A Randomized, Single-blind, Propofol-controlled Phase III Study Evaluating the Efficacy and Safety of Remimazolam in General Anesthesia in Adult Patients Undergoing Cardiac Surgery, including Follow-up Sedation in the Post-anesthesia Care Unit / Intensive Care Unit

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

Summary

ID

NL-OMON42664

Source
ToetsingOnline

Brief title
CNS7056-011

Condition

- Other condition
- Cardiac disorders, signs and symptoms NEC

Synonym
Anesthesia, narcosis

Health condition

narcose

Research involving
Human

Sponsors and support

Primary sponsor: PAION UK Limited
Source(s) of monetary or material Support: Paion UK Limited

Intervention

Keyword: Cardiac Surgery, General Anesthesia, Propofol-controlled

Outcome measures

Primary outcome

Successful sedation is defined as a Narcotrend index of 60 or less during at least 85% of the maintenance time and no rescue sedative medication administered. The maintenance starts at arrival at the operation theater and ends with the completion of the last skin suture. In clinics with no change in the location of the patient between induction and start of the surgery, maintenance starts when the anesthesiologist permits the surgical team to start the surgical procedure including preparation of the surgical site(s).

The primary endpoint is an efficacy endpoint.

Secondary outcome

The hemodynamic stability is expressed in terms of the amount of norepinephrine actually administered per body weight and time between start of the study medication (remimazolam or propofol) for induction of the general anesthesia

and the completion of the last skin suture. A lower amount of norepinephrine actually administered corresponds to a higher hemodynamic stability.

The key secondary endpoint is a safety endpoint.

Other Secondary Endpoints: Efficacy

* Use of rescue medication
* Time to loss of consciousness
* Time to intubation completed
* Course of Narcotrend index
* Intra-operative awakening/memory
* Body motion
* Time to post-operative awakening
* Time to extubation
* Time to discharge from ICU or PACU
* Time to discharge from hospital
* Amount of opioids administered
* Amount of neuromuscular blockers administered

Other Secondary Endpoints: Safety

* Adverse events
o Adverse events related to effects seen with medications known to be associated with abuse
o Adverse events related to renal function and coagulation
o Other adverse events

* Parameters of the cardiovascular and respiratory systems

o Blood pressure, heart rate

o Fall in mean arterial blood pressure by more than 30% from baseline at

induction of the general anesthesia

o Heart rate at induction below 50 bpm over at least one minute

o Low cardiac output syndrome

o Cardiac output index and ejection fraction

o Further parameters measured via PiCCO catheter

o Use of vasopressors and inotropes

o Use of milrinone together with epinephrine or norepinephrine

o Blood gas analysis

o Volume replacement

* Clinical laboratory: blood: hematology, clinical chemistry, coagulation

* Clinical laboratory: urine: standard parameters, viscosity

* Re-intubation

* Physical examination

* Electrocardiogram

* Cognitive function

* Post-operative delirium

Study description

Background summary

This study investigates drugs that lead to the loss of consciousness and maintain unconsciousness during the general anesthesia, also called narcosis.

Narcosis is required to perform the heart surgery that the patient needs to undergo. Narcosis is maintained until the planned surgical procedure on the heart is completed.

In addition to narcosis, pain reduction is required. This is to suppress reflexes of the body which could occur even under narcosis. Drugs that cause pain reduction are called analgesics. In the present study, pain reduction is achieved with the same analgesics that would be used if the patient was not in this study. The pain reduction is NOT subject of this study.
As a support to suppress reflexes, a medication for muscle relaxation will also be given during the narcosis, with the same medications as would be used as if the patient was not in this study. The muscle relaxation is also NOT a part of this study.

Based on the current medical standards, propofol is used very often as an anesthetic for heart surgery. It would also be possible to use narcotic gases. However, there is debate in the scientific community about narcotic gases having advantages over propofol or not. Benzodiazepines other than the drug tested in this study could also be used to achieve the necessary narcosis, but these *older* benzodiazepines have become less popular because of their comparably long off-set time.

In the present study, we would like to test a new drug from the class of benzodiazepines, which has a quick and predictable onset, and also offset of its effect at the end of the narcosis. Moreover, in contrast to other anesthetics, this new drug has an only minor impact on the performance of the heart and the circulatory system, i.e. the heart frequency and the blood pressure. This is extremely important during surgery on the heart.

The name of this new compound is remimazolam. Remimazolam is a drug under clinical investigation which means that it is not approved for narcosis by the competent authorities in Europe or any other region. By today, remimazolam was administered to approximately 920 subjects.

This study is conducted in several countries. A total of 530 patients are planned to be enrolled.

Study objective

The objectives are:
* to show non-inferiority of remimazolam compared with propofol in terms of successful maintenance of sedation defined as a Narcotrend index of 60 or less during at least 85% of the maintenance time without the use of rescue sedative medication.
* to show superiority of remimazolam compared with propofol in terms of hemodynamic stability defined as amount of norepinephrine administered per body weight and time during induction and maintenance.

* to assess the efficacy of remimazolam compared with propofol in terms of need for rescue sedative medication, time to loss of consciousness, time to intubation, depth of sedation as measured by Narcotrend, intra-operative awakening/memory, body motion, time to post-operative awakening, time to extubation after the end of the surgery, time to discharge from ICU (Intensive Care Unit) or PACU (Post-anesthesia Care Unit), time to discharge from hospital, amounts of opioids administered, and amount of neuromuscular blocker administered.
* to assess the safety of remimazolam compared with propofol in terms of adverse events (AEs), parameters of the cardiovascular and respiratory systems, the use of vasopressors and inotropes, physical examination, laboratory parameters, ECG, cognitive function, and post-operative delirium
* to investigate quality of life, pharmacokinetics, and to collect data potentially relevant for pharmacoeconomics in the setting of the study

Study design

Prospective, randomized, single-blind, active-controlled, multicenter, parallel-group, confirmatory, pivotal Phase III study

Intervention

* The screening phase (prior to the surgical procedure) includes recording of your medical history, the current diagnosis, the concomitant medication, the specification of the planned surgery, an electrocardiogram, laboratory tests and questionnaires regarding quality of life and mental performance. All of these elements can be collected within 21 days prior to the operation. Particularly for the results from standard laboratory tests done within 21 days prior to the operation, we ask the patient with the Informed Consent for his/her allowance to use them even if they were taken before signature on the Informed Consent Form. The aim is to avoid that samples for the same tests need to be taken again within a short time period. One blood sample only for the purposes of the study will be taken once during screening. The volume of blood taken by venipuncture will be 7.5 mL. At the end of the screening phase, randomization (the treatment allocation) will take place.
* The start of the general anesthesia: The monitoring systems routinely used during heart surgery will be connected (e.g. the electrocardiogram monitor). Moreover, an arterial catheter will be inserted to allow a study-specific monitoring system (PiCCO catheter) measuring and recording a number of parameters that are relevant for blood circulation. Together with other drugs that are used routinely for narcosis, the study medication (remimazolam) or the comparator medication (propofol) will be started. A central venous catheter will be inserted before or after the patient loses consciousness according to each hospital*s individual standards. There will be regular blood draws according to the standards of the hospital the patient is in, which would also be done if he/she was not in the study.

* The operation: During the operation, the administration of the study medication or the comparator medication will be continued to maintain the narcosis. At the same time, the parameters that are standard in heart surgery will be measured, which are blood pressure, heart frequency, electrocardiogram and other parameters. The PiCCO catheter will continue to measure and record parameters relevant for the blood circulation. Again, there will be regular blood draws according to the standards of the hospital the patient is in. One blood sample only for the purposes of the study will be taken once at the very end of the surgical procedure. The volume of blood taken will be 8.5 mL.
* The time in the Intensive Care Unit (ICU): Narcosis will be ended in a controlled manner which means that the study medication will be stopped so that the patient will wake up. While he/she is on the ICU, parameters relevant for blood circulation will be measured and recorded. One blood sample only for the purposes of the study will be taken once around 4 hours after the patient awoke. The volume of blood will be 7.5 mL, taken by venipuncture.
The patient will be discharged from the ICU as soon as the treating physicians are sure that you he/she is enough to breathe sufficiently and that he/she is in a stable medical condition. A few hours after the patient awoke, it will be checked whether he/she is clear about where he/she is and why why he/she in the clinic. Prior to discharge from the ICU or 24 hours after the end of the surgery (at the latest), the additional monitoring system (the PiCCO system) will be removed.
* Optional time on the ICU: If the patient needs medical care on the ICU beyond 4 hours after the end of the general anesthesia (in this context, the end of the narcosis is defined as the stop of the mechanical ventilation) or in case he/she needs medical care on the ICU for longer than 24 hours after the start of the general anesthesia, parameters relevant to assess the function of the heart, circulation and kidney function will be measured and recorded. If the patient receives the study medication for more than 24 hours in total, 4 extra blood samples will be taken around the time of the stop of the study medication if the patient agrees (see also point 2 below). The last of these blood draws will be performed 6 hours after the stop of the study medication. At that time, the patient might have been transferred from the ICU to another department. If the patient doesn*t agree with these last blood draws, he/she can participate in this study, nonetheless.
* Follow-up phase: This phase covers the time beginning after discharge or ICU and ending with discharge from hospital. During this time, there will be laboratory analyses from blood samples, electrocardiogram(s) and measurement of blood pressure and heart frequency. The patient will be asked to complete questionnaires regarding quality of life and mental performance again. Moreover, he/she will be asked about memories regarding the time before and after the narcosis.

During the entire duration of the study, the medication will be recorded completely. In case of adverse events or complications, these will be recorded, too.

As explained above, there will be blood samples only for the purposes of the study as follows:

1. For all patients: During screening, at the end of the surgery and a few hours after waking up from the narcosis. The total amount of blood needed for these 3 samples is 23.5 mL. This amount is roughly the contents of two tablespoons.

2. For patients who agree in taking extra blood if the study medication was given for more than 24 hours: a total of 12 mL will be taken. The amount of 12 mL is equal to one tablespoon.

Study burden and risks

The use of remimazolam can lead to adverse effects or complaints. The adverse effects or complaints observed so far comprise:

* Low blood pressure
* Slow heart rate
* Insufficient breathing
* Low blood oxygen
* Drowsiness
* Headache
* Unsteadiness
* Euphoric mood
* Agitation
* Feeling sick (nausea)
* Being sick (vomiting)
* Chills, feeling cold
* Low body temperature

To date, over 920 subjects have received remimazolam in studies, in doses lower and higher than that to be tested in this study.

As for other drugs of this class (benzodiazepines) there is a reversal medication available (called flumazenil) which has shown to reverse the effects of remimazolam. There is no such agent available for propofol.

It is possible that further risks emerge during the course of the study which are not known at this point in time.

The use of propofol can lead to the following adverse effects or complaints:

During anesthesia
* A feeling of pain at the site of injection (while the injection is given, before falling asleep)
* Low blood pressure

* Changes in the breathing pattern, shallow breathing
* Slow heart beat
* Twitching and shaking of the body, or a fit (may also happen while awake)
* Unusual color of the urine (may also happen while awake)
* Allergic reactions
* Stop of the heart beat
* Build up of fluid in lungs which can make very breathless (may also happen while awake)

After anesthesia
* Feeling sick (nausea)
* Being sick (vomiting)
* Headache
* Swelling and redness along a vein or blood clots
* Feeling sexually aroused
* High temperature (fever)
* Redness or soreness where the injection was given
* Being unconscious after the operation
* Tissue damage
* Pain and/or swelling at the site of injection

Other possible adverse effects
* Euphoric mood
* Involuntary movements
* Drug abuse or dependence
* Abnormal ECG
* Breakdown of muscle cells

The study procedures can be associated with risks or lead to complaints. The use of the study catheter (PiCCO catheter) comprises the insertion of an arterial line and of a central venous catheter. However, the insertion of a central venous catheter and and arterial line is a standard in heart surgery and would be performed also if the patient was not in the study. It might be though that the standard catheter used outside of this study is a different system (not PiCCO). Generally, intravenous or intraarterial lines (regardless whether PiCCO or any other system) can cause hematoma, infection, and thrombosis.

The study-specific physical examinations and blood draws can result in inconveniences or complaints.

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

* Patients scheduled for major non-emergency cardiac surgery assumed to require more than 2 hours of maintenance of general anesthesia and to require the use of extracorporeal circulation, including coronary bypass(es), valve replacement(s) and associated procedures and on-pump minimal invasive surgery
* Scheduled to receive mechanical ventilation via tracheal intubation (oropharyngeal or nasotracheal)
* Age at least 18 years
* Body Mass Index (BMI) 18 to * 40 kg/m2

Exclusion criteria

* Re-do cardiac surgery
* Surgical procedures that comprise the use of drugs and/or devices that are not approved for marketing
* Severe tricuspidal insufficiency

* Planned cooling below 32ºC
* History of or planned stop of circulation, e.g. due to repair of type A dissection of aorta or removal of thrombi from pulmonary artery
* Planned to receive epidural/spinal anesthesia together with general anesthesia
* Evidence of uncontrolled hepatic, central nervous system, respiratory, or metabolic dysfunction, or other clinically significant findings at screening that, in the investigator*s or medical monitor*s opinion, should exclude them from the study.
* Poorly controlled hypertension (e.g. systolic blood pressure *160 mmHg under antihypertensive medication at screening)
* Severe renal insufficiency or end-stage renal disease (creatinine clearance below 30 mL/min or estimated glomerular filtration rate below 30 mL/min/1.73 m2).
* Clinically uncontrolled coagulation abnormalities, or coagulation abnormalities not under adequate treatment
* Scheduled for heart or lung transplantation
* Infectious cardiac disorders (e.g. endocarditis, myocarditis)
* Sepsis
* Emergency surgery, status of shock or coma
* Ejection fraction from left ventricle of less than 20%
* Acute right heart failure

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-08-2015
Enrollment:	27
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Propofol 1% MCT Fresenius
Generic name:	Propofol
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Remimazolam
Generic name:	Remimazolam

Ethics review

Approved WMO Date:	28-09-2015
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	31-12-2015
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2014-004565-24-NL
ClinicalTrials.gov	NCT02523859
CCMO	NL54649.100.15