Evaluating the effects of intravenous LPS in healthy male volunteers on (neuro)inflammatory biomarkers in CSF and blood

Published: 30-01-2025
Last updated: 07-06-2025

Primary objectives:• To characterize the central inflammatory response to IV LPS by measuring biomarkers in CSF• To characterize the systemic inflammatory response to IV LPS by measuring biomarkers in blood • Characterize CSF/Blood ratios for each…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Central nervous system infections and inflammations
Study type	Observational invasive

Summary

ID

NL-OMON57284

Source
ToetsingOnline

Brief title
Effect of intravenous LPS on (neuro)inflammatory biomarkers

Condition

- Central nervous system infections and inflammations

Synonym
neuroinflammation

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research

Source(s) of monetary or material Support: CHDR

Intervention

Keyword: (neuro)inflammation, biomarkers, intravenous, LPS

Outcome measures

Primary outcome

Primary objectives:

• To characterize the central inflammatory response to IV LPS by measuring biomarkers in CSF

• To characterize the systemic inflammatory response to IV LPS by measuring biomarkers in blood

• Characterize CSF/Blood ratios for each biomarker over time

Primary endpoints:

• CSF inflammatory biomarkers including, but not limited to IL-1β, IL-18, IL-6, IL-8, TNF, CXCL10

• Systemic inflammatory biomarkers including, but not limited to IL-1β, IL-18, IL-6, IL-8, TNF, CXCL10

Secondary outcome

Secondary objectives:

• To evaluate complement activation after IV LPS administration.

• To evaluate if lumbar punctures cause an inflammatory response

Secondary endpoints:

• Complement activation products (e.g. C3a, sC5b) in plasma

• CSF inflammatory biomarkers including, but not limited to IL-1β, IL-18, IL-6,

IL-8, TNF, CXCL10

Study description

Background summary

Excessive activation of the central nervous system (CNS) inflammatory response has been implicated in a wide range of neurological diseases, including multiple sclerosis (MS), Parkinson's disease (PD), Alzheimer*s disease (AD) and amyotrophic lateral sclerosis (ALS). In these diseases, dysregulation of peripheral, systemic and central inflammatory cytokine signalling leads to vascular dysfunction and chronic activation of microglial cells with subsequent neuroinflammation and loss of neuronal function. The increasing evidence for the involvement of neuroinflammation in CNS diseases has resulted in the development of a broad range of investigational products targeting neuroinflammation. A well characterized, in vivo microglial activation/neuroinflammation model would be beneficial for the early clinical evaluation of pharmacological activity of these novel compounds, but currently isn*t readily available.

Lipopolysaccharide (LPS) is a large molecule found on the outer membrane of Gram-negative bacteria. It activates the transmembrane receptor toll-like receptor 4 (TLR4), leading to the activation of the central transcription factor nuclear factor-kB and secretion of pro-inflammatory cytokines such as Tumor necrosis factor (TNF), interferon gamma (IFN)-*, IFN-α, interleukin (IL)-6, IL-1b, IL-8, IL-17, and IL-23. Systemic administration of LPS has also been associated with activation of the complement system, which when hyperactivated, may also contribute to the pathophysiology of CNS diseases. At CHDR, administering intravenous (IV) LPS as a challenge agent is an established model to induce a systemic inflammatory response in a controlled manner. However, IV LPS has also been used by other researchers to induce microglia activation, which was assessed by positron emission tomography (PET) 18 kDa translocator protein (TSPO) brain imaging. Consequently, IV LPS could be potential challenge agent for establishing a neuroinflammation model.

While PET-TSPO imaging has been used to assess microglial activation following IV LPS administration, the use of blood and cerebrospinal fluid (CSF) biomarker measurements could offer complementary and potentially more detailed insights into the inflammatory process. However, no studies have systematically examined neuroinflammatory biomarkers in CSF following IV LPS administration, resulting in a knowledge gap regarding the optimal timing of CSF sampling and which biomarkers to measure. Addressing this gap is essential for advancing our

understanding of neuroinflammation and refining this potential in vivo neuroinflammation model for future phase 1 studies, particularly those evaluating novel compounds targeting neuroinflammation.

In this study, we aim to explore the potential of IV LPS as a model for neuroinflammation, by characterizing both the central and peripheral inflammatory response by analysis of inflammatory markers in CSF and in blood. Furthermore, we aim to evaluate complement protein activation. Additionally, an exploratory objective of this study is to assess the blood-brain-barrier permeability following LPS administration, with the goal of elucidating the intricate relationship between BBB disruption, systemic inflammation and neuroinflammation.

Study objective

Primary objectives:
• To characterize the central inflammatory response to IV LPS by measuring biomarkers in CSF
• To characterize the systemic inflammatory response to IV LPS by measuring biomarkers in blood
• Characterize CSF/Blood ratios for each biomarker over time

Secondary objectives:
• To evaluate complement activation after IV LPS administration.
• To evaluate if lumbar punctures cause an inflammatory response

Study design

This will be a double-blind, randomized, saline-controlled, exploratory study. It is a single-center, inflammatory challenge study, to evaluate neuroinflammation measured in blood and CSF after IV LPS administration in 27 healthy male volunteers. In this study healthy male volunteers (in 3 subgroups) will receive 1.0 ng/kg IV LPS as a challenge agent or saline (6:3) and CSF sampling (1 baseline and 2 post-LPS administration) and blood collection will be performed for the detection of central as well as systemic inflammation.

Study burden and risks

Burden
The burden of the participants is described in the Study Assessments
• Safety and tolerability assessments, including vital signs, weight and height, physical examination, electrocardiography, collection of blood samples
• Pharmacodynamic assessments, including blood (328.9 mL via an i.v. catheter placed in an antecubital vein in the arm, the indwelling catheter will be kept patent by saline flush after each blood sampling), and CSF (22.5 mL) via lumbar puncture.

Benefit
No medical benefit can be expected from this study for the participating subjects.

Risk assessment
Intravenous administration of LPS can lead to 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 involving administration of exogenous substance, rare side effects cannot be excluded beforehand. Reports of a decrease in cardiac contractility have been made following administration of 4 ng/kg bodyweight but were temporary and were resolved after 8 to 12 hours. Noteworthy, CHDR has extensive experience with in vivo LPS challenges and in this study, we will not administer a LPS dosage of more than 1 ng/kg to subjects, thereby minimizing the chance of stated adverse events ever happening.

For this study, it was concluded that a spinal catheter would be too burdensome for the participants. Previous experience at CHDR has shown significantly more AEs compared to lumbar punctures. The maximum amount of lumbar punctures per participant was set at three per participant to get enough data to answer the research questions, but to limit the burden as much as possible.

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)

Inclusion criteria

1. Healthy male volunteers aged 18 to 45 years, inclusive. Health 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. BMI in the range of 18 to 30 kg/m2, a minimum body weight of 50 kg.
3. Able to give written informed consent and willing to comply with all study-related procedures.
4.Has the ability to communicate well with the Investigator in the Dutch language and willing to comply with the study restrictions.

Exclusion criteria

1. Previous participation in a systemic (IV or inhaled) LPS challenge trial within a year before the first study day.
2. Antibiotic use, operation, or intervention by surgeon/dentist within one month before the first study day.
3. Any clinically significant febrile illness 30 days prior to the start of the study.
4. Any active inflammatory or infectious disease (e.g., periodontitis), excluding onychomycosis.
5. Any disease associated with immune system impairment, including auto-immune diseases. HIV, transplantation patients and active allergies when treated with medication.(non-active hay fever is acceptable)
6. History of trauma with likely damage to the spleen or surgery to the spleen.
7. History of sepsis, cardiovascular disease or malignancy.
8. History or presence of an abnormal ECG, including, but not limited to, complete left bundle branch block, second- or third-degree heart block, evidence of prior myocardial infarction, or any other abnormality that is clinically significant in the investigator*s opinion or precludes accurate interpretation and calculations of cardiac intervals (e.g., QT, QRS).
9. (A history of) any clinically significant medical condition or

abnormalities, as judged by the investigator.
10. 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.
11. Evidence of clinically significant hepatic or renal impairment in the opinion of the investigator, including alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1.5 the upper limit of normal (ULN) or bilirubin > 1.5 ULN. Patients with Gilbert syndrome without evidence of hepatic impairment may be enrolled.
12. Positive test results for Hepatitis B, Hepatitis C, HIV antibody or any other obvious disease associated with immune deficiency.
13. Use of immunosuppressive or immunomodulatory medication that affects the LPS response as judged by the investigator within 30 days of LPS administration, or less than 5 half-lives (whichever is longer) or planned to use during the study.
14. Use of any vitamin (including vitamin D), mineral, herbal, and dietary supplements within 7 days prior to dosing and/or LPS administration or within less than 5 half -lives (whichever is longer), until the EOS. Given the extensive half-life of vitamin D, incidental use is permitted between 5 half-lives (+/- 250 days) and 3 months prior to LPS administration if judged to be clinically irrelevant by the investigator.
15. Subjects who smoke more than 6 cigarettes or the equivalent in tobacco per day and are unwilling to abstain from smoking during the study period (from screening until end of study).
16. Any vaccination within the last 4 weeks before day 1 or intention to receive any vaccination(s) before the end of study.
17. Serious adverse reaction or serious hypersensitivity to any drug.
18. 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.
19. Subjects with a positive urine drug screen (Cocaine, amphetamines, opiates (morphine), benzodiazepines and cannabinoids) or alcohol test result at screening or first admission or a history of substance abuse.
20. Participation in an investigational drug, device or biomarker study, more than four times per year, and last dosing of previous study was within 30 days, or 5 half-lives (whichever is longest) prior to first LPS dosing of this study.
21. Loss or donation of blood over 500 mL within three months (males) prior to screening or intention to donate blood or blood products during the study.
22. Plasma donation within 14 days prior to screening.

Study design

Design

Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	06-02-2025
Enrollment:	27
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO

Date:	30-01-2025
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	NL87910.056.24