Fentanyl Blockade Study in OT 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...

Ethische beoordeling	Positief advies
Status	Werving nog niet gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON27786

Bron
NTR

Verkorte titel
CHDR1934

Aandoening

Drug interaction, pain

Ondersteuning

Primaire sponsor: CHDR
Overige ondersteuning: CHDR

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

• 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)

Toelichting onderzoek

Achtergrond van het onderzoek

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was conducted by CHDR in collaboration with the LUMC anaesthesiology department (CHDR1754, of which the results are yet unpublished), has shown that sustained high therapeutic levels of buprenorphine can inhibit the respiratory depressive effects of IV bolus fentanyl in OT patients.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.

Doel van het onderzoek

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.

Onderzoeksopzet

Up to -42 days till EOS

Onderzoeksproduct en/of interventie

Buprenorphine/placebo
Fentanyl boluses

Contactpersonen

Publiek

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen

(Inclusiecriteria)

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
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

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

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.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Cross-over
Toewijzing:	Gerandomiseerd
Blindering:	Dubbelblind
Controle:	Placebo

Deelname

Nederland

Status:	Werving nog niet gestart
(Verwachte) startdatum:	01-06-2021
Aantal proefpersonen:	12
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Toelichting
N.A.

Ethische beoordeling

Positief advies

Datum:	20-05-2021
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 51024
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL9467
CCMO	NL76423.056.21
OMON	NL-OMON51024

Resultaten

Samenvatting resultaten
N.A.