EFFECT OF ROUX-EN-Y GASTRIC BYPASS ON THE BIOAVAILABILITY OF METOPROLOL FROM IMMEDIATE AND CONTROLLED RELEASE TABLETS: A SINGLE ORAL DOSE STUDY BEFORE AND AFTER SURGERY

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ABSTRACT

Background
Roux-en-Y gastric bypass surgery (RYGB) induces major changes in the gastrointestinal tract that may alter the pharmacokinetics of orally administered drugs. However, results from pharmacokinetic studies are sparse.

Aim
To investigate the effect of RYGB on the bioavailability of metoprolol from immediate release (IR) and controlled release (CR) tablets in female patient volunteers before and after surgery.

Methods
An explorative, two-phase, single oral dose pharmacokinetic study of metoprolol in female patients undergoing RYGB was carried out. The dose was administered twice in each patient, 1 month before and 6 months after surgery. After intake of either 100 mg of metoprolol IR or CR tablet serum concentration-time profiles of metoprolol were determined. The endpoint was the ratio of $\frac{AUC_{after}}{AUC_{before}}$ of metoprolol.

Results
Twelve patients were included in the study (metoprolol IR: 7; metoprolol CR: 5). After intake of a metoprolol IR tablet large intra- and interindividual differences for $AUC$ were observed (range ratio $\frac{AUC_{0-10h \: after}}{AUC_{0-10h \: before}}$: 0.74-1.98). For metoprolol CR tablets a reduction in bioavailability of metoprolol was observed after surgery (range ratio $\frac{AUC_{0-24h \: after}}{AUC_{0-24h \: before}}$: 0.43-0.77).

Conclusions
RYGB may influence the bioavailability of metoprolol from an IR tablet. The magnitude of changes in bioavailability after RYGB require close monitoring of patients using metoprolol IR tablets and dose adjustment if deemed necessary. RYGB clearly reduces the bioavailability of metoprolol from a CR tablet. After RYGB clinicians may consider to increase the dose according to clinical response.

Trial Registration
INTRODUCTION

In 2013 Roux-en-Y gastric bypass (RYGB) was the most commonly performed bariatric procedure in the world [1]. RYGB achieves weight loss through restriction of food intake, altered neurohormonal signaling in body weight regulation, increased energy expenditure and altered bile salt metabolism due to changes in the gut microbiome. Although true malabsorption is rare after RYGB, changes in anatomy and function such as a reduced gastric volume, increased gastric pH, altered gastric emptying, reduced intestinal surface area for absorption, changed intestinal and hepatic first-pass metabolism, shorter intestinal transit time and more distal delivery of bile and pancreatic secretions, may all affect the absorption and thus the bioavailability of orally administered drugs [2-4]. The performance of oral formulation types such as slow release or delayed release may suffer from critical changes affecting adequate drug absorption and thereby their efficacy after RYGB [5].

Generally after restrictive-malabsorptive procedures, such as RYGB, it is recommended to substitute controlled release drug formulations into immediate release dosage forms [6]. This is reflected in the European guidelines on metabolic and bariatric surgery, stating that in the follow-up after bariatric surgery, patients should be advised to preferably use crushed and/or rapid release medication [7]. However, these recommendations are not evidence based. So far, only a few studies have been published on the influence of RYGB on the pharmacokinetics of drugs. Therefore, especially for drugs frequently used by patients after bariatric surgery, more studies are needed on the influence of bariatric surgery, in particular RYGB, on the pharmacokinetic behavior [8]. Although after restrictive-malabsorptive weight loss procedures, such as RYGB, a significant reduction in use of beta blockers has been reported, nonetheless a considerable number of patients still use a beta blocker [9-10]. Metoprolol, a lipophilic cardioselective β1-adrenoreceptor antagonist, has a long history of use in the treatment of hypertension, angina pectoris and other cardiovascular diseases, as well as for the prophylactic treatment of migraine. It is available as immediate and controlled release tablet. Although after oral administration absorption of metoprolol from the gastrointestinal tract is almost complete, due to an extensive first-pass hepatic metabolism only about 50% of the dose reaches the systemic circulation. In the liver metoprolol is metabolized for about 70-80% by cytochrome P450 2D6 (CYP2D6) into several metabolites. α-hydroxymetoprolol is an active metabolite, possessing only around one tenth of the β1-blocking activity of metoprolol. It is formed by CYP2D6, making it a suitable marker for CYP2D6 activity [11-12]. In urine approximately 7% of the administered dose of metoprolol is recovered as α-hydroxymetoprolol. Serum concentrations of α-hydroxymetoprolol vary depending on age and on the oxidation phenotype [12-13].
Possible variations in bioavailability after RYGB might be caused by changes in release of metoprolol from the oral tablet formulation. Therefore, in this study, in addition, the pharmaceutical availability and in vitro release characteristics of metoprolol from both oral immediate release (IR) and controlled release (CR) tablet formulations were established in a gastrointestinal simulation system (GISS) mimicking conditions before and after RYGB.

The aim of the present study was to investigate the effect of RYGB on the bioavailability of metoprolol and formation of its metabolite α-hydroxymetoprolol, after a single oral dose of metoprolol IR and CR tablet in female bariatric surgery patient volunteers before and after surgery.

MATERIALS AND METHODS

Metoprolol
In the present study the absorption of metoprolol from 2 different oral tablet formulations before and after RYGB was investigated. Metoprolol tartrate 100 mg immediate release tablet (Pharmachemie, Haarlem, The Netherlands; (metoprolol IR)), and metoprolol succinate 95 mg controlled release tablet, equivalent to 100 mg of metoprolol tartrate (Pharmachemie, Haarlem, The Netherlands; (metoprolol CR)) were used.

Participants
The study was conducted in female patients undergoing RYGB at Medical Centre Leeuwarden. Only female patients were enrolled in this study, since for metoprolol gender-related differences exist in the pharmacokinetics leading to greater drug exposure (higher C\text{max} and AUC) for women than men [14]. Moreover, almost 80% of the patients undergoing bariatric surgery are female [15]. The criteria for enrollment in this study were: age between 18-50 years, non-smokers, physiologically normal liver and kidney function, a normal ECG, and intermediate or extensive CYP2D6 metabolizer status, as evidenced by genotyping. Pregnant patients, patients who had previously undergone gastrointestinal surgery, and patients currently receiving metoprolol or with contraindications to treatment with metoprolol were excluded. Patients receiving medication which might interact with metoprolol or using a proton pump inhibitor or laxatives at the time of the study were also excluded. After having given written informed consent the subjects underwent a medical examination by an internal medicine specialist. Only patients meeting all criteria participated in the study, 7 in the metoprolol IR and 5 in the metoprolol CR part. All subjects underwent RYGB surgery resulting in the creation of a gastric pouch with a volume of 20-70 mL, a biliopancreatic limb of 80-150 cm and an alimentary limb of 150 cm. In this study subjects were their
own control, taking the same tablet formulation of metoprolol before and after RYGB. Patients were allowed to participate in the IR and CR part of the study with an interval of at least 7 days between administration of the two formulations of metoprolol.

The regional research ethics committee (RTPO Leeuwarden) reviewed and approved the study with EudraCT numbers 2013-002260-10 and 2013-002274-41.

Study design
An explorative, two phase single oral dose pharmacokinetic study of metoprolol was performed. A metoprolol IR or CR tablet was administered twice to each patient, 1 month before and 6 months after surgery. After an overnight fast of at least 10 hours subjects came to the clinical research unit of Medical Centre Leeuwarden. Usual medication of the patients was adjusted in a way that interference with the study was prevented and that the patient’s treatment was guaranteed. After insertion of a peripheral intravenous cannula participants ingested a metoprolol IR or CR tablet with 150 mL water (presurgery), or with as little water as possible (postsurgery). Blood samples were collected at 0, 0.5, 1, 1.5 (only IR), 2, 3, 4, 5, 6, 8, 10 and 24 (only CR) hour after intake. After the 10-hour blood sample was taken, subjects were allowed to go home. For subjects taking metoprolol CR a 24-hour blood sample was taken at the patient’s home. Blood samples were centrifuged as soon as possible and serum samples were stored at −24 °C until analysis. A standardized snack and standardized meals were served 2 h, 4 h and 10 h after administration of the tablet, respectively. During the first 6 hours after intake of the medication the patients were not allowed to lie down. For safety reasons blood pressure and heart rate were regularly monitored. Concentrations of metoprolol and its metabolite α-hydroxymetoprolol were determined by means of a validated LC-Orbitrap MS method [Postma-Kunnen, S, Yska JP, Hommema G, Koopmans S, Wilffert B, & van Roon EN; unpublished data]. The lower limit of quantitation of the assay was 2.0 ng/mL for metoprolol and 1.0 ng/mL for α-hydroxymetoprolol, respectively. Four months after surgery, before the start of the second phase of the study, the patients were asked about dumping syndrome symptoms by means of a questionnaire [16]. Complications of the surgery which might interfere with the study were also assessed. The subject was withdrawn from the study if she was suffering from the dumping syndrome or from interfering complications.

Pharmacokinetic parameters
The following pharmacokinetic parameters of metoprolol and α-hydroxymetoprolol were determined: maximum concentration \( C_{\text{max}} \) and time to maximum concentration \( T_{\text{max}} \) (metoprolol IR only), and area under the serum concentration versus time curve for 10 (metoprolol IR) or 24 h (metoprolol CR). The areas under the serum concentration versus time curves \( \text{AUC}_{0-10} \) or \( \text{AUC}_{0-24} \) were determined using the linear trapezoidal rule in Microsoft Excel (2013). The endpoint was the ratio \( \text{AUC}_{\text{after}} / \text{AUC}_{\text{before}} \) of metoprolol and α-hydroxymetoprolol for each participant.
Gastrointestinal simulation system

To study the in vitro release characteristics of metoprolol from metoprolol IR and CR tablets two variations of the gastrointestinal simulation system (GISS) mimicking conditions before and after RYGB were developed. The GISS is a system which is based on a pharmacopoeial dissolution method modified by Schellekens et al [17]. The GISS enables variation in parameters which are relevant to drug release in vivo: pH, volume, transit time, osmolality and agitation. During the test an oral drug formulation in a vessel with a rotating paddle at a temperature between 30-37 °C is exposed to solutions simulating in subsequent order the stomach, (duodenum), jejunum, ileum and the proximal colon in fasting conditions before and after RYGB. In simulated conditions before RYGB a total volume of 1000 mL of solution was used in the dissolution vessel. In simulated conditions after RYGB, bypassing the greater part of the stomach, the duodenum and the proximal jejunum, the total volume of solution was 500 mL. In the GISS the 2 different tablet formulations were tested (triplicate experiments). Release profiles were determined by measuring the concentrations of metoprolol spectrophotometrically. Further details of the in vitro experiments are presented in the Supplement (Supplementary Information 1 and Supplementary Tables 1-4).

RESULTS

Seven patients were included in the metoprolol IR part of the study, 5 patients in the metoprolol CR part. In Table 1 the characteristics of the participants of the pharmacokinetic study are shown. After intake of the single dose of metoprolol no side effects were reported. After surgery no complications from the gastric bypass surgery which might interfere with the study occurred and the participants did not suffer from symptoms of the dumping syndrome. No subjects were withdrawn from the study.

In Table 2 and Table 3 pharmacokinetic results after intake of metoprolol IR and CR, respectively, before and after RYGB are presented. Supplementary Figures 1 and 2, display the individual serum concentration-time profiles of metoprolol and α-hydroxymetoprolol after administration of either a single dose of metoprolol IR or CR, respectively, before and after RYGB. Figure 1 shows the change in AUC of metoprolol and α-hydroxymetoprolol for individual participants, after administration of metoprolol IR and CR, respectively, before and after RYGB. After intake of metoprolol IR tablet large intra- and interindividual differences for AUC of metoprolol before and after surgery were observed (range ratio $\frac{AUC_{after}}{AUC_{before}}$: 0.74-1.98). For α-hydroxymetoprolol ratios of $\frac{AUC_{after}}{AUC_{before}}$ ranged from 1.05 to 1.36. For metoprolol large differences occurred in $C_{max}$ and $T_{max}$ before and after surgery. For α-hydroxymetoprolol intra- and interindividual differences in $C_{max}$ and $T_{max}$ were less pronounced. After intake of metoprolol CR tablet a reduction in bioavailability of metoprolol was observed (range
ratio $\frac{\text{AUC}_{\text{after}}}{\text{AUC}_{\text{before}}}$: 0.43–0.77). For $\alpha$-hydroxymetoprolol ratios of $\frac{\text{AUC}_{\text{after}}}{\text{AUC}_{\text{before}}}$ ranged from 0.74 to 0.98.

For both metoprolol IR and CR extensive metabolizers for CYP2D6 had an AUC for metoprolol in the lower range, before as well as after surgery.

In Figure 2 GISS dissolution profiles of metoprolol from IR and CR tablets in simulated fasting conditions before and after RYGB are shown. Before RYGB complete release of metoprolol from IR tablets was reached within 30 minutes. In conditions simulating post-RYGB complete release was reached within 20 minutes. For metoprolol CR release profiles were the same for conditions simulating before and after RYGB.

**DISCUSSION**

In this study it was found that RYGB may influence the bioavailability of metoprolol from IR tablets. Large interindividual differences in the ratios of $\frac{\text{AUC}_{\text{after}}}{\text{AUC}_{\text{before}}}$ of metoprolol were observed. After intake of an IR tablet exposure of metoprolol after RYGB may be reduced or increased. For the individual patient the consequences of RYGB for dosing metoprolol IR tablets cannot be predicted. The magnitude of changes in bioavailability after RYGB require close monitoring of patients using metoprolol IR tablets and dose adjustment if deemed necessary.

The bioavailability of metoprolol from CR tablets is reduced after RYGB. Therefore, according to clinical response after RYGB, clinicians may consider to increase the dose.

**TABLE 1.** Characteristics of study participants.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Metoprolol Immediate Release tablet</th>
<th>Metoprolol Controlled Release tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>37 (8)</td>
<td>37 (5)</td>
</tr>
<tr>
<td>Intermediate CYP2D6 metabolizer, number</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Extensive CYP2D6 metabolizer, number</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>BMI, mean (SD), kg/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presurgery</td>
<td>39.9 (2.1)</td>
<td>38.6 (4.0)</td>
</tr>
<tr>
<td>5-6 months postsurgery</td>
<td>30.8 (2.3)</td>
<td>29.2 (4.3)</td>
</tr>
<tr>
<td>$-\Delta$</td>
<td>9.1 (1.2)</td>
<td>9.4 (0.7)</td>
</tr>
</tbody>
</table>

*SD standard deviation
BM*I Body Mass Index.
TABLE 2. Pharmacokinetic data after administration of a single oral dose of metoprolol tartrate 100 mg immediate release tablet.

<table>
<thead>
<tr>
<th>participant</th>
<th>metoprolol</th>
<th>α-OH metoprolol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC_{0-10 h} (ng.h/mL)</td>
<td>C_{max} (ng/mL)</td>
</tr>
<tr>
<td></td>
<td>before RYGB</td>
<td>after RYGB</td>
</tr>
<tr>
<td>IR1*</td>
<td>223</td>
<td>165</td>
</tr>
<tr>
<td>IR2*</td>
<td>197</td>
<td>389</td>
</tr>
<tr>
<td>IR3</td>
<td>372</td>
<td>399</td>
</tr>
<tr>
<td>IR4</td>
<td>551</td>
<td>515</td>
</tr>
<tr>
<td>IR5</td>
<td>569</td>
<td>670</td>
</tr>
<tr>
<td>IR6</td>
<td>425</td>
<td>380</td>
</tr>
<tr>
<td>IR7</td>
<td>398</td>
<td>604</td>
</tr>
</tbody>
</table>

* Extensive CYP2D6 metabolizer
Several factors that might affect bioavailability of metoprolol after RYGB should be considered. Metoprolol has been classified as a Biopharmaceutics Classification Scheme class I substance, having a high solubility and a high intestinal permeability, meaning that metoprolol will be easily dissolved and absorbed [18]. Metoprolol is not absorbed from the stomach, but may be well and similarly absorbed throughout the small intestine and colon. Thus, metoprolol administered as an oral formulation is expected to be absorbed from any region of the intestine in which it is released [19-21]. After RYGB the duodenum and proximal jejunum are no longer available for absorption, so reduced absorption may occur. In obese patients metoprolol, being a liposoluble compound, was found to have a higher volume of distribution with a lower $C_{\text{max}}$ compared with non-obese patients [22]. With a decreased BMI and body fat percentage after RYGB, one might expect a higher bioavailability.

Before enrollment in the study, participants were genotyped for CYP2D6 and poor metabolizers were excluded from participation. Although after intake of a metoprolol IR tablet exposure of metoprolol was either reduced or increased after RYGB, for $\alpha$-hydroxymetoprolol no reduction in AUC was observed after RYGB. After intake of a metoprolol CR tablet bioavailability of metoprolol was reduced, but, except for 1 patient, no reduction in AUC was observed for $\alpha$-hydroxymetoprolol after RYGB. Apparently, CYP2D6 activity is not influenced by RYGB.

As might be expected, extensive CYP2D6 metabolizers participating in this study showed a bioavailability of metoprolol in the lower range before as well as after RYGB. However, after intake of a metoprolol IR tablet, a decrease as well as an increase of bioavailability after RYGB was observed, depending on the subject.

In non-obese patients, apart from the interindividual variability in the hepatic first-pass metabolism, interindividual variability of intestinal absorption may be responsible for the substantial interindividual variability in the bioavailability of metoprolol. Fukao et al. studied the intestinal absorption mechanism of metoprolol using human intestinal epithelial LS180 cells. Cellular uptake of metoprolol was saturable, significantly decreased by acidification of extracellular medium pH, and decreased in the presence of hydrophobic cationic drugs [23]. It may be possible, that RYGB affects cellular uptake and/or hepatic first-pass metabolism of metoprolol through an influence on these mechanisms, among others.

In the present study after RYGB decreased bioavailability of metoprolol from CR tablet is observed. In normal patients systemic availability of controlled release metoprolol formulations is about 20 to 30% lower than that after administration of an IR tablet [13]. According to Plosker et al. the reduction in bioavailability is likely related to the relatively slow rate of drug delivery which enhances presystemic clearance of metoprolol because hepatic extraction is a saturable process. Moreover, since transit
TABLE 3. Pharmacokinetic data after administration of a single oral dose of metoprolol succinate 95 mg controlled release tablet.

<table>
<thead>
<tr>
<th>Participant</th>
<th>metoprolol</th>
<th>α-OH metoprolol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$AUC_{0-24h}$ (ng.h/mL)</td>
<td>ratio after-before</td>
</tr>
<tr>
<td>CR1*</td>
<td>200</td>
<td>105</td>
</tr>
<tr>
<td>CR2</td>
<td>514</td>
<td>309</td>
</tr>
<tr>
<td>CR3</td>
<td>262</td>
<td>113</td>
</tr>
<tr>
<td>CR4</td>
<td>548</td>
<td>421</td>
</tr>
<tr>
<td>CR5</td>
<td>281</td>
<td>177</td>
</tr>
</tbody>
</table>

* Extensive CYP2D6 metabolizer
FIGURE 2. Release profiles of metoprolol from metoprolol IR and metoprolol CR tablets in simulated fasting conditions before and after RYGB (triplicate experiments; mean ± SD).
time through the gastrointestinal tract can vary, some active drug may remain in the controlled release preparations at the time they are eliminated from the body, and this might also contribute to reduced systemic availability in some patients [13]. After RYGB, intestinal transit time might be a limiting factor for absorption from a controlled release formulation. However, data on intestinal transit time after RYGB are sparse and conflicting. Using a sulphasalazine tablet as a marker Carswell et al. found no influence of RYGB on oro-caecal transit time [24]. After a meal Dirksen et al. showed that 1.5 years after RYGB pouch emptying time was shorter, but small intestinal transit time was slower in patients than in control subjects. Colonic transit time did not differ [25]. In patients 5.7 years after RYGB Nguyen et al. found that pouch emptying and caecal arrival time were more rapid compared to control subjects. Pouch emptying tended to be faster after 150 mL than after 50 mL drinks [26]. In bioavailability studies oral tablet formulations are usually ingested with 150 mL of water. Because we did not want pouch emptying be influenced by the ingested volume of water, we decided to administer the metoprolol IR and CR tablets with 150 mL of water presurgery and with as little water as possible postsurgery.

Changes in bioavailability of medication after RYGB might in principle also be caused by changes in release characteristics from the different tablet formulations. However, the in vitro dissolution experiments showed that release patterns of metoprolol from IR and CR tablets in simulated RYGB conditions did not differ from those found in conditions before RYGB. From this, we conclude that the observed changes in bioavailability of metoprolol after RYGB are not caused by changes in release rate of metoprolol from the studied IR and CR tablet formulations as a result of environmental conditions.

For two drugs to be bioequivalent, the 90% confidence intervals for the ratio of the means of $C_{\text{max}}$ and AUC must lie within the range of 0.8-1.25 [27]. In the present study 3 out of 7 participants taking metoprolol IR and 5 out of 5 participants taking metoprolol CR had a ratio $\frac{\text{AUC}_{\text{after}}}{\text{AUC}_{\text{before}}}$ outside the range of 0.80-1.25, implying a clinically significant difference in drug exposure after RYGB, requiring dosage adjustment. As yet, for some drugs the influence of RYGB on pharmacokinetic properties has been evaluated in controlled clinical studies. However, well designed clinical studies with repeated measures before and after surgery, are scarce and not all effects of RYGB on drug exposure, reported so far, are of clinical importance [8, 28]. An example of a well-designed study is the repeated measure study by Mitrow-Winkelmolen et al.. They found a faster absorption of both acetylsalicylic acid and omeprazole after RYGB with a higher exposure of acetylsalicylic acid and an average decrease in bioavailability of omeprazole. Their findings have consequences for the dosing of omeprazole after RYGB (increase the dose in patients with inadequate response), but not for acetylsalicylic acid [29].

Gesquiere et al. performed a single-dose pharmacokinetic study of metoprolol tartrate
200 mg immediate and controlled release formulations in 14 healthy volunteers before and 6-8 months after RYGB. They concluded that the oral exposure of metoprolol from immediate and controlled-release formulations was not significantly different after RYGB compared with before, although there was a tendency towards higher exposure after surgery [30]. This different outcome compared with the results from our study, may be explained in terms of different design in the Gesquiere study. Although each patient served as his own control, women (10) as well as men (4) were included. Before inclusion the CYP2D6 genotype of the patients was not determined. In addition, no individual data were presented, only mean $\text{AUC}_{0-24\ h}$ with 95% confidence interval. Serum concentrations of metabolites of metoprolol were not measured. After RYGB participants ingested the tablets with 150 ml of water. By drinking this volume, pouch emptying might be accelerated [26]. Moreover, in daily practice patients may not swallow a tablet with such a volume of water.

This study has several limitations. The sample sizes of the metoprolol IR and CR part of the study were small. Despite the fact that this was an explorative pharmacokinetic study, the findings of this study may have implications for dosing metoprolol post-RYGB. Only women were included in this study. Although pharmacokinetics of metoprolol are different in women compared to men, the effects of RYGB on bioavailability of metoprolol after oral administration in men might be comparable. Moreover, more women undergo RYGB surgery than men. Postsurgery this study was performed 6 months after RYGB. Relatively soon after surgery or in the long term results might have been different. After RYGB intestinal adaptation may occur, whereby mucosal hypertrophy within the remaining intestine gives an increase in absorptive capacity over time. It is unknown, however, whether intestinal adaptation affects absorption [4].

In conclusion, RYGB may influence the bioavailability of metoprolol from an IR tablet. After RYGB clinicians may consider to adjust the dose according to clinical response. RYGB reduces the bioavailability of metoprolol from a CR tablet. After RYGB clinicians may consider to increase the dose according to clinical response.

ACKNOWLEDGMENTS

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This study was funded by a grant from the Science Fund (Wetenschapsfonds) Medical Centre Leeuwarden.
Additional Supporting Information may be found in the Supplement:

**Supplementary Information 1.** Description of the gastrointestinal simulation system simulating conditions before and after RYGB

**Supplementary Table 1.** Specifications of the five phases of the GISS before RYGB

**Supplementary Table 2.** Specifications of the four phases of the GISS after RYGB

**Supplementary Table 3.** Composition of the switch solutions GISS before RYGB

**Supplementary Table 4.** Composition of the switch solutions GISS after RYGB

**Supplementary Figure 1.** Individual serum concentration-time profiles of metoprolol and α-hydroxymetoprolol after administration of a single dose of metoprolol tartrate 100 mg immediate release tablet before and after RYGB

**Supplementary Figure 2.** Individual serum concentration-time profiles of metoprolol and α-hydroxymetoprolol after administration of a single dose of metoprolol succinate 95 mg controlled release tablet before and after RYGB.
REFERENCES

SUPPLEMENTARY INFORMATION TO CHAPTER 8
**SUPPLEMENTARY INFORMATION 1**

**Description of the gastrointestinal simulation system simulating conditions before and after RYGB**

An in vitro dissolution method simulating the conditions before and after Roux-en-Y gastric bypass might be a valuable tool to predict the behaviour of drugs with possible bioavailability problems in vivo. The gastrointestinal simulation system (GISS) mimicking conditions before and after RYGB was developed for investigating dissolution characteristics of oral medications. The GISS is a dissolution method which is based on a design by Schellekens et al [1]. They adjusted the paddle apparatus as described in USP 38 and the European Pharmacopoeia 8.0 to simulate conditions in consecutive sections of the gastrointestinal tract. The GISS enables variation in parameters which are relevant to drug release in vivo: pH, volume, transit time, osmolality and agitation. During the test in a dissolution vessel an oral drug formulation is exposed to solutions simulating stomach, (duodenum,) jejunum, ileum and colon in fasting conditions before and after RYGB. Tables 1 and 2 show the details of the phases as well as the biorelevant media which were applied to simulate conditions before and after RYGB, respectively. At the end of each phase a switch solution was added with a peristaltic pump in 5-10 minutes to obtain the required composition of the next phase. Tables 3 and 4 provide the composition of these switch solutions. The paddle was operated at 50 rpm and the system was kept at a temperature between 30-37 °C. Because of the smaller volume of the stomach (pouch) after RYGB, the length and diameter of the paddle were adjusted when simulating conditions after RYGB. Metoprolol immediate (IR) and controlled release (CR) tablets were tested in triplo. At regular time intervals samples were drawn from the dissolution vessel. Release profiles were determined by measuring the concentrations of metoprolol spectrophotometrically.


**SUPPLEMENTARY TABLE 1.** Specifications of the five phases of the GISS before RYGB.

<table>
<thead>
<tr>
<th>Phase</th>
<th>GI segment</th>
<th>Volume (mL)</th>
<th>Residence time (min)</th>
<th>pH</th>
<th>Osmolality (mosmol/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Stomach</td>
<td>500</td>
<td>120 (full) / 30 (empty)</td>
<td>1.2 ± 0.20</td>
<td>150 ± 25</td>
</tr>
<tr>
<td>II</td>
<td>Duodenum</td>
<td>550</td>
<td>15</td>
<td>5.5 ± 0.20</td>
<td>250 ± 50</td>
</tr>
<tr>
<td>III</td>
<td>Jejunum</td>
<td>630</td>
<td>120</td>
<td>6.8 ± 0.20</td>
<td>250 ± 50</td>
</tr>
<tr>
<td>IV</td>
<td>Ileum</td>
<td>940</td>
<td>30</td>
<td>7.5 ± 0.25</td>
<td>250 ± 50</td>
</tr>
<tr>
<td>V</td>
<td>Colon</td>
<td>1000</td>
<td>up to 1440</td>
<td>6.0 ± 0.25</td>
<td>250 ± 60</td>
</tr>
</tbody>
</table>
**SUPPLEMENTARY TABLE 2.** Specifications of the four phases of the GISS after RYGB

<table>
<thead>
<tr>
<th>Phase</th>
<th>GI segment</th>
<th>Volume (mL)</th>
<th>Residence time (min)</th>
<th>pH</th>
<th>Osmolality (mosmol/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Stomach (pouch)</td>
<td>50</td>
<td>120 (full) / 15 (empty)</td>
<td>5.0 ± 0.20</td>
<td>150 ± 25</td>
</tr>
<tr>
<td>II</td>
<td>Jejunum</td>
<td>130</td>
<td>70</td>
<td>6.8 ± 0.20</td>
<td>250 ± 50</td>
</tr>
<tr>
<td>III</td>
<td>Ileum</td>
<td>440</td>
<td>30</td>
<td>7.5 ± 0.25</td>
<td>250 ± 50</td>
</tr>
<tr>
<td>IV</td>
<td>Colon</td>
<td>500</td>
<td>up to 1440</td>
<td>6.0 ± 0.25</td>
<td>250 ± 60</td>
</tr>
</tbody>
</table>

**SUPPLEMENTARY TABLE 3.** Composition of the switch solutions GISS before RYGB.

<table>
<thead>
<tr>
<th>From</th>
<th>To</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>At start</td>
<td>Switch solution I</td>
<td>1.0 g sodium chloride, 3.5 ml hydrogen chloride 37%, demineralised water q.s. 500.0 mL</td>
</tr>
<tr>
<td>Switch solution I</td>
<td>Phase I Phase II</td>
<td>3.14 g potassium dihydrogen phosphate, 21.7 mL sodium hydroxide 2.0 M, demineralised water q.s. 50.0 mL</td>
</tr>
<tr>
<td>Switch solution II</td>
<td>Phase II Phase III</td>
<td>0.94 g potassium dihydrogen phosphate, 8.2 mL sodium hydroxide 2.0 M, demineralised water q.s. 80.0 mL</td>
</tr>
<tr>
<td>Switch solution III</td>
<td>Phase III Phase IV</td>
<td>2.04 g potassium dihydrogen phosphate, 10.8 mL sodium hydroxide 2.0 M, demineralised water q.s. 310.0 mL</td>
</tr>
<tr>
<td>Switch solution IV</td>
<td>Phase IV Phase V</td>
<td>10.0 mL hydrogen chloride 3.0 M, demineralised water q.s. 60.0 mL</td>
</tr>
</tbody>
</table>

**SUPPLEMENTARY TABLE 4.** Composition of the switch solutions GISS after RYGB.

<table>
<thead>
<tr>
<th>From</th>
<th>To</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>At start</td>
<td>Switch solution I</td>
<td>0.125 g sodium chloride, 5.0 µl hydrogen chloride 37%, demineralised water q.s. 50.0 mL</td>
</tr>
<tr>
<td>Switch solution I</td>
<td>Phase I Phase II</td>
<td>2.53 g potassium dihydrogen phosphate, 5.7 mL sodium hydroxide 2.0 M, demineralised water q.s. 80.0 mL</td>
</tr>
<tr>
<td>Switch solution II</td>
<td>Phase II Phase III</td>
<td>2.04 g potassium dihydrogen phosphate, 9.0 mL sodium hydroxide 2.0 M, demineralised water q.s. 310.0 mL</td>
</tr>
<tr>
<td>Switch solution III</td>
<td>Phase III Phase IV</td>
<td>8.0 mL hydrogen chloride 3.0 M, demineralised water q.s. 60.0 mL</td>
</tr>
</tbody>
</table>
SUPPLEMENTARY FIGURE 1. Individual serum concentration-time profiles of metoprolol and α-hydroxymetoprolol after administration of a single dose of metoprolol tartrate 100 mg immediate release tablet before and after RYGB (IR1, IR2: extensive metabolizer for CYP2D6).
Supplementary Figure S1. Individual serum concentration-time profiles of metoprolol and α-hydroxymetoprolol after administration of a single dose of metoprolol tartrate 100 mg immediate release tablet before and after RYGB (IR1, IR2: extensive metabolizer for CYP2D6).
SUPPLEMENTARY FIGURE 2. Individual serum concentration-time profiles of metoprolol and α-hydroxymetoprolol after administration of a single dose of metoprolol succinate 95 mg controlled release tablet before and after RYGB (CR1: extensive metabolizer for CYP2D6).
Supplementary Figure S2.

Individual serum concentration-time profiles of metoprolol and α-hydroxymetoprolol after administration of a single dose of metoprolol succinate 95 mg controlled release tablet before and after RYGB (CR1: extensive metabolizer for CYP2D6).
SECTION V

CONCLUSIONS AND PERSPECTIVES