Reversal of opioid-induced respiratory depression with opioid antagonists - a study in opioid naïve individuals and chronic opioid users under real-life conditions

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This study has been transitioned to CTIS with ID 2024-518041-16-00 check the CTIS register for the current data. The goal of the studies is multiple:1. To describe the pharmacokinetics of intravenously administered fentanyl and sufentanil;2. To...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON54257

Source
ToetsingOnline

Brief title
Reversal of OIRD

Condition

- Other condition

Synonym
opioid-induced respiratory depression

Health condition

PK en PD (farmacokinetiek en farmacodynamiek)

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: FDA (US)

Intervention

Keyword: Naloxone, Opioid, Respiratory depression, Reversal

Outcome measures

Primary outcome

Ventilation (L/min)

Secondary outcome

Pupil diameter (mm)

Withdrawal symptoms

Study description

Background summary

The opioid crisis has a significant socioeconomic impact worldwide but particularly in the US the number of opioid-related deaths is soaring. Opioid deaths are due to respiratory depression which is caused by the activation of μ-opioid receptors expressed on the surface of neurons in brainstem respiratory centers. Activation of these opioid receptors by both illicit opioids and prescription opioids may initiate respiratory compromise, which in many individuals is short-lived or reverts to normal breathing activity. In some individuals, often due to underlying disease, an opioid overdose or the combination of opioid use with other centrally depressant drugs (such as sleep medication or alcohol), diminished breathing progresses into irregular (or cyclic) breathing and eventually into apnea (the complete cessation of breathing). This may lead to cardiorespiratory collapse and ultimately death.3 The most effective treatment of opioid-induced respiratory depression is treatment with opioid receptor antagonists, most importantly naloxone.3,6 Naloxone is a competitive opioid receptor antagonist that is able to reactivate rhythmic respiratory activity although the optimal conditions of its effective

use in real-life (or street) conditions remain unknown.3 We previously studied the ability of intravenous naloxone to reverse opioid-induced respiratory conditions in healthy volunteers under experimental conditions, i.e. during inhalation of carbon dioxide.4,7 This was done to maximize the effect of naloxone and does lead to relevant and useful pharmacokinetic (PK) and pharmacodynamic (PD) data but is far off from real-life conditions of opioid overdoses in chronic opioid abusers and the use of other administration routes than intravenous, e.g. intranasal and nalmefene as opposed to naloxone.or intramuscular routes. As presented at research meetings, the FDA, under the supervision of David Strauss, has been using our prior experimental data in simulation studies to model naloxone doses to reverse the phenylpiperidines fentanyl and derivatives, however these simulations were based on (intravenous) experimental data and not on real-life conditions and were not performed in chronic opioid users.

Since it is important to study the ability of naloxone and nalmefene to reverse opioid-induced respiratory depression under real-life conditions induced by potent opioids, we designed a set of experiments to study the ability of intranasal and intramuscular naloxone and intravenous nalmefene to reverse respiratory depression induced by two potent opioids, fentanyl and sufentanil reverseved by intranasal naloxone (in Year 1) and fentanyl and sufentanil reversed by intramuscular intravenous naloxone and nalmefene (in Year 2). Studies are performed in volunteers without underlying disease and chronic opioid users. We will measure ventilation, end-tidal expired CO2, pupil diameter and drug concentrations in plasma under real-life conditions, i.e. without supplemental inhalation of carbon dioxide. In this study we mimic an opioid overdose under stable and highly monitored conditions by titrating the opioid to 40-60% depression of ventilation. Next, naloxone is administered at multiple times to characterize its effect on opioid affected ventilation. Importantly, we will measure the respiratory variables continuously on a breath-to-breath basis, while pupil diameter and plasma concentration are measured regularly allowing the precise matching of effects (ventilation and pupil diameter) and effects to plasma concentration.

The studies in the two populations (healthy subjects and chronic opioid users) will have a 2-arm cross-over and randomized design:

- In the first study (Year 1), all subjects will be tested twice with at least one week in between visits. On visit 1, the effect of 4 mg intranasal naloxone will be tested during fentanyl- or sufentanil induced respiratory depression with 2 administrations over time (4-5 h); on visit 2 the effect of 4 mg intranasal naloxone will be tested during fentanyl- or sufentanil-induced respiratory depression with 2 administrations over time (4-5 h). If the first visit is fentanyl, the second visit will be sufentanil and vice versa. At the end of each experiment 0.4 mg naloxone will be administered intravenously to determine its effect on ventilation and to allow calculation of naloxone intranasal bioavailability.

- In the second study (Year 2), all subjects will be tested twice with at least one week in between visits. On visit 1, the effect of an escalating intravenous dose of nalmefene or intravenous naloxone2 mg intramuscular naloxone will be tested during sufentanilfentanyl-induced respiratory depression with up to 4 or 513 administrations over time (2-31 h); on visit 2 the effect of 2 mgan escalating dose of intravenous nalmefene or intravenous naloxone intramuscular naloxone will be tested during fentanyl-induced respiratory depression with up to 4 or 513 administrations over time (2-31 h). The sequence of visits is sequential with first the fentanyl study and subsequently the sufentanil study. At the end of each experiment 0.4 mg naloxone will be administered intravenously to determine its effect on ventilation and to allow calculation of naloxone intramuscular bioavailability.

The choice of the two opioids is based on their pharmacokinetic properties. While fentanyl has a t*koff of 2 min, sufentanil*s t*koff equals 10 min. The koff determines the affinity of the opioid for the receptor; the longer t*koff the more difficult reversal by naloxone is. Apart from buprenorphine, fentanyl and sufentanil are the opioids with the greatest difference in t*koff for all clinically available opioids.

The collected data (ventilation, end-tidal PCO2, pupil dimeter, concentration opioid and concentration naloxone and nalmefene) will be analyzed using a population modeling approach to obtain reliable pharmacokinetic-pharmacodynamic data that allow precise description of opioid-induced respiratory depression and naloxone/nalmefene-induced respiratory stimulation, opioid- and naloxone/nalmefene-induced changes in pupil diameter , and opioid- and naloxone/nalmefene-induced changes in withdrawal. .

Study objective

This study has been transitioned to CTIS with ID 2024-518041-16-00 check the CTIS register for the current data.

The goal of the studies is multiple:
1. To describe the pharmacokinetics of intravenously administered fentanyl and sufentanil;
2. To describe the pharmacodynamics of intravenously administered fentanyl and sufentanil (important model parameters include receptor equilibration constants kon and koff and t*ke0, the blood-effect-site equilibration half-life of the opioid) for respiratory depression and miosis (reduction of pupil size).
3. To describe the pharmacokinetics of intranasal and intravenous naloxone and intravenous nalmefene;
4. To describe the pharmacodynamics of intranasal and intramuscular naloxone in its ability to reverse respiratory depression and miosis (important model parameters include C50, a measure of potency and t*ke0).
5. Finally, the results of these studies will allow us to perform simulation studies aimed at optimizing dosing regimens for intranasal and intramuscular

naloxone in individuals that overdosed on fentanyl and sufentanil, with respiratory depression ranging from moderate to severe. See quad chart.
6. Additionally, we will determine whether the dynamics of the surrogate biomarker, pupil diameter, mimics respiratory depression and hence may be used in the development of new opioid antagonists and study other routes of administration of current and new reversal agents.

Study design

Open label randomized crossover study

Intervention

Administration of an opioid and an opioid antagonist

Study burden and risks

In this pharmacokinetic-pharmacodynamic modeling study, the effect of IM and IN and IV naloxone is studied during infusion of two opioids, fentanyl and sufentanil, in mixed population of healthy volunteers and chronic opioid users. The PK/PD analysis will yield important information regarding dosing regimens of IM and IN naloxone at fentanyl and sufentanil doses much higher than we will administer here, but that may represent doses in case of an overdose both in clinical patients and opioid abusers.

Side effects related to the medication will be mild to moderate with most common side effects: nausea, vomiting, dizziness, somnolence, dry mouth and respiratory depression (from the opioids), and possibly mild withdrawal symptoms from naloxone. Side effects will dissipate over time while severe occurrences of nausea and vomiting will be treated with an antiemetic; severe occurrence of withdrawal symptoms will be treated with clonidine. Respiratory depression is the topic of the current study; severe occurrences (beyond the stopping rules) may be treated with intravenous naloxone. The participants will have no benefit from this trial in terms of disease burden reduction or disease alleviation.

The gained knowledge from the study is large as this is the first study to systematically study IM and IN naloxone dosing in chronic opioid users.

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

Healthy volunteers
1. Signed the informed consent form (ICF) and able to comply with the study requirements and restrictions listed therein;
2. Male and female subjects, age 18 to 70 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 serum pregnancy test prior to enrolment and must agree to use a medically acceptable means of contraception from screening through at least 1 month after the last dose of study drug;
4. Body Mass Index (BMI) 18 to 30 kg/m2, inclusive;
5. Healthy as defined by the Investigator, based on a medical evaluation that includes the subject*s medical and surgical history, physical examination, vital signs;
6. No history of substance use disorder;
7. Normal renal function, normal liver function
8. negative serology: HIV, hepatitic B and C

Chronic opioid users

1. Signed the consent form and able to comply with the requirements and restrictions listed therein;
2. Males or females age 18 to 70 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 serum 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 prescription opioids at daily doses >= 60 mg oral morphine equivalents (See Table 3);
6. Stable as defined by the Investigator, based on a medical evaluation that includes the subject*s medical and surgical history, physical examination, vital signs, 12-lead ECG, hematology, and blood chemistry;
7. positive opioid urine drug screening;
8. positive naloxone challenge.

Exclusion criteria

1. Currently meet the criteria for diagnosis of substance use disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria on any substance;
2. Any other active medical condition, organ disease or concurrent medication or treatment that may either compromise subject safety or interfere with study endpoints;
3. Consume, on average, >27 20 units/week of alcohol in men and > 20 13 units/week of alcohol in women (1 unit = 1 glass (250 mL) beer, 125 mL glass of wine or 25 mL of 40% spirit);
4. Previous or current treatment with opioid agonist, partial agonist, or antagonist treatment within 30 days prior to the first study drug administration;
5. Significant traumatic injury, major surgery, or open biopsy within the prior 4 weeks of informed consent;
6. 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;
7. Measured systolic blood pressure greater than 160 or less than 95 mmHg or diastolic pressure greater than 95 mmHg at screening;
8. History or presence of allergic response to fentanyl, sufentanil or naloxone or nalmefene;
9. Subjects 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;
10. 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;

11. Site staff or subjects affiliated with, or a family member of, site staff directly involved in the study;

Chronic opioid users
1. 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;
2. Any active medical condition, organ disease or concurrent medication or treatment that may either compromise subject safety or interfere with study endpoints;
3. 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);
4. Currently receiving medication-assisted treatment for the treatment of opioid-use disorder;
5. Significant traumatic injury, major surgery, or open biopsy within the prior 4 weeks of informed consent;
6. 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;
7. Measured systolic blood pressure greater than 160 or less than 95 mmHg or diastolic pressure greater than 95 mmHg at screening;
8. History or presence of allergic response to study medicationfentanyl, sufentanil, nalmefene or naloxone;
9. 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.
10. Estimated glomerular filtration rate <60 mL/min as estimated by the CKD-EPI equation;
11. Anemia at screening or donation of > 250 mL of blood or plasma within the last 3 months;
12. Positive serology tests for HIV, acute hepatitis B, or acute hepatitis C (OT patients with asymptomatic hepatitis B or C infection may be enrolled);
13. AST or ALT levels >3.0 times the upper limit of normal at screening;
14. 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;
15. Site staff or subjects affiliated with, or a family member of, site staff directly involved in the study.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	15-06-2022
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	fentanyl
Generic name:	Fentanyl
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Nalmefene
Generic name:	Nalmefene
Product type:	Medicine
Brand name:	naloxon
Generic name:	naloxon
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Narcan
Generic name:	Narcan
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Sufentanil
Generic name:	Sufentanil

Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	21-10-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	13-01-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	06-07-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	22-07-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	06-01-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	23-01-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	27-01-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	14-04-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	28-04-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	18-07-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	21-07-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	26-07-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	04-10-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	09-10-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	14-10-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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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
EU-CTR	CTIS2024-518041-16-00
EudraCT	EUCTR2021-005373-51-NL
CCMO	NL77759.058.21