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Using L-NAC to reverse breathing problems caused by opioid medication

Submission date
15/05/2023

Recruitment status
No longer recruiting

Registration date
31/05/2023

Overall study status
Completed

Last Edited
31/05/2023

Condition category
Signs and Symptoms

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

Plain English summary of protocol

Background and study aims
Opioid-induced respiratory depression (OIRD) is a serious problem that can occur when using opioids for medical treatment or when misusing them. Naloxone, a commonly used medication, is not very effective in reversing OIRD caused by powerful opioids like high-dose fentanyl. This means there is a need for alternative medications that can stimulate breathing without being specific to certain opioids. L-NAC (N-acetyl-N-cysteine or fluimicil) is a drug that is approved for treating paracetamol overdose, and it also has the ability to stimulate breathing. In this study, we will investigate whether giving L-NAC through an intravenous infusion can help reverse OIRD caused by fentanyl. We will conduct a randomized controlled trial where some participants will receive intravenous L-NAC while others will receive a placebo, and we will observe the effects on fentanyl-induced respiratory depression.

Who can participate?
Healthy volunteers aged 18 - 40 years.

What does the study involve?
The main goal of the study is to determine how L-NAC affects the amount of air a person breathes in and out (minute ventilation) when they receive an individualized intravenous dose of fentanyl. This specific dose of fentanyl is designed to cause a 40% decrease in breathing by the end of a 2-hour infusion of L-NAC or placebo.

First, the individualized intravenous fentanyl infusion will begin with the aim of achieving a 40% decrease in breathing compared to the person's normal breathing rate. Once the 40% decrease is achieved, either the L-NAC or placebo infusion will start and last for 1 hour with a dose of 75 mg/kg. Then, a second administration of L-NAC or placebo will be given over the next hour with a dose of 150 mg/kg. The dose of L-NAC may be adjusted based on the observations from previous participants, with a maximum increase of two times the initial dose.

Three hours after the start of the first infusion of L-NAC or placebo, the experiment will end, and all infusions will be stopped.

What are the possible benefits and risks of participating?
The healthy volunteers in this trial will not gain benefit from participating in this study. The benefit lies within the gained knowledge in our ability to treat, reverse and prevent opioid-inducted respiratory depression observed in patients treated with opioids and persons with an opioid use disorder. The burden of the study is related to the measurements and interventions. The used drugs have side effects. The application of iv lines could cause short-lasting pain and might result in a temporary, self-resolving hematoma.

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

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

Who is funding the study?
Leiden University Medical Center (the Netherlands)

Who is the main contact?
Dr Monique van Velzen, m.van_velzen@lumc.nl

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number
2023-503912-34

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
P23.033

Study information

Scientific Title
L-NAC (N-acetyl-N-cysteine or fluimicil) for reversal of opioid-induced respiratory depression

Acronym
ORNAC

Study objectives
L-NAC (N-acetyl-N-cysteine or fluimicil) is a drug, registered for treatment of paracetamol intoxication, that has also respiratory stimulatory effects. In the current study, we will investigate the ability of an intravenous infusion of L-NAC on OIRD induced by fentanyl.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 12/05/2023, Medical Research Ethics Committee Leiden the Hague Delft (Albinusdreef 2, 2333 ZA Leiden, the Netherlands; +31-71-5263241; metc-ldd@lumc.nl), ref: P23.033

Study design
Single center randomized placebo-controlled double-blind

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
University/medical school/dental school

Study type(s)
Safety, Efficacy

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet.

Health condition(s) or problem(s) studied
Reversal of opioid-induced respiratory depression

Interventions
Randomization (1:1) will be done by generating an electronic randomization list in R by an independent member of the department and sent to the pharmacy. The pharmacy is responsible for blinding the L-NAC/placebo syringes

Individualized intravenous fentanyl infusion will be initiated aimed at 40% respiratory depression compared to baseline. After 40% respiratory depression is attained, the L-NAC or placebo infusion will start over 1 h with dose 75 mg/kg. A second administration of L-NAC or placebo will be administered over hour the next hour with dose 150 mg/kg. The L-NAC dose may be adapted based on the results observed in previous subjects (max. increase with a factor of 2). Three hours after the first infusion of L-NAC or placebo, the experiment will end, and all infusions will be terminated.

Measurements made are: minute ventilation on a breath-to-breath basis through a facemask for 3 hours, end-tidal carbon dioxide partial pressure, respiratory frequency, tidal volume, oxygen saturation (all obtained on a breath-to-breath basis), arterial blood gas analysis: pH, pO_2, pCO_2, oxygen saturation (obtained at 15 min intervals), blood pressure by cuff (at 30 min interval) and plasma concentrations of fentanyl and L-NAC (at regular intervals). Total volume of blood drawn is 125 mL.

Intervention Type
Drug

Pharmaceutical study type(s)
Pharmacokinetic, Pharmacodynamic

Phase
Phase III/IV

Drug/device/biological/vaccine name(s)
L-NAC (N-acetyl-N-cysteine or fluimicil), fentanyl

Primary outcome measure
Minute ventilation during exposure measured through a facemask during the exposure period

Secondary outcome measures
1. End-tidal carbon dioxide partial pressure obtained on a breath-to-breath basis during the exposure period using pneumotachograph
2. Respiratory frequency obtained on a breath-to-breath basis during the exposure period using pneumotachograph
3. Tidal volume obtained on a breath-to-breath basis during the exposure period using pneumotachograph
4. Arterial blood gas analysis: pH, pO_2, pCO_2, oxygen saturation obtained at 15 min intervals during the exposure period using blood gas analyzer
5. Plasma concentrations of fentanyl and L-NAC measured using a blood sample at regular intervals using LC-MS/MS methods
6. Blood pressure measured by cuff (at 30 min interval) during the exposure period

Overall study start date
01/04/2023

Completion date
01/01/2024

Eligibility

Key inclusion criteria
1. Aged 18 - 40 years
2. Body mass index 19-30 kg/m²
3. Ability to read and understand the subject information in the Dutch language

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Upper age limit
40 Years

Sex
Both

Target number of participants
18

Key exclusion criteria
1. A medical history of medical or psychiatric disease;
2. Any allergy to food or medication;
3. Weekly ethanol intake of more than 3 units/day or more than 21 units/week in women and 5 units/day and 35 units/week in men;
4. Pregnancy;
5. 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 urine 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; Acceptable means of contraception include: hormonal methods (birth control pills), barrier
6. Methods (condoms, diaphragm), intrauterine devices, sterilization;
7. Participation in an investigational drug trial in the 3 months before the current study;
8. Illicit drug use in the 30 days before the current study;
9. A positive drug urine dipstick on the screening or study days, including benzodiazepines.

Date of first enrolment
01/06/2023

Date of final enrolment
01/11/2023

Locations

Countries of recruitment
Netherlands

Study participating centre
Leiden University Medical Center
Dept. of Anesthesiology
Albinusdreef 2
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Sponsor information

Organisation
Leiden University Medical Center

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Sponsor type
University/education

Website
https://www.lumc.nl/?setlanguage=English&setcountry=en

ROR
https://ror.org/05xvt9f17

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Leids Universitair Medisch Centrum

Alternative Name(s)
Leiden University Medical Center, LUMC

Funding Body Type
Government organisation

Funding Body Subtype
Local government

Location
Netherlands

Results and Publications

Publication and dissemination plan
The data will be published in a peer-reviewed scientific journal as soon as the data have been analyzed and the manuscript has been written, without any restrictions. This is in agreement with the
CCMO statement that (https://english.ccmo.nl/publications/publications/2002/03/01 /ccmostatement-
on-publication-policy)

Intention to publish date
01/06/2024

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from Albert Dahan a.dahan@lumc.nl

IPD sharing plan summary
Available on request