Investigation of posaconazole prophylaxis in children with chronic granulomatous disease (CGD): pharmacokinetics and tolerability (iPOD).

Published: 17-11-2008
Last updated: 06-05-2024

Primary: Dose finding for a twice daily regimen for PSZ as prophylactic treatment in children with CGD, based on the exposure to PSZ measured by PSZ trough levels.Secondary:To determine the tolerability of PSZ as prophylactic treatment in children...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Immune system disorders congenital
Study type	Interventional

Summary

ID

NL-OMON32626

Source
ToetsingOnline

Brief title
iPOD

Condition

- Immune system disorders congenital
- Immunodeficiency syndromes
- Fungal infectious disorders

Synonym
CGD, invasive fungal infection

Research involving
Human

Sponsors and support

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

Intervention

Keyword: CGD, children, pharmacokinetics, posaconazole

Outcome measures

Primary outcome

Individual trough PSZ plasma concentrations, on basis of which the PSZ dosage

for individual patients will be adjusted.

Base on the results a dosage for future prophylaxis with PSZ in children with

CGD will be defined.

Secondary outcome

Biochemical en hematological parameters of individual patients.

Information from patients and/or parents about possible side-effects

experienced during the trial.

Study description

Background summary

At this moment itraconazole is the drug of first choice in the prophylaxis of fungal infections in children with chronic granulomatous disease (CGD). Breakthrough fungal infections while on itra-conazole prophylaxis are described in literature indicating the need for a drug with a broader antifungal spectrum. Posaconazol (PSZ) might provide in this need. PSZ may also have a clinical safety and tolerability advantage over other antifungal agents. Because PSZ is metabolized through phase II glucuronidation it is less common to be subject to drug interactions. PSZ is known to be a CYP3A4 inhibitor, but does not inhibit other CYP enzymes, therefore it may exhibit fewer drug

interactions as com-pared with other azole antifungal agents.

Treatment of children from age 8 and older has been described in literatur, but it is still off-label use. No data have been published to date on the exposure of PSZ in children under the age of 8 or in children with CGD. Yet with the possibility of breakthrough fungal infections in CGD patients while on itraconazole prophylaxis, there is an urgent need to study the use of PSZ in these young children. Furthermore, the current regimen for antifungal prophylaxis requires a three times daily administration of PSZ. For this specific purpose less complex dosing schedules are warranted thus defining the need to examine a twice daily schedule.

As the tolerability and pharmacokinetics are unknown in patients under the age of 8 years and only limited data are available for age groups 8 to 16 years, we propose a feasibility study of a twice daily regimen of PSZ prophylaxis in CGD patients. With this information available we can suggest a dosage for future prophylaxis in this patient group.

Study objective

Primary:
Dose finding for a twice daily regimen for PSZ as prophylactic treatment in children with CGD, based on the exposure to PSZ measured by PSZ trough levels.

Secondary:
To determine the tolerability of PSZ as prophylactic treatment in children with CGD.

Study design

Open-label, non-randomised, non-controlled, multi-centre, phase II trial.

Patients receive posaconazole (PSZ) twice daily based on a PSZ dosing scheme for children (see Clinical Trial Protocol, 3.2.1 Dosing scheme, page 14).

On Day 10 the PSZ trough level is determined:
- if exposure to PSZ is adequate, prophylactic treatment with PSZ is continued,
- if exposure to PSZ is not adequate, the PSZ dosage is adjusted on Day 11.
On Day 20 the PSZ trough level is determined:
- if exposure to PSZ is adequate, prophylactic treatment with PSZ is continued,
- if exposure to PSZ is not adequate, the PSZ dosage is adjusted on Day 21.
On Day 30 the PSZ trough level is determined:
- the investigator and patient can agree to continue prophylactic treatment with PSZ instead of returning to itraconazole.

If the PSZ trough level is inadequate (i.e. lower than 0.5 mg/L) the PSZ dosage will be increased by 100%. In addition to the adjustment of the dosage instructions concerning the intake of PSZ with food should be given repeatedly. If the PSZ trough level is higher than 3 mg/L the PSZ dosage will be lowered by 50%.

An interim analysis will be presented after inclusion of 8 patients. If at this point more than 4 patients have an inadequate PSZ trough level at Day 10, the scheme for determining the starting dosage of PSZ will be revised. Additionally, if at this point more than 1 patient suffers from an invasive fungal infection, the trial will be terminated. This would imply a higher incidence of invasive fungal infections in these patients than under itraconazole prophylaxis (approximately 1 infection per 10 patients per year.2). At termination of the trial patients are to return to itraconazole as prophylactic treatment.

Intervention

Patients will be screend before entering the trial during a regular visit to the outpatient clinic. Blood samples will be taken and an ECG will be made. On Day 10 and 20 after start of intake of PSZ blood samples will be taken and patients will be asked about possible side-effects. Medication will be taken twice daily together with a meal.
During a regular visit to the outpatient clinic on Day 30 after start of intake of PSZ blood samples will be taken and the trial will be completed.

Study burden and risks

Possible side-effects of PSZ are headache, dizziness, somnolence, nausea, gastrointestinal problems and rash. These are the most frequently reported side-effects and appear in only 6% of populations of healthy volunteers and patients.

If the PSZ trough level is not high enough, a patient could be inadequately protected against invasive fungal infections. By regularly measuring the PSZ trough level and adjusting the individual PSZ dosage based on the trough level we prevent patients from being inadequately protected against invasive fungal infections.

The patient benefits from participation in this trial because posaconazole has a broader antifungal spectrum than itraconazole. The group of CGD patients benefits from this trial because a dosingscheme is defined for this specific patientgroup.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

1. Patient has CGD, rendering him/her at risk for invasive fungal infections hence requiring antifungal prophylaxis.
2. Patient is at least 2 years of age and younger than 17 years of age on the day of the first dosing.
3. Parents or legal representative, and children where appropriate, willing and able to give informed consent.

Exclusion criteria

1. Patient is suspected of an invasive fungal infection.

2. Therapy with any medicinal product for which an effect on posaconazol is expected (see Clinical Trial Protocol, appendix B, Table 1). If patient is undergoing therapy with any medicinal product which may be effected by posaconazol, the patient is included on condition that the investigator judges that the effects are not clinically relevant (see Clinical Trial Protocol, appendix B, Table 2). This should be clearly recorded.
3. Documented history of sensitivity/idiosyncrasy to posaconazol.
4. Results of serum biochemistry and hematology testing are not higher than 3x the upper limit of normal (see Clinical Trial Protocol, appendix A). If the results exceed these limits, the pa-tient is included on condition that the investigator judges that the deviations are not clinically relevant. This should be clearly recorded.
5. Relevant history or current condition that might interfere with drug absorption, distribution, metabolism or excretion.
6. Relevant history or presence of cardiovascular disorder or renal and hepatic dis-order.
7. History of or current abuse of drugs, alcohol or recreational substances.
8. Participation in a trial with an investigational drug within 60 days prior to the first dose.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-10-2008
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Noxafil
Generic name:	posaconazole

Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	17-11-2008
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-11-2008
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2008-004518-28-NL
CCMO	NL24490.091.08