ISRCTN21068708 https://doi.org/10.1186/ISRCTN21068708

Comparing the effects of giving various doses of medication through injection into the muscle versus using a nasal spray. This is to see which method works better in reversing the harmful effects of taking too many opioid drugs.

Submission date	**Recruitment status**	[_] Prospectively registered
22/08/2023	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[X] Statistical analysis plan
06/09/2023	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
20/05/2025	Other	

Plain English summary of protocol

Background and study aims

When people take strong pain-relieving medicines called opioids, sometimes their breathing can slow down too much, which is dangerous. This can happen if they use these medicines properly or misuse them. Right now, a medicine called naloxone is used to quickly reverse this slow breathing. But there's still a lot we don't know about the best way to give naloxone to make the breathing go back to normal quickly and completely. In our research, we will test two different forms of naloxone to see which one works better at fixing the slowed breathing caused by a strong pain-relieving medicine called fentanyl. We will do this test with both healthy volunteers and people who regularly take opioids for a long time.

Who can participate?

Healthy volunteers, aged 18 - 65 years and 6 chronic opioid users (minimal daily dose in morphine equivalents 90 mg).

What does the study involve?

In the study, we're testing things in a fair way, like flipping a coin. People will be involved in two separate sessions, with about a week apart (the order of how they get the medicine will be decided randomly).

First, after breathing pure oxygen for a short while, people will get a strong pain-relieving medicine called fentanyl through a vein. This will happen about 2 minutes after their breathing slows down. We'll do this repeatedly every 2 minutes until their breathing is back to normal.

There are two ways we'll give another medicine, naloxone. One way is by putting a needle into a muscle (5 mg). The other way is by squirting it into the nose (4 mg). We'll keep track of how much air they breathe in and out with each breath, and also the amount of a gas called PCO2 that comes out when they breathe.

At the end of the study, we'll give a single quick injection of naloxone through a vein (0.4 mg) to

see how well the naloxone from the needle and the nose works. We'll take small amounts of blood (about 5 mL each time) a total of 25 times during the study to check things.

What are the possible benefits and risks of participating?
The subjects themselves will not gain any benefit from participating in the study apart from a small financial gain (the reimbursement). Risks relate to the effect of the drugs, particularly fentanyl. Most importantly there is the risk of nausea and sedation. We will inform the subjects of this risk. One other risk relates to the primary outcome of the study, respiratory depression. This risk is however acceptable under the controlled conditions of this experiment and will not harm the subject. In case of nausea we can treat the subject with an antiemetic according to hospital policy. The risk of the arterial line is restricted to a hematoma at the end of the case due to insufficient pressure at the introduction site.

Where is the study run from?
Leiden University Medical Center (Netherlands)

When is the study starting and how long is it expected to run for?
June 2023 to September 2024

Who is funding the study?
1. DMP Pharma (Netherlands)
2. Leiden University Medical Center (Netherlands)

Who is the main contact?
Prof. Albert Dahan, a.dahan@lumc.nl

Contact information

Type(s)
Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
2023-505338-93-00

Protocol serial number
P23.055

Study information

Scientific Title
Comparison of multiple doses of intramuscular versus intranasal naloxone for reversal of opioid toxicity

Acronym
IMvIN

Study objectives
The objective is to compare the efficacy of multiple doses of intramuscular versus intranasal naloxone on fentanyl-induced respiratory depression.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 14/08/2023, METC-LDD (Albinusdreef 2, Leiden, 2333ZA, Netherlands; +31 0071-5263241; metc-ldd@lumc.nl), ref: P23.055

Primary study design
Interventional

Study design
Interventional randomized open design

Study type(s)
Treatment, Safety, Efficacy

Health condition(s) or problem(s) studied
Healthy volunteers and chronic opioid users

Interventions
The trial has a randomized open design. Subjects will be studied on two occasions with about 7-10 days in between study visits (the order of IM and IN will be randomized. Randomization is done in R by an independent person).

After a 5-10 min period of 100% oxygen breathing, subjects will receive 10 ug/kg intravenous fentanyl, administered over 90 s. The intervention will occur at t = 120 s following the start of respiratory depression and repeated at 2 min intervals until complete recovery to baseline ventilation. Intervention 1 is 5 mg IM naloxone, intervention 2 is 4 mg IN naloxone. We will measure minute ventilation and end-expired PCO2 on a breath to breath basis . At the end of the study we will administer a single bolus of 0.4 mg intravenous naloxone for determination of the bioavailability of IM and IN naloxone. We will draw twenty-five 5 mL blood samples at regular intervals during the study (total blood draw = 125 mL).

Intervention Type

Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Intranasal naloxon and intramuscular naloxon

Primary outcome(s)
The number IM and IN administrations needed to restore ventilation to baseline levels in healthy volunteers. aAter the fentanyl bolus we will give at 2-min intervals a maximum of 4 naloxone doses (intramuscular or intranasal; randomized). If the ventilation is within 80% of baseline ventilation (e.g. 8 liters/min if baseline ventilation was 10 liters/min), we will stop giving naloxone doses.

Key secondary outcome(s)
1. The number IM and IN administrations needed to restore ventilation to baseline levels in chronic opioid users
2. Naloxone-induced changes upon administration of naloxone (either IM or IN) in
2.1. Minute ventilation continuously measured during the experiment and saved per breath
2.2. End-tidal PCO2 continuously measured during the experiment and saved per breath
2.3. Plasma concentrations of naloxone measured at specific time points (-2, 0, 2, 4, 8, 10, 12, 14, 16, 18, 20, 25, 40, 60, 90, 120, 180, 240, 242, 244, 246, 250, 260, 275, 300 minutes relative from first IM/IN naloxone dose)
3. Effect of fentanyl and naloxone on pupil diameter and muscle tone will be analyzed by descriptive analysis. The pupil diameter will be measured using the CE-marked PLR-3000 (Neuroptics) that is in use in our laboratory for some time. Muscle tone is measured using the CE-marked MyotonPro (myotom.com), a device that elicits a small pressure on the skin and measure skin stiffness (in N/m) and that is in use in our laboratory (see Muckelt et al., Sci Rep 2022; 12: 13654).

Completion date
01/09/2024

Eligibility

Key inclusion criteria
Healthy volunteers + chronic opioid users:
1. Aged 18-65 years with body mass index 19 - 40 kg/m²

Additionally, for chronic opioid users:
2. Opioid users: use opioids at daily doses ≥ 60 mg oral morphine equivalents. No upper limit is set as would like to study as large as possible range of opioid use. It is our experience that the majority of patients use 60 - 600 mg oral morphine equivalents.
3. 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.

Participant type(s)
Healthy volunteer, Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
65 Years

Sex
All

Key exclusion criteria
Healthy volunteers + chronic opioid users:
1. A medical history of medical or psychiatric disease (incl. drug or alcohol addiction);
2. Pregnancy or lactation;
3. A positive drug urine dipstick on the screening or study days.
4. History or presence of allergic response to study medication;

Additionally, for chronic opioid users:
5. 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;
6. Any active medical condition, organ disease or concurrent medication or treatment that may either compromise subject safety or interfere with study endpoints;
7. Currently receiving medication-assisted treatment for the treatment of opioid-use disorder;
8. History or presence of allergic response to study medication;
9. Treatment with mixed agonists-antagonists (such as buprenorphine) or use of benzodiazepines.

Date of first enrolment
01/09/2023

Date of final enrolment
01/07/2024

Locations

Countries of recruitment
Netherlands

Study participating centre
Leiden University Medical Center
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Sponsor information

Organisation
Leiden University Medical Center

ROR
https://ror.org/05xvt9f17

Funder(s)

Funder type
Industry

Funder Name
DMP Pharma

Funder Name
Leids Universitair Medisch Centrum

Alternative Name(s)
Leiden University Medical Center, LUMC Leiden, LUMC

Funding Body Type
Government organisation

Funding Body Subtype
Universities (academic only)

Location
Netherlands

Results and Publications

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be 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?
Results article		19/05/2025	20/05/2025	Yes	No
Statistical Analysis Plan	version 1		12/09/2024	No	No