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

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

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This is part 2 of a two-article series that is aimed to address how pharmacotherapy is affected by bariatric surgery. The focus of this article is to review how each of the established bariatric procedures can affect pharmacokinetics based on information available in the literature. Other pertinent pharmacotherapy-related issues in patients with bariatric surgery, such as the risk of pill esophagitis, hormonal contraception, anticoagulant therapy, will be also addressed.

INTRODUCTION

In part I of this two-article series, the process of oral drug absorption was reviewed. It was concluded that in order to accurately predict drug responses after bariatric surgery, clinicians must take the following factors specific to the patient into account: the postoperative anatomy and physiology of the GI tract, the dosage form and pharmaceutical formulation of the medication to be used, and how food affects the absorption kinetics of the drug independent of the GI anatomy. This article will provide a comprehensive review of the published data in this area.

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PUBLISHED DATA FROM DRUG ABSORPTION STUDIES AND REPORTS IN PATIENTS WITH BARIATRIC SURGERY

There are very few clinical studies comparing the pharmacokinetics and pharmacodynamics of drugs before and after contemporary bariatric surgical procedures (i.e., proximal Roux-en-Y gastric bypass (RYGB), laparoscopic adjustable gastric banding (LAGB), sleeve gastrectomy). Historical data are available in the literature; however, the results are very inconsistent and difficult to interpret because: 1) most data were obtained from procedures currently no longer performed, such as jejunoileal bypass or vertically-banded gastroplasty; 2) the details of the bariatric procedures, such as the length of the GI tract bypassed, were not clearly described; and 3) in some studies, only combined results from several entirely different

Table 1.
Historical case reports and studies in oral drug absorption in patients with malabsorptive surgery (jejunoileal bypass (JIB) and gastroplasty. Note that the post-surgery anatomy of the GI tract of these procedures is different from RYGB. Results and findings may not be accurately extrapolated to recipients of RYGB or LAGB.

Drug affected	*Observed changes (Reference)*
Acetaminophen	Bioavailability unchanged after JIB (46 cm small intestine). (50)
Ampicillin	Bioavailability ↓ by 40% 2 weeks in patients with intestinal bypass (50 cm of small intestine remained). (51)
Cyclosporine	Reversal of JIB resulted in 3× ↑ in peak concentration and 20% ↓ in oral daily dose in a cardiac transplant patient. (52)
Digoxin	Absorption pattern and oral bioavailability unchanged after JIB (12 inches of jejunum connected to 6 inches of ileum with preserved ileocecal valve). (53)
Erythromycin	Variable changes in absorption in 6 patients with gastroplasty and 1 patient with RYGB (gastric pouch 50 mL, length of Roux-limb not reported). Overall a delayed absorption with an average of 41% reduction in absorption (range +57% to –90%). (54)
Ethambutol, isoniazid, and rifampin	Absorption adequate after JIB in 2 patients – 1 patient based on blood levels (rifampin and isoniazid); 1 patient based on resolution of symptoms of non-pulmonary tuberculosis. (55)
Hydrochlorothiazide	Urinary recovery of the drug ↓ by 31% after JIB (jejunum 40–55 cm; ileum 12–15 cm). (56)
Levonorgestrel, and D-Norgestrel	Absorption significantly reduced with peak concentration ↓ by 60% after JIB (jejunum 37 cm, ileum 12.5 cm) for levonorgestrel. (57)
	D-Norgestrel levels after JIB (small bowel 50 cm). (43)
Penicillin	Absorption ↑ by 100% based on 48-hour urinary excretion after JIB (46 cm small intestine). (50)
	Absorption not affected by stapled gastroplasty. (58)
Phenytoin	Absorption significantly ↓ after JIB in multiple patients. ↑ phenytoin dose by 75% Dosing in patients with 35 cm jejunum + 10 cm ileum. (59–61)
Propylthiouracil	No change in bioavailability and absorption pattern in up to 1 year after intestinal bypass (50 cm small intestine remained). (50)
Thyroxine	Severe malabsorption after JIB. (62,63)

bariatric procedures were published, which may be misleading (Table 1).

As of 2009, there are only a few full-length research articles and case reports published specifically in obese patients who have undergone RYGB surgery (Table 2) (1–8). Many of these reports did not include pre-surgical kinetic data for comparison, hence, the results are difficult to interpret. This confirms the scarcity of applicable information for the clinician in this area. Although a number of review articles have been published, the data and conclusions are not specific for contemporary bariatric surgical procedures; furthermore, details of the procedures are often not explained (9,10). At this time, careful and frequent monitoring of treatment responses and potential adverse events are strongly recommended. Patients and their care providers should be carefully educated about potential side effects and signs of treatment failure of the medications, along with the advice to inform their care providers about these symptoms and concerns at the earliest possible time.

EXTRAPOLATION OF DATA FROM OTHER GASTROINTESTINAL SURGICAL PROCEDURES

The surgical technique of Roux-en-Y anastomosis has been performed for decades. While this technique has recently become the most commonly adapted

Table 2. Summary of currently available pharmacokinetic/pharmacodynamic studies and reports in patients with contemporary bariatric surgical procedures.

Drug (Reference)	*No of patients*	*Length of Roux-limb*	*Reported changes*
Amoxicilin/ clavulanic acid (1)	1	Not reported	Possible treatment failure in a pregnant woman with repeated pyelonephritis.
Atorvastatin (2)	12	120 cm	Variable effects ranging from 3× ↓ to 2× ↑ in absorption. *(a)*
Haloperidol (3)	1	Not reported	No reference data for comparison; authors suggested that adequate absorption had taken place
Imatinib (4)	1	Sleeve gastrectomy only	↓ AUC by 45%, ↓ Cmax by 35%, suggesting decreased amount absorbed.
Mycophenolate (5)	4	Variable based on patients' weight in lbs. *(c)*	Significant inter- and intra-patient variability; reference data unavailable.
Sirolimus (5)	4	Variable based on patients' weight in lbs. *(b)*	Highly variable; overall lower AUC compared with historical kinetic data.
Tacrolimus (5)	5	Variable based on patients' weight in lbs. *(c)*	Reduced exposure of tacrolimus in RYGB patients compared with historical kinetic data. *(c)*
Tamoxifen (6)	3	Not reported *(d)*	↓ plasma tamoxifen concentrations compared with reference ranges.
Temozolomide (7)	1	Not reported	Absorption and total drug exposure were comparable to published reference values.
Warfarin (8)	1	Not reported *(e)*	Warfarin dose from 5–6 mg/day to 20 mg/day to maintain INR.

[a]Doses of atorvastatin used ranged from 20 to 80 mg.
[b]One-half the length being in the biliopancreatic limb and one half in the alimentary limb. For example, for a patient who weighs 300 lbs, Roux limb = 150 cm and biliopancreatic limb = 150 cm.
[c]Compared with historical data, RYGB patients received a lower doses based on dose per kilogram of total body weight.
[d]All three patients received partial gastrectomy and duodenal switch using the Roux-en-Y anastomosis. These procedures may cause a more significant malabsorptive effect than the currently performed proximal RYGB procedure.
[e]Patient received total gastrectomy and Roux-en-Y esophagojejunostomy secondary to gastric adenocarcinoma.

approach in bariatric surgery, it has also been used in the management of other GI diseases (e.g., gastric cancer, bile duct tumors) (11–13). Acetaminophen absorption kinetics, a marker to estimate gastric emptying rate, was performed in a study of patients who underwent gastrectomy for malignancy. In these patients, an esophageal jejunostomy was constructed using the Roux-en-Y technique. The results showed that the rate of acetaminophen absorption (administered as oral powder, mixed with a liquid meal) was significantly shortened in patients receiving this procedure, compared with healthy subjects (14). This observation was confirmed in our recently completed study in obese patients who received RYGB. Acetaminophen kinetics were determined preoperatively, as well as 3 months and 1 year after surgery. Acetaminophen was administered as oral liquid. We found that the mean peak acetaminophen concentration was nearly doubled

(continued on page 28)

(continued from page 26)

($p < 0.01$) following RYGB, and the mean time to peak concentration was significantly shortened, from about 45 minutes to around 10 minutes in both postoperative study visits (15). These preliminary results suggest that RYGB surgery is associated with a significant reduction of upper GI transit time, suggesting an increased risk of dumping.

PREDICTING THE IMPACT OF BARIATRIC SURGERY ON ORAL DRUG ABSORPTION: DOES THE ACIDIC/BASIC NATURE OF THE DRUG MATTER?

The impact of GI luminal pH changes on drug absorption can be unpredictable, especially for solid dosage forms (e.g., tablet, caplet). Although in principle, weak acids are less likely to be ionized in a low pH (acidic) environment that may favor their penetration across the GI epithelium, pH may also alter their solubility, depending on the physiochemical characteristics of the drug used. For example, the anti-cholesterol drug atorvastatin is a weak organic acid with a pKa of 4.46. Its solubility increases with higher pH, with an optimum solubility at pH of 6. Therefore, increased luminal pH may result in increased solubility of atorvastatin. However, this pH change also results in a shift of the equilibrium of atorvastatin toward the ionized form, which theoretically will have a reduced capacity for passive absorption across the membrane lipid of the intestinal epithelial cells (2,16). Therefore, the net effect of oral drug absorption, when given in solid dosage form, is highly unpredictable.

The notion that the acidic/basic nature of a drug determines how oral absorption is affected by luminal pH changes in the upper GI tract is further challenged by the results from historical studies conducted in patients with gastric surgeries. Oral absorption kinetics of an acidic drug, a neutral drug, and a basic drug were studied in patients with gastric or duodenal ulcer undergoing partial gastroduodenectomy with Bilroth I and jejunal transposition procedure, before and after their surgeries. In these studies, sulphafurazole was used as the acidic drug (pKa 4.8), quinidine as the basic drug (pKa 8.4), and isoniazid, a neutral drug, was used as the control. Regardless of their acidic/basic chemical nature, the rate of absorption for all 3 drugs was slightly increased with higher peak serum concentration attained. The change in absorption pattern was similar among the 3 drugs. The overall absorption, as estimated by the amount excreted in the urine, was comparable for sulphafenazole, but decreased for quinidine (17). These findings suggest that the achlorhydria (average postoperative basal gastric pH = 5.7) has little effect on the overall absorption of a drug, regardless of its acid-base profile. Another study conducted in patients undergoing antrectomy with gastroduodenostomy using similar design showed a delayed in oral absorption for all 3 drugs, although the postoperative change in absorption pattern was similar regardless of the acidic/basic chemical nature (18). The delayed in oral absorption is probably the result of the use of solid oral dosage form. Overall, these data suggest that the acidic/basic nature of the drug does not appear to predict the post-surgical absorption pattern. But the impact on oral drug absorption after bariatric surgery is affected by many factors and is difficult to predict. Data from these studies are more useful than those from other historical kinetic studies in patients with jejunoileal bypass or biliopancreatic diversion because the postoperative anatomy of the upper GI tract in these patients is more similar to those with proximal RYGB. Pharmacokinetic studies in patients with contemporary bariatric surgical procedures are desperately needed.

One issue that has not been addressed in any of published investigations and reports is the effect of dosage form. As discussed in Part I of this series, optimal absorption of solid dosage forms such as tablets and caplets requires the attainment of numerous favorable conditions to maximize disintegration and dissolution. On the contrary, fewer conditions need to be met for oral absorption of liquid medication. Using the before-and-after study design, our preliminary data suggests that the relative bioavailability of acetaminophen oral liquid was slightly increased after RYGB despite a significantly shortened transit time (15). Currently, studies aimed to compare the effect of dosage forms in RYGB patients are not available. But based on the principles of dosage form kinetics and our preliminary observation, a possible approach to maintain oral bioavailability after RYGB is to administered medications in liquid forms. Clearly, further investigations are necessary to confirm this hypothesis.

OTHER UNDER-INVESTIGATED ISSUES RELATED TO DRUG THERAPY

Use of Non-steroidal Anti-inflammatory Drugs (NSAID)

The chronic use of NSAID is associated with an increased risk for gastric ulcer. In post-bariatric surgery patients, there is evidence to suggest that NSAID use also increases the risk of marginal ulcerations (19). Marginal ulcers are GI ulcer of any depth in the jejunal mucosa, at or near the site of the gastrojejunal anastomosis. Marginal ulcers can develop at any time after RYGB. Its cause may be related to the surgery, such as disruption of the staple line, mucosal ischemia, or presence of foreign bodies (20–22). Non-surgery-related factors, such as smoking, NSAID use, or infection with *Helicobacter pylori*, can also contribute to the development of marginal ulcer (23–25). One study suggests that NSAID use may increase the risk of developing marginal ulcer by up to 11 times (25). Currently, there is no prospective study to assess the longitudinal risk of NSAID use after bariatric surgery. Further investigations are certainly needed.

Many bariatric surgery patients also have rheumatoid arthritis or osteoarthritis requiring chronic use of NSAID. At this point, clinicians should carefully weigh the risks and benefits of continuing NSAID therapy after RYGB (26). Concurrent use of a proton-pump inhibitor should be considered as this class of drugs has been shown to have a protective effect against peptic ulcer disease and marginal ulceration (25,27). Nevertheless, controlled trials are needed to determine the efficacy of proton pump inhibitors in this particular patient population and for this specific indication. Sucralfate is not expected to be effective for this indication, as it requires gastric acid and low luminal pH to be activated.

The Potential for GI Toxicity with Bisphosphonates After Bariatric Surgery

Esophageal injury has been reported with medications, especially with solid dosage forms (28–31). The factors that may affect the risk of developing pill esophagitis include the biochemical nature of the drug, the solubility of the ingredients in the pill, and contact time with the esophageal mucosal tissue (32). In bariatric surgery patients, the risk of pill esophagitis is increased if esophageal stricture, achalasia, or other factors that impair or obstruct the flow of swallowed material through the gastroesophageal junction are present. For instance, the contact time between the medication and the esophageal mucosa may be increased if the stoma of the adjustable gastric band is too tight, or if the gastrojejunal anastomosis is obstructed in a patient with RYGB surgery. The symptoms associated with pill esophagitis varies but may include odynophagia, dysphagia, or persistent retrosternal pain (32).

Pill esophagitis has been reported with the use of a number of drugs, including NSAID, some antibiotics (especially doxycycline), iron supplements, potassium supplements, phenytoin, and quinidine (30–32). But the most recognized agent is the bisphosphonate alendronate. Pathological evaluations from patients with alendronate-associated esophageal injury show inflammatory exudate and inflamed granulation tissue as characteristic of any ulcer site (33). The most recognized predisposing factors to the alendronate-associated esophageal injury include esophageal reflux, preexisting esophageal stricture, and esophageal obstruction of any kind leading to increased contact time between the drug and epithelial tissues, and incorrect administration technique of the medication. The bioadhesive characteristics of the dosage formulation may also play a role (34,35).

The use of bisphosphonate is particularly a potential concern for bariatric surgery patients. Weight loss increases bone demineralization (36–39). Together with decreased intake of micronutrients, particularly vitamin D and calcium, and possible malabsorption, the risk of developing osteoporosis after bariatric surgery is very high. Using bisphosphonates in addition to vitamin D and calcium supplementation may be beneficial in maintaining bone mass in post-bariatric surgery patients. However, if the post-surgical anatomy affects the smooth passing of the pill through the esophagus and the stomach, it can lead to serious adverse events. Therefore, clinicians should carefully weigh the risks versus benefits of oral bisphosphonate therapy in post-bariatric surgery patients before initiating therapy. Intravenous bisphosphonate therapy, such

as once yearly injection of zoledronic acid, can also be considered as an alternative therapy to minimize the risk of esophageal toxicity.

Oral Anticoagulant Therapy

Additional care and caution should be exercised in bariatric surgery patients with history of thromboembolic disorders requiring chronic warfarin therapy. Warfarin inhibits the synthesis of vitamin K-dependent coagulation factors. Therefore, in addition to the possible impact on oral bioavailability of warfarin, its clinical effects are also significantly affected by vitamin K intake. In bariatric surgery patients, especially during the early postoperative phase when oral intake is unstable, optimizing warfarin therapy to achieve stable international normalized ratio (INR) can be extremely challenging (8). Vomiting, variable intake of vitamin K-containing food, and changes in dietary habits may all affect the clinical effects of warfarin. More frequent monitoring of INR will be needed in these patients until oral intake becomes stable. During the period of unstable diet due to intolerance, postoperative GI complications, or poor dietary adherence, alternative antithrombotic therapy should be seriously considered. The antithrombotic agents with more established safety and efficacy profile in the bariatric surgery population include enoxaprin and unfractionated heparin. Both drugs are to be administered as subcutaneous injection and are available as prefilled syringes.

Hormonal Contraceptives

In obese women in childbearing age who are anovulatory (i.e., cessation of ovulation), weight loss often leads to restoration of ovarian function and improvement of menstrual cycle regularity (40-42). In sexually active women, these changes increase fertility, which may also lead to unplanned pregnancy. The most effective contraceptive approach for this patient population remains to be determined. The pharmacokinetics and pharmacodynamics of oral contraceptives have not been adequately evaluated in obese women. Studies in women with jejunoileal bypass surgery suggested that the overall absorption of estradiol, D-norgestrel, norethisterone and levonorgestrel is altered compared to non-operated morbidly obese women (43–46). However, similar studies have not been conducted in patients who received RYGB surgery. Therefore, whether RYGB surgery negatively impacts the efficacy of oral contraception is unknown. Although the absorption of implantable hormonal devices or transdermal patches should not be affected by bariatric surgery *per se*, obesity may affect the disposition of the drug (e.g., increased volume of distribution leading to lower plasma concentration of the hormone). Unfortunately, pharmacokinetic data for implantable and transdermal contraceptive devices are lacking in obese women. Based on limited available evidence, the efficacy of depot medroxyprogesterone acetate and combination contraceptive vaginal ring appears to not be affected by body weight. In the absence of established contraindications, these two products may be the preferred contraceptive agents for obese women (46–49).

SUMMARY

The impact of bariatric and other GI tract surgical procedures on oral drug absorption is under-investigated. The scarcity and significant limitation of the available published information greatly hinders their applicability in guiding patient management. At this point, practitioners should carefully monitor therapy in patients after RYGB or other bariatric procedures. Perform therapeutic drug monitoring whenever possible to optimize and stabilize the regimen. Thoroughly communicate with patients to watch for potential signs and symptoms related to sub-therapy or toxicity. While using oral liquids may be an option to minimize the potential for malabsorption, the bulkiness of the container may have a negative impact on medication adherence. Taking large volumes of oral liquid medication is also a potential concern for providing significant amounts of inabsorbable sugar such as sorbitol, which can contribute to dumping, diarrhea, and dehydration. Therefore, clinicians must carefully evaluate the regimens, dosage forms, and other therapy related issues such as cost, convenience, and palatability with the patient in order to optimize clinical outcomes. These concerns are not limited to medications, but vitamin and other micronutrient supplements as well.

Clearly, well-designed research in this area is necessary to address many of the concerns and to guide clinicians as to the best treatment approach. ■

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