Influence of dose interval on the pharmacokinetics of both unbound and total fractions of clozapine and norclozapine in psychiatric patients in the Netherlands

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

Summary

ID

NL-OMON48672

Source
ToetsingOnline

Brief title
INPUT study

Condition

- Schizophrenia and other psychotic disorders

Synonym
psychosis, Schizophrenia

Research involving

Human

Sponsors and support

Primary sponsor: Albert Schweitzer Ziekenhuis
Source(s) of monetary or material Support: Wetenschapscommissie ASz

Intervention

Keyword: clozapine, dose regimen, norclozapine, population pharmacokinetics

Outcome measures

Primary outcome

The main study parameters are the total and unbound clozapine and norclozapine plasma concentrations at specified time points. With these concentrations characterised pharmacokinetic profiles as well as metabolic ratio and protein binding of clozapine and norclozapine in OID and BID dosing regimens, will be determined.

Secondary outcome

Secondary endpoints are the frequency or discomfort of clozapine*s side effects.

Study description

Background summary

The antipsychotic clozapine has widely been recognised as the golden standard in treatment-resistant schizophrenia and partially responsive schizophrenia. The Dutch Guideline for the use of clozapine recommends that, preferably, clozapine should be given once daily (OID), before sleep, to relief the discomfort of side effects such as sedation, orthostatic hypotension and hypersalivation over the day, without assigning restrictions to a maximum dose. Accordingly, in the Netherlands there seems to be a shift towards OID dosing of clozapine at the end of the day. Though an OID regimen may be beneficial for drug adherence, benefits regarding relief of side effects have not been proven

yet. Moreover, all the available pharmacokinetic studies with clozapine are based on the twice-a-day (BID) regimen, as is the established clozapine threshold concentration for effect (0.30-0.35mg/l). However, in practice the same clozapine plasma reference concentrations, are used to guide therapy for both single and divided dose schedules, but it is not known whether this is legitimate or not.

Study objective

The aim of this study is to assess the differences in the pharmacokinetic properties of clozapine and norclozapine when clozapine is used OID or BID in psychiatric patients, examining both clozapine and norclozapine concentrations and its unbound fractions and total concentrations. Ultimately, the knowledge of the full pharmacokinetic profile will facilitate in developing an evidence based therapeutic window for clozapine when used OID. Additionally, we will explore the influence of dose frequency on the impact and frequency of clozapine*s side effects in relation with the clozapine plasma concentration found in this study, using the UKU (Udvalg for Kliniske Undersogelser) ratingscale.

Study design

This is a multicentre, non-randomised, open label study, using a limited sampling strategy and population pharmacokinetic analyses.

Study burden and risks

The study will be conducted among psychiatric in- and outpatients receiving clozapine therapy OID or BID as part of their regular treatment. Thus, patients are not designated to any investigational treatment nor to any dosing regimen different from their normal treatment. In participants using clozapine OID in total 9 (or 10) blood samples will be drawn at the study day (7 (or 8) for clozapine and norclozapine analysis and 2 for analysis of co-variates). All samples will be taken within 12 hours after the start of the study day, using the Venflon multiple sample sleeve, allowing collection of numerous samples through a single venepuncture and thereby reducing the number of venapunctures. A physician trained and competent in blood sampling will be installed at the study location for drawing blood at specified time points. He/she will also monitor both psychiatric and somatic signs of the participants in order to detect any psychiatric or somatic discomfort, stress or other disturbing signs during the study day.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* Age *18 * 70 years
* Clozapine use BID or OID
* Capacity to speak and read the Dutch language.
* Mental competency and decisional capacity with regard to participation in the current study
* Absence of active suicidality
* Clozapine use in *steady state* (i.e. same dose and frequency for *7 days)
* Signed Informed consent

Exclusion criteria

* *inbewaringstelling* (IBS)

* *rechterlijke machtiging* (RM)
* Pregnancy (if known)
* Initiation, cessation or dose change of the following co-medication within 7 days prior to blood sampling:
o Fluvoxamine
o Hormonal anti-conceptive,
o Ciprofloxacin,
o Phenytoin,
o Valproic acid,
o Carbamazepine
o Rifampicin.
* Acute inflammation / infection (derived from having fever (i.e. body temperature >38.0 degrees Celsius and/or using an antibiotic at time of blood sampling).
* Smoking (of tobacco containing products) initiation or cessation < 7 days before participation

Study design

Design

Study phase:	4
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-03-2019
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Leponex and Clozaril
Generic name:	Clozapine

Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	29-03-2018
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-09-2018
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-05-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-06-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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: 26619
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2017-004834-26-NL
CCMO	NL63635.101.18
OMON	NL-OMON26619