Clinical trial results:
Effect of High-dose Target-controlled Naloxone Infusion on Pain and Hyperalgesia in Patients following Groin-Hernia-Repair.
A companion study to: Pharmacokinetics of High-dose Target-controlled Naloxone Infusion.

Summary

EudraCT number	2015-000793-36
Trial protocol	DK
Global end of trial date	14 December 2015

Results information

Result version number	v1 (current)
This version publication date	20 May 2021
First version publication date	20 May 2021

Trial information

Trial identification

Sponsor protocol code	HighNxGHR

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Multidisciplinary Pain Center 7612, Neuroscience Center
Sponsor organisation address	Blegdamsvej 9, Copenhagen, Denmark, 2100
Public contact	Mads U. Werner, Multidisciplinary Pain Center 7612, Neuroscience Center, Rigshospitalet, 0045 28257703, mads.u.werner@gmail.com
Scientific contact	Mads U. Werner, Multidisciplinary Pain Center 7612, Neuroscience Center, Rigshospitalet, 0045 28257703, mads.u.werner@gmail.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 December 2015
Global end of trial reached?	Yes
Global end of trial date	14 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal aim of the study was to investigate the pharmacokinetic construct validity of a target-controlled-infusion (TCI) of naloxone.

Protection of trial subjects:

During infusion of naloxone, participants will be monitored with ECG and measurements of pulse oximetry, blood pressure and respiratory rate. When naloxone is given, a physician and a nurse will be present if potential side effects should need any kind of treatment.
If requested by the participant, the rapid-onset, analgesic, rescue-opioid, alfentanil, will be administered, which, in less than one min completely will antagonize the effects of naloxone. Alfentanil is a well- known drug used in anaesthesia for immediate relief of acute pain. Alfentanil is initially given 7-15 microg/kg (1-2 ml/70 kg) and is administered in a titrated fashion until the desired analgesic effect is achieved. Common dose-dependent side effects are nausea, vomiting and sedation (> 10%). During the naloxone-infusion, the participant's resting pain is monitored. The naloxone-infusion is immediately stopped if the participant experiences pain levels > 5 (NRS 0-10).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 November 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 8
Worldwide total number of subjects	8
EEA total number of subjects	8

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	8
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The PK-participants will be recruited from our registry of volunteers who previously have participated in experimental pain studies at the Multidisciplinary Pain Center 7612, Rigshospitalet.

Pre-assignment

Screening details:

Evaluation by a physician.

Pre-assignment period milestones

Number of subjects started	8
Number of subjects completed	8

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Naloxone

Arm description:

All subjects receiving naloxone infusion

Arm type	Experimental
Investigational medicinal product name	Naloxone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Naloxone 4 mg/ml is delivered in glass ampoules of 100 ml (total content 400 mg). Naloxone is dissolved in a 0.9% NaCl solution: 1 liter of solution contains 9 grams of sodium chloride in sterile water (sodium-chloride 154 mmol/l; osmolarity 308 mmol/l).
A total dose of 3.25 mg/kg of naloxone will be administered in a step-wise approach for 75 minutes as follows: In the first minute (0-1 min) a bolus of 0.02 mg/kg will be given followed by an infusion of 0.23 mg/kg during 24 minutes (1-25 min). Afterwards (25-26 min) a bolus of 0.06 mg/kg will be administered followed by a 24-minute infusion of 0.69 mg/kg (min 26-50). Finally, a bolus of 0.18 mg/kg (50-51 min) will be given followed by a 24-minute infusion of 2.07 mg/kg (51-75 min).

Number of subjects in period 1	Naloxone
Started	8
Completed	8

Baseline characteristics

Reporting groups

Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	8	8	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	8	8	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	25.9		
full range (min-max)	24.4 to 28.9	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	8	8	
Height Units: cm			
arithmetic mean	182		
full range (min-max)	177 to 194	-	
Weight Units: kg			
arithmetic mean	79.6		
full range (min-max)	61 to 92	-	

Subject analysis sets

Subject analysis set title	Final analysis
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects in the study adhered to the same analysis set.

Reporting group values	Final analysis		
Number of subjects	8		

Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	8		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean	25.9		
full range (min-max)	24.4 to 28.9		
Gender categorical Units: Subjects			
Female	0		
Male	8		
Height Units: cm			
arithmetic mean	182		
full range (min-max)	177 to 194		
Weight Units: kg			
arithmetic mean	79.6		
full range (min-max)	61 to 92		

End points

End points reporting groups

Reporting group title	Naloxone
Reporting group description:	
All subjects receiving naloxone infusion	
Subject analysis set title	Final analysis
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects in the study adhered to the same analysis set.	

Primary: Plasma concentration of naloxone

End point title	Plasma concentration of naloxone[1]
End point description:	
End point type	Primary
End point timeframe:	
Time-points during the TCI-infusion 17,20,23,41,44,47,67,70 and 75 min, and after 76,77,78, 79,80,82,86,94,110,142,206 and 334 min.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analyses made in the current study was by population pharmacokinetics. This cannot be described by the terms provided here. No pairwise comparisons were made.

End point values	Naloxone	Final analysis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	8	8		
Units: ng/ml				
geometric mean (confidence interval 95%)	455.37 (399.77 to 510.97)	455.37 (399.77 to 510.97)		

Attachments (see zip file)	Concentration-time profiles for naloxone/Figure 1.png

Statistical analyses

No statistical analyses for this end point

Primary: Plasma concentration of naloxone-3-glucuronide

End point title	Plasma concentration of naloxone-3-glucuronide[2]
End point description:	
End point type	Primary
End point timeframe:	
Time-points during the TCI-infusion 17,20,23,41,44,47,67,70 and 75 min, and after 76,77,78, 79,80,82,86,94,110,142,206 and 334 min.	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analyses made in the current study was by population pharmacokinetics. This cannot be described by the terms provided here. No pairwise comparisons were made.

End point values	Naloxone	Final analysis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	8	8		
Units: ng/ml				
geometric mean (confidence interval 95%)	1220.94 (1098.18 to 1343.69)	1220.94 (1098.18 to 1343.69)		

Attachments (see zip file)	Concentration-time profiles for naloxone/Figure 1.png

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From time 0 min when the infusion starts to time 340 min when the participant is discharged.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	22
Reporting groups	
Reporting group title	Naloxone
Reporting group description: All subjects receiving naloxone infusion	

Serious adverse events	Naloxone		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Naloxone		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 8 (12.50%)		
General disorders and administration site conditions			
Anxiety	Additional description: The subject experienced general discomfort and anxiety at the beginning of the naloxone infusion.		
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The values for the endpoints given as mean (95%CI) do not provide valuable information, since the main objective of the current study is to measure concentrations of naloxone. We refer to the attached chart under the endpoints section.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30915992