Enrichment randomized double-blind, placebo-controlled cross-over trial with PHEnytoin cream in patients with painful chronic idiopathic axonal polyNEuropathy

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The main objective is to evaluate the efficacy and safety of phenytoin cream in patients with neuropathic pain due to CIAP. The second objective is to determine the predictive value of a DOBRET to identify sustained responders.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Peripheral neuropathies
Study type	Interventional

Summary

ID

NL-OMON55278

Source
ToetsingOnline

Brief title
EPHENE study

Condition

- Peripheral neuropathies

Synonym
chronic idiopathic axonal polyneuropathy, nerve pain

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht

Source(s) of monetary or material Support: Prinses Beatrix Spierfonds

Intervention

Keyword: analgesic, phenytoin, polyneuropathy, topical

Outcome measures

Primary outcome

The primary endpoint is the change in pain intensity from baseline NRS to the mean NRS in the second week.

Secondary outcome

All secondary endpoints are for phenytoin 20% versus 10% versus placebo cream in DOBRET positive, negative and all participants.

The change between baseline and week 2 of each intervention is assessed for:

1) pain intensity measured on the NRS,

2) EQ5-5D-5L, subscales of the BPI, pain characteristics as assessed with the NPSI, worst pain characteristics

3) Correlations between the following items: duration of painful CIAP, baseline NRS level, PCS, pain treatment naïve versus pain treatment resistant participants, worst pain characteristic, pain reducing effect on NRS, DOBRET results and PGIC

4) 30% and 50% improvement (MEC30 and MEC50) or more on the NRS compared to placebo within one patient

5) Time of carry-over effects after a treatment period

6) Number of participants who are responders on the PGIC after a treatment period

7) Onset of analgesic effect after application

8) Duration of analgesic effect

9) Daily number of cream applications

10) Percentage of analgesic effect as rated by the patient

11) Local and/or systemic side effects

12) Detection of phenytoin in plasma

13) Predictive value of DOBRET

14) Use of escape pain medication

Study description

Background summary

CIAP is a slowly progressive distal symmetric sensory or sensorimotor axonal polyneuropathy without a known cause. Approximately one-third of CIAP patients have neuropathic pain. Until now, no randomized controlled trials have been conducted in painful CIAP. Peripheral neuropathic pain can be very debilitating and influences the quality of life considerably. For most patients current treatments have insufficient pain reducing effects, and/or give rise to considerable side effects. Therefore, more than half of the patients discontinue oral neuropathic pain medication within 3 months. New treatment strategies are needed to improve neuropathic pain management. Phenytoin cream could fulfill this need.

Study objective

The main objective is to evaluate the efficacy and safety of phenytoin cream in patients with neuropathic pain due to CIAP. The second objective is to determine the predictive value of a DOBRET to identify sustained responders.

Study design

Enrichment randomized double-blind, placebo-controlled cross-over trial with phenytoin cream in patients with painful CIAP (EPHENE study) with the duration of 6 weeks will be performed. At baseline a DOBRET with phenytoin 10% and placebo cream will be performed in each study participant to stratify participants according to their response to the DOBRET before entering the double-blind cross-over phase. DOBRET positive participants are those who experience within 30 minutes at least two points pain reduction on the 11-point

numerical rating scale (NRS) on the phenytoin 10% cream applied area and at least one-point difference on the NRS between phenytoin 10% and placebo cream area, in favour of the former.
For the randomized phase of the cross-over trial, 48 DOBRET positive participants will enter the DOBRET positive group and 24 DOBRET negative participants the DOBRET negative group. Participants will be assigned to a random order of the 3 treatments: phenytoin 10%, phenytoin 20% and placebo cream. The duration of each treatment period is two weeks. Participants will cross-over two times to each of the other treatments.
After the 6-week study, participants can choose to participate in a 1-year open label extension study with phenytoine 20% cream.

Intervention

Patients will test one of the following interventions every 2 weeks: phenytoin 20% cream, phenytoin 10% cream and placebo cream, with the instruction to apply the cream 2 to 4 times a day to the painful areas.

Study burden and risks

Burden of study participation consists of time needed to complete questionnaires and keep a daily pain diary, three extra hospital visits and one venipuncture for detection of phenytoin in plasma after the second week (T1). The risks are minimal, because we do not expect clinically relevant side-effects from the intervention and there is only once a minimally invasive procedure (venipuncture). The advantage of study participation is that participants can experience within a short timeframe if 10% and/or 20% phenytoin cream has a clinically relevant analgesic effect (personalized medicine).

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

* CIAP is defined as presence of symmetrical distal sensory or sensorimotor symptoms such as numbness, pins and needles, tightness, coldness, unsteadiness, muscle cramps, and weakness with onset in the feet, compatible with polyneuropathy; presence of symmetrical distal sensory or sensorimotor signs with evidence of large nerve fiber involvement such as decreased sense of touch, vibration, and propriocepsis, usually in the presence of decreased pin prick/temperature sense, decreased/absent tendon reflexes, or slight muscle weakness on neurologic examination, compatible with polyneuropathy; an insidious onset and slow or no progression of the polyneuropathy over the course of at least 6 months; no identifiable cause for the polyneuropathy after thorough history-taking, clinical examination, and extensive laboratory testing; no suggestion of a hereditary polyneuropathy based on detailed kinship history (i.e., one or more affected family member), neurologic examination, or confirmation by genetic analysis; and nerve conduction studies excluding a demyelinating polyneuropathy and confirming large nerve fiber involvement if the findings on neurologic examination are equivocal considering the patient*s age.
* Presence of chronic localized neuropathic pain due to CIAP
* Neuropathic pain localized in two anatomically symmetrical areas of feet/lower legs
* Duration of neuropathic pain * 3 months
* Duration of *1 hour neuropathic pain per day
* Neuropathic pain characteristics defined by a DN4 score *4
* Mean pain score of *4 and <10 on the NRS at study entry (baseline)
* Difference of pain intensity between left and right foot and/or lower leg of not more than 1 point on the NRS

Exclusion criteria

* Painful (poly)neuropathy other than CIAP
* Pregnancy or planned pregnancy in the study period
* Use of oral phenytoin
* Open wounds in the neuropathic pain area
* Current use of topical analgesics
* Presence of other pain syndromes such as the widespread pain syndrome or pain in joints
* Presence of serious psychological/psychiatric morbidity
* Addiction to intoxicants
* Hypersensitivity to the study medication (active substance and excipients)
* Insufficient mastery of the Dutch language
* Cognitive impairment and insufficiently capable to understand the purpose of the study

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-12-2020
Enrollment:	84
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	nvt
Generic name:	phenytoin 10% cream
Product type:	Medicine
Brand name:	nvt
Generic name:	phenytoin 20% cream

Ethics review

Approved WMO Date:	15-07-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	17-07-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	17-09-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-10-2021
Application type:	Amendment
Review commission:	METC NedMec

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
EudraCT	EUCTR2020-001340-25-NL
CCMO	NL73339.041.20

Study results

Date completed:	13-06-2023
Actual enrolment:	81