# Pharmacokinetic and Pharmacodynamic Alterations in the Roux-en-Y Gastric Bypass Recipients

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**Objective:** We conducted a pharmacokinetic (PK) study and a pharmacodynamic (PD) study to assess whether Roux-en-Y gastric bypass (RYGB) surgery is associated with significant changes to PK and PD of oral medications.

**Background:** The effect of RYGB on oral drug disposition is not well understood.

**Methods:** An oral cocktail of probe drugs for major drug-metabolizing enzymes (caffeine, tolbutamide, omeprazole, dextromethorphan, and oral and intravenous midazolam) was administered to 18 RYGB recipients and 18 controls. Timed blood and urine samples were obtained for PK analyses. Forty mg of oral furosemide was administered to 13 RYGB recipients and 14 controls, and urine and blood samples were collected for assessing furosemidePK , and urine volume and urine sodium excretion for PD analyses.

**Results:** Compared with controls, the RYGB group had significantly lower time to maximum plasma concentration ($t_{max}$) for caffeine (0.58 ± 0.5 vs 2.1 ± 2.2 hours, $P < 0.0001$), tolbutamide (1.4 ± 1.8 vs 2.1 ± 2.2 hours, $P = 0.0001$), omeprazole (1.1 ± 1.1 vs 4.4 ± 1.3 hours, $P < 0.0001$), and oral midazolam (0.5 ± 0.2 vs 0.7 ± 0.4 hours, $P < 0.01$). However, maximum plasma concentration, half-life, area under the curve, and oral bioavailability were not different. Compared with controls, the RYGB group had brisk natriuresis, with significantly lower $t_{max}$ for urine sodium (1.3 ± 0.5 vs 3.1 ± 2.3 hours, $P < 0.02$) and correspondingly lower $t_{max}$ for furosemide (1.8 ± 0.3 vs 4.2 ± 1.2 hours, $P = 0.006$). However, 6-hour urine sodium and 6-hour urine volume were not different between the two groups.

**Conclusions:** RYGB recipients have significantly shorter $t_{max}$ for the studied orally administered medications, but otherwise no other significant changes in PK were reported.

**Keywords:** CYP3A, drug metabolism, furosemide, gastric bypass, oral cocktail

(*Ann Surg* 2013;258: 262–269)

Extreme obesity, defined as a body mass index of 40 kg/m$^2$ or more, is particularly associated with higher mortality due to comorbid conditions such as diabetes mellitus, hypertension, cardiovascular disease, respiratory disorders, and cirrhosis from nonalcoholic steatohepatitis.[1–5] It is estimated that more than 9 million people in the United States suffer from extreme obesity.[6] When nonsurgical weight loss efforts fail to produce the desired effect, bariatric surgery is often considered for these individuals for its effective and sustained weight loss and improvement in the control of comorbid conditions and quality of life.[7–11] Among various surgical approaches, Roux-en-Y gastric bypass (RYGB) surgery is the most effective therapeutic modality, and, currently, it is the most frequently performed bariatric surgery accounting for 80% to 90% of all procedures.[12] RYGB is both a restrictive and maldigestive surgery and uses a small proximal gastric cardia pouch (≤50 mL) and Roux limb (∼150 cm) to delay the interaction of bile and pancreatic juices with food. The exclusion of the duodenal sweep and creation of this long Roux limb, although critical for effective and sustained weight loss, are however associated with several macro- and micronutrient deficiencies due to altered anatomy.[13–15] The effect of altered anatomy due to RYGB on oral drug absorption and bioavailability is currently unknown, often leading to confusion for the providers who prescribe medications for these patients.

Most drugs undergo biotransformation or metabolism to more water-soluble compounds for elimination by drug-metabolizing enzymes belonging to the cytochrome P450 (CYP) family. Various isoforms of CYP enzymes exist in many tissues throughout the body, but their expression is greatest in the liver and small intestine.[16,17] CYP3A isoform alone contributes to the metabolism of 50% of the orally administered drugs belonging to commonly used classes of medications such as calcium channel blockers, statins, HIV antiretrovirals, and immunosuppressants. Prior studies have shown the CYP3A enzyme activity is maximally expressed in the proximal small bowel (duodenum and jejunum).[18,19] Because the duodenum and proximal jejunum are bypassed during RYGB, it is anticipated that orally administered drugs are subjected to lesser gut wall metabolism, resulting in higher serum drug concentrations. On the contrary, the rapid transit of drugs through shortened length of small bowel may lead to lower drug absorption and lower serum drug concentrations. Previous studies that evaluated drug disposition in bariatric surgery recipients have focused on individual compounds (eg, metformin, sertraline, tacrolimus, and cyclosporine), and they yielded conflicting results.[20–24]

The drug-metabolizing profile of an individual can be evaluated by studying the catalytic activity of several CYP enzymes, all in one experimental session using probe substrates that are selective and specific for respective CYP enzymes. The term "pharmacokinetics" (PKs) is defined as the quantitative analysis of the processes of drug absorption, distribution, and elimination that determine the drug concentration achieved with time, whereas "pharmacodynamics" (PDs) deals with the relationship between the drug concentration and both the desired and adverse effects produced with time.[20] We hypothesized that RYGB will have a significant effect on oral bioavailability because of the profoundly altered anatomy, physiology, and intestinal first-pass metabolism. We performed a case-control PK-PD study to evaluate the differences in drug disposition in the subjects who underwent RYGB, using age-, sex-, race-, and body mass index-matched controls. For the PK study, we used an oral cocktail of probe drugs/substrates including caffeine, tolbutamide, omeprazole, dextromethorphan, and midazolam to study CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A, respectively. Oral and intravenous midazolam was administered in a semisimultaneous

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Disclosure: Supported by Clarian/IU Health Values Fund (VFR-278) and Indiana CTSI—Clinical Research Feasibility Funds to Dr Vuppalanchi and K24 DK069290 to Dr Chalasani. Dr Hall is currently an employee of Eli Lilly and Company, Indianapolis, IN.

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ISSN: 0003-4932/13/25802-0262
DOI: 10.1097/SLA.0b013e31827a0e82

fashion, as reported by Lee et al,[25] to evaluate the hepatic and intestinal CYP3A activity in each subject. In a proof-of-concept PD study, we evaluated the differences in urine volume and sodium excretion after administration of furosemide orally. The choice of furosemide for this study is based on its properties, such as low solubility and permeability resulting in poor absorption quality.[26,27] Moreover, it is primarily absorbed in the upper gastrointestinal tract following dissolution in the stomach.[28] In addition, prior studies have reported timed urine sodium output after oral furosemide administration as a valid PD end point.[20–22]

## METHODS

The institutional review board of Indiana University School of Medicine approved the PK and PD studies in concordance with the principles of the Declaration of Helsinki. All study volunteers gave written, informed consent before participating in the study.

### PK Study

#### *Study Design and Study Population*

Eighteen RYGB subjects and an equal number of age-, sex-, race-, and body mass index-matched (factors that may influence CYP3A activity) volunteers at least 18 years or older participated in this study. All RYGB volunteers satisfied the inclusion criteria of at least 1 year post-RYGB surgery before study enrollment to allow adequate time for the body to adapt to composition changes. For at least 2 weeks before the start of the study until its conclusion, participants were on a standard clinical pharmacology diet to avoid alterations in the CYP activity. Smokers were excluded, and the participants were instructed not to consume ethanol, caffeine, or xanthine-related products (coffee, tea, colas, chocolates, etc) for 2 days before the study. Subjects were excluded if they were taking medications known to induce or inhibit cytochrome P450 enzymes or had a history of hypersensitivity to drugs used in the cocktails. After adhering to the protocol diet for 2 weeks and fasting overnight, participants were admitted to the Indiana Clinical Research Center at Indiana University Medical Center for the duration of the study (24 hours). After a baseline blood sample was obtained, each subject received the "mini cocktail" of 5 drugs with 240 mL of distilled water, followed by 0.01 mg/kg of midazolam (Versed; Roche Pharmaceuticals, Nutley, NJ) intravenously over 30 minutes, 6 hours after the oral cocktail in a semisimultaneous fashion. *Mini cocktail* is a combination of 40 mg of oral caffeine (caffeine anhydrous powder 125 g/bottle; Spectrum Chemical, Gardena, CA), 20 mg of oral omeprazole (Prilosec OTC; Mckesson Medical, Grove City, OH), 100 mg of tolbutamide (Tolbutamide 500 mg; Mckesson Medical), 6 mg of dextromethorphan (Robitussin Pediatric Cough Syrup, 7.5 mg/5 mL; Mckesson Medical), and 1 mg of oral midazolam (Midazolam HCl 1 mg/mL 2-mL vial; Mckesson Medical). The doses used are one fifth of the doses, except for omeprazole, used in the previous cocktails.[23,24] Blood samples (n = 20, 3 mL each) were collected at the following times: 20, 30, 45, 60 and 90 minutes, 2, 4, and 6 hours after oral cocktail administration and at 15, 30, 40, 50, 75 and 90 minutes, 2, 4, 6, 10, 15, and 18 hours from the start of midazolam infusion. Urine was collected and pooled at 6-hour intervals. Serum and urine were harvested and frozen at −20°C until assayed.

#### *Analytical Methods*

Two accurate and precise methods were developed using high-performance liquid chromatography-tandem mass spectrometry to quantify all drugs and metabolites. One method, using 100 $\mu$L of plasma, was used to quantify caffeine, tolbutamide, metabolites, and internal standards. The other method, using 200 $\mu$L of plasma, was used to quantify dextromethorphan, omeprazole, midazolam, metabolites, and internal standards. The intraday accuracy and precision (% coefficient of variation) estimated that the lower limits of quantification for all compounds and metabolites were greater than 80% and less than 20%, respectively. The interday accuracy and precision estimates at the low quality control concentration for all compounds were greater than 90% and less than 15%, respectively.

#### *PK Analysis*

Pharmacokinetic parameters for the compounds including area under the curve (AUC), area under the moment curve (AUMC), and half-life ($t^{1}/_{2}$) were estimated using noncompartmental methods with Excel. The maximum plasma concentration ($C_{max}$) and time to $C_{max}$ ($t_{max}$) were obtained from the data. The AUC from zero to infinity ($AUC_{0\text{-}\infty}$) was estimated from the $AUC_{0\text{-}t}$ (time 0 to the last quantifiable concentration $C_{last}$) and the AUC from $C_{last}$ to infinity, $C_{last}/k_{el}$, where $k_{el}$ is the terminal rate constant of elimination. The $AUMC_{0\text{-}\infty}$ was estimated in an analogous manner. The systemic clearance (CL and CL/$F$, where $F$ is bioavailability) of the parent compounds was calculated from the dose and $AUC_{0\text{-}\infty}$. The apparent volume of distribution ($V_{dss}/F$) was estimated using the following equation: (dosage/$AUC_{0\text{-}\infty}$) × ($AUMC_{0\text{-}\infty}/AUC_{0\text{-}\infty}$).

For the CYP1A2 activity, AUC molar ratio of caffeine and its metabolite paraxanthine ($AUC_{paraxanthine}/AUC_{caffeine}$) was determined. CYP2C9 activity was assessed using AUC molar ratio of 1-OH tolbutamide/tolbutamide ($AUC_{1\text{-}OH\_tolbutamide}/AUC_{tolbutamide}$) and oral clearance of tolbutamide. The catalytic activity of CYP2C19 was estimated from the AUC molar ratio of 5-OH omeprazole and omeprazole ($AUC_{5\text{-}OH\_omeprazole}/AUC_{omeprazole}$) and oral clearance of omeprazole.

#### *Semisimultaneous Method*

The semisimultaneous approach for oral and intravenous midazolam has previously been shown to be a suitable approach to determine hepatic and intestinal CYP3A activity.[25] The oral bioavailability ($F_{po}$) of midazolam was determined from the ratio of the dose-normalized AUC obtained from oral and intravenous administration. The following equation was used for oral bioavailability:

$$F_{po} = \frac{Dose_{iv}}{Dose_{oral}} \times \frac{AUC_{oral}}{AUC_{iv}}$$

where $Dose_{iv}$ is intravenous dose and $AUC_{iv}$ is intravenous AUC. Hepatic midazolam clearance ($CL_H$) was assumed to be the same as systemic clearance and was calculated as (intravenous dose/intravenous AUC).

#### *Statistical Analysis*

The primary interest was CYP3A (probe: midazolam) activity because it is the predominant drug-metabolizing enzyme in the gut wall and liver. With 80% power and an $\alpha$ level of 0.05 assumed, a sample size of 18 (including the dropouts) allowed the detection of a 50% difference in CYP 3A activity using a 2-sided Student $t$ test. For each individual probe substrate, various PK parameters including $C_{max}$, $t_{max}$, $t_{1/2}$, AUC of parent compound, and phenotyping end points including $AUC_{metabolite}/AUC_{parent}$ and CL were compared between the groups. All the data were logarithmically transformed before statistical analysis. Student $t$ test compared the outcome variables between the groups. All results were expressed as geometric mean ± standard deviation except for $t_{max}$, which was expressed as median (interquartile range).

## PD Study

### Study Design and Study Population

Thirteen RYGB subjects and 14 age-, sex-, race-, and body mass index-matched volunteers participated in this study. All subjects were 18 years or older and free from any comorbid conditions that would affect their response to furosemide. After determining the eligibility criteria by a screening process, they were asked to consume a metabolic diet containing 2 g or 87 mEq of sodium and 60 to 80 mEq of potassium per day for 5 consecutive days in an outpatient setting until they equilibrated the metabolic diet, that is, the state of sodium balance as defined by having less than 20% variability in spot urine sodium and/or change in 2 consecutive daily weights of 1 kg or less on the last 2 days of metabolic diet. After an overnight fast, 1 dose of 40 mg of oral furosemide (Lasix 40 mg; Epic Pharma, Laurelton, NY) was given along with distilled water at 10 mL/kg of body weight and then blood and urine samples were collected at 0.5-, 1-, 1.5-, 2-, 2.5-, 3-, 4-, 6-, 8-, and 12-hour time points and stored at −20°C until assayed.

### Analytical Methods and Statistical Analysis

Serum furosemide levels were measured with high-performance liquid chromatography, using previously published methods.[29–31] Various PK parameters of furosemide such as $C_{max}$, $t_{max}$, $V_d/F$, and CL/$F$ were measured. Urine sodium and urine outputs were measured to calculate urine sodium excretion and urine output. Diuretic response to furosemide was assessed by measuring urine sodium excretion and urine output over a 6-hour period after the administration of furosemide. The primary end point was the total urinary sodium excretion over the first 6-hour period. Secondary end points included total urine output over 6 hours, timed sodium excretion and urine volume at 0- to 1-, 1- to 2-, 2- to 4-, and 4- to 6-hour intervals. In addition, furosemide PK parameters were compared between the 2 groups. The Student $t$ test compared the outcome variables and a $P$ value of less than 0.05 was considered to be significant.

# RESULTS

## PK Study

RYGB subjects were well matched with control subjects with respect to age, sex, race, and body mass index. Selected demographical and clinical characteristics of subjects in the PK study are given in Table 1.

### PK Measures of CYP3A (Probe: Oral and Intravenous Midazolam)

Compared with controls, the RYGB group had significantly shorter $t_{max}$ (0.5 ± 0.2 vs 0.8 ± 0.4 hour; $P = 0.01$), with no difference in $C_{max}$. The $AUC_{0\text{-}6\,h}$ of oral midazolam, which reflects the systemic exposure to oral midazolam, AUC ratio of 1-OH midazolam, and midazolam did not differ between the 2 groups. Oral bioavailability and clearance of oral midazolam were also similar between the 2 groups. $C_{max}$ and $t_{max}$ did not differ for the intravenously administered midazolam. However, compared with controls, RYGB subjects had significantly lower $AUC_{0\text{-}\infty}$ minus residual $AUC_{po}$ (8.6 ± 4.6 vs 14.6 ± 21, $P = 0.03$). The AUC ratio of 1-OH midazolam to midazolam ($AUC_M/AUC_P$) was lower in the RYGB group than in the control group, and this difference was of borderline statistical significance (0.09 ± 0.1 vs 0.05 ± 0.1, $P = 0.09$) (Table 2 and Fig. 1).

### PK Measures of CYP1A2 (Probe: Caffeine), CYP2C9 (Probe: Tolbutamide), and CYP2C19 (Probe: Omeprazole)

Compared with controls, $t_{max}$ in the gastric bypass group was significantly shorter for caffeine (0.6 ± 0.5 vs 2.1 ± 2.2 hours, $P < 0.0001$), tolbutamide (1.4 ± 1.8 vs 5.1 ± 1.7 hours; $P < 0.0001$), and omeprazole (1.1 ± 1.1 vs 4.4 ± 1.3 hours, $P = 0.0001$) (Table 3 and Fig. 2). $C_{max}$ of caffeine was significantly higher in the gastric bypass subjects than in the control subjects (910 ± 288 vs 620 ± 350 ng/mL, $P = 0.03$). However, $C_{max}$ for tolbutamide and omeprazole did not differ between the 2 groups. CYP1A2 activity (AUC molar ratio of paraxanthine and caffeine), CYP2C9 activity (AUC molar ratio of 5-OH tolbutamide and tolbutamide), and CYP2C19 activity (AUC molar ratio of 5-OH omeprazole and omeprazole) did not differ between the gastric bypass and the control group. In addition, $AUC_{0\text{-}\infty}$ and systemic clearance of the 3 probe substrates did not differ significantly. The CYP2D6 (probe: dextromethorphan) results are not presented because we could not quantify the dextromethorphan in 80% of the samples presumably due to low doses of dextromethorphan (6 mg) used in the oral cocktail (Table 3 and Fig. 2).

## PD Study

Of the 27 subjects who enrolled in the study, 13 were RYGB subjects and 14 were control subjects. The demographical and clinical characteristics at baseline did not differ between the 2 groups (Table 1). Measurements of sodium excretion and urine output at various time frames (0–1, 1–2, 2–4, 4–6 hours) revealed that the RYGB group had significantly higher sodium excretion over the initial 1- to 2-hour time frame than the controls (51 ± 39 vs 20 ± 15 mEq; $P = 0.01$) (Table 4 and Fig. 3). Urine output was similar at all time frames in the RYGB and control groups. Compared with controls, the $t_{max}$ of furosemide was significantly shorter in the RYGB group (1.8 ± 0.3 vs 4.2 ± 1.2; $P = 0.001$). There was no significant difference in the oral clearance of furosemide between the 2 groups (Table 4). Compared with controls, individuals with RYGB had significantly higher serum furosemide levels at 1 hour (38 ± 30 vs 347 ± 253 ng/mL; $P = 0.01$) and 2 hours (127 ± 116 vs 591 ± 418 ng/mL; $P = 0.02$), but there were no significant differences at time points 1.5, 2.5, 4, and 8 hours after furosemide dosing. Figure 3 shows the correlation between the serum furosemide concentration and urine sodium excretion at each time point for both the RYGB and control groups. Each point in the figure represents the mean of observations in 1 collection period for all subjects. The earlier absorption of furosemide appropriately correlated with earlier urinary sodium excretion produced by furosemide in the RYGB group compared with the control group.

# DISCUSSION

Because RYGB involves profound alterations to gastrointestinal anatomy and physiology, it has been suspected that patients undergoing RYGB may be at an increased risk for either adverse reactions or a suboptimal response due to altered pharmacokinetics and pharmacodynamics of orally administered drugs.[32,33] These alterations were initially attributed to changes in volume of distribution of the drug due to significant weight loss and loss of adipose tissue.[32,34,35] However, recent studies have shown contrasting results either because of altered bioavailability from decreased absorption or because of rapid transit or decreased first-pass metabolism from bypassing the drug-metabolizing enzymes in duodenum and proximal jejunum.[36,37] Skottheim et al[36] reported significantly altered systemic exposure to atorvastatin after RYGB, ranging from a 3-fold decrease to a 2-fold increase in AUC. However, this study was conducted within 6 weeks of bariatric surgery when the subjects were still undergoing rapid weight loss. More recently, Roerig et al[37] reported that the maximal

**TABLE 1.** Demographics and Clinical Characteristics of RYGB Subjects and Controls

| | PK Study | | PD Study | |
|---|---|---|---|---|
| | **RYGB (n = 18)** | **Controls (n = 18)** | **RYGB (n = 13)** | **Controls (n = 14)** |
| Age,* mean ± standard deviation, y | 40.9 ± 8.1 | 39.5 ± 8.6 | 44.8 ± 7.4 | 43.4 ± 7.4 |
| Female, % | 94 | 94 | 75 | 71 |
| White, % | 69 | 69 | 75 | 80 |
| Body mass index,* mean ± standard deviation, kg/m$^2$ | 29.1 ± 7.3 | 27.7 ± 5.9 | 29.2 ± 4.2 | 28.6 ± 3.4 |
| Date since surgery, mean ± standard deviation | 1.9 ± 0.8 | N/A | 1.9 ± 1.1 | N/A |
| Diabetes | | | | |
| Before RYGB | 3 (17%) | N/A | 1 (7%) | N/A |
| At the time of study enrollment | 0 | 0 | 0 | 0 |
| Hypertension | | | | |
| Before RYGB | 10 (56%) | N/A | 9 (69%) | N/A |
| At the time of study enrollment | 0 | 0 | 1 (7%) | 1 |
| Hyperlipidemia | | | | |
| Before RYGB | 0 | N/A | 5 (38%) | N/A |
| At the time of study enrollment | 5 (28%) | 0 | 0 | 1 (7%) |
| Sleep apnea | 5 (28%) | 0 | 1 (7.7%) | 0 |
| Depression | 6 (33%) | 0 | 5 (38%) | 0 |
| Gastroesophageal reflux disease | 4 (22%) | 2 (11%) | 3 (23%) | 1 |
| Medications | | | | |
| Antidepressants | 3 (17%) | 1 (6%) | 3 (23%) | 0 |
| Proton pump inhibitors | 2 (11%) | 1 (6%) | 2 15%) | 1 (7%) |
| Antihypertensive agents | 0 | 0 | 1 (7%) | 1 (7%) |
| Narcotics/NSAIDs | 2 (11%) | 3 (17%) | 0 | 1 |
| Birth control pills | 2 (11%) | 5 (28%) | 1 (7%) | 2 (11%) |

*No significant differences between RYGB subjects and controls were seen in the PK and PD studies.
N/A indicates not applicable; NSAID, nonsteroidal anti-inflammatory drug.

**TABLE 2.** Geometric Mean ± Standard Deviation Values of PK Parameters for Oral and Intravenous Midazolam

| | **RYGB (n = 18)** | **Control (n = 18)** | ***P*** |
|---|---|---|---|
| Oral midazolam | | | |
| $t_{max}$,* h | 0.5 ± 0.2 | 0.75 ± 0.4 | 0.01 |
| $C_{max}$, ng/mL | 1.9 ± 1.6 | 2.7 ± 11 | 0.25 |
| $t_{1/2}$, h | 3.0 ± 1.9 | 3.1 ± 1.7 | 0.11 |
| $AUC_{0\text{-}6\ h}$, (ng·h)/mL | 3.4 ± 2.5 | 6.0 ± 23 | 0.06 |
| $AUC_M/AUC_P$ | 0.3 ± 0.4 | 0.1 ± 0.2 | 0.12 |
| CL, L/h | 246 ± 147 | 168 ± 119 | 0.10 |
| CL, L/(h·kg) | 3.0 ± 1.9 | 2.1 ± 1.7 | 0.11 |
| $F_{po}$, % | 0.4 ± 0.2 | 0.3 ± 0.2 | 0.47 |
| Intravenous midazolam | | | |
| $t_{max}$, h | 0.5 ± 0.2 | 0.5 ± 0.1 | 0.94 |
| $C_{max}$, ng/mL | 6.5 ± 7.9 | 10 ± 16 | 0.09 |
| $t_{1/2}$, h | 3.0 ± 1.9 | 3.1 ± 1.7 | 0.11 |
| $AUC_{0\text{-}\infty}$ minus residual $AUC_{po}$, (ng·h)/mL | 8.6± 4.6 | 14.6 ± 21† | 0.03 |
| $AUC_M/AUC_P$ | 0.09 ± 0.1 | 0.05 ± 0.1 | 0.09 |
| $CL_H$, L/h | 94 ± 57 | 55 ± 46† | 0.03 |
| $CL_H$, L/(h·kg) | 1.2 ± 0.8 | 0.7 ± 0.6† | 0.04 |

*$t_{max}$ expressed in median (interquartile range).
†Significant difference at $P \leq 0.05$ versus control (Student *t* test).
AUC indicates area under plasma concentration-time curve for oral/intravenous midazolam; $AUC_M/AUC_P$, ratio of AUC of 1-OH midazolam (metabolite) and midazolam (parent drug) and this reflects the CYP3A activity.

plasma concentration and AUC of sertraline were significantly lower in RYGB subjects than in matched controls. Although this study was conducted after several months of bariatric surgery, the choice of sertraline, which is primarily metabolized in the liver through demethylation with no gut wall metabolism, does not necessarily address the alterations that may occur with drugs that are metabolized by CYP3A where gut wall metabolism plays a significant role.

In the current PK study, a rapid absorption (shorter $t_{max}$) of orally administered caffeine, tolbutamide, omeprazole, and midazolam was observed in the individuals with RYGB. The rapid emptying of small gastric pouch (~15–30 mL) may account for faster transfer of drugs into the jejunum, leading to earlier absorption of orally administered medications. This observation is consistent with prior studies that reported rapid and higher serum ethanol concentrations

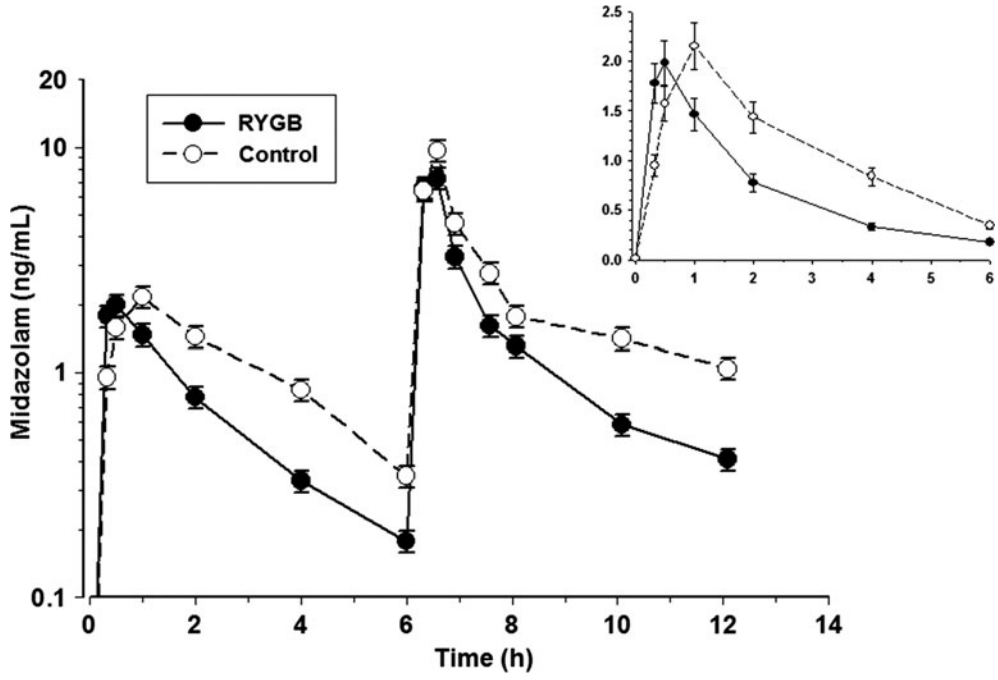


**FIGURE 1.** Oral and intravenous midazolam-CYP3A administered in a semisimultaneous fashion. Insert: $t_{max}$ of oral midazolam for the RYGB group is significantly shorter than the control group.

**TABLE 3.** PK Parameters for Caffeine, Tolbutamide, and Omeprazole

| | RYGB | Control | *P* |
|---|---|---|---|
| Caffeine (probe for CYP1A2) | | | |
| $t_{max}$,* h | **0.5 (0.3–1.0)** | **2.0 (1.0–4.0)** | **0.0001** |
| $C_{max}$, ng/mL | **910 ± 288** | **620 ± 350** | **0.02** |
| $t^1/_2$, h | 6.2 ± 2.9 | 4.7 ± 2.7 | 0.09 |
| AUC, ($\mu$g·h)/mL | 6.4 ± 5.4 | 5.2 ± 4.1 | 0.25 |
| $AUC_{paraxanthine}/AUC_{caffeine}$ | 0.6 ± 0.3 | 0.7 ± 0.3 | 0.23 |
| CL, L/h | 6.2 ± 3.4 | 7.7 ± 8.1 | 0.34 |
| CL, L/(h·kg) | 0.2 ± 0.1 | 0.1 ± 0.1 | 0.37 |
| CYP2C9 (probe: tolbutamide) | | | |
| $t_{max}$,* h | **1.1 (0.9–1.6)** | **5.9 (4.0–6.4)** | **0.0001** |
| $C_{max}$, ng/mL | 9.6 ± 2.7 | 9.4 ± 1.7 | 0.76 |
| $t^1/_2$, h | 8.8 ± 3.7 | 7.1 ± 2.3 | 0.07 |
| AUC, ($\mu$g·h)/mL | 115 ± 44 | 131 ± 40 | 0.23 |
| $AUC_{1\text{-}OH\_tolbutamide}/AUC_{tolbutamide}$ | 0.01 ± 0.01 | 0.01 ± 0.01 | 0.59 |
| CL, L/h | 0.84 ± 0.3 | 0.76 ± 0.2 | 0.38 |
| CL, L/(h·kg) | 0.01 ± 0.0 | 0.01 ± 0.0 | 0.59 |
| CYP 2C19 (probe: omeprazole) | | | |
| $t_{max}$,* h | **0.75 (0.8–1.5)** | **4.0 (4.0–6.0)** | **0.0001** |
| $C_{max}$, ng/mL | 441 ± 247 | 230 ± 871 | 0.43 |
| $t^1/_2$, h | 1.0 ± 0.8 | 1.1 ± 0.6 | 0.53 |
| AUC, ($\mu$g·h)/mL | 0.8 ± 0.7 | 0.8 ± 4.5 | 0.87 |
| $AUC_{5\text{-}OH\_omeprazole}/AUC_{omeprazole}$ | 0.4 ± 3.4 | 0.5 ± 1.8 | 0.82 |
| CL, L/h | 26 ± 82 | 23 ± 154 | 0.86 |
| CL, L/(h·kg) | 0.3 ± 1.1 | 0.3 ± 2.1 | 0.87 |

*$t_{max}$ expressed as median (interquartile range).
AUC indicates area under plasma concentration-time curve for oral/intravenous midazolam; CL, clearance.

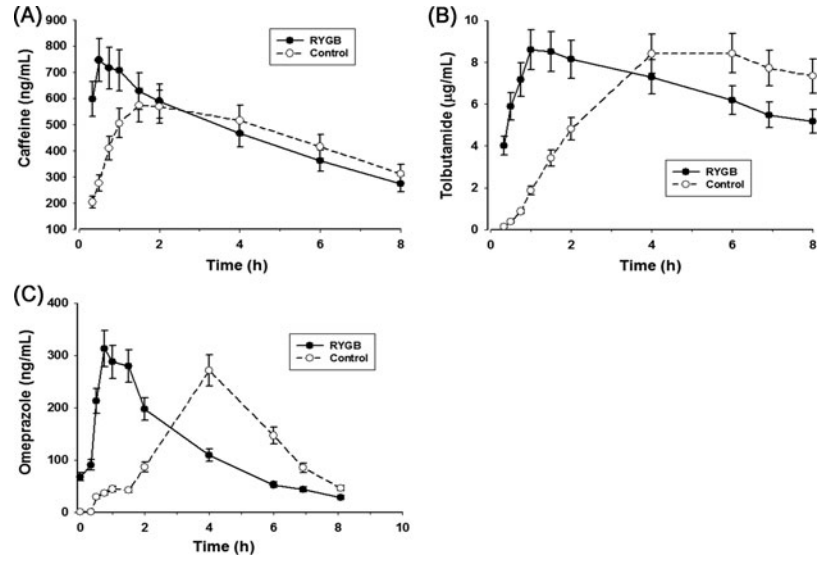


**FIGURE 2.** Mean plasma concentration versus time plots of caffeine-CYP1A2 (A); tolbutamide-CYP2C9 (B); and omeprazole-CYP2C19 (C). $t_{max}$ of caffeine, tolbutamide, and omeprazole for the RYGB group is significantly shorter than the control group.

**TABLE 4.** PD Results: Natriuresis and Diuresis After Administration of Oral Furosemide in RYGB Subjects and Controls

| | RYGB (n = 13) | Control (n = 14) | *P* |
|---|---|---|---|
| Natriuresis (urine sodium output), mmol | | | |
| Total 6-h urine sodium, mean ± standard deviation | 139 ± 80 | 125 ± 54 | 0.54 |
| Timed urine sodium output | | | |
| 0–1 h | 5.6 ± 6.2 | 4.0 ± 2.4 | 0.39 |
| 1–2 h | **51 ± 39** | **20 ± 15** | **0.02** |
| 2–4 h | 50 ± 33 | 54 ± 32 | 0.72 |
| 4–6 h | 31 ± 24 | 43 ± 43 | 0.32 |
| $t_{max}$, h | **1.34 ± 0.47** | **3.10 ± 2.3** | **0.005** |
| $V_{max}$, mmol/h | 42.0 ± 27.7 | 36.4 ± 14.5 | 0.87 |
| Diuresis (urine volume output), L | | | |
| Total 6-h urine volume, mean ± standard deviation | 2.9 ± 1.0 | 2.5 ± 0.8 | 0.39 |
| Timed urine output | | | |
| 0–1 h | 0.7 ± 0.4 | 0.6 ± 0.2 | 0.30 |
| 1–2 h | 0.9 ± 0.5 | 0.7 ± 0.3 | 0.09 |
| 2–4 h | 0.9 ± 0.3 | 0.8 ± 0.4 | 0.41 |
| 4–6 h | 0.7 ± 0.4 | 0.7 ± 0.4 | 0.95 |
| $V_{max}$, L/h | 0.85 ± 0.42 | 0.68 ± 0.24 | 0.12 |
| Serum furosemide pharmacokinetics | | | |
| $C_{max}$, ng/mL | 964 ± 368 | 1203 ± 388 | 0.57 |
| $t_{max}$, h | **1.8 ± 0.3** | **4.2 ± 1.2** | **0.006** |
| $t^{1}/_{2}$, h | 5.5 ± 2.1 | 3.7 ± 0.8 | 0.12 |
| $V_d$, L | 238 ± 108 | 176 ± 45 | 0.29 |
| CL, mL/min | 952 ± 155 | 798 ± 248 | 0.53 |

Values are expressed at mean ± standard deviation.
$t_{max}$ indicates time for maximal excretion rate; $V_{max}$, maximal excretion rate.

in RYGB subjects.[38–40] It has been suggested that the rapid absorption of alcohol with high blood alcohol levels may result in a more pronounced intoxicating effect resulting in alcohol addiction.[40] Similarly, orally administered drugs with intoxicating effects such as certain benzodiazepines and narcotics may have more rapid increases in plasma levels after ingestion, resulting in a greater intoxicating effect in RYGB subjects. Because the time of onset of the drug's intoxicating effect is critical, these subjects may be at risk for drug abuse.[41] Providers should thus exercise caution and avoid use of drugs with abuse potential, particularly those with rapid onset of action.

In contrast to prior reported studies, our study did not reveal any differences in the bioavailability and clearance of orally administered probe drugs. Although caffeine, omeprazole, and tolbutamide were not expected to have any variability in the PK parameters due to the lack of clinically significant expression of CYP1A2, CYP2C9, and CYP2C19 in the gut wall, the lack of difference in the midazolam PKs was surprising because, previously, studies have shown that up to 50% of the total CYP3A activity could be contributed by the gut wall.[42–44] This finding lends credence to the notion that there is intestinal adaptation of jejunum that is now contiguous to the gastric pouch and perhaps changing to a neoduodenum over time. Although

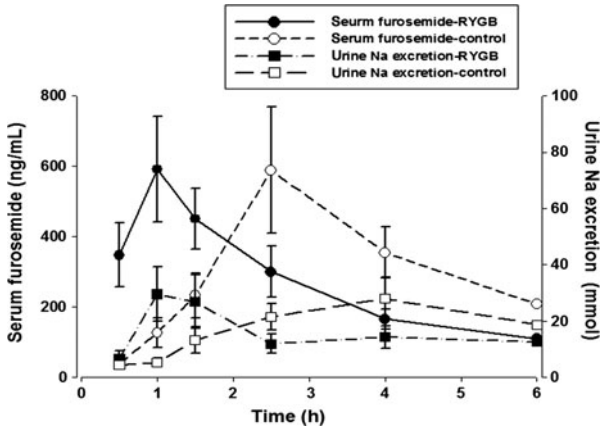


**FIGURE 3.** Serum furosemide and urine sodium in the RYGB and control groups at time 0 and after furosemide administration at following time points: 1, 1.5, 2.5, 4, 6, and 8 hours.

intestinal adaptation has been reported after short bowel syndrome,[45] there are limited data about such occurrence after RYGB surgery.[46,47] In a rat model by Taqi et al,[47] there was significant intestinal adaptation (increased bowel width, villus height, crypt depth, and proliferation) after RYGB surgery compared with sham surgery. The semisimultaneously administered midazolam in the current study permitted the differential evaluation of intestinal and hepatic CYP3A activity. Interestingly, we found that the hepatic CYP3A activity in RYGB subjects was higher on the basis of the lower AUCs and faster clearance of intravenous midazolam. We speculate that the unexpected finding of higher hepatic CYP3A activity in the RYGB group is possibly due to decreased hepatic steatosis after the RYGB. We have previously shown that hepatic steatosis is associated with significantly lower hepatic CYP3A activity[48] and it is well known that hepatic steatosis rapidly improves after bariatric surgery.[49] If this observation is confirmed in other studies, it may have important therapeutic implications, such as an RYGB patient requiring higher doses of intravenously administered CYP3A substrates (eg, diltiazem, midazolam) to avoid suboptimal response. Longitudinal studies with CYP3A activity measured before and after the RYGB are required to clarify the effect of hepatic steatosis on CYP3A activity.

The PD response to oral furosemide in the RYGB subjects occurred significantly earlier (Table 4), as evidenced by the increased urine sodium excreted during the 1- to 2-hour time frame. This finding likely results from postsurgical changes in the anatomy and physiology causing rapid gastric emptying and increased gastric pH resulting in shorter $t_{max}$ and a higher serum concentration of furosemide at 0.5 and 1 hour. A strong correlation was seen between serum furosemide and urine sodium excretion, with earlier peaking in both serum and urine values in the RYGB group (Fig. 3). Furosemide is a drug with low solubility and permeability that is most rapidly absorbed by the upper gastrointestinal tract after dissolution in the stomach.[50,51] Its aqueous solubility, however, increases with higher pH values.[51] However, the prompt natriuresis is not likely to occur unless accompanied by intestinal adaptation, with resultant improved absorption of furosemide in the neoduodenum.

This study contributes novel and clinically important data to the medical literature concerning the alterations in the PKs of the studied orally administered probe drugs in patients with RYGB. There is consistency between the results of PK and PD studies in which a significantly rapid absorption of orally administered medications after RYGB surgery was noted. Unlike prior studies that reported lower or higher bioavailability after gastric bypass, our study did not demonstrate any difference in oral bioavailability or oral clearance. It is likely that intestinal adaptation may play a role because all RYGB subjects in the current study were at least 1 year postsurgery, thus providing ample time for intestinal adaptation. Variability in oral bioavailability and absorption after gastric bypass may be in part related to the time interval between the PK study and RYGB surgery, resulting in variable intestinal adaptation. A critical review of the prior literature suggests that there is higher bioavailability when investigated in the immediate postoperative period, whereas lower bioavailability when investigated several months after the surgical procedure.[37] Thus, there is a need for conducting comprehensive PK studies before and at multiple time points after the RYGB procedure.

In summary, our study investigated the PK and PD changes in RYGB recipients using an oral mini-cocktail of probe drugs and furosemide and it shows that orally administered medications have veryrapid absorption and onset of action, but the overall exposure and clearance of the oral medicines remain similar to matched controls. Somewhat unexpectedly, we observed hepatic CYP3A activity to be significantly higher in RYGB recipients than in matched controls. Because our study consisted of individuals who had RYGB at least 1 year before participating in this study, we cannot exclude the possibility that there may have been significant PK and PD alterations in the early postoperative course that are reversed because of intestinal adaptation.

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