A randomised, double-blind, placebo-controlled crossover study to investigate the effect of buprenorphine on fentanyl induced effects on nociceptive thresholds and CNS functioning in opioid tolerant patients.

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Primary objectives- To evaluate the effects of buprenorphine on fentanyl induced analgesia using the PainCart test battery in OT patients, when compared to placebo.Secondary objectives- To evaluate the effects of buprenorphine on fentanyl induced...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Neurological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON51024

Source
ToetsingOnline

Brief title
Fentanyl Blockade Study in OT patients

Condition

- Neurological disorders NEC

Synonym
Drug interaction

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Buprenorphine, Fentanyl, Fentanyl blockade, Opioids

Outcome measures

Primary outcome

• Thermal pain: PDT (°C)

• Pressure Pain: PDT (kPa), PTT (kPa), area-under-the-curve (AUC) (kPa*mm) and post-test VAS (mm)

• Electrical Burst: PDT (mA), PTT (mA), AUC (mA*mm) and post-test VAS (mm)

• Electrical Stair: PDT (mA), PTT (mA), AUC (mA*mm) and post-test VAS (mm)

• Cold Pressor: pain detection threshold (PDT) (s), area-above-the-curve (AAC) (s*mm) and post-test visual analogue scale (VAS) (mm)

Secondary outcome

• Saccadic eye movement

o saccadic reaction time (s),

o saccadic peak velocity (°/s), and

o saccadic inaccuracy (%);

• Smooth pursuit eye movements:

o percentage of time the eyes of the subjects are in smooth pursuit of the target (%);

• Body sway:

o antero-posterior sway (mm);

• Adaptive tracking:

o average performance (%);

• Pupillometry (mm)

• VAS Bond & Lader (Alertness, mood, calmness) (mm)

• VAS Bowdle (internal perception, external perception, *feeling high*) (mm)

• ARCI-49

Exploratory

• Treatment-emergent (serious) adverse events ((S)AEs)

• Concomitant medication throughout the study at every study visit

• Pharmacokinetic parameters such as Cmax and AUC

Study description

Background summary

Buprenorphine is a partial agonist at the μ-opioid receptor (MOR) and is used for the medication assisted treatment of opioid use disorder (OUD). In recent years the use of opioids has increased in the U.S.A. and Europe, and an increase in the use of buprenorphine has been recorded. Buprenorphine has high affinity for the MOR and therapeutic plasma concentrations achieve >= 70% receptor occupancy. As a partial agonist, buprenorphine has a ceiling effect on respiratory depression such that it does not cause apnoea when administered alone and minute ventilation is not suppressed beyond 50 to 60%. This is in contrast with the effects of the full MOR agonist fentanyl, which does elicit complete respiratory depression when administered at high doses. Literature is inconclusive on whether buprenorphine has a ceiling effect on analgesia, in part due to insufficient investigation into the analgesic effect of high doses of buprenorphine, which can only be achieved in opioid-tolerant (OT) patients due to side effects of opioid treatment in healthy volunteers.

A previous study that was conducted by CHDR in collaboration with the LUMC

anaesthesiology department (CHDR1754, of which the results are yet unpublished), has shown that sustained high therapeutic levels of buprenorphine can inhibit the respiratory depressive effects of IV bolus fentanyl in OT patients. Buprenorphine formulations are being developed as a treatment for OUD, to prevent fentanyl-induced deaths. Worldwide, many patients are administered buprenorphine for various conditions, and it is expected that this number will increase in the coming years due to an increasing number of patients who are on medication assisted treatment of opioid use disorder. If buprenorphine is used by an increasing number of patients with OUD, the previous findings warrant additional research to be performed on the effects of buprenorphine on IV fentanyl induced analgesia and other CNS functions. In clinical practice, fentanyl is often used as an analgesic drug in the emergency and operating room. Patients with OUD who are being treated with buprenorphine will have sustained high plasma concentrations of buprenorphine, which might limit the analgesic properties of fentanyl when this drug is administered in a medical environment such as the ER. Hence, it is of great importance that knowledge is gained regarding the pharmacodynamic interaction of the two study drugs regarding the effects on pain.

The aim of this study is to evaluate the effects of buprenorphine on fentanyl induced analgesia and CNS effects in OT patients, when compared to placebo.

Study objective

Primary objectives
- To evaluate the effects of buprenorphine on fentanyl induced analgesia using the PainCart test battery in OT patients, when compared to placebo.
Secondary objectives
- To evaluate the effects of buprenorphine on fentanyl induced CNS effects using the NeuroCart test battery in OT patients, when compared to placebo.
Exploratory Objectives
- To develop a mathematical model describing the pharmacokinetic (PK)/pharmacodynamic (PD) interaction between buprenorphine and fentanyl concentrations and their effect on analgesia and CNS functions in OT patients.

Study design

This will be a randomised, double-blind, placebo-controlled, cross-over study to evaluate effects of buprenorphine on fentanyl induced analgesia and CNS effect in OT patients.

Buprenorphine/ placebo:
subjects are randomised to treatment group 1 or 2
treatment group 1: an initial bolus of 0.25 mg 70 kg-1 followed by continuous infusion of 0.1 mg 70 kg-1 h-1 / placebo
treatment group 2: an initial bolus of 1.25 mg 70 kg-1 followed by continuous

infusion of 0.5 mg 70 kg-1 h-1 / placebo

Fentanyl:
each treatment group will receive up to four boluses of 0.1 - 0.4 mg 70 kg*1

Intervention

Buprenorphine/placebo will be administered for 6 hours. Fentanyl boluses will be given by dose escalation +2HR,
+3HR, +4HR and +5HR after starting administration of buprenorphine/placebo to investigate the pharmacodynamic
interaction between buprenorhine and fentanyl.

Study burden and risks

Buprenorphine: adverse drug reactions commonly reported are sedation, dizziness, sleep, miosis, hypoventilation, nausea, vomiting, hyperhidrosis and headache. Hallucinations and other psychotomimetic effects can occur although more rarely. Hypotension leading to syncope can occur. Buprenorphine may cause significant respiratory depression when taken in combination with benzodiazepines or other CNS depressants. The planned doses are within the therapeutic range and have previously been safely administered to similar patient populations both in trials and in clinical practice.
Care will be taken when treating patients with impaired respiratory function or patients who are receiving drugs that can cause respiratory depression. Experience has shown that naloxone is beneficial in reversing a reduced respiratory rate. Respiratory stimulants such as doxapram are also effective.
The intensity and duration of action is affected in patients with impaired liver failure, which will be assessed during screening.
All healthy subjects will receive ondansetron 4 mg IV prior to buprenorphine infusion. A second dose of 4 mg can be administered as needed for management of nausea and vomiting. Patients administered chronic opioids can receive no more than two 4-mg IV doses of ondansetron as needed for management of nausea and vomiting.

Fentanyl: the most commonly reported adverse drug reactions are nausea, vomiting, muscle rigidity, hypotension or hypertension, bradycardia and sedation. Other adverse reactions that have been reported are dizziness, blurred vision, nausea, vomiting, hyperhidrosis, pruritus, urticaria, laryngospasm and anaphylaxis.

The planned doses in this study are not expected to cause respiratory insufficiency, based on a previous study performed at CHDR and LUMC (CHDR1754). However, fentanyl will be given only in an environment where the airway can be controlled and by personnel who will monitor the airway. Respiratory depression is dose-related and can be reversed by an antagonist such as naloxone. Multiple

doses of naloxone may be necessary because the respiratory depression will last longer than the duration of action of the opioid antagonist. Subjects will remain under appropriate surveillance. Resuscitation equipment and opioid antagonists will be readily available. Adequate spontaneous breathing must be established and maintained before discharge from the Post-Anaesthesia Care Unit (PACU).

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. Signed the ICF and able to comply with the requirements and restrictions listed therein;
2. Male and female, age 18 to 55 years, inclusive;
3. Women of childbearing potential (defined as all women who are not surgically

sterile or postmenopausal for at least 1 year prior to informed consent) must have a negative pregnancy test prior to enrolment and must agree to use a medically acceptable means of contraception from screening through at least 3 months after the last dose of study drug.
4. BMI 18 to 32 kg/m2, inclusive;
5. Opioid-tolerant patients administered opioids at daily doses >= 60 mg oral morphine equivalents (See Appendix A);
6. Stable as defined by the Investigator, based on a medical evaluation that includes the patient*s medical and surgical history, physical examination, vital signs, 12-lead ECG, haematology, blood chemistry, and urinalysis;
7. No current use of any CNS depressants, besides opioids, prescribed or otherwise for 5 half-lives of the product before first study drug administration unless assessed as safe by the principal investigator.

Exclusion criteria

1. Clinically significant risk factors of Torsades de Pointes (e.g., heart failure, hypokalaemia, family history of Long QT Syndrome) or an ECG demonstrating a Fridericia*s corrected QT interval (QTcF) > 450 msec in males and QTcF > 470 msec in females at screening;
2. Currently meet the criteria for diagnosis of moderate or severe substance use disorder according to the DSM-5 criteria on any substances other than opioids, caffeine, or nicotine;
3. Any active medical condition, organ disease or concurrent medication or treatment that may either compromise subject safety or interfere with study endpoints (including sleep apnoea, other significant respiratory illness, history or risk of difficult intubation, limited cervical spine mobility or limited oral excursion);
4. Not able to abstain from smoking cigarettes during each dose administration day;
5. Consume, on average, >27 units/week of alcohol in men and >20 units/week of alcohol in women (1 unit = 1 glass (250 mL) beer, 125 mL glass of wine or 25 mL of 40% spirit);
6. Use of buprenorphine 10 days prior to the first study drug administration;
7. Use of prescription or OTC medications that are clinically relevant CYP P450 3A4 or CYP P450 2D6 inducers or inhibitors from 14 days prior to study drug administration;
8. History of suicidal ideation within 30 days prior to informed consent or history of a suicide attempt in the 6 months prior to informed consent;
9. Measured systolic blood pressure greater than 160 or less than 95 mmHg or diastolic pressure greater than 95 mmHg prior to Day 1;
10. History or presence of allergic response to buprenorphine or fentanyl;
11. Opioid-tolerant patients who have demonstrated allergic reactions (e.g., food, drug, atopic reactions or asthmatic episodes) which, in the opinion of the Investigator and sponsor, interfere with their ability to participate in

the trial.
12. Estimated glomerular filtration rate <60 mL/min as estimated by the CKD-EPI equation;
13. Clinical significant anaemia at screening or donation of > 250 mL of blood or plasma within the last 3 months;
14. Positive serology tests for HIV, acute hepatitis B, or acute hepatitis C (OT patients with asymptomatic hepatitis B or C infection may be enrolled);
15. AST or ALT levels >3.0 times the upper limit of normal at screening;
16. Any current, clinically significant, known medical condition in particular any existing conditions that would affect sensitivity to cold (such as atherosclerosis, Raynaud*s disease, urticaria, hypothyroidism);
17. Treatment with another investigational drug within 3 months prior to dosing or having participated in more than 4 investigational drug studies within 1 year prior to screening;
18. Site staff or subjects affiliated with, or a family member of, site staff directly involved in the study.

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):	06-07-2021
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Fentanyl

Generic name:	Fentanyl
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Saline 0.9%
Generic name:	Placebo NaCl 0.9% solution
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Temgesic
Generic name:	Buprenorphine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	01-02-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-03-2021
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

ID: 27786
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2021-000012-39-NL
CCMO	NL76423.056.21
OMON	NL-OMON27786