Explorative, randomized, double-blind, placebo-controlled, 3-way cross-over study to assess the effects of oral cannabidiol 160 and 1500 mg in healthy male subjects on evoked pain tests and CNS using PainCart and NeuroCart test batteries.

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• To assess effects of a single oral dose of 160 and 1500 mg cannabidiol compared to placebo on a specific set of pain modalities• To assess effects of a single oral dose of 160 and 1500 mg cannabidiol compared to placebo on UVB- and capsaicin-...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON49760

Source
ToetsingOnline

Brief title
Cannabidiol, PainCart & NeuroCart

Condition

- Other condition

Synonym
Evaluation PD effects

Health condition

Pain and CNS assessments

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: Centre for Human Drug Research funded study

Intervention

Keyword: Cannabidiol, NeuroCart, PainCart

Outcome measures

Primary outcome

Change from baseline to each time point of measurement during each study period:

• Pressure Pain: Pain Detection Threshold (PDT), Pain Tolerance Threshold

(PTT), Area Under the Curve (AUC), post-test Visual Analogue Scale (VAS)

• Cold Pressor: PDT, PTT, Area Above the Curve (AAC), post-test VAS

• Electrical Stair and Burst (pre-cold pressor): PDT, PTT, AUC, post-test VAS

• Conditioned Pain Modulation (CPM) Response (change from electrical stair pre-

and post-cold pressor): PDT, PTT, AUC

• Von Frey: Total area of secondary algesia (mm2)

• Short Form McGill Pain Questionnaire (SF-MPQ) for all above pain tests,

except von Frey test and CPM

• Thermal pain (normal skin, capsaicin-sensitized skin and UVB-exposed skin

(the latter only for subjects with MED lower than 355 mJ/cm2 at screening):

PDT, and post-test VAS (mm).

• SF-MPQ for thermal pain

• Laser Speckle Contrast Imaging (LSCI)

o Dermal blood flow in capsaicin treated and control arm (au)

Observations at each time point of measurement during each study period:

• Saccadic eye movements:

o saccadic reaction time (second),

o saccadic peak velocity (degrees/second), and

o saccadic inaccuracy (%);

• Smooth pursuit eye movements:

o percentage of time the eyes of the subjects are in smooth pursuit of the

target (%);

• Adaptive tracking:

o average performance (%);

• Body sway:

o antero-posterior sway (mm);

• N-Back (working memory load)

o Mean reaction time for zero-back, one-back and two-back (ms)

o (nr correct - nr incorrect)/total for zero-back/one-back-two-back

• Pupil size (Pupil- and cornea diameter left/right eye)

o Pupil/iris ratio left/right eye

• Visual Analog Scales (VAS) according to Bond and Lader to assess:

o mood (mm)

o alertness (mm)

o calmness (mm)

• Visual Analog Scales (VAS) according to Bowdle to assess:

o Bowdle Psychotomimetic Effects Scores (mm)

During each study period:

• Visual Verbal Learning Test (VVLT) memory testing

o Immediate recall trial 3 (number correct)

o Delayed recall (number correct)

o Delayed recognition (number correct)

o Delayed recognition (reaction time correct) (msec)

• STROOP colour word

o Stroop card 1, 2 and 3

* Time completing cards (sec)

* Number of incorrect answers of cards

o Stroop effect: difference in reaction time between card 3 and 2 (sec)

• PBMCs isolation

• T cell proliferation

• Characterization immune subsets, including but not limited to:

o T cells

o NK cells

o Monocytes

• Cell viability

PK parameters of cannabidiol by non-compartmental analysis of the plasma concentration-time data:

• The maximum plasma concentration (Cmax);

• Time to maximum plasma concentration (Tmax)

• The area under the plasma concentration-time curve from zero to t of the last measured concentration above the limit of quantification (AUC0-last);

Other parameters as appropriate, as well as dose adjusted parameters, may be determined.

• Treatment-emergent (serious) adverse events ((S)AEs) throughout the study at every study visit

• Concomitant medication throughout the study at every study visit

• Vital signs (Pulse Rate (bpm), Systolic blood pressure (mmHg), Diastolic blood pressure (mmHg)) as per assessment schedule

• Clinical laboratory tests (Hematology, blood chemistry and urinalysis) as per assessment schedule

Secondary outcome

N.a.

Study description

Background summary

Cannabis sativa, or cannabis, is increasingly being approved as a medical treatment for a variety of illnesses. While historically more attention has been paid to the psychoactive component of the cannabis plant Δ9-tetrahydrocannabinol (THC), there have been fewer scientific studies on the

medical use of the cannabidiol (CBD) - a non-psychoactive component of the cannabis plant.
The pharmacology of CBD is complex, because more than 20 different mechanisms of action have been described. Like THC, CBD binds to both the CB1R and CB2R but acts as an antagonist at these receptors. Other targets include 5-HT1A receptor agonism, GPR55 antagonism, TRPV1 activation, PPARγ activation, and reuptake inhibition of e.g. anandamide and adenosine .

Following single oral doses of CBD in humans, maximum plasma concentrations are reached at approximately 4-5 hours post-dose. CBD elimination is multiphasic; the terminal elimination half-life is approximately 60 h and effective half-life estimates ranges from 10 to 17 h.
In contrast to THC CBD has few to no psychoactive effects. Single doses of 1500, 3000, 4500 or 6000 mg CBD are generally well tolerated with fatigue, diarrhea, changes in weight/appetite, and headache as the most reported side effects.

Clinical effects of CBD are being explored in a variety of illnesses, including epilepsy, anxiety disorders, cancer, anti-inflammatory effects, and schizophrenia. In the United States, the cannabidiol drug Epidiolex, up to a maximum recommended maintenance dosage of 20 mg/kg/day, was approved by the Food and Drug Administration in 2018 for the treatment of two epilepsy disorders.
The immune suppressive effects of CBD have been noted and its immune system suppression is thought to be mediated by direct inhibition of various cell types (microglial, innate, and T cells) and induction of apoptosis and regulatory cells. However, CBD*s anti-inflammatory effects are described in mice, but clinical data is lacking. Antinociceptive effects of CBD were reported for multiple nociceptive animal models. While the analgesic properties of THC in combination with CBD have been studied extensively, a recent literature review found only a few studies evaluating CBD in the treatment of chronic pain, highlighting the need for evidence on analgesic properties of CBD. Also, although cognitive test batteries have assessed the effect of CBD in psychiatric patients in a few studies, there is little research on neuropsychological and neurophysiological effects in healthy volunteers.

The NeuroCart is a CNS-test battery developed at CHDR to demonstrate the specific, time- and dose-dependent, neurophysiological and/or neuropsychological effects of a compound. The methods include (among others) tests for alertness, memory, visuomotor/motor coordination, and subjective drug effects.

The PainCart is a multimodal battery of evoked pain tests developed at CHDR to investigate the pharmacodynamic properties of (novel) analgesics. The PainCart aims to assess as objectively as possible the levels of pain induced in human subjects by a variety of potentially noxious stimuli, including electro-cutaneous, pressure, thermal and inflammatory stimuli.

This study aims to evaluate pharmacodynamic effects of CDB without THC using: the NeuroCart, PainCart and ex vivo immune characterization in a randomized, double blind, placebo-controlled 3-way cross-over trial in 12 healthy volunteers at two different dose levels.

Study objective

• To assess effects of a single oral dose of 160 and 1500 mg cannabidiol compared to placebo on a specific set of pain modalities
• To assess effects of a single oral dose of 160 and 1500 mg cannabidiol compared to placebo on UVB- and capsaicin-induced hyperalgesia
• To assess effects of a single oral dose of 160 and 1500 mg cannabidiol compared to placebo on a specific set of evoked pain tasks as measured by the NeuroCart
• To examine effects of a single oral dose of 160 and 1500 mg cannabidiol on immune cells as measured by flow cytometry.
• To assess pharmacokinetics (PK) of a single oral dose of 160 and 1500 mg cannabidiol in healthy subjects in the first 9 hours after administration.
• To assess safety and local tolerability of a single oral dose of 160 and 1500 mg cannabidiol.

Study design

This is a randomized, double-blind, placebo-controlled, 3-way crossover trial in 12 healthy male adults to evaluate PD effects of single oral doses of CBD at two different dose levels. Subjects will receive two single oral administrations of CBD (160 mg and 1500 mg) and one administration of placebo, divided over 3 separate study visits. The total duration of the study for each subject will be up to 13 weeks

Intervention

Cannabidiol or placebo

Study burden and risks

The cannabidiol formulation used in this study has a similar composition as Epidiolex, which has been approved by the FDA for the treatment of two epilepsy disorders (Lennox-Gastaut and Dravet syndrome) and is in line with the Epidiolex Summary of Product characteristics (SmPC)25.

Cannabidiol will be orally administered as a solution in oil and will contain no tetrahydrocannabinol (THC), which is the main psychoactive component of cannabis. Therefore, the study drug administration is not expected to cause an euphoric high or other psychotropic effects associated with cannabis use. Cannabidiol oil is considered safe and well tolerated26. The most frequently

reported side effects include fatigue, diarrhea, changes in weight/appetite, and headache. Occasionally reported are somnolence, dizziness, dry mouth and low blood pressure.

The adverse events after single doses are dose dependent and well tolerated up to a dose of 6000 mg. Therefore, the planned 160 mg and 1500 mg single doses in this study are expected to be safe and well tolerated. Cannabidiol oil is not considered a controlled substance in the Netherlands and it is sold as an over-the-counter health supplement. Cannabidiol is metabolized by CYP2C19 and 3A4, and may inhibit CYP1A2, 2B6 and 2C19. Therefore, medicinal and dietary ingredients with influence on these pathways are prohibited in this study.

The NeuroCart and PainCart test batteries are considered safe with minimal risk and have been used in many previous studies at CHDR17 22
The UVB-induced hyperalgesia model, apart from inducing sensitization, may also induce post-inflammatory hyperpigmentation (PIH), of which the incidence and duration decreases with the minimal erythema dose (MED) that is applied (i.e. lower incidence and shorter lasting PIH with 2x MED application compared to 3xMED)28. Hyperpigmentation following 2MED UVB exposure generally fades after six months, where PIH following 3MED UVB exposure may last for years. Following these safety measures and the UVB MED regimen of Sayre29, only subjects with a Fitzpatrick skin type I-III will be recruited, and only subjects with an MED < 355 mJ/cm2 at screening, will be exposed to 2MED during clinical conduct. The 2MED UVB-induced hyperalgesia model has been validated and used in clinical trials at CHDR (CHDR1650, CHDR1725, CHDR1834, CHDR1928).

To further reduce the risk of complications, only healthy male study participants will be included, aged between 18 and 55 years old. Subjects will be confined to the clinical unit during all study visits. They will be kept under medical supervision until approximately 9 hours after dosing.
No health benefit to study participants is expected.

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

1. Signed informed consent prior to any study-mandated procedure.
2. Healthy male subjects, 18 up and to 55 years of age, inclusive at screening.
3. Body mass index (BMI) between 18 and 30 kg/m2, inclusive at screening, and with a minimum weight of 50 kg.
4. All subjects must practice effective contraception during the study and be willing and able to continue contraception for at least 90 days after their last dose of study treatment.
5. Has the ability to communicate well with the investigator in the Dutch language and willing to comply with the study restrictions.

Exclusion criteria

1. Evidence of any active or chronic disease or condition that could interfere with, or for which the treatment of might interfere with, the conduct of the study, or that would pose an unacceptable risk to the subject in the opinion of the investigator (following a detailed medical history, physical examination, vital signs (systolic and diastolic blood pressure, pulse rate, body temperature) and 12-lead electrocardiogram (ECG)). Minor deviations from the normal range may be accepted, if judged by the investigator to have no clinical relevance.
2. Clinically significant abnormalities, as judged by the investigator, in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis). In the case of uncertain or questionable results, tests performed during screening may be repeated before

randomization to confirm eligibility or judged to be clinically irrelevant for healthy subjects.
3. Positive Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening.
4. Systolic blood pressure (SBP) greater than 140 or less than 90 mm Hg, and diastolic blood pressure (DBP) greater than 90 or less than 50 mm Hg at screening.
5. Abnormal relevant findings in the resting ECG at screening.
6. Participation in an investigational drug or device study (last dosing of previous study was within 90 days prior to first dosing of this study).
7. History of abuse of addictive substances (alcohol, illegal substances) or current use of more than 21 units alcohol per week, drug abuse, or regular user of sedatives, hypnotics, tranquilizers, or any other addictive agent
8. Positive test for drugs of abuse at screening.
9. Alcohol will not be allowed from at least 24 hours before screening or dosing.
10. Smoker of more than 10 cigarettes per day prior to screening or who use tobacco products equivalent to more than 10 cigarettes per day and unable to abstain from smoking whilst in the unit.
11. Excessive caffeine consumption (more than eight cups of coffee or equivalent per day
12. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug, multiple drug allergies (non-active hay fever is acceptable).
13. Loss or donation of blood over 500 mL within three months prior to screening or intention to donate blood or blood products during the study.
14. Any known factor, condition, or disease that might interfere with treatment compliance, study conduct or interpretation of the results such as drug or alcohol dependence or psychiatric disease.
15. Any current, clinically significant, known medical condition in particular any existing conditions that would affect sensitivity to cold (such as atherosclerosis, Raynaud*s disease, urticaria, hypothyroidism) or pain (disease that causes pain, hypesthesia, hyperalgesia, allodynia, paresthesia, neuropathy, etc.).
16. Subjects indicating pain tests intolerable at screening or achieving tolerance at >80% of maximum input intensity for the cold, pressure and electrical tests.
17. Subject indicating intolerable pain after capsaicin administration at screening.
18. History or presence of post-inflammatory hyperpigmentation.
19. Dark skin (Fitzpatrick skin type IV, V or VI), widespread acne, freckles, tattoos or scarring on the back.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	12
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	N.A.
Generic name:	Cannabidiol
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	18-08-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-09-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-08-2023

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2020-003162-39-NL
CCMO	NL74526.056.20