Interventional study to assess local pharmacodynamics and tolerability of topical allyl isothiocyanate in healthy male subjects.

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Primary objectiveTo evaluate the mechanism of AITC-induced vasodilationSecondary objectivesTo evaluate the tolerability of local AITC administrationTo evaluate the effect of whole-body heat on generation of NOTo evaluate the effect of AITC and whole...

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

Summary

ID

NL-OMON50731

Source
ToetsingOnline

Brief title
AITC model validation

Condition

- Other condition

Synonym
Neuropathic pain

Health condition

Vasodilation, Pain

Research involving

Human

Sponsors and support

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

Intervention

Keyword: AITC, Challenge, Pharmacodynamics

Outcome measures

Primary outcome

Laser speckle basal flow (AU) after

* AITC administration

* AITC in combination with whole body heating

Secondary outcome

* Treatment-emergent (serious) adverse events ((S)AEs) throughout the study at

every study visit

* Concomitant medication throughout the study at every study visit

* VAS pain and itch scores

* Serum nitrite, nitrate and peroxynitrite concentrations

* Multispectral camera parameters

* Clinician Erythema Assessment scale

* Skin colorimetry parameters

* Cold pain detection threshold (PDT)

* Heat PDT

* Pressure PDT

Study description

Background summary

The nitric oxide (NO) system is involved in a wide range of physiological processes and pathology. NO is produced by three isoforms of nitric oxide synthase (NOS). Endothelial NOS (eNOS) and neuronal NOS (nNOS) are expressed constitutively in respectively endothelial cells and neurons. eNOS is mainly responsible for endothelium-dependent vasodilation and peripheral cardiovascular homeostasis and has vasoprotective and anti-atherosclerotic effects. nNOS is implicated in synaptic plasticity and central regulation of blood pressure. The third form of NOS, inducible NOS (iNOS), is expressed in a wide variety of cells, especially immune cells, upon inflammatory stimuli. Given the wide variety of functions and locations of NOS isoforms, models separating the physiological pathways of NO function are an attractive target for development of pharmacological compounds targeting the NO system.

Allyl isothiocyanate (AITC), also known as *mustard oil*, is a transient receptor potential cation channel A1 (TRPA1)-agonist used in pain models in preclinical studies. Previous preclinical studies have shown that AITC induces a significant increase in local skin perfusion as measured using laser speckle contrast imaging (LSCI). In preclinical studies, this vasodilation is mediated by TRPA1 channel activation causing Ca2+ influx and production of nitric oxide (NO) by nitric oxide synthase (NOS). In this study, LSCI assessment of AITC induced vasodilation will be combined with a whole-body heat stress (WBHS) challenge. The WBHS response is partially dependent on nNOS. In addition, nitrate, nitrite and peroxynitrite (reaction products of NO) production can be measured in blood. The combination of the challenges and measurements allows targeted assessment of NO pathways. The present study aims to develop NOS isoform specific measurements as well as validate the AITC challenge model for further use in development of medicinal compounds.

Next to its use in preclinical context, AITC is also administered in human experimental pain studies to induce pain, sensitization, and neurogenic inflammation through activation of TRPA1. Readouts in previous studies completed by other research groups include thermal pain (heat and cold allodynia) and mechanical pain. (To validate the use of AITC as pain model at CHDR, pain will be assessed using the heat- and cold pain paradigms, (using the QSense TSAII device) and mechanical pain paradigm (using the AlgoMed device) following application of AITC on designated 3x3 cm area on the upper back. A non-stimulated area contralateral to that of application will serve as control. Reproducibility of results will be evaluated by having subjects report to the clinical unit for two identical study periods that are divided by at least one week.

Study objective

Primary objective
To evaluate the mechanism of AITC-induced vasodilation

Secondary objectives
To evaluate the tolerability of local AITC administration
To evaluate the effect of whole-body heat on generation of NO
To evaluate the effect of AITC and whole body heat on visual erythema and skin colorimetry
To evaluate the effect of AITC on heat pain thresholds, cold pain thresholds and mechanical (pressure) pain thresholds

Study design

Interventional and open-label study.

Intervention

Challenge drugs
25 *L of 15% allyl isothiocyanate solution in mineral oil applied topically to the skin within an O-ring or using a silicone square mall (3x3 cm, for applications on the back) for 30 seconds.

Study burden and risks

AITC is expected to induce pain at the application site. Symptoms such as redness, pain, swelling, and inflammation are also expected side-effects. AITC has been used in human subjects before as an inflammatory challenge agent.

Contacts

Public
Centre for Human Drug Research

Zernikedreef 8
Leiden 2333CL
NL
Scientific
Centre for Human Drug Research

Zernikedreef 8
Leiden 2333CL
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Healthy male subjects *18 and *65 years of age.
2. Signed informed consent before any study procedures.

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) and12-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. 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.
4. Use of any medications (prescription or over the counter [OTC]), within 14 days of study drug administration, or less than 5 half-lives (whichever is longer). Paracetamol (up to 4 g/day) and ibuprofen (up to 1g/day) are not allowed within 2 days before screening and before each study drug administration. Exceptions will only be made if the rationale is clearly

documented by the investigator.
5. Use of any 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 clearly documented by the investigator.
6. Participation in other investigational drug or device study (last dosing of previous study was within 90 days prior to first dosing of this study or dosed >3 times in the year 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, tranquillizers, or any other addictive agent
8. Positive test for drugs of abuse at screening.
9. Alcohol will not be allowed from 24 hours before screening or study days.
10. Smoking (i.e., smoking of any cigarettes within 3 months of study participation). Minor deviations may be accepted if judged by the investigator to have no clinical relevance.
11. Excess of caffeine consumption (more than eight cups of coffee or equivalent per day)
12. Known allergy to mustard oil, or any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug or food component, or multiple drug allergies (non-active hay fever is acceptable), or (history of) contact allergies, or history of atopic dermatitis, or history of food allergies.
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 skin disorders, excessive hair growth, tattoos, or other physical characteristics on the forearms or back that may interfere with study conduct.
16. Any current, clinically significant, known medical condition that would affect sensitivity to cold (such as atherosclerosis, Raynaud*s disease, urticaria, hypothyroidism) or pain (i.e., disease that causes pain, hypesthesia, hyperalgesia, allodynia, paraesthesia, neuropathy).
17. Participants indicating pain tests intolerable at screening.
18. History or presence of post-inflammatory hyperpigmentation
19. Participant is unable to remain in a warm water bath of 40°C for at least 20 minutes

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-11-2021
Enrollment:	12
Type:	Actual

Ethics review

Approved WMO

Date:	16-11-2021
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
CCMO	NL79322.056.21