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Multicentre open-label study of neurotransmitters and neuropeptides in schizophrenia

Submission date	Recruitment status	[_] Prospectively registered
07/01/2010	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
18/01/2010	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
08/10/2012	Mental and Behavioural Disorders	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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EudraCT/CTIS number

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Secondary identifying numbers

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Study information

Scientific Title
Multicentre open-label study of neurotransmitters and neuropeptides in schizophrenia: a multidisciplinary study of biological, pharmacokinetic, receptor occupancy and clinical relationships in patients suffering from schizophrenia treated with quetiapine (Seroquel®)

Study objectives
Quetiapine is an effective neuroleptic drug for the treatment of schizophrenia affecting dopaminergic and serotonergic neurotransmission. However, it is not known what changes in dopaminergic and serotonergic metabolism will be induced by quetiapine at central sites and in the periphery, whether these changes will be interrelated and whether these changes will be related to clinical response.

Therefore, the effect of quetiapine on serotonine and dopamine in man will be measured in a study in which cerebrospinal fluid (CSF) concentrations of 5-HIAA and HVA (metabolites of serotonine and dopamine) and of some neuropeptides (neuropeptide Y [NPY] and corticotropin releasing factor [CRF]) will be determined before (baseline) and after a 4 week administration (post-treatment) of quetiapine (600 mg/daily) in patients suffering from schizophrenia. Moreover, quetiapine will be measured in CSF and plasma to study the transport into the brain. Furthermore, we will assess whether the presumed change of CSF 5-HIAA, HVA and the improvement of clinical symptoms will be related to the receptor occupancy of quetiapine and to its pharmacokinetics in plasma and CSF.

This study design allows us to correlate pre- to post-treatment changes in biochemical variables as well as with psychopathological response.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics Committee of the Johann-Wolfgang-University of Frankfurt a. M., Germany approved on the 21st February 2007 (ref: 75/2006)

Study design
Single arm uncontrolled open label trial

Primary study design
Interventional

Secondary study design
Non randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Schizophrenia

Interventions
This study is designed as an open multicentre study to be performed in the Departments of Psychiatry and Psychotherapy, Klinikum Fulda gAG and the Philipps-University of Marburg, Germany. Recruitment of the subjects is expected to take 12 months, therefore the total study will last approximately 13 months. The protocol will be submitted to the Ethics Committee of the LÄK in Frankfurt a.M., Bundesinstitut für Arzneimittel und Medizinprodukte in Bonn and the Bundesamt für Strahlenschutz in Salzgitter, Germany. Written informed consent will be obtained from the patients after explanation of the purpose and design of the study.

Subjects: Selection and assessment
Twenty two patients with a DSM-IV (American Psychiatric Association 1994) diagnosis of schizophrenia assessed by SCID, aged 18 - 55 years, will be recruited. All patients will be assessed before treatment (baseline) after a 3 day wash-out period and then at weekly intervals during treatment by an expert clinician using PANSS and CGI for severity of illness and for improvement with treatment. All patients will undergo an extensive physical and laboratory check up, including haematology, clinical chemistry, toxicological urine tests, electroencephalogram (EEG), and electrocardiogram (ECG) before inclusion into the study.

Baseline - Collection (Metabolites, Neuropeptides) and PET imaging
The patients will be have to be free from drugs, which could possibly interfere with CNS amine metabolites for at least 3 days prior to the study. After a 3 day wash-out period (baseline), cerebrospinal fluid (CSF) samples will be obtained by lumbar puncture (LP) at 9:50 a.m. After this procedure D2 and 5-HT2A occupancy will be measured at 10:00 a.m. using positron emission tomography (PET) imaging.

Treatment
All 22 patients will be assigned to quetiapine (up to 600 mg/daily) treatment for 4 weeks distrubted over the day according individual tolerability. Patients receive per os, at breakfast, active treatment with quetiapine. The total daily dose for the first 4 days therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3), 300 mg (Day 4) and 600 mg on week 1.

Post-Treatment - Collection (Metabolites, Neuropeptides) and PET imaging
Due to the measurement of D2 and 5-HT2A occupancy on day 28 the daily dose (600 mg) has to be administered at 8:00 a.m., plasma and cerebrospinal fluid (CSF) samples will be obtained at 9: 50 a.m. After this procedure D2 and 5-HT2A occupancy will be measured at 10:00 a.m. using positron emission tomography (PET) imaging.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)

Quetiapine (Seroquel®)

Primary outcome measure
Level of HVA at baseline and after quetiapine treatment (4 weeks) in CSF

Secondary outcome measures
1. Pharmacokinetics and pharmacogenetics:
Atypical antipsychotic drugs are generally biotransformed to metabolites that have a different pharmacological and pharmacokinetic profile from that of the parent compound. Consequently, the hypothesis that metabolic and pharmacokinetic properties of a drug and its metabolites play an important role in their overall pharmacological activity is plausible and needs to be explored for quetiapine. Preliminary exploratory information will be obtained on:
1.1. The relative concentrations of quetiapine in cerebrospinal fluid (CSF) versus plasma, and on the plasma/CSF ratio-clinical effectiveness relationship in patients with schizophrenia, taking into account the phenotype/genotype of MDR1-polymorphism. To date no published data are available on this issue.
1.2. The role of the MDR1-polymorphism on the concentrations of quetiapine and 5-HIAA and HVA in CSF, and on the possible existence of a transport of quetiapine through the blood brain barrier

The hypothesis is that the relative concentrations of quetiapine in cerebrospinal fluid (CSF) are approximately half of those in plasma, measured after 4-week quetiapine treatment. Moreover, quetiapine administration should result in a highly significantly correlation between quetiapine in plasma and quetiapine in CSF concentrations.

2. Neurotransmitters and neuropeptides:
Dysregulation of the serotonergic and dopaminergic systems as well as altered hypothalamic-pituitary-adrenal (HPA) axis are likely, but not necessary involved in pathophysiology of schizophrenia. Thus, accumulated evidence indicates that NPY, as well as CRF, also play a role. Preliminary exploratory information will be obtained on:
2.1. The relative concentrations of neuropeptides e.g. NPY and CRF measured at pre-treatment and after quetiapine medication period and the relationship with clinical improvement. To date no published data are available on this issue.

The determinations of NPY and CRF in CSF, measured at baseline and after treatment will significant predict the degree of symptom improvement following 4 weeks quetiapine treatment (i.e. decrease in PANSS total score) and correlate with the availability of quetiapine in the central nervous system as shown by its CSF concentrations.

3. Neuroimaging:
The primary motive for seeking information on the occupancy of central nervous system (CNS) receptors by drugs is that the kinetics of a drug in brain may differ from its kinetics in plasma. The drug receptor complex may dissociate more slowly than the rate by which the concentrations of free drug is reduced in blood. It is also possible that the drug does not reach its target because of diffusion barriers or rapid peripheral metabolism. Kinetics of the drug at its target site can only be assessed by non-invasive imaging techniques like PET. Preliminary information will be obtained on:
3.1. The relationship between D2 and 5-HT2A occupancy and CSF kinetics of quetiapine, biochemical parameters (5-HIAA and HVA) and clinical improvement. To date no published data are available on this issue.

The determinations of D2 and 5-HT2A occupancy, measured at baseline and after treatment will significantly predict the degree of symptom improvement following 4 weeks quetiapine treatment (i.e. decrease in PANSS total score) and correlate with the availability of quetiapine in the central nervous system as shown by its CSF concentrations. Moreover, occupancy of dopamine D2 and serotonin 5-HT2A receptors correlate significantly with the changes in the CSF 5-HIAA and HVA concentrations.

4. Clinical variables:
For the evaluation of the clinical response of the patients under the neuroleptic treatment with quetiapine in exploratory way PANSS and CGI-ratings will be applied. In addition, PANSS-ratings will be related to the expected change in the primary variable to assess a probable relationship between the changes in 5-HIAA induced by quetiapine and the clinical state at the end of the treatment.

Overall study start date
01/12/2006

Completion date
31/12/2009

Eligibility

Key inclusion criteria
1. Diagnosis of schizophrenia by Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV)
1.1. Paranoid type (295.30)
1.2. Catatonic type (295.20)
1.3. Disorganised type (295.10)
1.4. Undifferentiated type (295.90)
1.5. Residual type (295.60)
2. Females and males aged 18 - 55 years
3. Clinical indication for a new treatment with antipsychotics (in case of an acute phase) or an adaptation or change of antipsychotic medication (due to an instable course)
4. Positive and Negative Syndrome Scale (PANSS) score at entry greater than 60
5. Female patients of childbearing potential must be using a reliable method of contraception and have a negative urine human chorionic gonadotropin (HCG) test at enrolment
6. Written informed consent
7. Capability to understand and comply with the requirements of the study
8. Patients without any medication affecting (serotonergic, dopaminergic and noradrenergic neurotransmission)
9. Patients with antipsychotic and/or antidepressive pre-treatment can be enrolled after a wash out period of 7 days. In case of fluoxetine at least 4 weeks.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
22

Key exclusion criteria
1. Any DSM-IV Axis I disorder not defined in the inclusion criteria
2. Predominantly organic psychosis
3. Any medical disease which will be related to psychopathology of the patient or will interfere with treatment requirements
4. Substance or alcohol dependence at enrolment (except dependence in full remission, and except for caffeine or nicotine dependence), as defined by DSM-IV criteria
5. Opiates, amphetamine, barbiturate, cocaine, cannabis, or hallucinogen abuse by DSM-IV criteria within 4 weeks prior to enrolment
6. Treatment with drugs affecting (serotonergic, dopaminergic and noradrenergic neurotransmission), especially neuroleptics, antidepressants, sedatives
7. Patients who had suffered from colzapine-induced agranulocytosis, or who had been treated with clozapine during two months prior to enrolment
8. Pregnancy or lactation
9. Patients who, in the opinion of the investigator, pose an imminent risk of suicide or a danger to self or others
10. Known intolerance or lack of response to quetiapine fumarate, as judged by the investigator
11. Use of any of the following cytochrome P450 3A4 inhibitors in the 14 days preceding enrolment including but not limited to: ketoconazole, itraconazole, fluconazole, erythromycin, clarithromycin, troleandomycin, indinavir, nelfinavir, ritonavir, fluvoxamine and saquinavir
12. Use of any of the following cytochrome P450 inducers in the 14 days preceding enrolment including but not limited to: phenytoin, carbamazepine, barbiturates, rifampin, St John's Wort, and glucocorticoids
13. Administration of a depot antipsychotic injection within one dosing interval (for the depot) before randomisation
14. Medical conditions that would affect absorption, distribution, metabolism, or excretion of study treatment
15. Unstable or inadequately treated medical illness (e.g. diabetes, angina pectoris, hypertension) as judged by the investigator
16. Involvement in the planning and conduct of the study
17. Previous enrolment or randomisation of treatment in the present study.
18. Participation in another drug trial within 4 weeks prior enrolment into this study or longer in accordance with local requirements

Date of first enrolment
01/12/2006

Date of final enrolment
31/12/2009

Locations

Countries of recruitment
Germany

Study participating centre
Klinikum Fulda gAG
Fulda
Germany
36043

Sponsor information

Organisation
Klinikum Fulda gAG (Germany)

Sponsor details
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Sponsor type
Hospital/treatment centre

Website
http://www.klinikum-fulda.de/allg/html/index/

ROR
https://ror.org/04jmqe852

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Klinikum Fulda gAG (Germany)

Results and Publications

Publication and dissemination plan

Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	genetic results	01/07/2011		Yes	No
Results article	NPY and CRF results	01/09/2012		Yes	No