Bioavailability of voriconazole in critically ill patients

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The objective of this study is to obtain the absolute bioavailability of voriconazole in critically ill ICU patients.

Ethical review	Approved WMO
Status	Will not start
Health condition type	Fungal infectious disorders
Study type	Interventional

Summary

ID

NL-OMON40908

Source
ToetsingOnline

Brief title
Bioavailability of voriconazole

Condition

- Fungal infectious disorders

Synonym
Suspected or prophylaxis of invasive aspergillosis, suspected or prophylaxis of invasive fungal infection.

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Bioavailability, Intensive care, Voriconazole

Outcome measures

Primary outcome

The primary endpoint is determining the bioavailability of voriconazole in ICU patients. Bioavailability will be calculated by determining the AUC of an intravenous and the AUC of an oral dose of voriconazole.

Secondary outcome

To get an indication of the influence of disease severity, determined with the APACHE IV score, and the degree of inflammation, determined with CRP, on the bioavailability of voriconazole.

Study description

Background summary

Voriconazole is considered to be a first line antifungal agent for the treatment of invasive aspergillosis. The bioavailability, based on healthy volunteers, is estimated to be >90%. Due to the high bioavailability of voriconazole, switching between oral and intravenous administration is permitted if clinically allowed. Few data are available for the bioavailability of voriconazole in critically ill patients. However, to obtain a therapeutic concentration of voriconazole, one study showed that a higher oral dose is required compared with the intravenous dose to obtain this therapeutic concentration. Therefore, the pharmacokinetics can be changed in critically ill patients, including bioavailability. When a patient switch from intravenous to oral administration, lower voriconazole levels might occur. If this leads to insufficient effect the attending physician may decide to stop voriconazole and switch to a less favorable second line antifungal drug, likely with a less favorable outcome where an increased dosing would be more appropriate. The dosage of voriconazole might be adjusted to maintain a therapeutic concentration. To cope with this problem, knowledge about the bioavailability of voriconazole in critically ill ICU patients is required. This would probably result in keeping more patients on first line treatment, voriconazole, and

maintaining efficacy.

Study objective

The objective of this study is to obtain the absolute bioavailability of voriconazole in critically ill ICU patients.

Study design

An intervention study will be performed in patients treated with oral voriconazole and admitted to an ICU at the University Medical Center Groningen. Whether a patient will be treated with voriconazole or not depends on the choice of the attending physician, as well as the dose and route of administration. Patients eligible for this study received at least four doses of voriconazole. To be eligible for inclusion patients must receive oral voriconazole.

ICU patients who received at least four doses of voriconazole and receive voriconazol orally at time of inclusion, will receive one intravenous administration of voriconazole in the same dose as the oral dose. A full concentration-time curve of voriconazole/voriconazole N-oxide will be obtained to determine the AUC of an intravenous dose of voriconazole. Plasma samples, 1 ml per sample, are taken before administration, immediately after administration of the infusion volume and 0,5; 1; 1,5; 2; 4; 8 and 12 hour after start of the infusion. The next dose of voriconazole will be given orally as prescribed and plasma samples will be drawn before oral administration of voriconazole and 0,5; 1; 1,5; 2; 4; 8; and 12 after administration of voriconazole for determining the AUC of the oral dose. The bioavailability will be determined, comparing the intravenous AUC (100%) and the oral AUC. For determining pharmacogenetics an extra blood sample of 4 ml will be taken.

The day the full concentration-time curve of voriconazole will be obtained, the APACHE IV score will be determined based on clinical parameters that are routinely recorded for ICU patients.

Intervention

An intravenous dose of voriconazole.

Study burden and risks

As ICU patients have vascular access via an indwelling arterial catheter, the extra plasma samples taken for this study, 1 ml per sample, are not seen as an extra burden. Subjects benefit from this study because a sub therapeutic voriconazole level will be noticed and dose adjustments can be made to reach a therapeutic level. Whether or not dose adjustments will be made depends on the

choice of the attending physician.
Future patients may benefit from the results of this study as efficacy is maintained when patients treated with voriconazole, switching from intravenous treatment to oral treatment.
This study cannot be performed without these patients, since they are the subjects of the investigation.

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

Aged * 18 yrs;
Treatment with voriconazole;
Admission to an ICU;
Written informed consent.

Exclusion criteria

Blood sampling by central venous catheter or peripheral cannula not possible;
Concomitantly using a strong inhibitor or inducer of cytochrome P450.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	13
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Vfend
Generic name:	voriconazole
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	15-05-2014
Application type:	First submission

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-07-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2014-001222-15-NL
ClinicalTrials.gov	NCT02110316
CCMO	NL47955.042.14