Modafinil as a Stimulant for Military Aviators

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INTRODUCTION: Modafinil is a wakefulness-promoting stimulant that has been approved by the Republic of Singapore Air Force (RSAF) as a fatigue countermeasure medication since 2011. Each RSAF aircrew member must undergo a ground test to exclude operationally relevant adverse drug effects prior to consuming the medication for operational reasons. This study describes the RSAF's modafinil ground testing outcomes over a 7-yr period.

METHODS: This is a retrospective case series of 243 RSAF aircrew members who underwent modafinil 100-mg test dosing over the 7-yr period from September 2011 to September 2018.

RESULTS: The median age was 31 yr (range, 21–53 yr) and mean age was 31.7 yr ± 6.19 yr. Of the aircrew members, 234 (96.3%) were men and all were of Asian ethnicity. Of the subjects, 237 (97.5%) were medically cleared for the operational use of modafinil. Among the six (2.47%) who failed modafinil ground testing, headache (cumulative incidence, 1.65%), anxiety (cumulative incidence, 0.41%), diarrhea (cumulative incidence, 0.41%), and insomnia (cumulative incidence, 0.41%) were reported as the side effects experienced. None of the aircrew members experienced major adverse drug events.

DISCUSSION: Our findings suggest a low occurrence of adverse drug effects among military aircrew members who undergo modafinil test dosing prior to using the drug operationally. To our knowledge, this is the single largest published case series of modafinil ground testing outcomes among Asian military aviators.

KEYWORDS: Asian, side effects, adverse drug events, fatigue, pilots.

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Modafinil was first developed by Laboratoire Lafon in 1994 and was approved by the U.S. Food and Drug Administration (FDA) for the treatment of narcolepsy in 1998.[1] In 2003, the U.S. FDA expanded the approved use of the drug to the management of shift work disorder and adjunctive treatment of obstructive sleep apnea/hypopnea syndrome.[15] Studies have also explored the use of modafinil in the treatment of disease-related fatigue, attention-deficit disorder, depression, and jet-lag.[9] In the area of human performance maximization, the U.S. Air Force and Army[4], Indian Air Force,[13] French Air Force,[10] and Canadian Space Agency[16] have reported their use of modafinil as a fatigue countermeasure medication.

The Republic of Singapore Air Force (RSAF) has approved modafinil as a fatigue countermeasure medication since 2011. The drug is employed for operations that require aircrew members to function during their circadian trough and are anticipated to be particularly fatiguing based on bio-mathematical modeling, such as extended flying operations, consecutive early morning sorties, and flights that entail the crossing of multiple time zones. As a policy, the use of modafinil as a fatigue countermeasure medication is strictly voluntary. All aircrew members who elect to consume modafinil for operational reasons, including ground testing, are provided with a patient information sheet that includes details on the relevant known side effects of the drug as part of the informed consent process.

Prior to consuming modafinil for operational reasons, each RSAF aircrew member must undergo a ground test to exclude operationally relevant adverse drug effects. This involves a brief to educate the aircrew on the physiological effects, duration of action, and common side effects of modafinil, followed by the self-administration of oral modafinil at a dose of 100 mg at least 8 h prior to usual bedtime. A washout period of at least 24 h is observed if an aircrew member is also undergoing ground

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testing for other RSAF-approved fatigue countermeasure medications, such as zolpidem.[8] Aircrew members are also instructed to limit factors that may interfere with the ground test, with specific examples given being concurrent illness, the concomitant intake of alcohol, caffeine, or other psychoactive substances, and recent dietary changes.

Following consumption of modafinil on the ground, aircrew members are required to complete a standardized paper-based questionnaire the next day. The questionnaire provides the following common side effects for selection: "diarrhea," "dizziness/giddiness," "feverish/flu-like symptoms," "fast heartbeat," "chest pain," "headache," "change in vision," "breathing difficulties," and "anxiety/nervousness," as well as an "others" option for an aircrew member to record any symptom not listed in the preceding list. Completed questionnaires are reviewed by a flight surgeon to determine the individual's suitability for modafinil use, and all ground testing results are subsequently entered into an electronic database at the RSAF Aeromedical Center. To our knowledge, this is the single largest published database of modafinil ground testing outcomes among Asian military aviators to date.

METHODS

This is a retrospective case series of 243 RSAF aircrew who underwent the modafinil 100-mg test dosing over the 7-yr period from September 2011 to September 2018. The aircrew members were identified using the RSAF Aeromedical Center's electronic database of modafinil ground testing outcomes, and their age at time of ground testing and ethnicity were obtained from the aircrew members' electronic health records. The database records and paper-based questionnaires of those who were not medically cleared for the operational use of modafinil were retrieved and scrutinized to identify the reasons for failing ground testing. This study was approved by the Singapore Armed Forces Joint Medical Committee (Research).

RESULTS

The median age of the aircrew members was 31 yr (range, 21–53 yr) and mean age was 31.7 yr $\pm$ 6.19 yr. Of the 243 aircrew members, 234 (96.3%) were men and 9 (3.7%) were women. Based on their medical records, all were of Asian ethnicity. None of the aircrew members declared a history of psychiatric disorders, or pre-existing cardiac, renal, or liver impairment.

A total of 237 (97.5%) aircrew members were medically cleared for the operational use of modafinil. Of the six (2.47%) aircrew members who failed ground testing, four reported headaches (cumulative incidence, 1.65%), one experienced diarrheal side effects (cumulative incidence, 0.41%), and one experienced insomnia resulting in 21 h of prolonged wakefulness (09:00 to 06:00 the next day) (cumulative incidence, 0.41%). One of the four aircrew members who developed headache also reported concurrent anxiety (cumulative incidence, 0.41%). Two aircrew members reported transient mild palpitations (cumulative incidence, 0.82%) that did not preclude them from the operational use of modafinil. None of the aircrew members experienced major adverse drug events.

DISCUSSION

Modafinil (2-[(diphenylmethyl)sulfinyl]acetamide) is a wakefulness promoting stimulant that is thought to achieve its effect by elevating extracellular catecholamines, glutamate, serotonin, and histamine, activating the orexinergic system, and decreasing gamma-aminobutyric acid (GABA).[6] Modafinil 400 mg has been found comparable to caffeine 600 mg in reducing fatigue-related performance decrements on psychomotor vigilance testing,[17] with lower doses proven effectual in sustaining wakefulness for extended periods not exceeding 24 h.[18] Modafinil has a longer half-life than caffeine (12–15 h vs. 4–6 h) and, hence, requires lower frequency of doses to maintain serum concentrations. It is also less likely to have tolerance and dependency issues vis-à-vis caffeine and, therefore, has less interindividual response variability.

While the exact mechanism of action of modafinil remains elusive, the drug's pharmacological profile is certainly distinct from that of amphetamines.[12] Of direct relevance to aviation is modafinil's superior subjective side effect profile when compared to those of amphetamines and caffeine; while more than 50% of those in the amphetamine and caffeine groups report adverse symptoms, those in the modafinil group experienced side effects at a frequency that was not significantly different from the placebo group.[9] It also has a much lower propensity for abuse than amphetamines and does not induce the rebound hypersomnia that is characteristic of amphetamines.[11] Conversely, modafinil has relatively little negative impact on sleep quality even if the drug is administered close to a sleep episode.[3] Modafinil may also weakly improve cognitive functions, even among healthy non-sleep-deprived adults.[7] Due to the combination of its favorable side effect profile, low propensity for abuse, and minimal impact on subsequent sleep, modafinil confers distinct pharmacological advantages over amphetamines and caffeine in the aviation context.

An unpublished study conducted by the RSAF in 2010 to determine the optimal dosing of modafinil to sustain 40 h of continuous wakefulness among an ethnically Asian study population found that, following oral ingestion of modafinil 200 mg, peak plasma concentration was achieved at 2.75 h $\pm$ 1.5 h and the drug half-life was 12.3 h $\pm$ 1.5 h. These findings were consistent with published studies involving other Asian and Caucasian populations[19,20] and informed the RSAF's operational regimen of a loading dose of modafinil 200 mg followed by subsequent maintenance doses of modafinil 100 mg every 8 h to a limit of 400 mg cumulative dosing within any 24-h period. As a safeguard against the unknown effects of protracted modafinil usage, RSAF aircrew members are not permitted to maintain continuous wakefulness beyond 48 h while on modafinil. From a performance viewpoint, this 48-h limit is supported by the

observation that a 2-h nap is equivalent to or more effective than modafinil after 48 h of sleep deprivation.[14] Other works also suggest that the employment of modafinil and napping in combination for prolonged wakefulness may yield better performance than either alone.[2]

Notwithstanding the pharmacological evidence that modafinil has a superior side effect profile compared to amphetamines and caffeine, the RSAF requires its aircrew members to undergo a modafinil test dose under medical supervision before any operational usage to ensure the absence of duty-relevant side effects. In this regard, it is important to note that that the aim of the ground test is to identify aircrew who experience adverse effects of an idiosyncratic nature (type B reactions), rather than the dose-dependent reactions observed in previous studies.[4]

Placebo-controlled clinical trials found that the most frequent adverse drug effects resulting in the discontinuation of modafinil treatment were headache (2%), nausea, anxiety, dizziness, insomnia, chest pain, and nervousness (each $< 1\%$).[15] Our study of the RSAF Aeromedical Centre's modafinil ground testing outcomes similarly found that the most common reason for failure was the development of headache, occurring at a cumulative incidence of 1.64%. A plausible explanation for the lower incidence of headaches in our case series is the use of a 100-mg dose for ground testing, rather than the more commonly administered doses of 200 mg to 600 mg administered as part of clinical studies.[15] Nonetheless, our finding that headache occurred at $< 2\%$ cumulative incidence among aircrew members undergoing ground testing with modafinil 100 mg is useful in supporting our use of modafinil 100-mg maintenance doses from a safety perspective, in addition to its proven efficacy in countering cognitive fatigue due to sleep deprivation.[2]

Anxiety and diarrhea were the two other reported symptoms that resulted in RSAF aircrew members failing ground testing, with each occurring at a cumulative incidence of 0.41%. Anxiety has been found to be a dose-dependent adverse effect in placebo-controlled clinical trials using doses of 200, 300, and 600 mg $\cdot$ d^{-1} of modafinil,[15] while diarrhea after consuming modafinil occurred in 6% of patients[15] and has been reported to be significant enough in some cases to cause the discontinuation of its use among narcolepsy patients.[5] Again, the lower incidences of anxiety and diarrhea in our study is probably due to the use of a lower dosage for modafinil ground testing, compared to the higher doses administered for clinical indications.

Although palpitations are a known side effect of modafinil (cumulative incidence of 2%), clinical studies have found no consistent change in the mean values of heart rate or systolic and diastolic blood pressure.[15] It was therefore reasonable for the flight surgeon to clear the two RSAF aircrew members who experienced transient mild palpitations to use modafinil operationally. On the other hand, studies have found an increase in antihypertensive medication use among patients on modafinil (2.4%) compared to those on placebo (0.75%), and symptoms of cardiac ischemia along with ischemic ECG changes have been reported in patients with left ventricular hypertrophy and mitral valve prolapse while on modafinil.[15] As such, the RSAF does not permit the use of modafinil among aviators with poorly controlled hypertension and/or a history of cardiac disease.

To date, most safety studies on modafinil were conducted in experimental or clinical settings. Our case series of 243 aircrew members who underwent modafinil test dosing is, as far as we are aware, the first to provide real-world data demonstrating a low incidence of adverse effects to the drug among aviators. A particular strength of our study is its applicability to young Asian aircrew populations, with the mean age being 31.7 yr. However, we acknowledge intrinsic limitations of our study: first, its case series design is intrinsically prone to bias; our retrospective analysis was also limited by the information available within our database and the aircrew members' electronic health records; and finally, the findings of our study should not be extrapolated to dose-dependent reactions that occur at higher dosages or for hypersensitivity reactions that occur with repeated exposure. Notwithstanding, our study does suggest a low occurrence of adverse effects in military aircrew members who undergo ground testing of modafinil and adds to the evidence base in support of the employment of modafinil as a fatigue countermeasure medication in aviation.

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