# Development of an optimal sampling strategy for clozapine to predict area under the concentration-time curve ratios and the clinical validation of the dried blood spot analysis for clozapine

Published: 13-05-2014
Last updated: 23-04-2024

- To establish a model for TDM and calculate the AUC in patients treated with clozapine.- To clinically validate the DBS analysis method for clozapine. - To determine which sample points or combination of sample point(s) gives the best estimate of...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Schizophrenia and other psychotic disorders |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON40128

**Source**
ToetsingOnline

**Brief title**
Optimal sampling model and clinical validation of DBS for clozapine

### Condition

- Schizophrenia and other psychotic disorders

**Synonym**
schizophrenia

**Research involving**
Human

## Sponsors and support

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

## Intervention

**Keyword:** Clozapine, Dried Blood Spot analysis, Optimal sampling model

## Outcome measures

### Primary outcome

Developing a model for the calculation of the clozapine area under the plasma concentration-time curve from 0 to 12 hours (AUC0-24).

### Secondary outcome

- Comparing the clozapine drug levels obtained by venous blood sampling with the clozapine drug levels obtained by finger prick DBS sampling and venous DBS sampling.
- to determine which sample points or combination of sample point(s) using the developed model gives the best estimate of the AUC of clozapine (optimal sampling).
- To perform an external validation of the model using concentration-time data of clozapine from Russian patients.

# Study description

### Background summary

Clozapine is one of the most effective antipsychotic drugs currently available that is particularly used in patient who are refractory or intolerant to other antipsychotics. The plasma concentration of clozapine is very important for the treatment efficacy of the medicine. Unfortunately, no clear linear correlation between the dose and plasma concentration of clozapine is observed. This is

caused by various genetic, individual and environmental factors and also co-morbidity may influence the plasma concentration.
Since many factors affect the clozapine plasma concentration in patients, therapeutic drug monitoring (TDM) is highly recommended and prevailed in clozapine treatment. Concentration measurements have become common practice in the treatment of a patient with clozapine. The clozapine plasma concentration is generally determined at the start of the therapy, when there is a poor response on the drug, in case of expected interactions, the suspicion of an intoxication, infections, the stop or start of smoking or control therapy in case of higher doses. Plasma levels above 350 µg/L seem to give a better therapy-response, although response may also occur below 350 µg/L.
By TDM, both the clozapine plasma levels and the levels of its major metabolite desmethylclozapine are determined using the trough level concentration. The relationship between the clozapine and desmethylclozapine concentrations gives an impression of the pharmacokinetic profile of clozapine However, trough-level monitoring for clozapine/ desmethylclozapine is probably not optimal in all cases. Patients with the same trough concentration may not have the same drug exposure as judged by the pharmacokinetic profile. The area under the plasma concentration time curve (AUC) might be a better indicator of clozapine exposure. However, clozapine AUC-0-12h measurement requires multiple samples from patients over 12 hours, what makes it intensive, time-consuming and uneconomical. A limited-sampling model that can estimate the AUC of clozapine from a reduced number of blood samples may help to overcome these problems. In this research, we are going to determine which sample point or combination of sample point(s) gives the best estimate of the AUC of clozapine using a population PK model of clozapine.
In order to make TDM even more easier and patient friendly, Dried Blood Spot (DBS) sampling will be used. DBS samples are dry, more stable and easier to obtain as compared to conventional samples. We assume that the DBS method is suitable for determining clozapine plasma levels in patients with schizophrenic disorders especially in the ambulatory setting. However, the DBS method needs to be validated in a clinical setting to ensure its reliability. Therefore in this research protocol, analysis of venous blood samples is compared with analysis of dried blood spots.
In future research the correlation between the clozapine plasma concentration, the given dosage and the clinical effect will be examined. A model to predict the exposure as determined by AUC based on a population PK model with limited sampling, will be very useful in this research. Furthermore, DBS sampling will be a great advantage in collecting and transporting blood samples in different settings, DBS samples are dry and stable and easy to transport with usual transport systems (postal mail). In addition, they can be stored at ambient conditions and a refrigerator is not requirement as is with liquid samples.

## Study objective

- To establish a model for TDM and calculate the AUC in patients treated with clozapine.

- To clinically validate the DBS analysis method for clozapine.
- To determine which sample points or combination of sample point(s) gives the best estimate of the AUC using the developed population PK model.
- To perform an external validation of the model using concentration-time data of clozapine from Russian patients.

**Study design**

a) Recruitment of 15 schizophrenic patients (male or female; Caucasian ethnicity; aged 18 till 55 years) under stable mono-therapy with 200 - 600 mg clozapine in a single morning dose for at least two weeks and excluding the usage off all predefined concomitant medication. All used co-medication should be recorded including dosage used and generic names.

b) Collecting venous blood samples of about 5 ml before intake of clozapine and at 2, 4, 6, 8, and 12 hrs after oral administration of clozapine (when 12 hrs is feasible).

c) Finger prick DBS (2-3 blood drops) before intake of clozapine and at 2, 4, 6, 8 and 12 hrs after oral administration of clozapine.

d) Venous DBS before intake of clozapine and at 2, 4, 6, 8 and 12 hrs after oral administration of clozapine prepared by pipetting 3 * 50 µl of the venous blood sample onto a dried blood spot paper.

e) Storage of all obtained venous plasma samples at -80C.

f) Clozapine serum concentration-time data for external validation will be made available by
The Mental Health Research Institute Tomsk, as part of a collaborative partnership.

**Study burden and risks**

Patients may experience minor discomfort from blood sampling and the finger prick. The finger prick is however widely applied for self-test glucose monitoring in diabetic patients and self-test INR control in patients using anticoagulants and discomfort is estimated to be mild. There are no advantages for the participant in this study.

# Contacts

**Public**
Universitair Medisch Centrum Groningen

hanzeplein 1
Groningen 9713 GZ
NL
**Scientific**
Universitair Medisch Centrum Groningen

hanzeplein 1
Groningen 9713 GZ
NL

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

Stable treatment with clozapine for at least two weeks
Caucasian ethnicity
Age between 18 and 55 years

## Exclusion criteria

Patients who start a treatment with any of the drugs descriped below less than three days before blood sampling are excluded from participation in this study (in case of amidaron within 6 months). Patients who already use these drugsfor longer than three days are not excluded from the study, unless there is a change in usage or dosage less than three days before sampling.
Amiodarone
Cimetidine
Fluoroquinolones
Fluvoxamine
Furafylline
Interferon

Methoxsalen
Mibefradil
Insulin
Methylcholanthrene
Modafinil
Nafcillin
Beta-Naphthoflavone
Omeprazole

# Study design

## Design

**Study type:** Observational invasive

| | |
|---|---|
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 01-06-2014 |
| Enrollment: | 15 |
| Type: | Actual |

# Ethics review

Approved WMO

| | |
|---|---|
| Date: | 13-05-2014 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |

# 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 |
|---|---|
| Other | clinicaltrials.gov |
| CCMO | NL46635.042.13 |