Walking the Isobole of drug Interaction: Comparison of hemodynamic effects, cerebral and tissue oxygenation for 4 equipotent combinations of propofol and remifentanil

Published: 09-07-2013
Last updated: 22-04-2024

To investigate the effects of the different combinations of propofol and remifentanil on the isobole of TOL90 and to compare hemodynamics, cerebral and tissue oxygenation for each equipotent combination. To describe the combination of propofol and...

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

Summary

ID

NL-OMON40328

Source
ToetsingOnline

Brief title
Walking the isobole

Condition

- Other condition

Synonym
general anaesthesia

Health condition

anesthesie

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: anaesthesia, drug interaction, general anaesthesia, haemodynamical effects, Propofol, remifentanil, TCI

Outcome measures

Primary outcome

1) Absolute blood pressure, heart rate, cardiac output, cerebral and tissue

oxygenation and 2) changes in blood pressure, heart rate, cardiac output,

cerebral and tissue oxygenation from baseline (awake), which will be recorded

during standardized induction and maintenance of anesthesia using 4 different

combinations of remifentanil and propofol.

3) Total dose of atropine and ephedrine required to maintain heart rate >

40/min and mean arterial blood pressure > 50 mmHg, respectively.

4) Probability of tolerance of laryngoscopy, which will be tested after

induction and during a steady-state maintenance of anesthesia.

Secondary outcome

-

Study description

Background summary

In anesthesia, the synergistic interaction between hypnotics and opioids is

used daily to give adequate anesthesia and analgesia at significantly lower doses than would be needed if only one type of drug was given to reach the same effect. A lot of research has been done on the interaction of drugs on the desired effects, but the simultaneous interaction on the unwanted side effects is less well described. The response surface model of Bouillon et al. predicts all combinations of propofol and remifentanil effect-site concentrations that lead to an equipotent desired effect. Due to this model we now are able to predict which combinations of propofol and remifentanil will lead to, for instance, a desirable 90% probability of tolerance of laryngoscopy (TOL90) in the population. However, at this time we don*t know whether some of the combinations of propofol and remifentanil have a more favorable hemodynamic stability compared to other combinations on the same isobole, i.e. what the relationship is between these equipotent combinations and the undesired side effects such as hemodynamic instability (hypotension, changes in heart rate or cardiac output), decreases in cerebral or tissue oxygenation (both measured with near infrared spectroscopy).

Study objective

To investigate the effects of the different combinations of propofol and remifentanil on the isobole of TOL90 and to compare hemodynamics, cerebral and tissue oxygenation for each equipotent combination. To describe the combination of propofol and remifentanil on the TOL90 isobole with the least hemodynamic side effects. This study will help the anesthesiologist to increase the safety of induction and maintenance of anesthesia as we will be able to provide a priori information on those combinations with the least side effects. Currently, the post hoc (after the induction) monitoring of side effects is the only way to guarantee safety.

Study design

The goal of this study is to compare the hemodynamic effects (and tissue oxygenation) of different combinations of remifentanil and propofol that are known to produce an equipotent anesthetic effect (TOL90). This is a blinded interventional randomized study. Patients will be randomized to one of four pre-calculated combinations of propofol and remifentanil effect site concentration that produce TOL90. The anesthesiologist (staff member) in charge of airway management will be blinded for the medication administration and will quantify responsiveness to interventions. This allows maximal prevention of observation bias while the anesthesiologist or research assistant (medical doctor) in charge of drug administration and overall management has full knowledge of any administered medication and can intervene if required for patient safety. All study parameters will be determined and recorded by fully-automatic data management system.

Intervention

Patients will be randomized to receive one of four different combinations of remifentanil and propofol. All combinations are within the ranges used in normal clinical practice for induction and maintenance of anesthesia, but differ in their position on the TOL90 isobole.

Study burden and risks

All patients will receive a letter with information on this study at least one week before the planned operation date. Eligible patients will be asked for a written informed consent prior to the procedure. Patients will then be randomized to receive one of four predefined combinations of propofol and remifentanil. These drugs will be administered through commercially available target controlled infusion pumps. All concentrations and doses fall within the normal ranges used in clinical practice for induction of anesthesia, and within the ranges that patients would receive if they weren*t included in this study. Hemodynamic side effects are expected, (as always when inducing anesthesia) and if necessary these will be countered using escape medication mentioned in the protocol, which are also regularly used in clinical practice to counteract the same side effects. Respiratory side effects are also expected, as in any general anesthesia, and when these occur, they will be addressed using normal clinical routines such as airway maneuvers (such as chin lift, jaw thrust etc.) and manually assisted ventilation, as necessary. After the end of the study period, additional propofol or remifentanil will be administered if deemed necessary by the anesthesiologist to achieve the proper depth of anesthesia to allow tracheal intubation and mechanical ventilation, as in normal clinical practice.

All additional monitoring devices that are not part of normal clinical practice (cardiac output, cerebral and tissue oxygenation) are non-invasive and cause no harm, but provide considerably more detailed information on hemodynamics compared to blood pressure and heart rate alone. Therefore this study will not extend the burden or risks for the patients compared to normal clinical practice.

Contacts

Public
Universitair Medisch Centrum Groningen

hanzeplein 1
groningen 9713 EZ
NL
Scientific
Universitair Medisch Centrum Groningen

hanzeplein 1
groningen 9713 EZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- General anesthesia required for the procedure
- Age: 18 years and older
- American Society of Anesthesiologists (ASA) physical status I to III
- Written informed consent

Exclusion criteria

- Refusal to participate in this study
- Contra-indications for the use of propofol or remifentanil
- BMI > 35 kg/m2
- Central nervous system disorders (i.e. cerebrovascular accident, dementia, seizures, psychiatric disorders)
- Relevant hepatic disease (Child B or higher)
- Regular use of medication that affects the central nervous system (i.e. benzodiazepines, antidepressants, antipsychotics, antiepileptic drugs)
- Use of alpha-agonists or beta-blockers
- Overt signs of alcohol abuse
- Use of preoperative benzodiazepines (on the day of the study)
- Overt signs of drugs abuse
- Beta Blockers eye drips

Study design

Design

Study type: Interventional

Masking:	Single blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-03-2014
Enrollment:	80
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Propofol-Lipuro
Generic name:	Propofol
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Remifentanil HCl Mylan
Generic name:	Remifentanil HCl
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	09-07-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-09-2013
Application type:	First submission

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-12-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-01-2015
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	EUCTR2013-002883-20-NL
CCMO	NL45424.042.13