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The effect of cebranopadol, oxycodone, and placebo on respiration, the central nervous system, and pain perception

Submission date
26/07/2022

Recruitment status
No longer recruiting

Registration date
27/07/2022

Overall study status
Completed

Last Edited
27/07/2022

Condition category
Other

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Opioids (strong painkillers like morphine, and oxycodone (classical opioids)) are one of the most commonly used drugs for pain relief. However, opioids can have serious side effects like nausea, itchiness, sedation and addiction. Respiratory depression is another serious side effect of opioid use. In severe cases, a person may stop breathing at all, which can be life threatening and potentially lethal if not treated. For this reason, there is a need for effective painkillers that cause less respiratory depression than the classic opioids.
Cebranopadol is designed to alleviate pain while limiting the possibility of harmful side effects such as respiratory depression. Cebranopadol targets Mu-opioid-receptor (MOP) and nociception /orphanin FQ receptor (NOP). In previous research it has been shown that the side effects of opiates are less, when the NOP receptor is also activated. In animal studies,cebranopadolproduced much less respiratory depression compared to classic opioids.Cebranopadolcould provide a safer option for many pain patients than the currently available opioids. The main objective therefore is to study the effects of cebranopadol, oxycodone and a placebo on respiratory function and pain relief using tests as described below.

Cebranopadol is a new experimental drug that is being developed for treatment for acute and chronic pain. In this study, we are looking at how safe cebranopadol is, how it is absorbed and processed in the body. We are testing different strengths of cebranopadol in healthy subjects. Painkiller drugs like cebranopadol can lead to respiratory depression (slow and shallow breathing) when taken in high doses. This is an effect that can be very serious and sometimes fatal outside the controlled setting. Because respiratory depression can have these severe consequences, we will look at the effects of cebranopadol on breathing in this study. Cebranopadol has been administered to many (over 2100) humans before and has been tested previously in the laboratory and on animals. However, the highest dose of cebranopadol that will be tested in this study (1000 µg) has not yet been studied as a single dose without titration yet. Titration is when doses are gradually increased to accustom the body to the drug and so limit side effects. It is thus unknown exactly how safe the 1000 µg as single dose is. It is important that you take these aspects into consideration before deciding to participate.

We compare the effects and safety of cebranopadol with the effect and safety of oxycodone. Oxycodone is already registered for routine clinical use for the treatment acute and chronic pain. We also compare the effect and safety of cebranopadol with the effect of a placebo. A placebo is a product without the active ingredient: a 'fake medicinal product'.
Additionally, the data collected in this research can be used to gain more knowledge about the disease(s) that the medicine is being developed for and the treatment of these disease(s). This is done to ultimately find the best possible treatment for patients.

Who can participate?
This study needs 30 healthy adult men and women aged 18-45 years old who are deemed eligible for participation by in and exclusion criteria.

What does the study involve?
For the study, subjects need to visit the research center of CHDR in combination with the LUMC 4 times in approximately 12 weeks. A visit lasts approximately 40 hours. Between the start of each study period there will be a period of at least 2 weeks. Each period consists of 3 days (day -1, day 1 and day 2). On the study day (Day 1) at the LUMC, ventilatory measurements, and other measurements such electrical pain test, pressure pain test, blood withdrawal, ECG, pupil diameter measurements (pupillometry) and other (vital sign) measurements including BP and heart rate are performed twice. Hereafter the study drug, in the form of 8 capsules is administered orally with 240 ml of water. The measurements will then be performed repeatedly throughout the day. Vital signs (heart rate, BP, oxygen saturation) will continuously be monitored throughout the experiment. At the end of the study day, subjects will be transferred back to CHDR. The next morning (Day 2) all measurements from the previous day will be repeated twice in the LUMC. Hereafter subjects will be discharged home. After approximately 7 days after the last study drug administration subjects will return for a final follow-up visit.

What are the possible benefits and risks of participating?
For new drugs such as cebranopadol not all side effects are known yet. Thus there may be unexpected side effects, for example an allergic or hypersensitivity reaction. Cebranopadol and oxycodone are both types of opioid drugs. Side effects that are frequently reported for opioids include difficulty emptying your bowels, nausea, vomiting, drowsiness, headache, and itching. Decreases in blood pressure can occur with opioids, making you feel dizzy if you get up too fast from sitting or lying down. In addition, the use of opioid drugs can cause abuse, addiction, and opioid withdrawal (when taken for a prolonged period of time and then stopped), however for this study that is unlikely with the administrations on only four occasions as in this study. Respiratory depression (a decrease in the ability to inhale and exhale and/or breathing frequency) may occur at higher doses of opioids and can be serious resulting in a decreased oxygen level in the blood: this is the effect we aim to measure in this study. In an uncontrolled (non-medical) setting this may become life-threatening and potentially lethal. During an episode of respiratory depression one can experience fatigue, confusion, light headedness, nausea, headaches, shortness of breath, apnea or seizures. At CHDR and the LUMC, there is adequate medical supervision to ensure your safety when being administered cebranopadol or oxycodone. Should a serious respiratory depression develop, we will administer naloxone if necessary. Naloxone is an antidote to the action of opiates. Naloxone’s effects are shorter than opiates, therefore we may need to administer naloxone several times.
Ondansetron is a common anti-nausea drug (also known as anti-emetic). The most common side effects related to ondansetron are headache, heat flashes, difficulty emptying your bowels and local infusion site reactions

Where is the study run from?
The Centre for Human Drug Research (CHDR) and Leiden University Medical Centre (LUMC).

When will the study start and how long is it expected to run for?
September 2021 to May 2023

Who is funding the study?
Park Therapeutics Inc. (USA)

Who is the main contact?
Dr Simone Jansen, Project Leader, clintrials@chdr.nl
Prof. dr. Geert Jan Groeneveld, Prinicpal investigator, clintrials@chdr.nl

Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2021-006701-30

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
PARK-104-VRH

Study information

Scientific Title
A randomized, double blind, four-period, six-treatment, double-dummy, placebo controlled, partial-crossover study to explore and compare the ventilatory response to hypercapnia (VRH) of cebranopadol, oxycodone, and placebo in healthy subjects

Acronym
PARK-104-VRH

Study objectives
The present study is designed to investigate if:
1. Cebranopadol produces less respiratory depression than oxycodone
2. Cebranopadol respiratory effects have a ceiling at supratherapeutic doses and
3. Cebranopadol does not produce significant respiratory depression, as measured in this study design with 30 subjects, at any dose in the VRH model

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 15/07/2022, Medical Ethics Committee Leiden the Hague Delft (Leiden University Medical Hospital, Albinusdreef 2, 2333 ZA Leiden, South Holland, The Netherlands; +31(0)71 52 63241; metc-ldd@lumc.nl), ref: p22.026

Study design
Randomized double blind four-period six-treatment double-dummy placebo controlled partial-crossover study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Ventilatory drive, central nervous system and pain in healthy subjects

Interventions
This randomized, double blind, four- period, six-treatment, double-dummy, placebo controlled, partial-crossover study will investigate the effects of cebranopadol on the ventilatory response to hypercapnia (VRH), nociceptive thresholds, pharmacokinetics (PK) and safety. Thirty healthy subjects, aged 18 – 45years (inclusive) will complete the study.

All treatments will be over-encapsulated to ensure double blinding. Based on the assigned treatment sequence, each subject will be randomly allocated to receive a single oral dose in each of the 4 periods, with at least 14 days between dosing days. Each period, subjects will receive an oral dose of identically appearing capsules that will contain one of the following treatments:
• Cebranopadol tablets (strength: 200µg); single oral doses of 600µg, 800µg, and 1000µg
• Oxycodone IR capsules (strengths: 10mg and 20mg); single oral doses of 30mg and 60mg
• Matching placebo for cebranopadol and oxycodone

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Cebranopadol, oxycodone, placebo

Primary outcome(s)
Respiratory drive measured by the VRH by maximum decrease in minute ventilation(L)after administration ofcebranopadol, oxycodone, and placebo.

Key secondary outcome(s))
1. Pupil diameter(mm) measured by pupillometrypredoseand at multiple time points after administration ofcebranopadol, oxycodone, and placebo
2. Sensitivity of the ventilatory response to hypercapnia aftersingleoral administration ofcebranopadol, oxycodone, and placeboby measuring:
2.1. Minute ventilation (expired minute volume; L)
2.2. Respiratory rate (breaths/min)
2.3. Flow rates (peak expired flow; L/min)
2.4. Tidal volume (expired tidal volume; mL)
2.5. End tidal CO2(partial pressure)
2.6. O2Saturation peripheral(%)
3. Analgesic activity ofcebranopadoland oxycodone, compared to each other and placebo, following single oraladministration, on theelectrical and pressure paintests by measuring the mean:
3.1. Pain Detection Threshold (PDT)
3.2. Pain Tolerance Threshold (PTT – electrical pain only)
4. Clinical safety data from adverse event (AE) reporting, clinical observations, 12-lead electrocardiograms (ECGs)(Heart rate (bpm), PR, RR, QRS, QT,QTcF), vital signs (blood pressure, heart rate, respiratory rate, body temperature, oxygen saturation, and safety laboratory tests following administration ofcebranopadol, oxycodone, and placebo.
5. Blood samples will be collected to evaluate pharmacokinetics(PK) ofcebranopadol(and its metabolites)and oxycodoneby determining the following parameters
5.1. The maximum plasma concentration observed (Cmax)
5.2. Time to reach Cmax(tmax)
5.3. The area under the concentration–time curve from time zero to time of last quantifiable concentration (AUClast)
5.4. The area under the concentration–time curve from time zero to24hours (AUC0-24)
5.5. Other parameters as appropriate, as well as dose adjusted parameters, may be determined

6. Pharmacokinetic-pharmacodynamic (PK/PD)analysiswill be conducted

Completion date
25/05/2023

Eligibility

Key inclusion criteria
1. Signed informed consent prior to any study-mandated procedure.
2. Subject is able to speak, read, and understand Dutch and voluntarily provide written informed consent to participate in the study.
3. Adult men or women aged 18to45years, inclusive.
4. Subjects are in good health as indicated by medical history, physical examination, vital signs, oxygen saturation, clinical laboratory tests, and 12-lead ECG.
5. Body mass index between18.0kg/m2and 32.0kg/m2and body weight greater than50kg,inclusive.
6. Adequate contraception is being used or women of nonchildbearing potential may be enrolled

if surgically sterile (i.e.,after hysterectomy) or postmenopausal for at least 2years (based on subject's report).
• For women of childbearing potential:
- A medically acceptable and highly effective method of birth control is defined as any form of contraception with a low failure rate defined as <1% per year.
- For example:
• Hormonal contraceptives for at least 8weeks prior toscreeningand at least until 4weeks after theFollow-up visit.
• An intra-uterine device.
• Additional barrier contraception should be used by the partner for the duration of the trial, defined as from the time ofscreeninguntil 4weeks after thefollow-up visit. A single barrier method alone is not acceptable.
• For men:
- Subjects must be willing to use medically acceptable and highly effective methods of birth control. Subjects must be willing to use barrier contraception (condom) during sexual intercourse with females from the first administration of IMP until 4weeks after theFollow-up visit.
- Subjects must be willing to take care that their female sexual partner uses at least 1additional method of contraception with a low failure rate defined as <1% per year (e.g.,hormonal contraceptives, diaphragm) during this time

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. History or presence of clinically significant cardiovascular(incl. a history of risk factors for torsade de pointes e.g., heart failure, hypokalaemia, family history of long QT syndrome, history of myocardial infarction, ischaemic heart disease, clinically significant arrhythmia or uncontrolled arrhythmia or cardiac failure), pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, or psychiatric disease(e.g., anxiety); or any other condition (e.g., hyperventilation disorder), which, in the opinion of the Investigator, would jeopardize the safety of the subject or the validity of the study results.
2. History of known difficult airway access or uncontrolled gastroesophageal reflux disease (GERD), gastric motility disorders, or delayed gastric emptying
3. Hasclinically significantabnormalitieson ECGat screening or Day -1,as defined by the following:
a. prolonged corrected QT interval (Fridericia-corrected QT interval [QTcF] > 450msin males and >470 ms in females) demonstratedon ECG;
b. Left bundle branch block at Screening or Baseline
4. Systolic blood pressure (BP) >150 or <90 mmHg or diastolic BP >95 or <50 mmHg at Screening

or Baseline, or history of clinically significant orthostatic hypotension.
5. Heart rate (HR) <40 beats per minute (bpm) or >100 bpmat Screening.
6. Is currently enrolled in another clinical study or used any investigational drug or device within 3 months prior to dosing or has participated in more than 4 investigational drug studies within 1 year prior to Screening.
7. Has any condition in which an opioid is contraindicated (e.g.,significant respiratory depression, acute or severe bronchial asthma or hypercarbia, or has or is suspected of having paralytic ileus).
8. Have a history of chronic obstructive pulmonary disease or any other lung disease (e. g.,asthma, bronchitis, obstructive sleepapnoea, exercise-induced asthma) that would cause CO2retention.
9. History of opioid use disorder per Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) classification, or other drug/substance or alcohol dependency or abuse(excluding nicotine and caffeine) within the last 5yearsbefore Screening,which, in the opinion of the Investigator, would jeopardize the safety of the subject or the validity of the study results
10. Has a positivealcohol test orurine drug screen for drugs of abuse (amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine and opioids)at Screening orDay -1.
11. Use of nicotine-containing products within 4 weeks before the Screening visit and not able to withhold from smoking during the study.
12. Pregnant or breastfeeding.
13. Subjects indicating pain test intolerability at Screening or achieving pain tolerance at >80% of maximum input intensity for the pain tests.
14. Demonstrated allergic reactions (e.g., food, drug, atopic reactions, or asthmatic episodes) which, in the opinion of the Investigator, interfere with the subject’s ability to participate in the trial.
15. Positive hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (Anti-HBc), hepatitis C antibodies (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at Screening.
16. Use of prescription, non-prescription medications or herbal preparations containing St. John’ s Wort, within 14 days or 5 half-lives prior to dosing, whichever is longer. An exception is made for contraceptives and incidental use of paracetamol or ibuprofen, which is allowed up to 48 hours before start of each visit. Other exceptions are allowed only when clearly documented by the investigator.
17. No vitamin, mineral, herbal, and dietary supplements will be permitted within 7 days prior to study drug administrations, or less than 5 half-lives (whichever is longer, and during the course of the study.
18. Any clinically significant lifetime history of suicidal behaviour or ideation and/or poses a current (within the past12 months) suicide risk, as assessed by scores on the Columbia Suicide Severity Rating Scale (C-SSRS) at Screening per Investigator judgment
19. Receipt of blood products within 4 weeks, blood donation or blood loss >250 mL within 8 weeks, or donation of plasma within 1 week of any Study Drug dose administration.
20. Is employed byTris, Park, the Centre for Human Drug Research (CHDR), or the Investigator or study site (permanent, temporary contract worker, or designee responsible for the conduct of the study), or is immediate family* of aTris, Park, CHDR, Investigator, or study site employee.

Date of first enrolment
20/07/2022

Date of final enrolment
02/04/2023

Locations

Countries of recruitment
Netherlands

Study participating centre
Center for Human Drug Research
Zernikedreef 8
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Study participating centre
Leiden University Medical Hospital
Albinusdreef 2
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Sponsor information

Organisation
Park Therapeutics Inc

Funder(s)

Funder type
Industry

Funder Name
Park Therapeutics Inc

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes