A randomized, double blind, placebo-controlled, double dummy, three-way crossover study to investigate the effects of an intravenous ethanol clamp and a morphine infusion on resting state functional magnetic resonance imaging in healthy male volunteers

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Primary Objectives:• To investigate the effects of a stable level of alcohol (0.6 g/L) on fMRI activation patterns in healthy male volunteers,• To investigate the effect of a stable level of morphine (80 nmol/L) on fMRI activation patterns in…

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

Summary

ID

NL-OMON31294

Source
ToetsingOnline

Brief title
Effects of ethanol and morphine on fMRI

Condition

- Other condition

Synonym
not applicable

Health condition

Er zal bij deze studie niet gekeken worden naar de aandoening die het middel behandelt. De farmacodynamische effecten van morfine/ethanol op resting state networks in de hersenen zullen worden bestudeerd.

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: CHDR

Intervention

Keyword: alcohol, ethanol, fMRI, morphine

Outcome measures

Primary outcome

CNS Pharmacodynamics

• Visual Analogue Scales (VAS) to assess mood, alertness and calmness (Bond

and Lader),

• VAS to assess the subjective effects of ethanol,

• VAS to assess the subjective feeling of nausea,

• VAS to assess psychedelic effects (Bowdle).

fMRI

• Resting State Network (RSN) activity

Pharmacokinetics

• Breath ethanol concentrations,

• Plasma morphine, morphine-3-glucuronide (M3G) and morphine-6-

glucuronide (M6G) levels.

Secondary outcome

not applicable

Study description

Background summary

Although fMRI has been available for close to a decade, it has never gained wide application in drug development. This is mainly due to technical limitations in the way fMRI was elicited. In traditional setups, fMRI-signals were brought about by repeated administration of a certain cognitive, sensory or motor task, basically subtracting post- from pre-stimulatory scans. Consequently, the alterations in brain activation highly depended on the characteristics of the stimulus paradigm. Studies have been performed that show how drugs change such stimulus-related fMRI-patterns. However, there are practical limitations to the tasks that can be performed in a MRI-scanner, and it has not been possible to design meaningful paradigms for all drugs. Ideally, drug-induced fMRI-changes would be stimulus-independent, and merely related to the concentrations and pharmacological effects of the drugs on different brain areas. Until recently, this was not technically possible, but recent innovations in signal analysis now allow the accurate detection of resting-state, unactivated fMRI-signals. So far, no drug studies have been performed with this innovative technique. The main objective of the current study is to detect drug induced fMRI-effects. Alcohol as well as morphine have been chosen for this study. Accurate infusion paradigms have been developed for both ethanol and morphine. These paradigms allow the maintainance of stable drug levels, with well-known CNS-effects. These fixed levels provide a stable stimulus that should reduce the variability of the Resting State-pharmaco-MRI (RS-phMRI) signal, which is considered an advantage at this early stage of development. Ethanol was chosen because it induces a wide range of changes in the central nervous system, which could be associated with different areas of fMRI activation. Despite its mild to sometimes serious side effects, morphine remains one of the most valuable analgesics in clinical practice. Because of its common use in the clinical setting and because of the major experience with this prototype μ-opioid receptor agonist within our research group (Dahan et al.), morphine will also be investigated for its effects on brain activation with fMRI.

Study objective

Primary Objectives:

• To investigate the effects of a stable level of alcohol (0.6 g/L) on fMRI activation patterns in healthy male volunteers,
• To investigate the effect of a stable level of morphine (80 nmol/L) on fMRI activation patterns in healthy male volunteers.

Secondary Objectives:
• To assess the feasibility of PK/PD-analyses for alcohol-induced fMRI-activation patterns,
• To assess the feasibility of PK/PD-analyses for morphine-induced fMRI-activation patterns

Study design

This will be a randomized, double blind placebo-controlled, double dummy, three-way crossover study. Washout periods will be at least seven days.

One study team member, who is not involved in any of the measurements, will obtain the BrAC-measurements and adapt the infusion regimen accordingly. The rest of the study team will remain blinded to the treatment randomisation.

Intervention

Ethanol 10% w/v solution in 5% glucose will be delivered by intravenous infusion to maintain blood ethanol concentration near 0.60 g/L for 150 minutes. The target concentration of 0.60 g/L is expected to be well tolerated, since this concentration has been safely employed in several previous CHDR studies (CHDR0313 and CHDR0502 - data on file) for even longer periods (up to 5 hours). In these previous studies the 0.6 g/L ethanol clamp showed statistically significant pharmacodynamic CNS effects. Furthermore these levels are routinely achieved during social drinking.

To avoid local pain in the beginning of the ethanol infusion, a parallel infusion with glucose 5% will be given.

Prior to the administration of morphine, ondansetron 4 mg will be administered intravenously to avoid nausea. A matching placebo will be administered prior to the other occasions. During *morphine-occasions* an initial morphine dose of 100 µg/kg will be administered in one minute, followed by a continuous infusion of 30 µg/kg/h for 2.5 hours in order to reach a stable morphine plasma concentration of 80 nmol/L. Prior morphine studies using the same bolus, but a 30 µg/kg/h infusion for only 1 hour show that this infusion paradigm can safely be used to create a stable serum level of 80 nmol/L with detectable pharmacodynamic effects. The total amount of morphine administered during 1 occasion using this dosage scheme, will be about 14 mg for an average weighted male subject, infused over a time period of 2.5 hours. This dose is considered a safe and rational dose, since it is within the therapeutic range of morphine

(i.e. 2.5 mg-15 mg in 4-5 ml in 4-5 minutes intravenously, for acute pain) according to the *Farmacotherapeutisch Kompas*.

Glucose 5% will be used as placebo.

Study burden and risks

Side effects of ethanol: 'drunkness', nausea, 'hangover'.
Side effects morphine: constipation, sedation, nausea (will be antagonized by ondansetron), itching.
Rare side effects of morphine, not to be expected at the proposed dose: psychomimetic effects, respiratory depression and release of histamine.
fMRI: claustrophobia.

Screening: 1 venapunction (22.5 ml in total).
Three intravenous cannulas will be inserted during every study day (there are 3 study days in total). One cannula will be used for the administration of morphine/placebo, the second cannula will be used to administer ethanol/placebo and the third cannula will be used for the pharmacokinetic bloodsampling of morphine. 10 ml blood will be drawn 11 times, during each study day, to assess morphine blood concentrations. 500 ml ethanol/placebo and 60 ml morphine/placebo will be administered via the other two cannulas. To diminish the vessel irritating, burning effect of ethanol during the beginning of the ethanol infusion, 20 ml of glucose will also be administered during the first 10 minutes of infusion.
Follow-up visit: 1 venapunction (12.5 ml). The total amount of blood drawn during the complete study period will be approximately 365 ml.

Serious or rare adverse events are not likely to appear during this project using the doses described in the protocol, especially not since only healthy subjects will be included in this study. The outcome of this study will contribute to the development of fMRI as a biomarker in early drug development.

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. Subject is a legally competent male adult between 18 and 40 years old, extremes included.;b. Subject is neither grossly overweight nor underweight for height and body build. BMI of 18 - 26 kg.m-2, extremes included.;c. Subject is familiar with the procedures of the study, and agrees to participate in the study program by giving oral and written informed consent.;d. Subject is familiar with the use and effects of alcohol.

Exclusion criteria

a. Subject has a (history of) a significant medical disorder that may pose a risk for the subject or jeopardize the aims of the study, based on medical history, physical examination, ECG and safety laboratory parameters.;b. Subject has a positive screen for Hepatitis B, C and HIV.;c. Subject uses more than 4 alcoholic consumptions per day, on average.;d. Subject has a significant history of any cardiac or vascular disorder, asthma or other pulmonary disease, major gastrointestinal abnormalities/peptic ulceration, hepatic, neurological, psychiatric, haematological (including bleeding disorders), endocrine, renal, or major genitourinary disease or uses any kind of concomitant medication that - in the opinion of the investigator - may interfere with the study.;e. Subject has a history of illness or any condition that, in the opinion of the investigator, might interfere with optimal participation, confound the results of the study or pose additional risk in administering ethanol or morphine to the subject (e.g. opioid allergy).;f. Subject smokes more than 5 cigarettes per day or is unable to refrain from smoking on the study days.;g. Subject has participated in a trial within 3 months prior to the start of the study or subject has participated in more than 4 clinical trials in the last year.;h. Subject has donated blood (including blood sampling during clinical trails) in the past 3

months.;i. Subject is a habitual and heavy consumer of caffeinated beverages (more than 6 cups of coffee or equivalent/day) at the time of the study.;j. Subject is currently a regular user (including *recreational uses*) of any illicit drugs, or has (a history of) drug or alcohol abuse.;k. Subject is unable to refrain from quinine containing products and grapefruit or grapefruit juice from 14 days prior to study start until the last study day.;l. Subject is provided with metal medical devices like pacemakers, knee or hip prothesis, earimplants, vesselclips, subcutaneous insuline pumps or carries metal particles (e.g. metal splinter in the eye) inside the body.;m. Subject has a significant history of claustrophobia.;n. Subject has a professional involvement in the study or is an investigator*s relative.;o. Subject is not able to maintain a regular diurnal rhythm.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2007
Enrollment:	12
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	morphine
Generic name:	morphine HCL CF 10 mg/ml
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Zofran

Generic name:	Ondansetron ratiopharm 4 mg/2 ml injectie, solution for injection 2mg/ml
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	17-07-2007
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	29-11-2007
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2007-001593-93-NL
Other	NA
CCMO	NL17581.058.07