PK STUDY.

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON27257

Source
Nationaal Trial Register

Health condition

The interaction between proposal and ketamine when given for sedation in the ICU after cardiac surgery.

Sponsors and support

Primary sponsor: Leiden University Medical Center
Source(s) of monetary or material Support: Leiden University Medical Center

Intervention

Outcome measures

Primary outcome

Concentration of pharmaca in plasma.

Secondary outcome

Hemodynamic and sedation parameters.

Study description

Background summary

Postoperative sedation in patients requiring care in the intensive care unit (ICU) generally is achieved with the administration of short acting intravenous hypnotic agents that often are combined with longer acting morphinomimetic analgesics.

Propofol is an often used intravenous anesthetic agent with strong sedative effects with a rapid onset and short duration of action and a preferable recovery profile. Propofol that exerts its action through facilitation of the GABAA receptor, is widely used as sedative for induction and maintenance of anesthesia but also as sedative agent in patients in the ICU or PACU. Next to its sedative effects, propofol exhibits significant side effects jeopardizing hemodynamic stability and spontaneous respiration. These side effects are relatively mild in otherwise healthy patients but may induce serious unwanted effects in critically ill patients. Blood pressure is reduced in the presence of propofol both through direct vasodilatation as well as by myocardial depression. The respiratory depressant effects of propofol are central of origin and result in a reduced response to arterial pCO2 and may become clinically evident as a reduction in minute ventilation. Ketamine, a NMDA-receptor antagonist is another commonly used intravenous anesthetic agent with strong analgesic effects. Next to its analgesic and sedative effects S(+)-ketamine has hallucinogenic properties that limit its use in awake patients. In patients sedated through coadministration of an intravenous hypnotic agent like propofol, ketamine may however, be advantageous for it combines its sedative-analgesic properties with hemodynamic stimulatory effects that may reduce the hemodynamic side effects of intravenous hypnotic agents and may even limit the requirements of sympaticomimetics. In addition, several studies suggest that ketamine may attenuate the inflammatory response to cardiac surgery as induced by blood contact with the surface of the extracorporeal circuit apparatus, surgical trauma and reperfusion injury.

The pharmacodynamic interaction between 2 agents acting at similar receptor systems is often additive. This, in contrast to the interaction between agents that propagate their effect at different receptor sites that often is found to be synergistic. Synergism implies that one needs less of the combination of two agents than expected from the potency of the two agents separately. Because propofol is known for its action at the GABAA receptor and ketamine for its antagonism of the NMDA receptor one may expect the interaction between these agents to be synergistic. Next to the pharmacodynamic interaction propofol and ketamine may well also affect each other distribution and/or clearance and thus may also affect each other’s pharmacokinetics. The hemodynamic stimulatory effects of ketamine may influence the distribution and hepatic clearance of propofol. Propofol is known as a high hepatic extraction ratio drug, its clearance therefore may be sensitive to changes in hepatic blood flow.

In summary, propofol and ketamine may well be a promising anesthetic combination for sedation of patients after cardiac surgery ((coronary artery bypass grafting (CABG) and aortic valve surgery) in the ICU. This study aims to evaluate the interaction between these 2 agents with respect to their pharmacokinetics (distribution, redistribution and elimination) and pharmacodynamics (sedation, hemodynamic side effects and attenuation of the inflammatory response) in patients after cardiac surgery.

Study objective

1. To quantify the influence of propofol on the distribution, redistribution and elimination of ketamine and to evaluate the importance of hemodynamic parameters on the pharmacokinetics of ketamine;

2. To quantify the influence of ketamine on the distribution, redistribution and elimination of propofol and evaluate the importance of hemodynamic parameters on the pharmacokinetics of propofol;

3. To evaluate the pharmacodynamic interaction between propofol and ketamine with respect to the sedative and hemodynamic effects during sedation in patients sedated in the ICU.

Study design

From 1 hour post-operative until 5 hours afterwards.

Intervention

The study contains 2 study arms. Patients will be randomly assigned to one of these arms.

During arm A, 21 ICU patients will be sedated using a target controlled infusion of propofol at one of 3 fixed target propofol concentrations in addition to a target controlled infusion of S(+) ketamine with a variable target ketamine concentration to assure adequate sedation to a Ramsay sedation score of 4.
After 15 min of propofol infusion, and stabilization at the ICU, control values will be gathered and the ketamine infusion will be started. The target propofol concentration is maintained constant for the entire study period while the target ketamine concentration will be increased in a stepwise manner. Each step will be maintained for 12 min. After 48 minutes, the ketamine infusion will be terminated and eventually the target concentration of propofol will be adjusted to a level that is associated with a Ramsay score of 4 with a comfortable patient. 5 hours after initiation, the study is finished and propofol infusion may be terminated when the patient status meets the standard criteria for termination of mechanical ventilation and extubation.
During the the first hour, every 3 min the level of sedation is scored on the basis of the Ramsey sedation scale and hemodynamic parameters will be gathered. The last four hours,

sedation and hemodynamic parameters are collected at increasing intervals ranging from 15 to 60 min.

During arm B, 21 ICU patients will be sedated using a target controlled infusion of S(+) ketamine at one of 3 fixed target ketamine concentrations in addition to a target controlled infusion of propofol with a fixed and a variable target propofol concentration to assure adequate sedation to a Ramsay sedation score of 4.
After 15 min of ketamine infusion, and stabilization at the ICU, control values will be gathered and the variable propofol target controlled infusion will be started. The target ketamine concentration is maintained constant for the entire study period while the target propofol concentration will be increased in a stepwise manner. Each step will be maintained for 12 min. After 48 minutes, the propofol infusion will be lowered to 1 µg/ml and eventually the target concentration of ketamine will be adjusted to a level that is associated with a Ramsay score of 4 with a comfortable patient.
5 hours after initiation, the study is finished and ketamine and propofol infusion may be terminated when the patient status meets the standard criteria for termination of mechanical ventilation and extubation.
During the the first hour, every 3 min the level of sedation is scored on the basis of the Ramsey sedation scale and hemodynamic parameters will be gathered. The last four hours, sedation and hemodynamic parameters are collected at increasing intervals ranging from 15 to 60 min.

The fixed target concentrations of propofol and ketamine may be adjusted to the patients need when required to assure adequate sedation.

Contacts

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Eligibility criteria

Inclusion criteria

1. Scheduled for ventilation and sedation at the ICU post cardiac surgery;

2. Aged 18-80 years;

3. Being able to give written informed consent.

Exclusion criteria

1. Unable to give written informed consent;

2. Increased intracranial pressure;

3. Poor ventricular function;

4. Epilepsy;

5. Psychosis;

6. Glaucoma;

7. History of cerebrovascular incident < 1 year;

8. Pregnancy;

9. Documented or suspected soybean protein and/or drug allergy;

10. Morbid obesity (BMI > 35).

Study design

Design

Study type: Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-11-2011
Enrollment:	42
Type:	Anticipated

Ethics review

Positive opinion

Date:	13-11-2011
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 34050
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL2992
NTR-old	NTR3140
CCMO	NL32985.058.10

Register	ID
ISRCTN	ISRCTN wordt niet meer aangevraagd.
OMON	NL-OMON34050

Study results

Summary results
N/A