the release of excitatory amino

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This manuscript was received for review in November 2021. It was accepted for publication in March 2022.

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DOI: https://doi.org/10.3357/AMHP.6032.2022

acid transmitters, and the inhibition of GABA release.[13] The transmitter of excitatory amino acids is closely related to signal transmission in the peripheral vestibular nervous system, central nervous system, and balance-related cerebral cortex.[12] Therefore, there is a theoretical basis for modafinil to have a possible influence on the vestibular and equilibrium systems. Furthermore, physiological and psychological fatigue caused by long flights and intensive cognitive load will lead to a decrease in vestibular function and equilibrium ability, which manifest as decreased abilities regarding acceleration perception and spatial orientation.[4,9] Thus, it is necessary to evaluate whether modafinil has adverse side effects on vestibular function.

The present study specifically aimed to assess the safety of modafinil on equilibrium and vestibular function. To this end, we compared the vestibular effects of modafinil and placebo through a series of vestibular function examinations in healthy volunteers using a randomized, double-blind, placebo-controlled crossover design.

METHODS

This study used a randomized, double-blind, placebo-controlled crossover design and was performed in a single center in China (Aerospace Clinical Medical Center, Air Force Medical University). The study was conducted according to the Declaration of Helsinki (Hong Kong Amendment), Good Clinical Practices (European Guidelines), and pertinent national legal and regulatory requirements. Subjects were free to withdraw from the study at any time for any reason.

Subjects

The project was approved by the Ethics Committee of the First Affiliated Hospital of the Fourth Military Medical University (KY20192110-F-1), and informed consent was obtained from each subject. The study included 10 healthy male volunteers whose physical condition met the strict pilot medical selection criteria. The mean ($\pm$ SD) age of the subjects was 24.5 $\pm$ 8.37 yr. No subject had previous vestibular disability or clinically significant balance impairment. Any subject with an ongoing clinically relevant condition, currently receiving medication likely to interfere with the outcomes of the study, or with a history of modafinil allergy was excluded from the study.

Procedures

The study consisted of three phases. The subjects were randomly assigned to receive a single 200-mg dose of modafinil or placebo by a balanced, nonadaptive randomization method with a 1:1 ratio. The reason that we administered a single dose of 200 mg modafinil is because the commonly used medication regimen is doses of 200 mg to pilots who perform missions greater than 12 h in duration according to previous studies from the U.S. Army.[8] Modafinil and placebo were provided by Welman Pharmaceutical (181,101; Hunan, China). This period was followed by a 3-d washout phase. During the second treatment phase, subjects were crossed over to alternative treatment for a single dose of placebo or modafinil. Equilibrium function was assessed using the sensory organization test (SOT) and adaptation test (ADT), and semicircular function was assessed with the video head impulse test (v-HIT). These tests were performed 2 h after the administration of modafinil or placebo because it takes approximately 2 h for modafinil to achieve peak levels in blood according to previous studies.[18] Healthy volunteers, investigators, and individuals involved in the analysis of the study were blinded to group assignment.

SOT. All subjects were evaluated by the SOT (Equitest System, NeuroCom International, Clackamas, OR, USA). The SOT protocol includes six test conditions which reflect the functions of visual, vestibular, and proprioceptive sensory systems in maintaining postural balance. The six SOT test conditions were as follows: 1) eyes open with fixed surroundings and platform (C1); 2) eyes closed with a fixed platform (C2); 3) sway-referenced surroundings with a fixed platform (C3); 4) eyes open with fixed surroundings and a sway-referenced platform (C4); 5) eyes closed with a sway-referenced platform (C5); and 6) sway-referenced surroundings and a platform (C6). Three trials were conducted under each condition, leading to a total of 18 trials. After each test, anterior to posterior center of gravity (COG) displacement was automatically measured, and an equilibrium score was calculated by comparing the angular difference between the patient's maximum anterior to posterior COG displacement to the theoretical limits of stability. An equilibrium score ranging between 0% (fall) and 100% (did not sway at all) was obtained. Additionally, the composite score was calculated by independently averaging the equilibrium scores for conditions SOT1 and SOT2, adding these two scores to the equilibrium scores from each of three trials of condition SOT3 through SOT6, and dividing the sum by the total number of performed trials. The composite score is the first parameter used to interpret SOT results because it provides an overall determination of normal versus abnormal performance in postural stability. Sensory ratio analysis in SOT is described as follows. 1) Somatosensory ratio: ratio of the mean values of C2/C1. 2) Visual ratio: ratio of the mean values of C4/C1. 3) Vestibular ratio: ratio of the mean values of C5/C1. 4) Visual preference: ratio of the mean values of (C3 + C6)/(C2 + C5). Each sensory analysis ratio was considered "abnormal" when it was lower than the age-specific normative data given by the computerized dynamic posturography manufacturer. Abnormally low somatosensory, visual, and vestibular ratios indicate that patients make poor use of each sensory system in postural stability. A low visual preference ratio means that patients rely on visual cues even when they are inaccurate (such as in moving visual surroundings).[14,16]

ADT. The adaptive balance function of each subject while standing was measured using an Adaptation Test via a computerized dynamic posturography machine (Smart Equitest; NeuroCom International). This test assesses the motor system's ability to adapt to repeated support surface rotation that causes the ankles to dorsiflex or plantar flex and thus triggers

the toes to move up or down without significantly displacing the subject's COG. During the test, the subject stood and looked straight forward while maintaining postural stability. The subject was then exposed to a series of five sudden platform rotations for each toe-up or toe-down cycle. The physiological postural control system is initially prepared to actively resist ankle joint dorsiflexion/plantar flexion. However, resisting ankle joint rotations in the ADT is destabilizing when the support surface rotates. Therefore, by the fourth or fifth platform rotation of the series, the automatic postural control system attenuates ankle joint resistance and reduces COG sway during the recovery period. A nondimensional sway energy score (SES) was generated based on the velocity and acceleration of the COG (i.e., body sway) of the subject during each testing trial of both toe-up and toe-down platform rotations. SES is an accurate measure of the overall functional effect of changes in adaptive balance. Mean SESs were calculated for both the toe-up and toe-down conditions and used to quantify the amount of body sway and define the overall adaptation of the motor system. A smaller mean SES represents less body sway and better adaptive automatic postural responses to repeated platform rotations. The SESs of both the toe-up and toe-down conditions in each trial were used for the analysis.[2,14]

v-HIT. The subjects were instructed to sit in front of a laser dot on a screen at a distance of 1.20 m in a dimly lit room and were instructed to look at the target. To test each semicircular canal, 20 head impulses in each direction were manually delivered by the examiner with random timing and direction. The peak head velocity of the impulses ranged from 50~250° · s^{-1} (acceleration = 750 to 5000/s^2; amplitude = 5~20°). Eye position was calculated using a pupil detection method. HITs that did not meet the standard criteria were excluded from the tests. Vestibular performance was calculated with measurements of the vestibulo-ocular reflex (VOR), the gain of which was obtained by dividing the eye velocity by the head velocity.[1]

Statistical Analysis

Statistical analyses were performed using Prism version 8.0 computer software (GraphPad Software, San Diego, CA, USA). The normal distribution of differences between the two groups was tested by the Shapiro-Wilk normality test. Then, the statistical significance of paired comparisons was assessed by a paired *t*-test (for normally distributed variables) or the Wilcoxon rank sum test (for non-normally distributed variables). An estimate was considered to be statistically significant if the *P*-value was < 0.05.

RESULTS

Overall results of vestibular function tests are described below. The VOR gain values in v-HIT are presented in **Table I**, the scores in SOT are presented in **Table II** and **Table III**, and the SES in the ADT are presented in **Table IV** and **Fig. 1**.

Table I. VOR Gain Values of the Six Semicircular Canals in the Placebo and Modafinil Groups.

	PLACEBO GROUP		MODAFINIL GROUP		
	MEAN/ MEDIAN	SD	MEAN/ MEDIAN	SD	*P*-VALUE
GLL	0.939	0.065	0.962	0.056	0.186*
GRL	1.029	0.066	1.032	0.083	0.858*
GLA	0.815	0.094	0.762	0.051	0.162*
GRP	0.919	0.094	0.893	0.145	0.624*
GRA	0.892	0.103	0.835	0.116	0.099*
GLP	0.855		0.845		0.592†

VOR, vestibular-ocular reflex; GLL, gain of the left lateral canal; GRL, gain of the right lateral canal; GLA, gain of the left anterior canal; GLP, gain of the left posterior canal; GRA, gain of the right anterior canal; GRP, gain of the right posterior canal. $N = 10$ in each group.
*This variable was found to be normally distributed according to the Shapiro–Wilk test, and no statistically significant differences were found by paired *t*-test.
†This variable was found to be nonnormally distributed according to the Shapiro–Wilk test, and no statistically significant differences were found by the Wilcoxon rank sum test.

The v-HIT was applied to assess the different functional statuses of the six semicircular canals between the modafinil and placebo groups. All gain values of the six semicircular canals in the two groups were in the normal range, and there were no significant gain differences between the two groups for any of the six semicircular canals. Table I shows the statistical data of VOR gain values of the six semicircular canals in the modafinil and placebo groups. These results suggest that the VOR works well at high frequencies related to natural head movements with a single dose of modafinil.

The SOT was implemented to assess changes in equilibrium function in the modafinil and placebo groups. The individual equilibrium scores indicate the postural stability during each of the six SOT conditions (C1–C6), whereas the composite score is a weighted average that combines all six SOT conditions. All the scores in the two groups were in a normal range and there were no significant differences between the two groups for any of the scores in the six SOT conditions and composite score. Sensory analysis ratios (somatosensory, visual, and vestibular ratios) indicate how well the subject can use information from somatosensory, visual, and vestibular systems. The preference

Table II. Equilibrium Scores of the Six SOT Conditions in the Modafinil and Placebo Groups.

	PLACEBO GROUP		MODAFINIL GROUP		
	MEAN	SD	MEAN	SD	*P*-VALUES
C1	94.87	1.86	94.60	1.80	0.731
C2	93.77	2.22	93.90	1.81	0.835
C3	93.47	2.39	93.23	2.75	0.826
C4	86.03	5.76	86.67	5.19	0.733
C5	77.30	5.41	74.73	8.82	0.413
C6	69.27	10.26	72.93	10.11	0.254
CS	83.30	3.86	83.70	4.47	0.747

SOT: sensory organization test; C1 stands with eyes open; C2 stands with eyes closed; C3 stands with eyes open, visual surroundings are sway-referenced; C4 stands with eyes open, force platform is sway-referenced; C5 stands with eyes closed, force platform is sway-referenced; C6 stands with eyes open, visual surroundings and force platform are sway-referenced; CS composite score is a weighted average that combines all six SOT conditions. This variable was found to be normally distributed according to the Shapiro–Wilk test, and no statistically significant differences were found by paired *t*-test. $N = 10$ in each group.

Table III. Sensory Ratios and Preference Ratio in the SOT in the Modafinil and Placebo Groups.

	PLACEBO GROUP		MODAFINIL GROUP		
	MEAN	SD	MEAN	SD	*P*-VALUES
Somatosensory	0.9885	0.02	0.9928	0.02	0.584
Visual	0.9071	0.06	0.9158	0.05	0.636
Vestibular	0.8148	0.06	0.7904	0.10	0.460
Preference	0.9510	0.05	0.9857	0.04	0.103

Somatosensory ratio: score of condition 2 compared to condition 1; visual ratio: score of condition 4 compared to condition 1; vestibular ratio: score of condition 5 compared to condition 1; preference ratio: sum scores of conditions 3 and 6 compared to sum scores of 2 and 5. This variable was found to be normally distributed according to the Shapiro-Wilk test and no statistically significant differences were found by paired *t*-test. $N = 10$ in each group.

Table IV. SES in the Adaptation Test in the Modafinil and Placebo Groups.

	PLACEBO GROUP		MODAFINIL GROUP		
	MEAN	SD	MEAN	SD	*P*-VALUES
Toe-up					
Trials 1	80.90	26.12	83.80	25.55	0.518
Trials 2	73.10	20.46	60.90	13.22	0.048‡
Trials 3	64.10	15.45	55.80	11.41	0.077
Trials 4	57.30	15.13	52.70	5.58	0.353
Trials 5	55.40	15.71	54.50	7.56	0.831
Toe-down					
Trials 1	52.60	10.19	48.60	7.47	0.245
Trials 2	41.40	8.57	44.10	7.33	0.372
Trials 3	42.50	5.17	39.10	7.43	0.251
Trials 4	39.60	4.33	38.20	6.53	0.419
Trials 5	39.30	5.95	38.70	9.48	0.842

There was a significant difference ($P < 0.05$) between the two groups in trial 2 of toe-up ADT. This variable was found to be normally distributed according to the Shapiro–Wilk test, and no statistically significant differences were found by paired *t*-test in all trials of the toe-down test and in trials 1, 3, 4, 5 of the toe-up test. $N = 10$ in each group.

sensory ratio indicates the degree to which the subject relies on visual information to help them maintain their balance. All the ratios fell within normal limits and statistical analysis via paired *t*-tests did not reveal significant differences between the modafinil and placebo groups for the somatosensory, visual, and vestibular preference ratios. Tables II and III show the SOT results of the modafinil and placebo groups. These data suggest that the equilibrium function and sensory preference were not affected by a single dose of modafinil.

ADT was used to reflect equilibrium adaptation ability. The SES was generated based on the velocity and acceleration of the COG during each testing trial of both toe-up and toe-down platform rotations. SES is an accurate measure of adaptive balance functional changes. A smaller SES represents less body sway and better reflex postural responses to repeated platform rotations. No significant differences were observed between the placebo and modafinil groups in either the toe-up or toe-down condition in ADT Trial 1, Trial 3, Trial 4, or Trial 5. The total SES decreased by 16.7% in the modafinil group relative to the placebo group ($P = 0.048$) in toe-up Trial 2, and no such change was observed in the toe-down condition. Table IV shows the statistical data of the modafinil and placebo groups in the ADT test. Fig. 1 shows the differences in the Adaptation test between the modafinil and placebo groups. These data suggest that the adaptive balance function might be improved (or at least was not impaired) by a single dose of modafinil.

DISCUSSION

The aim of this randomized, double-blind, placebo-controlled, crossover study was to investigate the safety of modafinil on vestibular function and equilibrium ability in healthy volunteers. The results showed that the administration of a single dose of 200 mg modafinil did not cause any impairment. More specifically, vestibular function evaluated by v-Hit examination did not differ between the modafinil and placebo groups. None of the index analyses of the sensory organization test, which reflects equilibrium ability, showed any difference between the modafinil and placebo groups. Surprisingly, the total SES decreased by 16.7% in the modafinil group relative to the placebo group in toe-up Trial 2 of the adaptation test, which indicated that modafinil did not impair the adaptive postural response, and there was a small possibility that modafinil might have a positive effect.

Modafinil is widely used in those who engage in special occupations, such as military pilots, astronauts, and military fighter aircrew, due to its benefits in cognitive enhancement, alertness maintenance, and fatigue countermeasure.[9] Pharmacodynamic studies have shown that modafinil has short-term effectiveness and a relatively short half-life of 12–15 h.[7] These safety and effectiveness characteristics enable modafinil to act as a wake-promoting and vigilance-maintaining agent. However, drug safety challenges still exist during the application of modafinil in specific military situations, especially flight missions. These challenges mainly come from the uncertain effects of modafinil on vestibular function and equilibrium ability; a disrupted vestibular sensory system might lead to spatial disorientation, loss of situational awareness, and equilibrium disability under flight situations.[6] Thus, even though there has been a long history of modafinil application in pilots, it is necessary to evaluate the vestibular safety of modafinil.

An early study investigated the positive effects of modafinil on vestibular function during 24-h sleep deprivation, in which the visual-vestibular optokinetic reflex and optokinetic nystagmus were used to reflect vestibular function.[19] However, the peripheral vestibular system, vestibulo-spinal reflex, and equilibrium ability were not fully assessed in this study. Thus, the vestibular- and equilibrium-related safety effects of modafinil have been raised as a crucial concern while using it as a wake-promoting agent in aircrew and astronauts.

There are a series of commonly used vestibular function tests, such as subjective postural, spatial memory, and subjective visual vertical tests, and it is necessary to use comprehensive examination methods to evaluate vestibular medication safety. Considering the features of flight work, we mainly chose v-HIT and SOT examinations. The v-HIT examination, a high-frequency vestibular function test, is considered to be the most appropriate method to reflect vestibulo-ocular reflection,

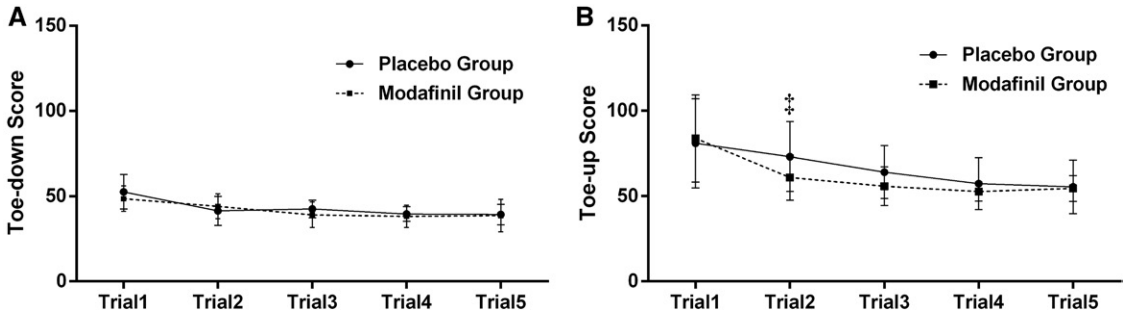

Fig. 1. SES in the Adaptation test in the modafinil and placebo groups. A) Toe-down score in ADT and B) toe-up score in ADT. Data are shown as the mean ± SD, $N = 10$ in each group. A statistically significant difference is indicated by an ‡.

which is in line with vestibular functioning in daily life.[1] The SOT is an objective test to reflect human balance function and to determine the main sensory system that is responsible for maintaining balance.[16] Considering that posturography tests might have certain learning and memory effects in evaluating vestibular function, we adopted a crossover design to avoid the bias of experimental results caused by memory effects in the experimental designs.

Our study suggests that a single dose of modafinil does not have adverse effects on vestibular function and equilibrium ability. In the adaptation test, the indices of the modafinil group were better than those of the placebo group in trial 2, suggesting that a single dose of modafinil might have a positive effect on balance adaptation. Regarding equilibrium function, direct evidence of modafinil effects has not been observed in previous studies. A functional brain network study indicated that modafinil induced a positive change in functional connectivity in the cortex and cerebellum among elderly people,[17] which might be one of the reasons for the positive effect on balance adaptation in our study.

According to previous studies, a single 200-mg dose of modafinil in 24 h is commonly used to produce satisfactory antifatigue effects.[8] Thus, we adopted a single 200-mg oral dose as the medication regimen in this clinical study. However, one of the limitations of this study is that it has not been determined whether a higher dose or a long duration use of modafinil will affect vestibular and equilibrium function. Actually, a daily dose of 200 mg is the maximum recommended medication dose and the short half-life of modafinil guarantees its safety on vestibular organs. The vestibular safety of modafinil in extra workload, such as fatigue, stress, and multiple tasks, has not yet been evaluated. Previous studies have indicated that equilibrium is disrupted under fatigue, stress, and multitask load conditions,[5] in which modafinil's positive effects on cognitive function and attention were observed.[3] According to the results of the current study, multiple administrations or increased doses are theoretically inferred to have a positive effect on vestibular and equilibrium function, especially under the conditions of fatigue, long flights, and attention consumption.

In addition, the sample size of this study was small, which is due to the limited number of test subjects in aerospace medical research. Unlike usual clinical studies, aerospace medical human research requires special volunteers whose physical condition meets the pilot medical selection criteria and who are to carry out preliminary flight simulation training. Thus, although this study has a small sample size, the results of the current study are useful for aviation pilots.

In conclusion, we found that a single 200-mg dose of modafinil did not have adverse effects on high-frequency vestibular function and equilibrium ability in healthy volunteers. Therefore, our findings preliminarily provide clinical evidence of the vestibular safety of modafinil, which might have meaningful value for its application in aviation medicine. Further studies are needed to delineate whether a single dose or multiple administrations of modafinil would affect vestibular and equilibrium function under realistic combat flight missions.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Xiaocheng Wang, Dr. Xutao Zhang, Ms. Yajuan Li, and M.M. Kehai Zang of the Aerospace Clinical Medical Center of the Air Force Medical University, as well as Ms. Tingting Shi of the Clinics Research Center of Aerospace for their assistance with this study.

All authors have read and agreed to the published version of the manuscript. Fengzhou Liu and Min Zhang contributed equally to this study and share first authorship.

Trial registration number: ChiCTR2000031407.

Financial Disclosure Statement: This study was funded by the Military Medicine Foundation (Grant Numbers: BKJ19J024 and 2018HKZL07). The authors have no conflicts to disclose.

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