Evaluation of pharmacokinetic and *dynamic characteristics of norepinephrine for the augmentation of arterial blood pressure in healthy volunteers prior to and during general anesthesia

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Primary Objective:To assess the effect of the administration of norepinephrine on ABP while subjects are awake and subsequently, to study the effects of the interactions of norepinephrine and anesthetics (propofol and remifentanil) on ABP under...

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

Summary

ID

NL-OMON51910

Source
ToetsingOnline

Brief title
VASOCONTROL-I

Condition

- Other condition

Synonym
narcose, sleep medication

Health condition

general anaesthesia

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Interaction, Norepinephrine, Pharmacodynamics, Pharmacokinetics

Outcome measures

Primary outcome

- The relationship between plasma concentrations of norepinephrine and hemodynamics in terms of heart rate, cardiac index (CI), stroke volume index (SVI), and systolic, diastolic and mean arterial blood pressure (SAP, DAP, MAP, respectively) in awake circumstances.

- The relationship between plasma concentrations of norepinephrine and hemodynamics in terms of heart rate, cardiac index (CI), stroke volume index (SVI), and systolic, diastolic and mean arterial blood pressure (SAP, DAP, MAP, respectively) during standardized general anesthesia using propofol and remifentanil administration.

- The hemodynamic effects will be related to drug concentrations using PKPD analysis / modelling.

Secondary outcome

- Evaluation of the effect of the interaction between propofol, remifentanil and norepinephrine on hemodynamics during the induction of general anesthesia.

- Evaluation of the effect(s) of endogenous norepinephrine plasma concentration

and observed arousal on the relationship between administered dose (and plasma concentration) of norepinephrine and induced hemodynamic alteration(s).

- Internal validation of the Beloeil norepinephrine TCI PKPD model and acquisition of data in order to improve this model performance.

- Assessment of changes in mean systemic filling pressure prior to and after induction of general anesthesia, as assessed by arm stop-flow measurements by application of a rapidly inflated tourniquet.

- Evaluation of the dose-dependent effect of administered norepinephrine on plasma melatonin concentrations prior to and after induction of general anaesthesia.

- As a post-hoc exploratory analysis, mathematical indices reflecting the complex changes in raw EEG will be investigated to assess the effects of norepinephrine on consciousness.

Study description

Background summary

Intraoperative hypotension is an important risk-factor for the development of renal, myocardial and cerebral complications following surgery. Therefore, vasopressors such as norepinephrine, are commonly used for maintaining or restoring arterial blood pressure (ABP) during general anesthesia. There is however surprisingly little information on the dose-response of norepinephrine, both in awake patients, and in patients under general anesthesia. Also, the administration of norepinephrine is reactive, i.e. follows when hypotension has already occurred, and should ideally be proactive, i.e. to prevent hypotension from developing, ultimately minimizing the risk of postoperative organ injury.

Study objective

Primary Objective:
To assess the effect of the administration of norepinephrine on ABP while

subjects are awake and subsequently, to study the effects of the interactions of norepinephrine and anesthetics (propofol and remifentanil) on ABP under steady-state conditions during general anesthesia.

Secondary Objective(s):
- Evaluation of the effect of the interaction between propofol, remifentanil and norepinephrine on hemodynamics during general anesthesia.
- Evaluation of the effect(s) of endogenous norepinephrine plasma concentration on the relationship between administered dose (and plasma concentration) of norepinephrine and induced hemodynamic alteration(s).
- Evaluation of the Beloeil norepinephrine PKPKD model.
- Assessment of changes in mean systemic filling pressure prior to and after induction of general anesthesia, as assessed by arm stop-flow measurements by application of a rapidly inflated tourniquet.
- Evaluation of the dose-dependent effect of administered norepinephrine on plasma melatonin concentrations prior to and after induction of general anaesthesia.
- Evaluation of the dose-dependent effect of administered norepinephrine on EEG indices both during awake states and during general anesthesia.

Study design

This study is a prospective, single center, single period, crossover healthy volunteer study.

Intervention

After application of standard non-invasive cardiopulmonary monitoring, a peripheral intravenous line will be inserted. Subsequently, a radial artery catheter will be placed under local anesthesia for continuous monitoring of ABP and stroke volume/cardiac output. While the subject is awake, norepinephrine will be administered in a standardized step-up dosing scheme. After a wash-out phase, general anesthesia will be induced using a standardized propofol * remifentanil dosage administration. Once steady-state has been achieved, norepinephrine will be administered, again in a standardized step-up dosing scheme and surgical incision will be mimicked using noxious electrical tetanic stimulation.
During interventions, arterial blood samples will be drawn for the determination of drug concentrations. Hemodynamic effects (including ABP) will be continuously monitored.

Study burden and risks

In this study, we will provide standard anesthesia which we use normally in daily standard clinical practice. Subjects will be paid volunteers. An intravenous line (drug and fluid infusion) and an arterial line for blood

sampling and blood pressure/cardiac output monitoring, will be inserted on the non-dominant hand under local anesthesia, by a certified anesthesiologist using state-of the art techniques used daily during routine perioperative anesthetic care. Possible risks include hematoma, infiltration, embolism and phlebitis, but these risks are considered rare, especially in healthy volunteers. The total volume of blood sampling has no clinical impact. All other monitoring will be non-invasive and will not harm the subject. The application of noxious tetanic stimulation will have no negative impact since it will be applied solely under general anesthesia only, and will be used within the limitations as set by the manufacturer. Theoretically, tetanic stimulation may result in skin burns at the location of the electrodes. Norepinephrine, as well as propofol and remifentanil, are routinely used drugs in daily clinical practice. The use of these drugs in a controlled environment in healthy volunteers is safe. The administration of norepinephrine will remain within the dosing guidelines provided by the manufacturer. Well defined cessation criteria will prevent individuals from reaching a dangerously high ABP. The anesthesiologist remains in control of drug dosing.
During recovery, the subject may experience a sore throat secondary to airway manipulation while being under general anesthesia. Subjects may experience mild side-effects after recovery from general anesthesia that are directly related to the administration of anesthetic drugs. In general, current medical conditions may *worsen* temporarily in the period of the administration of general anesthesia. Nausea may occur directly after recovery. Also, the subject may experience a subtle drowsiness in the days following the administration of general anesthesia. Finally, it may appear that subjects experience a temporary sleeping disorder and/or a diminished ability to concentrate

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713 GZ
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713 GZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- American Society of Anesthesiologists (ASA) Physical Status I or II
- No exclusion criterion is present
- Informed, and willing to give written informed consent.

Exclusion criteria

- Refusal of the volunteer to participate
- Pregnancy
- Diseases 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)
- A difference > 15 mmHg in measured systolic or diastolic blood pressure value (SBP, DBP) between the left and right upper arm, as determined by non-invasive cuff oscillometry during the screening visit.
- An increased risk of difficult mask ventilation or tracheal intubation, as judged by the anesthesiologist-researcher.
- Pulmonary disease
- Gastric or endocrinologic diseases
- End-stage liver or kidney failure
- Use of tricyclic antidepressive medication or MAO inhibitors.

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):	21-07-2021
Enrollment:	36
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Noradrenalin, CF
Generic name:	Norepinephrin, Noradrenalin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Propofol, MCT/LCT Fresenius
Generic name:	propofol
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	remifentanil Mylan (Ultiva)
Generic name:	remifentanil
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	21-04-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	21-07-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-02-2022
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	EUCTR2020-005886-15-NL
CCMO	NL76998.056.21
Other	NL9312