A randomized, double-blind, double dummy, placebo-controlled, four-way cross-over study to investigate the analgesic effects and CNS effects of morphine and pregabalin in healthy subjects

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Primary• To evaluate the analgesic effects of morphine, pregabalin and the two drugs as combination using PainCartSecondary• To evaluate the drug-sensitive central nervous system (CNS) functioning of morphine, pregabalin and the two drugs as...

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

Summary

ID

NL-OMON51629

Source
ToetsingOnline

Brief title
Pharmacodynamic study of a novel analgesic combination treatment

Condition

- Other condition

Synonym
Chronic Pain

Health condition

Chronic Pain

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: The EU provides financial support for the study via Horizon 2020 European Union grant: QSPainRelief (H2020-SC1-BHC-2018-2020). CHDR is the sponsor of the study.

Intervention

Keyword: Analgesic effects, CNS effects, Morphine, Pregabalin

Outcome measures

Primary outcome

• Pressure Pain: Pain Detection Threshold (PDT), Pain Tolerance Threshold

(PTT), Area Under the Curve (AUC), post-test Visual Analogue Scale (VAS)

• • Heat pain (pre-cold pressor: unexposed/normal and UVB-exposed skin, the

latter only for subjects with MED lower than 355 mJ/cm2 at screening): PDT, and

post-test VAS

• Cold Pressor: PDT, PTT, Area Above the Curve (AAC), post-test VAS

• Electrical Stair test: PDT, PTT, AUC, post-test VAS

• Electrical burst test: PDT, PTT, AUC, post-test VAS

• Conditioned Pain Modulation (CPM) Response (change from heat pain pre- and

post-cold pressor): PDT

• Short Form McGill Pain Questionnaire (SFMPQ) for pressure pain, heat

pain, cold pressor, electrical stair test and electrical burst test.

Secondary outcome

• Body sway:

o antero-posterior sway (mm);

• Visual Analog Scales (VAS) according to Bond and Lader to assess:

o mood (mm),

o alertness (mm), and

o calmness (mm).

• Visual Analog Scales (VAS) according to Bowdle to assess:

o Feeling high (mm)

o Internal perception (mm)

o External perception (mm)

• N-back

o Average reaction time (ms) (zero-, one-, two-back)

o Number of correct targets (zero-, one-, two-back)

o Number of incorrect targets (zero-, one-, two-back)

•o Number of faulty non-target responses (zero-, one-, two-back)

• Adaptive Tracking

o Average performance (%);

• Visual Verbal Learning Test (VVLT) memory testing

o Immediate recall trial 3 (number correct)

o Delayed recall (number correct)

o Delayed recognition (number correct)

o Delayed recognition (reaction time correct) (msec)

• Electroencephalography

o Frequency ranges for spectral analysis, Delta, Theta, Alpha, Beta, Gamma

• Simple Reaction Time Task (SRT)

o Reaction time (ms)

Questionnaires:

• State-Trait Anxiety Inventory (STAI)

o State anxiety score

• Brief Symptom Inventory (BSI)

o General somatic symptoms

o Cognitive symptoms

o Interpersonal sensitivity

o Depressed mood

o Anxiety

o Hostility

o Phobic anxiety

o Paranoid thoughts

o Psychoticism

o Global severity index

• PK parameters of morphine (and metabolite: morphine-6-glucuronide),

pregabalin by noncompartmental analysis of the plasma concentration-time data:

• AUCinf, AUClast, CL(/F), Cmax, t1/2, tlag, tmax, Vz(/F)

• Treatment-emergent (serious) adverse events ((S)AEs) throughout the study at every study visit

• Concomitant medication throughout the study at every study visit

• Vital signs (Pulse Rate (bpm), Systolic blood pressure (mmHg), Oxygen saturation, Diastolic blood pressure (mmHg)) as per assessment schedule

• Clinical laboratory tests (Hematology, blood chemistry, glucose, and urinalysis) as per assessment schedule

• ECG parameters (Heart Rate (HR) (bpm), PR, QRS, QT, QTcF) as per assessment schedule

Study description

Background summary

Chronic pain is one of the most prevalent and complex medical conditions in the Western world. In general, around 20% of the population in Europe experiences chronic pain, resulting in a large socio-economic burden, including the effect on the patient*s environment and the health care system. Current pain drug treatment options include opioids, anti-depressants, antiepileptics, benzodiazepines and nonsteroidal anti-inflammatory drugs (NSAIDs).

60% of patients treated for chronic pain responds poorly to the above-mentioned therapies. Prescription of opioids, currently the most effective class of analgesics for moderate to severe chronic pain, has furthermore led to complications related to their adverse effects, including sedation, cognitive side-effects, and drug abuse liability. A solution for this may be by adding a non-opioid analgesic to treatment with an opioid, which may lead to an opioid-sparing effect . For example, therapies with combinations of morphine and anti-epileptics (e.g., pregabalin) or anti-depressants(e.g., amitriptyline), may lead to an improved balance of therapeutic benefit and adverse effects, tailored to the needs of individuals and stratified patient groups.

To obtain a better understanding of combination pain therapies a consortium was

established through a Horizon 2020 European Union grant: QSPainRelief (H2020-SC1-BHC-2018-2020). The consortium will investigate alternative novel drug combinations with improved analgesic-, and reduced adverse effects in the context of a full translational program: from in-silico modelling via in-vitro models to two healthy volunteer studies and eventually in studies with pain patients. All studies are performed by consortium members (www.qspainrelief.eu).

So far, in-silico, in-vitro, and preclinical research has been performed by the QSPainRelief consortium to investigate which combination therapy may provide the optimal analgesic-adverse effect profile. [Data not yet published] Data have been gathered in the QSPainRelief model. Initial discussion and results indicate that for this healthy volunteer study morphine (a potent μ-opioid receptor) in combination with pregabalin (a α2-δ subunit specific, voltage-dependent calcium channel ligand) may yield improved clinical utility over either drug used as monotherapy.

PainCart and NeuroCart are two comprehensive and validated test batteries commonly used in early-phase drug studies to profile pharmacodynamic effects of (novel) drugs. PainCart consists of an evoked pain test battery that was used previously to amongst others profile pregabalin and the opioid fentanyl. NeuroCart is a Central Nervous System (CNS) test battery that is used to assess drug-induced changes in CNS functioning. The batteries have previously been used together to evaluate possible synergistic effects of two analgesics, and to determine the CNS and analgesic profile of a novel investigational drug.

The aim of this first human experimental pain study, the QSPainRelief-novel A trial, is to investigate the analgesic effects and effects on CNS functioning of morphine and pregabalin as an analgesic combination in healthy subjects, compared to each of the two analgesics alone and to placebo. A second, similarly designed study is to follow in a year after this trial, to evaluate a different combination of an opioid and a non-opioid analgesic that is proposed by the QSPainRelief model.

Study objective

Primary
• To evaluate the analgesic effects of morphine, pregabalin and the two drugs as combination using PainCart

Secondary
• To evaluate the drug-sensitive central nervous system (CNS) functioning of morphine, pregabalin and the two drugs as combination by biomarker profiling and the NeuroCart
• To evaluate the blood pharmacokinetic parameters of morphine, pregabalin and the two drugs as combination
• To evaluate the safety and tolerability of morphine, pregabalin and the two

drugs as combination

Study design

This is a single centre, double blind, placebo-controlled, study to investigate the effect of morphine and pregabalin on pain thresholds and cognitive functioning.

Intervention

Investigational drug

Pregabalin
Pregabalin (Teva), 300 mg will be orally administered.

Morphine
Morphine hydrochloride (HCl) 3 mg and 7 mg will be administered intravenously.

Comparative drug
Matching placebo

Study burden and risks

No medical benefit is expected for study participants; however, this study will provide more insight in a combination treatment for patients suffering from chronic pain. Morphine and pregabalin are registered drugs which are widely used in the clinic, amongst other analgesics. The safety profiles of these compounds are well known. Both analgesic and adverse effects are likely to occur. Symptoms such as, sedation, somnolence, dizziness, fatigue, reduced vigilance, are to be expected following administration for both compounds, but will be closely monitored by medically trained staff as part of the study objectives. Subjecten will experience pain when the pain tests are performed. These tests are validated rigorously and have a safety cut-off to prevent too much pain and/or harm.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Healthy subjects, 18 to 65 years of age, 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) between 18 and 30 kg/m2, inclusive, and with a minimum weight of 50 kg and a maximum weight of 100 kg.
3. Able to participate and willing to give written informed consent and 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. Positive Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening.
4. 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.
5. 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 < 45 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
6. Use of any medications (prescription or over-the-counter [OTC]), within 14 days of study drug administration, or less than 5 half-lives (whichever is longer). Exceptions are paracetamol (up to 4 g/day) and ibuprofen (up to 1g/day), which are allowed up to 2 days before screening and 2 days before each study drug administration. Other exceptions will only be made if the rationale is clearly documented by the investigator.
7. Use of any vitamin, mineral, herbal, and dietary supplements within 7 days of study drug administration, or less than 5 half-lives (whichever is longer). Exceptions will only be made if the rationale is clearly documented by the investigator.
8. Participation in an investigational drug or device study (last dosing of previous study was within 90 days prior to first dosing of this study).
9. History of abuse of addictive substances (alcohol, illegal substances) or current use of more than 21 units (for males) or 14 units (for females) of alcohol per week, drug abuse, or regular user of sedatives, hypnotics, tranquillisers, or any other addictive agent
10. Positive test for drugs of abuse at screening or pre-dose.
11. Alcohol will not be allowed from at least 24 hours before screening or each admission.
12. Current use of tobacco or nicotine products and unable to abstain from use of these products within the previous 3 months before the first dose administration.
13. Is demonstrating excess in caffeine consumption (more than eight cups of coffee or equivalent per day).
14. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug, or multiple drug allergies (non-active hay fever is acceptable).
15. 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.
16. If a woman, pregnant, or breast-feeding, or planning to become pregnant during the study.
17. Not willing to practice effective contraception during the study and not willing and able to continue contraception for at least 90 days after their last dose of study treatment.
18. 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.
19. Known hypersensitivity to the investigational drug or comparative drug or drugs of the same class, or any of their excipients.
20. Fitzpatrick skin type IV, V and VI, wide-spread acne, tattoos or scarring interfering with the area of interest (i.e. upper back).
21. Any current, clinically significant, known medical condition in particular any existing conditions that could have affected sensitivity to cold (such as atherosclerosis, Raynaud*s disease, urticaria, hypothyroidism) or pain (paraesthesia, etc.).
22. Subjects who indicated nociceptive tests intolerable at screening or who achieved tolerance at >80% of maximum input intensity for the cold pressor or electrical pain tasks.

Study design

Design

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):	04-04-2022
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Morphine HCl CF 10 mg/ml, solution for injection
Generic name:	Morphinehydrochloride.
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Pregabalin Teva 300 mg hard capsules
Generic name:	Pregabalin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	30-11-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-01-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-02-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-02-2022
Application type:	Amendment
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
EudraCT	EUCTR2021-005826-39-NL
CCMO	NL79589.056.21