Trigeminovascular Activation in Preventive Treatment of Headache Disorders

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This study aims to evaluate the effect of preventive treatment with monoclonal antibodies targeting CGRP or the CGRP receptor and of treatment with candesartan on trigeminovascular activation in migraine and cluster headache patients. We want to...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Headaches
Study type	Observational non invasive

Summary

ID

NL-OMON50257

Source
ToetsingOnline

Brief title
TAPTHA

Condition

- Headaches

Synonym
Migraine and Cluster headache

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: oa Spinoza premie prof.M.D.Ferrari

Intervention

Keyword: Capsaicin, Headache disorders, Preventive treatment, Trigeminovascular system

Outcome measures

Primary outcome

Dermal blood flow response (Emax measured in Arbitrary Units) to capsaicin

application and electrical stimulation.

Secondary outcome

plasma concentration of CGRP

Study description

Background summary

Headache disorders such as migraine and cluster headache are highly disabling for patients and have a large impact on their environment and society.
The pathophysiology of migraine is not fully understood and is probably multifactorial. In migraine, a crucial role in the development of an attack is attributed to the activation of the trigeminovascular system.
This system consists of sensory neurons of the trigeminal nerve and the cranial blood vessels they innervate. Upon stimulation of the trigeminal nerve, the neuropeptide CGRP (calcitonin gene-related peptide) is released from the nerve endings surrounding the meningeal blood vessels.
Cluster headache is one of the trigeminal autonomic cephalalgias. A trigeminal-autonomic reflex is assumed to play an important role in the pathophysiology of an attack.
A number of pharmacological treatment options are currently being used as preventive treatment for migraine and cluster headache.
Efficacy rates of preventive treatment are mediocre and unpredictable and side effects often occur.
Because CGRP is attributed an important role in the pathogenesis of headache attacks in migraine and in cluster headache, drugs aimed at reducing the function of CGRP or the CGRP receptor have been developed.
When looking at responder rates, there seems to be a subset of patients that respond very well to CGRP (receptor) blocking therapy, while others do not.

Candesartan is the most frequently prescribed migraine prophylactic drug in the LUMC. How this anti-migraine effect is achieved, is unknown. Previously, we

have demonstrated that trigeminovascular CGRP release is inhibited by the acutely acting antimigraine drug sumatriptan(5-HT1B/1D receptor agonist), as well as by the prophylactic antimigraine drug propranolol (ß-adrenoceptor antagonist). Thus, it may well be that the trigeminovascular pathway, involving CGRP release, is a common pathway that can be triggered via different pharmacological mechanisms,

CGRP can be released from the trigeminal nerve endings by external electrical, mechanical, chemical or thermal stimuli. Capsaicin, the pungent ingredient of red hot chili peppers, activates the TRPV1 channel (transient receptor potential cation channel subfamily V member 1) in the trigeminal nerve, causing vasodilation, which most likely is a CGRP-mediated process, resulting in an increase in blood flow. The change in dermal blood flow after application of capsaicin to the skin can be measured with laser Doppler perfusion imaging. Electrical stimulation can directly stimulate the trigeminal nerve, causing an increase in blood flow, without involving the TRPV1 release pathway. The increase in dermal blood flow in response to electrical stimulation is probably not (completely) mediated by CGRP. It is also not influenced by the menstrual cycle, while stimulation with capsaicin is. This trigeminovascular model has been used as a biomarker for changes in trigeminovascular activation by acute antimigraine drugs.
The effect of preventive pharmacological treatment on the trigeminovascular activation has so far not been studied. Knowledge of how trigeminovascular activity changes due to reduced CGRP pathway function and whether trigeminovascular (de)activation is correlated to the clinical response to treatment with anti-CGRP (receptor) antibodies could give us more insight in how this treatment works. Being able to predict the clinical response to preventive treatment would be a major advance for clinical practise.

We hypothesise that capsaicin induced trigeminovascular activation is reduced by treatment with antibodies directed against CGRP or its receptor.
We hypothesise that the reduction in trigeminovascular activation is predictive for the clinical response.
We hypothesise that the trigeminovascular model is indicative for trigeminovascular activation exclusively mediated by CGRP.

Study objective

This study aims to evaluate the effect of preventive treatment with monoclonal antibodies targeting CGRP or the CGRP receptor and of treatment with candesartan on trigeminovascular activation in migraine and cluster headache patients. We want to explore the predictive value of trigeminovascular activation for the clinical response to this treatment.
Objectives are:
I. To explore the predictive value of trigeminovascular activation for the clinical response to treatment with anti-CGRP (receptor) antibodies and to treatment with candesartan

II. To quantify the effect of treatment with anti-CGRP (receptor) antibodies and with candesartan on trigeminovascular activation in patients with migraine and cluster headache.
III. To establish whether the trigeminovascular model is an indicator for exclusively CGRP mediated trigeminovascular activation.

Study design

This is an exploratory longitudinal study, during which the trigeminovascular activation will be measured twice.

Study burden and risks

Subjects must come to the hospital twice for a 45 minute measurement. Subjects are asked to refrain from eating heavy meals <2 hours before the measurement. Data are recorded about drug use, diet and any comorbidity. During the measurement, subjects should be silent and applied capsaicin solution to the skin, applied electrical stimulation and measured blood pressure.
All products and equipment used during this investigation are used within the registered indication. Theoretical risks arise from the use of capsaicin solution and by the use of the laser dimming device. The eyes are shielded to prevent them from coming into contact with capsaicin or the laser.
There is no benifit for individual subjects.

Contacts

Public
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333ZA
NL
Scientific
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333ZA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Humans aged *18 years, with a history of migraine or cluster headache

Exclusion criteria

1. History of using neurostimulation devices within the last 2 months
2. History of botulin toxin injections in the forehead skin within the last year
3. Dermal diseases or other abnormalities on the forehead that might interfere with the measurement
4. History of sensitivity to the fruits of capsicum plants (e.g. chilli peppers)
5. Medication overuse headache
6. current use of preventive migraine/cluster headache medication.
7. Alcohol or drug abuse
6. Body mass *30kg/m2

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-12-2018
Enrollment:	138
Type:	Actual

Ethics review

Approved WMO Date:	26-11-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	08-07-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	18-09-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	NL61805.058.17