Clinical trial results:
Observational study of lidocaine levels in children after airway topicalisation during direct laryngotracheobronchosopy (DLTB).

Summary

EudraCT number	2014-005207-25
Trial protocol	GB
Global end of trial date	10 July 2018

Results information

Result version number	v1 (current)
This version publication date	05 April 2020
First version publication date	05 April 2020

Trial information

Trial identification

Sponsor protocol code	R03818

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	UK Research Ethics Service: 16/NW/0004

Notes:

Sponsors

Sponsor organisation name	Manchester University NHS Foundation Trust
Sponsor organisation address	Oxford Road, Manchester, United Kingdom,
Public contact	Dr Lynne Webster, Manchester University NHS Foundation Trust, +44 01612764125, research.sponsor@mft.nhs.uk
Scientific contact	Dr Lynne Webster, Manchester University NHS Foundation Trust, +44 01612764125, research.sponsor@mft.nhs.uk

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	10 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 July 2018
Global end of trial reached?	Yes
Global end of trial date	10 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To identify the peak blood levels of lidocaine in children undergoing an endoscopic examination of their airways under anaesthesia. The local anaesthetic lidocaine, is routinely applied to the airway during this procedure as part of the anaesthetic technique.

Protection of trial subjects:

The potential risks of insertion of a supplementary intravenous cannula include bruising, localized skin infection, and allergy to the antiseptic solution used (chlorhexidine gluconate 2% in ethanol 70%), or to the cannula dressing. However, these final two risks are not additional to standard, as all children are routinely cannulated during DLTB. The 0.9% saline flush used for cannula patency poses negligible risk, even in the case of extravasation. The blood samples would total 5.5ml of venous blood, and thus do not pose a risk of anaemia to our participants. In order to minimise any risk, this procedure will be performed by an senior anaesthetic registar or consultant anaesthetist in accordance with trust guidelines.

Background therapy:

In our current practice at Royal Manchester Children’s Hospital, general anaesthesia for direct laryngotracheobronchoscopy (DLTB) in children is carried out using a spontaneously breathing technique, and is routinely supplemented by lidocaine applied topically to the airway. This is applied to both the supraglottis and subglottis. The method of application is by a mucosal atomisation device. Varying doses, between 3 to 5mg per kg, are being used.
The study does not involve any change to the routine clinical care given to children undergoing DTLB. All children undergoing this procedure will receive lidocaine as described above, therefore the risk associated with the investigational medicinal product lidocaine in this clinical trial is no greater than the risk to which participants would be exposed were they to undergo DTLB at this hospital and not enter the trial.
The trial differs from routine care only in the measurement of lidocaine levels: a supplementary intravenous cannula will be inserted during general anaesthesia, in order to obtain four blood samples for lidocaine plasma levels.
This off-label use of lidocaine is established practice in our and other hospitals.

Evidence for comparator:

The population from which participants will be selected are children undergoing elective direct laryngotracheobronchosopy as part of their clinical management by the ENT surgeons in Royal Manchester Children's Hospital. There is no change to their primary procedure or anaesthetic technique. The only additional procedure they will undergo as part of the study is the insertion of a supplementary intravenous cannula during general anaesthesia, in order to obtain four blood samples for lidocaine plasma levels.

Actual start date of recruitment	01 November 2015
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	United Kingdom: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

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)	30
Children (2-11 years)	20
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The population from which participants will be selected are children undergoing elective direct laryngotracheobronchosopy as part of their clinical management by the ENT surgeons in RMCH. UK only study, recruitment period 18/01/2017 to 17/01/2018.

Pre-assignment

Screening details:

The population from which participants will be selected are children undergoing elective direct laryngotracheobronchosopy as part of their clinical management by the ENT surgeons in Royal Manchester Children's Hospital.

Period 1

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

Arms

Arm title	Whole cohort
Arm description: -	
Arm type	Whole cohort
Investigational medicinal product name	Lidocaine Hydrochloride Injection BP 2% w/v
Investigational medicinal product code	01502/0036
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Endotracheopulmonary use

Dosage and administration details:

3-5mg/kg total was the maximum dose

Number of subjects in period 1	Whole cohort
Started	50
Completed	50

Baseline characteristics

Reporting groups

Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	50	50	
Age categorical Units: Subjects			
< 1 year	12	12	
1-3 years	22	22	
> 3 years	16	16	
Age continuous Units: months			
median	23.5		
inter-quartile range (Q1-Q3)	12.25 to 37.75	-	
Gender categorical Units: Subjects			
Female	28	28	
Male	22	22	
Surgical Procedure Units: Subjects			
Diagnostic	27	27	
Therapeutic	23	23	
Weight Units: kg			
arithmetic mean	12.43		
standard deviation	± 5.11	-	
Dose Units: mg			
arithmetic mean	58.5		
standard deviation	± 23.94	-	
Dose Units: mg/kg			
median	5.0		
inter-quartile range (Q1-Q3)	4.93 to 5.00	-	
Volume Units: ml			
arithmetic mean	2.94		
standard deviation	± 1.16	-	
Plasma at 5mins Units: ng/ml			
arithmetic mean	2575.8		
standard deviation	± 1185.47	-	
Plasma at 10mins Units: ng/ml			
arithmetic mean	2960.0		
standard deviation	± 1154.45	-	

Plasma at 15mins Units: ng/ml arithmetic mean standard deviation	 2851.0 ± 1078.01	 -	
Plasma at 20mins Units: ng/ml arithmetic mean standard deviation	 2614.0 ± 986.85	 -	

Subject analysis sets

Subject analysis set title	Whole cohort
Subject analysis set type	Full analysis

Subject analysis set description:
Whole cohort

Reporting group values	Whole cohort		
Number of subjects	50		
Age categorical Units: Subjects			
< 1 year 1-3 years > 3 years			
Age continuous Units: months median inter-quartile range (Q1-Q3)			
Gender categorical Units: Subjects			
Female Male	28 22		
Surgical Procedure Units: Subjects			
Diagnostic Therapeutic			
Weight Units: kg arithmetic mean standard deviation	 ±		
Dose Units: mg arithmetic mean standard deviation	 ±		
Dose Units: mg/kg median inter-quartile range (Q1-Q3)			
Volume Units: ml arithmetic mean standard deviation	 ±		

Plasma at 5mins Units: ng/ml arithmetic mean standard deviation	±		
Plasma at 10mins Units: ng/ml arithmetic mean standard deviation	±		
Plasma at 15mins Units: ng/ml arithmetic mean standard deviation	±		
Plasma at 20mins Units: ng/ml arithmetic mean standard deviation	±		

End points

End points reporting groups

Reporting group title	Whole cohort
Reporting group description: -	
Subject analysis set title	Whole cohort
Subject analysis set type	Full analysis
Subject analysis set description:	
Whole cohort	

Primary: Peak plasma

End point title	Peak plasma[1]
End point description:	
End point type	Primary
End point timeframe:	
Full study	

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: Linear regression models were used to assess the relationship between peak plasma concentration and variables of age, weight, volume and dose. These do not compare groups as this is a single arm trial and do not fit in this system.
There is a significant quadratic relationship between peak plasma level and age (p=0.00973).
There is a significant quadratic relationship between volume of local anaesthetic utilised and peak plasma levels (p=0.0352).

End point values	Whole cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: ng/ml				
arithmetic mean (standard deviation)	3275 (± 1164.43)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to peak plasma

End point title	Time to peak plasma
End point description:	
End point type	Secondary
End point timeframe:	
Whole study	

End point values	Whole cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: mins				
median (inter-quartile range (Q1-Q3))	10 (10 to 15)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma over toxicity level

End point title	Plasma over toxicity level

End point description:

End point type	Secondary

End point timeframe:

Whole study

End point values	Whole cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: Subjects				
Yes	4			
No	46			

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse Effect

End point title	Adverse Effect

End point description:

End point type	Secondary

End point timeframe:

Whole Study

End point values	Whole cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: Subjects				
Yes	0			
No	50			

Statistical analyses

No statistical analyses for this end point

Secondary: Fluid bolus

End point title	Fluid bolus

End point description:

End point type	Secondary

End point timeframe:

Whole study

End point values	Whole cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: Subjects				
Yes	7			
No	43			

Statistical analyses

No statistical analyses for this end point

Secondary: Signs of LA toxicity

End point title	Signs of LA toxicity

End point description:

End point type	Secondary

End point timeframe:

Whole study

End point values	Whole cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: Subjects				
Yes	0			
No	50			

Statistical analyses

No statistical analyses for this end point

Secondary: Second cannula removed

End point title	Second cannula removed

End point description:

End point type	Secondary

End point timeframe:

Whole Study

End point values	Whole cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	50			
Units: Subjects				
Yes	45			
No	5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All adverse events and adverse reactions up to 24hours after surgery were to be recorded on the Adverse Events Recording form and will be reviewed by the sponsor at routine study monitoring visits.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	1

Reporting groups

Reporting group title	Whole cohort

Reporting group description: -

Serious adverse events	Whole cohort		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 50 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Whole cohort		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 50 (0.00%)		

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: There were no adverse events within this trial.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 December 2016	Substantial amendment 1: 1. Change to laboratory providing analysis for primary endpoint. 2. Addition of further protocol authors.
01 March 2017	Substantial amendment 2: 1. Change to protocol to allow initial approach to the parents of potential trial participants by telephone and letter. 2. Extension to study to July 2018 (planned date of last participant last visit). 3. Minor typographical and administrative changes to protocol. 4. Addition of new covering letter to send with study information leaflet to potential recruits.

Notes:

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.

None.

Notes: