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The effect of esketamine on the hypoxic ventilatory response

Submission date
20/06/2023

Recruitment status
No longer recruiting

Registration date
27/06/2023

Overall study status
Completed

Last Edited
20/11/2024

Condition category
Respiratory

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Opioids and anesthetics are given to patients before surgery and have an important effect on breathing. While we know that opioids are potent respiratory depressants, including depression of the hypoxic ventilatory response (HVR; the increase in breathing caused by low blood oxygen), few human studies have addressed the effect of ketamine on the hypoxic ventilatory response. Since esketamine is frequently used to reduce opioid consumption before surgery and hypoxia following surgery is quite common, it is important to study the effect of ketamine (this study will use esketamine) on the hypoxic ventilatory response in a population of healthy male and female volunteers. In the first set of experiments, the researchers expect to observe that esketamine alone does not affect the HVR. Next, they will test whether the reduced HVR by the opioid remifentanil is restored by adding esketamine.

Who can participate?
Healthy volunteers aged 18 - 45 years

What does the study involve?
In part 1 of the study the researchers will infuse four esketamine doses and during each dose they will measure the HVR. In part 2, they will test the dose that effectively sustains the HVR in part 1, and will determine whether that dose is able to reverse remifentanilinduced depression of the HVR.

What are the possible benefits and risks of participating?
Participants will not benefit from participating in this study. The benefit lies within the gained knowledge about how to treat, reverse and prevent opioid-inducted respiratory depression in patients treated with opioids and people 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 (bruise).

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?
February 2023 to April 2024

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

Who is the main contact?
S. C. Jansen, s.c.jansen@lumc.nl

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2023-504229-37-00

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
2

Study information

Scientific Title
Hypoxic ventilatory response (HVR): Effect of Esketamine

Acronym
HE-o-E

Study objectives
Opioids and anesthetics are given to patients perioperatively and have an important effect on breathing. While it is known that opioids are potent respiratory depressants, including depression of the hypoxic ventilatory response (HVR), few human studies addressed the effect of ketamine on the hypoxic ventilatory response. Since esketamine is frequently used to reduce opioid consumption postoperatively and hypoxia following surgery is quite common, it is important to study the effect of ketamine (this study will use the S-enantiomer, esketamine) on the hypoxic ventilatory response in a population of healthy male and female volunteers. In the first set of experiments, the researchers expect to observe that esketamine alone does not affect the HVR. Next, they will test whether the reduced HVR by the opioid remifentanil is restored by adding esketamine. It was showed earlier that esketamine enhances remifentanil-induced depressed isohypercapnic ventilation in healthy volunteers. The researchers will do so in a randomized controlled trial of esketamine versus placebo during remifentanil infusion.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 12/06/2023, Medisch-Ethische Toetsingscommissie Leiden | Den Haag | Delft (LUMC Albinusdreef 2 Secretariaat: Kamer P5-22, routenummer 953 Spreekkamer: Kamer P5-40, routenummer 953, Leiden, 2333 ZA, Netherlands; Monday +31(0)71 52 63241; Tuesday +31(0)71 52 66045; Wednesday +31(0)71 52 63003; Thursday +31(0)71 52 66963; Friday +31(0)71 52 63241; metc-ldd@lumc.nl), ref: P23.039

Study design
Part 1: Single-center dose-finding study; Part 2: Single-center randomized placebo-controlled trial

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
The effect of esketamine on the hypoxic ventilatory response

Interventions
The study intervention is the administration of esketamine.

In part 1 of the study the researchers will infuse four esketamine doses and during each dose, they will measure the HVR: In part 1 of the study, for esketamine the dosing regimen is set at dose 0 (control condition for 60 min), followed by dose 16 (16 mg given over 60 min), dose 24 (24 mg given over 60 min) and finally dose 32 (32 mg over 60 min); all doses are per 70 kg. This dosing regimen is identical to that used earlier by (Jonkman et al. BJA 2018; https://clinicaltrialregister.nl/nl/trial/24921).

In part 2, the researchers will test the dose that effectively sustains the HVR in part 1, and will perform an RCT (esketamine vs placebo) to determine whether that dose is able to reverse remifentanilinduced depression of the HVR. Participants will be studied three times with at least 2 days in between study visits.

Intervention Type
Drug

Pharmaceutical study type(s)
Pharmacokinetic, Pharmacodynamic

Phase
Phase III/IV

Drug/device/biological/vaccine name(s)
Remifentanil, esketamine

Primary outcome measure
Hypoxic ventilatory response as determined from the change in ventilation and the change in oxygen saturation, ie. ΔVentilation/ΔSaturation with unit L/min per % desaturation, where Δ stands for the difference between the variable observed at baseline and observed during hypoxia. Measured through measuring minute ventilation by facemask during the exposure period (i.e. l/min/% desaturation).

Secondary outcome measures
1. Plasma esketamine concentrations over time, measured using blood samples at 0, 2, 5, 30, 60, 62, 65 and 75 min following the start of each of the esketamine infusions
2. Psychomimetic side effects assessed by the Bowdle and Bond & Lader questionnaires during hypoxic breathing

Overall study start date
22/02/2023

Completion date
23/04/2024

Eligibility

Key inclusion criteria
1. Aged 18 - 45 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
45 Years

Sex
Both

Target number of participants
18

Total final enrolment
18

Key exclusion criteria
1. A history of clinically significant (as deemed by the investigators) medical or psychiatric disease; These include: clinically significant illness or disease (e.g., psychiatric disorders, disorders of the gastrointestinal tract, liver, kidney, respiratory system, endocrine system, hematological system, neurological system, or cardiovascular system, or any clinically significant abnormal symptom or organ impairment, as judged by the investigator, found by medical history, physical examinations or vital signs at screening
2. Any allergy to food or medication
3. Weekly alcohol 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 or lactation
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. By contraception we mean for women: intrauterine device (IUD), diaphragm with spermicide, oral contraceptive, injectable progesterone, subdermal implant or a tubal ligation. Males who are sexually active and whose partners are females of childbearing potential must agree to use condoms
6. Participation in an investigational drug trial in the 3 months before the current study
7. Illicit drug use in the 30 days before the current study
8. A positive drug urine dipstick on the screening or study days

Date of first enrolment
31/07/2023

Date of final enrolment
01/01/2024

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
Government

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
01/07/2024

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

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		07/11/2024	20/11/2024	Yes	No