Does dose frequency influence the plasma concentration of clozapine and norclozapine in psychiatric patients in the Netherlands?

Gepubliceerd: 30-11-2017 Laatst bijgewerkt: 15-05-2024

Clozapine is highly protein bound and theoretically protein binding can become saturated when higher peak concentrations are reached after once daily (OID) dosing of clozapine. Also higher peak concentrations after OID dosing, could theoretically...

Ethische beoordeling	Positief advies
Status	Werving gestopt
Type aandoening	-
Onderzoekstype	Observationeel onderzoek, zonder invasieve metingen

Samenvatting

ID

NL-OMON26619

Bron
Nationaal Trial Register

Verkorte titel
INPUT study

Aandoening

schizophrenia, clozapine, pharmacokinetics, dose interval, protein binding

Schizofrenie, clozapine, farmacokinetiek, doseerfrequentie, eiwitbinding

Ondersteuning

Primaire sponsor: Albert Schweitzer hospital, Dordrecht, the Netherlands
Overige ondersteuning: Scientific committee, Albert Schweitzer hospital, Dordrecht, the Netherlands

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

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

Toelichting onderzoek

Achtergrond van het onderzoek

Background of the study:

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/1). 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.

Objective of the study:

The aim of this multicentre, non-randomised, open label 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.

Doel van het onderzoek

Clozapine is highly protein bound and theoretically protein binding can become saturated

when higher peak concentrations are reached after once daily (OID) dosing of clozapine. Also higher peak concentrations after OID dosing, could theoretically lead to saturation of clozapine’s metabolic enzymes and thus might alter its linear elimination rate into a non-linear relation, influencing its elimination rate. Finally, since norclozapine has a longer terminal elimination half-life than clozapine, it is possible that the metabolic ratio of clozapine to norclozapine is increased when switching from BID dosing to OID dosing. This underlines the need for a population pharmacokinetic study comparing both total and free clozapine and norclozapine concentrations when clozapine is adminis-tered OID or BID.

Onderzoeksopzet

-T = 0 hours : trough concentration

-T = 20 minutes: absorption phase begins

-T = 2 hours and 4 hours: maximum concentration (Cmax) is expected to be reached after 1-3 hours

-T = 8 hours: for BID dosing, this time point will be on the slope between the Cmax and the trough concentration

-T = 12 hours: for OID dosing, this time point will be halfway the concentration time curve; for BID dosing, the concentration at t=12 hours is expected to be equal to the concentration at t= 0 hours (trough concentration).

Onderzoeksproduct en/of interventie

At the study day(s), multiple blood samples will be drawn from the included patients. Sampling times depend on the patient’s clozapine dosing regimen.
In addition, a standardised assessment tool for measuring the side-effects of clozapine will be filled out by the participants during the study day

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

 Age ≥18 – 65 years

 Clozapine use BID or OID *1

 Capacity to speak and read the Dutch language.

 Mental competency and decisional capacity with regard to participation in the current study *2

 Absence of active suicidality *2

 Clozapine use in ‘steady state’ (i.e. same dose and frequency for ≥7 days)

 Informed consent

 Admission to the same ward or assisted living accommodation for ≥7 days *3

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

 ‘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 Phenytoin,

o Valproic acid,

o Carbamazepine

o Rifampicin.

 Acute inflammation / infection (derived from having fever (i.e. body temperature >38 degrees Celsius and/or using an antibiotic at time of blood sampling).

 Smoking initiation or cessation < 7 days before participation

Onderzoeksopzet

Opzet

Type:	Observationeel onderzoek, zonder invasieve metingen
Onderzoeksmodel:	Anders
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestopt
(Verwachte) startdatum:	01-02-2018
Aantal proefpersonen:	50
Type:	Werkelijke startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Ethische beoordeling

Positief advies

Datum:	30-11-2017
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 48672
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL6913
NTR-old	NTR7108
CCMO	NL63635.101.18
OMON	NL-OMON48672

Resultaten