Liposomal amphotericin B (Ambisome) pharmacokinetics given as a single intravenous dose to obese patients (ASPEN).

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

Summary

ID

NL-OMON47120

Source
ToetsingOnline

Brief title
ASPEN

Condition

- Fungal infectious disorders

Synonym
Aspergillosis / Invasive Fungal Infection

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum

Source(s) of monetary or material Support: Gilead Inc.

Intervention

Keyword: Bariatric Surgery, Liposomal Amphotericin B, Obesity, Pharmacokinetics

Outcome measures

Primary outcome

The primary outcome measurement will be area under the plasma concentration* time curve (AUC) from time 0 to infinitive (inf) post infusion (AUC0* inf) values of AmBisome. The AUC0inf will be determined by use of the linear up, log down trapezoidal rule. Peak plasma concentrations (Cmax) will be directly observed from the data. The elimination rate constant (ke) will be determined by linear regression of the terminal points of the log-linear plasma concentration time curve. Clearance (CL) will be calculated as dose/AUC0* inf. Volume of distribution (Vd) will be calculated as dose/AUC0-inf * ke.

Secondary outcome

N/A

Study description

Background summary

Obesity represents one of the most important public health issues according to the World Health Organization. Despite increased pharmacotherapy among obese patients, there is a paucity of dosing guidelines for this population. Pharmacokinetic (PK) studies are necessary to determine the appropriate dosing regimen as obese patients have a different body composition compared to normal-weight individuals, which influences the volume of distribution (Vd) and clearance (CL) of drugs.
Ambisome is currently used in the setting of treatment for Aspergillus fumigatus (both susceptible and resistant species) as well as less common pathogens such as Mucor species and Fusarium or Scedosporium species.

AmBisome is dosed on a weight basis. However, the implied assumption of a linear relationship between exposure and bodyweight is not always appropriate in obese subjects. In general, the Vd of hydrophilic drugs relates to Ideal Body Weight because of poor penetration into adipose tissue. A weight-based dose of AmBisome (a drug with a low log P and a small Vd) may therefore result in higher exposure in obese patients. Unfortunately, AmBisome exhibits severe concentration dependent toxicity. This may then be more pronounced in obese patients who receive a higher absolute dose.
In the current literature, only one single (unpublished) abstract on the use of AmBisome in obese adults has been reported. At equivalent doses, obese patients reported significantly more toxicity in comparison to non-obese patients (serum creatinine increased, GFR decreased, hypokalemia). However, AmBisome plasma concentrations were not measured.
In the absence of solid evidence to safely treat this patient population, it seems prudent to conduct a pharmacokinetic study in a cohort of (morbidly) obese patients who receive AmBisome and describe the pharmacokinetics in order to establish an optimal dosing regimen for obese patients. These data will be compared with normal-weight subjects.

Study objective

The overall aim is develop a rational dosing regimen of liposomal amphotericin B in obese patients. To achieve this goal we have defined the following objectives:

Primary objective:
* To determine the pharmacokinetics of liposomal amphotericin B administered as a single, intravenous dose (1 mg/kg or 2 mg/kg) to obese patients with a BMI * 40 kg/m2.

Secondary objective:
* To determine optimal dosing strategy (multiple dose) in obese patients trough Monte Carlo simulations based on the developed PK model.
* To compare the PK of liposomal amphotericin B in obese patients to a normal weight reference population.

Study design

Prospective, open-label, non-randomized, single-centre, single-dose, multiple dose level trial (1 mg/kg and 2 mg/kg).

* Group 1 (n=8) in this study will receive a single dose of AmBisome 1 mg/kg. An interim analysis on the data after inclusion of subject group 1 will be performed to review safety before inclusion of subject group 2 (2 mg/kg; n= 8).

* Day 1: A single dose of AmBisome 1 mg/kg IV (subject group 1) or 2 mg/kg

(subject group 2) will be administered in 45 minutes and 90 minutes, respectively (prior to surgery).

* A PK curve will be determined after administration of a single, 1 day pre-surgery dose of AmBisome at t = 0.5, 0.75 (end of infusion), 1.5, 2, 4, 6, 8, 10, 12, 24, and 48 and (if feasible) 72 hours post infusion (n=12 samples) for group 1 (1 mg/kg), 8 patients.The PK curve of group 2 (2 mg/kg, 8 patients) will be similar to group 1, except for the t=1.5 hour sampling point, which will be end of infusion due to the infusion time of 90 minutes.

* Blood samples of 4.0 mL will be taken to obtain at least 2.0 mL of plasma.

* Patients are considered to have completed the study if at least 9/11 samples of the PK curve up until 48 hours have been collected.

Intervention

Indwelling venous cannula /venflon for study
A single dose of liposomal amphotericin B 1 mg/kg (n=8) or 2 mg/kg (n=8) will be administered in 45 or 90 minutes, respectively (pre-surgery).

A PK curve will be determined after administration of a single, (1 day) pre-surgery dose of AmBisome at t = 0.5, 0.75 (end of infusion), 1.5, 2, 4, 6, 8, 10, 12, 24, and 48 and (if feasible) 72 hours post infusion (n=12 samples) for group 1 (1 mg/kg), 8 patients.
The PK curve of group 2 (2 mg/kg, 8 patients) will be similar to group 1, except for the t=1.5 hour sampling point, which will be end of infusion due to the infusion time of 90 minutes.

Study burden and risks

Since this population of morbidly obese patients is admitted to a hospital for planned bariatric surgery, these patients will remain in the hospital for approximately 72 hours under the constant supervision of medical staff (anaesthesiologist, surgeon, ward physician, nursing personnel). This study design can be suitably incorporated with surgery procedures and associated patient care, while the level of interference is expected to be minimal. Therefore, this cohort of patients seems crucial in answering the primary research question.
Bariatric surgery will proceed according to schedule and will not be altered due to study participation, with the only exception of sampling a maximum amount of 48 millilitres of blood (12 samples, maximum of 72 hours) from an indwelling venous catheter. The catheter will be placed in addition to a regular intravenous catheter used for standard clinical care. The sampling of blood is expected to have no influence on patient recovery. In addition, this patient population is not expected to be administered any co-medication

interacting with the pharmacokinetics of AmBisome and are considered (relatively) healthy despite their weight status.
Furthermore, bariatric surgery procedures can be prone to various kinds of infections (including candida-infections). A prospective study reported frequent fungal (and bacterial) overgrowth in the stomach and small bowel after gastric bypass surgery in bariatric patients. Another study found similar results, reporting the presence of Candida spp. after surgery in obese patients. Although the patients normally do not receive antifungal prophylaxis during surgery, the invasiveness of the procedure in the gastro-intestinal region and the risk of the development of fungal infections justify the prophylactic use of single dose AmBisome during bariatric surgery in this trial.
In addition, a previous study by our group with a similar design was granted approval in 2014 (anidulafungin pharmacokinetics in 8 morbidly obese patients receiving 100 mg single dose pre-surgery, CMO # 2013/533, NL46907.091.13)

The single dose used in our study is much lower than the recommended dose by the manufacturer of 5 mg/kg (for treatment of invasive fungal infections caused by Aspergillus-species) and the 10 mg/kg dose used in Mucor species infections. By using a single dose design, we intend to reduce possible toxicity of AmBisome in comparison with multiple dose trials. Furthermore, the single dose in our study is considerably lower than doses used in other clinical trials (up to 15 mg/kg single dose, which resulted in few of the common adverse advents of AmBisome (i.e. hypokalemia, nephrotoxicity) and infusion-related adverse events).
The safety of AmBisome in the 1 mg/kg group will be assessed in an interim analysis, before proceeding to the second group receiving a dose of 2 mg/kg. The infusion time of the 2 mg/kg dose will be longer than the 1 mg/kg dose (90 minutes instead of 45 minutes), to limit possible infusion-related adverse events.

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. Patient has a BMI *40 kg/m2 and is undergoing bariatric surgery.
2. Subject is at least 18 years of age on the day of screening.
3. Subject or legal representatives are able and willing to sign the Informed Consent before screening evaluations.

Exclusion criteria

1. Documented history of sensitivity to medicinal products or excipients similar to polyene antifungal agents.
2. History of, or current abuse of drugs, alcohol or solvents (up until a maximum of three months before enrolment).
3. Inability to understand the nature of the trial and the procedures required.
4. Administration of nephrotoxic medication (aminoglycosids, immunosuppressants, antivirals, antineoplastic agents) up until a maximum of one month before enrolment.

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):	22-03-2018
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AmBisome
Generic name:	Liposomal Amphotericin B
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	18-12-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-01-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-11-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-03-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	28-05-2018
Application type:	Amendment
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	EUCTR2014-003306-33-NL
CCMO	NL51820.091.14

Study results

Date completed:	03-11-2018
Results posted:	03-11-2020
Actual enrolment:	16

First publication
30-05-2019