Validation of the capsaicin (1%) sensitization model in the context of the PainCart test battery

Published: 06-04-2017
Last updated: 04-01-2025

Primary objectivePart A• Evaluating the effect and reproducibility of the capsaicin sensitization model on the predefined primary endpoints in both primary and secondary hyperalgesia areas for LS• Evaluating the effect and reproducibility of the...

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON45379

Source
ToetsingOnline

Brief title
Capsaicin validation study

Condition

- Other condition

Synonym
Neuropathic pain

Health condition

pain

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Capsaicin, Neuropathic pain models, PainCart, Validation

Outcome measures

Primary outcome

Part A

Erythema

• Area of flare on capsaicin treated and control arm (mm2)

• Intensity of flare on capsaicin treated and control arm (A.U.)

• Increase in blood perfusion on capsaicin treated and control arm (%)

Primary and secondary hyperalgesia

• Thermal pain: peripheral sensitization capsaicin treated area - Pain

Detection Threshold (PDT) (°C)

• Thermal pain: peripheral sensitization control area - Pain Detection

Threshold (PDT) (°C)

• von Frey hair stimulation: Area of secondary hyperalgesia (mm2)

Psychophysical

• Detection thresholds in primary, secondary and control area (mA) (IES only)

• Rate of detection in primary, secondary and control area (%) (IES only)

• Slope of psychophysical curve in primary, secondary and control area (mA-1)

(IES only)

• Reaction time in primary, secondary and control area (ms)

• Subjective pain perception after LS on primary, secondary and control area

o LS-NRS: Numeric rating scale (0-10 with 0=no pain & 10=worst pain imaginable)

o McGill Pain Questionnaire

Electrophysiological

• LEP and IESEP (in primary, secondary and control area)

o Amplitude (µV) of N1, N2, P1, P2, N2P2 peaks

- For the following IES stimulus amplitudes:

• 1x detection threshold

• 1.5x detection threshold

• 2x detection threshold

o Latency (ms) of N1, N2, P1, P2, N2P2 peaks

- For the following IES stimulus amplitudes:

• 1x detection threshold

• 1.5x detection threshold

• 2x detection threshold

• Regions of interest in time-frequency analysis in primary, secondary and control area using LS

• Regions of interest in scalp distribution analysis in primary, secondary and control area using LS

• Regions of interest in time-frequency analysis in primary, secondary and control area using IES

• Regions of interest in scalp distribution analysis in primary, secondary and control area using IES

Capsaicin pain

• Cap-NRS: Numeric Rating Scale (0-10 with 0=no pain & 10=worst pain imaginable)

Baseline is defined as the average or first value prior to dosing.

Part B

Primary (thermal) hyperalgesia

• Thermal pain: peripheral sensitization capsaicin treated area - Pain

Detection Threshold (PDT) (°C)

• Thermal pain: peripheral sensitization control area - Pain Detection

Threshold (PDT) (°C)

Psychophysical

- Reaction time in primary, secondary and control area (ms)

Electrophysiological

• LEP (in primary, secondary and control area)

o Amplitude (µV) of N1, N2, P1, P2, N2P2 peaks

o Latency (ms) of N1, N2, P1, P2, N2P2 peaks

- Regions of interest in time-frequency analysis in primary, secondary and

control area using LS

- Regions of interest in scalp distribution analysis in primary, secondary and

control area using LS

PainCart parameters

• Electrical Stair (pre-cold pressor): Pain Detection Threshold (PDT), Area

Under the VAS pain Curve (AUC), and post-test VAS.

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

• Conditioned Pain Modulation Response (change from electrical stair pre- and post cold pressor): PDT, PTT, AUC.

• Pressure Pain: PDT, AUC, and post-test VAS.

• Cold Pressor: PDT, AUC, and post-test VAS.

• VAS Bond & Lader (Alertness, mood, calmness)

• VAS Bowdle (internal perception, external perception, *feeling high*)

Capsaicin pain

• Cap-NRS: Numeric Rating Scale (0-10 with 0=no pain & 10=worst pain imaginable)

Secondary outcome

Not applicable

Study description

Background summary

Human experimental pain models may help to better understand the nociceptive processing, efficacy, dose levels and profile of analgesic properties. Pain models in healthy individuals have been established as cost-reducing tools in early drug development for assessing the efficacy of analgesic drugs on healthy subjects. Evoking pain under controlled circumstances is advantageous, because analgesic effects on specific pain conditions may be investigated without the influence of other symptoms.

One model which is commonly used to induce one of the symptoms of neuropathic pain is the topical application of capsaicin. This substance selectively activates the primary nociceptive afferents of C-fibers and multimodal Aδ-fibers via the Transient Receptor Potential cation channel subfamily V member 1 (TRPV1) receptor [1]. Previous studies have shown that topical application of capsaicin can induce peripheral and (possibly) central sensitization shown

respectively by primary mechanical/thermal hyperalgesia and by secondary mechanical hyperalgesia/allodynia [2], [3]. This pain model can therefore be used to study novel analgesic compounds targeting these typical symptoms of neuropathic pain [4]-[6], [23].

To quantify the effects of this pain model, both psychophysical and electrophysiological parameters will be assessed on the capsaicin sensitized area on the right forearm and the control area on the left forearm. Both laser stimulation (LS) and intra-epidermal electrical stimulation (IES) have been proven to be successful stimulation techniques to activate the nociceptive system [24], [25], [16], [26]-[28]. LS uses high intensity electromagnetic energy to rapidly increase the temperature of the skin, resulting in Aδ- and C-fiber activation. LS shows disadvantages in possible first degree skin burns, receptor habituation, painful experience and co-activation of C-fibers [29]. IES uses micro-needles to deliver a low current in the epidermis, thereby preferentially stimulating Aδ fibers without painful experience. IES shows disadvantages in possible Aβ-fiber co-activation and stimulation time needed to estimate the characteristics of the psychophysical curve [26], [30]. Which method shows the most reproducible parameters in a neuropathic pain model is still unclear. Therefore, an exploratory study using capsaicin sensitization combined with LS and IES will be performed to investigate the reproducibility of psychophysical and electrophysiological endpoints in a neuropathic pain model.
After evaluation of both stimulation methods, two analgesic compounds, tramadol 100 mg and duloxetine 60 mg, will be used to further validate the quality of the pain model. Therefore, this study is divided into two parts:
Part A will be a validation study of the capsaicin model with topical application of 1% capsaicin crème. Assessments will be done by heat pain assessment (TSA, Medoc, Israel, laser stimulation (Stimul1340, Electronic Engineering S.p.A., Firenze, Italia) and IES [28], [31].
Part B will be carried out to evaluate the analgesic properties of 2 established analgesic compounds using the PainCart test battery of evoked pain models, now including the newly developed capsaicin/LEP model.

Study objective

Primary objective
Part A
• Evaluating the effect and reproducibility of the capsaicin sensitization model on the predefined primary endpoints in both primary and secondary hyperalgesia areas for LS
• Evaluating the effect and reproducibility of the capsaicin sensitization model on the predefined primary endpoints in both primary and secondary hyperalgesia areas for IES

Part B
• To evaluate the analgesic efficacy of tramadol and duloxetine on the

capsaicin induced allodynia model chosen in Part A.

Secondary objectives
Part A
• To evaluate peripheral sensitization using thermal hyperalgesia in the primary area
• To evaluate the area and intensity of the flare and increase in blood perfusion following a single dose of topical administration of 1% capsaicin using Laser speckle contrast imaging and multispectral imaging
• To determine the secondary area of hyperalgesia using von Frey hair stimulation
• To evaluate the safety and tolerability of capsaicin following a single dose of topical administration of 1% capsaicin in combination with LS and IES
• To evaluate the intra-subject variability of the capsaicin induced hyperalgesia
• To evaluate the effect of pre-/rekindling
• To investigate new potential reproducible parameters in time-frequency and scalp distribution analyses

Part B
• To evaluate the ability of tramadol and duloxetine to demonstrate analgesic properties in healthy subjects for pre-specified secondary endpoints using a panel of evoked pain tests.
• To evaluate the pharmacokinetic / pharmacodynamic relationship of any observed efficacy of tramadol and duloxetine at any measured endpoints.
• To evaluate the safety and tolerability of capsaicin, tramadol and duloxetine following a single dose of topical administration of capsaicin 1% in combination with oral tramadol and duloxetine.

Study design

Part A
This is a method validation study of the capsaicin induced hyperalgesia model and of LS & IES. It will be an open-label, parallel-group study in young healthy male subjects. There are a number of published clinical studies in which capsaicin was used to induce hyperalgesia [4], [9], [11], [14], [15], [89] to characterize the capsaicin model. Effects of LS [24], [25], [89]-[91] and IES [26], [92] have been tested before as well. In those studies, doses ranging between 0.075% - 3% were administered for 30 minutes to 24 hours. We will use 1% capsaicin cream based on the study by Roberts et al. [4] in order to prove a valid pain model that can be used as a part of the PainCart.
There will be 2 groups, both with 2 occasions. Each group will contain 10 subjects.
Both groups will follow the same schedule of assessment, except that pre-/rekindling is included to the schedule of assessments of group 2 only.
• The screening phase will take about 2 hours

• Two investigational periods of 1 day each with a washout period of at least 7 days.
• Follow-up will be by telephone and will take a maximum of 10 minutes.

Part B
This will be a Proof-of-Concept study. It will be a double-blind, single dose, randomized, placebo-controlled 3-way cross-over study. In this study duloxetine and tramadol are the compounds under investigation. These compounds are known to be effective in neuropathic pain and have been used in the clinic for this indication [19], [18], [20], [21]. In total 18 male subjects will attend the clinic on five separate occasions (Screening, Period 1 - 3 and Follow-up).
• The screening phase will take about 2 hours
• Three investigational periods of 1 day each with a washout period of at least 7 days.
• Follow-up will be by telephone and will take a maximum of 10 minutes.

Intervention

During the course of the study (part B), on every one of the study days, a subject will get, in random order:
- Duloxetine 60mg
- Tramadol 100mg
- Placebo

Study burden and risks

Part A
The risks associated in this study can be divided into topical capsaicin, LS and IES related risks.

Topical capsaicin
Topical capsaicin can lead to both sensitization and defunctionalization of TRPV1 containing nerve fibres, depending on the concentration and application frequency. Sensitization could result in transient burning sensations, hyperalgesia, allodynia and erythema. Defunctionalization due to overstimulation could result in increased tactile and nociceptive thresholds. Both consequences are reversible in respectively hours and weeks. In addition, as mentioned in 1.3.1, nerve defunctionalization is not expected in this study, given the eightfold lower dose.

LS
For skin burn reasons, LS should not be repeated on the exact same location within minutes. Therefore, the location of stimulation is varied within every stimulation block of multiple stimulations. In addition, the laser energy has been limited to 2 J with a diameter of 5 mm to prevent skin damage. For more

information on the stimulation method, please read Paragraph 8.1.

IES
Extensive literature is available regarding IES and specifically the IES set-up that will be used in this study. In none of the studies listed above, or in other studies on the subject, negative effects of the electrical stimulation either through needle electrodes or flat-plate electrodes have been described. Therefore, it is not expected that electrical stimulation would cause any negative effects when stimulation duration and intensity is kept low.
The stimulator used for the measurements (NociTRACK AmbuStim PT, University of Twente, Enschede) was used in several studies and is proven to be safe (Roosink et al., University of Twente, Enschede, NL17316.080.07, and NL26665.044.09). The stimulator is a prototype and does not have a CE mark, but an IMDD brochure is available. The stimulator is powered by an internal rechargeable battery. The maximum current is set to 25 mA, with a maximal output voltage of 120V. Stimulation immediately stops when the button is released. In addition, the examiner can switch off the stimulator at all times. The electrodes used for the NPT measurements are reusable electrodes and consists of 5 small needles (with a length of about 0.5mm). After each use, the electrodes are put in a sterilization pouch and sterilized in an autoclave with a minimum temperature of 121 degrees Celsius for at least 15 minutes.

Part B
Tramadol
Tramadol is a commonly used analgesic. Symptoms such as nausea, dizziness are to be expected (>10%). Also constipation, vomiting, dry mouth, sweating, confusion, headache, drowsiness and fatigue (1-10%) can occur. In few occasions, diarrhea, orthostatic hypotension, cardiovascular deregulation (palpitations, tachycardia) rash, pruritus, urticaria and erythema may be present (0.1-1%). Subjects should not drive a car and should not engage in activities that require operating vehicles or dangerous machinery following administration of tramadol for as long as necessary in the opinion of the investigator. Thus, the subjects will remain in the clinic under supervision and will be discharged >10 hours after administration of tramadol.

Duloxetine
Duloxetine is a commonly used analgesic. Symptoms such as nausea, dry mouth, drowsiness, headache are to be expected (>10%). Also, anxiety, dizziness, hypertension, yawning, vomiting, constipation and diarrhea, could be present (1-10%). In few occasions, disorientation, apathy, gastroenteritis, gastritis, increased liver enzymes (ALAT, AST, alkaline phosphatase), hepatitis, acute liver injury and muscle stiffness may be present [39]. Subjects should not drive a car and should not engage in activities that require operating vehicles or dangerous machinery following administration of duloxetine for as long as necessary in the opinion of the investigator. Thus, the subjects will remain in the clinic under supervision and will be discharged >10 hours after

administration of duloxetine.

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

Part A
1. Healthy male subjects, 18 to 45 years of age, inclusive. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs and urinanalysis.
2. Body mass index (BMI) between 18 and 30 kg/m2, inclusive.
3. Able to participate and willing to give written informed consent and to comply with the study restrictions.;Part B
1. Healthy male subjects, 18 to 45 years of age, inclusive. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and

surgical history, a complete physical examination including vital signs, 12-lead Electrocardiogram (ECG), haematology, blood chemistry, and urinalysis
2. Body mass index (BMI) between 18 and 30 kg/m2, inclusive.
3. Able to participate and willing to give written informed consent and to comply with the study restrictions.

Exclusion criteria

Part A
1. History or symptoms of any significant disease including (but not limited to), neurological, psychiatric, endocrine, cardiovascular, respiratory, gastrointestinal, hepatic, or renal disorder.
2. Positive test for drugs of abuse at screening or pre-dose. Positive tests at screening may be repeated once.
3. Use of any medications (prescription or over-the-counter [OTC]), vitamin, mineral, herbal, and dietary supplements within 14 days prior to first study day, or less than 5 half-lives (whichever is longer). Exceptions will only be made if the rationale is discussed and clearly documented by the Investigator.
4. Clinically significant abnormalities, as judged by the Investigator. 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.
5. Participation in an investigational drug or device study within 3 months prior to screening.
6. Concomitant disease or condition that could interfere with, or for which the treatment of might interfere with, the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the subject in this study.
7. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against capsaicin specific
8. Dark skin (Fitzpatrick skin type V - VI), wide-spread acne, tattoos or scarring on the volar forearm.
9. Subject indicating a Numeric Rating Scale (NRS)(0-10) of more than 8 at screening after administration of capsaicin.
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.
11. Consume, on average, >8 units/day of (methyl)xanthines (e.g. coffee, tea, cola, chocolate) and not able to refrain from use during each stay at the CHDR clinic.
12. Unwillingness or inability to comply with the study protocol for any other reason.
13. Subject indicating prekindling process intolerable ;Part B
1. Positive test for drugs of abuse at screening or pre-dose. Positive tests at screening may be repeated once.
2. History (within 3 months of screening) of alcohol consumption exceeding 2 standard drinks per day on average (1 standard drink = 10 grams of alcohol). Alcohol consumption will be prohibited during study confinement and at least 24 hours before screening, before dosing, and before each scheduled visit.
3. History or clinical evidence of alcoholism or drug abuse.
4. History or symptoms of any significant disease including (but not limited to), neurological, psychiatric, endocrine, cardiovascular, respiratory, gastrointestinal, hepatic, or renal disorder.

5. Positive Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening.
6. Systolic blood pressure (SBP) greater than 145 or less than 90 mm Hg, and diastolic blood pressure (DBP) greater than 90 or less than 50 mm Hg.
7. Use of any medications (prescription or over-the-counter [OTC]), vitamin, mineral, herbal, and dietary supplements within 7 days of study drug administration, or less than 5 half-lives (whichever is longer). Exceptions will only be made if the rationale is discussed and clearly documented between the Investigator and the sponsor.
8. 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.
9. Participation in an investigational drug or device study within 3 months prior to screening.
10. Loss or donation of blood over 500 mL within three months (males).
11. Concomitant disease or condition that could interfere with, or for which the treatment of might interfere with, the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the subject in this study.
12. Smoker of more than 10 cigarettes per day prior to Screening or who use tobacco products equivalent to more than 10 cigarettes per day.
13. Consume, on average, >8 units/day of (methyl)xanthines (e.g. coffee, tea, cola, chocolate) and not able to refrain from use during each stay at the CHDR clinic.
14. Any of the following findings in the resting ECG.
a. QTcF> 450 or < 300 msec at screening or baseline visit;
b. Notable resting bradycardia (HR < 45 bpm) or tachycardia (HR > 100 bpm) at screening or baseline visit;
c. Personal or family history of congenital long QT syndrome or sudden death;
d. Screening or baseline ECG with QRS and/or T wave judged to be unfavourable for a consistently accurate QT measurement (e.g., neuromuscular artefact that cannot be readily eliminated, arrhythmias, indistinct QRS onset, low amplitude T wave, merged T- and U-waves, prominent U waves);
e. Evidence of atrial fibrillation, atrial flutter, complete branch block, Wolf-Parkinson-White Syndrome, or cardiac pacemaker at screening or baseline visit.
15. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug, or multiple allergies (non-active hay fever is acceptable).
16. Dark skin (Fitzpatrick skin type V - VI), wide-spread acne, tattoos or scarring on the forearm.
17. Subject indicating a NRS (0-10) of more than 8 at screening after administration of capsaicin.
18. Subject indicating pain test intolerable at screening or achieving tolerance at > 80% of maximum input intensity for any pain test for cold, pressure, and electrical tests.
19. Unwillingness or inability to comply with the study protocol for any other reason.

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	18-05-2017
Enrollment:	38
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Capsaicin creme FNA
Generic name:	capsaicin
Product type:	Medicine
Brand name:	Duloxetine 60 mg
Generic name:	duloxetine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tramadol 100 mg
Generic name:	Tramadol
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	06-04-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-05-2017
Application type:	First submission
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	EUCTR2017-000480-32-NL
CCMO	NL60793.056.17

Study results

Date completed:	12-12-2017
Results posted:	11-01-2023

First publication
04-03-2020