The effects of THC on Resting State fMRI.

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON20151

Source
NTR

Brief title
N/A

Health condition

Resting State fMRI
Pharmacology
THC
PK/PD

Sponsors and support

Primary sponsor: CHDR in cooperation with LUMC
Source(s) of monetary or material Support: VIDI grant

Intervention

Outcome measures

Primary outcome

- Resting state network (RSN) activity

- Arterial spin labeling (ASL)

- THC and its metabolites 11-hydroxy-THC and 11-nor-9-carboxy-THC

Secondary outcome

- Visual Analogue Scale (VAS) mood & alertness (Bond and Lader)

- VAS feeling high, internal & external perception (Bowdle)

- Heart rate

- Prolactin, LH, FSH, cortisol levels

Study description

Background summary

Title:

A randomized, double blind, placebo-controlled, 2-way cross-over study to investigate the effects of inhaled THC on resting state functional magnetic resonance imaging in healthy volunteers.

Investigator/trial location:

CHDR, Leiden, The Netherlands
LUMC, Leiden, The Netherlands.

Rationale:

Cannabinoid receptor (CB) ligands could have beneficial effects on several disorders associated with impairments of certain regions of the central nervous system (CNS), such as obesity, substance abuse and pain.

To gain understanding of the pharmacological activity of CNS drugs, pharmacodynamic (PD) effects are assessed using a variety of validated PD measures. Functional Magnetic Resonance Imaging (fMRI) measures blood oxygen level dependent (BOLD) signals that are associated with neuronal activity, and can thus give information on brain activation patterns of a CNS-active drug. Ideally, drug-induced fMRI-changes would be independent of tasks, and merely related to the concentrations and pharmacological effects of the drugs on different

brain areas. Until recently, this was not technically possible, but innovations in signal analysis now allow the accurate detection of resting-state fMRI-signals, activated by a pharmacological compound instead of by a task. The main objective of the current study is to detect resting-state fMRI-effects induced by CB-agonist Ä9-tetrahydrocannabidiol (THC).

Study objectives:

Primary Objective:

To investigate the effects of THC on fMRI activation patterns in healthy volunteers.

Secondary objectives:

1. To assess the feasibility of pharmacokinetic/pharmacodynamic (PK/PD)-analyses for THC-induced fMRI-activation patterns;

2. To assess the pharmacokinetics of THC;

3. Other pharmacodynamic effects (visual analogue scales).

Study design:

1. Randomized, double blind, placebo-controlled, 2-way cross-over design;

2. Treatment arms;

3. THC (2, 6, 6 mg);

4. Placebo THC;

Wash-out period: 2 weeks.

Study population:

Total expected number of subjects:

12 (6 male, 6 female).

Main selection criteria:

Healthy right-handed occasional cannabis users (< 1/week).

Investigational products:

Dosing rationale:

THC doses that will be used have shown to be effective in inducing effects on CNS and heart rate in previous studies performed at CHDR.

Formulations:

1. THC 2, 4 and 6 mg in ethanol 200, 600 and 600 µL, in 8 l of air;

2. THC Placebo: ethanol 200, 600 and 600 µL, in 8 l of air.

Routes of administration:

Intrapulmonary.

Dose regimen/duration:

Single repeated doses of THC 2, 6, 6 mg with 1.5 hour intervals.

Endpoints:

1. Pharmacodynamics:

2. Resting state network (RSN) activity;

3. Arterial spin labeling (ASL): whole brain, voxel-wise cerebral blood flow (CBF) (milliliters of blood per 100g of tissue per minute) and CBF changes due to drug administration;

4. Visual Analogue Scale (VAS) mood & alertness (Bond and Lader);

5. VAS feeling high, internal & external perception (Bowdle);

6. Heart rate;

7. Prolactin, LH, FSH, cortisol levels;

8. Pharmacokinetics:

THC and its metabolites 11-hydroxy-THC and 11-nor-9-carboxy-THC.

Assessment schedule:

On study days, subjects will inhale THC or placebo at three time points with 1.5 h intervals. The dosages of THC are 2, 6, and 6 mg. One scanning sessions is planned before dosing, and two scanning sessions after each inhalation. After the last inhalation, two extra scanning sessions are scheduled.

Duration of study period (per subject):

In total per subject: approximately 28 days (4 weeks or 1 month).

14 days for screening.

14 days for wash out period.

2 study periods (1 day).

Study objective

THC causes changes in resting state brain activity that can be visualized by fMRI

Study design

time = 0:00 h -2 mg THC / placebo

time = 1:30 h -6 mg THC / placebo

time = 3:00 h -6 mg THC / placebo

Intervention

Triple dose of delta9-tetrahydrocannabidiol (THC) intrapulmonary with 1.5 hour intervals. Fist dose 2 mg, second dose 6 mg, third dose 6 mg

Triple dose of visual identical placebo intrapulmonary with 1.5 hour intervals

Contacts

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Eligibility criteria

Inclusion criteria

1. Subject is a legally competent Caucasian male/female from 18 up to and including 45 years old (extremes included) on the day the informed consent is signed.

2. Subject is right-handed.

3. Subject is able to speak, read and understand the local language of the investigational site, is familiar with the procedures of the study, and agrees to participate in the study program by giving oral and written informed consent prior to screening evaluations.

4. Subject is a mild cannabis user for at least one year: cannabis use of no more than once a week, and able to refrain from using cannabinoids from at least 2 weeks prior to the first

treatment period to the end of the last study day.

Exclusion criteria

1. Subject has a BMI below 18 or above 28.5 kg/m2.

2. Subject has a significant history of any cardiac or vascular disorder, asthma or other pulmonary disease, major gastrointestinal abnormalities, peptic ulceration, hepatic, neurological, psychiatric, haematological (including bleeding disorders), endocrine, renal, or major genitourinary disease or uses any kind of concomitant medication that - in the opinion of the investigator - may interfere with the study.

3. Subject has a (history of) a significant medical disorder that may pose a risk for the subject or jeopardize the aims of the study, based on medical history, physical examination, ECG and safety laboratory parameters.

4. Subject has a history of clinically significant psychiatric illness in first degree relatives.

5. Subject has a history of hereditary neurological illness in first- or second degree relatives.

6. Female subjects not using the NuvaringÂ® nor one of the monophasic oral contraceptives (including Diane-35), who are unable and unwilling to also skip the pill/ring-free week, from the screening until the end of the study.

7. Pregnant subjects.

8. Breast feeding subjects.

9. Left-handed handed subjects
10. History of sensitivity / idiosyncrasy to THC, compounds chemically related to these compounds, or excipients which may be employed in the study or to any other drug used in the past.

11. Use of any drug or substance that is known to induce or inhibit drug-metabolizing enzymes within one month prior to the first dose.

12. Use of any drug or substance within one week prior to each dosing, except for paracetamol or some topical medication (i.e. creams, ointments, gels or lotions to induce a local effect without systemic exposure), however, use of such medication have to be reported to the investigator.

13. Subject is currently a regular user (including â€œrecreational usesâ€) of any illicit drugs, or has (a history of) drug or alcohol abuse (alcohol consumption > 40 grams/day or 4 units/day).

14. Subject smokes more than 5 cigarettes or equivalent per day and/or not able to refrain from smoking on study days.

15. Subject is a habitual and heavy consumer of caffeinated beverages (more than 6 cups of coffee or equivalent/day) at the time of the study and/or is not able to refrain from use of (methyl) xanthines (e.g. coffee, tea, cola, chocolate) from 12 hours prior to dosing until the end of the study day.

16. Unable to refrain from all use of grapefruit and containing products from 2 weeks prior to the first dose until the last study day.

17. Unable to refrain from all use of quinine from 48 hours before dosing until discharge.

18. Unable to refrain from use of alcohol from 48 hours before dosing until discharge, and positive alcohol breath test at screening or admission.

19. Positive urine screen at screening for other drugs than THC, i.e., cocaine, opioids, benzodiazepines, MDMA, methamphetamine and amphetamines.

20. Positive drug test, including THC prior to admission.

21. Positive test result on hepatitis B surface antigen, hepatitis C antibody or HIV antibody test.

22. Unable to refrain from strenuous physical exercise from 24 h prior to each dosing until the end of a study day.

23. Unable to maintain a regular diurnal rhythm.

24. Participation in an investigational drug study within 90 days prior to the first dose and/or participation in more than 4 clinical trials in the last year.

25. Donation of blood/plasma outside limits of Sanquin Blood Supply Foundation guidelines.

26. Subject is provided with a metal medical device like pacemaker, knee or hip prosthesis, ear-implant, vessel-clip, subcutaneous insulin pump, or carries metal particles (e.g. metal splinter in the eye) inside the body.

27. Subject has a significant history of claustrophobia.

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2009
Enrollment:	12
Type:	Anticipated

Ethics review

Positive opinion

Date:	13-11-2008
Application type:	First submission

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
NTR-new	NL1464

Register	ID
NTR-old	NTR1533
Other	: chdr0826
ISRCTN	ISRCTN wordt niet meer aangevraagd

Study results

Summary results
N/A