# 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)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over | | | |
| Age continuous | | | |
| Mean 20.6, sd 1.29 | | | |
| Units: years<br>arithmetic mean<br>standard deviation | <br>20.6<br>± 1.29 | | |
| Gender categorical | | | |
| Subjects all male | | | |
| Units: Subjects | | | |
| Female<br>Male | 0<br>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:<br>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:<br>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:<br>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:<br>Addition of non-smoking/light smoker criteria no 18 to inclusion criteria this has been added to ensure the safety of the participants .<br>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.<br>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.<br>Spielberger State Anxiety Inventory (SSAI) added in prior to dosing in addition to all previous timepoints.<br>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