Pharmacokinetics of Paracetamol before and after Roux-en-Y gastric bypass

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To assess the effect of a Roux-en-Y gastric bypass on the pharmacokinetics of a single oral dose of 1000 mg paracetamol before the surgery. within one month after the surgery and 6 months after the surgery.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gastrointestinal therapeutic procedures
Study type	Interventional

Summary

ID

NL-OMON55190

Source
ToetsingOnline

Brief title
PAPAYA

Condition

- Gastrointestinal therapeutic procedures

Synonym
Roux en Y gastric bypass; gastric bypass

Research involving
Human

Sponsors and support

Primary sponsor: Albert Schweitzer Ziekenhuis
Source(s) of monetary or material Support: Promotiefonds ASz

Intervention

Keyword: paracetamol, pharmacokinetics, Roux en Y gastric bypass

Outcome measures

Primary outcome

The primary end point is the pharmacokinetics of paracetamol after a single oral dose of 1000 mg paracetamol before and after RYGB.

Amendement:

In 6 RYGB patients the primaire end point is the pharmacokinetics of paracetamol after a single oral dose of 1000 mg paracetamol, followed by a single intravenous dose of 1000 mg paracetamol at 6 months after RYGB.

Secondary outcome

A secundary end point will be the pharmacokinetics of the metabolites paracetamol glucuronide (PCM-GLU), paracetamol sulfate (PCM-SUL), paracetamol mercatopurate (PCM-MER) and paracetamol cysteine (PCM-CYS).

Additional secundary end points are aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), gamma-glutamyltransferase (γ-GT) and bilirubin values before, after 6h and 24h after a single oral dose of 1000 mg paracetamol before and after RYGB.

Study description

Background summary

The number of bariatric procedures performed in the Netherlands is increasing, especially the Roux-en-Y gastric bypass (RYGB). Little is known about the effect of RYGB on the pharmacokinetics of drugs, neither the surgery procedure itself nor the loss of weight in the long term. It is unclear how to dose drugs both shortly and long after the surgery.

Paracetamol (PCM) is a widely used analgesic used by patients because of RYGB, but it can also be used for other reasons. The common dosage is 500-1000 mg, maximally four times a day.

PCM is a potential hepatotoxic drug when used in too high dosages. In morbidly obese people, pharmacokinetics of PCM is different compared to healthy non-obese volunteers. The peak concentration (Cmax) of and total exposure (AUC, area under the plasma concentration versus time curve) to PCM are lower in morbidly obese people. The metabolism of PCM was shown to be increased with higher activity of glucuronidation, sulfatation and CYP2E1-mediated metabolism, resulting in faster forming and higher concentrations of toxic metabolite concentrations. The effect on liver toxcity was demonstrated after administration of a single dose of 2 g PCM. It is unknown whether normalization of weight may result into normalization of the pharmacokinetics of PCM.

Another pharmacokinetic study showed that at 6 months after bariatric surgery, the absorption of 500 mg PCM in RYGB patients was faster compared to healthy subjects. It also showed that Cmax and AUC increased gradually to values that are comparable to non-obese patients. An important limitation of this study is that metabolism of PCM was not studied.

In short, morbid obesity, RYGB surgery and the normalization of weight affect the pharmacokinetics of PCM, including both absorption as elimination, as well as the formation of toxic metabolites. A higher dosage of PCM could be considered to overcome the lower Cmax and AUC, but this option may be limited by the additional forming of toxic metabolites.

This is why all these aspects will be combined in this research to understand the pharmacokinetics of PCM before and after RYGB surgery.

Study objective

To assess the effect of a Roux-en-Y gastric bypass on the pharmacokinetics of a single oral dose of 1000 mg paracetamol before the surgery. within one month after the surgery and 6 months after the surgery.

Study design

This study is an open-label, longitudinal pharmacokinetic study. 20 morbidly obese patients will be included, who are planned to undergo a Roux-en-Y gastric bypass surgery. Pharmacokinetics of a single oral dose of 1000 mg paracetamol (PCM) will be assessed at 3 time points: up to 2 months before RYGB, and at 2 weeks - 1 month after and 5-7 months after surgery.

The moments for pharmacokinetic sampling will be combined with regular visits of the patients to the hospital to avoid unnecessary burden for the patients. Furthermore, eight healthy non-obese volunteers will be included to assess the pharmacokinetics of a single oral dose of 1000 mg PCM.

All participants will be screened and asked for informed consent.

Amendment:
A semi-simultaneous design will be applied to part of the participants. At 5-7 months after surgery, 6 morbidly patients will get an oral dose, followed by an intravenous dose of 1000 mg PCM 4h later. By comparing the data from the different dosing regimens, oral bioavaibility (F) can be assessed.

Intervention

See study design: pharmacokinetics of a single oral dose of 1000 mg paracetamol (PCM) will be assessed at 3 time points: up to 2 months before RYGB, and at 2 weeks - 1 month after and 5-7 months after surgery.

Amendement:
At the last time points, pharmmacokinetics of a single oral dose of 1000 mg paracetamol (PCM), followed by an intravenous dose of 1000 mg PCM will be assessed in 6 RYGB patients

Study burden and risks

The potential risk for the patients and healthy volunteers is assessed to be minimal. All subjects will receive a usual dose of paracetamol (PCM). With this dosage PCM and metabolites can be measured in relevant concentrations. A higher dosage - even after a single dose - could lead into liver toxicity.

In this study, pharmacokinetics of a single oral dose of 1000 mg PCM will be assessed at three time points in subjects who are on the waiting list to undergo RYGB surgery: once before, between 2 weeks - 1 month and between 5-7 months after RYGB. Pharmacokinetics of a single oral dose of 1000 mg PCM will be assessed once in healthy volunteers.

For this study, patients will be asked to extend their stay in the hospital on visit days to at least 6 hours. At 9 time points, blood samples will be drawn. To minimize burden for patients, they will receive a intravenous canula

allowing multiple blood sampling via the same venepuncture for the first 8 time points. The last sample will Always be drawn via venepuncture. The subject can decide whether this will take place at their home or in the hospital the next day. The number of sampling is necessary to assess the absorption and metabolism of PCM and the metabolites before and after RYGB. The outcomes of this research outweight the burden, because the understanding of pharmacokinetic changes will help us to assess whether patients after RYGB are adequately treated with the standard dose of PCM.

It is necessary to include a control group of 8 healthy subjects to compare the results of patients before and after RYGB with healthy volunteers without overweight who do not undergo RYGB. Only then can be assessed if the pharmacokinetics of morbidly obese patients return to the same profiles as of healthy subjects without obesity. Based on the results of this comparison, a new dosage regimen can be suggested.

Moreover, visits of patients will be combined with regular visits of participants, so that they do not need to come to the hospital for an extra time. Blood sampling will be done by trained personnel. Thus, risks during withdrawal of blood are minimized as much as possible.*

Addendum:
6 RYGB patients will get at the last time point a single oral dose of 1000 mg PCM intravenously via a second intravenous canula in the other arm. 4 additional blood samples will be withdrawn. The length of stay in the hospital for these RYGB patients remains the same.

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

- at least 18 years old
- on the waiting list of getting a Roux en Y gastric bypass
- mentally competent
- provided informed consent

Exclusion criteria

- patient undergoing different types of bariatric surgery, such as gastric band, gastric sleeve, mini gastric bypass or revision RYGB
- patient who previously underwent a gastric surgery, such as gastric band, RYGB or gastric sleeve
- liver failure
- taken paracetamol <24 h before blood sampling at t=0
- allergy or intolerance for paracetamol
- not being able to take paracetamol orally
- to vomit after intake of paracetamol
- to be pregnant

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:	Recruiting
Start date (anticipated):	13-02-2020
Enrollment:	28
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Panadol
Generic name:	acetaminophen
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	14-10-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-12-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-02-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	12-04-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2018-005006-62-NL
CCMO	NL70329.078.19
Other	NL8280