Trial Description

Title

Studies on permeability of the blood brain interface for escitalopram related to the genotype of the ABCB-1 gene -effects on sleep

Trial Acronym

Escitalopram and sleep

URL of the trial

http://www.mpipsykl.mpg.de/1988842/studie_antidepressivum

Brief Summary in Lay Language

Escitalopram (brand name: Cipralex) is a marketed drug for the treatment of episodes of major depression, panic disorder, social phobia, generalized anxiety and obsessive compulsive disorder. We want to investigate how escitalopram influences sleep depending on genotype. In order to be effective antidepressants must reach the target, the brain. To this end at first these drugs must be absorbed in the gut and then they must pass the so-called blood-brain barrier. Certain proteins located in the cellular wall inhibit the absorption of substances in the gut and their transfer from blood into the brain as well by transporting them back. One of these proteins is called P-glycoprotein (P-Gp). A certain gene (molecular unit of heredity), the so-called ABCB-1 gene provides the construction plan of P-Gp. There exist various types of this gene so-called genotypes. In our Institute it was demonstrated, that clinical effects of antidepressants in depressed patients with different genotypes of the ABCB-1 gene are different. Therefore we suggest that different amounts of antidepressants reach the brain depending from these types. We want to clarify this issue with this study. It is known that most antidepressants including escitalopram exert an influence on sleep particularly by suppression of rapid eye movement (REM) sleep, a kind of sleep that occurs in intervals during the night and is characterized by rapid eye movements and more dreaming. We assume that the extent of REM suppression after escitalopram depends on the amount of the drug in the brain and herewith from the ABCB-1 genotype. We hope that this clinical trial will help to understand better the action of antidepressants and will help to treat depression, anxiety and obsessive compulsive disorder better. In a first pilot phase (A) we want to delineate the minimal dosage of escitalopram which is required to reduce the time spent in REM sleep. In the main phase (B) we want to test, whether the effects of escitalopram after the dosage determined in phase A on sleep differ between genotypes of the ABCB-1 gene.

We are searching healthy male volunteers, 20-35 years old, as participants of this study. Persons who are interested to participate in the study will be informed about the aims of the trial. After signing informed consent so-called genotyping will be performed in order to determine the ABCB-1 genotype of the volunteer. In addition the genotype of the so-called cytochrome gene will be determined to assess how fast drugs are metabolized. Before admission to the trial a thorough medical examination will be performed. The study consists of seven days. The subjects spend in all six nights during phase A (dose finding) or four nights during phase B (main study) in the so-called sleep laboratory of our hospital, in a single

room. The first (and during phase B also the third) night serve as adaptation nights. During the other nights in the sleep laboratory sleep-EEG recording is performed between 23:00 and 07:00. To that end electrodes will be fixed in the head region by paste to record electrical signals from the brain (so-called electroencephalogram, EEG), eye movements (electrooculogram, EOG) and the muscle tone of the chin (EMG). These recordings are not dangerous and are painless. They allow later analysis for sleep stages incuding the amount of REM sleep. After the second night in the sleep lab until the last night, that is for four days, daily escitalopram is given. During phase A the daily dosage rises from 2 to 3 to 4 and finally to 5 mg in order to delineate the minimal dosage which suppresses REM sleep. This dosage is given during phase B during four days. The plasma concentration of the substance is determined by blood sampling.During the total trial 250 mg blood will be collected during phase A and 200 mg blood will be collected during phase B, respectively. Between one week and 12 vdays after the final night in the sleep laboratory a control examination including blood sampling will be performed.

Brief Summary in Scientific Language

Only about 60% of all patients with depression are responders to antidepressants and only about 40% show full remission of depressive symptomatology after such treatment. Apart from other causes one possible reason for poor response to antidepressants is their inadequate penetration into the central nervous system, which depends on their ability to pass the blood-brain barrier (BBB). This barrier includes active transporters that are expressed at the luminal membrane of the endothelial cell lining, the small blood capillaries that form the BBB. These molecules actively transport the substrates against the concentration gradient out of the cells back to the blood circulation, thus potentially keeping brain drug concentration low. One of these transporter molecules is P-glycoprotein (P-Gp) which is coded by the ABCB-1 (multidrug-resistance <MDR>-1) gene (Hoffmeyer et al., 2000). Animal studies showed that knockout mice of this gene with a lack of P-Gp had 2-3 fold elevated levels of antidepressants including citalopram in the brain compared to the wildtype (Uhr and Grauer, 2003; Uhr et al., 2008). In patients with epilepsy it was shown that endogenous differences of the ABCB-1 gene which concern one single nucleotide polymorphism (SNP) correlated with a different risk to be therapy resistant (Siddiqui et al., 2003). In the Max Planck Institute of Psychiatry in the same gene another SNP, rs2032583 with similar properties was identified. Related to the genotype of this gene distinct differences in the therapy response were found in patients with depression. CC- and CT-carriers of this SNP showed significantly higher remission. rates after treatment with antidepressants which are substrate P-Gp than TT-cariers (Uhr et al., 2008). According to this finding we suggest that in subjects with different genotypes of this SNP different amount of antidepressants reach the brain.

The sleep EEG provides biomarkers for central nervous system effects of antidepressants (Steiger and Kimura, 2010). Selective serotonin reuptake inhibitors like citalopram induce suppression or REM sleep and enhance fragmentation of sleep related to an increase of nocturnal awakenings. Sleep changes after antidepressants are most distinct during the first week of active treatment. Sleep EEG is appropriate to assess these changes (Wilson et al., 2004). We hypothesize an association between the brain concentrations of antidepressants like escitalopram and their effects on sleep, particularly the degree of REM sleep suppression. Our previous studies suggest a relationship between plasma concentrations of antidepressants and their effect on sleep (Steiger, 1988). In a recent unpublished study we found an influence of the ABCB-1 genotype on sleep EEG of drugfree healthy subjects. Administration of 10 mg

escitalopram for four days suppressed, as expected, REM sleep. An influence of the genotype on the amount of this sleep-EEG change was not found however. Possibly in this study the dosage was too high to identify an influence of the genotype on sleep-EEG changes. Therefore the aim is to test whether after a lower dosage of escitalopram such difference occurs.

In a pilot study (phase A) which runs before the main study (phase B) the minimal dosage of escitalopram will be delineated, which is necessary to suppress REM sleep.

Organizational Data

- DRKS-ID: **DRKS00006241**
- Date of Registration in DRKS: **2014/11/12**
- Date of Registration in Partner Registry or other Primary Registry: **[---]***
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **Approved**
- (leading) Ethics Committee Nr.: **280-14 fed , Ethik-Kommission der Medizinischen Fakultät der Ludwig-Maximilians-Universität München**

Secondary IDs

- EudraCT-No.
(for studies acc. to Drug Law): **2014-001304-21**

Health condition or Problem studied

- Free text: **healthy volunteers**

Interventions/Observational Groups

- Arm 1: **The effect of escitalopram on sleep EEG is examined. First during phase A the minimal REM suppressing dosage is determined. In order to do this during four consecutive nights 2, 3, 4 and 5 mg escitalopram are given. In the main study (phase B) the effect of the dosage determined in phase A is given for four days in order to compare its effects in the genotypes CC or CT vs. TT on sleep EEG.**

Characteristics

- Study Type: **Interventional**
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Study Type Non-Interventional: **[---]***

- Allocation: **Single arm study**
- Blinding: **[---]***
- Who is blinded: **[---]***
- Control: **Uncontrolled/Single arm**
- Purpose: **Pharmacogenetics**
- Assignment: **Single (group)**
- Phase: **IV**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **No**

Primary Outcome

The main objective is to investigate whether in healthy subjects who are carriers of the C/C or C/T genotype of the ABCB-1 gene, SNP rs2032583, the time spent in REM sleep is significantly less than in carriers of the T/T genotype after 4 days of treatment with escitalopram in the minimal dosage suppressing REM sleep as delineated by dose finding.

Secondary Outcome

Secondary objectives include to investigate whether in healthy subjects after treatment with the minimal REM sleep suppressing dosage of escitalopram for four days
•further objective sleep variables [as the time spent in various sleep stages, sleep continuity, etc.] differs significantly from baseline [interval before tretament], indpendently from the genotype,
•those subjects who are carriers of the C/C or C/T genotype of the ABCB-1 gene show significantly more distinct changes of the objective sleep variables mentioned before than the carriers of the T/T genotype,
•further SNPs characterizing the transporter proteins of the blood brain interface exerte influences on objective sleep variables,
•low molecular substances exert influences on objective sleep variables,
•plasma concentrations of escitalopram exert influences on objective sleep variables,
•the gene expression differs significantly from baseline.

Countries of recruitment

- DE **Germany**

Locations of Recruitment

- Medical Center **Max-Planck-Institut für Psychiatrie, München**

Recruitment

- Planned/Actual: **Actual**
- (Anticipated or Actual) Date of First Enrollment: **2014/11/07**
- Target Sample Size: **27**
- Monocenter/Multicenter trial: **Monocenter trial**
- National/International: **National**

Inclusion Criteria

- Gender: **Male**
- Minimum Age: **20 Years**
- Maximum Age: **35 Years**

Additional Inclusion Criteria

1)Male healthy volunteers, 20 to 35 years old
2) each subject must understand the aims of the study and must give written informed consent

Exclusion criteria

1) Participation in another study either at the same time or during the last month prior to entering the study,
2)Psychiatric disorder, acute or in the own history,
3) Sleep disorders, acute or during the last 3 months,
4) Nocturnal shift work during the last 3 months,
5) Transmeridian flight during the last 3 months,
6) Serious acute or chronic physical disorder,
7) Any drug intake lasting more than two days during the last 3 months, any drug intake during the last month
8) Smoking,
9) Use of alcohol, more than moderate,
10) more than 2 cups of coffee per day,
11) drug abuse during the last 4 months,
12) intolerance of escitaolpram or additives

Addresses

- **Primary Sponsor**

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Sources of Monetary or Material Support

- **Private sponsorship (foundations, study societies, etc.)**

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Status

- Recruitment Status: **Recruiting complete, follow-up complete**
- Study Closing (LPLV): **2018/07/06**

Trial Publications, Results and other documents

** This entry means the parameter is not applicable or has not been set.*

**** This entry means that data is not displayed due to insufficient data privacy clearing.*