Clinical trial results:
Paracetamol and setrons : drug interactions in the management of pain after tonsillectomy in children

Summary

EudraCT number	2011-002213-12
Trial protocol	FR
Global end of trial date	12 June 2012

Results information

Result version number	v1 (current)
This version publication date	27 May 2021
First version publication date	27 May 2021
Summary attachment (see zip file)	Article (Ramirez_et_al-2015-European_Journal_of_Pain.pdf)

Trial information

Trial identification

Sponsor protocol code	I10 005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01432977
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CHU de Limoges
Sponsor organisation address	2 Avenue Martin Luther King, Limoges, France,
Public contact	Principal Investigator, Pr Nathan-Denisot, nathan@unilim.fr
Scientific contact	Principal Investigator, Pr Nathan-Denisot, 33 5 55 05 63 00, nathan@unilim.fr

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 October 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 June 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectif of this study is to demonstrate that the association paracetamol / ondansetron is not as effective as the association paracetamol / droperidol in the treatment of pain in children following tonsillectomy.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable french regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. The following additional measure(s) were in place for the protection of trial subjects:
All patients will receive injectable paracetamol at a dose of 15 mg / kg slowly from the start of surgery, then 15 mg / kg every 6 hours for the first 24 hours. The patient will therefore receive a total dose of 60 mg / kg per day in 4 administrations. In addition, Nifluril®, intra-rectally started in the operating room, at a dose of 400 mg / 10 kg in two doses per day will be administered to all patients for 24 hours.
During surgery, the anesthesiologist will administer an IV bolus of morphine of 75 µg / kg. Then in SSPI, a morphine titration at a dose of 25 µg / kg i.v. every ten minutes for a CHEOPS scale <8 at rest will be used.
If pain persists (CHEOPS scale> 8 at rest) after discharge from the SSPI in the department, codeine syrup (Codenfan®) will be administered at a dose of 0.5 mg / kg every 4 hours. If the pain persists (CHEOPS scale> 8 at rest), the dose of codeine administered will then be 0.75 mg / kg. Finally, in case of still persistent pain, a dose of codeine of 1 mg / kg will be administered. In case of persistent pain despite these treatments, a doctor will be contacted to decide on the patient's management.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	01 August 2011
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	France: 69
Worldwide total number of subjects	69
EEA total number of subjects	69

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)	69
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 study was carried out in the Hôpital Mère-Enfant of the Limoges University Hospital Center between October 2011 and June 2012. A total of 70 patients aged between 2 and 7 years scheduled for tonsillectomy ± adenoidectomy were included.

Pre-assignment

Screening details:

Patients aged between 2 and 7 years scheduled for tonsillectomy ± adenoidectomy were enrolled Exclusion criteria included a hospital stay of less than 24 hours, patients already on pain medication, and allergic patients with a contraindication to one of the study drugs.

Period 1

Period 1 title	Overal trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

The protocol will be carried out in simple blind. The two anti-emetics to be administered will not be known to the patient included, nor to the person collecting the CHEOPS and PONV scores, but may be known by the anesthesiologist or the nurse of the SSPI or the department.
This is because the first dose of ondansetron or droperidol will be administered during the surgery by the anesthesiologist or anesthesia nurse; but the person collecting the scores will not be able to know which substance.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ondansetron

Arm description:

Patient will receive intravenously ondansetron at a dose of 0.1 mg / kg (dose1) along with betamethasone. After surgery, if the ANCOVA score is> 1, then the patient will receive a new ondansetron dose at a dose of 0.1 mg / Kg IV (dose 2).
Thereafter, if the ANCOVA score is still> 1 droperidol dose at 0.05mg/kg will be administered (dose3).

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

Dosage and administration details:

Patient will receive intravenously ondansetron at a dose of 0.1 mg / kg (dose1) along with betamethasone. After surgery, if the ANCOVA score is> 1, then the patient will receive a new ondansetron dose at a dose of 0.1 mg / Kg IV (dose 2).

Arm title	dorperidol

Arm description:

Patient will receive intravenously dorperidol at a dose of 0.05 mg / kg (dose1) along with betamethasone. After surgery, if the ANCOVA score is> 1, then the patient will receive again droperodol at a dose of 0.05 mg / kg (dose 2).
Thereafter, if the ANCOVA score is still> 1 ondesetron at a dose of 0.1mg/kg will be administered (dose3).

Arm type	Active comparator

Investigational medicinal product name	dorperidol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Patient will receive intravenously dorperidol at a dose of 0.05 mg / kg (dose1) along with betamethasone. After surgery, if the ANCOVA score is> 1, then the patient will receive again droperodol at a dose of 0.05 mg / kg (dose 2).
Thereafter, if the ANCOVA score is still> 1 ondesetron at a dose of 0.1mg/kg will be administered (dose3).

Number of subjects in period 1	Ondansetron	dorperidol
Started	35	34
Completed	35	34

Baseline characteristics

Reporting groups

Reporting group title	Ondansetron

Reporting group description:

Patient will receive intravenously ondansetron at a dose of 0.1 mg / kg (dose1) along with betamethasone. After surgery, if the ANCOVA score is> 1, then the patient will receive a new ondansetron dose at a dose of 0.1 mg / Kg IV (dose 2).
Thereafter, if the ANCOVA score is still> 1 droperidol dose at 0.05mg/kg will be administered (dose3).

Reporting group title	dorperidol

Reporting group description:

Patient will receive intravenously dorperidol at a dose of 0.05 mg / kg (dose1) along with betamethasone. After surgery, if the ANCOVA score is> 1, then the patient will receive again droperodol at a dose of 0.05 mg / kg (dose 2).
Thereafter, if the ANCOVA score is still> 1 ondesetron at a dose of 0.1mg/kg will be administered (dose3).

Reporting group values	Ondansetron	dorperidol	Total
Number of subjects	35	34	69
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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	4.43	4.18	
standard deviation	± 1.6	± 1.4	-
Gender categorical Units: Subjects			
Female	10	20	30
Male	25	14	39

End points

End points reporting groups

Reporting group title	Ondansetron

Reporting group description:

Patient will receive intravenously ondansetron at a dose of 0.1 mg / kg (dose1) along with betamethasone. After surgery, if the ANCOVA score is> 1, then the patient will receive a new ondansetron dose at a dose of 0.1 mg / Kg IV (dose 2).
Thereafter, if the ANCOVA score is still> 1 droperidol dose at 0.05mg/kg will be administered (dose3).

Reporting group title	dorperidol

Reporting group description:

Patient will receive intravenously dorperidol at a dose of 0.05 mg / kg (dose1) along with betamethasone. After surgery, if the ANCOVA score is> 1, then the patient will receive again droperodol at a dose of 0.05 mg / kg (dose 2).
Thereafter, if the ANCOVA score is still> 1 ondesetron at a dose of 0.1mg/kg will be administered (dose3).

Primary: postoperative pain score

End point title	postoperative pain score

End point description:

Assessed using CHEOPS (Children’s Hospital of Eastern Ontario Pain Scale)
It's a behavioural scale for evaluating post-operative pain in young children (McGrath et al., 1985). It has been validated
for children aged between 1 and 7 years [scores of 4 (normal) to 13 (maximum pain)] and it was used in this study.Pain scores were recorded by research nurses 30 min after admission and when leaving the recovery room, and then on the ward at 4 h after acetaminophen administration

End point type	Primary

End point timeframe:

4 h after the intraoperative co-administration of acetaminophen and ondansetron or droperidol,

End point values	Ondansetron	dorperidol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	34		
Units: Score				
median (standard deviation)	4.97 (± 0.89)	5.35 (± 1.18)		

Statistical analyses

Statistical analysis title	Wilcoxon
Comparison groups	Ondansetron v dorperidol

Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2355
Method	Wilcoxon (Mann-Whitney)

Secondary: Analysis of morphine and codeine consumption for 24 hours post intervention

End point title	Analysis of morphine and codeine consumption for 24 hours post intervention

End point description:

Comparison of the averages of morphine titrations in SSPI between group 1 and group 2.

End point type	Secondary

End point timeframe:

24 hours post intervention

End point values	Ondansetron	dorperidol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	34		
Units: µl				
arithmetic mean (standard deviation)	279.50 (± 271.53)	97.65 (± 201.53)		

Statistical analyses

Statistical analysis title	Wilcoxon
Comparison groups	Ondansetron v dorperidol
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0041
Method	Wilcoxon (Mann-Whitney)

Secondary: Comparison of the cumulative incidences of nausea and vomiting 24 hours after surgery between group 1 and group 2

End point title	Comparison of the cumulative incidences of nausea and vomiting 24 hours after surgery between group 1 and group 2

End point description:

Comparison of the cumulative incidences of nausea and vomiting 24 hours after surgery between group 1 and group 2

End point type	Secondary

End point timeframe:
At 24 h after suirgery

End point values	Ondansetron	dorperidol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	34		
Units: Number of patients	4	6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Until 24 h after the last patient visit	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups	
Reporting group title	Ondansetron

Reporting group description:

Patient will receive intravenously ondansetron at a dose of 0.1 mg / kg (dose1) along with betamethasone. After surgery, if the ANCOVA score is> 1, then the patient will receive a new ondansetron dose at a dose of 0.1 mg / Kg IV (dose 2).
Thereafter, if the ANCOVA score is still> 1 droperidol dose at 0.05mg/kg will be administered (dose3).

Reporting group title	dorperidol

Reporting group description:

Patient will receive intravenously dorperidol at a dose of 0.05 mg / kg (dose1) along with betamethasone. After surgery, if the ANCOVA score is> 1, then the patient will receive again droperodol at a dose of 0.05 mg / kg (dose 2).
Thereafter, if the ANCOVA score is still> 1 ondesetron at a dose of 0.1mg/kg will be administered (dose3).

Serious adverse events	Ondansetron	dorperidol	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 35 (5.71%)	0 / 34 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Feeding disorder			

subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ondansetron	dorperidol	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 35 (11.43%)	9 / 34 (26.47%)	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Nervous system disorders			
Hypersialorrhea			
subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Peroperative bleeding			
subjects affected / exposed	0 / 35 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Postoperative bleeding			
subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
fever			
subjects affected / exposed	1 / 35 (2.86%)	0 / 34 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Mouth ulceration			
subjects affected / exposed	0 / 35 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	0 / 35 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Pain			

subjects affected / exposed	1 / 35 (2.86%)	1 / 34 (2.94%)	
occurrences (all)	1	1	
Vomiting			
subjects affected / exposed	0 / 35 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Desaturation			
subjects affected / exposed	0 / 35 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	0 / 35 (0.00%)	1 / 34 (2.94%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
HYPERTHERMIA			
subjects affected / exposed	1 / 35 (2.86%)	1 / 34 (2.94%)	
occurrences (all)	1	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