Effects of Modafinil and Caffeine on vigilance in low, medium and high caffeine consumers during the circadian trough in healthy RNLAF aircrew: a randomized controlled trial

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To investigate the effect of modafinil (200 mg) and caffeine (300 mg) on vigilance in low, medium and high caffeine consumers during the circadian trough in order to determine the best pharmacological agent to target fatigue.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON44344

Source
ToetsingOnline

Brief title
MOCAFFE

Condition

- Other condition

Synonym
fatigue

Health condition

fatigue

Research involving
Human

Sponsors and support

Primary sponsor: Center for Man in Aviation
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: aircrew, Caffeine, Modafinil, vigilance

Outcome measures

Primary outcome

Objective and subjective measurements with regard to vigilance. The following

primary parameters will be measured:

Vigilance & Tracking Test (VigTrack)

- Root mean square of tracking error

- Percentage omissions

- Reaction time

Psychomotor Vigilance Task (PVT):

- Reaction time

- Lapses

- Misses

Secondary outcome

Secondary parameters include:

Besides these objective measures, subjective measurements with regard to

measuring sleepiness will be performed including the Stanford Sleepiness scale

(SSS) and the Epworth Sleepiness scale (ESS). Two consecutive days before the

test day, they will have to keep a journal concerning their fatigue level,

their sleeping hygiene and habits, and daily caffeine intake.

Bloodsamples (intravenous) will be conducted to determine exact objective

caffeine- and modafinil levels.

Study description

Background summary

One of the main risks for aircrew during missions is fatigue. This concerns pilots operating aircraft, but also loadmasters (responsible for everything that occurs in the back of an aircraft), boom operators (supplying fighter jets with kerosene in mid-air) and doctors and nurses giving emergency care to casualties and the sick. Previous trials have shown that modafinil and caffeine both have a positive effect on fatigue in aviation, and increase vigilance (reference). However, almost all of those trials had either subjects with chronic fatigue or subjects that were sleep deprived for 36 to even 72 hours before medication was administered. It is however, incredibly unlikely that personnel will execute missions after being awake for so long. The maximum duration of a working day seems to be 20 hours, with extremes up to 24 hours. Twenty hours is roughly the time when an individual starts his circadian trough, the time when melatonin production is maximum, and cortisol levels are low, which makes one very prone to falling asleep. Prior research has shown that cognition, including vigilance is impaired during this time of day.
A single pharmacotherapeutic treatment of fatigue in aviators during this circadian trough is not available through literature. I In addition many crew in the field complain about the low efficacy of caffeine to target this problem while there is a relative high caffeine intake by many of them. The aim of this research project is to provide flight surgeons with an advice what to prescribe to individual aircrew members to combat fatigue without disregarding their daily caffeine intake. The hypothesis of an increase in vigilance with both modafinil and caffeine will be evaluated in the proposed study.

Study objective

To investigate the effect of modafinil (200 mg) and caffeine (300 mg) on vigilance in low, medium and high caffeine consumers during the circadian trough in order to determine the best pharmacological agent to target fatigue.

Study design

This is a randomized, double-blind, placebo controlled, three treatment, three nights, crossover-intervention study. Groups will be selected based on their

daily caffeine intake. All groups will spend three non-consecutive nights at the research centre in which they will be given 200 mg modafinil, 300 mg of caffeine and a placebo.
Prior to the first day, but after being included in the study, all subjects will be send a letter to instruct them before the start of the first day. Two consecutive days before the test day, they will have to keep a journal concerning their fatigue level and their sleep hygiene and habits.
On the test day they will be welcomed and the procedures for the day will be explained. Also, they will need to fill out the Epworth and Stanford Sleepiness Scales. After procedures have been explained, first bloodsamples of subjects will be taken to determine caffeine levels. Also the subjects* vital parameters will be measured, including blood pressure, temperature (aural or oral) and pulse. A pregnancy test will be performed on every test day. The Psychomotor Vigilance Task (PVT) and Vigilance & Tracking Test (VigTrack) will be practiced and explained to them.
During the three test days subjects are allowed to do whatever they want for the rest of the day, although they cannot leave the test center without being chaperoned. Also, subjects are not allowed to fall asleep. Based on the amount of caffeine intake that they habitually use, they should take their normal amount of caffeine based products, no caffeine consumption is allowed after 17:00. At 18:00 first baseline characteristics will be measured, including blood pressure, pulse, temperature, bloodsamples, Stanford Sleepiness scale and a series of VigTrack and PVT tests.
At 0:00 another baseline measure with a set of VigTrack, PVT tests and bloodsamples will be done, and directly after, subjects will get their test medication (modafinil or caffeine or placebo). From then on, at 2:00, 3:00, 4:00, 6:00 and 8:00 subjects will do another set of VigTrack and PVT and blood will be sampled the same way as mentioned before.

Intervention

To investigate the effect of 200 mg of modafinil and 300 mg of caffeine on vigilance tasks, compared with a placebo in healthy aircrew.

Study burden and risks

Burden on test subjects will not be very high. They will be required to stay in the test center for 3 non-consecutive 24 hour periods in which they will not be allowed to fall asleep. Prior to starting the trials and at arrival of each day they will have to fill out a questionnaire regarding their current health, caffeine use and sleep hygiene. During 2 of the nights they will receive medication (modafinil and caffeine) in dosages that are already approved by the European Medicines Agency and its Dutch subsidiary College ter Beoordeling van Geneesmiddelen. The other night they will receive a placebo. There will always be a doctor on site and an AED and ACLS medication will be present in the test center.

The main benefit is that flight surgeons will be able to give a personal advice to aircrew members to diminish their fatigue during flight, with respect to their daily caffeine intake. This will increase flight safety in general and during the circadian trough in particular. A total of 4 bloodsamples will be collected to determine exact caffeine and modafinil levels. This will be done by a qualified nurse working at the CML.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
I. The potential participant has given informed and written consent and is able to comply with all study assessments scheduled in the protocol.

II. All personnel need to be aircrew members of the Royal Netherlands Air Force, irrespective of their position.
III. All subjects need to be between 18 and 60 years of age.
IV. All subjects need to be in good health, and may not have any chronic diseases.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:;Exclusion criteria are mostly based on possible side effects or interactions of one or both of the medicines.
i. Pregnant or nursing women are not eligible, modafinil is possibly teratogenic. There has not been enough research to prove modafinil safe for use during pregnancy. A pregnancy test will be performed on every test day (in the morning).;ii. People with known heart, kidney or liver disease or neurological complaints are not eligible;People who use medication that is being metabolized through CYP3A4/5, CYP2C19 of CYP2C9, since this might alter the plasma levels of the used medication and modafinil. It does not change the levels of Modafinil.
iii.
iv. A history of psychiatric illness disqualifies for the trials; this includes sleeping disorders;v. One week prior to starting every trial day, all subjects need to be (and remain) in a time zone that is a maximum of 4 time zones away from the CET time zone in which the research center lies. (GMT+1, daylight savings GMT+2). This to exclude jet lags that might confound the test results.;vi. Known allergies for caffeine, modafinil or any of its ingredients or metabolites.
;Women using hormone based birth control (e.g. oral contraceptives, intra-uterine device) will be very well informed prior to taking part due to the interference between hormones and modafinil. There will be no interference with the working mechanism of modafinil or its efficacy, but there is a known decreased effect of the contraceptive when used simultaneously with modafinil. Women using hormone-based contraceptives can therefore participate if they are willing to use other non-hormone based contraceptives as well. It is therefore not a direct exclusion criterion, but women will be informed concerning the lower efficacy of hormonal contraceptives.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-12-2018
Enrollment:	36
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	Caffeine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	N/A
Generic name:	Modafinil
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	03-10-2017
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

Approved WMO

Date:	24-01-2018
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-002288-16-NL
CCMO	NL62145.028.17