A study on the effect of gastric bypass on the absortpion of metoprolol immediate release tablet.

Gepubliceerd: 19-05-2013 Laatst bijgewerkt: 18-08-2022

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....

Ethische beoordeling	Positief advies
Status	Werving nog niet gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON29306

Bron
NTR

Aandoening

Roux- en-Y gastric bypass;

Metoprolol

immediate release tablet
absorption

gastric bypass
metoprolol
directe afgifte tablet
absorptie

Ondersteuning

Primaire sponsor: Medisch Centrum Leeuwarden
Overige ondersteuning: Wetenschapsfonds MCL

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

Parameters that will be determined before and after surgery are Cmax, Tmax, and AUC0-10 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.

Toelichting onderzoek

Achtergrond van het onderzoek

Rationale: Bariatric surgery induces changes in the gastrointestinal tract that might alter the pharmacokinetics of drugs.

Hypothesis: Bariatric surgery influences the rate and extent of absorption of a lipophilic drug like metoprolol from a tablet with an immediate release (IR) profile.

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 100 mg of metoprolol IR tablet in 10 female bariatric surgery patient volunteers, before and after surgery.

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

Study population: 10 female bariatric surgery patient volunteers between 18 and 50 years old.

Intervention: One month before and six months after Roux-en-Y gastric bypass the patient takes a single oral dose of 100 mg of metoprolol IR tablet.

Main study parameters/endpoints: Parameters that will be determined before and after surgery are Cmax, Tmax and AUC0-10 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.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: There will be no direct benefit for included patients. After having given written

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 a month before the scheduled surgery and the second visit six months after surgery. The procedure of both days is the same. A single dose of 100 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 the day, 11 blood samples of each 5 ml will be collected according to a time schedule. 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.

Doel van het onderzoek

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 also 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.
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 an immediate 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 (CR) formulation. Therefore another pharmacokinetic study with metoprolol CR will be performed. However, to determine the effect of Roux-en-Y gastric

bypass on the absorption of an immediate release formulation a study with metoprolol IR is also essential. For this reason metoprolol IR will be used in this study. To determine the effect of the Roux-en-Y gastric bypass, the rate and extent of absorption of metoprolol IR before and after this surgery will be compared. In this study, the patient is his own control.

Onderzoeksopzet

Two studyphases, one month before and six month after Roux-enY gastric bypass

Onderzoeksproduct en/of interventie

One month before and six months after Roux-en-Y gastric bypass the patient takes a single oral dose of 100 mg of metoprolol IR tablet

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 tartrate 100 mg immediate release tablet will be used.

- The patient will stay at the MCL for 10 hours.

- Each visit, a total of 11 blood samples of 5 ml will be collected

- 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.

Contactpersonen

Publiek

Medisch Centrum Leeuwarden
Henri Dunantweg 2
J.P. Yska
Leeuwarden 8934 AD
The Netherlands
+31 (0)58 2866604

Wetenschappelijk

Medisch Centrum Leeuwarden
Henri Dunantweg 2
J.P. Yska
Leeuwarden 8934 AD
The Netherlands
+31 (0)58 2866604

Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

- 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.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

- 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

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Cross-over
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving nog niet gestart
(Verwachte) startdatum:	01-09-2013
Aantal proefpersonen:	10
Type:	Verwachte startdatum

Ethische beoordeling

Positief advies

Datum:	19-05-2013
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL3832
NTR-old	NTR4000
Ander register	MCL-metoprolol-IR : RTPO 898
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Resultaten