Reversal through TRH of opioid-induced respiratory depression (OIRD) in healthy volunteers

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To study the effect of TRH on opioid-induced respiratory depression in healthy volunteers.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON46759

Source
ToetsingOnline

Brief title
RETRO

Condition

- Other condition

Synonym
opioid-induced respiratory depression

Health condition

opiaat-geinduceerde ademdepressie

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: opioids, Respiratory depression, TRH

Outcome measures

Primary outcome

Ventilation

Secondary outcome

-

Study description

Background summary

odern medicine relies heavily on opioids for suppression of moderate to severe pain. Strong opioids are use observed during anesthesia to suppress autonomic responses, during procedural sedation to reduce nociception, and given for treatment of acute (postoperative) pain and chronic pain. However, the use of opioids comes with serious side effects of which opioid-induced respiratory depression (OIRD) is most dangerous. OIRD may be related to sedation, loss of upper airway patency and central depression of rhythm generation. There are various options to prevent or treat OIRD. We previously showed that the K+-channel blocker GAL021 effectively reverses OIRD. GAL021 is still experimental and will require many years of additional research before it may be used in clinical practice. Alternatives to GAL021 that may be used clinically are scarce. We recently tested the effect of the NMDA receptor antagonist ketamine on OIRD (P16.117) and observed a partial relief of OIRD is 75% of volunteers (Fig. 1). Still, the use of ketamine is not without consequences. First, it stimulates the sympathetic system and has psychomimetic effects. Albeit mild, these effects preclude its general use. Second, ketamine is a registered anesthetic and is given via the intravenous route. Hence, its application in OIRD is limited to the perioperative setting.

One possible treatment of OIRD is with the hormone TRH (thyrotropin-releasing hormone, tripeptide Glu-His-Pro-NH2). Few studies tested the effect of TRH on

breathing. In 1991, Nink et al. (Acta Physiol Scand 1991; 141: 309-318) studied low-dose TRH (200 and 400 µg or 15 µg/min) on breathing in healthy volunteers and observed brisk but short-lived respiratory effect. TRH is used in humans, especially as diagnostic tool in endocrine disorders and for treatment of spinal muscle atrophy (Tzeng et al. Am J Phys Med Rehab 2000; 79: 435-440).

In the current study, we will investigate the effect of intravenous TRH on remifentanil-induced respiratory depression.

Study objective

To study the effect of TRH on opioid-induced respiratory depression in healthy volunteers.

Study design

Double blind randomised

Intervention

Infusion of TRH and measurement of ventilation

Study burden and risks

Side effect are transitory and mild. The gain of this research is large with possibly even the development of a complete new treatment strategy to overcome OIRD. This is highly relevant taken the large opioid epidemic in the US.

Most common side effects of TRH reported in the literature are flushing, nausea, vomiting, and small increases in blood pressure and heart rate. All reported side effects were short-lived and mild.

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 male or female volunteers;
- Age: 18 - 40 years;
- Body mass index < 30 kg/m2;
- Able to give informed consent.

Exclusion criteria

- Known or suspected neuromuscular or a (family) history of any neuromuscular disease;
- A history of allergic reaction to food or medication including study medication;
- Any current or previous medical (including high blood pressure), neurological or psychiatric illness (including a history of anxiety);
- Alcohol abuse (> 21 units/week);
- Illicit drug use in the past 30 days before inclusion;
- Pregnancy or lactation;
- Participation in any medical or drug trial in the month prior to the current study.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-04-2018
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Protirelin
Generic name:	TRH
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	07-03-2018
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	09-04-2018
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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
EudraCT	EUCTR2017-004973-15-NL
CCMO	NL64429.058.17

Study results

Date completed: 23-08-2018

Actual enrolment: 7

Summary results
Trial ended prematurely