The effect of Roux-en-Y gastric bypass on the rate and extent of absorption of metoprolol from a controlled release tablet in female bariatric patient volunteers: a single oral dose study before and after surgery

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To investigate the effect of Roux-en-Y gastric bypass on the rate and extent of absorption of metoprolol and its main active metabolite α-OH metoprolol, after a single oral dose of 95 mg metoprolol CR tablet in 10 female bariatric surgery patient...

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

Summary

ID

NL-OMON38920

Source
ToetsingOnline

Brief title
Effect of RYGB on the absorption of metoprolol controlled release.

Condition

- Gastrointestinal therapeutic procedures

Synonym
Roux-en-Y gastric bypass, weight loss surgery

Research involving

Human

Sponsors and support

Primary sponsor: Medisch Centrum Leeuwarden
Source(s) of monetary or material Support: wetenschapsfonds MCL

Intervention

Keyword: absorption, controlled release tablet, metoprolol, Roux- en Y gastric bypass

Outcome measures

Primary outcome

Parameters that will be determined before and after surgery are Cmax, Tmax and

AUC0-24 of metoprolol and its main active metabolite α-OH metoprolol.

The main endpoint is the ratio of AUCafter/AUCbefore of metoprolol and α-OH

metoprolol.

Secondary outcome

Secondary endpoint is the quotient of the ratios of the AUC of metoprolol and

its metabolite after and before.

Other study parameters

Blood pressure and heart rate measured at t = 0, 2, 4, 8 and 10 hours after

intake of metoprolol.

Further analysis

After completion of the other pharmacokinetic study with metoprolol immediate

release tablet relevant parameters may be compared for further analysis.

Study description

Background summary

Obesity is a growing world wide problem. In The Netherlands, about 10% of all men and women have a BMI of 30 kg/m2 or more. Obesity is a chronic, uncurable metabolic disorder, which is characterised by excessive fatstorage at unfavorable places. Obese people have a higher risk to develop comorbidities like diabetes mellitus II, cardio vascular diseases and osteoarthritis. Morbid obesity, a BMI >= 40 kg/m2, is also associated with reduced life expectancy. Bariatric surgery is an operation for obese people with a BMI >= 40 kg/m2 or >35 kg/m2 with a comorbidity, who are not able to lose weight by themself. The number of patients undergoing bariatric surgery is rapidly increasing. Several metabolic operations can be divided into a restrictive (gastric band, sleeve gastrectomy), a malabsorptive (biliopancreatic deviation) and a combined restrictive/malabsorptive (gastric bypass) procedure. In The Netherlands the Roux-en-Y gastric bypass is the most frequently performed operation, with the best long term results. Bariatric surgery has been shown to lead to sustained weight loss, resolution of comorbidities and improved life expectancy.
Theoretically, bariatric surgery may alter the pharmacokinetics of orally taken drugs. Depending on the type of operation, different factors might influence drug absorption. A gastric restriction has influence at gastric mixing, gastric pH and gastric emptying. These changes may influence drug absorption by an altered drug disintegration and dissolution. Secondly, because of the reduced functional gastrointestinal length after a bypass procedure the absorption of drugs across the duodenum and jejunum might be reduced. This might be counterbalanced by *intestinal adaptation*, whereby mucosal hypertrophy within the remaining intestine results in an increased absorptive capacity.
Altered drug absorption will be a problem especially for oral formulations with a coating or with a modified release profile. These technological formulations are developed to disintegrate at a higher pH, or to dissolute slowly. In the USA investigators advocate that formulations with controlled release should not be used after bariatric surgery. However this is based on theoretical aspects and not on clinical studies.
The absorption of lipophilic drugs might be decreased because bile salts may emulsify the lipophilic drugs for absorption much later. Results showed that after a partial gastric resection the absorption of the lipophilic β-blocker propranolol is significantly decreased compared to the hydrophilic β-blocker atenolol. Although bariatric surgery may theoretically have effect on the pharmacokinetics of drugs, there is little known about the pharmacokinetics of drugs after bariatric surgery. In this study we want to investigate the pharmacokinetic profile of a controlled release lipophilic drug before and

after a Roux-en-Y gastric bypass.
Preliminary results of a retrospective study show that metoprolol belongs to the top 15 of most used drugs by bariatric surgery patients. The majority of these patients use metoprolol as a controlled release formulation. For these reasons metoprolol CR will be used in this study. However another pharmacokinetic study with metoprolol immediate release will also be performed. To determine the effect of the Roux-en-Y gastric bypass, the rate and extent of absorption of metoprolol CR before and after this surgery will be compared. In this study, the patient is his own control.

Study objective

To investigate the effect of Roux-en-Y gastric bypass on the rate and extent of absorption of metoprolol and its main active metabolite α-OH metoprolol, after a single oral dose of 95 mg metoprolol CR tablet in 10 female bariatric surgery patient volunteers, before and after surgery.

The pharmacokinetic parameters that will be determined are:
- Cmax The maximum serum concentration of metoprolol.
- Tmax The time after oral administration of metoprolol when the maximum serum concentration is reached.
- AUC t=0-24 The area under the serum concentration-time curve, a measurement of the bioavailability of metoprolol until 24 hours after intake.

The effect can be determined according to the following ratios as listed in the studyprotocol.

Study design

A single dose, fasting, explorative pharmacokinetic study before and after surgery, with the patient as his own control.

This study concerns an explorative two-phase single oral dose pharmacokinetic study of metoprolol under fasting conditions in patients undergoing bariatric surgery. The single dose will be administered twice in each patient, once before and once after bariatric surgery.

The study will be performed in 2013-2014.

The study takes place at the clinical research unit of the MCL. Analysis of the samples will take place in the Laboratory for Drug Analysis and Clinical

Toxicology of the Department of Clinical Pharmacy and Clinical Pharmacology MCL.

Details
- A total of 10 female bariatric surgery patient volunteers will participate in this study.
- The study is divided into two periods. One period before scheduled surgery and one after surgery.
- Metoprolol succinate 95 mg controlled release tablet will be used.
- The patient will stay at the MCL for 10 hours.
- Each visit, a total of 10 blood samples of 5 ml will be collected
- 24 hours after the intake of the tablet a blood sample of 5 ml will be collected at the patient*s home
- Blood pressure and heart rate will be monitored.
- Four months after surgery before the start of the second phase of the study the patient will be asked about dumping syndrome symptoms by means of a questionnaire. Dumping syndrome is characterized by symptoms of nausea, shaking, sweating, diarrhea, light-headedness, flushing, tachycardia (fast heart rate) and possibly fainting shortly after eating foods containing high amounts of refined sugars and when eating too fast. Side effects of metoprolol might resemble these symptoms. If the patient is suffering from the dumping syndrome, the patient will be withdrawn from the study.

Intervention

One month before and six months after Roux-en-Y gastric bypass the patient takes a single oral dose of 95 mg of metoprolol CR tablet.

Study burden and risks

There will be no direct benefit for included patients. After having given written informed consent to participate in the study, the patient is required to undergo a medical examination. The patient has to visit the MCL for two days. The first visit is scheduled one month before the surgery and the second visit six months after surgery. The procedure of both visits is the same. A single dose of 95 mg of metoprolol may cause side effects like hypotension, headache and dizziness, but these side effects are moderate. Blood pressure and heart rate will be monitored regularly. The patient is not allowed to lie down during the first six hours of the study. During each phase, 11 blood samples of 5 ml each will be collected according to a time schedule by a venous cannula. An intensivist is available for questions and safety of the patient. The patient has to stay at the clinical research unit, but is not confined to bed.

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

- Female gender
- Age 18-50 years
- Scheduled for Roux-en-Y gastric bypass surgery
- Good liver and kidney function
- Normal ECG
- Intermediate or extensive CYP 2D6 metabolizer, evidenced by genotyping.

Exclusion criteria

Pregnancy
- Smoking
- Alcohol: more than 7 drinks a week or 4 or more drinks during a single occasion (12)
- Use of alcohol during the period 24 hours before until 48 hours after the start of each phase of the study

- Use of metoprolol
- The use of CYP 2D6 inhibiting, inducing or metabolising drugs
- The use of drugs that may interact with metoprolol
o Calcium antagonist
o Lidocaine
o Digoxin
- An existing contraindication for the use of metoprolol (8)
o Sick-sinus syndrome
o Second and third degree heart block
o Systolic blood pressure less than 100 mmHg
o Cardiogenic shock
o Sinus bradycardia
o Cardiac failure, overt
o Cardiac failure, moderate to severe
o Untreated pheochromocytoma
o Heart rate less than 45 beats/minute
o First degree heart block (P-R interval 0.24 sec or greater)
o Severe bronchial asthma or a history of severe bronchospasm
o Hypersensitivity to metoprolol, related derivatives, other beta-blockers, or any component of the product
o Severe peripheral arterial circulatory disorders
- Previous surgery of the upper gastrointestinal tract
- Disease or any other condition that may interfere with gastrointestinal absorption
- Suffering from dumping syndrome after RYGB surgery

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-11-2013
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	metoprolol succinate 95 mg controlled release tablet
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	06-06-2013
Application type:	First submission
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	11-07-2013
Application type:	First submission
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)

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	EUCTR2013-002274-41-NL
CCMO	NL44935.099.13