ISRCTN13923422 https://doi.org/10.1186/ISRCTN13923422

Investigation into the effects of inflammation on pain response

Submission date	Recruitment status	[_] Prospectively registered
05/02/2019	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
08/02/2019	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
28/05/2020	Signs and Symptoms	

Plain English summary of protocol

Background and study aims
LPS is a molecule found in the outer membrane of gram-negative bacteria. By intravenously administering sterilized LPS (i.e. into a vein), a controlled immune response can evoked. By performing a battery of pain tests and sampling blood at certain timepoints, the aim of this study is to validate a model to study new analgesics (painkillers) in early phase clinical research, and find new state-of-the art biomarkers that may help treat inflammatory pain.

Who can participate?
Healthy male volunteers aged 18 to 55

What does the study involve?
Participants are randomly allocated to be treated with LPS or a placebo (dummy drug) over 2 days, undergo a series of pain tests and provide blood samples.

What are the possible benefits and risks of participating?
No medical benefit can be expected from this study for the participants. LPS can cause influenza-like symptoms (e.g. chills, headache, eye sensitivity to light, nausea, myalgia and arthralgia), increase in core temperature and pulse rate, and decline in mean arterial pressure. Most symptoms are dose-related and resolve within 2-6 hours. As with any study, rare side effects cannot be excluded beforehand. There have been reports of a decrease in cardiac contractility, but these were temporary and were resolved after 8 to 12 hours. CHDR has extensive experience with the use of LPS and will not use a dose of more than 2 ng/kg, reducing the chance of side effects.

Where is the study run from?
Centre for Human Drug Research (Netherlands)

When is the study starting and how long is it expected to run for?
February 2018 to October 2018

Who is funding the study?
Centre for Human Drug Research (Netherlands)

Who is the main contact?
Dr Hemme Hijma

Contact information

Type(s)
Scientific

Contact name
Mr Hemme Hijma

Contact details
Zernikedreef 08
Leiden
Netherlands
2333 CL

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CHDR1749

Study information

Scientific Title
Extended characterization of human endotoxemia: LPS-induced hyperalgesia and inflammatory responses

Study objectives
The human endotoxemia model is a suitable to create an effect on pain-related markers (functional assessments of nociceptive pain with PainCart, cell surface markers, soluble markers) and on state-of-the-art inflammatory biomarkers.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Stichting Beoordeling Ethiek Biomedisch Onderzoek (Stichting BEBO), Dr. Nassaulaan 10 9401 HK Assen, Tel: +31 (0)592 405871, Email: info@stbebo.nl, 19/04/2018, ref: NL65264.056.18

Study design

Single-centre observational study with interventional measurements

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Other

Study type(s)
Other

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Hyperalgesia, pain

Interventions
Randomization: double-blind. Randomization created by study-independent statistician using SAS 9.4 for Windows or newer (SAS Institute Inc., Cary, NC, USA), and in accordance with CHDR's applicable standard operating procedures.

Methodology: Per cohort, 11 of 12 subjects were assigned to the following treatment order: saline administration on study day 2 and LPS administration on study day 3. To one subject, LPS was administered on study day 2 and saline on study day 3. This way, both the investigator and subjects were blinded for treatment allocation.

1. Lipopolysaccharide (1 ng/kg in cohort 1 and either 0.5 ng/kg or 2 ng/kg in cohort 2)
2. Saline NaCl 0.9%, via intravenous administration)

Pain test battery (electrical pain tasks, pressure pain task, heat pain task, cold pressor pain task) at -1h, 0h, 2h, 4h, 8h, 10h and 24h* (*: only on study day 3).

The total duration was a maximum of 80 days.

Intervention Type
Other

Primary outcome measure
1. Electrical Stair (pre-cold pressor): Pain Detection Threshold (PDT) (mA), Area Under the VAS pain Curve (AUC) (mA*mm), and post-test VAS (mm) at -1h, 0h, 2h, 4h, 8h, 10h and 24h* (*: only on study day 3)
2. Electrical Stair (post-cold pressor): PDT (mA), PTT (mA), AUC (mA*mm), and post-test VAS (mm) at -1h, 0h, 2h, 4h, 8h, 10h and 24h* (*: only on study day 3)
3. Conditioned Pain Modulation Response (change from electrical stair pre- and post-cold pressor): PDT (mA), PTT (mA), AUC (mA*mm) at -1h, 0h, 2h, 4h, 8h, 10h and 24h* (*: only on study day 3)

4. Pressure Pain: PDT (kPa), AUC (kPa*mm), and post-test VAS (mm) at -1h, 0h, 2h, 4h, 8h, 10h and 24h* (*: only in on study day 3)
5. Cold Pressor: PDT (°C), AUC (°C*mm), and post-test VAS (mm) at -1h, 0h, 2h, 4h, 8h, 10h and 24h* (*: only on study day 3)
6. Thermal pain: peripheral sensitization on primary and control area - Pain Detection Threshold (PDT) (°C) at -1h, 0h, 2h, 4h, 8h, 10h and 24h* (*: only on study day 3)
7. Short Form McGill Pain Questionnaire (SF-MPQ) scores after each of the above pain tests

Secondary outcome measures
1. Cytokines (including, but not limited to IL-1β, IL-6, IL-8, IL-10, TNF-α and IL-1ra; IL-17), measured with ELISA on study day 2 at 0h, 2h, 4h, 10h. On study day 3 at 0h, 5min, 15min, 30min, 1h, 2h, 3h, 4h, 10h and 24h
2. LPS, CRP, LBP, PCT, sTREM-1, presepsin; measured with electrochemiluminescence on study day 3 at 0h, 5min, 15min, 30min, 1h, 2h, 3h, 4h, 6h, 8h, 10h, 24h and at follow-up visit
3. Antibody glycosylation patterns measured with Nano-LC-ESI-MS on study day 3 at -1h, 2h, 8h and at follow-up visit
4. Molecular inflammatory markers: Bradykinin, Kallikrein, cortisol and Prostaglandin E2, measured on study day 2 at 0h, 2h, 3h, 4h, 8h. On study day 3 at 0h, 2h, 3h, 4h, 8h, 24h
5. Activation of complement pathways: classical, alternative and lectin route, measured with WIELISA on study day 3 at 0h, 4h
6. Mitochondrial membrane potential (MMP); measured with flow cytometry on study day 2 at -1 h, 3h, 6h. On study day 3 at -1h, 3h, 6h, 24h
7. Neutrophil activation markers measured with ELISA on study day 2 at 0h, 3h. On study day 3 at 0h, 3h, 24h and at follow-up visit
8. Cytokines (including, but not limited to IL-1β, IL-6, IL-8, IL-10, TNF-α and IL-1ra; IL-17); measured with ELISA see above for timepoints
9. LPS, CRP, LBP, PCT, sTREM-1, presepsin: measured with ELISA see above for timepoints

Overall study start date
15/02/2018

Completion date
01/10/2018

Eligibility

Key inclusion criteria
1. Healthy male volunteers aged 18 to 55 years, 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 ECG, haematology, blood chemistry, and urinalysis
2. Body Mass Index (BMI) in the range of 18 to 28 kg/m2, and a minimum body weight of 50 kg
3. Be able to abstain from smoking between the screening visit and the study discharge visit
4. No history of alcohol or drug abuse
5. No history of trauma with likely damage to the spleen or surgery to spleen
6. Free from any clinically significant febrile illness 30 days preceding study day 1
7. Non-atopic constitution, including non-asthmatic
8. No use of any prescription drugs, including aspirin or other non-steroid anti-inflammatory drugs
9. Able to give written informed consent and willing to comply with all study-related procedures

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Sex
Male

Target number of participants
24

Total final enrolment
24

Key exclusion criteria
1. History of sepsis, cardiovascular disease, previous syncope or malignancy
2. Reported unintended weight loss or gain of at least 5 kg in four weeks at screening
3. Haemorrhagic diathesis (easy bruising, epistaxis, gastro-intestinal bleeding)
4. First degree family history of premature cardiovascular disease event (if diagnosed before 50 years of age)
5. Previous participation in a LPS challenge trial or prior exposure to endotoxin
6. Recent antibiotic use, operation or intervention by surgeon/dentist
7. Any active inflammatory or infectious disease (e.g. periodontitis)
8. Hypertension (defined as systolic blood pressure RR > 160 mmHg or diastolic blood pressure RR > 90 mmHg, repeatedly measured after 5 minutes in resting supine position)
9. Hypotension (defined as systolic blood pressure RR < 100 mmHg or diastolic blood pressure RR < 50 mmHg)
10. Clinically significant abnormalities on the 12-lead ECG (QRS complex > 120 ms, PR interval > 240 ms, QTcF interval > 470 ms)
11. Positive test results for Hepatitis B, Hepatitis C, HIV or any other obvious disease associated with immune deficiency
12. Renal insufficiency as defined by plasma creatinine ≥ 120 µmol/L
13. Biochemical diagnosis of diabetes mellitus
14. Biochemical diagnosis of hypo- or hyperthyroidism (TSH <0.3 or >4.8 mU/L)
15. Any medical condition or abnormal laboratory value that is judged clinically significant by the investigator
16. Other medical or psychological conditions which, in the opinion of the investigator, might create undue risk to the subject or interfere with the subject's ability to comply with the protocol
17. Donation of blood within 3 months prior to screening or donation of plasma within 14 days prior to screening
18. Participation in an investigational drug or device study within 3 months prior to screening or more than 4 times in the past year
19. Not having a general practitioner
20. Not willing to accept information transfer which concerns participation in the study, or information regarding health, like laboratory results, findings at anamnesis or physical examination and eventual adverse events to and from his general practitioner
21. Not willing to give permission to have the general practitioner to be notified upon

participation in this study
22. 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 (i.e., disease that causes pain, hypesthesia, hyperalgesia, allodynia, paraesthesia, neuropathy)
23. Subjects indicating pain tests intolerable at screening or achieving tolerance at >80% of maximum input intensity for any pain test for cold, pressure and electrical tests

Date of first enrolment
08/05/2018

Date of final enrolment
10/09/2018

Locations

Countries of recruitment
Netherlands

Study participating centre
Centre for Human Drug Research
Zernikedreef 08
Leiden
Netherlands
2333 CL

Sponsor information

Organisation
Centre for Human Drug Research

Sponsor details
Zernikedreef 08
Leiden
Netherlands
2333 CL
+31 (0)71 5246 400
clintrials@chdr.nl

Sponsor type
Research organisation

Website
https://chdr.nl/

ROR
https://ror.org/044hshx49

Funder(s)

Funder type
Research organisation

Funder Name
Centre for Human Drug Research

Results and Publications

Publication and dissemination plan
Results will be published in a peer-reviewed scientific journal

Intention to publish date
30/06/2020

Individual participant data (IPD) sharing plan
Contact: M. Moerland, Principal Investigator and H.J. Hijma, project leader
email: clintrials@chdr.nl
Only completely anonymized data can be made available. Specifics regarding datasets and for what purposes will be determined per request, all ethical and legal restrictions apply.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/08/2020		Yes	No