Clinical trial results:
Pharmacodynamic interactions between remifentanil and dexmedetomidine (PIRAD)

Summary

EudraCT number	2017-000945-37
Trial protocol	NL
Global end of trial date	23 February 2018

Results information

Result version number	v1 (current)
This version publication date	23 March 2022
First version publication date	23 March 2022

Trial information

Trial identification

Sponsor protocol code	PIRAD-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03143972
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Medical Center Groningen
Sponsor organisation address	Hanzeplein 1, Groningen, Netherlands,
Public contact	spanjersberg, umcg, r.spanjersberg@umcg.nl
Scientific contact	spanjersberg, umcg, r.spanjersberg@umcg.nl

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	24 January 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 February 2018
Global end of trial reached?	Yes
Global end of trial date	23 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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 electrical stimuli, response to laryngoscopy and electroencephalogram (EEG) derived indices. These effects will be related to drug concentrations using pharmacokinetic/pharmacodynamic (PKPD) modeling

Protection of trial subjects:

A complete anaesthesia work station including a ventilator, were present in the study room. The study team included a board certified anaesthetist and nurse anaesthetist ensured the safety of our volunteers. Volunteers were well informed in advance, local anesthesia was given before inserting the arterial canula. We ensured someone was present in the room at all times so volunteers could indicate problems at all times.

Background therapy:

NA

Evidence for comparator:

NA

Actual start date of recruitment	28 June 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	27
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

We recruited healthy volunteers through an online advertisement on www.medians.nl, approved by the ethical committee. We recruited between 25-5-2017 and 31-1-2018 in the Netherlands.

Pre-assignment

Screening details:

Screened: 48
Included: 35 (including replacement of 5 drop-outs before second session)
Reasons for drop-out: failure of arterial cannula placement (n=3), withdrawal after 1st session by participant (n=1), withdrawal after 1st session by physician due to too much anxiety of volunteer during 1st session (n=1)

Period 1

Period 1 title	Dexmedetomidine
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Dexmedetomidine
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Dexmedetomidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Volunteers received dexmedetomidine via target-controlled infusion (Supplemental Digital Content 2, http://links.lww.com/ALN/C13). This target-controlled infusion was based on the pharmacokinetic model developed by Hannivoort (Hannivoort LN, Eleveld DJ, Proost JH et al.: Development of an optimized pharmacokinetic model of dexmedetomidine using target-controlled infusion in healthy volunteers. Anesthesiology 2015; 123:357–67) expanded with an equilibration rate constant (ke0) for the effect site of the MOAA/S estimated in the pharmacodynamic model by Colin (Colin PJ, Hannivoort LN, Eleveld DJ, et al: Dexmedetomidine pharmacokinetic–pharmacodynamic modelling in healthy volunteers: 1. Influence of arousal on bispectral index and sedation. Br J Anaesth 2017; 119:200–10). To avoid hypertensive
reactions, the infusion of dexmedetomidine was limited to 6 μg · kg−1 · h−1 for the first three infusion steps and was increased to 10 μg · kg−1 · h−1 for the two highest targets of 5 and 8 ng/ml.

Number of subjects in period 1	Dexmedetomidine
Started	30
Completed	30

Period 2	
Period 2 title	Remifentanil
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Remifentanil

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	remifentanil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A computer-controlled infusion, based on the pharmacokinetic–pharmacodynamic model developed by Eleveld et al. (Eleveld DJ, Proost JH, Vereecke H, Absalom AR, Olofsen E, Vuyk J, Struys MMRF: An allometric model of remifentanil pharmacokinetics and pharmacodynamics.Anesthesiology 2017; 126:1005–18) was used to target remifentanil effect-site concentrations.

Number of subjects in period 2	Remifentanil
Started	30
Completed	30

Period 3	
Period 3 title	Interaction
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Interaction

Arm description: -

Arm type	Experimental

Investigational medicinal product name	Dexmedetomidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Volunteers received dexmedetomidine via target-controlled infusion (Supplemental Digital Content 2, http://links.lww.com/ALN/C13). This target-controlled infusion was based on the pharmacokinetic model developed by Hannivoort (Hannivoort LN, Eleveld DJ, Proost JH et al.: Development of an optimized pharmacokinetic model of dexmedetomidine using target-controlled infusion in healthy volunteers. Anesthesiology 2015; 123:357–67) expanded with an equilibration rate constant (ke0) for the effect site of the MOAA/S estimated in the pharmacodynamic model by Colin (Colin PJ, Hannivoort LN, Eleveld DJ, et al: Dexmedetomidine pharmacokinetic–pharmacodynamic modelling in healthy volunteers: 1. Influence of arousal on bispectral index and sedation. Br J Anaesth 2017; 119:200–10). To avoid hypertensive
reactions, the infusion of dexmedetomidine was limited to 6 μg · kg−1 · h−1 for the first three infusion steps and was increased to 10 μg · kg−1 · h−1 for the two highest targets of 5 and 8 ng/ml.

Investigational medicinal product name	remifentanil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A computer-controlled infusion, based on the pharmacokinetic–pharmacodynamic model developed by Eleveld et al. (Eleveld DJ, Proost JH, Vereecke H, Absalom AR, Olofsen E, Vuyk J, Struys MMRF: An allometric model of remifentanil pharmacokinetics and pharmacodynamics.Anesthesiology 2017; 126:1005–18) was used to target remifentanil effect-site concentrations.

Number of subjects in period 3[1]	Interaction
Started	29
Completed	29

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: During the remifentanil period, one participant experienced thorax rigidity (known side effect of remifentanil). This person completed the remifentanil period, but did not enter the interaction period.

Baseline characteristics

Reporting groups	
Reporting group title	Dexmedetomidine

Reporting group description: -

Reporting group values	Dexmedetomidine	Total	
Number of subjects	30	30	
Age categorical			
Our total of 30 volunteers completing both study sessions were stratified into three age categories (18 to 34, 35 to 49, and 50 to 70 yr) with five males and five females in each category. Volunteers ranged from 18 to 67 yrs of age.			
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)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
All Subjects (18-70 years)	30	30	
Gender categorical Units: Subjects			
Female	15	15	
Male	15	15	

End points

End points reporting groups

Reporting group title	Dexmedetomidine
Reporting group description: -	
Reporting group title	Remifentanil
Reporting group description: -	
Reporting group title	Interaction
Reporting group description: -	
Subject analysis set title	All subjects (18-70 years)
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects within the study	

Primary: Tolerance of laryngoscopy

End point title	Tolerance of laryngoscopy
End point description:	
End point type	Primary
End point timeframe:	
At the end of each infusion step	

End point values	Interaction	All subjects (18-70 years)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	29	29[1]		
Units: yes / no				
tolerant	12	12		
non-tolerant	17	17		

Notes:

[1] - One person experienced thoraxi rigidity in period two, and did not enter period 3.

Attachments (see zip file)	Response surface - Tolerance of laryngoscopy/Tolerance of

Statistical analyses

Statistical analysis title	non-linear mixed effects modeling
Statistical analysis description:	
non-linear mixed effects modeling was used to describe exposure-response relationships of either drug alone (dexmedetomidine / remifentanil) and in combination (interaction).	
Comparison groups	Interaction v All subjects (18-70 years)

Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other[2]
Method	nonlinear mixed effects modeling
Parameter estimate	EC50
Point estimate	35
Confidence interval	
level	90 %
sides	2-sided
lower limit	25
upper limit	54

Notes:

[2] - nonlinear mixed-effects modeling

Adverse events

Adverse events information

Timeframe for reporting adverse events:

As per protocol, all adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. Serious adverse events will be reported to ethical comittee by PI through webportal ToetsingOnline

Assessment type	Non-systematic

Dictionary used

Dictionary name	Not applicable
Dictionary version	NA

Reporting groups

Reporting group title	All subjects-all periods

Reporting group description: -

Serious adverse events	All subjects-all periods		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	All subjects-all periods		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 30 (100.00%)		
Cardiac disorders			
Hypotension			
subjects affected / exposed	30 / 30 (100.00%)		
occurrences (all)	40		
Hypertension			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Bradycardia			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	6		
Syncope	Additional description: orthostatic syncope		

subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	11 / 30 (36.67%)		
occurrences (all)	13		
Vomiting			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure	Additional description: thoracic rigidity (known complication of remifentanil)		
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Respiratory depression			
subjects affected / exposed	25 / 30 (83.33%)		
occurrences (all)	40		

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.

Results are not interpretable in this online format. Please read article for results.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31425170