Pharmacodynamic interactions between remifentanil and dexmedetomidine (PIRAD)

Published: 01-05-2017
Last updated: 13-04-2024

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

Summary

ID

NL-OMON45644

Source
ToetsingOnline

Brief title
PD interaction of REMI and DMED

Condition

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

Synonym
Anesthesia administration, Anesthesia monitoring

Health condition

gezonde vrijwiligers welk onder anesthesie worden gebracht

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: Dexmedetomidine, Interaction, Pharmacodynamic, Remifentanil

Outcome measures

Primary outcome

Our primary objective is to observe changes in anesthetic depth measured by hypnotic and analgesic endpoints (MOAA/S, response to laryngoscopy and electroencephalogram (EEG) derived indices, during administration of dexmedetomidine or remifentanil and their combination, and to relate these effects to drug concentrations using PKPD modeling (see ch.8 for details).

Secondary outcome

- To improve existing EEG-indices by gaining full EEG-recordings and relate these to the anesthetic effects.
- To validate two previously developed TCI models (a dexmedetomidine model and a remifentanil model, see references in our protocol)
- To relate ventilatory changes induced by each of the agents and by the combination of both drugs, to the measured drug plasma concentrations.
- To relate hemodynamic changes induced by each of the agents and by the combination of both drugs, to the measured drug plasma concentrations.

Study description

Background summary

Dexmedetomidine (DMED) is an *2-adrenoceptor agonist which is used as a sedative in intensive care units and during surgical or diagnostic procedures. It has sedative, analgesic and anxiolytic properties and only minimally affects respiration. Studies investigating the analgesic properties of dexmedetomidine found that exposure resulting in mild to deep sedation seems to lack analgesic efficacy. This study is designed to investigate the interaction of dexmedetomidine with the potent analgesic remifentanil (REMI). Remifentanil is a strong analgesic, but lacks sedative potency. As such, these drugs might prove an interesting combination.
This study is designed to investigate whether the use of a combination of dexmedetomidine and remifentanil is clinically useful to provide anesthesia during surgical and diagnostic procedures and whether it could be used for anesthetic induction. Furthermore we aim to gain better insights in the required dosing regimens, the inter-individual variability in response towards the combination and the associated side effects. We are convinced that 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 oversedation, side effects and recovery times.

Study objective

Our objective is to map the pharmacokinetic / pharmacodynamic interaction between dexmedetomidine and remifentanil by observing changes in anesthetic depth, measured by hypnotic and analgesic endpoints such as modified observer*s assessment of alertness and sedation scale (MOAA/S), response to laryngoscopy and electroencephalogram (EEG) derived indices. These effects will be related to drug concentrations using pharmacokinetic/pharmacodynamic (PKPD) modeling.

Study design

Pharmacokinetic/pharmacodynamic modelling of a drug-drug interaction.

Intervention

All volunteers will receive 2 standardized anesthesia sessions with a washout period of at least one week between sessions. During the first session volunteers will receive dexmedetomidine, during the second session they will first receive remifentanil and afterwards the combination of drugs will be administered. Anesthetic depth will be evaluated by MOAA/S scores (see table 2) and testing of tolerance to laryngoscopy. Furthermore multichannel EEG-data will be collected to get insight in the drug dependent characteristics.
Measured effects will be related to drug plasma concentrations.

Study burden and risks

Dexmedetomidine and remifentanil are both frequently used drugs in clinical

practice. They are safe to use in controlled settings, such as an operating room or intensive care unit. The targets for dexmedetomidine used in this study will be higher than the package insert indicates, but our cessation criteria will prevent individuals from reaching dangerously high concentrations. Other studies using similar criteria have had individuals reaching target concentrations of up 14-16 ng/ml. Our maximum target concentration will be 8 ng/ml. An intravenous line (drug and fluid infusion) and an arterial line (for blood sampling and blood pressure/cardiac output monitoring) will be inserted before starting the study. Possible risks include hematoma, infiltration, embolism and phlebitis, but these risks are considered rare, especially in healthy volunteers. All other monitoring will be non-invasive.

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

- American Society of Anesthesiologists (ASA) Physical Status 1;- No medical history of significance;- No chronic use of medication, drugs, tobacco or more than 20 gr alcohol daily (oral contraceptives excluded). ;- Concerning the cognitive function: Volunteers are considered to have sufficient cognitive reserve if they are able to read and comprehend the patient information form, if they can adequately answer the anamnestic questions during the screening process and if they are allowed to provide legitimate written informed consent. ;- No selection will be made regarding ethnic background;- No exclusion criterium is present

Exclusion criteria

- Known intolerance to dexmedetomidine or remifentanil;- Volunteer refusal ;- Age < 18 years or >70 years ;- Pregnancy, or currently nursing;- Hairstyle with dreadlocks (EEG-monitoring will not be possible);- Body mass index (BMI) <18 or >30 kg/m2. ;- Neurological disorder (epilepsy, the presence of a brain tumor, 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). ;- 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)
- Recent use of psycho-active medication (benzodiazepines, anti-epileptic drugs, parkinson medication, anti-depressant drugs, opioids) or more than 20 g of alcohol daily.
- Bilateral non-patent a. ulnaris
- Any other condition relevant to the study

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):	01-05-2017
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Dexdor
Generic name:	Dexmedetomidine hydrochloride
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Remifentanil, HCL Mylan
Generic name:	Remifentanil
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	01-05-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-07-2017
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	EUCTR2017-000945-37-NL
Other	na
CCMO	NL61190.056.17