

# Multicentre open-label study of neurotransmitters and neuropeptides in schizophrenia

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| <b>Submission date</b><br>07/01/2010   | <b>Recruitment status</b><br>No longer recruiting             | <input type="checkbox"/> Prospectively registered    |
| <b>Registration date</b><br>18/01/2010 | <b>Overall study status</b><br>Completed                      | <input type="checkbox"/> Protocol                    |
| <b>Last Edited</b><br>08/10/2012       | <b>Condition category</b><br>Mental and Behavioural Disorders | <input type="checkbox"/> Statistical analysis plan   |
|  |   | <input checked="" type="checkbox"/> Results          |
|  |   | <input type="checkbox"/> Individual participant data |

**Plain English summary of protocol**  
Not provided at time of registration

## Contact information

**Type(s)**  
Scientific

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## Additional identifiers

**Protocol serial number**  
Version Nr: 1.3; D1449L00033

## 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 serotonin and dopamine in man will be measured in a study in which cerebrospinal fluid (CSF) concentrations of 5-HIAA and HVA (metabolites of serotonin 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

### **Study type(s)**

Treatment

### **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 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-HT<sub>2A</sub> 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 distributed 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-HT<sub>2A</sub> 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-HT<sub>2A</sub> 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(s)**

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

## **Key secondary outcome(s))**

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 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.

## 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-HT<sub>2A</sub> 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-HT<sub>2A</sub> 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-HT<sub>2A</sub> 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.

## 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

## Healthy volunteers allowed

No

## Age group

Adult

## Lower age limit

18 years

## Sex

All

## 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 clozapine-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)

**ROR**

<https://ror.org/04jmqe852>

# Funder(s)

## Funder type

Hospital/treatment centre

## Funder Name

Klinikum Fulda gAG (Germany)

# Results and Publications

## 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? |
|---|-------------------------------|--------------|------------|----------------|-----------------|
| <a href="#">Results article</a>               | genetic results               | 01/07/2011   |            | Yes            | No              |
| <a href="#">Results article</a>               | NPY and CRF results           | 01/09/2012   |            | Yes            | No              |
| <a href="#">Participant information sheet</a> | Participant information sheet | 11/11/2025   | 11/11/2025 | No             | Yes             |