Pharmacokinetics of posaconazole (Noxafil(R)) as prophylaxis for invasive fungal disease

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• To determine the pharmacokinetics of posaconazole (new solid oral and IV) given as prophylaxis to patients who are at risk for developing fungal infections after receiving conditioning therapy (except strictly non myeloablative (NMA)) for…

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

Summary

ID

NL-OMON43127

Source
ToetsingOnline

Brief title
PIRAÑA

Condition

- Fungal infectious disorders

Synonym
fungal prophylaxis, pharmacokinetics

Research involving
Human

Sponsors and support

Primary sponsor: Afdeling Apotheek
Source(s) of monetary or material Support: Merck Sharp & Dohme (MSD),pharmaceutical company

Intervention

Keyword: fungal infections, mucositis, pharmacokinetics, posaconazole

Outcome measures

Primary outcome

Data will be analyzed using non-linear mixed effects modeling (NONMEM). NONMEM is a one-stage analysis that simultaneously fixed (e.g. clearance, volume of distribution, covariate effects)and random (e.g. inter- and intra-individual variability and residual error) effects. Since allowance can be made for individual differences, this method can be used with both intensive sampling and sparse data (and in the occasion of missing values: an unbalanced number of data points per patients).

Multiple compartment models with first-order or saturable elimination will be tested. Between subject variability (BSV) and, when applicable, between occasion variability (BOV) will be included on all pharmacokinetic parameters. Residual unexplained variability (RUV) will be estimated with additive or proportional error models. The first-order conditional estimation method with interaction will be used. Citrulline will be tested as a binary covariate on bioavailability. Dose linearity

Secondary outcome

not applicable

Study description

Background summary

Posaconazole is licensed for treatment of invasive fungal infections in patients intolerant to first line therapy and for prophylaxis of invasive fungal infections in patients receiving remission induction chemotherapy for AML/MDS expected to have prolonged neutropenia and HSCT recipients undergoing high-dose immunosuppression for GVHD.

Despite the proven clinical effectiveness of posaconazole in these patients; low posaconazole plasma concentrations, possibly leading to breakthrough infections, have been reported in literature . According to the ECIL guidelines, posaconazole trough concentrations >0.5-0.7 mg/L for prophylaxis and >1mg/L for treatment are related to higher efficacy.
Low plasma concentrations are due to very unpredictable bioavailability of the oral suspension. Posaconazole is a highly lipophilic, weak base with low solubility in water, all limiting the absorption. Furthermore, the unpredictable bioavailability is attributed to underlying diseases (e.g. diarrhea, neutropenia, mucositis) and used co-medication such as proton pump inhibitors. This has limited the use of posaconazole, despite its extensive in vitro spectrum potential.

The new oral formulation with a pH dependent polymer matrix shows more consistent absorption compared to the oral solution. Doses of the new formulations (IV and tablet) for both prophylaxis and treatment are 300mg BID on day 1, followed by 300mg QD on following days. This dose regimen is profoundly different compared to the dose regimens of the oral solution (dependent on indication 200mg BID-QID).
The new formulations offer new treatment possibilities, specifically in patients previously unable to attain adequate exposure to posaconazole.

Already some data are published on the pharmacokinetics; however strictly selected to patients and healthy volunteers. However, important specific aspects related to the pharmacokinetics remain unsolved, such as data on the impact of different phases of mucositis on the pharmacokinetics, as it is unknown whether mucosal barrier injury impacts the absorption of posaconazole or alters presystemic clearance. Even though vanStraelen et al found that posaconazole plasma concentrations remained >0.5mg/L in six allogeneic stem cell transplant patients receiving posaconazole tablets as prophylaxis; it remains unkown whether the pharmacokinetics will be impacted by mucositis and adequate exposure will be attained in a larger group of patients or when given as treatment where higher plasma concentrations are pursued (>1.0 mg/L).

With this trial we think we can resolve the pharmacokinetics of the new formulations of posaconazole in a cohort of haematological patients. A step-down in posaconazole dose will provide information on linearity of the absorption. In theory, step-down from 300mg QD to consecutively 200mg QD and

100mg QD would provide rich information on linearity; however it remains unknown if 100mg QD will ensure adequate exposure to ensure prophylaxis. Therefore only step-down to 200mg QD will be performed.

Posaconazole can then serve as a model substrate to determine the impact of mucositis on the pharmacokinetics of other drugs as well, allowing direct translation of findings to the clinical practice and assists us in further improving treatment of invasive fungal infections in this vulnerable group of patients.

For the purpose of resolving our primary research question, we have selected a group of patients that will experience a severe degree of mucositis either induced by the conditioning regimen or severe GvHD and whom are a target population for receiving posaconazole prophylaxis. As a general statement, we hypothesize that altered absorption is more likely than altered clearance in hematology patients. We expect that a difference in rate of absorption or bioavailability or presystemic clearance is largest in patients with mucosal barrier injury. A marker of mucosal damage (citrulline) will also be used to identify the influence of mucositis on posaconazole pharmacokinetics. In order to identify changes in absorption, this is the cohort best used to address the question.

Study objective

• To determine the pharmacokinetics of posaconazole (new solid oral and IV) given as prophylaxis to patients who are at risk for developing fungal infections after receiving conditioning therapy (except strictly non myeloablative (NMA)) for allogeneic stem cell transplant (SCT(, remission induction chemotherapy for acute myeloid leukemia (AML)/ myelodysplastic syndrome (MDS) or being treated for severe Graft versus Host Disease (GvHD).
• To determine the impact of mucositis on changes in drug absorption or presystemic clearance.

Study design

Open-label, multi-centre, randomised, multiple-dose, multiple dose-level, sequential therapy, phase IV trial

Intervention

- 10 subjects (group A) will start with posaconazole 300mg IV BID on day 1, followed by 300mg IV QD on days 2-7, followed by 300mg PO QD on days 8-12, followed by 200mg PO QD on days 13-16.

- 10 subjects (group B) will start with posaconazole 300mg PO BID on day 1, followed by 300mg IV PO on days 2-7, followed by 300mg IV QD on days 8-12,

followed by 200mg IV QD on days 13-16.

Study burden and risks

The risk-classification is assessed as negligible to the patient population receiving study drug at the current regimens. The drug is licensed for the use investigated in this protocol. There is no attributable risk for the application of the study protocol to the haematology patients at risk for fungal infections.

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. Subject is able and willing to sign the Informed Consent Form prior to screening evaluations.
2. Subject is at least 18 years of age on the day of providing informed consent.
3. Patient receives immunosuppressive therapy for acute GVHD, (non)myeloablative or reduced intensity conditioning regimens for SCT, or remission induction chemotherapy for AML/MDS.
4. In case of acute GVHD grade II-IV, patient has received less than 1 week of immunosuppressive therapy.
5. If a woman, is neither pregnant nor able to become pregnant and is not nursing an infant.
6. Has an ALAT <=200U/L, ALAT <=225U/L, alkaline phosphatase <=60 U/L and a bilirubin level <=50 µmol/L.
7. Subject is capable of receiving oral tablets.
8. Subject is managed with a central venous or arterial catheter.

Exclusion criteria

1. Documented history of sensitivity to medicinal products or excipients similar to those found in the posaconazole preparation.
2. Relevant history or presence of cardiovascular disorders (specific QTc time prolongation).
3. Inability to understand the nature of the trial and the procedures required.
4. Any sign or symptoms of invasive fungal disease or the use of antifungal drugs within the previous month.
5. Has previously participated in this trial.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	10-01-2017
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Noxafil
Generic name:	posaconazole
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	20-07-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
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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	EUCTR2016-001182-87-NL
CCMO	NL58150.091.16

Study results

Date completed: 09-02-2019

Actual enrolment: 10

Summary results

Trial is onging in other countries