Study of the cerebral effects of sevoflurane, propofol and remifentanil as measured by the spontaneous electro-encephalogram

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

Summary

ID

NL-OMON40298

Source
ToetsingOnline

Brief title
Improving the measurement of cerebral anesthetic drug effects

Condition

- Other condition
- Nervous system, skull and spine therapeutic procedures

Synonym
Anesthesia administration, Anesthesia monitoring

Health condition

gezonde vrijwilligers die onder anesthesie worden gebracht

Research involving
Human

Sponsors and support

Primary sponsor: MASIMO
Source(s) of monetary or material Support: Masimo Corporation;40 Parker;Irvine;CA 92618 USA

Intervention

Keyword: Electroencephalogram, Hypnotic drug effects, Inhalation Anaesthesia, Intravenous Anaesthesia

Outcome measures

Primary outcome

The predicted population plasma and effect-site concentration of propofol and

remifentanil at every steady state step during induction and recovery and

during bolus dose administration.

The measured individual plasmaconcentration of propofol and remifentanil at

every steady state step during induction and recovery and during bolus dose

administration.

The total dose administered over time for all drugs involved

The end-tidal sevoflurane concentration for every steady state step during

inductie and recovery and during the bolus administration

The multichannel raw EEG signals during the total study duration

The observers assesment of alertness and sedation scale at every steady state

step during the induction and during recovery fase.

The presence or abcense of a somatic response after a standardized tetanic

stimulation during every steady state step during induction and recovery.

Secondary outcome

The heart frequency, oxygen saturation (plethysmogram), non invasive bloodpressure measurement and end-tidal CO2 monitoring, as well as the signal of the Rainbow Acoustic Monitor (Masimo, Irvine, CA, USA) will be stored to ensure and document the safety of the volunteers throughout the study. Moreover, hemodynamic effects may also be set in relation to drug concentration changes in order to observe the timecourse differences between desired EEG effects and

Study description

Background summary

Multiple electroencephalographically derived indices have been developed to measure the cerebral hypnotic drug effect during anesthesia, using a variety of mathematical algorithms such as bispectral index, spectral entropy and spectral edge frequency. The complexity of the raw EEG is reduced to -an easy to interpret- number. It varies generally between 100 (fully awake patient) to 0 (an excessively sedated patient). The anesthesiologist adjusts his dosing scheme to target a number between a predefined range. (e.g. between 40 and 60)

These monitors are currently solidly integreted in clinical practice although they keep being hampered by several limitations. The most important problem is that they are not extracted from a direct neuro-physiological phenomenon that is known to be closely related to loss and return of consciousness, rather they have a probabilistic nature, indicating whether your probability of responsivenessis is high or low. You are never sure which EEG phenomenon relates to the index. Also, the number that relates to loss of consciousness rarely is the same as the number that indicates return of consciousness, which decreases the predictive value during recovery of anesthesia. Additionally, the dose response relationship differs on multiple parameters between each monitors. As such the performance of one monitor cannot be extrapolated to another. Finally, although the detection capacity of responses to verbal command is fairly good, EEG extracted numbers perform worse on correlation with movement after a noxious stimulus.

Most problems are related to the limited understanding of the relationship

between the changes in EEG and the underlying (insufficiently understood) neurophysiological mechanism that evokes (un)consciousness during anesthesia. Secondly, at the time of development of most monitors, the methods of drug administration were less reproducible to allow a more rational drug titration in a population of different demographics. The last two decades, major progress has been made on both issues. Therefore, new insights in neuro-physiology and better drug titration systems opens new perspectives to improve EEG derived data extraction.

Recently, Mashuire et al found a typical EEG characteristic that is correlated consistently with the loss and return of responsiveness, independent of the anesthetic used (inhalation or intravenous) and independent of the species tested (rats and humans). These findings do suggest that new information can be extracted from the raw EEG that has a much closer connection with the essential neurophysiological processes involved to evoke consciousness/unconsciousness or responsiveness/unresponsiveness. In this study we want to collect data that allows us to recognize these patterns on the EEG as a better measurement of consciousness/unconsciousness.

Additionally, we have the ability to use (clinically availlable) target controlled infusion techniques for propofol (plasma- and/or effect-site controlled) and end-tidal titrated sevoflurane (through a Zeus Ventilator (Draeger)) If we titrate our hypnotics through these more advanced and pharmacologically more rational titration methods, we may detect a more relevant correlation between the dose given and the EEG behavior. By adding remifentanil, we will also explore the alteration of performance of EEG derived information during interaction with opioids.

The obtained data may result in a breakthrough in the methodology to titrate anesthesia in a more predictable and reproducible way, because the extracted information relates closer to a neuro-physiological process related to (un)responsiveness. Moreover, the index may produce more consistent results whether inhaled anesthetics or intravenous drugs are given.

Study objective

Our first goal is collecting high quality raw EEG waves, - measured simultaneously on multiple locations of the brain - during a pharmacological reproducible anesthesia. The goal is to observe EEG patterns that allow the development of technology to monitor anesthesia drug effect more effectively. As we use the same neural network as a benchmark (all healthy volunteers will receive all 4 anesthesia regimens, we can detect typical EEG characteristics that are evoked by either sevoflurane (inhaled anesthesia) or propofol (intravenous anesthesia) with or without the addition of remifentanil. (powerful pain killer)
Our methodology allows to describe the following dose response relationships:
1) The dose response relationship in an identical population of healthy

volunteers between raw EEG effects at one hand and the responsiveness to noxious and non-noxious stimuli at the other hand evoked by steady state propofol concentrations.
2) The dose response relationship in an identical population of healthy volunteers between raw EEG effects at one hand and the responsiveness to noxious and non-noxious stimuli at the other hand evoked by steady state sevoflurane concentrations.
3) The dose response relationship in an identical population of healthy volunteers between raw EEG effects at one hand and the responsiveness to noxious and non-noxious stimuli at the other hand evoked by steady state propofol concentrations with addition of a high or low dose of remifentanil.
4) The dose response relationship in an identical population of healthy volunteers between raw EEG effects at one hand and the responsiveness to noxious and non-noxious stimuli at the other hand evoked by steady state sevoflurane concentrations with addition of a high or low dose of remifentanil.
5) In all upper situations the typical EEG characteristics compatible with loss and return of consciousness will be explored. (We hypothesize that loss and return of consciousness occur at very different drug concentrations but may have comparable features in EEG behavior)
6) After a step up steady state induction towards unconsciousness and a step down steady state recovery, a non steady-state bolus dose will be administered to evaluate the hysteresis between bolus dose and EEG effect. Both steady state and non steady state conditions need to be tested as they are a reflection of respectively the maintenance and induction of anesthesia.
7) Based on the observed dose response phenomena, we want to develop an optimized EEG derived index that meets the demands of the anesthesiologist better compared to other contemporary monitoring systems
These seven goals imply the need for some interventions:
1) Use of adjusted drug titration technology for the administered molecules.
2) Blood sampling at multiple intervals (only for the sessions with propofol and/or remifentanil) to adapt the predicted population concentration according to the individual measured pharmacokinetic-dynamic behavior. For sevoflurane this is not necessary as the end tidal concentration is already an individualized measurement.
3) Simultaneous high quality EEG monitoring on multiple locations of the brain
4) At every steady state, we need to determine whether the patient responds to the observers assessment of alertness and sedation scale.
5) At every steady state, we need to determine whether the patient responds to a standardized noxious stimulus (tetanic electrical current for short duration). This test is not performed when the patient is responsive to verbal stimuli.
6) The availability of a pharmacometricist who knows how to use NONMEM software. (Department of anesthesiology, UMCG)
7) The availability of signal processing engineers to develop and test multiple algorithms for EEG data extraction. (Masimo research and development department)
During all measurements, all hemodynamic and respiratory parameters (ECG, SpO2,

NIBP and ETCO2), as well as the non invasive Rainbow Acoustic Monitor (Masimo, Irvine, CA, USA)) are stored on a computer with Automated Data Collection software (ADC, Masimo Inc) en RUGLOOPII software (Demed, Temse, Belgium) for further posthoc analysis.
All data (inclusive residual bloodsamples) will be stored in order to allow future research that relates anesthetic effect with EEG response and humoral or endocrine stress responses.

Study design

Prospective randomized and stratified observational study with healthy volunteers.

Intervention

ll volunteers receive 4 standardized anesthesia sessions with at least one week recovery between each session. EEG characteristics are collected using a Masimo multichannel EEG recorder and compared post hoc for drug dependent characteristics. No off label drug use is applied in this study. All monitors used are CE approved and clinically applied in common anesthesia practice.

Study burden and risks

In this study, we will administer anesthesia in conditions that are comparable to clinical practice. The volunteers will be under the supervision of a certified anesthesiologist at all times and all techniques and methods described in this study are performed according to current state of the art daily practice. The risks of canulations may be haematoma, infiltrations of drug, embolisation of air and trombi, and flebitis. These are very rare complications in a healthy volunteer population.
The arteriel line will be placed in the arteria radialis of the non dominant hand under local anesthesia. It will be used for blood pressure measurements and blood sampling. The total volume of blood taken has no clinical consequences.
The small intravenous canulae will be introduced in a vein of the back of the hand or forearm, which may cause a slight temporary pain. Patients receive cristaloids through that canula. (Ringer Lactate 500ml).
All sensors used for vitale parameters are used routinely in clinical practice and are CE certified. They do not evoke any risk for the patient.
If the study takes longer than three hours a bladder scan will be performed at the end of the study and if deemed necessary, a single bladder catheterization will be performed.

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 volunteers aged 18 to 70 years.
18-35 y 6 men / 6 women
35-50 y 6 men / 6 women
50-70 y 6 men / 6 women

Exclusion criteria

Volunteer refusal
- Volunteer < 18 years and >70 years
- Exclusion criteria are weight less than 70% or more than 130% of ideal body weight
- Neurological disorder

- 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)
- Pulmonary diseases
- Gastric diseases
- Endocrinologic diseases
- Recent use of psycho-active medication or more than 20 g of alcohol daily.
-Drug abuse

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-01-2014
Enrollment:	36
Type:	Actual

Medical products/devices used

Generic name:	Electroencephalographic (EEG) monitoring with multiple electrodes
Registration:	Yes - CE intended use
Product type:	Medicine
Brand name:	Propofol Lipuro B Braun
Generic name:	propofol
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Remifentanil HCl Mylan

Generic name:	remifentanil
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	ULTANE
Generic name:	sevoflurane
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	08-02-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	31-07-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-06-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2013-000119-25-NL
CCMO	NL43238.042.13