A biomarker assessment study to investigate the influence of high-frequency chest wall oscillations on the clearance of cerebrospinal fluid biomarkers

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Assess amyloid beta clearance from CSF to serum in response to HFCWO in healthy volunteers:- Change from baseline in amyloid beta 40 (ng/ml) in CSFAssess endogenous protein biomarker clearance from CSF to serum in response to HFCWO in healthy…

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

Summary

ID

NL-OMON51372

Source
ToetsingOnline

Brief title
Cerebrospinal fluid biomarker clearance

Condition

- Other condition

Synonym
Cerebrospinal fluid clearance

Health condition

Method Development

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Biomarker, Cerebrospinal fluid

Outcome measures

Primary outcome

• Change in neurofilament light chain

• Change in amyloid beta

• Change in tau

• Change in total amount of neural derived exosomes.

Secondary outcome

n.a.

Study description

Background summary

Cerebrospinal fluid (CSF) outflow from the central nervous system (CNS) compartment has been a topic of interest for a long time due to its critical role in CNS homeostasis. Pathways of CSF clearance to the peripheral circulation have been studied extensively but have not yet been fully elucidated. Currently, the strongest evidence points to clearance via perineural outflow pathways along nerve sheaths, across arachnoid villi, through dural lymphatics and possibly by re-entry into the CNS parenchyma via the glymphatic system . The majority of work on perineural outflow pathways have found that both the olfactory nerve and the optic nerve may be large sites of CSF clearance. However, few studies have focused on peripheral CSF outflow pathways (PCOPs) along the brain stem and spinal cord, where perineural pathways are also thought to exist along multiple cranial and spinal nerves.

Differential outflow pathways mediate clearance of distinct CSF molecular classes as in vivo evidence found that there were size-dependent differences in the rate of molecular outflow from CSF.

CSF functions in part to remove several toxic metabolites and proteins from the CNS parenchyma. Accumulation of such toxic metabolites is believed to play a role in various neurodegenerative diseases. CSF measurement of various toxic molecules as disease biomarkers is in fact commonplace in clinical diagnosis. A recently resurgent hypothesis suggests that Aβ accumulation seen in Alzheimer*s Disease (AD) may not only be due to increased production of Aβ but that reduced clearance of CSF from the CNS may also be an important factor. The rate of clearance of Aβ has indeed been shown to be significantly lower in AD patients compared to the healthy population. Similarly, previous research also found altered CSF dynamics in amyotrophic lateral sclerosis patients. Furthermore, aging was also found to be associated with reduced clearance rates of CSF in humans and this may significantly contribute to the age-related reduction of CNS Aβ clearance rates. Surprisingly, it was recently demonstrated that clearance of CSF proteins, like Aβ, could be increased through exercise in mouse models of AD. These studies also showed that exercise improved overall cognition in these mouse models. This supports observations of improved cognitive function in AD patients following intervention with exercise programs. Physical exercise is known to have a significant protective role in neurodegeneration, but the exact mechanism underlying this is unclear. Physical exercise markedly stimulates cardiac and ventilatory function, both of which are known to promote oscillatory movements of the CSF given the proximity of the heart and lungs to the spinal column. This may enhance CSF clearance and thus provide one mechanism underlying the benefit of exercise in neurodegeneration. Together these findings hint at an important role for CSF clearance rates in the pathology of various neurodegenerative diseases and call for additional research in understanding the impact of exercise on this process.

Understanding mechanisms affecting perineural outflow of CSF constituents is also critical for optimizing intrathecal (IT) drug administration. Previous research has found significant inter-individual variability in CSF concentrations after IT drug administration. Moreover, only a small amount of IT administered drug may reach CNS parts most distant from site of administration. Several factors may impact the variability in CSF drug concentrations between individuals following IT dosing, including dosing procedures as well as the size and molecular nature of the drug compound administered. This is supported by rodent studies, where CSF half-lives of various IT dosed compounds differed greatly. Neuraxial spread from the administration site is required for IT dosed drugs to reach their CNS targets. Peripheral perineural outflow may be a significant factor in clearing drugs from CSF and could thus reduce neuraxial spread and IT drug delivery to CNS target sites. Therefore, a better understanding of CSF molecular clearance via perineural outflow paths may improve IT modelling and help to optimize IT dosing.

This study attempts to contribute to the understanding of CSF clearance through the PCOP by employing high-frequency chest wall oscillation (HFCWO) to mimic the effects of exercise on CSF clearance. HFCWO is commonly used to enhance ventilation and airway clearance in many diseases. A recent study has shown that CSF molecular clearance can be modulated by HFCWO. This study aims to investigate this by direct quantification of endogenous CSF proteins before and after HFCWO.

Study objective

Assess amyloid beta clearance from CSF to serum in response to HFCWO in healthy volunteers:
- Change from baseline in amyloid beta 40 (ng/ml) in CSF

Assess endogenous protein biomarker clearance from CSF to serum in response to HFCWO in healthy volunteers
- Change from baseline in neurofilament light chain (pg/ml) in serum
- Change from baseline in neurofilament light chain (pg/ml) in CSF
- Change from baseline in amyloid beta 40 (ng/ml) in serum
- Change from baseline in amyloid beta 42/40 (ng/ml) in serum
- Change from baseline in amyloid beta 42/40 (ng/ml) in CSF
- Change from baseline in total-tau (pg/ml) in serum
- Change from baseline in total-tau (pg/ml) in CSF
- Change from baseline in total neuronal derived exosomes in CSF
- Change from baseline in total neuronal derived exosomes in serum

Study design

This study will investigate the impact of HFCWO on CSF protein biomarker clearance. The participant population will consist of 34 healthy volunteers. Participants will be randomized to receive the HFCWO intervention or no intervention in a 1:1 ratio (HFCWO to no HFCWO). They will be admitted on day -1 to the study clinic for safety measurements, blood draws and lumbar puncture for baseline CSF measurement. On Day 1, HFCWO will be applied for 30 minutes at 0, 60, 120, 210, 300 and 420 minutes with blood drawing performed directly after this application. After the final HFCWO session (at 420 minutes) a second lumbar puncture and safety assessments will be performed. Physical examinations and vital signs will be collected regularly during Day 1. A final follow-up safety visit is planned on Day 8.

This design allows us to determine CSF clearance from the CNS and the identification of the effect of biomechanical modulation on the peripheral cerebrospinal fluid outflow pathway in healthy subjects. This will enable us to better interpret results from future trials with intrathecally administered study medication.

Intervention

Participants will be randomized to receive the intervention to no intervention in a 1:1 ratio (HFCWO to no HFCWO).

Study burden and risks

The risks of venepuncture and lumbar puncture are well known, and will be done by experienced medical personnel following current safety and hygiene guidelines, thereby minimizing risk of the aforementioned possible adverse effects. The risks of HFCWO are minimal.
The frequency of lumbar punctures being performed in the current study is limited to the minimum amount necessary, which further minimizes risks. Additionally, all possible adverse effects are well monitorable and well manageable.
Taking the risk, the minimization thereof and the scientific benefits of the study in consideration, it is deemed acceptable to perform the procedures as described in the protocol.

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. Signed informed consent prior to any study-mandated procedure
2. Healthy male or female subjects, 18 to 50 years of age, inclusive at screening.
3. Body mass index (BMI) between 18 and 30 kg/m2, inclusive at screening, and with a minimum weight of 50 kg.
4. All women of childbearing potential must practice effective contraception during the study.
5. Has the ability to communicate well with the Investigator in the Dutch language and willing to comply with the study restrictions.

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) and 12-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. History of malignancy not deemed cured by their treating physician.
4. Positive Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening.
5. 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.
6. Abnormal findings in the resting ECG at screening defined as:
a. QTcF> 450 or < 300 msec for men and QTcF> 470 or < 300 msec for women
b. Notable resting bradycardia (HR < 40 bpm) or tachycardia (HR > 100 bpm)
c. Personal or family history of congenital long QT syndrome or sudden death;
d. 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
7. Participation in an investigational drug or device study (last dosing of previous study was within 90 days prior to first dosing of this study)
8. 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, tranquillisers, or any other addictive agent
9. Positive test for drugs of abuse at screening. A retest may be performed at the discretion of the investigator.
10. Alcohol will not be allowed from at least 24 hours before each visit, including screening and follow-up
11. Smoker of more than 10 cigarettes per day prior to screening or who use tobacco products equivalent to more than 10 cigarettes per day and unable to abstain from smoking whilst in the unit.
12. Is demonstrating excess in caffeine consumption (more than eight cups of coffee or equivalent per day)
13. Loss or donation of blood over 500 mL within three months (males) or four months (females) prior to screening or intention to donate blood or blood products during the study.
14. If a woman, pregnant, or breast-feeding, or planning to become pregnant during the study.
15. For CSF sampling, any of the criteria below:
a. History of clinically significant hypersensitivity to local anesthetics that may be used for LP (e.g., lidocaine).
b. Criteria that would preclude an LP, such as a local infection at the site of the LP, <100 × 103/µl platelet count at screening or clinically significant coagulation abnormality or significant active bleeding, or treatment with an anticoagulant or treatment with more than two antiplatelet agents.
c. History of clinically significant back pathology and/or back injury (e.g., degenerative disease, spinal deformity, or spinal surgery) that may predispose to complications or technical difficulty with LP.
16. Allergic to iodine.
17. 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.
18. Positive screening cultures for Multidrug resistant bacteria (BRMO) and/or Methicillin resistant staphylococcus aureus (MRSA) or no consent to perform BRMO and MRSA culture in case of increased risk for colonization with these bacteria.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	06-03-2023
Enrollment:	34
Type:	Actual

Ethics review

Approved WMO Date:	23-12-2022
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	NL82938.056.22