Drug disposition and modelling before and after gastric bypass: immediate and controlled release metoprolol formulations

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Summary

AIMS
To evaluate the disposition of metoprolol after oral administration of an immediate and controlled release formulation before and after Roux-en-Y gastric bypass (RYGB) surgery in the same individuals and to validate a physiologically-based pharmacokinetic (PBPK) model for predicting oral bioavailability following RYGB.

METHODS
A single-dose pharmacokinetic study of metoprolol tartrate 200 mg immediate release (Lopresor®) and controlled release (Slow-Lopresor®) was performed in 14 volunteers before and six to eight months after RYGB. The observed data were compared with predicted results from the PBPK modelling and simulation of metoprolol tartrate immediate and controlled release formulation before and after RYGB.

RESULTS
After administration of metoprolol immediate and controlled release, no statistically significant difference in the observed AUC\(_{0-24h}\) was shown, although a tendency towards an increased oral exposure could be observed as AUC\(_{0-24h}\) was 32.4% (95% CI [1.36, 63.5]) and 55.9% (95% CI [5.73, 106])% higher following RYGB for the immediate and controlled release formulation, respectively. This could be explained by surgery related weight loss and a reduced presystemic biotransformation in the proximal GI-tract. The PBPK modelling and simulation predicted values were similar to the observed data, confirming its validity.

CONCLUSIONS
The disposition of metoprolol from an immediate release formulation and a controlled release formulation was not significantly altered after RYGB; there was a tendency to an increase, which was also predicted by PBPK modelling and simulation.
What is known about this subject?

- RYGB has an influence on a number of factors known to govern drug absorption including an increased gastric pH, delayed inlet of bile acids, and reduced small intestinal surface area.
- There are only a few studies conducted, in which changes in oral drug exposure after RYGB have been observed.

What this study adds to our knowledge?

- The disposition of metoprolol was not significantly different post-RYGB, although a tendency to a higher exposure was seen.
- The disposition of metoprolol controlled release remained unaltered following RYGB.
- The study added to the body of work illustrating the validity of a PBPK modelling and simulation approach in predicting trends in oral drug exposure pre- to post-RYGB.
Introduction

Over the last decades, the prevalence of obesity has increased dramatically [1]. This has led to an increased demand for bariatric surgery, especially Roux-en-Y gastric bypass (RYGB), which is the only available treatment leading to major and sustainable weight reduction in morbid obese patients (BMI ≥ 40 kg/m² or BMI ≥ 35 kg/m² with obesity-related diseases) [2]. RYGB results in an altered anatomical structure of the gastrointestinal tract by reducing the gastric capacity and bypassing the duodenum and the proximal jejunum. Changes to the anatomical structure of the gastrointestinal tract following RYGB can alter the pharmacokinetics of a given drug by an increase in gastric pH (due to gastric resection and the widespread use of antacid medication following surgery), a delayed inlet of bile acids, a reduced small intestinal surface area available for absorption and a potential bypass of intestinal regions with high abundance of drug metabolising enzymes [3,4]. All of the above stated changes may impact oral drug absorption and bioavailability. However, the extent to which absorption is hampered for a specific drug, or class of drugs, remains unknown. The few studies that have been conducted illustrate that a trend in oral drug exposure before to after RYGB is not easy to predict. On the one hand, oral exposure can be reduced following RYGB, as reported for azithromycin [5]; on the other hand, it can remain unaltered, as reported for levothyroxine, or be increased, as for metformin [6,7]. A systematic approach to study the influence of RYGB on oral drug exposure is lacking as previously conducted studies vary in design and are poorly standardised based on how surgery is conducted, which makes the results difficult to compare.

Drug substances can be classified according to their solubility and permeability, which forms the basic concept of the Biopharmaceutical Classification System (BCS) [8]. Based on its absorption characteristics, we have chosen to investigate the influence of RYGB on metoprolol, a BCS class I compound, which is characterized by a high solubility and high permeability. Metoprolol is a β₁-blocker, and β-blockers are widely used cardiovascular drugs. Metoprolol (pKₘ = 9.18) is known to cross the intestinal mucosa by passive diffusion [9]. It is mainly metabolized by cytochrome P450 2D6 (CYP2D6) and in healthy volunteers, the half-life of metoprolol amounts to 3-4 h [10,11]. For the investigation of the influence of RYGB surgery on the disposition of metoprolol, we have chosen for an immediate release formulation and for a controlled release formulation; so far, controlled release formulations have never been studied in RYGB patients. It is generally advised to avoid formulations with a controlled release after bariatric surgery, but this advice is purely eminence based [12]. An additional aim of this study was to serve as an ongoing validation of a previously developed physiologically-based pharmacokinetic (PBPK) model [13] for predicting oral drug exposure following RYGB in order to validate its use for dose adjustments following surgery. This way, potential dangerous over- or underdosing of drugs can be avoided, which is especially a risk for drugs with a narrow therapeutic range.
Hence, this paper reports on two types of investigations: (1) evaluation of the oral pharmacokinetic parameters of metoprolol tartrate, a β₁-blocker belonging to class I of the BCS (high solubility/high permeability), immediate and controlled release in obese patients before and after RYGB; (2) comparison of the in vivo data to the predictions from the PBPK modelling of metoprolol tartrate immediate and controlled release formulation before and after RYGB.
Methods

Selection of patients

For this study (EudraCT number is 2012-001244-22), 14 obese patients with a planned RYGB surgery at the University Hospitals Leuven, Belgium, were recruited. Patients who had previously undergone bariatric surgery or who had renal and hepatic impairment were not included in the study. Pregnant and breastfeeding women were also not included. RYGB surgery was performed in all recruited patients by the same surgeon. In brief, the jejunum was divided 30 cm from the ligament of Treitz and anastomosed to a 30 mL proximal gastric pouch. The jejunum was reanastomosed 120 cm distally to the gastrojejunostomy. All mesenteric defects were closed. The study was approved by the Medical Ethics Committee of the University Hospitals Leuven (ML8433) and all patients gave written informed consent.

Study design and procedure

A single-dose pharmacokinetic study of metoprolol tartrate (referred to as metoprolol) 200 mg immediate release (Lopresor®) and controlled release (Slow-Lopresor®) was performed before and six to eight months after RYGB (on average 6.6 months [SD 0.63]; further referred to as six months after RYGB). Both formulations were tested in all patients before and after RYGB, with an interval of at least 5 days between administration of the two formulations. The relative extent of oral exposure of metoprolol from both formulations was estimated by the determination of the area under the curve (AUC$_{0-24h}$), the peak plasma concentration of metoprolol after oral administration ($C_{\text{max}}$) and the time to reach peak concentration ($T_{\text{max}}$). The AUC$_{0-24h}$ reflects drug absorption and drug elimination; in this paper we have mainly focused on drug absorption as a RYGB mainly influences the absorption through the formation of a gastric pouch and bypass of the proximal part of the small intestine.

Following an overnight fast of at least 10 hours, subjects came to the clinical pharmacology unit of the University Hospitals Leuven. Weight and height of the subjects were measured with calibrated equipment. The weight was measured to the nearest 0.1 kg, with the subjects having an emptied bladder and wearing indoor clothing with empty pockets and without shoes. BMI (kg/m$^2$) was calculated by dividing the weight (kg) by the square of the height (m$^2$). A Dual Energy X-ray Absorptiometry (DXA) was performed to measure the amount of body fat mass [14].

After the insertion of an intravenous catheter, the subjects ingested 200 mg of metoprolol (2 tablets of Lopresor® 100 mg or 1 tablet of Slow-Lopresor® 200 mg) with 150 mL of water. The tablets were taken without being broken or crushed. After oral administration, blood samples were collected into heparinised tubes at 15; 30; 60; 90 minutes and 2; 2.5; 3; 3.5; 4; 5; 6; 7; 8; 9; 10 and 24 hours. The blood samples were centrifuged immediately after collection (1800 g, 10 min, 4°C) and plasma
samples were stored at -20°C until analysis. At each time-point, the systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate were determined with Omron, Model M6, Digital automatic blood pressure monitor, Intellisens™.

A standardised meal and a standardised snack were administered 4 hours and 8 hours after drug administration, respectively. Participants had to consume the entire meal. The use of water was allowed ad libitum, except for one hour before and four hours after drug administration. During the first 4 hours after administration of metoprolol, the patients had to remain semi-supine in bed. After the 10h-blood sample, the subjects were discharged and they had to return the next morning for the 24-h blood sampling. As proton pump inhibitors, H₂-receptor antagonists and antacids could influence the absorption of drugs, the recruited patients were asked to stop these drugs during the week preceding the study. Other prescription drugs were checked to verify that there were no pharmacokinetic interactions with the study drug. The morning of the study, the patients were not allowed to take their medication.

All procedures were in accordance with the ethical standards of the Medical Ethics Committee of the University Hospitals Leuven.

**HPLC analysis**

The determination of the concentration of metoprolol was performed by a validated HPLC method with fluorescence detection (ex.271nm, em.302nm; Waters 2475 Multiwavelength Fluorescence Detector). Metoprolol was extracted after adding 1.25 mL of 0.2M HCl, 0.10 mL of 200 nM propranolol (as internal standard), 0.50 mL of 2M NaOH and 10.00 mL of CH₂Cl₂ to 0.50 mL of plasma by repeatedly vortexing. After extraction for one minute, it was centrifuged (4000 rpm, 10 min, 4°C) and the supernatant was removed. The remaining organic solution was evaporated and the residue was dissolved in MeOH. This solution was evaporated again and resuspended in 0.15 mL of transport medium, which was injected into the HPLC system, equipped with an Alliance 2695 separations module and a Novapak C-18 column under radial compression (Waters, Milford, MA, USA).

A gradient run was performed with 25 mM acetate buffer pH 3.5:methanol (51:49 v/v) during the first three minutes, followed by six minutes 25 mM acetate buffer pH 3.5:methanol (45:55 v/v). Then the column was rinsed with acetonitrile:water (90:10 v/v). The flow rate amounted to 1.10 mL/min resulting in a retention time of 4.2 min and 8.2 min for metoprolol and the internal standard, respectively.

Calibration curves were made based on a stock solution of metoprolol in dimethyl sulfoxide and linearity was observed between 1337 ng/mL and 5 ng/mL. The intra-day accuracy and precision errors were 3.3% and 6.4%, respectively, for a
concentration of 535 ng/mL (corresponding to 2000 nM) and 3.0% and 8.6%, respectively, for a concentration of 53 ng/mL (corresponding to 200 nM). The inter-day accuracy and precision errors were 6.1% and 1.0%, respectively, for a concentration of 535 ng/mL, and 4.8% and 3.5%, respectively, for a concentration of 53 ng/mL.

Data and chapter analysis

The AUC$_{0-24h}$ of the concentration-versus-time profiles was determined using the linear trapezoidal rule. Data are presented as mean (95% confidence interval, CI), unless otherwise mentioned. To evaluate the effect of RYGB on the pharmacokinetic parameters of metoprolol, AUC$_{0-24h}$, $C_{\text{max}}$ and $T_{\text{max}}$ obtained before and after surgery were compared. The paired data were analysed with SPSS Statistics 22, performing a paired t-test as the assumption for normal distribution of the data was accepted (Shapiro-Wilk test). The AUC$_{0-24h}$ of the controlled release formulation was transformed with the logarithmic function to achieve normality. For the data analysis of $T_{\text{max}}$, a Wilcoxon signed-rank test was performed as normality was not achieved. Multiple linear regression analysis was performed to control for confounding factors between the difference in oral exposure of metoprolol and: gender, age, BMI, fat percentage as measured by DXA, weight loss, systolic and diastolic blood pressure and heart rate were included. No significant confounding factors were identified for AUC$_{0-24h}$; so no adjustments for these factors were made. To compare the baseline pharmacodynamic parameters a paired t-test was performed, and the comparison of the pharmacodynamic profiles was carried out using a linear mixed model. Statistical significance was set at $p<0.05$.

Physiologically-based pharmacokinetic modelling and simulation

PBPK modelling and simulation was employed using the previously developed and validated RYGB PBPK absorption model, based on the obesity model by Ghobadi et al. (2011) available in the Simcyp Simulator, considering obesity related changes in drug disposition [15]. The RYGB PBPK absorption model was coupled to the minimal PBPK model incorporated into the Simcyp Simulator version 13.1, in order to elucidate the potential mechanism behind the observed trend in oral drug exposure of metoprolol immediate and controlled release formulation before to after RYGB [13,16,17]. Metoprolol immediate and controlled release compound files were developed based on the pre-validated metoprolol compound as supplied in the Simcyp compound library. Distributional parameters describing a two-compartmental distribution behaviour ($V_{ss}$, $V_{sac}$, $k_{in}$, $k_{out}$) were estimated based on intravenous data from Regardh et al. [18] using the parameter estimation toolbox, obtaining the following estimates: 2.58 L/kg, 1.89 L/kg, 5.75 h$^{-1}$ and 5.09 h$^{-1}$ for $V_{ss}$, $V_{sac}$, $k_{in}$ and $k_{out}$, respectively. Clearances via cytochrome P450 isoforms 3A4 and 2D6 were estimated using the retrograde model, back-calculating intrinsic clearance (CL$_{int}$) from intravenous clearance assuming a 7% contribution by CYP3A4 (Simcyp Simulator v13.1).
vitro release profiles of metoprolol immediate and controlled release formulations were obtained from Oosterhuis et al. [19] and Polli et al. [20] and were fitted to a Weibull function using Matlab R2012a (Mathworks, Natick, MA, USA). For the immediate release metoprolol formulation the Weibull function describing the dissolution profile derived from simulated gastric fluid was directly implemented into the Simcyp Simulator. Dissolution of the controlled release formulation was scaled by in vitro-in vivo correlation (IVIVC) based on fast, medium and slow extended release profiles and plasma concentration-time data as reported by Eddington et al. [21]. The IVIVC produced a correction factor of 0.93 using the module in Simcyp Simulator v13.1. The RYGB absorption model was adapted as per Darwich et al. [16] in order to account for population-specific demographics (body weight, height, age and gender) pre and post RYGB, and surgical dimensions. Furthermore, oral bioavailability ($F_{oral}$) was calculated using the following equation:

$$F_{oral} = F_A \times F_G \times F_H$$

where $F_A$ stands for fraction of drug absorbed; $F_G$ is the fraction of drug escaping gut wall metabolism and $F_H$ stands for the fraction of drug entering the portal vein escaping first pass metabolism in the liver.
Results

In this study, we recruited 14 patients (10 women, 4 men) with a mean age of 44.4 years (95% CI [38.0, 50.7]). The main characteristics of the participants are shown in Table 1.

The observed and predicted pharmacokinetic data are summarised in Table 2 and the observed concentration-time profiles are shown in Fig. 1.

The AUC$_{0-24h}$ of metoprolol immediate release was 32.4% (95% CI [1.36, 63.5]) higher 6 months following RYGB than before surgery. However, this difference was not statistically significant (paired t-test: $p=0.07$). C$_{max}$ for metoprolol immediate release tended to be 29.0% (95% CI [-1.86, 59.8]) higher after RYGB, but this difference did not reach statistical significance (paired t-test: $p=0.07$). The time to reach maximum plasma concentration was also not statistically significant different, but with a trend of T$_{max}$ being shorter after the operation: T$_{max}$ decreased from 1.36 h (95% CI [1.03, 1.69]) to 1.25 h (95% CI [0.89, 1.61]) (Wilcoxon: $p=0.68$). These trends were similar to the predicted data from the PBPK simulation and modelling: AUC$_{0-24h}$ and C$_{max}$ were also higher after RYGB by 16.0% and 34.0%, respectively; T$_{max}$ was shorter with a decrease from 1.72 h to 1.25 h after RYGB. The half-life increased from 4.2 h (95% CI [3.1, 5.3]) before RYGB to 4.9 h (95% CI [3.2, 6.6]) after RYGB; this difference was not significant.

After administration of the metoprolol controlled release formulation, no statistically significant difference in AUC$_{0-24h}$ of metoprolol was observed, although a tendency towards increased oral exposure could be observed after RYGB as the AUC$_{0-24h}$ after oral administration of the controlled release formulation was 55.9% (95% CI [5.73, 106]) higher than before RYGB (paired t-test: $p=0.30$). The same observation was made for the predicted data. In Fig. 2 the data from the in vivo pharmacokinetic study and the predicted data for metoprolol immediate and controlled release before and after RYGB are shown along with the segmental fraction of dose absorbed along the small intestine.

[Insert Table 1]

[Insert Table 2]

[Insert Figure 1]

[Insert Figure 2]

[Insert Table 3]
In the simulated data, a very small reduction of 3% in oral bioavailability ($F_{oral}$) following RYGB was predicted (see Table 3).

During the pharmacokinetic study, pharmacodynamic parameters were also monitored (Fig. 3). Before administration of the metoprolol immediate release formulation, baseline systolic blood pressure ($p=0.02$) and heart rate ($p=0.00$) were significantly lower after RYGB; before administration of metoprolol controlled release, baseline systolic blood pressure ($p=0.01$) was significantly lower after RYGB. After administration of metoprolol immediate release, there was a significant interaction between time-point after administration and moment of the experiment (before or after surgery) for heart rate ($p=0.029$) and systolic blood pressure ($p<0.001$), but not for diastolic blood pressure. After administration of the controlled release formulation, there were no significant interaction effects regarding the pharmacodynamic parameters.

[Insert Figure 3]
Discussion

As the knowledge regarding the impact of gastric bypass on drug disposition is very limited, this study aimed to investigate the disposition of BCS class I compound metoprolol from an immediate and controlled release formulation before and after RYGB, which would also serve as further validation of a previously developed RYGB PBPK absorption model. No significant differences were observed in the pharmacokinetic parameters of disposition of both formulations.

Metoprolol (pK_a = 9.18) is known to cross the intestinal mucosa through passive diffusion [9]. As this compound has a high solubility and high permeability [8,22], its absorption is not expected to be altered significantly after RYGB, which was indeed confirmed in this study, despite the observed tendency towards a higher oral drug exposure.

Besides its high solubility (>700 mg metoprolol tartrate/mL in water at 37°C) and high permeability, the absorption of metoprolol by the gastrointestinal tract is rapid and complete; no site dependent absorption occurs over a large part of the intestine [22,23]. However, in view of the reduced length of the gastrointestinal tract after RYGB, the absorption may be decreased. Additionally, surgery associated weight loss might result in a reduced distribution volume, which therefore may compensate for a possible reduction in oral absorption postoperatively. In a previous study in obese patients, the apparent distribution volume for metoprolol was shown to be higher in obese patients compared to non-obese patients with a lower peak concentration [24]. This can also contribute to the tendency towards an increased oral exposure post-RYGB, since the BMI and fat percentage is decreased six months post-RYGB compared to baseline.

Furthermore, metoprolol undergoes metabolism in the liver by CYP2D6 and to a small extent by CYP3A4, resulting in the formation of metabolites (O-desmethylmetoprolol and α-hydroxymetoprolol) without a significant beta-blocking effect, [25]. As no significant changes were observed in the pharmacokinetic parameters of disposition and the half-life of metoprolol before and after surgery, CYP2D6 metabolism is probably the same before and after RYGB as metoprolol is a validated probe drug for CYP2D6 activity [26]. Also for the controlled release formulation, no significant differences in the disposition of metoprolol were observed. Both formulations contained the same salt, metoprolol tartrate, and we could therefore expect these two formulations to display the same solubility properties. Previous studies have shown that the extent of absorption of metoprolol is comparable along the gastrointestinal tract [27,28]. This may explain the absence of an effect on AUC_0-24h for the controlled release formulation before and after RYGB as the absorption in more distal parts of the intestine can compensate for the bypassed proximal segment of the small intestine. Furthermore, for a controlled release formulation based on a matrix system, as is the case here, the intestinal transit time becomes an important factor in limiting absorption. In only a few studies the intestinal transit time after RYGB has been investigated. Dirksen et al. have shown that...
the small intestinal transit time after a meal was slower in patients more than one year post-RYGB than in control subjects, while the colonic transit rate did not differ between the groups [29]. These observations do not entirely correspond with the findings of Morinigo et al., who have shown that the oro-caecal transit time, which includes pouch emptying and small intestinal transit, was shorter in RYGB-patients. Other studies have already shown that the gastric emptying for liquids is accelerated after RYGB [30-32]. Carswell et al. also reported on the oro-caecal transit time using sulphasalazine; in this study, RYGB had no impact on the oro-caecal transit time [33]. Overall, these studies indicate that the transit time before and after RYGB is probably comparable, which contributes to the similar disposition of metoprolol after administration of the controlled release formulation. Although, the oral exposure after administration of the controlled release formulation had also the tendency to be increased; this might be explained by the characteristics of the compound, as discussed for the immediate release formulation.

Because it is impossible to test all the drugs on the market in clinical trials in specific patient populations, PBPK modelling may be considered a complimentary approach in that it may provide potential insights as to what factors are mainly responsible for observed differences in drug exposure between populations. During the last few years, PBPK modelling has indeed seen an expanding area of applications, including that of post bariatric surgery patients. A pharmacokinetic model was created for the different types of bariatric surgery, including RYGB, by Darwich et al [13]. The observed data of metoprolol immediate and controlled release were compared to matched simulations utilising the PBPK RYGB model. The trends observed in the clinical studies were comparable to the predictions made using the PBPK modelling and simulation approach. However, an overprediction occurred in the first part of the concentration-time profiles, especially for the slow release formulation which could probably be attributed to the lack of well-established in-vitro in-vivo correlation methods. Despite this minor overprediction, the observed data were well within the 95% prediction intervals. According to simulations, the trend of an increased oral exposure was mainly due to weight loss as the oral bioavailability remained almost constant before and after surgery. For the observed data, weight loss could contribute to the tendency of the increased exposure of metoprolol post-RYGB.

Based on the current results one could conclude that the PBPK modelling and simulation provides a good platform for reasoning around what factors will be the most significant in determining the disposition of metoprolol following RYGB. As already mentioned, metoprolol is metabolized by CYP2D6, which has a genetic heterogeneity; a different CYP2D6 genotype and metabolizer phenotype may thus influence the pharmacokinetics of metoprolol [11,34]. Therefore, it may be advantageous to determine the genotype of the volunteers, which was not performed in this study. However, the fact that we
followed the same group before and after the operation (i.e. the genotype in both groups was the same) rules out the absolute necessity of genotyping.

It also has to be kept in mind that the expression of cytochrome P450 enzymes is the highest in duodenum and jejunum and decreases towards to more distal sites of the small intestine [35]; bypassing parts of the proximal small intestine with a high abundance of CYP enzymes may therefore lead to a different effect on the bioavailability of drugs metabolized by CYP enzymes, depending on the genotype. Bypassing first-pass metabolism in the proximal small intestine may also contribute to the tendency of an increased exposure of metoprolol after RYGB as it results in a decreased presystemic biotransformation. A similar effect has been described by Skottheim et al. [36] concerning the exposure of atorvastatin following gastric bypass surgery.

In this study, we also explored the influence of both formulations on the pharmacodynamic parameters; the blood pressure and heart rate at baseline were lower after the operation. This can be explained by the improvement of cardiovascular parameters after RYGB [37].

Overall, the strength of this study lies in the fact that it was performed in the same patient group before and after the operation, and that the same type of surgery was performed by the same surgeon. This design helps to minimize inter-individual differences in metoprolol exposure before and after surgery, which is important as there are several factors contributing to the inter-individual variability in the pharmacokinetics of metoprolol (such as age, first-pass metabolism and intestinal absorption) [9].

In the future, more challenging drugs will be studied, including low solubility compounds for which solubilisation depends on intraluminal bile salt concentrations or on the residence time in the acidic environment of the stomach.

To conclude, the oral exposure of metoprolol immediate release and controlled release formulation was not significantly different before compared to after RYGB, although a tendency towards higher exposure existed following surgery, which could be explained by weight loss and a reduced presystemic biotransformation in the proximal GI-tract. The PBPK modelling and simulation predicted values were similar to the observed data, confirming its validity in daily clinical practice.
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Conflict of Interest/Disclosure

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare: AD had support from Innovative Medicines Initiative (IMI) for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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Table legends

Table 1 Characteristics of the participants, shown as mean (95% CI).

Table 2 Pharmacokinetic results and predicted results for the immediate (IR) and controlled release (CR) formulation of metoprolol before and after surgery.

Table 3 Predicted results for the bioavailability of metoprolol. $F_A$, fraction of drug absorbed; $F_G$, fraction of drug escaped gut metabolism; $F_{H}$, fraction escaped first pass metabolism; $F_{oral}$, oral bioavailability.

Figure legends

Fig. 1 Observed plasma concentration-time profiles of metoprolol over 24h after the administration of an immediate release dosage form before and after RYGB (A) and a controlled release dosage form before and after RYGB (B), shown as mean concentration±sem ($n=14$).

Fig. 2 Mean plasma concentration-time profiles from the in vivo pharmacokinetic study and predicted mean plasma concentration-time profiles over 24h for the immediate release (A) and controlled release formulation (B) and predicted mean of segmental fraction of dose absorbed along the intestine for immediate release (C) and controlled release formulation (D).

Fig. 3 Pharmacodynamic parameters: systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate at the different time-points after administration of the immediate formulation (A and B) and controlled release formulation (C and D), shown as mean concentration±SD.