Fluconazole pharmacokinetics, including bioavailability, in Obese subjects after an Intravenous and oral Administration (FOLIA).

Published: 23-07-2018
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Primary objective: To determine the effect of obesity (BMI *35 kg/m2) on the pharmacokinetics, including oral bioavailability of fluconazole.Secondary objective: To develop an optimal dosing regimen for obese patients.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Fungal infectious disorders
Study type	Interventional

Summary

ID

NL-OMON45817

Source
ToetsingOnline

Brief title
FOLIA

Condition

- Fungal infectious disorders

Synonym
Fungal infection/candidiasis

Research involving
Human

Sponsors and support

Primary sponsor: Klinische Farmacie

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Fluconazole, Obese, Pharmacokinetics

Outcome measures

Primary outcome

A farmacokinetic model using Non Linear Mixed Effects Modelling (NONMEM). Model

validation using bootstrap

method or Sampling Importance Resampling (SIR). The final model will be used

for Monte Carlo simulation for multiple-dosing regimens and higher dosages.

Secondary outcome

NA

Study description

Background summary

The incidence of obesity (Body Mass Index (BMI) > 30 kg/m2) is increasing worldwide. Dosing guidelines are based on clinical trials in which obese subjects are often excluded. Pharmacokinetic studies are necessary to determine the appropriate dosing regimen for obese patients, as obesity and morbid obesity are associated with many physiological changes affecting pharmacokinetics.

There is clear evidence indicating that heavier patients are receiving a sub-optimal dose of fluconazole if the current guidelines are used (see H1.1 'Background and rationale' of the protocol). Fluconazole is registered for the treatment of invasive candidiasis and is a drug of first or second choice, depending on the Candida species. A sub-optimal dose can result in therapy failure with an increased risk of mortality, so adequate dosing is needed at start of treatment.

Fluconazole is available as an oral and intravenous formulation. However, information on bioavailability of the oral form in obese patient and in patient who had undergone bariatric surgery, is not known.

Therefore it seems prudent to conduct a trial in a cohort of obese patients who receive fluconazole oral (400 mg, registered dose), followed by an intravenous dose of 400 mg fluconazole and define the pharmacokinetics, including oral bioavailability. These will then be compared to the pharmacokinetics in a normal-weight group. Both groups receive 400 mg fluconazole oral, followed by 400 mg fluconazole intravenous

This study aims to provide clinical information that will be used to determine an optimal dosing strategy for obese patients thru modeling and simulation.

Study objective

Primary objective: To determine the effect of obesity (BMI *35 kg/m2) on the pharmacokinetics, including oral bioavailability of fluconazole.

Secondary objective: To develop an optimal dosing regimen for obese patients.

Study design

This is a prospective, open-label, non-randomized, multi-centre trial.

An oral dose of fluconazole (400 mg) followed by an intravenous dose of fluconazole (400 mg) is administered.
A PK curve is taken from t = 0.25 to 48 hours.

Intervention

Placin a venous cathether for blood sampling.
Administration of an oral dose of fluconazole (400 mg) followed by an intravenous dose of fluconazole (400 mg) administered according to SPC.
Sampling of a total of 100 ml of blood (including PK Curve, lab values, hematology)

Study burden and risks

The risk-classification is assessed as negligible to the patient population receiving study drug at the current regimen. The drug is licensed on the Dutch market for the 400 mg dosages administered in this trial. The medication will be administered as two doses, but none of the two groups (1 obese and 1 non-obese) will receive a dose resulting in an exposure that is higher than studied in the registrations studies. Fluconazole is considered to be safe up to a dose of 1600 mg. Therefore, there is no attributable risk for the application of the study protocol to the subjects.

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

1. Subjects BMI:
a. obese groups: subject must have a BMI *35 kg/m2 at the time of inclusion;
b. non-obese group: subject must have a BMI *18.5 and <30 kg/m2 at the time of inclusion;
2. Subject is at least 18 of age on the day of screening and not older than 65 years of age on the day of dosing;
3. Subject able and willing to sign the Informed Consent before screening evaluations.
4. If a woman, is neither pregnant nor able to become pregnant and is not nursing an infant.;For the non-obese subjects the following additional inclusion criteria applies:;5. Subject is in good age-appropriate health condition as established by medical history, physical examination, electrocardiography, results of biochemistry, hematology and urinalysis testing within 6 weeks prior to study drug administration. Results of biochemistry, hematology and urinalysis testing should be within the laboratory's reference ranges (see

Appendix A). If laboratory results are not within the reference ranges, the subject is included based on the investigator*s judgment that the observed deviations are not clinically relevant. This should be clearly recorded.

Exclusion criteria

1. Documented history of sensitivity to fluconazole or similar azole-compound.
2. Documented history of the long QT syndrome (LQTS)
3. History of, or known abuse of drugs, alcohol or solvents (up until a maximum of three months before study drug administration);
4. Use of medication that has known relevant interaction with study drug as determined by the investigator up to 1 weeks prior to study drug administration;
5. Donation of blood or plasma to a blood bank or in a clinical study (except a screening visit) within 4 weeks prior to study drug administration;
6. Blood transfusion within 8 weeks prior to study drug administration;
7. Treatment with the concerning study drug up to 7 days before administration of the study drug;
8. Any other sound medical, psychiatric and/or social reason as determined by the investigator.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-11-2019
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Diflucan
Generic name:	Fluconazole
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	23-07-2018
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-11-2018
Application type:	First submission
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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-002613-35-NL
CCMO	NL66611.100.18

Study results

Date completed:	23-03-2021
Actual enrolment:	25

Summary results
Trial is onging in other countries