OBES SURG (2016) 26:2051–2058
DOI 10.1007/s11695-016-2065-8

ORIGINAL CONTRIBUTIONS

The Effect of Roux-en-Y Gastric Bypass Surgery in Morbidly Obese Patients on Pharmacokinetics of (Acetyl)Salicylic Acid and Omeprazole: the ERY-PAO Study

Lieke Mitrov-Winkelmolen[1] · Marie-Christine W. van Buul-Gast[2] · Dingeman J. Swank[3] · Hans W P M Overdiek[4] · Ron H. N. van Schaik[5] · Daan J. Touw[6]

Published online: 21 January 2016

Abstract
Background Data on the absorption of orally administered drugs following Roux-en-Y gastric bypass (RYGB) surgery in obese patients are limited and inconclusive. As it is difficult to predict changes in absorption, studies on frequently used drugs in this population are necessary. Acetylsalicylic acid (ASA) and omeprazole are two commonly prescribed drugs in obese patients.
Methods In this repeated measures study, omeprazole and salicylic acid (SA) serum concentrations were measured before and after RYGB in 34 morbidly obese subjects. Time to maximum concentration (Tmax), lag time (Tlag), maximum concentration (Cmax), and area under the serum concentration versus time curve (AUC) were calculated for both drugs to determine possible differences in drug absorption after the procedure.
Results For SA, Tmax significantly decreased after RYGB, while both Cmax and $AUC_{0–24}$ significantly increased. For omeprazole, both Tmax and Tlag significantly decreased after RYGB, while Cmax significantly increased. Mean $AUC_{0–12}$ significantly decreased post-surgery. The difference in $AUC_{0–12}$ before and after surgery varied between subjects.
Conclusions Our study shows a faster absorption of both ASA and omeprazole after RYGB. The exposure to ASA is higher post-surgery, but the standard dose of 80 mg does not need to be modified, considering its range in effective dose. The exposure to omeprazole is, on average, decreased after surgery. Clinicians should be aware to increase the dose of omeprazole if symptoms suggest inadequate response.

Keywords Roux-en-Y gastric bypass · Drug absorption · Acetylsalicylic acid (Aspirin) · Omeprazole

The ERY-PAO study was conducted at the department of clinical pharmacy, Central Hospital Pharmacy, Medical Centre The Hague, The Hague, The Netherlands and the Dutch Obesity Clinic West, The Hague, The Netherlands.

✉ Lieke Mitrov-Winkelmolen
l.mitrov@ikazia.nl

1 Department of Clinical Pharmacy, Ikazia Hospital and Maasstad Hospital, Rotterdam, The Netherlands

2 Department of clinical pharmacy, BovenIJ Hospital, Amsterdam, The Netherlands

3 Dutch Obesity Clinic West, The Hague, The Netherlands

4 Central Hospital Pharmacy, Medical Centre The Hague, The Hague, The Netherlands

5 Department of Clinical Chemistry, Erasmus University Medical Center, Rotterdam, The Netherlands

6 Department of Clinical Pharmacy and Pharmacology, University Medical Centre Groningen Groningen, University of Groningen, Groningen, The Netherlands

Introduction

Worldwide, obesity prevalence has doubled since the 1980s. In 2014, 13 % of the adult population was obese, defined as a body mass index (BMI) of >30 kg/m^2. Obesity is related to many co-morbidities and increased mortality [1]. Bariatric surgery has shown to be the most effective method to treat morbid obesity (BMI > 35 kg/m^2) and related co-morbidities. Roux-en-Y gastric bypass surgery (RYGB) is one of the most commonly performed procedures in bariatric surgery. In RYGB, the stomach is reduced to a small gastric pouch. The duodenum is bypassed by connecting the jejunum to this pouch. The duodenum is connected to a lower part of the jejunum to ensure passage of gastric acid, bile salts, and pancreatic enzymes [2].

Food and drugs first pass the newly created gastric pouch, before passing directly into the shortened jejunum. Changes in volume and pH of the gastric pouch, and bypassing the greater part of the stomach and the entire duodenum, could affect the absorption of nutrients and drugs [3–6]. It is well recognized that RYGB results in problems regarding vitamin and nutrient absorption, and patients are eligible for life-long vitamin and nutrient supplementation [7].

In contrast, limited well-controlled prospective data are available on absorption of orally administered drugs after RYGB. The literature consists mostly of case reports, small studies, or in vitro research. Results of these publications are inconclusive. Some authors report decreased absorption for drugs; others report unchanged or better absorption. It is not possible to predict easily whether drugs undergo any change in absorption after RYGB [5, 8–18]. Therefore, studies should be performed with frequently used drugs in this population. Acetylsalicylic acid (ASA) and omeprazole are two drugs commonly prescribed to obese patients and patients after RYGB.

Acetylsalicylic Acid

In the Netherlands, ASA is one of the most commonly prescribed drugs, and is usually administered in a dose of 80 mg as a platelet-inhibitory agent, to prevent thrombotic disease in high-risk patients [19, 20]. Low-dose ASA (75–150 mg) once daily has been proven to be an effective dose in preventing death, myocardial infarction, and stroke. The efficacy has, however, not been proven in doses lower than 75 mg once daily, except for stroke [21]. If RYGB would result in a decreased absorption of ASA, the efficacy might be insufficient for preventing myocardial infarction and death.

Omeprazole

Omeprazole is a selective and irreversible proton pump inhibitor, inhibiting the proton pump in the parietal cells of the stomach and therewith resulting in a less acidic stomach. It is prescribed in reflux disease and treatment and prophylaxis of ulcerations. Omeprazole is mainly metabolized by the liver enzyme Cytochrome P450 2C19 (CYP2C19). Polymorphisms of CYP2C19 can lead to increased or decreased blood levels of omeprazole [19, 22]. After RYGB, treatment with 20 mg omeprazole twice daily during a period of 6 months is prescribed to patients to prevent ulcerations of the anastomosis [23–25]. If the absorption of omeprazole would be decreased after RYGB, this post-surgery prophylaxis could possibly be ineffective.

We aimed to study and to compare the pharmacokinetics of ASA and omeprazole in morbidly obese subjects before and after RYGB, to identify possible changes in absorption of these drugs after the procedure, and to possibly relate omeprazole outcomes to CYP2C19 phenotype.

Materials and Methods

This open-label longitudinal repeated measures study was performed in morbidly obese subjects undergoing RYGB at the Dutch Obesity Clinic (NOK) West. The RYGB resulted in the creation of a gastric pouch of approximately 5 by 7 cm with a residual volume of 35–50 cc, a biliary limb of circa 75 cm and an alimentary limb of 150 cm. Subjects with at least one of the following criteria were excluded: previously performed bariatric surgery, increased bleeding risk, malabsorption disorder, inability to swallow whole tablets, allergy to any of the study medication, or the use of other medication with an interaction with the study medication.

The absorption of omeprazole and ASA was investigated before and after RYGB. Therefore, two intervention periods were defined: one period more than 2 weeks before the scheduled surgery and one period more than 6 weeks after the performed surgery. During the intervention periods, subjects were instructed to take the study medication omeprazole 20 mg twice daily for 1 week. On day 7 of each period, an outpatient visit was planned at the study site, where the study medication omeprazole (20 mg) and ASA (80 mg) were administered, and data collection took place. Omeprazole was administered as a whole tablet to preserve the enteric coating; ASA was dispersed in 25 ml of water directly before administration. In the pre-operative intervention period, subjects were instructed to continue the use of 20 mg omeprazole twice daily due to safety considerations after ASA intake [26]. After surgery, administration of 20 mg omeprazole twice daily was routine practice for all subjects for the duration of 6 months. During the intervention periods, subjects were instructed to register the times of omeprazole intake, the use of other medications, and side effects. Body weight, body height, BMI, and fat percentage were measured during scheduled visits in the obesity clinic before and after the surgery. Both body weight and fat percentage were determined on the TANITA SC330 body composition analyzer (WEDA BV, Naarden, the Netherlands).

On day 7 of both intervention periods, blood was drawn five times: once before administration of the study medication ($T=0$) and four times after the administration of the medication: at 30 ($T=30$), 60 ($T=60$), 120 ($T=120$), and 240 min ($T=240$). One extra sample was drawn on one of both days for genotyping. In Fig. 1, the study procedures are summarized.

Blood samples were collected in ethylenediaminetetraacetic acid (EDTA) and Clot Activator tubes (BD, Plymouth, UK). As ASA is rapidly hydrolyzed to salicylic acid (SA) after administration, SA was measured as a marker for ASA. Samples for SA and omeprazole drug concentration

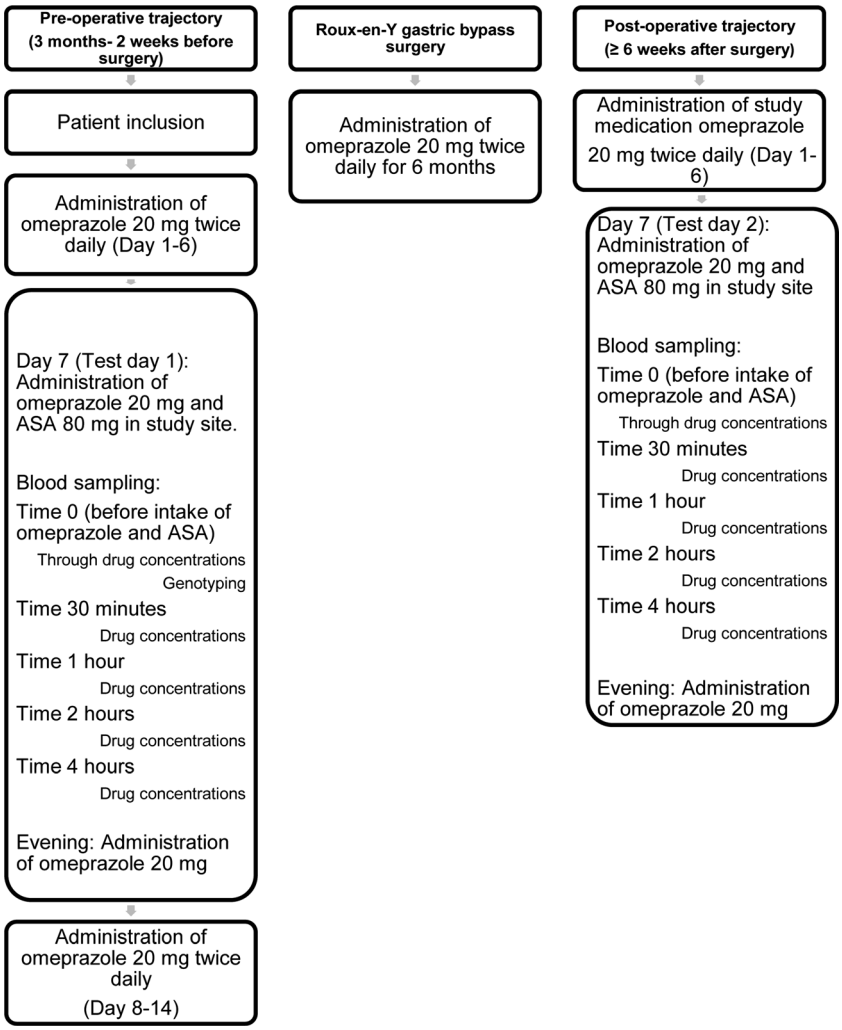

Fig. 1 Summary of ERY-PAO study procedures

measurements were kept at room temperature for a maximum of 5 h and then centrifuged for 10 min at 2530*g*. Serum was then aliquoted. Samples for genotyping were not centrifuged. All samples were stored at −80 °C until further use.

Concentrations of SA and omeprazole were analyzed in serum using a validated liquid chromatography-mass spectrometry (LC/MS/MS) (Agilent 6460 MS, Agilent 1290 LC) method (LLOQ omeprazole 0.01 mg/l, linearity 0.026–2.64 mg/l; LLOQ SA 0.2 mg/l, linearity 0.25–10 mg/l). Concentrations for SA were expressed in milligram per liter (mg/l) and for omeprazole, in microgram per liter (μg/l). Genotyping was performed on 10-ng DNA using TaqMan probes, as described earlier [27] and translated to a CYP2C19 predicted phenotype.

Using validated pharmacokinetic software MWPharm (version 3.70 Mediware, Groningen, the Netherlands), time to maximum concentration (Tmax), lag time (Tlag), maximum concentration (Cmax), and area under the serum concentration versus time curve for 12 or 24 h ($AUC_{0–12}$ or $AUC_{0–24}$) were calculated for omeprazole and SA.

Results are reported as mean ± standard deviation (SD). Data were analyzed using SPSS statistics version 20 (IBM, Armonk, NY, USA). Data were tested for normality. A paired *t* test was performed on the obtained data before and after surgery. A bivariate analysis was performed on omeprazole data and phenotype. A p value of <0.05 was considered significant.

Approval for the study was obtained from the local ethics committee of The Hague (METCZWH, The Hague, the Netherlands). Before participating in the study, informed consent was obtained from all individual study subjects.

Results

Forty subjects were included in the study and completed test day 1. Both study days were completed by 34 subjects. Patient recruitment and inclusion are described in Fig. 2. The acquired numerical data passed the test for normality.

The mean age of the subjects on the surgery date was 48.7 ± 10 years. Of the subjects, 79 % was female. Subjects did not

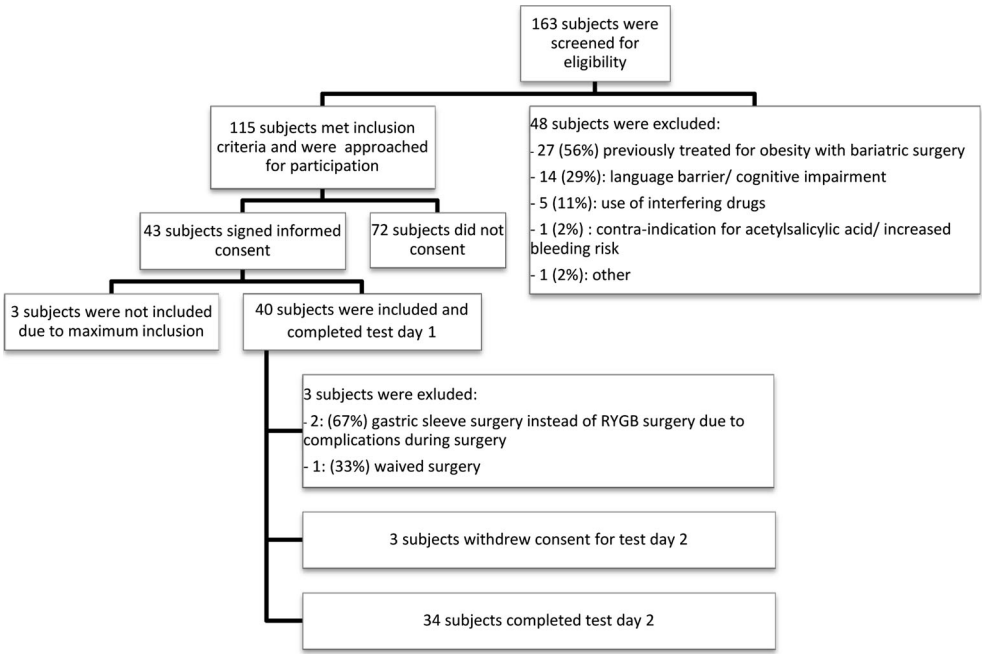

Fig. 2 Inclusion of study subjects for the ERY-PAO study

use interacting medication during both test periods. Test days were performed on an average of 63 ± 18 days before (test day 1) and 58 ± 18 days after (test day 2) the date of surgery.

Mean weight before the surgery was 128.9 ± 18.7 kg with a mean BMI of 44.9 ± 6 and a percentage of body fat of 48.4 ± 6.3. After surgery, the average percentage of total weight loss (TWL) was 11.5 % with a decrease in body fat of 5 %. Results are shown in Table 1. In Table 2 various pharmacokinetic values of SA and omeprazole before and after the surgery are displayed. Figure 3 shows an absorption curve before and after surgery for both SA and omeprazole.

Salicylic Acid

The Tmax of SA after RYGB was significantly shorter than before surgery: 0.7 and 1 h, respectively ($p < 0.001$). Both Cmax and $AUC_{0–24}$ were significantly higher after surgery compared to the pre-surgery data: Mean Cmax increased from 3.5 ± 1 to 4.6 ± 0.9 mg/l ($p < 0.001$) and mean $AUC_{0–24}$ increased from 11.4 ± 5.2 to 14.1 ± 6.4 mg/l ($p < 0.001$). Figure 4 shows the difference in $AUC_{0–24}$ of SA for each individual subject. For each subject, an increase in SA $AUC_{0–24}$ was observed.

Omeprazole

For omeprazole, both Tmax and lag-time, the time necessary for the drug formulation to release the drug for absorption (Tlag), were significantly shorter after surgery. The Tmax after surgery was 0.9 h compared to 2.1 h before surgery ($p < 0.001$). Tlag after surgery was 0.4 h compared to 1 h before surgery ($p < 0.001$).

The Cmax of omeprazole was significantly higher after (958.6 ± 300.8 μg/l) than before surgery (731.1 ± 339.0 μg/l, $p < 0.001$). In contrast, mean $AUC_{0–12}$ after surgery was significantly lower compared with mean $AUC_{0–12}$ before surgery: 2834.1 ± 1560.4 and 3737.4 ± 21932 μg h/l, respectively ($p < 0.001$). Figure 5 displays the difference in $AUC_{0–12}$ of omeprazole displayed for each individual subject and shows variation between subjects. No correlation between phenotype and difference in $AUC_{0–12}$ was found.

Discussion

The pharmacokinetics of ASA and omeprazole appear to change after RYGB. In this study, the absorption of ASA was faster and better after RYGB. Absorption of omeprazole after surgery was also faster, but the mean total exposure was lower.

Salicylic Acid

To the best of our knowledge, this is the first study that investigated absorption of ASA before and after RYGB. ASA is regularly absorbed by passive diffusion as unionized drug in the stomach and partly as ionized drug in the duodenum. In our study population, although the stomach and the duodenum were bypassed after surgery, both Cmax and $AUC_{0–24}$ significantly increased after surgery. This suggests that absorption of ionized ASA can also take place in the jejunum, replacing the stomach and duodenum as an absorption site. According to our data, absorption in the jejunum is even better, explaining the higher exposure. The low volume of

Table 1 Subject characteristics before and after RYGB

	Test day 1 (pre-surgery)	Test day 2 (post-surgery)	Mean total difference	Ratio post-surgery/ pre-surgery	*p* value
Age(years) on surgery date	48.7 ± 10		NA	NA	NA
Female (%)	79		NA	NA	NA
Weight (kg)	128.9 ± 18.7	114.1 ± 17.0	−14.8 ± 4.7	0.89	$p < 0.001$
BMI (kg/m^2)	44.9 ± 6.0	39.8 ± 5.4	−5.2 ± 1.6	0.89	$p < 0.001$
Body fat (%) [a]	48.4 ± 6.3	45.9 ± 6.7	−2.4 ± 3.2	0.95	$p < 0.001$
CYP2C19 Genotype (%)	*1/*1: 24 % *1/*2: 32 % *1/*17: 32 % *2/*2 : 6 % *2/*17: 3 % *17/*17: 3 %		NA	NA	NA
CYP2C19 Phenotype (%)	Poor metabolizer: 6 % Intermediate metabolizer: 32 % Extensive metabolizer: 27 % Extensive/ultra-rapid metabolizer: 32 % Ultra-rapid metabolizer 3 %		NA	NA	NA

Subject characteristics before (test day 1) and after (test day 2) RYGB a) $N = 30$

NA not applicable; *BMI* body mass index, *CYP2C19* cytochrome P450 2C19

distribution of SA (0.17 l/kg) suggests a negligible effect of the weight loss after surgery on serum concentrations of salicylic acid.

After absorption, ASA is rapidly hydrolyzed in the liver to SA. A small part of this conversion already happens in the intestinal wall during absorption [28]. After RYGB, transit time through the stomach to the intestinal wall is shorter [3] and hydrolysis of ASA starts faster. This might explain the reduced Tmax of salicylic acid after surgery.

Sufficient absorption of ASA after gastric or bowel surgery is important, given the effect of ASA in preventing cardiovascular complications. The ERY-PAO study shows no decreased absorption of ASA (80 mg) and therefore suggests an adequate effect of ASA after RYGB. Although the increase in Cmax and $AUC_{0–24}$ of SA is statistically significant, it is not clinically relevant and can be compared with a dose of 100 mg, still within the recommended dosing range of ASA as a platelet aggregation inhibitor.

Table 2 Pharmacokinetic data for salicylic acid and omeprazole before and after RYGB

	Test day 1 (pre-surgery)	Test day 2 (post-surgery)	Mean total difference	Ratio post-surgery/ pre-surgery	*p* value
Salicylic acid					
Cmax (mg/l)	3.5 ± 1.0	4.6 ± 0.9	1.1 ± 1.1	1.30	$p < 0.001$
Tmax (hours)	1.0 ± 0.3	0.7 ± 0.2	−0.3 ± 0.4	0.71	$p < 0.001$
$AUC_{0–24}$ (mg h/l)	11.4 ± 5.2	14.1 ± 6.4	2.7 ± 3.4	1.24	$p < 0.001$
Omeprazole [b]					
Cmax (μg/l)	731.1 ± 339.0	958.6 ± 300.8	226.6 ± 319.3	1.31	$p < 0.001$
Tmax (hours)	2.1 ± 1.0	0.9 ± 0.3	−1.2 ± 1.0	0.42	$p < 0.001$
Tlag (hours)	1.0 ± 0.5	0.4 ± 0,1	−0.6 ± 0,5	0.43	$p < 0.001$
$AUC_{0–12}$ (μg h/l)	3737.4 ± 2193.2	2834.1 ± 1560.4	−903.3 ± 1183.7	0.76	$p < 0.001$

Pharmacokinetic data for salicylic acid and omeprazole before (test day 1) and after (test day 2) RYGB

Cmax maximum serum concentration, *Tmax* time to maximum serum concentration, *Tlag* lag time, time for the drug to be released from the tablet for absorption, $AUC_{0–24}$ area under the serum concentration versus time curve between 0 and 24 h after administration, $AUC_{0–12}$ area under the serum concentration versus time curve between 0 and 12 h after administration b) $N = 33$

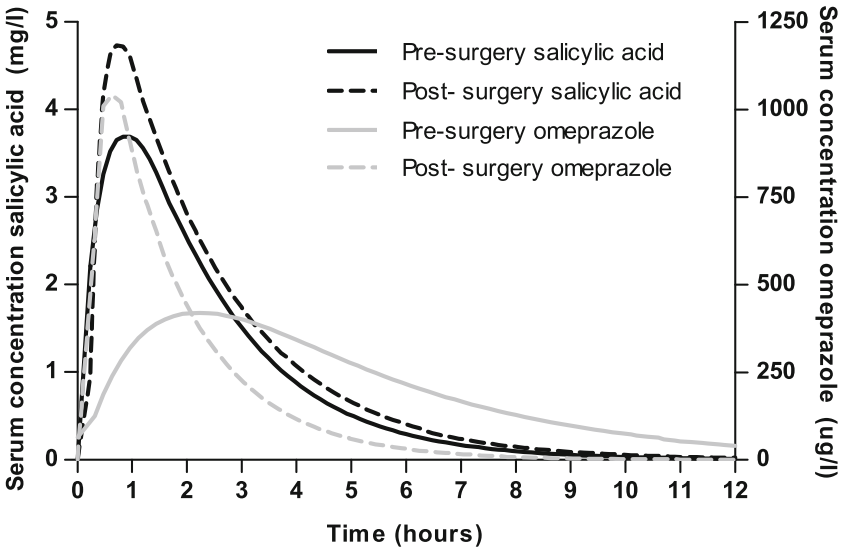

Fig. 3 Absorption curve of salicylic acid and omeprazole in a subject before and after RYGB

Omeprazole

Omeprazole is formulated as an enteric-coated tablet. In normal physiology, after passing the acidic stomach, the coating dissolves and omeprazole is absorbed. After RYGB, the coating will dissolve faster due to an increased gastric pouch pH. In addition, because of the shorter transit time, omeprazole will be available for absorption sooner after administration. This is shown in the reduced Tlag and Tmax after surgery.

Our results are similar to a previously published case-control study of Tandra et al., showing a faster absorption and increased Cmax in operated versus non-operated subjects [29]. The higher Cmax is presumably caused by the faster absorption of omeprazole after surgery. As BMI was similar between both subject groups, the increase in Cmax cannot be explained alone by weight loss after surgery. In addition, the low volume of distribution of omeprazole (0.3 L/kg) suggests only a minor effect of weight loss on omeprazole concentrations in our study population. Tandra et al. reported a similar exposure to omeprazole (AUC) in both subject groups, while we found a mean lower $AUC_{0–12}$ post-surgery, with wide variation between individual subjects. Great inter-individual variability in omeprazole pharmacokinetics has been reported previously [22]. This discrepancy in the change in exposure may be due to differences in the study design; the use of matched controls versus our repeated measures design. Furthermore, in the case-control study, only a single dose of 20-mg omeprazole was administered. Only after repeated intake of omeprazole would a steady-state situation exist, by a decrease in first-pass effect due to auto-inhibition of CYP2C19, thereby reducing the inter- and intra-individual variability in CYP2C19 capacity and reflecting the normal outpatient situation.

The degree of acid inhibition by omeprazole is related to AUC. However, a clear lower limit of efficacy has not been established [22, 30]. A significant decrease in omeprazole $AUC_{0–12}$ was seen in a substantial number of our subjects.

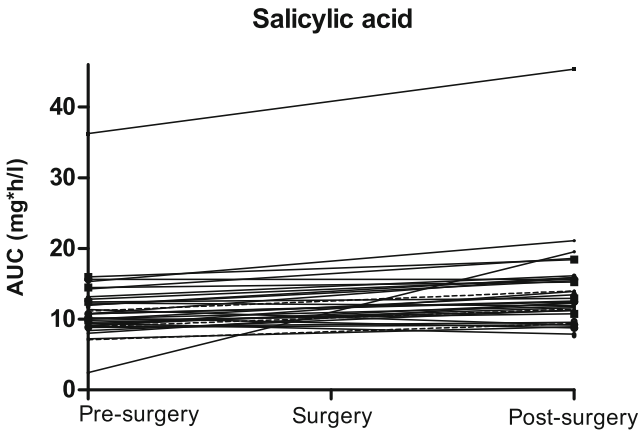

Fig. 4 Changes in area under the serum concentration versus time curve 0–24 h ($AUC_{0–24}$) of salicylic acid for each individual subject before and after RYGB

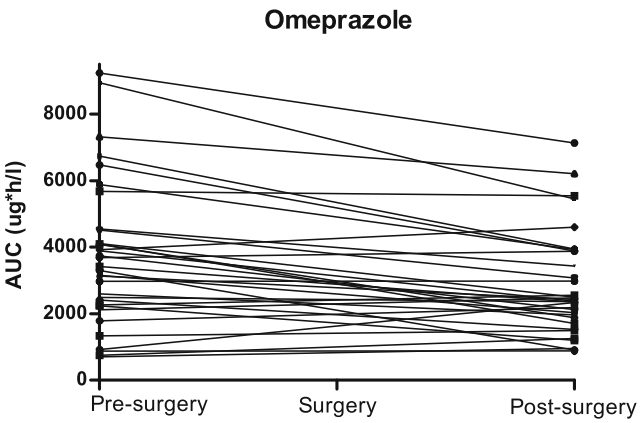

Fig. 5 Changes in area under the serum concentration versus time curve 0–12 h ($AUC_{0–12}$) of omeprazole for each individual subject before and after RYGB

Possibly, this can result in inadequate acid inhibition, leading to an increased risk of ulcerations. Symptoms in patients after RYGB could indicate insufficient exposure to omeprazole. In these cases, omeprazole dose could be increased after exclusion of other possible causes for lower exposure, such as drug-drug interactions.

Our study has some strengths and limitations. Compared to previously published articles describing drug absorption before and after RYGB, our study has a relatively large study population. Another advantage is the repeated measures study design, wherein the subjects act as their own controls to minimize variability between the pre-surgery and post-surgery situation. Because of the applied exclusion criteria, pharmacokinetics was not influenced by interacting medication. A possible limitation of our study is the determination of SA as a measure for ASA absorption. However, since ASA is readily and completely transformed to SA and no SA was measured in serum on $T=0$, we consider the SA serum concentration a good surrogate marker for ASA absorption. For ethical considerations, no dietary restrictions were imposed on the subjects during the study. Differences in food consumption might have influenced the rate of absorption for both drugs. However, dietary variation during the study reflects the reality, and therefore, our results can be extrapolated to daily practice.

In conclusion, our study shows a faster absorption of both ASA and omeprazole after RYGB. The exposure to ASA is higher post-surgery, but the standard dose of 80 mg once daily does not need to be modified. The exposure to omeprazole is, on average, lower after surgery. Clinicians should be aware to increase the dose of omeprazole if symptoms suggest inadequate response.

Acknowledgments The authors would like to thank Central Hospital Pharmacy, The Hague, Medical Centre Haaglanden, The Hague, and the Dutch Obesity Clinic West, The Hague for funding this study, Henk Trumpie for the analysis of the samples, and Anne Hanschke, Piet Sturm, Yolanda Ooms, and Caroline Wiersma for their contribution in performing the study.

Compliance with Ethical Standards

Funding This study was funded by Central Hospital Pharmacy, The Hague, Medical Centre Haaglanden, The Hague, and the Dutch Obesity Clinic West, The Hague.

Conflicts of Interest All authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Approval for the study was obtained from the local ethical committee of The Hague (METCZWH, The Hague, the Netherlands). The study was registered in the Dutch Trial Register (NTR3939).

Informed Consent Informed consent was obtained from all individual participants included in the study.

References

1. World Health Organization. WHO factsheet Obesity and Overweight. 1-1-2015. 13-9-2015. Ref Type: Online Source http://www.who.int/mediacentre/factsheets/fs311/en/.
2. Canadian Agency for Drugs and Technologies in Health. Bariatric surgical procedures for obese and morbidly obese patients: a review of comparative clinical and cost-effectiveness, and guidelines. 24-4-2014. 13-9-2015. Ref Type: Online Source http://www.ncbi.nlm.nih.gov/books/NBK264224/.
3. Edwards A, Ensom MH. Pharmacokinetic effects of bariatric surgery. Ann Pharmacother. 2012;46(1):130–6.
4. Padwal R. A systematic review of drug absorption following bariatric surgery and its theoretical implications. Obes Rev. 2010;11(1):41–50.
5. Yska JP, van der Linde S, Tapper VV, Apers JA, Emous M, Totte ER, et al. Influence of bariatric surgery on the use and pharmacokinetics of some major drug classes. Obes Surg. 2013;23(6):819–25.
6. Titus R, Kastenmeier A, Otterson MF. Consequences of gastrointestinal surgery on drug absorption. Nutr Clin Pract. 2013;28(4):429–36.
7. Sawaya RA, Jaffe J, Friedenberg L, Friedenberg FK. Vitamin, mineral, and drug absorption following bariatric surgery. Curr Drug Metab. 2012;13(9):1345–55.
8. Fuller AK, Tingle D, DeVane CL, Scott JA, Stewart RB. Haloperidol pharmacokinetics following gastric bypass surgery. J Clin Psychopharmacol. 1986;6(6):376–8.
9. Hamad GG, Helsel JC, Perel JM, Kozak GM, McShea MC, Hughes C, et al. The effect of gastric bypass on the pharmacokinetics of serotonin reuptake inhibitors. Am J Psychiatry. 2012;169(3):256–63.
10. Magee SR, Shih G, Hume A. Malabsorption of oral antibiotics in pregnancy after gastric bypass surgery. J Am Board Fam Med. 2007;20(3):310–3.
11. Prince RA, Pincheira JC, Mason EE, Printen KJ. Influence of bariatric surgery on erythromycin absorption. J Clin Pharmacol. 1984;24(11–12):523–7.
12. Roerig JL, Steffen K, Zimmerman C, Mitchell JE, Crosby RD, Cao L. Preliminary comparison of sertraline levels in postbariatric surgery patients versus matched nonsurgical cohort. Surg Obes Relat Dis. 2012;8(1):62–6.
13. Skottheim IB, Stormark K, Christensen H, Jakobsen GS, Hjelmesaeth J, Jenssen T, et al. Significantly altered systemic exposure to atorvastatin acid following gastric bypass surgery in morbidly obese patients. Clin Pharmacol Ther. 2009;86(3):311–8.
14. Wills SM, Zekman R, Bestul D, Kuwajerwala N, Decker D. Tamoxifen malabsorption after Roux-en-Y gastric bypass surgery: case series and review of the literature. Pharmacotherapy. 2010;30(2):217.
15. Rogers CC, Alloway RR, Alexander JW, Cardi M, Trofe J, Vinks AA. Pharmacokinetics of mycophenolic acid, tacrolimus and sirolimus after gastric bypass surgery in end-stage renal disease and transplant patients: a pilot study. Clin Transplant. 2008;22(3):281–91.
16. Rubio IG, Galrao AL, Santo MA, Zanini AC, Medeiros-Neto G. Levothyroxine absorption in morbidly obese patients before and after Roux-En-Y gastric bypass (RYGB) surgery. Obes Surg. 2012;22(2):253–8.
17. Hamilton R, Thai XC, Ameri D, Pai MP. Oral bioavailability of linezolid before and after Roux-en-Y gastric bypass surgery: is dose modification necessary in obese subjects? J Antimicrob Chemother. 2013;68(3):666–73.
18. De Smet J, Colin P, De PP, Ruige J, Batens H, Van NY, et al. Oral bioavailability of moxifloxacin after Roux-en-Y gastric bypass surgery. J Antimicrob Chemother. 2012;67(1):226–9.

19. Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie. KNMP Kennisbank. 1-9-2015. 13-9-2015. Ref Type: Online Source https://kennisbank.knmp.nl/.
20. Stichting Farmaceutische Kengetallen. Data en Feiten 2015. 1-8-2015. 13-9-2015. Ref Type: Online Source https://www.sfk.nl/nieuws-publicaties/data-en-feiten/data-en-feiten-2015.
21. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002;324(7329):71–86.
22. Hunfeld NGM. Clinical effects of proton pump inhibitors, Focus on pharmacogenetics, kinetics and dynamics. Rotterdam: Erasmus University Rotterdam; 2010.
23. D'Hondt MA, Pottel H, Devriendt D, Van RF, Vansteenkiste F. Can a short course of prophylactic low-dose proton pump inhibitor therapy prevent stomal ulceration after laparoscopic Roux-en-Y gastric bypass? Obes Surg. 2010;20(5):595–9.
24. Dallal RM, Bailey LA. Ulcer disease after gastric bypass surgery. Surg Obes Relat Dis. 2006;2(4):455–9.
25. Garrido Jr AB, Rossi M, Lima Jr SE, Brenner AS, Gomes Jr CA. Early marginal ulcer following Roux-en-Y gastric bypass under proton pump inhibitor treatment: prospective multicentric study. Arq Gastroenterol. 2010;47(2):130–4.
26. Kwaliteitsinstituut voor de gezondheidszorg C. NSAID-gebruik en preventie van maagschade. Van Zuiden communications BV; 2003. http://www.diliguide.nl/document/2188
27. van Schaik RH, Kok M, Sweep FC, van Vliet M, van Fessem M, Meijer-van Gelder ME, et al. The CYP2C19*2 genotype predicts tamoxifen treatment outcome in advanced breast cancer patients. Pharmacogenomics. 2011;12(8):1137–46.
28. Pharmachemie. SmPC Acetylsalicylzuur 80 mg. 3-10-2014. 13-9-2015. Ref Type: Online Source http://db.cbg-meb.nl/IB-teksten/h102651.pdf.
29. Tandra S, Chalasani N, Jones DR, Mattar S, Hall SD, Vuppalanchi R. Pharmacokinetic and pharmacodynamic alterations in the Roux-en-Y gastric bypass recipients. Ann Surg. 2013;258(2):262–9.
30. AstraZeneca. SmPC Losec MUPS 20 mg. 27-8-2014. 13-9-2015. Ref Type: Online Source http://db.cbg-meb.nl/IB-teksten/h21684.pdf.