



Clinical trial results:

Pharmacokinetics of subcutaneously given dexmedetomidine in healthy volunteers

Summary

EudraCT number	2015-004698-34
Trial protocol	FI
Global end of trial date	30 November 2017

Results information

Result version number	v1 (current)
This version publication date	25 October 2020
First version publication date	25 October 2020
Summary attachment (see zip file)	ScDex_journal_article (41_Uusalo_ScDex_EJCP_in_press.pdf)

Trial information

Trial identification

Sponsor protocol code	ScDex_v1.0
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Turku University Hospital
Sponsor organisation address	Kiinamyllynkatu 4-8, Turku, Finland, 20520
Public contact	Department of Anesthesiology and In, University Of Turku, teijo.saari@utu.fi
Scientific contact	Department of Anesthesiology and In, University Of Turku, teijo.saari@utu.fi

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	30 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 May 2016
Global end of trial reached?	Yes
Global end of trial date	30 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this study is to investigate the pharmacokinetics of subcutaneously administered dexmedetomidine in healthy volunteers. The absolute bioavailability of subcutaneously administered dexmedetomidine will be calculated.

Protection of trial subjects:

Heart rate, intra-arterial blood pressure, and peripheral oxygen saturation were monitored throughout the clinical phase of the study (18 hours after dexmedetomidine dosing). The local tolerability of dexmedetomidine was assessed by the study participants and by visual inspection by the investigator immediately prior to drug administration (baseline) and at 1, 5, and 10 h. Subjects were instructed to inform the researchers any drug-related effects. Possible local dermal irritation, inflammation, bleeding, and swelling were monitored 18 hours after dexmedetomidine dosing.

Background therapy:

None

Evidence for comparator:

NA

Actual start date of recruitment	01 February 2016
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	Finland: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

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)	10
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	10
Number of subjects completed	10

Period 1

Period 1 title	First period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Intravenous arm

Arm description:

Subjects randomized to intravenous arm were administered 1-µg/kg doses of dexmedetomidine intravenously. Dexmedetomidine (Dexdor® 100 µg/ml, Orion Pharma, Espoo, Finland) were diluted in 0.9% saline solution (Natriumchlorid B. Braun® 9 mg/ml, B. Braun, Melsungen, Germany) and administered at a concentration of 8 µg/ml during 10 min by infusion (Perfusor® Space Infusion Pump, B. Braun).

Arm type	Active comparator
Investigational medicinal product name	dexmedetomidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

1-µg/kg dose, administered intravenously at a concentration of 8 µg/ml during 10 min by continuous infusion

Arm title	Subcutaneous arm
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Arm description:

Subjects randomized to subcutaneous arm were administered 1-µg/kg doses of dexmedetomidine intravenously. Dexmedetomidine (Dexdor® 100 µg/ml) was diluted in 0.9% saline solution and administered at a concentration of 50 µg/ml during 10 min by continuous infusion (Perfusor® Space Infusion Pump, B. Braun).

Arm type	Active comparator
Investigational medicinal product name	dexmedetomidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

1-µg/kg dose administered subcutaneously at a concentration of 50 µg/ml during 10 min by continuous infusion.

Number of subjects in period 1	Intravenous arm	Subcutaneous arm
Started	5	5
Completed	5	5

Period 2

Period 2 title	Second period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Intravenous arm

Arm description:

Subjects randomized to intravenous arm were administered 1-µg/kg doses of dexmedetomidine intravenously. Dexmedetomidine (Dexdor® 100 µg/ml, Orion Pharma, Espoo, Finland) was diluted in 0.9% saline solution (Natriumchlorid B. Braun® 9 mg/ml, B. Braun, Melsungen, Germany) and administered at a concentration of 8 µg/ml during 10 min by infusion (Perfusor® Space Infusion Pump, B. Braun).

Arm type	Active comparator
Investigational medicinal product name	dexmedetomidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

1-µg/kg dose, administered at a concentration of 8 µg/ml during 10 min by continuous infusion

Arm title	Subcutaneous arm
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Arm description:

Subjects randomized to subcutaneous arm were administered 1-µg/kg doses of dexmedetomidine intravenously. Dexmedetomidine (Dexdor® 100 µg/ml) was diluted in 0.9% saline solution and administered at a concentration of 50 µg/ml during 10 min by continuous infusion (Perfusor® Space Infusion Pump, B. Braun)

Arm type	Active comparator
Investigational medicinal product name	dexmedetomidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

1-µg/kg dose administered at a concentration of 50 µg/ml during 10 min by continuous infusion.

Number of subjects in period 2	Intravenous arm	Subcutaneous arm
Started	5	5
Completed	3	5
Not completed	2	0
Consent withdrawn by subject	1	-
Physician decision	1	-

Baseline characteristics

Reporting groups

Reporting group title	First period
Reporting group description: -	

Reporting group values	First period	Total	
Number of subjects	10	10	
Age categorical			
Units: Subjects			
Adults, 18-84 years	10	10	
Age continuous			
Units: years			
arithmetic mean	22.6		
standard deviation	± 2.2	-	
Gender categorical			
Units: Subjects			
Male	10	10	
Ethnic group			
Units: Subjects			
Caucasian	10	10	

Subject analysis sets

Subject analysis set title	Pharmacokinetics
Subject analysis set type	Full analysis

Subject analysis set description:

Data were log-transformed before statistical analysis, but nontransformed results are reported. The peak plasma concentrations and corresponding peak plasma concentration times were observed directly from the data. For each subject, the terminal log-linear phase of the plasma dexmedetomidine concentration-time curve was identified visually, and the elimination rate constant was determined by regression analysis on the basis of at least four time points. The elimination half-life was then calculated from the equation $t_{1/2} = \ln 2 / k_{el}$. The area under the dexmedetomidine plasma concentration-time curve was calculated using the trapezoidal method, with the linear trapezoidal rule for increasing concentrations and the logarithmic trapezoidal rule for decreasing concentrations. Apparent clearance and apparent volume of distribution of dexmedetomidine during the elimination phase were also calculated, with noncompartmental methods based on statistical moment theory.

Subject analysis set title	Pharmacodynamics
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Heart rate, intra-arterial blood pressure, and peripheral oxygen saturation were recorded at times of blood sampling (immediately prior to administration of dexmedetomidine (baseline) and thereafter at 5, 10, 15, 30, and 45 min and 1, 1.5, 2, 3, 5, 8, and 10 h after the start of dexmedetomidine administration). At the same time points, also psychomotor drug effects on vigilance and performance were assessed with visual analog scales (VAS). Subjective assessments (alert to drowsy, very good performance to very poor performance) were recorded with 100-mm horizontal VAS lines. For each pharmacodynamic variable, the AUC was determined using the trapezoidal rule.

Subject analysis set title	Local tolerability
Subject analysis set type	Safety analysis

Subject analysis set description:

The local tolerability of SC and IV administered dexmedetomidine was assessed with VAS scores by the study participants and by visual inspection by the investigator immediately prior to drug administration (baseline) and at 1, 5, and 10 h. Subjective effects (no local pain/strong pain, no irritation/strong

irritation, no pruritus/strong pruritus, no numbness/total numbness) were recorded. In the visual inspection by the investigator, possible local dermal irritation, inflammation, bleeding, and swelling were recorded. For each assessment, the AUC was calculated using the trapezoidal rule.

Reporting group values	Pharmacokinetics	Pharmacodynamics	Local tolerability
Number of subjects	10	10	10
Age categorical Units: Subjects			
Adults, 18-84 years	10	10	10
Age continuous Units: years			
arithmetic mean	22.6	22.6	22.6
standard deviation	± 2.2	± 2.2	± 2.2
Gender categorical Units: Subjects			
Male	10	10	10
Ethnic group Units: Subjects			
Caucasian	10	10	10

End points

End points reporting groups

Reporting group title	Intravenous arm
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Reporting group description:

Subjects randomized to intravenous arm were administered 1-µg/kg doses of dexmedetomidine intravenously. Dexmedetomidine (Dexdor® 100 µg/ml, Orion Pharma, Espoo, Finland) were diluted in 0.9% saline solution (Natriumchlorid B. Braun® 9 mg/ml, B. Braun, Melsungen, Germany) and administered at a concentration of 8 µg/ml during 10 min by infusion (Perfusor® Space Infusion Pump, B. Braun).

Reporting group title	Subcutaneous arm
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Reporting group description:

Subjects randomized to subcutaneous arm were administered 1-µg/kg doses of dexmedetomidine intravenously. Dexmedetomidine (Dexdor® 100 µg/ml) was diluted in 0.9% saline solution and administered at a concentration of 50 µg/ml during 10 min by continuous infusion (Perfusor® Space Infusion Pump, B. Braun).

Reporting group title	Intravenous arm
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Reporting group description:

Subjects randomized to intravenous arm were administered 1-µg/kg doses of dexmedetomidine intravenously. Dexmedetomidine (Dexdor® 100 µg/ml, Orion Pharma, Espoo, Finland) was diluted in 0.9% saline solution (Natriumchlorid B. Braun® 9 mg/ml, B. Braun, Melsungen, Germany) and administered at a concentration of 8 µg/ml during 10 min by infusion (Perfusor® Space Infusion Pump, B. Braun).

Reporting group title	Subcutaneous arm
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Reporting group description:

Subjects randomized to subcutaneous arm were administered 1-µg/kg doses of dexmedetomidine intravenously. Dexmedetomidine (Dexdor® 100 µg/ml) was diluted in 0.9% saline solution and administered at a concentration of 50 µg/ml during 10 min by continuous infusion (Perfusor® Space Infusion Pump, B. Braun).

Subject analysis set title	Pharmacokinetics
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Subject analysis set type	Full analysis
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Subject analysis set description:

Data were log-transformed before statistical analysis, but nontransformed results are reported. The peak plasma concentrations and corresponding peak plasma concentration times were observed directly from the data. For each subject, the terminal log-linear phase of the plasma dexmedetomidine concentration-time curve was identified visually, and the elimination rate constant was determined by regression analysis on the basis of at least four time points. The elimination half-life was then calculated from the equation $t_{1/2} = \ln 2 / k_{el}$. The area under the dexmedetomidine plasma concentration-time curve was calculated using the trapezoidal method, with the linear trapezoidal rule for increasing concentrations and the logarithmic trapezoidal rule for decreasing concentrations. Apparent clearance and apparent volume of distribution of dexmedetomidine during the elimination phase were also calculated, with noncompartmental methods based on statistical moment theory.

Subject analysis set title	Pharmacodynamics
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

Heart rate, intra-arterial blood pressure, and peripheral oxygen saturation were recorded at times of blood sampling (immediately prior to administration of dexmedetomidine (baseline) and thereafter at 5, 10, 15, 30, and 45 min and 1, 1.5, 2, 3, 5, 8, and 10 h after the start of dexmedetomidine administration). At the same time points, also psychomotor drug effects on vigilance and performance were assessed with visual analog scales (VAS). Subjective assessments (alert to drowsy, very good performance to very poor performance) were recorded with 100-mm horizontal VAS lines. For each pharmacodynamic variable, the AUC was determined using the trapezoidal rule.

Subject analysis set title	Local tolerability
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Subject analysis set type	Safety analysis
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Subject analysis set description:

The local tolerability of SC and IV administered dexmedetomidine was assessed with VAS scores by the study participants and by visual inspection by the investigator immediately prior to drug administration (baseline) and at 1, 5, and 10 h. Subjective effects (no local pain/strong pain, no irritation/strong irritation, no pruritus/strong pruritus, no numbness/total numbness) were recorded. In the visual inspection by the investigator, possible local dermal irritation, inflammation, bleeding, and swelling were

recorded. For each assessment, the AUC was calculated using the trapezoidal rule.

Primary: Bioavailability

End point title	Bioavailability
End point description:	
End point type	Primary
End point timeframe:	
0-10 hours	

End point values	Intravenous arm	Intravenous arm	Subcutaneous arm	Subcutaneous arm
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	5	5
Units: percent				
median (full range (min-max))	100 (100 to 100)	100 (100 to 100)	81 (49 to 97)	81 (49 to 97)

End point values	Pharmacokinetics			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: percent				
median (full range (min-max))	50 (0 to 100)			

Statistical analyses

Statistical analysis title	Comparison of pharmacokinetic parameters
Comparison groups	Intravenous arm v Intravenous arm v Subcutaneous arm v Subcutaneous arm
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Kruskal-wallis

Primary: Area under the plasma concentration-time curve

End point title	Area under the plasma concentration-time curve
End point description:	
End point type	Primary

End point timeframe:

0-10 hours

End point values	Intravenous arm	Intravenous arm	Subcutaneous arm	Subcutaneous arm
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	5	5
Units: nanogram x minutes per liter				
arithmetic mean (standard deviation)	117 (± 20)	117 (± 29)	74 (± 21)	74 (± 21)

End point values	Pharmacokinetics			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: nanogram x minutes per liter				
arithmetic mean (standard deviation)	117 (± 20)			

Statistical analyses

Statistical analysis title	Comparison of pharmacokinetic parameters
Comparison groups	Intravenous arm v Intravenous arm v Subcutaneous arm v Subcutaneous arm
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Kruskal-wallis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

0-10 hours

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	10
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Reporting groups

Reporting group title	Local tolerability
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Reporting group description: -

Reporting group title	Vital signs
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Reporting group description: -

Serious adverse events	Local tolerability	Vital signs	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Local tolerability	Vital signs	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	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

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29666901>