Cyp3A4 metabolism before and after surgery induced weight loss in morbidly obese patients, using midazolam as a model drug

Published: 05-09-2011
Last updated: 27-04-2024

To compare midazolam pharmacokinetics in morbidly obese patients before/during bariatric surgery and 0.5-2 year after surgery.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal therapeutic procedures
Study type	Observational invasive

Summary

ID

NL-OMON39456

Source
ToetsingOnline

Brief title
MEMO study

Condition

- Gastrointestinal therapeutic procedures

Synonym
obesity or overweight

Research involving
Human

Sponsors and support

Primary sponsor: Sint Antonius Ziekenhuis
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: CYP3A4, Midazolam, Morbid obesity, weight reduction

Outcome measures

Primary outcome

- Difference in midazolam clearance (CL) in morbidly obese patients

before/during bariatric surgery and 0.5-2 year after surgery.

Secondary outcome

Secondary:

- Difference in midazolam rate of absorption (Ka), bioavailability (F) and

volume of distribution (V) in morbidly obese patients before/during bariatric

surgery and 0.5-2 year after surgery.

- Difference in midazolam pharmacokinetics in morbidly obese patients (both

during and 0.5-2 years post bariatric surgery) and 12 healthy volunteers (from

an earlier clinical trial by the Centre for Human Drug Research, CHDR; EudraCT

2009-010331-40).

- Differences in protein binding before and 0.5-2 years after bariatric

surgery.

Study description

Background summary

The prevalence of morbid obesity is rising worldwide1-2. Several general physiologic alterations associated with obesity have been described in the literature, however the impact of obesity on specific drug metabolic and elimination pathways needs to be determined, particularly in view of the ongoing increase in bodyweights worldwide.
Approximately 50% of all drugs are metabolised by the enzyme system CYP450

3A43, which predominantly occurs in the liver. Morbidly obese patient suffer from low-grade inflammation4. The large lipid compartment consists of adipocytes and macrophages that excrete many different adipokines and inflammation factors, such as leptin, adiponectin, IL-6 and TNF-α5-7. In vitro and animal studies have shown that inflammation factors, decrease cytochrome p450 3A4 expression, following down regulation of CYP3A4 mediated metabolism8-11. This phenomenon was confirmed in humans where critically ill patients exhibit decreased CYP3A4 metabolism12-13.
Kotlyar and Carson (1999)14, reviewed studies comparing clearance parameters of individual CYP3A4 mediated compounds in obese and control subject and demonstrated a trend of lower CYP3A4 mediated clearance values in obese as compared to non-obese individuals.
However, the studies summarized by Kotlyar and Carson (1999)14 only included obese (BMI>30) and no morbidly obese patients (BMI>40). The influence of morbid obesity (BMI>40), as seen in the clinic today, on CYP3A4 mediated clearance has not been studied yet.
In addition to the liver, CYP3A4 enzymes are also located in the intestines where they play a role in oral drug absorption. So far, no studies have assessed the influence of weight on CYP3A4-mediated drug absorption.
In this study we hypothesize that a reduction in weight will increase CYP3A4 mediated metabolism in morbidly obese patients. To adequately test this hypothesis we aim to assess CYP3A4 metabolism in morbidly obese patients using midazolam as a (CYP3A4) model drug before weight reducing surgery and after the significant loss of weight one year post surgery. In order to assess both oral absorption and clearance, a semi-simultaneous administration design is applied. This design will facilitate the quantification of the reduction of intestinal and hepatic CYP3A4 metabolism and interpretation of its clinical relevance in the morbidly obese population.

Study objective

To compare midazolam pharmacokinetics in morbidly obese patients before/during bariatric surgery and 0.5-2 year after surgery.

Study design

This is a prospective observational intervention study and will be performed in morbidly obese patients before/during and 0.5-2 year after bariatric surgery. At the day of surgery patients will receive both oral (7.5 mg) and intravenous (5 mg) midazolam. Oral midazolam will be administered 2.5 hours before surgery and the intravenous dose will be given at the induction of anesthesia. Venous blood samples will be collected until 390 min post i.v. midazolam dose.
As after 0.5-2 years patients will be at their weight loss optimum, patients are invited to the hospital to participate in the second part of the study. A similar schedule of oral and i.v. midazolam will be used and blood samples will

be drawn over the same time span (until 390 minutes after the i.v. midazolam dose).

Study burden and risks

Oral and intravenous midazolam are frequently used as premedication or for induction of anesthesia in routine clinical practise. The doses used in this study protocol are considered low and are associated with minimal risk. This study will take place during clinical practice (first visit) and outside clinical practice (second visit). During the second visit, vital functions are monitored by a physician.

Clinical practice (first visit)
During and after surgery a maximum amount of 75 millilitres of blood will be sampled from an indwelling venous catheter (placed for clinical practice).

Second visit
For the second visit, patients will stay at the observatory for one day. Again an oral and intravenous dose of midazolam will be administered and a maximum amount of 75 millilitres of blood will be sampled from an indwelling venous catheter before, placed for the purpose of this study.

Contacts

Public
Sint Antonius Ziekenhuis

Koekoekslaan 1
Nieuwegein 3435 CM
NL
Scientific
Sint Antonius Ziekenhuis

Koekoekslaan 1
Nieuwegein 3435 CM
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- 20 Morbidly obese subjects scheduled for bariatric surgery. We will stratify subjects to 4 weight groups: 100-120 kg; 120-145 kg; 145-170 kg; >170 kg
- Age 18-60 year old

Exclusion criteria

- Prescription or use of either CYP3A4-activity inducing or decreasing medication.
- Use of product containing grapefruit, wild grape, banpeiyu, pomegranate, star fruit, and black berry within 2 weeks prior to a study visit
- Pregnancy, breastfeeding
- Renal insufficiency
- OSAS

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-01-2012
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Versed
Generic name:	Midazolam
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	05-09-2011
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-09-2011
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-11-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Not approved Date:	16-12-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-01-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-12-2012
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-02-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2011-003293-93-NL
CCMO	NL35861.100.11