

Carol Rees Parrish, R.D., M.S., Series Editor

Drug Therapy-Related Issues in Patients Who Received Bariatric Surgery (Part I)



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With the number of bariatric surgical procedures performed on the rise, clinicians will inevitably be involved in the care of patients who have received one of these procedures. How bariatric surgical procedures affect drug absorption has not been systematically investigated. This is part 1 of a two-article series that is aimed to address how pharmacotherapy is affected by bariatric surgery. The current article is aimed to provide a detailed review of process and factors that affect drug absorption from the gastrointestinal tract. The discussion may help clinicians better predict how bariatric procedures may affect oral drug absorption and pharmacotherapy.

INTRODUCTION

As the obesity trend continues to rise in North America, more people become eligible for bariatric surgery, since it remains to be the most effective therapy both in inducing, and maintaining, weight loss for patients with class II and class III obesity (i.e., BMI >35 and 40, respectively) (1–4). It is estimated that over 220,000 patients underwent

bariatric surgery in the United States in 2008 alone (5). This figure included only those patients who had bariatric surgeries performed in the United States alone. It is believed that many patients also seek treatment in other countries. Annually, it is expected that the number of bariatric surgeries performed will continue to increase worldwide. Based on these figures, clinicians will encounter patients with bariatric surgery, regardless of the practice setting.

How bariatric surgical procedures affect drug absorption has not been widely investigated. The quality of data in the existing literature is often poor (e.g.,

(continued on page 28)

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(continued from page 26)

small number of patients studied, surgical procedures not clearly explained, dosage forms used not characterized). In the older studies or case reports, surgical technique and procedures involved were often very different from contemporary practice. Since the anatomy of the gastrointestinal (GI) tract affects the process of drug absorption, speculating drug responses and dispositions based on data from dissimilar procedures may lead to inaccurate prediction. The objectives of this article are to review the process and factors that affect drug absorption from the GI tract, discuss the existing data, albeit limited, on how bariatric procedures affect pharmacokinetics, dispel misconceptions regarding how the bariatric procedures alter drug disposition, and discuss other pertinent pharmacotherapy-related issues in patients who have undergone bariatric surgery.

TYPES OF BARIATRIC SURGICAL PROCEDURE COMMONLY PERFORMED

All current bariatric surgical procedures that result in significant weight loss and sustained weight maintenance involve at least one of the following mechanisms: (1) malabsorption, which decreases the absorptive capacity of nutrients from the GI tract; (2) restriction, which involves limiting food intake. In the United States, the leading bariatric surgical procedures are Roux-en-Y gastric bypass surgery and adjustable laparoscopic gastric banding. This article will focus on the implications of these surgical procedures for drug therapy.

Roux-en-Y Gastric Bypass

Roux-en-Y gastric bypass (RYGB) is considered a combined restrictive and malabsorptive procedure, with the restriction component likely the primary mechanism in inducing weight loss. The procedure involves gastric volume reduction by creating a small gastric pouch typically between 15–30 mL by staple partition or staple transection of the stomach. A narrow anastomosis is formed between the pouch along the lesser curvature and the jejunum, usually divided 30 to 40 cm distal from the ligament of Treitz (Figure 1). This “bypassed limb,” also known as the alimentary

limb or the roux-limb, is the passage for foodstuff and other swallowed matter from the gastric pouch to the lower GI tract. The biliary limb, which includes remnant stomach, the intact duodenum and portion of the proximal jejunum where food is excluded, is reattached back to the jejunum distally through a jejuno-jejunal anastomosis. The purpose of this reconstruction is to allow the entrance of pancreatic enzymes, bile salts, and other enterohepatic hormones into the lower part of the GI tract (6–8). It is suspected that weight loss is achieved and maintained after RYGB by early satiety due to the small capacity of the stomach pouch. Additionally, incomplete digestion of food and mild malabsorption of nutrients through the exclusion of some functional absorptive units (duodenum, proximal jejunum) and poor mixing with pancreatobiliary secretions likely further contribute to weight loss.

Proximal RYGB is currently the most commonly performed version of this procedure. In proximal RYGB, the magnitude of malabsorption is likely limited because the typical length of the Roux-limb (i.e., the bypass limb) is between 75 and 90 cm with over two-thirds of the functional small intestine remaining fully intact. In some bariatric programs, distal RYGB is performed for more obese patients. The roux-limb of distal RYGB is usually over 150 cm. This leads to more significant nutrient malabsorption and should promote more significant weight loss. Nonetheless, micronutrient deficiencies are also more likely to occur with a longer Roux-limb.

The rate of weight loss after RYGB is usually very rapid. Maximal weight loss is commonly achieved within the first 2 years achieving up to 40% loss of original weight. According to the long-term data from the Swedish Obese Subjects Study Group, the average weight loss from RYGB after 15 years is close to 30%, which is significantly higher than banding (around 14%) and conventional therapy (2%). A survival benefit was also observed in RYGB recipients over those receiving conventional therapy (diet, exercise, lifestyle changes, and counseling) (9–11).

Laparoscopic Adjustable Gastric Banding

In principle, laparoscopic adjustable gastric banding surgery (LAGB) involves inserting a silicone band

lined with an inflatable donut-shaped balloon. The band is tied around the neck of the stomach about 1 to 2 cm below the gastroesophageal junction to create an approximate 30-mL upper gastric pouch. The liquid-filled balloon is connected to a port implanted under the skin of the abdomen. Adjusting the extent of inflation of the balloon affects the magnitude of gastric restriction and limits food intake (7,8,12,13). LAGB is a purely restrictive procedure. Reduced food and nutrient intake leads to nutritional deficiency. Nutrient malabsorption is not expected to play a role.

Compared with RYGB, LAGB is associated with slower rate of weight loss. The rate of weight loss peaks around the fourth or the fifth year after the procedure. The total percent of weight loss in year 5 may be up to

56%, which is comparable to RYGB; however, long-term efficacy data are not yet available (13–15).

UNDERSTANDING THE PROCESS OF DRUG ABSORPTION FROM THE GASTROINTESTINAL TRACT

By definition, a drug is considered 100% bioavailable if administered by the intravenous route. This is because all the drug molecules will enter the blood stream through direct injection, whether it is a bolus injection or continuous infusion, thus potentially allowing the entire dose to be available for therapeutic action. On the other hand, the bioavailability of a drug after oral administration, also known as oral bioavail-

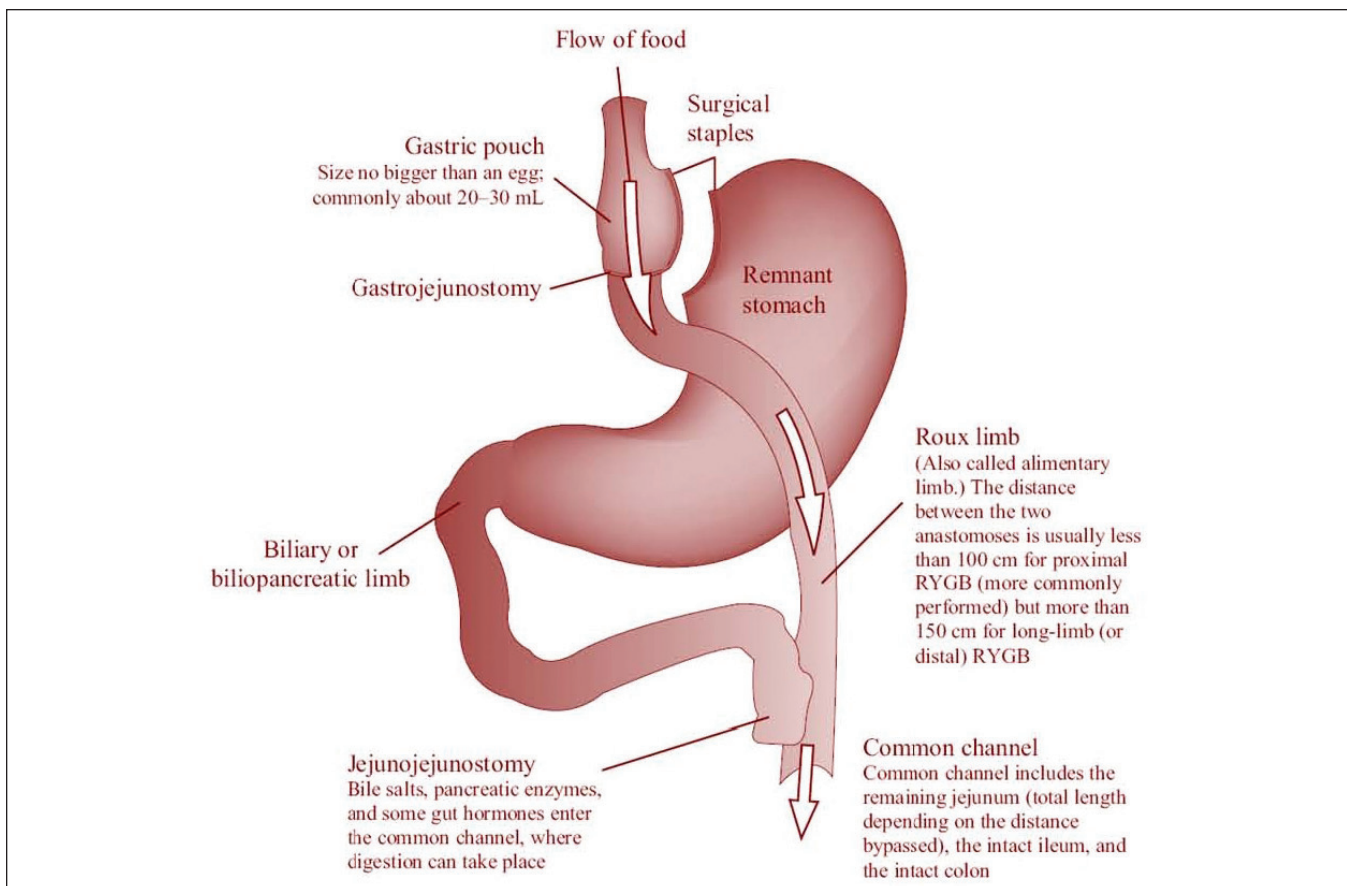


Figure 1. Illustration of contemporary proximal Roux-en-Y gastric bypass surgery. Reprinted with permission from Chan L, Downing J: Management of Patients Receiving Bariatric Surgery, In: Richardson MM, Chant C, Cheng JWM, Chessman KH, Hume A, Hutchinson L, et al., eds. Pharmacotherapy Assessment Program, 6th ed. Gastroenterology and Nutrition. Lenexa, KS: American College of Clinical Pharmacy, 2007, 67.).

ability, varies significantly and is affected by at least four main processes:

1. Disintegration and Dissolution

This process occurs primarily in the stomach. The presence of saliva, gastric acid, and the grinding-and-mixing action provided by gastric contractility helps dissolve and break down the size of the solid oral dosage forms, such as tablets, caplets, capsules, and powders (16). The presence of a lower pH is especially important for the dissolution of some drugs, as solubility is often pH dependent. For example, the dissolution rate of the antifungal agent itraconazole is extremely poor in the absence of gastric acid (17–20). Impaired dissolution may significantly decrease the oral bioavailability of some drugs. Disintegration and dissolution are important processes for oral absorption of drugs in solid dosage forms since large particle sizes are poorly absorbed across the GI epithelium. However, it is important to point out that disintegration and dissolution apply only to solid dosage forms. Oral solutions do not need to undergo dissolution as the drug molecules have already been dissolved. Therefore, lack of gastric acid usually has little impact on the oral bioavailability of liquid medications. Using itraconazole again as an example, its oral absorption is not affected by concurrent use of a proton-pump inhibitor when administered as itraconazole oral solution (19).

2. Passive Diffusion

The absorption process begins after disintegration and dissolution. Theoretically, drug molecules that are lipophilic and electrically neutral are more efficiently absorbed across the GI epithelium by passive diffusion. Passive diffusion of a drug may be affected by the luminal concentration of the drug (i.e., the dose), luminal pH, and the ionization state of the drug. The dose of the drug is usually the primary determinant of its luminal concentration. Luminal pH and the ionization state of the drug are often inter-related. Based on the relationship described by the Henderson-Hasselbalch equation, drugs that are weak acids are most likely in their electrically neutral (i.e., non-charged) state in the stomach where the pH is low; whereas

drugs that are weak bases are mostly in the electrically neutral state in the small bowel where the intestinal luminal pH is basic.

3. Transport Functions

The absorption efficiency of many drugs is affected by both efflux and uptake transporters. Uptake transport proteins facilitate the transluminal absorption of drugs into the systemic circulation. Efflux transport proteins export compounds that have already absorbed in the cytoplasmic region of the epithelial tissue back to the lumen, thus causing a negative effect on oral absorption. The oral absorption of a number of oral antibiotics, such as oseltamivir, valacyclovir, and some beta-lactam class of antibiotics, is greatly enhanced by the uptake transport protein PepT1 (21–23). On the other hand, intestinal efflux pumps such as P-gp and MRP acts to reduce the absorption of a larger number of drugs (24,25). There is regional difference in the distribution of these transporters along the GI tract. For example, PepT1 distribution and activity peak in the jejunum, whereas the expression of human peptide transporter 1 (HPT1), another important uptake transporter that regulates drug absorption, appears to be relatively uniform along the small and large intestine. For efflux transporters, the expression of P-gp appears to gradually increase from the jejunum toward the colon, whereas the expression of MRP2 is mostly limited to the jejunum (26). How bariatric surgery affects drug absorption depends on how the bypass or resected region of the intestine changes the overall activities of these transporters. For instance, our preliminary data suggest that proximal RYGB appears to have very limited effect on the oral absorption of digoxin, a drug transported by P-gp (27).

4. Pre-systemic Metabolism

This refers to the metabolism/biotransformation of certain drugs by the intestine and the liver before reaching systemic circulation. The intestine, especially small intestine, is a highly metabolically active organ (28,29). Many enzymes involved in drug metabolism are commonly present in the intestinal epithelial tissues. Bariatric surgical procedures that cause the flow

Table 1. Examples of drugs with significantly increased oral bioavailability when taken with food. Reduced food intake associated with bariatric procedures may decrease oral absorption of these compounds regardless of the surgery performed.

- Atovaquone (Mepron[®])
- Carbamazepine (Tegretol[®])
- Cefuroxime (Ceftin[®])
- Cefpodoxime (Vantin[®])
- Chloroquine (Aralen[®])
- Clofazimine (Lamprone[®])
- Ganciclovir (Cytovene[®])
- Griseofulvin (Grifulvin[®])
- Hydralazine (Apresoline[®])
- Itraconazole capsule (Spranox[®])
- Ketoconazole (Nizoral[®])
- Lithium
- Mefloquine (Larium[®])
- Methylphenidate (Ritalin[®])
- Nelfinavir (Viracept[®])
- Propranolol (Inderal[®])
- Propoxyphene (Darvon[®], other combination products)
- Ritonavir (Norvir[®], other combination products)
- Saquinavir (Invirase[®], Fortovase[®])
- Selegiline (Eldepryl[®])
- Spironolactone (Aldactone[®])
- Ziprasidone (Geodon[®])

of drugs to bypass the tissues with high metabolic activities can alter oral bioavailability.

Based on these characteristics, one may speculate that purely restrictive procedures, such as adjustable gastric banding and possibly sleeve gastrectomy, would have less impact on oral drug absorption, whereas malabsorptive procedures, such as biliopancreatic diversion or even distal RYGB, would be more likely to alter the magnitude and/or pattern of oral drug absorption. However, restrictive procedures can still indirectly affect oral bioavailability of drugs. With a successful restrictive procedure, food intake by the patient is significantly reduced postoperatively. If the absorption of a particular drug is dependent on food intake, reduced food intake may significantly alter its oral bioavailability. Our clinical experience also appears to confirm this. In a number of our patients, the daily doses of ziprasidone (Geodon[®]) needed to be

increased to maintain efficacy after LAGB surgery. Table 1 provides examples of drugs with increased oral absorption when taken with food. Extra caution and additional monitoring and assessment of treatment responses are recommended, especially if the patient has already established a stable treatment response towards these medications before bariatric surgery, as the oral bioavailability of these drugs may be negatively affected after bariatric surgery. The impact of combined restrictive and malabsorptive procedures, such as proximal RYGB, on oral drug absorption is particularly difficult to predict and information is lacking in the literature.

SUMMARY

Oral drug absorption is a complex process that is regulated by multiple factors. To more accurately predict drug responses after bariatric surgery, clinicians must have a reasonable understanding of each patient's anatomy and physiology of the GI tract after the surgery and the dosage form and pharmaceutical formulation of the medication to be used. In addition, it is also helpful to know how food affects the absorption kinetics of the drug independent of the GI anatomy. It is important to remember that GI tract surgery may significantly alter bioavailability, or simply change the pattern and rate of absorption without affecting the overall amount absorbed. ■

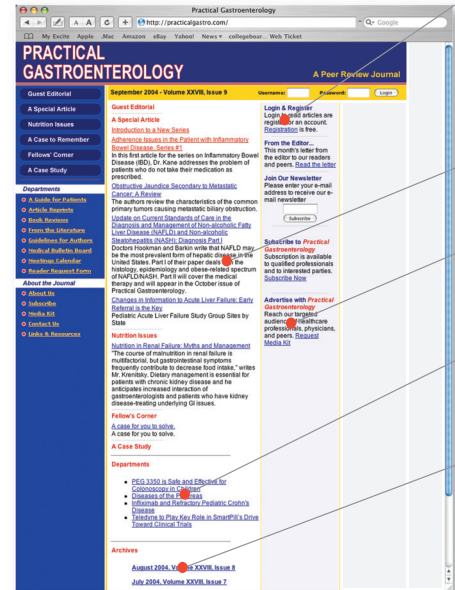
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