Clinical trial results:
Phase 1 study of use of 5% Carbogen in treatment of paediatric non-convulsive status epilepticus

Summary

EudraCT number	2011-005318-12
Trial protocol	GB
Global end of trial date	12 January 2015

Results information

Result version number	v1 (current)
This version publication date	29 July 2016
First version publication date	29 July 2016

Trial information

Trial identification

Sponsor protocol code	NCTU:CONCEPT1

Additional study identifiers

ISRCTN number	ISRCTN80717736
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	EudraCT: 2011-005318-12, UKCRN ID: 12223

Notes:

Sponsors

Sponsor organisation name	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Sponsor organisation address	Freeman Hospital, Freeman Road,, Newcastle upon Tyne, United Kingdom, NE7 7DN
Public contact	Dr Rob Forsyth, The Newcastle upon Tyne Hospitals NHS Foundation Trust, 44 191 256 3820, r.j.forsyth@newcastle.ac.uk
Scientific contact	Dr Rob Forsyth, The Newcastle upon Tyne Hospitals NHS Foundation Trust, 44 191 256 3820, r.j.forsyth@newcastle.ac.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	07 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 January 2015
Global end of trial reached?	Yes
Global end of trial date	12 January 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the feasibility of the protocol and of data collection (blood gases, respiratory rate, breathlessness) and to confirm recruitment rates to inform the design of a definitive randomised controlled trial.

Protection of trial subjects:

DMC suggested extension of EEG monitoring of participants post inhalation of IMP from 2 to 15 minutes and this was incorporated into substantial amendment 3 to the protocol.

Background therapy:

Participants attended hospital with non-convulsive status epilepticus for control of seizure therefore there were no restrictions on concurrent medications to be used.

Evidence for comparator: -

Actual start date of recruitment	11 March 2013
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	United Kingdom: 6
Worldwide total number of subjects	6
EEA total number of subjects	6

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)	5
Adolescents (12-17 years)	1
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The parents of eligible children known to the paediatric neurology services at site and deemed "at risk" of developing non-convulsive status epilepticus (NCSE) were notified, by letter, of the trial. Otherwise the parents of potentially eligible children were approached upon presentation at hospital.

Pre-assignment

Screening details:

The trial was conducted in an emergency setting therefore screening was performed upon presentation of the child at hospital with suspected NSCE. Consent in principal was obtained from the child's parent or guardian before EEG was performed to confirm presence of NCSE and confirmation of normal blood gas result.

Pre-assignment period milestones

Number of subjects started	6
Number of subjects completed	6

Period 1

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

Arms

Arm title	5% Carbogen

Arm description:

Inhalation of 5% Carbogen

Arm type	Experimental
Investigational medicinal product name	5% carbon dioxide/oxygen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Medicinal gas, compressed
Routes of administration	Inhalation use

Dosage and administration details:

Administration of 5% carbogen by spontaneous inhalation administered via a loosely attached face mask (flow rate 15 litres/minute) for a period of 120 seconds.

Number of subjects in period 1	5% Carbogen
Started	6
Completed	6

Period 2	
Period 2 title	Immediately post-inhalation
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	5% Carbogen

Arm description:

Inhalation of 5% carbogen over a 120 second period

Arm type	Experimental
Investigational medicinal product name	5% carbon dioxide/oxygen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Medicinal gas, compressed
Routes of administration	Inhalation use

Dosage and administration details:

Administration of 5% carbogen by spontaneous inhalation administered via a loosely attached face mask (flow rate 15 litres/minute) for a period of 120 seconds.

Number of subjects in period 2	5% Carbogen
Started	6
Completed	6

Period 3	
Period 3 title	24 hours post-inhalation
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	5% Carbogen

Arm description:

Inhalation of 5% Carbogen

Arm type	Experimental

Investigational medicinal product name	5% carbon dioxide/oxygen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Medicinal gas, compressed
Routes of administration	Inhalation use

Dosage and administration details:

Administration of 5% carbogen by spontaneous inhalation administered via a loosely attached face mask (flow rate 15 litres/minute) for a period of 120 seconds.

Number of subjects in period 3	5% Carbogen
Started	6
Completed	6

Period 4

Period 4 title	7 days post-inhalation
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	5% Carbogen

Arm description:

Inhalation of 5% Carbogen

Arm type	Experimental
Investigational medicinal product name	5% carbon dioxide/oxygen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Medicinal gas, compressed
Routes of administration	Inhalation use

Dosage and administration details:

Administration of 5% carbogen by spontaneous inhalation administered via a loosely attached face mask (flow rate 15 litres/minute) for a period of 120 seconds.

Number of subjects in period 4	5% Carbogen
Started	6
Completed	0
Not completed	6
Lost to follow-up	6

Baseline characteristics

Reporting groups	
Reporting group title	Preinhalation
Reporting group description:	
Inhalation of 5% carbogen	

Reporting group values	Preinhalation	Total	
Number of subjects	6	6	
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)	5	5	
Adolescents (12-17 years)	1	1	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	1	1	
Male	5	5	
Pre-inhalation (baseline) blood pH level Units: pH			
arithmetic mean	7.4		
standard deviation	± 0.03	-	
Pre-inhalation (baseline) capillary PO2 level Units: kPa			
arithmetic mean	7.78		
standard deviation	± 1.83	-	
Pre-inhalation (baseline) capillary respiratory rate Units: Breaths per minute			
arithmetic mean	24.5		
standard deviation	± 9.33	-	
Pre-inhalation pCO2			
pCO2 level prior to inhalation of carbogen.			
Units: kPa			
arithmetic mean	4.97		
standard deviation	± 0.51	-	

Subject analysis sets	
Subject analysis set title	Carbogen Tolerability
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects that underwent treatment with carbogen.

Reporting group values	Carbogen Tolerability		
Number of subjects	6		
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)	5		
Adolescents (12-17 years)	1		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Gender categorical Units: Subjects			
Female	1		
Male	5		
Pre-inhalation (baseline) blood pH level Units: pH			
arithmetic mean	7.4		
standard deviation	± 0.03		
Pre-inhalation (baseline) capillary PO2 level Units: kPa			
arithmetic mean	7.78		
standard deviation	± 1.83		
Pre-inhalation (baseline) capillary respiratory rate Units: Breaths per minute			
arithmetic mean	24.5		
standard deviation	± 9.33		
Pre-inhalation pCO2			
pCO2 level prior to inhalation of carbogen.			
Units: kPa			
arithmetic mean	4.97		
standard deviation	± 0.51		

End points

End points reporting groups

Reporting group title	5% Carbogen
Reporting group description: Inhalation of 5% Carbogen	
Reporting group title	5% Carbogen
Reporting group description: Inhalation of 5% carbogen over a 120 second period	
Reporting group title	5% Carbogen
Reporting group description: Inhalation of 5% Carbogen	
Reporting group title	5% Carbogen
Reporting group description: Inhalation of 5% Carbogen	
Subject analysis set title	Carbogen Tolerability
Subject analysis set type	Full analysis
Subject analysis set description: All subjects that underwent treatment with carbogen.	

Primary: Tolerated period of carbogen inhalation

End point title	Tolerated period of carbogen inhalation[1]
End point description: In line with the feasibility focus, the key primary endpoint for this study was the tolerated period of carbogen inhalation. The protocolised period of inhalation was 120 seconds of inhalation of 5% carbogen.	
End point type	Primary
End point timeframe: End of scheduled inhalation period.	

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: No applicable statistical analyses. The primary objective of the trial was to determine the feasibility of the protocol. As only 6 out of a target of 30 participants were recruited in the designated time period the DMC determined that the trial was not feasible.

End point values	5% Carbogen			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Seconds				
Inhalation period	120			

Statistical analyses

No statistical analyses for this end point

Secondary: Respiratory rate before inhalation

End point title	Respiratory rate before inhalation

End point description:

End point type	Secondary

End point timeframe:
Immediately prior to inhalation of carbogen

End point values	5% Carbogen			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Breaths per minute				
arithmetic mean (standard deviation)	24.5 (± 9.33)			

Statistical analyses

No statistical analyses for this end point

Secondary: Respiratory rate immediately post inhalation

End point title	Respiratory rate immediately post inhalation

End point description:

End point type	Secondary

End point timeframe:
Immediately after inhalation of carbogen

End point values	5% Carbogen			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Breaths per minute				
arithmetic mean (standard deviation)	26.17 (± 7.65)			

Statistical analyses

No statistical analyses for this end point

Secondary: Capilllary pO2 post inhalation

End point title	Capilllary pO2 post inhalation

End point description:

End point type	Secondary

End point timeframe:
Immediately post inhalation of carbogen

End point values	5% Carbogen			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: kPa				
arithmetic mean (standard deviation)	11.78 (± 2.77)			

Statistical analyses

No statistical analyses for this end point

Secondary: Capilllary pCO2 post inhalation

End point title	Capilllary pCO2 post inhalation

End point description:

End point type	Secondary

End point timeframe:
Immediately post inhalation of carbogen

End point values	5% Carbogen			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: kPa				
arithmetic mean (standard deviation)	5.05 (± 0.58)			

Statistical analyses

No statistical analyses for this end point

Secondary: Blood pH post inhalation

End point title	Blood pH post inhalation

End point description:

End point type	Secondary

End point timeframe:
Post inhalation of carbogen

End point values	5% Carbogen			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: pH				
arithmetic mean (standard deviation)	7.41 (± 0.04)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Adverse events were reported from time of consent until 7 days post IMP administration.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	None used
Dictionary version	0

Reporting groups	
Reporting group title	5% Carbogen
Reporting group description: Inhalation of 5% Carbogen	

Serious adverse events	5% Carbogen		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (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	5% Carbogen		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)		
General disorders and administration site conditions			
More sleepy			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Desaturation	Additional description: Period of desaturation on saturation number. No colour change or respiratory duress.		
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash	Additional description: Rash on back of neck		

subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Clammy			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Psychiatric disorders			
Distress	Additional description: Minimal distress at having mask on face		
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 October 2012	Due to the face mask for administering the IMP being loosely applied to the face, for participant comfort, there was a risk of the carbogen being diluted by room air. Therefore, this amendment proposed to increase the flow rate of carbogen administration to counteract any possible dilution.
03 January 2013	Addition of two research sites.
13 November 2013	Removal of the requirement for participants to remain in hospital for 24h after inhalation as this was seen as burdensome and a reason for nonparticipation in the study by families. The Trial Steering Committee strongly recommended that this requirement be relaxed and follow-up arrangements be more proportionate to risks of the study. Participants allowed home before the 24h observation point were to be followed up by an outpatient review on the first day after inhalation. In addition the day 7 review was modified to allow it to take place by telephone rather than face to face review. The end of the follow-up period was standardised at seven days, rather than seven days or duration of inpatient stay whichever was the longer.

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.

Recruitment to the trial was extremely difficult and 6 participants were recruited from a target of 30. On the advice of the data monitoring committee, the study was then terminated for lack of feasibility therefore analyses are descriptive only.

Notes: