Pharmacokinetics of escalating doses of clonidine in ICU patients

Published: 30-11-2015
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Primary objective:Plasma levels of clonidine, in order to describe pharmacokinetic and pharmacodynamic properties of intravenous clonidine in critically ill ventilated ICU patients.Secondary objectives are: * to evaluate the effect of a 3-hr loading...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Deliria (incl confusion)
Study type	Interventional

Summary

ID

NL-OMON42780

Source
ToetsingOnline

Brief title
Clonidine kinetics 1.1

Condition

- Deliria (incl confusion)

Synonym
delirium

Research involving
Human

Sponsors and support

Primary sponsor: Deventer Ziekenhuis
Source(s) of monetary or material Support: door het deventer ziekenhuis zelf;evt aangevuld met subsidie van derden

Intervention

Keyword: clonidine, ICU, kinetics, ventilated patients

Outcome measures

Primary outcome

Pharmacokinetic data:

Clonidine plasma concentration at start of infusion at t=2, t=4, t=8 and t=12 h

Clonidine plasma concentration during study, once daily

Clonidine plasma concentration after stopping infusion at t=*+8, t=*+16, t=*

+24 h, and t=*+48 h (*= end of infusion).

clonidine concentrations in CVVH fluids

Secondary outcome

Hemodynamic parameters:

Heart rate, blood pressure, 2-hrly for the first 12 h, 8-hrly thereafter.

Laboratory parameters:

Serum creatinine daily

Albumin concentrations at study entry

12hrly urine creatinin clearance

Clinical parameters:

CAM-ICU delirium scale 8-hrly

RASS sedation scale 8-hrly

Need for fixation

CVVH or dialysis

Medication:

Total amounts and average daily doses of:

Noradrenalin, dobutamine, midazolam, morfine, propofol, haloperidol, other

antipsychotics.

Safety parameters:

Adverse events

Serious adverse events

Study description

Background summary

Many patients in intensive care units (ICU*s) require sedation and analgesia to tolerate mechanical ventilation and other ICU procedures. Commonly used GABA-ergic anaesthetics like propofol, midazolam and morphine have potential adverse effects that may increase morbidity, prolong ICU stay and provoke delirium. Recent studies have shown that sedation with alpha-2-adrenergic agonists may lead to a reduction of the total amount of GABA-ergic anaesthetics and reduction of delirium In clinical practice the alpha-2-adrenergic agent clonidine is widely used off label as an add-on sedative in mechanically ventilated patients who suffer from delirium, but there are no large studies proving that this therapy is effective and safe. Limited information exists on the pharmacokinetics of iv clonidine, especially in ICU patients. Besides, dosing regimens of clonidine differ widely among ICU*s in the Netherlands, and in the literature.

Study objective

Primary objective:
Plasma levels of clonidine, in order to describe pharmacokinetic and pharmacodynamic properties of intravenous clonidine in critically ill ventilated ICU patients.

Secondary objectives are:
* to evaluate the effect of a 3-hr loading schedule on serum levels and the time to reach steady state concentrations

* Plasma clonidine concentrations in patients with impaired renal function, renal replacement therapy and in patients with an altered distribution volume
* Hemodynamic parameters
* Sedation levels

Study design

This study is a single centre, prospective, open-label, non-randomized, dose escalation cohort study in 32 ICU patients.

Intervention

Clonidine is added to standard sedation at the time of first interruption of sedation. Three cohorts of eight will receive continuous infusions of iv clonidine in doses of 600, 1200, and 1800 µg/24h. The first half of each dosing group will not receive a loading dose and the second half will receive a loading dose of intravenous clonidine (triple infusion velocity during four hours). A fourth cohort with 8 patients will receive no clonidine, and serves as a control group

Study burden and risks

The burden associated with participation is minimal. Once daily blood samples, CAM-ICU scales, RASS scales and physical examinations required for the study are all routine daily practice on the ICU. Extra blood samples will be taken for pharmacokinetic modelling (7 + once daily from day 1 until end of infusion). Blood samples will be drawn from arterial catheters already in place. The addition of clonidine for sedation of critically ill patients is common practice in many ICU*s in the Netherlands and is generally thought to be safe. Although clonidine can cause hypotension and bradycardia, this is not considered a safety risk in a monitored environment.
The benefit of participation is the possibility to reduce the period of delirium during ICU stay. The relevance of this study lies in the widespread off-label use of clonidine in critically ill patients and the lack of consensus on administration and dosing. The purpose of this study is to develop a dosing regimen to achieve sufficient sedation without significant cardiovascular side effects.

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

* at least 18 years of age
* intubated
* sedated
at the start of the study. Because of the high incidence of delirium on the ICU in all age categories, all age groups > 18 years will be included.

Exclusion criteria

* Severe neurotrauma,
* Severe dementia (living in a nursing home)
* Inability to speak Dutch or English, which is one of the causes of not being able to use the CAM-ICU.
* The use of clonidine during the 96 hours before the start of the study.
* Bradycardia (<50/min)
* Severe hypotension (MAP < 65 after volume resuscitation and vasopressors)
* Pregnancy and lactation (pregnancy test are routinely performed in premenopausal women on the ICU).
* Epilepsy

* Known clonidine intolerance
* Liver cirrhosis (Child Pugh class C)
* Recent and acute myocardial infarction
* Severe heart failure (LVEF < 30%)
* Second or third degree AV-block without a permanent pacemaker
* Expected transfer to another hospital
When renal failure (eGFR <30ml/min): maximum dose of clonidine will be 1200mcg

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-02-2016
Enrollment:	32
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Catapresan
Generic name:	clonidine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	30-11-2015

Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	01-12-2015
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	13-07-2016
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

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	EUCTR2015-001699-23-NL
ClinicalTrials.gov	NCT02466373
CCMO	NL53097.075.15