Single-centre, randomised, prospective, open-label, three-period, Phase 1 clinical trial for assessment of the pharmacodynamic and pharmacokinetic interaction of remimazolam and remifentanil

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The primary objective is to quantify the remimazolam exposure-response relationship with and without remifentanil in regard to various stages of MOAA/S for procedural and ICU sedation and general anaesthesiaSecondary objectives are:- Quantification...

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

Summary

ID

NL-OMON51001

Source
ToetsingOnline

Brief title
Remix2 study

Condition

- Other condition

Synonym
sedation, unconsiousness

Health condition

general anesthesia

Research involving
Human

Sponsors and support

Primary sponsor: PAION UK Limited
Source(s) of monetary or material Support: Funding by industry

Intervention

Keyword: pharmacodynamic interaction, pharmacokinetic interaction, remifentanil, remimazolam

Outcome measures

Primary outcome

An exposure-response model describing the relationship between effect-site

concentrations of remimazolam and plasma concentrations of remifentanil and

MOAA/S corresponding to mild, moderate and deep sedation

Secondary outcome

Pharmacokinetics

An exposure-response model describing the relationship between effect-site

concentrations of remimazolam and plasma concentrations of remifentanil and BIS

corresponding to mild, moderate and deep sedation

Performance characteristics for the TCI models used (RMZ and remifentanil)

according to Varvel et al. [1]. These include median absolute prediction error,

median prediction error, wobble and divergence.

Pharmacodynamics

Exposure response models for:

1. tolerance to laryngoscopy,

2. tolerance to tetanic stimulus,

3. BIS,

4. hemodynamic alterations in terms of heart rate, arterial blood pressure

(ABP), mean arterial pressure (MAP), stroke volume and cardiac output.

5. respiratory depression.

6. raw EEG data will be used for explorative comparison with the listed PD

parameters

Safety

* Heart rate and arterial blood pressure

* Number and incidence of adverse events by drug-relatedness, seriousness, and

severity during each treatment period.

* Clinical laboratory parameters (at screening, prior to each period and End of

Trial), ECG, vital signs, physical examination at Screening and End-of-Trial

(end of Treatment Period 3). Modified Aldrete score (prior to discharge after

each treatment period).

Study description

Background summary

This trial is designed to quantify the pharmacodynamic (PD) and pharmacokinetic (PK) interaction(s) between an anaesthetic drug (remimazolam) and an opioid (remifentanil). Remimazolam is a new anaesthetic drug with a sedative effect, which, in combination with an opioid can be used to achieve general anaesthesia.

Remimazolam exhibits its anaesthetic effects via the benzodiazepine binding site at the GABAA receptor, as does midazolam. The compound is rapidly metabolised and inactivated by tissue esterases that are abundantly distributed throughout the body. Remimazolam was found to be generally safe and well tolerated in all clinical trials conducted to date. Safety results from the completed trials show a lower overall incidence of hypotension compared to both midazolam and propofol.

To date, however, no clinical trials have been conducted to specifically assess the potential for drug-drug interactions between remimazolam and remifentanil. A better characterization of this drug-drug interaction will lead to more precise dosing regimens, which in turn, will lead to a reduction in the occurrence of over sedation, side effects and recovery times.

Study objective

The primary objective is to quantify the remimazolam exposure-response relationship with and without remifentanil in regard to various stages of MOAA/S for procedural and ICU sedation and general anaesthesia

Secondary objectives are:
- Quantification of the remimazolam exposure-response relationship with and without remifentanil in regard to various BIS values for procedural and ICU sedation and general anaesthesia.
- Validation of the Remimazolam (RMZ) 3-compartmental PK model (Final PopPK model from Nuventra*s *procedural sedation* report, NPS2981) under TCI conditions based on arterial blood samples taken during steady-state and non-steady-state conditions.
- Evaluation of various haemodynamic parameters of this combination under various concentrations at steady state.
- Explorative pharmacokinetic comparison of remimazolam alone and with different remifentanil concentrations.
- Evaluation of standard safety assessments of this combination under various concentrations at steady state.

Study design

This is a single-centre, open-label, three-period, randomised treatment sequence, trial

Subjects will be screened up to 28 days before Day 1 of Treatment Period 1. Each subject will be randomised to a sequence of 3 consecutive treatment periods. In each treatment period, subjects will enter the clinic on the late afternoon/evening before dosing (Day 1) for a restricted screening (see 7.2.2). They will return early in the next morning and remain in the unit until completely recovered on the evening of the treatment (Day 1). There will be at

least 5 days between each of the 3 treatment periods. A follow-up visit will be performed just before discharge after recovery in Period 3. A follow-up per telephone will be performed one day after each treatment period .

Intervention

In each cohort, 2 males and 2 females will be randomised to each Treatment Sequence (1 or 2, respectively). Sequences 1 and 2 will be identical for Periods 1 and 2. Dosing for remifentanil will be randomised in Period 3.

In each period, remifentanil will be dosed to a fixed effect concentration (EC) throughout:
Period 1: 0 ng/mL,
Period 2: 0.5 ng/mL,
Period 3: 0.1 ng/mL [Sequence 1] or 1.0 ng/mL [Sequence 2]).

In each period, remimazolam will be dosed in a series of up to 11 predefined 30 minute EC dose steps (6 ascending steps followed by 5 descending steps).

Study burden and risks

Small risks in this trial are associated with the administration of the IMP and remifentanil (see 2.3.1 of protocol), the catheterization of the A. radialis, the insertion of venous cannulae, the bladder catheterization and with the total blood loss of up to 275 mL over the 3 treatment periods.

Furthermore, subjects will:
- need to refrain from alchol, nicotine and recreational drugs prior to and during study participation,
- fast before the study days (6 hours concerning solid food, 2 hours concerning clear liquids)
- need to use highly effective birth control from the last menstrual cycle prior to the start of the IMP until the end of the trial follow-up procedures (females) or prevent their partner from becoming pregnant during the study procedure (males)

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 adults *18 to *70 years old
* American Society of Anesthesiologists (ASA) Physical Status 1
* Body mass index (BMI) >18 or <30 kg/m2
* Bilateral patent a. radialis
* For female volunteers of childbearing potential: Negative results of 2 pregnancy tests, the first test taken at the start of Screening and the second test taken from the morning urine within 3 hours before the start of the administration of the IMP as well as consent to use highly effective birth control from the last menstrual cycle prior to the start of the IMP until the end of the trial follow-up procedures. For definition of childbearing potential and highly effective birth control, see protocol.
* For male participants, their partner must not become pregnant during the trial. They should inform their partner about this.
* Subject agrees not to use alcohol for 2 days, not to use nicotine for 1 week, and not to use recreational drugs for 2 weeks prior to the first period until End of Trial
* Understanding of the trial procedures and be willing to follow the instructions of the Investigator or centre staff during the course of the clinical trial
* Written informed consent obtained from the subject

Exclusion criteria

* Known intolerance to benzodiazepines, flumazenil, opioids or any ingredients of the remimazolam drug products (e.g., dextran, lactose)
* Pregnancy, or currently breastfeeding
* Have current neurological disorder(s) (epilepsy, the presence of a brain tumour, a history of brain surgery, hydrocephalic disorders, depression needing treatment with anti-depressive drugs, a history of brain trauma, a subarachnoidal bleeding, TIA or cerebral infarct, psychosis or dementia, schizophrenia, alcohol or drug abuse).
* Have a disease(s) involving the cardiovascular system (hypertension, coronary artery disease, prior acute myocardial infarction, any valvular and/or myocardial disease involving decrease in ejection fraction, arrhythmias, which are either symptomatic or require continuous medication/pacemaker/automatic internal cardioverter defibrillator)
* Recent (<3 months) use of psycho-active medication (benzodiazepines, anti-epileptic drugs, Parkinson*s medication, neuroleptics, anxiolytics, anti-depressant drugs, opioid analgesics)
* A history of illicit drug or alcohol abuse within two years prior to screening
* Any ongoing condition considered by the Investigator as potentially relevant to the trial
* Any medical history considered by the Investigator as potentially relevant to the trial
* An employee or direct relative of an employee of the trial site, the CRO or the Sponsor.
* Resting HR <45 bpm or *90 bpm OR resting SABP <90 mmHg or *140 mmHg OR resting DABP <50 mmHg or *90 mmHg, except for those cases of mild hypertension or tachycardia which is considered to be secondary to anxiety or known white coat hypertension.
* Positive urine drug screening test (amphetamines, methamphetamines, benzodiazepines, barbiturates, marijuana, cocaïne, and opioids).
* Positive Covid-19 screening test
* Any participant as judged by the PI or Sub-Investigator to be inappropriate for the trial for any other reason
* Clinically significant, as judged by the Investigator abnormal ECG
* Clinically significant abnormal laboratory values
* Participation in a clinical trial of an Investigational Drug or Medical Device within three months prior to the Screening Visit
* Blood donation of *500mL within three months prior to Screening Visit
* Prior participation in this clinical trial. However, non-dosed drop-outs can participate in the trial again but will need to be-rescreened.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	31-03-2021
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	remifentanil, Ultiva GlaxoSmithKline GmbH Co KG
Generic name:	remifentanil
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	remimazolam
Generic name:	remimazolam

Ethics review

Approved WMO Date:	18-01-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-01-2021
Application type:	First submission

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-12-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2020-003806-30-NL
ClinicalTrials.gov	NCT04670471
CCMO	NL75782.056.20