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Using the antidote flumazenil to treat coma following unintentional drug overdose

Submission date
22/12/2023

Recruitment status
Recruiting

Registration date
08/03/2024

Overall study status
Ongoing

Last Edited
22/06/2026

Condition category
Injury, Occupational Diseases, Poisoning

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
In 2021, the UK witnessed 4,390 unintentional drug overdose deaths, primarily associated with opioid drugs such as morphine and heroin, often combined with benzodiazepine drugs (often simply called ‘benzos’), including diazepam (Valium), etizolam, and alprazolam (Xanax).

We currently have an effective antidote (a medicine that aims to reverse an overdose) for opioids, called naloxone. Naloxone has saved many lives from unintentional drug overdoses. The use of other recreational drugs such as benzos can sometimes also cause people to fall into a coma (become unconscious) and their breathing to slow down, or even stop. Unintentional overdose of these drugs can be fatal - a problem that has become increasingly common over the past ten years in the UK.

Although an antidote for benzo overdose already exists (called flumazenil), we currently don’t use it for this purpose. This is because some of the first patients to receive it had seizures (fits) after treatment. On reflection, this is likely to be because they had taken another medicine which caused seizures. However, as a result of this problem, the flumazenil antidote is not being used to reverse benzo overdoses.

The purpose of this research study is to find out whether flumazenil, when given by injection into the muscles (IM) of the arm, thigh or buttock, can safely treat people who are unconscious after a probable benzo overdose without causing unacceptable side effects. It is now really important to find out whether IM flumazenil can be given to treat coma, without causing seizures. This route of administration will allow treatment to start before patients arrive at hospital in the future.

Who can participate?
Patients aged 16 years or older admitted to hospital while unconscious from a drug overdose, which the ambulance crew and doctors think is most likely due to benzos, will be able to take part.

What does the study involve?
Patients will be unconscious due to their drug overdose on recruitment to the study. On waking,

they will be informed about the study they have been in and their consent to continue sought. Discussions by the study's lived experience co-investigator with benzodiazepine user support groups across Scotland indicate that the study population consider the question extremely important and would be keen to take part.

The patients' condition and, where available, medical notes will be checked to make sure it's safe to administer flumazenil (or placebo) before you are entered into the study. Patients will be put at random by a computer programme into one of two treatment groups and given either a dose of flumazenil, or a placebo control (salty water). The treatment is given by IM injection, and you will be monitored closely for 1 hour afterwards.
Patients will have several blood samples taken over 1 hour (up to five samples - around 40 ml in total, about a third of a small wine glass) to monitor the oxygen levels in their blood and to work out why you were unconscious (identify what drugs were in your system). All other treatments or tests will be decided by the hospital team treating you.

Patients entered into the study in Edinburgh will have one other blood sample (5 ml, one teaspoon) taken around 2.5 hours after they entered the study. Some of their blood will be tested straight away. Some plasma, extracted from the blood sample, will be collected, processed and sent to a secure laboratory for analysis.

In Edinburgh, the researchers will also take some breath samples.

What are the possible benefits and risks of participating?
It is hoped that flumazenil can help treat people who have overdosed on benzos. The knowledge we gain from this study will improve the care of people in the future.

Flumazenil is commonly used in hospitals for patients who have received too much diazepam for a procedure such as an operation or telescope test (endoscopy). Common side effects include gastrointestinal symptoms (such as feeling sick), allergic reactions, anxiety, emotional lability, insomnia (inability to sleep), somnolence (feeling sleepy), vertigo, headache, agitation, tremor, dry mouth, hyperventilation (breathing fast), speech disorder, paraesthesia, diplopia or strabismus (double vision), crying, palpitations, flushing, hypotension (low blood pressure), orthostatic hypotension (low blood pressure on standing up), transient increased blood pressure, nausea, vomiting, hiccup, sweating, and pain at the injection site. A few people (less than 1%) have a fit that is over within a minute or two. This is usually reported when very high doses of flumazenil are used, or when people are prone to seizures due to epilepsy or brain injuries.

Where is the study run from?
The study has been organised by researchers from the University of Edinburgh with the support of the Edinburgh Clinical Trials Unit (UK)

When is the study starting and how long is it expected to run for?
January 2025 to July 2028

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Prof. Michael Eddleston, M.Eddleston@ed.ac.uk

Contact information

Type(s)
Scientific, Principal investigator

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Additional identifiers

Integrated Research Application System (IRAS)
1008964

Protocol serial number
AC23145

Study information

Scientific Title
Repurposing flumazenil for intramuscular treatment of coma due to unintentional drug overdose - a dose-finding safety and efficacy phase II/III study

Study objectives
Hypothesis:
That IM flumazenil can safely and efficaciously reverse benzodiazepine-induced coma.

Primary objective:
Stage 1: Identify two likely safe (regarding tonic-clonic seizures) and efficacious IM doses of flumazenil.
Stage 2: Gain more precise estimates for efficacy for these two IM doses (identified in stage 1).
Stage 3: Establish the incidence of tonic-clonic seizures for an effective IM dose of flumazenil (identified in stage 2), compared to placebo.

Secondary objective 1. Gain more information on reversal of sedation through assessment of blood gases and sedation scores over 1 h post-administration of IM flumazenil.
Secondary objective 2. Establish the safety profile of IM flumazenil

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 26/02/2024, Scotland A Research Ethics Committee (2nd Floor, Waverley Gate, 2-4 Waterloo Place, Edinburgh, EH1 3EG, UK; +44 (0)781 460 9032; sesres@nhslothian.scot.nhs.uk, manx.neill@nhslothian.scot.nhs.uk), ref: 24/SS/0009

Primary study design
Interventional

Study design
Randomized placebo-controlled double-blind dose-escalation then parallel-group

Study type(s)
Efficacy, Safety

Health condition(s) or problem(s) studied
Benzodiazepine overdose

Interventions
This is a multicentre, Phase II/III, randomised, double-blind, dose-escalation then parallel-group study to evaluate the safety and efficacy of intramuscular (IM) flumazenil. The study will first identify two likely safe and efficacious doses of IM flumazenil in a dose-escalation design, then gain more precise estimates of efficacy for these two doses, before measuring safety (incidence of seizures) in the lowest efficacious IM dose in a non-inferiority comparison to placebo. The study will be conducted in three stages.

Stage 1
In Stage 1, there will be up to six dose escalation cohorts, each including 12 participants. Participants will be randomised to flumazenil or saline placebo in a 5:1 ratio for each cohort of 12 participants (10 flumazenil: 2 placebo). The first four dose cohorts will receive 0.2 mg, 0.4 mg, 0.8 mg and 1.2 mg of flumazenil by IM injection over <10 sec, as long as dose escalation is recommended by the Data Monitoring Committee (DMC). The last two dose cohorts are currently proposed as 2.0 mg and 3.0 mg but these doses may be modified if there has been a clear response at the 1.2 mg dose.

Stage 2
The two doses identified by the DMC as being effective in stage 1 will be given to participants in stage 2. The first dose in stage 1 which elicits an improvement in consciousness, as shown by an increase in RASS score in >50% of participants, and does not induce tonic-clonic seizures will be the first dose for stage 2. A decision on whether to escalate to the next proposed dose level or a different dose will be made by the DMC. Up to 189 participants will be randomised to one of the two flumazenil doses or placebo in a 1:1:1 ratio in stage 2.

Stage 3
The most efficacious flumazenil dose (improved consciousness as shown by increased RASS scores in the -2 to 0 range) from stage 2 will be selected for stage 3. Up to 374 participants in stage 3 will be randomised in a 1:1 ratio to the most efficacious flumazenil dose or placebo.
A total of up to 635 patients will be recruited across the three stages and the maximum dose in the study will not exceed 3 mg.
For all stages of the trial, randomisation will be carried out using a web-based randomisation service and random permuted blocks will be used to ensure the appropriate allocation ratio. No other restrictions on randomisation (minimisation or stratification) will be implemented.

Intervention Type
Drug

Phase
Phase II/III

Drug/device/biological/vaccine name(s)
Flumazenil

Primary outcome(s)
Stage 1
Primary Endpoint (safety)
The occurrence of a tonic-clonic seizure as measured by visual observation of the participant by an experienced clinician up to 1 h after drug administration

Primary Endpoint (efficacy)
The level of sedation as measured using the Richmond Agitation-Sedation Score (RASS) score is in the -2 [light sedation] to 0 [alert, calm] range at 15 min after drug administration

Stage 2
Primary Endpoint (efficacy)
The level of sedation as measured using the Richmond Agitation-Sedation Score (RASS) score is in the -2 [light sedation] to 0 [alert, calm] range at 15 min after drug administration

Stage 3
Primary Endpoint (safety)
The occurrence of a tonic-clonic seizure as measured by visual observation of the participant by an experienced clinician up to 1 h after drug administration

Key secondary outcome(s)
Current key secondary outcome(s) as of 22/06/2026:

Stage 1
1. Reversal of respiratory depression measured using falling $PaCO_2$ on venous (alternatively arterial) blood-gas analysis at 15 and 30 min
2. Level of sedation measured using RASS, Glasgow Coma Scale/Score (GCS), and Alert, Voice, Pain, Unresponsive (AVPU) scores over 60 min post drug administration
3. Need for/duration of intubation, or death, recorded until hospital discharge
4. Adverse events (AEs) and serious adverse events (SAEs) recorded from the time of administration of flumazenil or placebo until hospital discharge

Stage 2
1. Reversal of respiratory depression measured using falling $PaCO_2$ on venous (alternatively arterial) blood-gas analysis at 15 and 30 min
2. Level of sedation measured using RASS, GCS, and AVPU scores over 60 min post drug administration
3. Need for/duration of intubation, or death, recorded until hospital discharge
4. AEs and SAEs recorded from the time of administration of flumazenil or placebo until hospital discharge

Stage 3
1. Reversal of respiratory depression measured using falling PaCO2 on venous (alternatively arterial) blood-gas analysis at 15 and 30 min
2. Level of sedation measured using RASS, GCS, and AVPU scores over 60 min post drug administration
3. Need for/duration of intubation, or death, recorded until hospital discharge
4. AEs and SAEs recorded from the time of administration of flumazenil or placebo until hospital discharge

Physiological secondary endpoints measured using blood and breath samples until 150 min.
Other secondary endpoints measured until hospital discharge.

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Previous key secondary outcome(s):

Stage 1
1. Reversal of respiratory depression measured using falling PaCO2 on venous (alternatively arterial) blood-gas analysis at 15 and 30 min
2. Level of sedation measured using RASS, Glasgow Coma Scale/Score (GCS), and Alert, Voice, Pain, Unresponsive (AVPU) scores over 60 min post drug administration
3. Need for/duration of intubation, or death, recorded until hospital discharge
4. Adverse events (AEs) and serious adverse events (SAEs) recorded from the time of administration of flumazenil or placebo until hospital discharge

Stage 2
1. Reversal of respiratory depression measured using falling PaCO2 on venous (alternatively arterial) blood-gas analysis at 15 and 30 min
2. Level of sedation measured using RASS, GCS, and AVPU scores over 60 min post drug administration
3. Need for/duration of intubation, or death, recorded until hospital discharge
4. AEs and SAEs recorded from the time of administration of flumazenil or placebo until hospital discharge

Stage 3
1. Reversal of respiratory depression measured using falling PaCO2 on venous (alternatively arterial) blood-gas analysis at 15 and 30 min
2. Level of sedation measured using RASS, GCS, and AVPU scores over 60 min post drug administration
3. Need for/duration of intubation, or death, recorded until hospital discharge
4. AEs and SAEs recorded from the time of administration of flumazenil or placebo until hospital discharge

Physiological secondary endpoints measured using blood and breath samples and both eye and pupil movement, until 150 min.
Other secondary endpoints measured until hospital discharge.

Completion date
31/07/2028

Eligibility

Key inclusion criteria
1. Acute suspected unintentional BZD overdose presenting to hospital with reduced consciousness after administration of clinically adequate doses of naloxone. Mixed overdoses suspected to include BZDs will be included
2. Other common causes of reduced consciousness (such as hypoglycaemia) will have been excluded
3. RASS score of -5 (unrousable) to -3 (moderate sedation)
4. Aged, or believed to be aged, 16 years and over

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
16 Years

Upper age limit
100 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. RASS score above -3
2. Past medical history of epilepsy or chronic brain injury
3. Seizure pre-hospital following the overdose or after hospital admission, before recruitment
4. Clinically apparent pregnancy or medical record of current pregnancy (urine-HCG test not practicable in patients with reduced consciousness)
5. Prolonged QRS duration (>120 msec, unless due to pre-existing bundle branch block) on electrocardiogram
6. Prisoner or under arrest
7. Currently detained under the Mental Health Act
8. HIV positive with detectable virus load, or no virus load data from previous 12 months, or not currently on therapy
9. Patients who have previously participated in the study (according to the recruitment log).

In Stage 1, as we explore the safety of flumazenil, we will have additional exclusion criteria to further reduce the risk of seizures.
10. No access to medical records at recruitment
11. Unknown patient (precluding use of medical records).

To ensure external validity for future clinical practice, when medical records will usually not be immediately available, these will not be used once stage 1 has identified potentially safe doses.

The risk of seizures in these patients with a dose found to be safe in Stage 1 is likely to be outweighed by the chance of benefit if used pre-hospital in future.

Date of first enrolment
23/01/2025

Date of final enrolment
31/01/2028

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
Royal Infirmary of Edinburgh at Little France
51 Little France Crescent
Old Dalkeith Road
Edinburgh
Lothian
Scotland
EH16 4SA

Study participating centre
Royal Berkshire NHS Foundation Trust
Royal Berkshire Hospital
London Road
Reading
England
RG1 5AN

Study participating centre
Victoria Hospital
Hayfield Rd
Kirkcaldy
Scotland
KY2 5AH

Study participating centre

Queen Elizabeth University Hospital
1345 Govan Road
Glasgow
Scotland
G51 4TF

Sponsor information

Organisation
University of Edinburgh

ROR
https://ror.org/01nrxwf90

Funder(s)

Funder type
Government

Funder Name
UK Research and Innovation

Alternative Name(s)
UKRI

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request. All requests for study data, including participant-level data and statistical code, will be made in writing via e-mail to ECTUdatashare@ed.ac.uk in the first instance and will be reviewed in accordance with ECTU-SOP-OP-15 Data Access Request and Application Management.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Study website	Study website	11/11/2025	11/11/2025	No	Yes