A double blind, randomised, multicentre, active controlled, parallel-group, phase III trial to evaluate the efficacy, safety and pharmacokinetics of clonidine (hydrochloride) for sedation in children from birth to less than 18 years of age

Published: 12-02-2015
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Primary:To assess the non-inferiority of the sedative properties of continuous intravenous (i.v.) clonidine compared to continuous i.v. midazolam in mechanically ventilated children and adolescents (0 -

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

Summary

ID

NL-OMON42245

Source
ToetsingOnline

Brief title
CloSed

Condition

- Other condition

Synonym
Sedation

Health condition

sedatie

Research involving
Human

Sponsors and support

Primary sponsor: Universitätsklinikum Erlangen
Source(s) of monetary or material Support: Europese Unie- FP7

Intervention

Keyword: Clonidine, Paediatric Intensive Care, Sedation

Outcome measures

Primary outcome

The primary endpoint is defined as sedation failure within the study treatment

period (a maximum of seven days).

Sedation failure is defined as:

When a subject*s assessment results are:

Numerical Rating Scale (NRS) score <4 and COMFORT-B score >22

OR

Numerical Rating Scale (NRS) score <4 and COMFORT-B score <=22->=11 AND Nurse*s

Interpretation of Sedation (NISS) score 1

at a point during the study where no further increase in IMP dose is permitted

as described in the dose escalation scheme.

Secondary outcome

* Primary PK parameters estimated will be clearance (CL), volume of

distribution (VD) and inter-compartmental clearance (Q). Additional parameters

include Cmax, AUC, t1/2, Csteadystate, Ctrough. PK measurements will be made

using sparse opportunistic sampling.

* PK-PD modelling will seek to elucidate the relationship between IMP pharmacokinetics and sedation as measured by COMFORT-B score.

* The PK-PD covariate model will include demographics (e.g. age, weight), clinical characteristics (e.g. reason for admission) and pharmacogenomics (see Genetic parameters in Section 4.3.1)

* General safety and tolerability assessments

* Extent of withdrawal effects using the Sophia Observation withdrawal Symptoms- Paediatric Delirium (SOS-PD) scale measured three times a day in subjects who receive sedatives and/or opioids for 5 days or more and after cessation of treatment in all subjects for at least 24 hours after treatment.

* The extent of delirium measured by the SOS-PD scale.

* Rebound hypertension monitored for at least 72 hours post cessation of treatment.

* Percentage of respiratory depression per group.

* Adverse event reporting of symptoms indicative of post-ICU stress (e.g. nightmares, confusion, hallucinations).

* Neurodevelopment of subjects recruited in lower age group (from birth to 27 days)

Study description

Background summary

Although clonidine is recommended by PICU guidelines as an alternative to midazolam in critically ill children requiring i.v. sedation, there are limited clinical data on PK, efficacy and safety available which by no means meet the criteria for obtaining regulatory approval. Therefore, paediatricians are

forced to use the drug off-label in their patients. Moreover, age- and weight-adapted parenteral formulations are lacking. Clonidine might have favourable properties regarding tolerance and withdrawal, however, this has never been studied.

Study objective

Primary:
To assess the non-inferiority of the sedative properties of continuous intravenous (i.v.) clonidine compared to continuous i.v. midazolam in mechanically ventilated children and adolescents (0 - <18 years) admitted to a paediatric intensive care unit (PICU).

Secondary:
* To evaluate the safety and tolerability (including withdrawal effects) of clonidine compared with midazolam in ventilated children and adolescents admitted to PICU.
* To determine clonidine dose-dependent effects on sedation.
* To establish the pharmacokinetics - pharmacodynamics (PK-PD) relationship of clonidine for sedation in PICU.
* To compare the cumulative total morphine consumption/kg between the two arms in the first 48 hours of investigational medical product (IMP) administration.
* To determine if candidate genes predict adequate response to clonidine and midazolam in critically ill paediatric patients.
* To identify polymorphisms of clinical relevance to the sedative action of clonidine, midazolam and morphine.
* To correlate midazolam pharmacokinetics to polymorphisms of candidate genes.
* To correlate clonidine pharmacokinetics to polymorphisms of candidate genes.
* To correlate morphine pharmacokinetics to polymorphisms of candidate genes.

Study design

This is a double blind, randomised, active-controlled, parallel group, multicentre, phase III study.

Intervention

Clonidine as sedative with midazolam as active control.

Study burden and risks

Participants are at risk of inadequate sedation, therefore a dose escalation scheme has been established with frequent assessments of sedation.
There is a risk of cardiovascular side effects of clonidine which are easily manageable in the PICU setting.
The active control group receivesthe most likely drug to be administered for

this purpose anyway, its use in the framework of the clinical study does not cause any additional, study-related risk due to its pharmacological properties.

Subjects will have no direct benefits from their participation in the study other than particularly close monitoring of sedation levels and the application of a rational IMP dosing regimen based on PK-PD modelling.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Male or female aged from birth >34 weeks gestational age [GA] to <18 years
Admitted to PICU
Ventilated and anticipated need for sedation for at least 24 hours

Informed consent obtained from the subject*s parent(s) or legal guardian(s).

Exclusion criteria

Body weight less than 1200g and/ or gestational age of less than 34 weeks.
Body weight greater than 85kg.
Subjects under sedation for more than 72 hours
Post-resuscitation less than 24 hours.
Severe organ insufficiency
Abnormalities of the central nervous system impairing the judgement of sedation
Acute asthma
Known hypersensitivity to (non-)investigational medical products
Treatment on ECMO
Relatives to investigators or employees of study site
No informed consent obtained

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-11-2016
Enrollment:	150
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Catapresan
Generic name:	Clonidine hydrochloride
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Dormicum
Generic name:	Midazolam
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	12-02-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-06-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-03-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-05-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-02-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	01-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2014-003582-24-NL
CCMO	NL51551.078.15