Clemastine fumarate as remyelinating treatment in internuclear ophthalmoparesis and multiple sclerosis

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This study has been transitioned to CTIS with ID 2024-513099-17-00 check the CTIS register for the current data. To assess the (long-term) efficacy of clemastine fumarate in improving dysconjugacy of eye movements in patients with internuclear...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Ocular neuromuscular disorders
Study type	Interventional

Summary

ID

NL-OMON52129

Source
ToetsingOnline

Brief title
RESTORE

Condition

- Ocular neuromuscular disorders
- Demyelinating disorders

Synonym
Multiple sclerosis (MS); internuclear ophthalmoparesis (eye movement disorder)

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC
Source(s) of monetary or material Support: Stichting VUmc fonds

Intervention

Keyword: Clemastine, Internuclear ophthalmoparesis, Multiple sclerosis, Remyelination

Outcome measures

Primary outcome

The primary outcome measure is the change in versional dysconjugacy index (VDI) of area under the curve (AUC) measured by infrared oculography.

Secondary outcome

Secondary outcome measures include changes in other VDI measures (peak velocity per amplitude (PV/Am) and peak velocity (PV)), changes in VDI after single fampridine dose, other oculography parameters (e.g. saccadic latency, anti-saccades), (peripheral) retinal nerve fibre layer (pRNFL) and (macular) ganglion cell inner plexiform layer (mGCIPL) thickness measured by Optical Coherence Tomography (OCT), Symbol Digit Modalities Test (SDMT), Expanded Disability Status Scale (EDSS), high and low contrast visual acuity, subjective visual functioning (NEI-VFQ-25 and NOV-AU questionnaire), quality of life (EQ5D-5L) and fatigue (CIS20R and NFI-MS questionnaire).

Study description

Background summary

There are currently no satisfying remyelinating therapies available for multiple sclerosis (MS). Clemastine fumarate has been identified as potential remyelinating therapy in vitro, animal studies and two small randomized controlled trials. The long-term remyelinating effects of clemastine, the effect of longer treatment periods and the effect in other models than optic neuropathy are still unknown. Internuclear ophthalmoparesis (INO) may provide a suitable clinical model for investigating remyelinating therapies because INO reflects the function of a few (demyelinated) axons which can be quantified by

measuring horizontal eye movements with infrared oculography. The selection of MS patients that may benefit from remyelinating therapy remains a challenge because axonal damage may be too great in some individuals to benefit from remyelination. An earlier study showed that fampridine was able to temporarily improve INO is some MS patients. Improvement of INO after a single dose of fampridine may predict whether an individual will benefit from clemastine treatment. This single-centre randomized placebo-controlled trial aims to investigate the (long-term) effects of clemastine fumarate on the dysconjugacy of horizontal eye movements as measured by infrared oculography in INO and MS. Additionally, it will investigate whether response to fampridine can predict the effects of clemastine treatment.

Study objective

This study has been transitioned to CTIS with ID 2024-513099-17-00 check the CTIS register for the current data.

To assess the (long-term) efficacy of clemastine fumarate in improving dysconjugacy of eye movements in patients with internuclear ophthalmoparesis and multiple sclerosis. Secondly, to assess whether a response to a single dose of fampridine can predict the effects of clemastine treatment.

Study design

A single-centre double-blind randomized placebo-controlled trial consisting of a 6 months treatment period followed by a 30 months follow-up period.

Intervention

The intervention group will receive 4 mg of clemastine fumarate twice daily (8 mg/day) for 6 months, the control group will receive an equivalent amount of placebo. At baseline all participants will receive a single 10 mg dose of fampridine.

Study burden and risks

Participation in the study will consist of a total of 7 study visits, including screening, baseline and 5 follow-up visits at 3, 6,12 24, and 36 months. Study visits will include physical/neurological examination, infrared oculography, OCT, visual acuity tests, a cognition test (SDMT), 5 questionnaires and blood samples at 4 of the visits for safety laboratory tests. Participants will be given either clemastine twice daily for 6 months or equivalent placebo. Clemastine is a well-established and relatively safe drug with fatigue or drowsiness as its most important side-effect. Clemastine was used in an earlier trial with MS patients at a higher dosage than the current study without serious adverse events. Participants are legally prohibited from driving will

using the study drug (6 months). At baseline participants will receive a single 10 mg dose of fampridine. Fampridine is a registered drug, which has been used in an earlier study in MS patients with INO. Transient dizziness was the most common side effect. No serious adverse events were reported.
Risks of the current study are mainly a result of the medication used in the study. Considering both drugs are registered and have been used in clinical practice the risk of unexpected reactions is deemed low. Using careful participant selection to reduce known risks results in an acceptable level of overall risk for study participants.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. A clinically definite diagnosis of multiple sclerosis.

2. Diagnosis of internuclear ophthalmoplegia determined by the first infrared oculography at screening with either cut-off of 1.174 of the versional dysconjugacy index area under the curve (VDI-AUC) of 15° saccades or 1.180 of the versional dysconjugacy index peak velocity/saccadic amplitude (VDI-PV/Am) of 15° saccades.
3. Age 18-70 (inclusive)
4. Use of disease modifying therapies is not a contraindication.
5. Ability to understand the purpose and risks of the study and provide signed and dated informed consent.

Exclusion criteria

MS-related exclusion criteria:
1. Changes in immunomodulatory therapy for multiple sclerosis in the 6 months before inclusion into the study.
2. Clinical relapse of MS or high dosage corticosteroid use within 30 days before inclusion into the study.

IMP and medication related exclusion criteria:
3. Contraindications to clemastine use, such as known porphyria or hypersensitivity to clemastine, other antihistamines with a similar chemical structure or any of the excipients.
4. Contraindications to fampridine use, such as hypersensitivity to fampridine or any of the excipients, history of epilepsy, kidney disease (GFR <50 ml/min absolute contraindication; GFR = 50-80 ml/min relative contraindication), use of Organic Cation Transporter 2 (OCT2) inhibitors or history of significant cardiac arrhythmias or conduction block.
5. Concomitant use of Fampridine or any other formulation of 4-aminopyridine (4AP) or diamino4ap that cannot be temporarily suspended prior to each study visit.
6. Changes in the use of medication currently being investigated in remyelination trials within 6 months before screening, including but not limited to domperidone, liothyronine, quetiapine, testosterone and bazedoxifene.
7. Non-incidental use of central nervous system depressants including but not limited to hypnotics, anxiolytics, monoamine-oxidase inhibitors (MAOI*S), tricyclic antidepressants, opioid analgesics and other antihistamines with sedating properties (e.g. promethazine).

Other medical history and concomitant disease exclusion criteria:
8. History of significant cardiac conduction block.
9. History of malignancy of any organ system (other than localized squamous or basal cell carcinoma of the skin or adequately treated cervical cancer), treated or untreated, within the past 3 years, regardless of whether there is evidence of local recurrence or metastases.
10. Estimated glomerular filtration rate (eGFR) < 50 ml/min/1.73 m2; AST, ALT,

or alkaline phosphatase > 3 times the upper limit of normal.
11. Any ophthalmological disease which may prevent accurate infrared oculography assessment.
12. Suicidal ideation or behaviour in 6 months prior to baseline.
13. History of drug or alcohol abuse within the past year.
14. Clinically significant cardiac, metabolic, hematologic, hepatic, immunologic, urologic, endocrinologic, neurologic, pulmonary, psychiatric, dermatologic, allergic, renal or other major diseases that in the PI*s judgement may affect interpretation of study results or patient safety.
15. History of or presence of clinically significant medical illness or laboratory abnormality that, in the opinion of the investigator would preclude participation in the study.

General exclusion criteria:
16. Pregnancy at the time of inclusion into the study or planning on breastfeeding within the first 7 months after inclusion in the study.
17. Involvement in other study protocol simultaneously without prior approval.
18. Insufficient proficiency in reading Dutch or English.
19. Unable or unwilling to suspend driving for a duration of 6 months.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	30-08-2022
Enrollment:	80
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Clemastine
Generic name:	Clemastine fumarate
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Fampyra
Generic name:	Fampridine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	16-12-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-02-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-06-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-09-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-06-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-07-2024

Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
EU-CTR	CTIS2024-513099-17-00
EudraCT	EUCTR2021-003677-66-NL
ClinicalTrials.gov	NCT05338450
CCMO	NL78363.029.21