Slow continuous subcutaneous flumazenil infusion for benzodiazepine dependence: a pilot study

Published: 05-10-2015
Last updated: 13-04-2024

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON41934

Source
ToetsingOnline

Brief title
Subcutaneous flumazenil infusion for benzodiazepine dependence

Condition

- Other condition

Synonym
benzodiazepine withdrawal

Health condition

verslavingsziektes

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Radboudumc/ Nijmegen Institute for Scientists-Practitioners in Addiction. Novadic-Kentron netwerk voor verslavingszorg

Intervention

Keyword: benzodiazepines, detoxification, flumazenil, withdrawal

Outcome measures

Primary outcome

Subjective Withdrawal Scale (in dutch: Subjectieve Onthoudings Schaal (SOS))

Objective Withdrawal Scale (in dutch: objective Onthoudings Schaal (OOS).

BWSQ (Benzodiazepine Withdrawal Symptom Questionnaire)

Registration of any adverse event

Registration of Intericatal Epileptiform Discharges (IEDs) during two nights

with a combined Electroencephalography (EEG)/ Polysomnography (PSG)

Secondary outcome

Spielberger State-Trait Anxiety Inventory

Mini International Neuropsychiatric Interview (MINI)

SCL-90R

Emotional Stroop Test

Pittsburgh Sleep Quality Index (PSQI)

Sleep Wake Diary

Registration of sleep during two nights with a combined Electroencephalography

(EEG)/ Polysomnography (PSG)

psychomotor vigilance test (PVT)

A 5-point Likert scale questionnaire on the burden and recommendation of the

treatment to others and preparedness to repeat the treatment if needed

Abstinence rates after infusion, one month and three month

EuroQuol 5d (EQ-5d)

Study description

Background summary

In the Netherlands, about 200,000 people are benzodiazepine dependent resulting in a reduced quality of life and increased risk of accidents. Detoxification of high-dose benzodiazepines by tapering is long, difficult for the patient and is often not successful (<30% abstinence after one year). Flumazenil infusion could solve this problem. In Australia and Italy about 1500 people have been treated for about four days with a low dose of flumazenil. All participants finished the detoxification with generally few withdrawal symptoms.
In this study, 30 patients with high-dose benzodiazepine will be treated with flumazenil. Not only withdrawal symptoms and safety (EEG recordings) will be examined but also the effects on anxiety and sleep. In addition, research is being done on the effectiveness after three months. If the results are positive then offers this perspective for all people with benzodiazepine dependence.

Study objective

The primary objective is to demonstrate that detoxification of benzodiazepines in high-dose benzodiazepine dependent patients using continuous subcutaneous infusion of flumazenil is feasible and safe.
Secondary goals of the study are to explore
1) Percentage completers and abstinence rate after three month.
2) The effect of flumazenil detoxification on anxiety and sleep during and after detoxification.
3) Patient satisfaction of flumazenil detoxification.

Study design

Open label pilot study

Intervention

All patients are given a subcutaneous flumazenil infusion with a rate of 4 mg/ 24 hrs during 4-6 days. A low dose of oxazepam will be given orally during the first three nights. Use of all other benzodiazepines stops with the start of

the infusion.

Study burden and risks

The burden will consist of four days of subcutaneous infusion, completing various questionnaires, performing computer tasks, twice taking an EEG during sleep, and two additional visits to the outpatient clinic of the Radboud University Nijmegen Medical Centre. There may be an increased risk of seizures in respect to regular treatment. The advantages that are opposite are: a shorter hospital stay of one week instead of about six weeks, accompanied by fewer withdrawal symptoms, and a greater chance of successful cessation of benzodiazepines.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• A primary diagnosis of benzodiazepine dependence with an average daily dose of at least 30 mg of diazepam or equivalent according table 2
OR
A diagnosis of benzodiazepine dependence with an average daily dose of at least 30 mg of diazepam or an equivalent with a co-morbid diagnosis of alcohol or cannabis dependence. Prior to the baseline measurement and flumazenil infusion patients must be abstinent from alcohol and cannabis for at least two months.
• Age between 21 and 65 years.
• Participants should master Dutch language sufficiently to provide informed consent and participate in all measurements (including self report questionnaires).
• Motivation for and availability of a regular treatment after the detoxification procedure at a regional (addiction) care facility.

Exclusion criteria

• History of epilepsy or IEDs on EEG or other serious neurological disorders;
• History of a serious medical condition, including heart disease (myocardial infarction or arrhythmias), lung disease (COPD gold stage II or higher), acute liver or kidney disease (indexed by ASAT ALAT max three times the norm or increased Creatinine/Ureum);
• Diagnosis of a current severe psychiatric disorder (psychosis, mania, severe depression);
• Diagnosis of a primary organic sleep disorders e.g. hypersomnia, disorders of the sleep wake schedule and sleep apnoea;
• A positive urine screening for cocaine, heroin, amphetamine, ecstasy, cannabis, opiates, buprenorphine and methadone;

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-02-2017
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Anexate, Lanexat, Mazicon, Romazicon
Generic name:	flumazenil
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-10-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-03-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-12-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-06-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-02-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-000420-15-NL
CCMO	NL49414.091.15