Clinical and Translational Science

ARTICLE OPEN ACCESS

Pharmacokinetic Profiles of Lansoprazole in Patients With Morbid Obesity Post-Roux-en-Y Gastric Bypass Surgery

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Received: 26 August 2024 | **Revised:** 28 February 2025 | **Accepted:** 6 March 2025

Funding: This study was funded by the Ratchadapiseksomphot Fund, Faculty of Medicine, Chulalongkorn University, grant number RA 64/036.

Keywords: lansoprazole | morbid obesity | pharmacokinetics | Roux-en-Y gastric bypass

ABSTRACT

Data on the effects of Roux-en-Y gastric bypass (RYGB) surgery on lansoprazole pharmacokinetics in morbidly obese patients are limited. This study aimed to evaluate the impact of RYGB surgery on the pharmacokinetic profile of lansoprazole in Thai morbidly obese patients. Participants received 30 mg of lansoprazole twice daily for 7 days before surgery and continued the regimen for 6 weeks post-surgery. Plasma lansoprazole concentrations were measured at predose (0), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 8 h after dosing, both pre- and post-surgery, using a validated high-performance liquid chromatography technique. *CYP2C19* genotyping classified participants as normal metabolizers (**1/*1*) or intermediate metabolizers (**1/*2* and **1/*3*). Pharmacokinetic parameters, including the area under the plasma concentration-time curve from 0 to 8 h (AUC_{0-8h}), maximum plasma concentration (Cmax), and time to maximum concentration (Tmax), were compared before and after surgery. A total of 13 patients (mean age 37.0 ± 3.9 years; body mass index 54.0 ± 4.8 kg/m^2) were enrolled. Post-surgery, AUC_{0-8h} and Cmax decreased by 16% ($p = 0.009$) and 31% ($p = 0.003$), respectively, while Tmax remained unchanged. A 30% reduction in Cmax ($p = 0.007$) was observed in *CYP2C19* normal metabolizers, whereas no significant changes were noted in intermediate metabolizers. In conclusion, RYGB surgery significantly reduced lansoprazole systemic exposure, particularly in *CYP2C19* normal metabolizers. Further studies are needed to explore the clinical implications of these pharmacokinetic changes and develop optimized treatment strategies for post-RYGB patients.

Trial Registration: ClinicalTrials.gov identifier: TCTR20220118001

1 | Introduction

Obesity is a major global public health concern. According to the World Health Organization (WHO), as of 2022, approximately 2.5 billion adults were classified as overweight (body mass index (BMI) ≥ 25 kg/m^2), with over 890 million categorized as obese (BMI ≥ 30 kg/m^2) [1]. Obesity is associated with an increased risk of numerous comorbidities and a significantly increased rise in mortality rates [2, 3]. The World Obesity Atlas 2023 projects a concerning trend, forecasting a rise in global obesity prevalence from over 2.6 billion individuals in 2020 (38% of the global population) to more than 4 billion by 2035 (50% of the global

Summary

- What is the current knowledge on the topic?
  - Roux-en-Y gastric bypass (RYGB) is a preferred surgical procedure for patients with morbid obesity. Lansoprazole is widely used to prevent marginal ulcers following RYGB surgery. Currently, there are no pharmacokinetic data available on lansoprazole in morbidly obese patients undergoing RYGB surgery.
- What question did this study address?
  - This study aimed to investigate the changes in lansoprazole pharmacokinetics in morbidly obese patients after RYGB surgery.
- What does this study add to our knowledge?
  - RYGB surgery resulted in a significant reduction in lansoprazole plasma concentrations, with a 16% decrease in AUC_{0-8h} (mean difference: -647.01 ± 202.77 ng·h/mL, $p = 0.009$, 95% CI: −1093.30, −200.71) and a 31% decrease in Cmax (mean difference: -251.86 ± 67.27 ng/mL, $p = 0.003$, 95% CI: −399.93, −103.80). A 30% reduction in Cmax (mean difference: -211.06 ± 58.37 ng/mL, $p = 0.007$, 95% CI: −345.66, −76.46) was observed in *CYP2C19* normal metabolizers, with no significant changes in intermediate metabolizers.
- How might this change clinical pharmacology or translational science?
  - RYGB surgery significantly reduces lansoprazole systemic exposure, particularly in CYP2C19 normal metabolizers. Further studies are required to explore the clinical implications of these pharmacokinetic changes and to develop strategies for optimizing treatment outcomes in this population.

population) [4]. Similarly, data from the Thai Health Project indicate a growing prevalence of obesity in Thailand, increasing from 34.7% in 2008–2009 to 37.5% in 2014 [5].

In Thailand, metabolic and bariatric surgery is an established treatment for obesity, particularly for individuals with a BMI $\geq 37.5\,kg/m^2$, or $\geq 32.5\,kg/m^2$ when accompanied by comorbidities such as severe gastroesophageal reflux disease (GERD) or type 2 diabetes mellitus [6]. Among the available surgical options, Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy are the most commonly performed procedures. RYGB is particularly recommended for patients with a BMI $> 50\,kg/m^2$ due to its superior efficacy in achieving substantial weight loss and its lower reoperation rates compared to sleeve gastrectomy [7].

A subset of patients (1%–16%) undergoing RYGB surgery may develop marginal ulcers in the gastrointestinal tract due to acid reflux. These ulcers can lead to complications such as bleeding, perforation, strictures, gastrointestinal obstruction, and chronic pain [8, 9]. Proton pump inhibitors (PPIs) are commonly prescribed to reduce acid secretion and promote ulcer healing [10]. However, studies have reported reduced plasma concentrations of omeprazole in patients following RYGB surgery, likely due to altered drug absorption [11]. The changes in oral drug absorption post-RYGB surgery are theoretically linked to multiple factors. These include impaired disintegration of oral medications and a diminished drug dissolution process, influenced by reduced gastric volume, elevated gastric pH, and shortened gastric transit time. Additional contributing factors include modifications in gastric emptying and gastrointestinal transit time, a decreased absorptive surface area in the small intestine, and reduced exposure to bile acids and enterohepatic circulation [12, 13].

The effects of RYGB surgery on drug pharmacokinetics remain inconsistent across studies [14]. Some research has reported reduced drug absorption and plasma concentrations for medications such as paracetamol, tramadol/paracetamol, rivaroxaban, dabigatran, mycophenolic acid, tacrolimus, sirolimus, and omeprazole [15–21]. Conversely, other studies have observed increased maximum plasma concentrations (Cmax) for drugs such as morphine, cyclosporin, tacrolimus, mycophenolate sodium, sirolimus, and metformin [22–24]. Despite these findings, the clinical relevance of these pharmacokinetic changes remains unclear in many cases [13]. Altered pharmacokinetic profiles, such as earlier and higher peak concentrations with lower trough concentrations or delayed peaks with higher trough concentrations, can have varying implications depending on the drug's therapeutic window and pharmacodynamic properties. However, many studies do not evaluate or report the clinical consequences of these pharmacokinetic alterations. These findings underscore the complexity of drug absorption and metabolism following RYGB surgery, emphasizing the critical need for further research to elucidate the clinical implications of pharmacokinetic changes and to develop optimized pharmacological strategies for post-RYGB patients.

Lansoprazole is widely used to treat acid-related disorders such as GERD and peptic ulcer disease [25]. It is also frequently prescribed to prevent marginal ulcers in patients following RYGB surgery [10]. After oral administration, lansoprazole is rapidly absorbed, with a bioavailability exceeding 85% [26]. The drug reaches its maximum plasma concentrations (Tmax) within 1.2 to 2.1 h, with reported Cmax values ranging from 0.92 to 1.15 mg/L. [23] The area under the plasma concentration-time curve (AUC) is reported between 2.4 and 2.93 mg/L·h, with an elimination half-life of 0.9 to 2.1 h [27]. Lansoprazole undergoes extensive hepatic metabolism via the cytochrome P450 (CYP450) enzyme system, primarily involving the CYP2C19 isoenzyme [28]. However, no pharmacokinetic data are currently available for lansoprazole in morbidly obese patients post-RYGB surgery. The anatomical and physiological changes induced by RYGB surgery, particularly the bypass of significant portions of the gastrointestinal tract, are likely to influence drug absorption and metabolism [29]. These alterations may affect lansoprazole's pharmacokinetics and therapeutic efficacy, highlighting the need for further investigation.

This study aimed to evaluate changes in lansoprazole pharmacokinetics in morbidly obese patients before and after undergoing RYGB surgery.

2 | Methods

This clinical pharmacokinetic study was registered in the Thai Clinical Trials Registry and received ethical approval from

the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University. The study was conducted in accordance with the Declaration of Helsinki and adhered to the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP). Written informed consent was obtained from all participants prior to enrollment.

2.1 | Participant Recruitment and Eligibility Criteria

Participants were recruited from the Obesity Clinic at King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand. Eligible participants were adults (≥ 18 years) with a BMI of ≥ 37.5 kg/m^2 or a BMI of ≥ 32.5 kg/m^2 with at least one comorbidity. Individuals who smoked or were continuous users of non-steroidal anti-inflammatory drugs (NSAIDs), defined by daily NSAID use for more than 1 month, were excluded. Prior to surgery, all participants underwent *Helicobacter pylori* detection using the campylobacter-like organism (CLO) test. Those who tested positive for *Helicobacter pylori* received a two-week eradication treatment before proceeding with surgical intervention.

2.2 | Surgical Procedures

RYGB surgery was performed laparoscopically on all participants using a standardized technique by the same surgeon. The procedure began with the creation of a gastric pouch with a capacity of approximately 20–30 mL. A 50 cm biliopancreatic limb and a 150 cm Roux limb were constructed in an antecolic, antegastric orientation. Anastomosis was achieved using a side-to-side jejunojejunostomy technique. A gastrojejunostomy anastomosis was then performed between the end of the Roux limb and the gastric pouch using a 2.5 cm circular staple. To prevent internal herniation, the mesenteric and pseudo-Petersen defects were meticulously closed with sutures. Finally, a gastroscopy was conducted to evaluate the integrity of the intraluminal anastomosis and confirm the success of the procedure.

2.3 | Lansoprazole Administration, Sample Collection, and Gastric Ulcer Evaluation

Participants received 30 mg of lansoprazole twice daily for 1 week prior to surgery. On the seventh day of treatment (prior to surgery, in fasting state), venous blood samples (3 mL) were collected in EDTA tubes at predetermined time points: predose (0 h), and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 8 h post-dose. Blood samples were immediately stored at 4°C, then centrifuged at 4500 *g* for 10 min to separate plasma. The plasma samples were subsequently stored at −80°C until analysis.

After surgery, participants continued the same lansoprazole regimen (30 mg twice daily) for 24 weeks. Blood sample collection was repeated at week 6 post-surgery in fasting conditions using the same time-point schedule and procedures as described above (Figure 1). Gastric ulcer evaluation was conducted at 6 and 24 weeks post-RYGB by the same physician using clinical examination and patient history assessment to monitor symptoms and signs of ulcer formation.

2.4 | Bioanalysis of Lansoprazole in Plasma

Lansoprazole concentrations in plasma were quantified using a fully validated high-performance liquid chromatography (HPLC) method. Plasma sample (500 μL) and 10 μL of rosiglitazone, which served as the internal standard, and 3 mL of ethyl acetate were combined. The mixture was vortexed for 2 min and then centrifuged at 2500 rpm at 10°C for 5 min to extract lansoprazole. The organic layer was evaporated to dryness and reconstituted with 200 μL of a solution consisting of acetonitrile, methanol, and 10 mM potassium dihydrogen phosphate (pH 6.4) in a 1:1:1 (v/v/v) ratio. A 50 μL aliquot of the reconstituted extract was injected into the HPLC system, equipped with a UV detector set at a wavelength of 285 nm, to measure lansoprazole concentrations.

2.5 | Validation of the Analytical Method

The analytical method validation was performed in accordance with the guidelines of the European Medicines Agency [30] and the US Food and Drug Administration [31]. Selectivity was assessed by screening six different sources of blank plasma to identify any interference peaks. The results confirmed no interference peaks from endogenous components at the retention times of lansoprazole or the internal standard in all blank plasma samples.

Linearity was evaluated using eight standard points of lansoprazole, ranging from 20.100 to 4020.000 ng/mL in plasma. The lower limit of quantification (LLOQ) was established at 20.100 ng/mL. Three calibration curves demonstrated excellent linearity, with back-calculated lansoprazole concentrations showing accuracy between 90.985% and 103.379%. The correlation coefficient (R^2) consistently exceeded 0.99975, meeting the

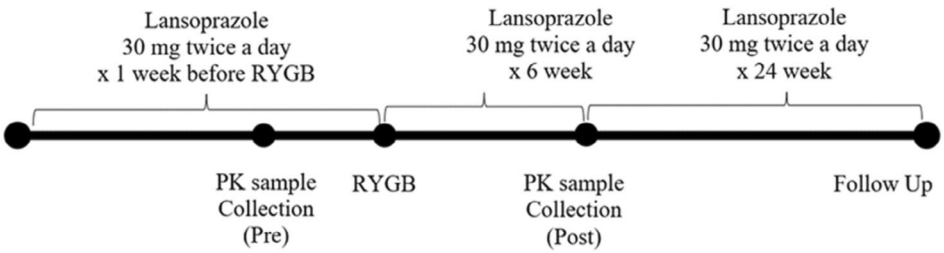

FIGURE 1 | Research framework. RYGB, Roux-en-Y gastric bypass.

required criteria of ±15% accuracy for all levels, except for the LLOQ, which required ±20% accuracy and an R^2 value greater than 0.99.

The intra-batch accuracy and precision of the method were determined using five replicates of four quality control (QC) concentrations: LLOQ, low QC (LQC), medium QC (MQC), and high QC (HQC). Inter-batch accuracy and precision were evaluated across three independent batch runs. The acceptance criteria for both intra-batch and inter-batch assessments required accuracy within ±15% of the nominal values and precision within 15% coefficient of variation (CV), except for the LLOQ, which required 80%–120% accuracy and ≤ 20% CV. For this method, the intra-batch %accuracy ranged from 83.591% to 110.547%, with a precision of 6.582% CV. Inter-batch %accuracy ranged from 92.471% to 101.330%, with a precision of 14.179% CV.

Recovery was evaluated by comparing the mean detected responses of five replicates at LQC and HQC levels for lansoprazole and the internal standard in plasma from pre-extracted and post-extracted samples. The recovery rates for lansoprazole were 73.583% at LQC and 76.720% at HQC, while the recovery rate for the internal standard was 71.205%. The precision for lansoprazole ranged from 0.719% to 4.154% CV, and the internal standard showed a precision of 8.159% CV.

Post-preparative stability was evaluated by preparing lansoprazole samples at LQC and HQC levels, analyzing them as freshly prepared samples, and re-analyzing extracted samples that were stored in an autosampler at 15°C after 24 h. Stability was confirmed if deviations were within ±15%. The results showed deviations of 12.595% for LQC and −1.934% for HQC, indicating that lansoprazole remained stable for at least 24 h under these conditions. Long-term stability was assessed after 342 days of storage at −70°C. Three replicates of QC samples at LQC and HQC levels were analyzed and compared to freshly prepared samples. The deviations were 12.624% for low QC and 11.140% for high QC, confirming that lansoprazole remained stable within the acceptable range of ±15% during long-term storage.

Carryover was evaluated by injecting blank plasma samples following a calibration curve at the upper limit of quantification (ULOQ). No significant carryover was detected, as peak responses for lansoprazole and the internal standard in blank plasma samples were below the acceptable thresholds of < 20% for LLOQ and < 5% for internal standard. The carryover test sequence—blank sample, ULOQ, blank sample, ULOQ, blank sample, blank sample, and LLOQ—confirmed the absence of detectable residual analytes. These results ensure that the analytical method was free from carryover.

2.6 | *CYP2C19* Genotyping

DNA was extracted from whole blood using PureLink Genomic DNA Mini Kits (Invitrogen, USA). DNA concentration and purity were assessed using a NanoDrop spectrophotometers (Thermo Scientific, USA), with an absorbance ratio at 260/280 nm ≥ 1.8 indicating acceptable purity.

Genotyping for *CYP2C19*2* (rs4244285), *CYP2C19*3* (rs4986893), and *CYP2C19*17* (rs12248560) was performed using TaqMan Real-Time Polymerase Chain Reaction (PCR) assays (Applied Biosystem, ThermoFisher Scientific). PCR amplification was conducted on a StepOnePlus Real-Time PCR System (Thermo Fisher Scientific). Predicted phenotypes and * allele designations for *CYP2C19* were assigned based on the PharmGKB database (https://www.pharmgkb.org/page/cyp2c19RefMaterials). The *CYP2C19*1* represents normal enzyme function, while *CYP2C19*2* and *CYP2C19*3* are classified as no-function alleles. In contrast, the *CYP2C19*17* allele is associated with increased enzyme function. *CYP2C19* phenotypes were classified as normal metabolizers (*CYP2C19*1/*1*), intermediate metabolizers (*CYP2C19*1/*2* and **1/*3*), poor metabolizers (*CYP2C19*2/*2, *2/*3*, and **3/*3*), rapid metabolizers (*CYP2C19*1/*17*) and ultrarapid metabolizers (*CYP2C19*17/*17*).

2.7 | Pharmacokinetic and Statistical Analysis

Non-compartmental pharmacokinetic analysis was conducted using the WinNonlin program. The pharmacokinetic parameters reported included Tmax, Cmax, area under the plasma concentration-time curve from time 0 to 8 h ($AUC_{0-8\,h}$), and area under the curve extrapolated to infinity (AUC_{0-inf}). Statistical analyses were performed using SPSS version 28.0. Continuous data were expressed as mean ± standard deviation (SD) unless otherwise specified. The paired Student's *t*-test was used to compare pharmacokinetic parameters before and after surgery. Additionally, changes in all parameters between the pre- and post-surgery periods were also quantified as the differences (post-surgery value minus pre-surgery value) and presented as mean difference ± standard error of the mean (SEM). A $p < 0.05$ was considered statistically significant.

3 | Results

3.1 | Participant Characteristics and Outcomes of RYGB Surgery

A total of 13 Thai morbidly obese patients were enrolled in the study, with approximately 60% being male. Several participants presented with comorbidities, including diabetes mellitus, dyslipidemia, hypertension, and obstructive sleep apnea (Table 1). Two participants tested positive for *Helicobacter pylori* and underwent a two-week eradication treatment before surgery.

Following RYGB surgery, all participants experienced significant reductions in BMI (mean difference: −4.6 ± 1.6 kg/m^2, $p = 0.014$, 95% CI: −8.087, −1.113). Significant improvements were also observed in clinical parameters (Table 1), including blood urea nitrogen (mean difference: −3.6 ± 1.5 mg/dL, $p = 0.034$, 95% CI: −6.869, −0.331) and HbA1c (mean difference: −0.8% ± 0.2%, $p = 0.002$, 95% CI: −1.235, −0.365).

During the 6 weeks post-surgery, all participants were prescribed a multivitamin and calcium supplement in addition

TABLE 1 | Baseline characteristics.

Parameters	Baseline	6-week post RYGB	Mean differences[a]	*p* (95% CI)
Age (years)	37.0 ± 3.9	na	na	na
Male (*n* (%))	8 (61.5)	na	na	na
Co-morbidity diagnosed before surgery (*n* (%))				
Diabetes mellitus	4 (30.8)	na	na	na
Dyslipidemia	6 (46.2)	na	na	na
Hypertension	10 (76.9)	na	na	na
Obstructive sleep apnea	4 (30.8)	na	na	na
Body build				
Weight (kg)	141.1 ± 22.5	129.8 ± 21.1	−11.3 ± 8.6	0.213 (−30.039, 7.439)
Body mass index (kg/m^2)	54.0 ± 4.8	49.4 ± 3.4	−4.6 ± 1.6	0.014 (−8.087, −1.113)
Laboratory investigation				
Hemoglobin (mg/dL)	13.0 ± 1.2	12.6 ± 1.6	−0.4 ± 0.6	0.517 (−1.705, 0.905)
White blood cell count (×10^3)	10.8 ± 4.4	7.9 ± 2.2	−2.9 ± 1.4	0.061 (−5.952, 0.152)
Platelets (×10^3)	289 ± 64	258 ± 56	−31 ± 24	0.221 (−83.290, 21.290)
Blood urea nitrogen (mg/dL)	13.9 ± 3.8	10.3 ± 3.9	−3.6 ± 1.5	0.034 (−6.869, −0.331)
Creatinine (mg/dL)	0.7 ± 0.2	0.7 ± 0.3	0.0 ± 0.1	1.000 (−0.218, 0.218)
Fasting plasma glucose (mg/dL)	101.8 ± 16.3	94.8 ± 15.5	−7.0 ± 6.2	0.281 (−20.506, 6.506)
HbA1C (mg%)	5.8 ± 0.6	5.0 ± 0.4	−0.8 ± 0.2	0.002 (−1.235, −0.365)
CYP2C19 phenotypes				
Normal metabolizers (**1/*1*)	9 (69.2)	na	na	na
Intermediate metabolizers (**1/*2* & **1/*3*)	4 (30.8)	na	na	na
Concomittent medication after surgery				
Multivitamin	na	13 (100.0)	na	na
Calcium	na	13 (100.0)	na	na
Amlodipine	na	2 (15.4)	na	na
Carvedilol	na	1 (7.7)	na	na
Enalapril	na	1 (7.7)	na	na
Manidipine	na	1 (7.7)	na	na
Insulin	na	1 (7.7)	na	na
Meformin	na	1 (7.7)	na	na
Simvastatin	na	1 (7.7)	na	na

Note: Data are presented as mean ± standard deviation unless otherwise specified.
Abbreviations: 95% CI, 95% confidence interval; na, not applicable; RYGB, Roux-en-Y gastric bypass.
[a]Data are presented as mean ± standard error of the mean.

to lansoprazole. Five participants received antihypertensive medications, including amlodipine ($n = 2$), manidipine ($n = 1$), enalapril ($n = 1$), and carvedilol ($n = 1$). One participant was prescribed insulin injections alongside metformin and simvastatin. Notably, none of the participants exhibited symptoms of gastric ulcers 6 weeks post-RYGB surgery.

3.2 | Pharmacokinetic Profiles of Lansoprazole and the Effect of RYGB Surgery

The pharmacokinetic profiles of lansoprazole before and 6 weeks after RYGB surgery are summarized in Table 2 and Figure 2. Significant reductions in plasma lansoprazole

TABLE 2 | Pharmacokinetic parameters of lansoprazole before and 6 weeks after Roux-en-Y gastric bypass surgery.

Parameters	Baseline	6-week post RYGB	Mean difference[a]	*p* (95% CI)
Plasma concentrations (ng/mL)				
C0	22.35 ± 33.66	45.05 ± 88.93	22.70 ± 22.16	0.332 (−27.432, 72.836)
C0.5	193.22 ± 132.93	197.09 ± 130.89	3.87 ± 65.67	0.955 (−164.953, 172.683)
C1	339.20 ± 384.02	230.45 ± 70.01	−108.75 ± 126.95	0.414 (−395.929, 178.437)
C1.5	375.55 ± 263.25	296.36 ± 148.61	−79.19 ± 108.85	0.484 (−321.715, 163.340)
C2	531.67 ± 226.27	366.72 ± 140.82	−164.94 ± 84.25	0.079 (−352.670, 22.782)
C2.5	537.09 ± 280.09	387.11 ± 226.27	−149.99 ± 47.06	0.010 (−254.846, −45.124)
C3	479.09 ± 238.11	369.99 ± 198.57	−109.10 ± 35.87	0.012 (−189.036, −29.173)
C4	404.28 ± 176.27	327.95 ± 194.25	−76.32 ± 23.69	0.009 (−129.102, −23.545)
C6	305.17 ± 119.38	283.58 ± 160.70	−21.59 ± 24.76	0.406 (−77.613, 34.429)
C8	219.93 ± 110.29	207.64 ± 133.80	−12.29 ± 14.93	0.438 (−47.598, 23.024)
Pharmacokinetics parameters				
Tmax (h)	1.93 ± 0.91	2.90 ± 1.66	0.98 ± 0.59	0.126 (−0.323, 2.274)
Cmax (ng/mL)	704.10 ± 273.72	452.24 ± 144.66	−251.86 ± 67.27	0.003 (−399.931, −103.796)
AUC_{0-8h} (ng h/mL)	2613.63 ± 1003.50	1966.63 ± 1142.56	−647.01 ± 202.77	0.009 (−1093.300, −200.708)

Note: Data are presented as mean ± standard deviation.
Abbreviations: 95% CI, 95% confidence interval; AUC_{0-8h}, area under the concentration-time curve from time 0 to 8 h; C, plasma concentration; Cmax, maximum plasma concentration; RYGB, Roux-en-Y gastric bypass; Tmax, time to maximum plasma concentration.
[a]Data are presented as mean ± standard error of the mean.

concentrations were observed at specific time points post-surgery, particularly at C2.5, C3, and C4. The mean differences were as follows: C2.5: −149.99 ± 47.06 ng/mL, $p = 0.010$, 95% CI: −254.846, −45.124; C3: −109.10 ± 35.87 ng/mL, $p = 0.012$, 95% CI: −189.036, −29.173; and C4: −76.32 ± 23.69 ng/mL, $p = 0.009$, 95% CI: −126.102, −23.545. Both AUC_{0-8h} and Cmax were significantly reduced post-surgery (mean difference for AUC_{0-8h}: −647.01 ± 202.77 ng·h/mL, $p = 0.009$, 95% CI: −1093.300, −200.708, approximately 16% reduction and Cmax: −251.86 ± 67.27 ng/mL, $p = 0.003$, 95% CI: −399.931, −103.796, approximately 31% reduction). No significant differences were observed in Tmax.

3.3 | Influence of *CYP2C19* Phenotypes on the Pharmacokinetic Profiles of Lansoprazole

When analyzed by *CYP2C19* phenotypes, notable differences emerged in the pharmacokinetic parameters of lansoprazole before and after RYGB surgery. In the normal metabolizers (*CYP2C19*1/*1*), significant reductions were observed in Cmax (mean difference: −211.06 ± 58.37 ng/mL, $p = 0.007$, 95% CI: −345.664, −76.460) and at time points C2.5 (mean difference: −157.67 ± 62.71 ng/mL, $p = 0.040$, 95% CI: −305.944, −9.393), C3 (mean difference: −120.64 ± 47.81 ng/mL, $p = 0.040$, 95% CI: −233.684, −7.597), and C4 (mean difference: −86.02 ± 30.34 ng/mL, $p = 0.025$, 95% CI: −157.773, −14.269). These findings are presented in Table 3 and Figure 3A,C. In contrast, no statistically significant changes were observed in intermediate metabolizers (*CYP2C19*1/*2* and *CYP2C19*1/*3*) post-surgery (Table 3, Figure 3B,D).

4 | Discussion

This study demonstrates a significant alteration in the pharmacokinetic profile of lansoprazole following RYGB surgery, as evidenced by a decrease in AUC_{0-8h} and Cmax in Thai morbidly obese patients. These findings underscore the impact of the anatomical and physiological changes, along with weight loss, on drug pharmacokinetics in post-RYGB patients. Moreover, the influence of *CYP2C19* phenotypes on lansoprazole metabolism highlights the crucial role of pharmacogenetics in drug disposition among post-RYGB individuals.

The administration of PPIs during the early postoperative period (3–4 months) is essential as a prophylactic measure against gastric ulcers [32]. Emerging evidence suggests that newer PPIs, such as lansoprazole, may offer advantages over omeprazole in treating gastric ulcers, with studies reporting a 15% increase in healing rates at 4 weeks [33]. Based on this evidence, lansoprazole was selected as the PPI of choice for all participants in this study.

RYGB surgery is likely to alter drug absorption, leading to pharmacokinetic changes that are theoretically attributed to several factors. These include limited disintegration of oral drugs and a reduced drug dissolution process, influenced by factors such as decreased gastric volume, increased gastric pH, and reduced gastric transition time. Additional contributing factors include altered gastric emptying and gastrointestinal transit time, a reduced absorptive surface area in the small intestine, and decreased exposure to bile acids and enterohepatic circulation [13, 14, 29, 34]. Consistent with these theoretical considerations,

our findings demonstrated significant alterations in lansoprazole pharmacokinetics post-RYGB surgery. Specifically, lansoprazole absorption was reduced, as evidenced by a 16% reduction in AUC_{0-8h} and a 31% reduction in Cmax.

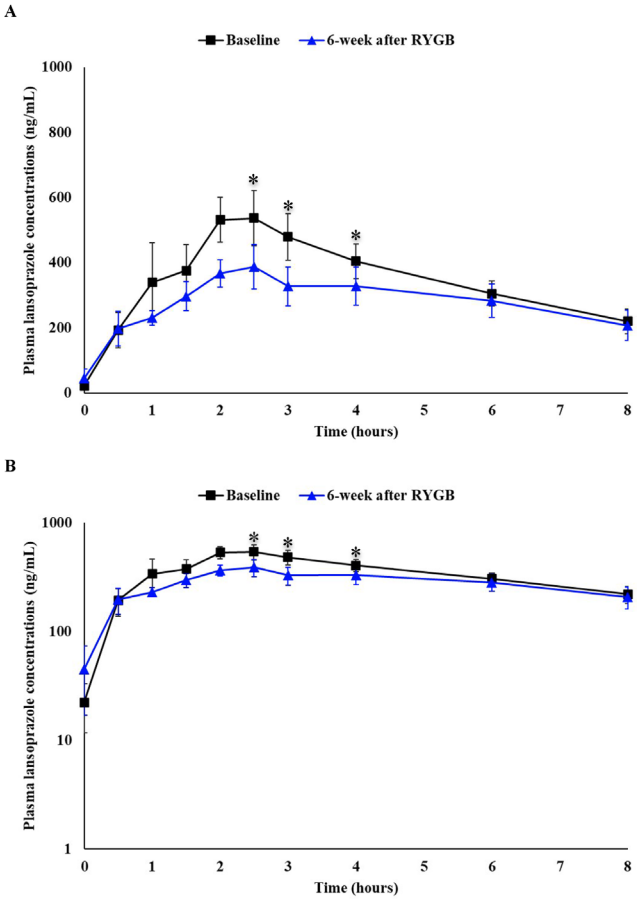

FIGURE 2 | Plasma lansoprazole concentration-time profiles from 0 to 8 h after administration of 30 mg lansoprazole in morbidly obese patients, comparing pre- and post-RYGB surgery. Data are presented as mean ± standard error of the mean. (A) linear scale, (B) semi-logarithmic scale.*$p < 0.05$ for baseline versus 6-week post RYGB. RYGB, Roux-en-Y gastric bypass.

Our results align with previous studies reporting significant reductions in drug absorption and pharmacokinetic parameters of PPIs following RYGB surgery. For example, a study evaluating omeprazole pharmacokinetics in 14 RYGB patients and 24 controls found significant reductions in both AUC and Cmax at 1 and 6 months post-surgery compared to baseline ($p < 0.001$ and $p = 0.001$, respectively) [20]. Similarly, another study assessing early post-surgical effects on omeprazole absorption in 20 participants reported a significant reduction in plasma omeprazole concentrations at 90 min post-administration compared to both pre-surgery levels ($p = 0.02$) and control groups ($p < 0.01$) [21]. However, our findings contrast with a previous study involving 34 morbidly obese patients post-RYGB, which examined omeprazole pharmacokinetics before and after RYGB surgery. While this study observed a significant reduction in AUC_{0-12h} ($p < 0.001$), it also reported an unexpected increase in Cmax ($p < 0.001$) [11].

The profound weight loss following RYGB surgery significantly influences drug pharmacokinetics, particularly volume of distribution (V) and clearance (CL) [14, 29]. After surgery, the substantial reduction in adipose and lean body mass can lead to a decrease in V, particularly for lipophilic drugs such as lansoprazole, due to reduced distribution into fat stores. Consequently, this reduction in V may result in higher plasma concentrations for a given dose, potentially altering drug efficacy and toxicity.

The decrease in CL following RYGB is multifactorial, driven by changes in hepatic metabolism, renal function, and intestinal drug transport [14]. The metabolic capacity of the liver may be altered due to modifications in drug-metabolizing enzyme activity, including CYP450 enzymes, secondary to weight loss and overall metabolic improvements. Moreover, renal CL can be affected by postoperative alterations in glomerular filtration rate, which initially increase due to obesity-associated hyperfiltration but normalize with weight loss. However, due to the lipophilicity of lansoprazole, its elimination primarily depends on hepatic metabolism rather than renal CL. Our pharmacokinetic data was insufficient to fully characterize the changes in CL and V of lansoprazole in our patient cohort. However, we observed a reduction in AUC_{0-8h} of lansoprazole after surgery and weight loss. Since AUC is inversely proportional to total CL when the

TABLE 3 | Pharmacokinetic parameters of lansoprazole before and 6 weeks after Roux-en-Y gastric bypass surgery classified by *CYP2C19* phenotypes.

***CYP2C19* phenotypes**	**Parameters**	**Baseline**	**6-week post RYGB**	**Mean differences[a]**	***p* (95% CI)****
Normal metabolizers (**1/*1*)	Tmax (h)	2.01 ± 1.01	2.59 ± 1.57	0.58 ± 0.70	0.431 (−1.031, 2.189)
	Cmax (ng/mL)	683.97 ± 249.30	472.91 ± 157.71	−211.06 ± 58.37	0.007 (−345.664, −76.460)
	AUC_{0-8h} (ng h/mL)	2640.91 ± 1153.20	2066.39 ± 1320.48	−574.52 ± 262.91	0.060 (−1180.785, 31.752)
Intermediate metabolizers (**1/*2* & **1/*3*)	Tmax (h)	1.67 ± 0.58	3.83 ± 1.89	2.17 ± 0.93	0.145 (−1.826, 6.159)
	Cmax (ng/mL)	764.50 ± 395.20	390.23 ± 89.00	−374.27 ± 220.66	0.232 (−1323.698, 575.164)
	AUC_{0-8h} (ng h/mL)	2531.79 ± 453.49	1667.32 ± 161.42	−864.47 ± 208.74	0.054 (−1762.623, 33.689)

Note: Data are presented as mean ± standard deviation.
Abbreviations: 95% CI, 95% confidence interval; AUC_{0-8h}, area under the concentration-time curve from time 0 to 8 h; Cmax, maximum plasma concentration; RYGB, Roux-en-Y gastric bypass; Tmax, time to maximum plasma concentration.
[a]Data are presented as mean ± standard error of the mean.
**$p < 0.05$ for baseline versus 6-week post RYGB within the phenotype group.

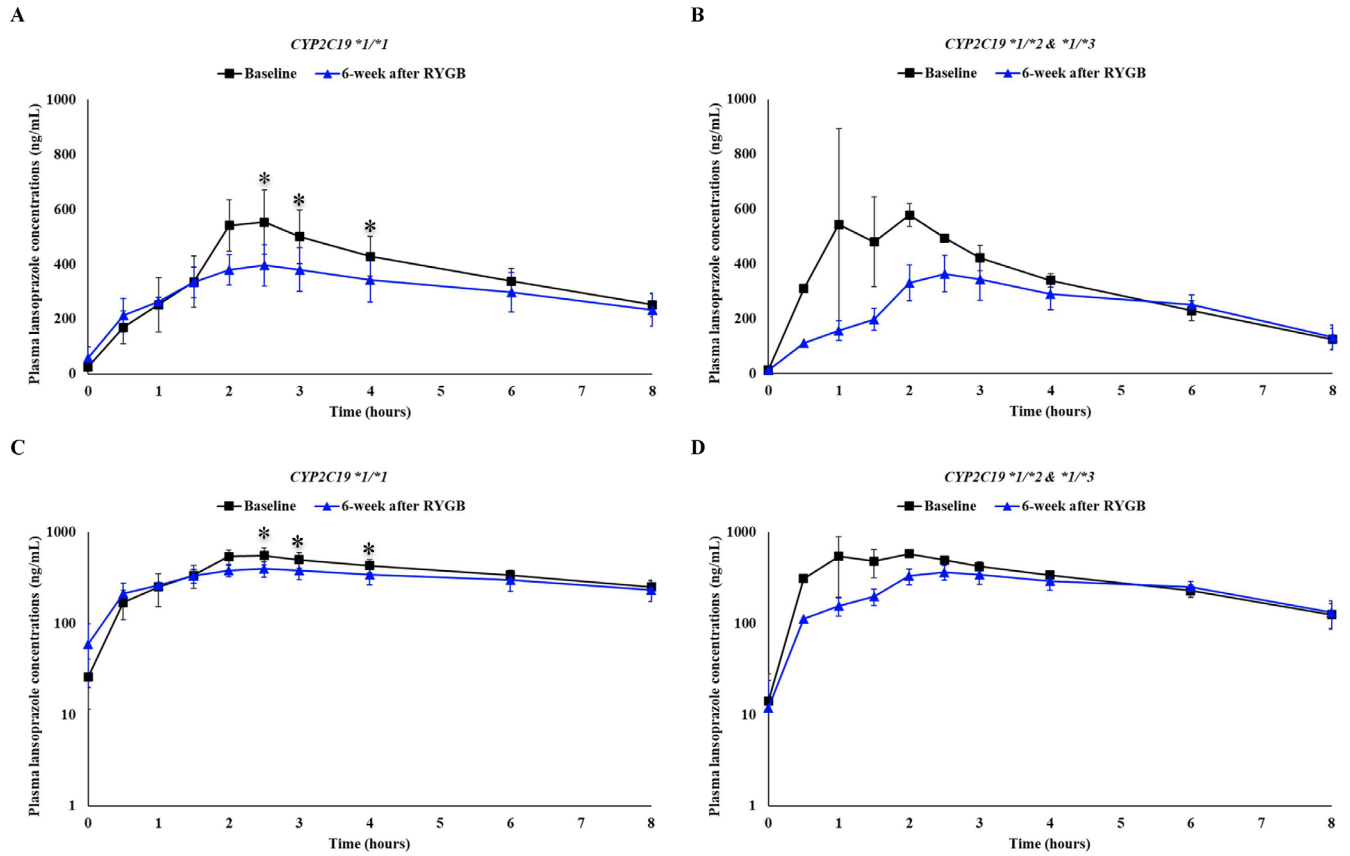

FIGURE 3 | Plasma lansoprazole concentration-time profiles from 0 to 8 h after administration of 30 mg lansoprazole in morbidly obese patients, comparing pre- and post-RYGB surgery, classified by *CYP2C19* phenotypes. Data are presented as mean ± standard error of the mean. (A, B) linear scale, (C, D) semi-logarithmic scale.*$p < 0.05$ for baseline versus 6-week post RYGB. RYGB, Roux-en-Y gastric bypass.

dose remains constant, our finding suggested that the total CL of lansoprazole (hepatic metabolism + renal clearance) may have increased in our patients after surgery.

To further elucidate the effect of hepatic metabolism on lansoprazole pharmacokinetics, we also investigated the influence of genetic variations in CYP2C19, the primary drug metabolizing enzyme responsible for the lansoprazole biotransformation [35]. A previous study by Kvitne et al. involving 40 obese individuals post-RYGB, 41 diet-induced weight loss, and 18 controls found that baseline CYP2C19 enzyme activity, represented by the 5-hydroxyomeprazole/omeprazole metabolic ratio, was 2.7-fold lower in obese patients compared to controls ($p < 0.05$). Following RYGB surgery, CYP2C19 enzyme activity increased by 43% within the first 3 weeks and by an additional 30% over the next 6 weeks [36]. Other studies have also reported increased CYP2C19 enzyme activity, reflected by a significant reduction in systemic omeprazole exposure within 1 to 6 months post-surgery [11, 20]. Our findings support this evidence, as we observed that *CYP2C19* normal metabolizers (*CYP2C19 *1/*1*) generally exhibit lower systemic exposure to lansoprazole at 6 weeks post-RYGB, with a significant reduction in Cmax. In contrast, no significant pharmacokinetic changes were observed in *CYP2C19* intermediate metabolizers (*CYP2C19 *1/*2 & *1/*3*) post-surgery. Based on these results, we suggest that CYP2C19 enzyme activity increases after RYGB surgery, particularly in *CYP2C19* normal metabolizers. The increases in enzyme activity, leading to enhanced hepatic CL, are likely associated with weight reduction and decreased liver fat content, as described above.

Drug–drug interaction may influence the pharmacokinetics of lansoprazole. CYP2C19 inhibitors, such as fluconazole, fluoxetine, fluvoxamine, and ticlopidine, are likely to increase systemic exposure of lansoprazole [37]. Conversely, CYP2C19 inducers, including apalutamide, rifampicin, efavirenz, enzalutamide, and phenytoin, may decrease systemic exposure of the drug [37]. However, none of these medications were coadministered to participants in this study.

Regarding treatment outcomes, none of the patients developed marginal ulcers during the 24-week follow-up period post-surgery. These findings suggest that dose adjustments for marginal ulcer prophylaxis may not be necessary for RYGB patients receiving lansoprazole, which contrasts with previous data [20, 21]. The discrepancies between our findings and earlier studies may be attributed to differences in study methodologies, including the type of PPI used (primarily omeprazole in prior research [11, 20, 21]), differences in dosages and timing of blood sample collection, ethnicity, and the baseline body weight of the participants.

One limitation of this study is the restricted pharmacokinetic sampling duration (up to 8 h post-dose), which does not allow for accurate estimation of AUC_{0-inf}. While this limitation affects the ability to fully characterize the elimination phase, the chosen

sampling timeframe was based on lansoprazole's pharmacokinetic properties. Given the logistical constraints of prolonged sampling in the studied patients, we prioritized capturing the absorption phase and early elimination phase to assess the impact of RYGB on lansoprazole exposure. Additionally, ethical considerations and patient burden associated with extended sampling periods were factors in determining the study design. Despite this limitation, the collected pharmacokinetic data provide meaningful insights into RYGB's impact on lansoprazole absorption. The observed reductions in AUC_{0-8h} and Cmax indicate a significant decrease in systemic exposure, which aligns with prior reports of altered pharmacokinetics following RYGB [20, 21]. These findings contribute to the growing body of evidence suggesting that gastrointestinal anatomical changes post-RYGB influence drug absorption, particularly for medications with pH-dependent solubility and extensive first-pass metabolism.

A full characterization of the elimination phase is necessary to determine total systemic exposure, but our results still provide valuable insights into the influence of RYGB on lansoprazole disposition. The observed reduction in Cmax, particularly in *CYP2C19* normal metabolizers, suggests increased first-pass metabolism or altered absorption post-surgery. Prior studies have demonstrated that CYP2C19 enzyme activity is suppressed in obesity and increases following significant weight loss [11, 20, 36, 38]. Our findings align with this trend, as the pharmacokinetic changes observed post-RYGB suggest enhanced metabolism in *CYP2C19* normal metabolizers. However, further investigation is needed to comprehensively understand the metabolic shifts occurring in post-RYGB patients.

This study included only *CYP2C19* normal and intermediate metabolizers. The effects of ultrarapid (*CYP2C19 *17/*17*), rapid (*CYP2C19*1/*17*), and poor metabolizers (*CYP2C19 *2/*2 & *3/*3*) on lansoprazole pharmacokinetics remain unexplored. A recent COCKTAIL pharmacokinetic study demonstrated that obesity downregulates CYP2C19 and CYP3A enzyme activity, with diabetes mellitus further suppressing CYP2C19 enzyme activity beyond obesity-related effects. Notably, enzyme activities increased with weight loss [38]. Unfortunately, our cohort included only one patient with diabetes mellitus, and CYP3A variability was not assessed in our analysis.

While our study design did not originally incorporate a modeling approach, population pharmacokinetic modeling could provide additional insights by integrating covariates such as body weight changes, CYP2C19 genotype, and gastric pH alterations. Given the relatively small sample size of our study, such an approach would require careful consideration of identifiability constraints and appropriate assumptions to ensure robust model performance. Future research incorporating population pharmacokinetic modeling could help refine dose recommendations for post-RYGB patients and further elucidate the interplay between weight loss, hepatic metabolism, and drug absorption.

Although no symptoms of marginal ulcers were observed in our participants, early esophagogastroduodenoscopy (EGD) at 24 weeks post-surgery was not performed to confirm this outcome. Additionally, our study lacked the power to assess the efficacy of lansoprazole in gastric ulcer prevention. Previous studies have reported that 7.6% of patients may develop marginal ulcers within the first 2 months post-RYGB, even in the absence of dyspeptic symptoms [39]. Moreover, marginal ulcers onset following RYGB surgery can occur as early as 1 month and as late as 6 years post-surgery [40]. Therefore, both short- and long-term EGDs are essential to validate our findings and comprehensively assess the long-term risk of marginal ulcers in RYGB patients receiving lansoprazole.

In conclusion, this study provides valuable insights into lansoprazole pharmacokinetic alterations in Thai morbidly obese patients before and after RYGB surgery, demonstrating a significant reduction in systemic exposure. While the limited sampling duration precludes a full characterization of elimination kinetics, the observed reductions in AUC_{0-8h} and Cmax provide meaningful evidence of altered absorption and metabolism post-RYGB. The influence of *CYP2C19* variability on lansoprazole pharmacokinetics underscores the critical role of pharmacogenetics in drug metabolism among post-RYGB patients. These findings highlight the potential need for dose adjustments in post-RYGB patients to maintain therapeutic efficacy. Future studies incorporating prolonged sampling, population pharmacokinetic modeling, and clinical outcomes assessment are warranted to further optimize treatment strategies for this population.

Author Contributions

S.C., N.B., S.P., P.K., S.U., and P.C. wrote the manuscript. W.W., P.S., W.L., S.U., and P.C. designed the research. S.C., N.B., S.P., P.K., W.W., P.S., W.L., and S.U. performed the research. N.T. and P.C. analyzed the data. P.C. contributed reagents/analytical tools.

Acknowledgments

The authors express their gratitude to all participants and collaborators for their invaluable support throughout this study. We extend our thanks to the Maha Chakri Sirindhorn Clinical Research Center, Faculty of Medicine, Chulalongkorn University, for their assistance with plasma sample collection, and to the Chula Pharmacokinetic Research Center, Faculty of Medicine, Chulalongkorn University, for performing plasma lansoprazole quantification. Additionally, we are grateful to our research assistants for their support in managing the manuscript preparation and submission process.

Conflicts of Interest

The authors declare no conflicts of interest.

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