Fluconazole versus Micafungin in neonates with suspected or culture-proven Candidiasis: a randomized pharmacokinetic and safety study

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Primary Objectives 1. To evaluate the pharmacokinetics of fluconazole and micafungin both administered after randomization in neonates with suspected or culture-proven Candidiasis in order to validate their optimal dosage and identify covariates...

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

Summary

ID

NL-OMON41553

Source
ToetsingOnline

Brief title
Fluconazole versus Micafungin in neonates

Condition

- Fungal infectious disorders

Synonym
Infection, sepsis

Research involving
Human

Sponsors and support

Primary sponsor: INSERM

Source(s) of monetary or material Support: European Commission (Health Co-operation Work Program of the 7th Framework Program)

Intervention

Keyword: Candidiasis - Fluconazole - Micafungin - Pharmacokinetic study

Outcome measures

Primary outcome

Primary study parameters/outcome of the study: protocol pg. 21

- Time to reach the AUC breakpoint and the ratio of AUC/MIC90s in the two treated groups.

- The theoretical MIC90s against the common pathogens responsible for the infection to be treated will be used by opposition with the *real MIC90* of the agent really involved that is rarely isolated.

Secondary outcome

Secondary study parameters/outcome of the study: protocol pg 21-25

Covariates collection:

The following procedures or evaluations will be performed on the days of PK study and the data recorded as indicated:

1. Record study drug dosing information.

2. Record all concomitant antimicrobials including drug name and dosing information.

3. Record nutrition information.

4. Weight, height, postnatal age, gestational age.

5. Associated pathology.

6. The following clinical laboratories values: a. Hematology: hematocrit, hemoglobin, white blood cell count with differential, absolute neutrophil count, platelet count b. Serum chemistry: creatinin, blood urea nitrogen, sodium, potassium, chloride, calcium, magnesium, total protein, albumin c. Liver function tests: aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, total bilirubin, conjugated bilirubin d. Renal function tests: urine protein.

The tolerability and safety criteria evaluation will include the collection of: Adverse Event/Adverse Reaction, reasons for withdrawal, global physical examination, vital signs, laboratory test evaluations.

Study description

Background summary

The epidemiology of candidiasis is rapidly changing; recent estimates are that nearly 50% of Candida bloodstream isolates are non-albicans Candida species requiring the use of treatments active against them. Because of the high risk associated with candida infection in premature babies, fluconazole prophylaxis is now recommended in NICUs with a high incidence in fungal infections. Both Fluconazole and Amphotericine B are routinely used in neonates when there is a suspected or proven invasive Candidiasis. Micafungin is hardly prescribed in neonates since Pk-data is limited. However, the main advantages is a better sensitivity for non-albicans Candida-strains.

As candida infection is difficult to prove and requires an urgent treatment, in particular to avoid CNS infection, treatment is often started in high risk patients when the infection is only suspected, i.e. on clinical arguments without waiting for positive cultures (10% of cases).

Fluconazole has not been approved for use in the treatment of neonatal candidiasis. In contrast, the efficacy of echinocandins for the treatment of invasive candidiasis has been suggested by pre-clinical and clinical studies. Related to Micafungin, the available data support the idea that only dosages that are greater than what currently recommended in infants (that is, 2 to 4 mg/kg/day) may ensure adequate coverage of the CNS given that ability of low dosages of micafungin to penetrate the cerebrospinal compartment and to diffuse in the cerebrospinal fluid is deemed suboptimal.

Therefore, the current study is designed to determine whether micafungin is as efficacious as the current standard of fluconazole, as well as, compare the safety of the drugs in the treatment of proven neonatal candidiasis. It is also designed to further elucidate the pharmacokinetics of the two products in the growing and developing neonate and premature infant.

The doses that will be administered are higher that currently used in order to optimize efficacy. The concept of a loading dose is present in antifungal treatment strategies for adults, but it has never been applied to infants and preterm neonates. It will be used for both drugs in the present project.

The protocol should be able to recommend fluconazole for prophylaxis and micafungin for the treatment of fungal infections in newborns.

Study objective

Primary Objectives

1. To evaluate the pharmacokinetics of fluconazole and micafungin both administered after randomization in neonates with suspected or culture-proven Candidiasis in order to validate their optimal dosage and identify covariates that impact pharmacokinetics including drug interactions and pharmacogenetic factors.
2. To compare the time to reach the target drug exposure, i.e. the area under the concentration-time curve from 0 to 24 h (AUC0-24) for candidiasis by the two randomly administered drugs.

Secondary Objectives

1. To evaluate the tolerability of fluconazole and micafungin in neonates with suspected or culture-proven Candidiasis.
2. To describe short-term safety.
3. To describe short term outcome of treated episodes.

Study design

This is a phase 2-3, randomized, multicenter, parallel group comparing pharmacokinetics and safety of fluconazole and micafungin. This study will have 2 arms, with 1 group randomized to fluconazole and 1 group randomized to micafungin.

Intervention

• Treatment: Randomization (1:1): Fluconazole (25mg/kg loading dose; 12mg/kg or 20 mg/kg daily according to gestational and postnatal age) OR Micafungin (15mg/kg loading dose; 10 mg/kg daily)

• Pharmacokinetics (fluconazole or micafungin treatment):

If the gestational age <= 32 weeks (at the time of recording / randomization) :
Group A: Hours of sampling on day 1 and day 5 of treatment: at 2 h & 12 h; Total blood volume: 400 µL
Group B: Hours of sampling on day 1 and day 5 of treatment: at at 2 h & 18 h; Total blood volume: 400 µL

If the gestational age >= 32 +1 weeks (at the time of recording / randomization) :
Group C: Hours of sampling on day 1 and day 5 of treatment: at 2 h, 4 h & 16 h; Total blood volume: 600 µL
Group D : Hours of sampling on day 1 and day 5 of treatment: at 2.5 h, 10 h & 24 h; Total blood volume: 600 µL

Pharmacokinetic samples at Day 1 and 5 will only be drawn if there is a central line or if peripheral blood is taken for medical reasons

• Pharmacogenetic sample (protocol pg.36): It is aimed to extract DNA from the cells left over after centrifugation of the plasma EDTA samples to reduce the amount of blood taken from the neonate therefore no additional sample will be required.

• Cerebrospinal fluid sample (CSF) (protocol pg.36): CSF sample will not specifically be performed for the study. Only if it is performed for routine diagnostic procedure, a sample (0,2 ml) will be taken for the study.

Study burden and risks

- The additional blood samples are drawn from a line (arterial line) already in place for his treatment or if the child has to be already punctured for his standard care.

- Fluconazole and Micafungin: Both drugs are used for many years in neonates:

fluconazole for over fifty years and micafungin more recently as this drug has been approved for neonate use since 2008. Use of both drugs hold very little risk. This risk includes biological abnormalities related to the liver, such as an increase in the transmaminases.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

1. Neonates and infants between 24 up to 42 weeks gestational age AND with a post-natal age of 48 hours of life up to day of life (DOL) 120 at the time of culture acquisition.
2. Requiring antifungal therapy according to medical decision by the attending physician for microbiologically documented or clinically suspected candida infection independently from the availability of any positive culture for Candida spp (see protocol appendix 1)
3. Written informed consent from the parents or the legally authorized representative must be obtained prior to entry.

4. Infant must have sufficient venous access to permit administration of study medication and monitoring of safety variables.

Exclusion criteria

1. Infant exposed to fluconazole or micafungin prophylaxis prior to inclusion
2. Infant who has received more than 48 hours of systemic antifungal therapy (any product) prior to the first dose of study drug for treatment of the current Candida infection.
3. Infant with a concomitant medical condition, whose participation, in the opinion of the Investigator and/or medical advisor, may create an unacceptable additional risk.
4. Infant previously enrolled in this study.
5. Infant who is co-infected with a non-Candida fungal organism.
6. Neonates with isolated candiduria
7. Infant with any history of a hypersensitivity or severe vasomotor reaction to any echinocandin or fluconazole product
8. Infant with pre-existing hepatic or renal disease
9.Infants with baseline Candida spp. Isolate resistant to fluconazole or micafungin according to EUCAST/CLSI clinical breakpoints (see section 5.2.2 for interpretative MIC criteria) or with an isolate for which treatment with an alternative antifungal agent is indicated, i.e. there is insufficient evidence that the species in question is a good target for therapy with either fluconazole or micafungin.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-07-2014
Enrollment:	18

Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Fluconazole KABI
Generic name:	Fluconazole
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Mycamine
Generic name:	Micafungin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	10-06-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-01-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-05-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2012-001916-41-NL
CCMO	NL45035.078.14