Effects of methylphenidate on the development of the dopaminergic system in the brain

Published: 02-12-2010
Last updated: 15-05-2024

Primary objective of the study: 1. To report on the effectmodification by age of MPH treatment on the outgrowth of the DA system using state-of-the-art Magnetic Resonance Imaging (MRI) techniquesSecondary objectives:1. To report on the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Structural brain disorders
Study type	Interventional

Summary

ID

NL-OMON39033

Source
ToetsingOnline

Brief title
ePOD-MPH

Condition

- Structural brain disorders
- Cognitive and attention disorders and disturbances

Synonym
attention deficit hyperactivity disorder (ADHD); attention disorder

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: dopamine, methylphenidate, neurodevelopment, neuroimaging

Outcome measures

Primary outcome

Primary study parameters/endpoints:

- phMRI: % change in ASL signal from baseline in response to acute oral MPH challenge before and after 16 weeks of MPH treatment

- DTI: % change in FA and MD values from baseline after 16 weeks of MPH treatment

- Resting state fMRI (rs-fMRI): % change in functional connectivity (FC) within specific (DA) neuronal networks

Secondary outcome

Secondary study parameters/endpoints:

- fMRI: % change in task related BOLD signal from baseline

- Neuropsychological functioning: change in outcome of several well-validated neuropsychological (computer) tasks addressing emotional processing and impulsivity/behavioral inhibition compared to baseline measurements.

- Sleep log and actigraphy: % change from baseline

Study description

Background summary

50-90% of prescribed pediatric drugs have never been tested or licensed in children, only in adults. Approximately 100 million children in the European Union are prescribed off-label or unauthorized drugs and in doing so risk adverse reactions or do not respond to treatment at all. In fact, medication

doses used in children are no more than *guestimates*. Clearly, there are potential dangers in assuming that children will have the same response to therapy as adults. Methylphenidate (MPH) is primarily used as treatment for attention deficit hyperactivity disorder (ADHD), effectively reducing symptoms of inattention, hyperactivity, and impulsivity in up to 70% of children. It is assumed MPH does this by blocking the DA transporter (DAT) thus increasing extracellular DA in the brain. Its efficacy and safety has been documented in many studies. However, there is still a gap of knowledge concerning the influence of MPH on brain development and its effect on brain structure and function. Studies in animals raise serious concerns and call for further investigation of possible effects on brain structure and function.

Study objective

Primary objective of the study:
1. To report on the effectmodification by age of MPH treatment on the outgrowth of the DA system using state-of-the-art Magnetic Resonance Imaging (MRI) techniques

Secondary objectives:
1. To report on the effectmodification by age of MPH on the outgrowth of the DA system using several functional outcome measures (functional MRI (fMRI), neuropsychological test battery)
2. To report on the effects of MPH on restless legs syndrome (RLS) symptoms and insomnia.

Study design

A pharmacological MRI (phMRI) study for assessment of dopaminergic function and connectivity in an 18-week multicenter randomized, double-blind, placebo-controlled trial with methylphenidate in 100 children-, and adult male ADHD patients in which the effect of age is investigated before and after treatment. Patients will be stratified into two age groups: adolescents (10-12 years of age) and adults (23-40 years of age) and randomly assigned to receive a flexible dose of either MPH or placebo, resulting in four groups consisting of 25 subjects each.

Intervention

- Random assignment to a flexible dose of methylphenidate or placebo drug treatment for a period of 16 weeks with a 1 week washout period.
- 3.0 Tesla MRI scan. Total duration 2 x 30 minutes (with a 90 minute break in between scans) including a pharmacological phMRI (phMRI), diffusion tensor imaging (DTI), functional connectivity (rs-fMRI) and task-related fMRI scans before and after a DA challenge with oral MPH (0.5 mg/kg). Before, during and after trial end. The MRI scan during the trial will last 30 minutes, without a

DA challenge.
- Assessment of a neuropsychological (NPO) test battery and questionnaires (duration approximately 1 hour), Before, during and after trial end. The NPO during the trial will last 30 minutes.
- Assessment of sleep architecture using a questionnaire, actigraph and a sleep log during 3 x 5 days: Before, during and after trial end.

Study burden and risks

Since we study the effect of methylophenidate use on outgrowth of the dopaminergic system in the maturing brain, it is essential to include individuals in which brain development is still ongoing, thus minors.

Burden:
• Ingestion of study medication (tablets) during 16 weeks daily (methylphenidate or placebo, doubleblind).
• Screeningvisit and exit-interview during which confronting or uneasy questions can be asked.
• Three times 5 days of actigraphy (wearing a bracelet), and completing a sleeplog and short questionnaire.
• Two times assessment of neuropsychological tests and questionnaires (approximately 1 hour), and once for 30 minutes only.
• Three times MRI scan:
-Twice one hour (2 x 30 minutes) with in between an orale challenge with methylphenidate (0.5 mg/kg) followed by a 90 minutes break between scans.
-Once 30 minutes preceded, without oral challenge

Risks and burden: The risks and burden of study participation are related to
1) Pharmacotherapy: there is no added risk because the pharmacotherapy is part of normal clinical practice treatment. There may only be a negligible delay in start of the treatment in the placebo group. There is a small but negligible added burden in the placebo group, because after the trial end they can/must start active treatment. However, the placebo group receives the studymedication in the period that they would normally be on a waiting list for treatment. Ths they don*t experience any disadvantage of study participation, rather a potential benefit. All patients, including the placebo group will receive adequate care and monitoring and they can switch after trial end to an active treatment.
2) MRI: No added risk. MRI studies in children of 8 years and older have previously been approved by the METC of the AMC (e.g., MEC 06.053). There are no risks involved in MRI scanning. It is a non-invasive technique, and we will do everything in our potential to make the children at ease. The burden is considered minimal. There will be fun tasks to do in the scanner. In our experience children experience the tasks in the MRI scanner often amusing, rather than boring.
3) Oral challenge during the MRI scan: Negligible added risk. Oral challenge

with methylphenidate (0.5 mg/kg) as a kind of probe during the MRI examination to turn the dopamine system 'on'. The dose is well tolerated in children of 4-14 year old (see also page 10-11 of the study protocol). They may experience an inrease in heartbeat and blood pressure, but no significant side effects, thus a minimal added burden.
4) Actigraphy, neuropsychological examination and questionnaires: no added risk, minimal burden because these are non-invasive examinations that children in general find quite amusing.

The added risk of this study is thus negligible and the burden is minimal.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

50 adolescent (10-12 years of age) and 50 adult (23-40 years of age) male outpatients diagnosed with type ADHD, all subtypes as defined in the DSM-IV, and in need of pharmacotherapy according to existing guidelines.

Exclusion criteria

-Co-morbid Axis I psychiatric disorders requiring treatment with medication at study entry, and a history of epilepsy and traumatic brain injury. ;-IQ < 70 (subtest Wechsler Intelligence Scale for children-Revised (WISC-R; Wechsler 1981) or National Adult Reading Test (NART; Nelson 1991, Dutch translation Schmand et al. 1991) ;- Current or previous treatment with medications that influence the DA system (for adults before 23 years of age) such as: neuroleptics, antipsychotics, D2/D3 agonists (pramipexole and ropinirole);-Current or previous (ab)use of drugs that influence the DA system (for adults before 23 years of age), such as: MDMA, amphetamine, methamphetamine, cocaine, heroine and LSD ;-Contraindications to MPH treatment: cardiovascular diseases such as hypertension, arrhythmia, hyperthyroidism, glaucoma, suicidality, psychosis, Tourette disorder.;-Prenatal use of MPH by mother of the patients.;-Contraindications to MRI (metal implants, pacemakers, claustrophobia, etc.)

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-06-2011
Enrollment:	100

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ritalin
Generic name:	methylphenidate
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	02-12-2010
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-03-2011
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-12-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-06-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-08-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Not approved Date:	25-10-2012

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-01-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-04-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-12-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 20266
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2010-023654-37-NL
CCMO	NL34509.000.10
OMON	NL-OMON20266