Effects of obesity, non-alcoholic fatty liver disease and bariatric surgery on systemic cytochrome P450-mediated drug metabolism using a COCKTAIL approach.

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Primary objectives: To examine the effects of: (I) RYGB surgery, (II) obesity and (III) liver fat on drug metabolism using a cocktail approach. Secondary objectives: To examine the effects of: (I) RYGB surgery, (II) obesity and (III) NAFLD, on…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON50513

Source
ToetsingOnline

Brief title
COCKTAIL TRIAL

Condition

- Other condition
- Hepatic and hepatobiliary disorders

Synonym
Obesity and non-alcoholic fatty liver disease

Health condition

Obesitas

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Metabole Fonds

Intervention

Keyword: Gastric bypass surgery, Non-alcoholic fatty liver disease, Obesity, Pharmacokinetics

Outcome measures

Primary outcome

Primary study endpoints are the differences in area under the plasma concentration versus time curve (AUC) for each drug following the administration of the cocktail in four different situations/ disease states: (1) early (= anatomical) and (2) late and (3) very late (= weight reduction dependent) post-RYGB surgery compared to the pre-RYGB surgery situation.

Secondary outcome

Secondary endpoints include the differences in the PK parameters clearance, volume of distribution, absorption rate, mean residence time and elimination half-life in the above mentioned situations / disease states.

Study description

Background summary

Obesity rates are at an all-time high. This phenomena goes hand in hand with increasing prevalences of non-alcoholic fatty liver disease (NAFLD) and Roux-en-Y gastric bypass (RYGB) surgery. Thus far, quality studies investigating the human pharmacokinetic effects in these disease states are

lacking.

Study objective

Primary objectives: To examine the effects of: (I) RYGB surgery, (II) obesity and (III) liver fat on drug metabolism using a cocktail approach.
Secondary objectives: To examine the effects of: (I) RYGB surgery, (II) obesity and (III) NAFLD, on pharmacokinetic parameters, including: clearance, volume of distribution, absorption rate, mean residence time, and elimination half-life.

Study design

An open-label, single-dose, intervention study.

Study burden and risks

The burden of this study includes a screening visit, five overnight fasts and four twelve-hour hospital admissions during which the drug cocktail is administered (five times). For all participants, one urine sample will be collected to perform an urinary drug screening. Blood samples will be drawn for pharmacokinetic analysis, monitoring of laboratory parameters and for pharmacogenetic analysis of liver enzymes. A maximum total volume of 350 ml blood will be obtained over an one-year period. During the scheduled surgery a liver biopsy will be taken. Risks associated with this liver biopsy (bleeding from the biopsy site) will be kept to a minimum by providing several measures to check for and promote hemostasis. This study will generate information regarding the drug metabolizing activity in obese with and without NAFLD and bariatric surgery recipients with an altered gastrointestinal tract.
Information gathered from this study will enhance the ability of medical professionals to produce recommendations on what changes should be made to dosing regimen in these disease states; ultimately, reducing medication errors and thereby drug-associated morbidity and mortality.

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

In order to be eligible to participate in this study, a subject must meet the following criteria:
- Capability to provide informed consent and to comply with the requirements and restrictions listed on the informed consent form;
- Stable weight 3 months prior to inclusion;
- Obese, but otherwise healthy, with the exception of NAFLD, females, aged between 18 - 45 years;
- Eligible and scheduled for laparoscopic RYGB surgery (in accordance with the national guidelines (74)).

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- Any medical disorder (with the exception of NAFLD and metabolic syndrome);
- Major illness in the past 3 months;
- History of cholecystectomy or other bile duct anomalies;
- (History of) (an) eating disorder(s);
- Use of prescription or non-prescription drugs and herbal or dietary supplements that affect the CYP enzymes of interest within 30 days prior to the administration of the drug cocktail, except for oral contraceptives;
- Diabetes;
- Drug abuse or alcoholism (>2 units of alcohol per day);

- Strenuous exercise for at least 3 days prior to each study day, defined as more than 1 hour of exercise per day;
- Difficulty in donating blood or limited accessibility of a vein;
- Use of tobacco products (induction of liver enzymes).

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	21-10-2019
Enrollment:	17
Type:	Actual

Ethics review

Approved WMO Date:	13-08-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	13-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-05-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
CCMO	NL65040.018.18