Pharmacokinetics and optimal dosage of caspofungin in critically ill patients with suspected invasive candidiasis.

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Determine the pharmacokinetics of caspofungin, and the optimal dosage of caspofungin in relation to adequate exposure in critically ill patients.

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

Summary

ID

NL-OMON40105

Source
ToetsingOnline

Brief title
Optimal dosage of caspofungin in critically ill.

Condition

- Fungal infectious disorders

Synonym
Suspected invasive candidiasis, suspected 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: Caspofungin, Intensive care, Optimal dosage, Pharmacokinetics

Outcome measures

Primary outcome

The main study parameter is the optimal dosage of caspofungin in relation to adequate exposure in critically ill patients. The AUC of caspofungin is used as a measure for the exposure. The optimal dosage can be given as a starting dosage for empirical treatment with caspofungin in critically ill patients.

Secondary outcome

1) Pharmacokinetic parameters of caspofungin in critically ill patients.

2) Correlation of pharmacokinetic parameters and the plasma concentration of caspofungin with disease severity scores.

3) Correlation of the plasma concentration of caspofungin with candida eradication.

4) Correlation of the plasma concentration of caspofungin with inflammation parameters.

5) AUC/MIC ratio and Cmax/MIC ratio.

6) Constructing a pharmacokinetic model of caspofungin in critically ill patients.

7) Drug-related adverse events of caspofungin.

8) The amount of caspofungin that is lost in dialysis.

Study description

Background summary

Intensive care unit (ICU) patients are especially at risk for invasive candidiasis due to the presence of risk factors. Prompt initiation of effective antifungal therapy in the appropriate dosage is required to improve outcome in patients with candidemia. An efficacy study showed a lower response rate for caspofungin among patients with a higher disease severity score. Furthermore, it is known that in critically ill patients, alterations in function of various organs and body systems can influence the pharmacokinetics and hence the plasma concentration of a drug. A study of caspofungin in ICU patients has found a high inter- and intra-individual variability in caspofungin trough concentration. The pharmacokinetic parameters of caspofungin in critically ill patients are most likely different, however, this has not been specifically studied to date. As a result of the altered pharmacokinetics, under-exposure of caspofungin can occur in critically ill patients and a higher dosage might be necessary in these patients.

Study objective

Determine the pharmacokinetics of caspofungin, and the optimal dosage of caspofungin in relation to adequate exposure in critically ill patients.

Study design

Intervention study. On day 3 (± 1 day) of treatment with caspofungin, blood samples are taken just before administration of caspofungin and 1, 2, 3, 4, 6, 8, 12 and 24 hours after the start of the infusion, to determine the AUC (Area Under the concentration-time Curve) and pharmacokinetic parameters of caspofungin. The AUC is used as a measure for the exposure, an AUC of >= 98 mg*h/L is established as an adequate exposure. A decline in AUC of >= 20% below 98 mg*h/L is considered a clinically relevant decline in AUC, and in this case a dose adjustment of caspofungin is required. An AUC > 200 mg*hr/L is considered too high and in this case the dosage will be reduced. If the caspofungin dosage is adjusted, blood samples are taken on day 3 (± 1 day) after dose adjustment, just before administration of caspofungin and 1, 2, 3, 4, 6, 8, 12 and 24 hours after the start of the infusion, to determine the AUC at the adjusted dosage. When the patient is on an adequate dosage regimen, trough levels will be followed every three days during treatment on the ICU, with a maximum of 28 days, to evaluate potential fluctuations in caspofungin concentration over time.
On the day the first AUC of caspofungin is obtained, blood samples are drawn for determination of procalcitonin, interleukin-6 and interleukin-8 to assess correlation of caspofungin concentration with inflammation parameters.
If the patient is on dialysis, samples from the dialysate will be obtained at the same time points as the blood sampling to determine the amount of caspofungin that is lost in dialysis.

Different disease severity scores will be calculated to evaluate their correlation with the plasma concentration and pharmacokinetic parameters of caspofungin. The calculation of the different scores is based on clinical parameters that are routinely recorded for ICU patients. The APACHE II, APACHE IV, LODS, MODS, MPM II, ODIN, SAPS 3 and SOFA score will be calculated on the day the first AUC of caspofungin is obtained.

Intervention

Dose-adjustment of caspofungin in case of under-exposure (AUC >= 20% below AUC that is required for an adequate exposure), or in case of over-exposure (AUC > 200 mg*hr/L, twice the AUC for an adequate exposure).

Study burden and risks

Dose adjustment in case of under- or over-exposure leads to an adequate exposure of caspofungin and can lead to a better outcome among the subjects included in this study. Caspofungin has shown good tolerability in dosages up to 200 mg per day. Results of this study can contribute to future dosing schedules in critically ill patients treated with caspofungin and to practical decision rules for therapeutic drug monitoring. The extra blood samples needed to study exposure and the pharmacokinetic parameters of caspofungin are a minor burden as these patients already have an indwelling vascular catheter. This study cannot be conducted without these patients, as they are the subjects of 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

Treatment with caspofungin.
Admission to an ICU.
Age >= 18 years.
Suspected invasive candidiasis.

Exclusion criteria

Blood sampling by central venous catheter or peripheral cannula not possible.

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):	01-12-2013
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cancidas
Generic name:	Caspofungin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	08-11-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-01-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-10-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-10-2014
Application type:	Amendment
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
Other	clinicaltrials.gov
EudraCT	EUCTR2012-003617-34-NL
CCMO	NL41676.042.12