Mapping serotonergic function using pharmacologic Magnetic Resonance Imaging (phMRI) in healthy subjects and users of ecstasy

Published: 18-05-2009
Last updated: 05-05-2024

- To assess the usefulness of 5-HT phMRI (BOLD-, PWI and ASL based phMRI) in assessing cerebral 5-HT neurotoxicity when compared to SERT SPECT.- To assess which MRI technique (BOLD-, PWI or ASL) is best in assessing cerebral 5-HT neurotoxicity when...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON33100

Source
ToetsingOnline

Brief title
MDMA-MRI

Condition

- Other condition
- Neurological disorders NEC

Synonym
brain damage, Neurotoxicity

Health condition

Drugsgebruik

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: NWO (VENI)

Intervention

Keyword: MDMA, phMRI, Serotonin, SPECT

Outcome measures

Primary outcome

BOLD: % change in BOLD SI from baseline (ROI)

PWI: % change in ratio from baseline (ROI: rCBV/white matter rCBV)

ASL: % change in CBF from baseline (ROI CBF/100 mg tissue)

SPECT: SERT ratio (striatal ROI binding/binding in cerebellum)

Visual analogue rating scale (VAS)

Secondary outcome

Not applicable

Study description

Background summary

Previous studies have suggested neurotoxicity of the recreational drug ecstasy (3,4-methylenedioxymethamphetamine, MDMA) to the serotonergic system. This is illustrated by reductions of serotonin transporter densities (SERT) assessed using single photon emission computed tomography (SPECT) in cortical brain regions in male (Semple et al, 1999) and female (Reneman et al, 2001b) ecstasy users. However, these findings are still debated because of the presumed limited sensitivity of [123I]*-CIT SPECT imaging to measure SERT density in the cerebral cortex (Heinz et al, 2000; Ricaurte and McCann 2001; Kish 2002). Recent work suggests that the serotonin (5-HT) system can also be evaluated non-invasively using magnetic resonance imaging (MRI) by measuring hemodynamic

changes following a
5-HT challenge, called pharmacological MRI (phMRI). There are three ways of assessing pharmacological-induced changes in hemodynamic responses with MRI: using BOLD (blood oxygenation-level dependent) contrast, perfusion weighted imaging (PWI) and arterial spin labelling (ASL). However, the reliability of these techniques in assessing 5-HT function have not yet been assessed and directly compared to each other. Therefore, this study will assess the reliability of BOLD-, PWI and ASL based phMRI by assessing cerebral 5-HT function when compared to SERT (123I *-CIT) SPECT in 10 healthy male volunteers, and 10 users of ecstasy in order to identify the best phMRI technique in doing so. Ultimately, it is expected that 5-HT phMRI will add crucial information on the effects of ecstasy in adolescents and young adults using this drug.

Study objective

- To assess the usefulness of 5-HT phMRI (BOLD-, PWI and ASL based phMRI) in assessing cerebral 5-HT neurotoxicity when compared to SERT SPECT.
- To assess which MRI technique (BOLD-, PWI or ASL) is best in assessing cerebral 5-HT neurotoxicity when compared to SERT SPECT.

Study design

BOLD-, PWI and ASL 5-HT-phMRI studies will be conducted and compared to a SERT SPECT scan as reference (gold standard). First, a SERT SPECT scan will be conducted. With an interval of 2-3 weeks, the BOLD and ASL 5-HT-phMRI studies can be studied in one scan session following a low dose challenge with the serotonin reuptake inhibitor (SSRI) citalopram. In a second MRI study with gadolinium (PWI based phMRI), again a low dose citalopram challenge will be given.

Intervention

Non-invasive 3.0 Tesla MR imaging of cerebral hemodynamics following an intravenous bolus injection of citalopram (7,5 mg). For the PWI studies in addition two intravenous bolus injections of a contrast agent (gadobutrol; Gadovist) will be administered. For the SPECT studies a registrated and well-validated radioligand ([123I]*-CIT) will be administered intravenously.

Study burden and risks

No serious side effects are foreseen. MRI itself is a non-invasive imaging modality. In this study, a low dose citalopram challenge (7.5 mg injected over 7.5 min.) will be administered during the two MRI studies, along with a contrast agent during the PWI MRI study. There is no expected risk associated with participation. Gadobutrol (Gadovist, Bayer) is routinely administered for

contrast enhanced MRI studies at the departments of Radiology worldwide, also in healthy human volunteers. Intravenous citalopram (5*10 mg) has been developed as probe of central 5-HT function by measuring increased prolactin secretion following its administration (Seifritz et al. 1996; Attenburrow et al. 2001), and has also been used as a probe for 5-HT modulation in phMRI studies (for review see Anderson et al., 2008, McKie 2005). It is the only SSRI available for intravenous administration. This formulation has been shown to increase the plasmatic concentration of the molecule faster than the oral one with a larger therapeutic effect in either controlled and open trials with depressed patients. Citalopram infusion followed by oral citalopram may be an effective and well-tolerated treatment for severely depressed patients, also being not associated with higher severity of side effects. In fact * 50% patients report no adverse events during chronic treatment with i.v.citalopram at much higher doses (20-60 mg) than employed in this study (Svestka et al. 1993a, b; Schöny 1992). Of the patients who did experience side effects, tremor, somnolence and dizziness were reported by * 10% (Charbonnier et al. 1987). The most common adverse events associated with i.v. citalopram are nausea, headache, tremor, and somnolence (Bouchard et al. 1997; Baumann et al. 1998; Guelfi et al. 2000). The radiation exposure of the SPECT scan is classified as category II, and routinely conducted at the AMC also in healthy human volunteers. Moreover, [123I]*-CIT is a registered radioligand, which is produced routinely using GMP-criteria. In conclusion, the nature of the burden is classified as moderate, considering that subjects will have to come to the AMC on 3 different occasions, undergo 3 different types of scans, involving venous 3 venous punctures and i.v. administration of either or a combination of a radioligand, citalopram or contrast agent. The risks involved are negligible, as all the agents and techniques employed are registered for their use and/or routinely performed at the AMC. There is no direct potential benefit for the participants, other than indirect benefits as the current study will hopefully be able to shed a new light on the discussion on the presumed neurotoxic effects of ecstasy in users of this drug.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
1105 AZ
Nederland
Scientific
Academisch Medisch Centrum

Meibergdreef 9

1105 AZ
Nederland

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

-Male
-Between 18 and 30 years of age

Exclusion criteria

-Serious general medical condition or one that could interfere in the interpretation of results
-use of (5-HT) medication within the last 2 weeks
-excessive consumption of alcohol (>21 units/ week), caffeine (greater than eight cups of coffee per day) or cigarettes (greater than ten cigarettes per day).
-Contraindications for MRI (e.g. osteosynthetic material, pacemaker, artificial cardiac valves), claustrophobia
-Contraindications for contrast agent: renal disease (serum creatinine * 110 mmol/L).

Study design

Design

Study type:	Observational invasive
Intervention model:	Other

Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-05-2009
Enrollment:	20
Type:	Anticipated

Ethics review

Approved WMO

Application type:	First submission
Review commission:	METC Amsterdam UMC

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
CCMO	NL27513.018.09