Clinical trial results:
Further development of a new model of GAD: The effect of a clinically effective and noneffective dose of lorazepam on CO2 induced anxiety

Summary

EudraCT number	2006-001085-17
Trial protocol	GB
Global end of trial date	29 August 2008

Results information

Result version number	v1 (current)
This version publication date	21 April 2019
First version publication date	21 April 2019
Summary attachment (see zip file)	Publication (Diaper_et_al-2012-Human_Psychopharmacology__Clinical_and_Experimental.pdf)

Trial information

Trial identification

Sponsor protocol code	P1V-S01-03-06

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University of Bristol
Sponsor organisation address	Queens Road, Bristol, United Kingdom, BS8 1QU
Public contact	Dr Alison Diaper, University of Bristol, alison_diaper@hotmail.com
Scientific contact	Dr Alison Diaper, University of Bristol, alison_diaper@hotmail.com

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	29 August 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 August 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

A human model of GAD will be useful to investigate how GAD symptoms occur, and to test potential medications in healthy volunteers and in patients. To be effective, any potential model needs to reliably reproduce anxiety in healthy people and the degree of anxiety provoked should be repeatable and measurable. In addition the effects of known anxiolytics should mirror those in patients. We have developed a possible model of GAD using the inhalation of increased levels of carbon dioxide (7.5% CO2) for 20 minutes (Bailey et, al 2005). In healthy volunteers, this challenge induces anxiety and increases blood pressure and heart rate. To further validate the 7.5% CO2 challenge as a model of GAD, it is essential to know whether the dose of lorazepam required to alleviate anxiety is similar between subjects in the model and patients with GAD. This model could then be used to test the effectiveness of potential medications on GAD and stress.

Protection of trial subjects:

The Psychopharmacology Unit is experienced in managing and conducting human research in patient and healthy volunteer populations. Experience with the effects of inhaling 7.5% CO2 has been obtained from research completed over the last 8 years, using the procedure on hundreds of subjects.
The study was performed in accordance with ICH Good Clinical Practice, with approval from the Local Research Ethics Committee (Central and South Bristol Research Ethics Committee), relevant Health Service Trust regulatory approval (United Bristol Healthcare Trust), and the Medicines and Healthcare products Regulatory Agency (MHRA). Approval in writing was received prior to starting the study. Aspects of the Data Protection Act were adhered to. The case report forms were completed and stored appropriately. Data held on the computer were anonymised.
Volunteers were recruited using advertisements approved for that reason by the Ethics Committee. After initial contact, the subjects received the Participant Information Sheet and were given at least 48 hours to read it and consider the implications of their participation in the study. They were given the time to raise any questions with the investigators prior to making the decision to participate. Each subject was then asked to give their written informed consent after one of the investigators had explained the nature, purpose and risks of the study, by signing the Informed Consent Forms.
A letter was sent to the subjects' general practitioners informing them of their patients' participation in the trial.
Emergency out-of-hours contact telephone numbers for study medic were given to all participants, and adverse events were recorded during and after test days.

Background therapy:

The inhalation of carbon dioxide (CO2) has a lengthy history in psychiatry. The technique of inhaling a low concentration (5-7.5%) of CO2 for 15 or 20 minutes was developed by Gorman et al. (1984) who used 5% CO2 as a control gas for an experiment in which patients with panic disorder were asked to hyperventilate. However, more patients panicked in the CO2 group than the hyperventilation group. This discovery that the inhalation of 5% CO2 produces panic in patients with panic disorder, but not in subjects without anxiety, has been replicated and validated and is a well recognised experimental model. In patients with panic disorder, the anxiety resulting from a CO2 challenge has been shown to be sensitive to treatment with acute and chronic alprazolam (Sanderson et al., 1994; Woods et al., 1986). Although much of the published literature on CO2-induced anxiety has focussed on panic anxiety in patients with panic disorder, recent interest has focussed away from the idea that only patients with panic disorder are sensitive to the effects of CO2. We have recently reported that the inhalation of 7.5% CO2 for 20 minutes in healthy subjects produces an increase in blood pressure and heart rate, and increased feelings of anxiety, fear and tension (Bailey et al., 2005). These results suggest that the inhalation of 7.5% CO2 produces a state that is more like generalized anxiety rather than panic. Also, recent studies by us, and others, have reported that the inhalation of 35% CO2 activates the stress response system in healthy volunteers (Argyropoulos et al., 2002; Kaye et al., 2004; van Duinen et al., 2005).

Evidence for comparator:

Bailey et al. (2005) have postulated that the state produced by inhalation of 7.5% CO2 is more like that seen in a state of generalised anxiety, rather than a panic attack. This hypothesis was further explored using two proven anxiolytic therapies for GAD: a benzodiazepine (lorazepam) and a selective serotonin reuptake inhibitor (SSRI; paroxetine; Bailey et al., 2007). Benzodiazepine agonists effectively treat acute anxiety, whereas SSRIs are commonly used for longer periods to treat both panic and generalised anxiety disorder. New research has shown that drugs acting on the GABAA receptor may be effective in attenuating 7.5% CO2-induced anxiety more than other anxiolytics (Bailey et al., 2009).
It is unclear if these drug effects on the CO2 challenge are general or dose-dependent. This study was therefore conducted to determine the dose-¬related effects of 0.5mg (considered not clinically effective) and 2.0mg (clinically effective) of the benzodiazepine lorazepam on anxiety induced by inhalation of 7.5% CO2 for 20 minutes.

Actual start date of recruitment	09 May 2008
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: 18
Worldwide total number of subjects	18
EEA total number of subjects	18

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)	18
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited using existing databases at the Psychopharmacology Unit, University of Bristol (UoB), via advertisements on the UoB careers website, and posters around the UoB.

Pre-assignment

Screening details:

99 participants made contact, 89 PISs sent out, 43 screened by telephone (basic information about smoking and drinking habits, estimated height and weight, and illnesses/medications), 37 invited for screening. Screen fails included: taking part in another drugs study, worried about side effects, history or family history of psychiatric problems.

Pre-assignment period milestones

Number of subjects started	99[1]
Intermediate milestone: Number of subjects	Received PIS: 89
Intermediate milestone: Number of subjects	Telephone screen: 43
Intermediate milestone: Number of subjects	Invited to face-to-face screening: 37
Intermediate milestone: Number of subjects	Attended face-to-face screening: 32
Intermediate milestone: Number of subjects	Passed screening: 18
Number of subjects completed	18

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Taking part in another drugs study: 1
Reason: Number of subjects	Lack of availability: 8
Reason: Number of subjects	Concern about potential side effects: 1
Reason: Number of subjects	History or family history of psychiatric problems: 4
Reason: Number of subjects	Family reasons: 2
Reason: Number of subjects	Effort not worth the recompense: 1
Reason: Number of subjects	No reason given: 2
Reason: Number of subjects	Did not meet eligibility criteria: 62

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The pre-assignment number includes all volunteers, and is not a count of participants actually enrolled on the study.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

Study drugs were provided by the Pharmacy department of Bristol Royal Infirmary. Lorazepam 0.5mg and 2mg and placebo were prepared in matching blue capsules in individual containers labelled ‘Period 1’, ‘Period 2’ and ‘Period 3’, and were randomised by the Pharmacy.

Arms	
Are arms mutually exclusive?	No
Arm title	Lorazepam 2mg
Arm description: Lorazepam 2mg, one off dose	
Arm type	Experimental
Investigational medicinal product name	Lorazepam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 2mg, one off dose, oral overencapsulated.	
Arm title	Lorazepam 0.5mg
Arm description: Lorazepam 0.5mg, one off dose	
Arm type	Experimental
Investigational medicinal product name	Lorazepam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 0.5mg, one off dose, oral overencapsulated.	
Arm title	Placebo
Arm description: Matched placebo	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: Placebo, oral, overencapsulated.	

Number of subjects in period 1	Lorazepam 2mg	Lorazepam 0.5mg	Placebo
Started	18	18	18
Completed	18	18	18

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial
Reporting group description:	
18	

Reporting group values	Overall trial	Total	
Number of subjects	18	18	
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			
Mean 20.6, sd 1.29			
Units: years			
arithmetic mean	20.6		
standard deviation	± 1.29	-	
Gender categorical			
Subjects all male			
Units: Subjects			
Female	0	0	
Male	18	18	

Subject analysis sets	
Subject analysis set title	All subjects
Subject analysis set type	Full analysis
Subject analysis set description:	
Cross over study of 18 male participants. Each participant completed one test day on each comparator (lorazepam 2mg, 0.5mg and placebo) with a week washout in between each test session.	

Reporting group values	All subjects		
Number of subjects	18		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			

Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Mean 20.6, sd 1.29			
Units: years arithmetic mean standard deviation	 20.6 ± 1.29		
Gender categorical			
Subjects all male			
Units: Subjects			
Female Male	0 18		

End points

End points reporting groups

Reporting group title	Lorazepam 2mg
Reporting group description: Lorazepam 2mg, one off dose	
Reporting group title	Lorazepam 0.5mg
Reporting group description: Lorazepam 0.5mg, one off dose	
Reporting group title	Placebo
Reporting group description: Matched placebo	
Subject analysis set title	All subjects
Subject analysis set type	Full analysis
Subject analysis set description: Cross over study of 18 male participants. Each participant completed one test day on each comparator (lorazepam 2mg, 0.5mg and placebo) with a week washout in between each test session.	

Primary: Last subject last measurement

End point title	Last subject last measurement
End point description:	
End point type	Primary
End point timeframe: Last participant, last test session, last test.	

End point values	Lorazepam 2mg	Lorazepam 0.5mg	Placebo	All subjects
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	18	18	18	18
Units: Test points	54	54	54	54

Statistical analyses

Statistical analysis title	PSI
Statistical analysis description: Panic Symptom Inventory	
Comparison groups	Lorazepam 2mg v Lorazepam 0.5mg v Placebo
Number of subjects included in analysis	54
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	> 0.05
Method	ANOVA

Statistical analysis title	GAD-C
Statistical analysis description: Anxiety measure	
Comparison groups	Lorazepam 2mg v Lorazepam 0.5mg v Placebo
Number of subjects included in analysis	54
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	> 0.05
Method	ANOVA

Statistical analysis title	VAS Fearful
Statistical analysis description: Visual Analogue Scale - fearful	
Comparison groups	Lorazepam 2mg v Lorazepam 0.5mg v Placebo
Number of subjects included in analysis	54
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	< 0.05 [1]
Method	Friedman

Notes:

[1] - A repeated measures Friedman test showed a significant effect of Drug at time points 10 minutes after the Air inhalation (Air + 10 mins; $\chi 2(2, n=17)=6.28$, $p<0.05$), Peak CO2 ($\chi 2(2, n=17)=7.13$, $p<0.05$).

Statistical analysis title	VAS Stressed
Statistical analysis description: Visual Analogue Scale - Stressed	
Comparison groups	Lorazepam 2mg v Lorazepam 0.5mg v Placebo
Number of subjects included in analysis	54
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	< 0.05 [2]
Method	Friedman

Notes:

[2] - A repeated measures Friedman test showed a significant effect of Drug at time point 10 minutes after the Air inhalation (Air + 10 mins; $\chi 2(2, n=17)=7.06$, $p<0.05$).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Participants encouraged to report AEs from any time after signing Informed Consent Form. AEs taken during test days and by follow-up telephone call the day after test days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11

Reporting groups

Reporting group title	Lorazepam 2mg
Reporting group description: -	
Reporting group title	Lorazepam 0.5mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Lorazepam 2mg	Lorazepam 0.5mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)	0 / 18 (0.00%)	0 / 18 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Lorazepam 2mg	Lorazepam 0.5mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 18 (55.56%)	7 / 18 (38.89%)	4 / 18 (22.22%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 18 (22.22%)	2 / 18 (11.11%)	0 / 18 (0.00%)
occurrences (all)	4	2	0
Headache			
subjects affected / exposed	1 / 18 (5.56%)	4 / 18 (22.22%)	1 / 18 (5.56%)
occurrences (all)	1	4	1
General disorders and administration site conditions			

Somnolence			
subjects affected / exposed	5 / 18 (27.78%)	0 / 18 (0.00%)	1 / 18 (5.56%)
occurrences (all)	5	0	1
Fatigue			
subjects affected / exposed	3 / 18 (16.67%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Coordination abnormal			
subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Vessel puncture site haematoma			
subjects affected / exposed	0 / 18 (0.00%)	2 / 18 (11.11%)	2 / 18 (11.11%)
occurrences (all)	0	2	1
Psychiatric disorders			
Feeling abnormal			
subjects affected / exposed	3 / 18 (16.67%)	0 / 18 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 January 2008	Addition of inclusion criteria and clarification/change of timings of subjective ratings and inclusion of additional subjective rating questionnaire: Addition of non-smoking/light smoker criteria no 18 to inclusion criteria this has been added to ensure the safety of the participants . Clarification of the timing of subjective ratings - Panic Symptom Inventory (PSI) and Generalised Anxiety Disorder Criteria Inventory (GAD(C)), this has been added in to add clarity to the timepoints in which these ratings are performed. Movement in the timing of the Anxiety Sensitivity Index (ASI) from screening to Day 1. It is a more appropriate time to conduct the rating at Day 1 prior to dosing than at screening. Spielberger State Anxiety Inventory (SSAI) added in prior to dosing in addition to all previous timepoints. Spielberger Trait Anxiety Inventory (STAI) added in to Day 1, this rating was not previously specified, but is used in conjunction with the SSAI.

Notes:

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/23027657