

Medication and nutrient administration considerations after bariatric surgery

APRIL D. MILLER AND KELLY M. SMITH

Obesity in the United States is increasing at an alarming rate. Obesity, defined as a body mass index (BMI) ≥ 30 , affects approximately 50 million Americans.^{1,2} Of those, 12 million are morbidly obese (BMI ≥ 40). Morbid obesity is associated with many comorbidities (e.g., type 2 diabetes mellitus, hyperlipidemia, hypertension, obstructive sleep apnea, heart disease, stroke, asthma, degenerative joint disease, cancer, depression)¹ and can shorten life expectancy.^{1,2} Pharmacologic therapies, such as orlistat and sibutramine, produce only modest weight loss and have various adverse effects.³ Thus, radical and innovative treatments for obesity are often pursued.

The number of bariatric surgeries performed in the United States has increased dramatically. According to the American Society for Bariatric Surgery, an estimated 16,000 procedures were performed annually in the early 1990s, increasing to approximately 103,000 procedures by 2003.⁴ A recently published study demonstrated that patients who had undergone gastric bypass procedures were twice as likely to be admitted to the hospital in the year after surgery

Purpose. Medication and nutrient administration considerations after bariatric surgery are discussed.

Summary. Bariatric surgery is categorized by surgical technique (i.e., restrictive procedure or a combination of restrictive and malabsorptive procedures). Roux-en-Y gastric bypass is the most frequently performed bariatric surgery in the United States. Patients who have undergone this surgery are at risk for nutrient deficiencies. Several factors, such as pH and absorption sites, should be considered when providing these patients with appropriate supplementation. Drug solubility and surface area for absorption are also affected by gastric bypass procedures. By bypassing major portions of the small intestine, Roux-en-Y procedures drastically reduce the surface area for absorption. These changes may warrant manipulation in drug route or dose to ensure adequate delivery. Drugs with long absorptive phases that remain in the intestine for extended periods are likely to exhibit decreased bioavailability in these patients. The reduced size of the stomach after surgery can place patients at risk for adverse events associated with

some medications. Medications implicated in such adverse events include nonsteroidal antiinflammatory drugs, salicylates, and oral bisphosphonates. Drugs that are rapidly and primarily absorbed in the stomach or duodenum are likely to exhibit decreased absorption in patients who have had combination restrictive-malabsorptive procedures. Because reduced drug absorption may result in decreased efficacy rather than toxicity, increased patient monitoring for therapeutic effects can help detect potential absorption problems.

Conclusion. Selection of appropriate nutrient salts can improve nutrient replacement in patients who have undergone bariatric surgery. Changes in dosage forms based on drug characteristics can improve bioavailability.

Index terms: Absorption; Antiinflammatory agents; Bisphosphonates; Dosage; Dosage forms; Drugs, availability; Drugs, body distribution; Gastric bypass; Nutrition; Obesity; Salicylates; Solubility; Surface area; Toxicity

Am J Health-Syst Pharm. 2006; 63:1852-7

than in the year preceding it.⁵ Given the increase in bariatric surgeries performed, many health professionals have become involved in the

postoperative care of these patients. Concerns related to medication administration in the obese population and nutrient intake in patients who

APRIL D. MILLER, PHARM.D., is Critical Care Specialty Resident and Chief Resident, Department of Pharmacy Services, University of Kentucky Health Care, Lexington. KELLY M. SMITH, PHARM.D., is Associate Professor, Department of Pharmacy Practice and Science, University of Kentucky College of Pharmacy, Lexington.

Address correspondence to Dr. Smith at the Department of Pharmacy Services, University of Kentucky Chandler Medical Center, 800 Rose Street, C-117, Lexington, KY 40536-0293

(ksmit1@email.uky.edu).

Jillena Leonard and Kelly Barker are acknowledged for their assistance in preparing Table 1.

Copyright © 2006, American Society of Health-System Pharmacists, Inc. All rights reserved. 1079-2082/06/1001-1852\$06.00.
DOI 10.2146/ajhp060033

have undergone bariatric surgery are well documented.^{2,6-12} However, there is a paucity of literature on how to manage these concerns.

Literature review

A systematic search of MEDLINE (1966 to September 2005), International Pharmaceutical Abstracts (1970 to September 2005), and the Internet (through September 2005) for the terms gastric bypass, bariatric surgery, weight-loss surgery, medications, and absorption was conducted. Pertinent citations from retrieved articles were also reviewed for information. In addition, a number of weight-loss surgery center websites were examined to gain an understanding of the patient information provided. The lack of primary literature in this area necessitated the use of some review articles and meta-analyses. Information regarding the sites of absorption for specific drugs and nutrients was obtained from manufacturers and published data whenever possible.

Types of bariatric surgery

Bariatric surgery is categorized by surgical technique (i.e., restrictive procedure or a combination of restrictive and malabsorptive procedures).^{2,13,14} During restrictive procedures, a small pouch is created at the top of the stomach. Food passes through a small hole (≈ 1 cm) created at the bottom of the pouch and then through the remainder of the gastrointestinal tract. The smaller pouch limits the quantity of food that patients can consume, and the small opening slows emptying to create a prolonged sensation of satiety.^{2,13} Restrictive procedures include vertical-banded gastroplasty and adjustable gastric banding. With vertical-banded gastroplasty, a vertical section of the upper stomach is stapled to form a pouch. A small stoma is formed at the bottom of the pouch using a polypropylene band (Figure 1A).¹³ Adjustable gastric banding involves

placement of a silicone ring around the upper portion of the stomach. The diameter is adjusted by adding saline to partition off the stomach and create a small opening at the bottom (Figure 1B).¹⁴ Adjustable gastric banding has been widely performed in Australia and recently performed in the United States. Both procedures produce less dramatic weight loss than do combination procedures and are performed less commonly than combination restrictive and malabsorptive procedures in the United States.^{2,13,14}

The combination restrictive-malabsorptive procedures most commonly performed include biliopancreatic diversion and the Roux-en-Y gastric bypass. Biliopancreatic diversion involves removal of up to 75% of the stomach. The small intestine, which produces digestive enzymes essential for the breakdown and absorption of fats and proteins, is reconnected to bypass the duodenum, the jejunum, and all but the last 50–100 cm of the ileum. By bypassing a majority of the small intestine and limiting the amount of food exposed to digestive enzyme, very little consumed fat and protein are absorbed. While this procedure is very effective, the drastic reduction in functional intestine length places patients at high risk for nutritional deficiencies that can be difficult to replace and is generally reserved for patients with a BMI of ≥ 50 .^{2,13}

Roux-en-Y gastric bypass is the most frequently performed bariatric surgery in the United States (Figure 1C).^{2,13,14} The restrictive portion of the procedure entails separating, by stapling or transection, a 30–60-mL pouch in the stomach to restrict food intake. The small pouch produces much less gastric acid and has a higher pH than the stomach as a whole. The small intestine is cut 45 cm from the base of the stomach, and the lower intestine (termed the Roux limb) is connected to the pouch at the top of the stomach. The connection to the intestine is ≈ 1 cm

in diameter to slow emptying from the stomach and maintain a feeling of fullness for an extended period of time. The portion of the small intestine connected to the lower portion of the stomach is also connected to the Roux limb to allow some acid and digestive enzymes to reach passing food and facilitate digestion. By bypassing the lower stomach and a majority of the small intestine, malabsorption occurs.^{2,13} Patients who have undergone this surgery are also at risk for nutrient deficiencies. However, unlike with biliopancreatic diversion, supplementation can easily be achieved in these patients. Several factors, such as pH and absorption sites, should be considered when providing these patients with appropriate supplementation. Because this surgical approach is the most common and is associated with more pharmacologic issues, it is the primary focus of this article.

Drug absorption after bariatric surgery

The solubility of a drug, surface area for absorption, and blood flow to the gastrointestinal tract influence oral absorption and bioavailability. Drug solubility and surface area for absorption are affected by gastric bypass procedures. Drugs in aqueous solution are more rapidly absorbed than those in oily solutions, suspensions, or solid form.¹⁵ When medications are given as tablets, the times to disintegration and dissolution of the tablet affect absorption. In early drug trials, these factors are accounted and adjusted for to ensure adequate absorption in patients with unaltered gastrointestinal tracts. However, reductions in the amount of functioning gastrointestinal tract after gastric bypass surgery lead to decreased time to drug absorption and reduced drug bioavailability.

The solubility of drugs is affected by pH. Drugs that are more soluble at an acidic pH are absorbed in the stomach, and those soluble in al-

Figure 1A. Vertical-banded gastroplasty. A vertical section of the stomach is stapled to form a pouch. A small stoma is formed at the bottom of the pouch using a polypropylene band. Illustration by Marie Dauenheimer, CMI. Adapted, with permission, from Medscape General Medicine. www.medscape.com/viewarticle/471952.

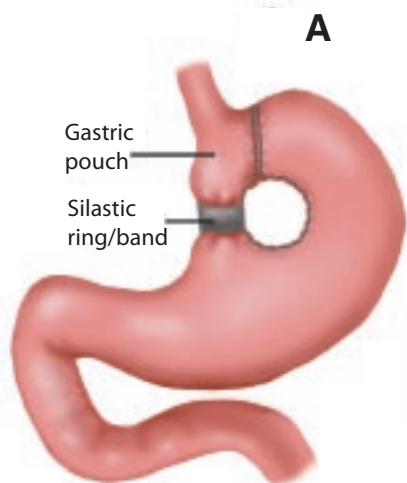


Figure 1B. Adjustable gastric banding. This involves placement of a silicone ring around the upper portion of the stomach. The diameter is adjusted by adding saline to partition off the stomach and create a small opening at the bottom. Illustration by Marie Dauenheimer, CMI. Adapted, with permission, from Medscape General Medicine. www.medscape.com/viewarticle/471952.

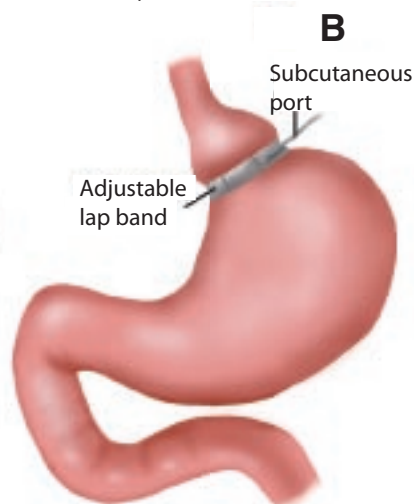
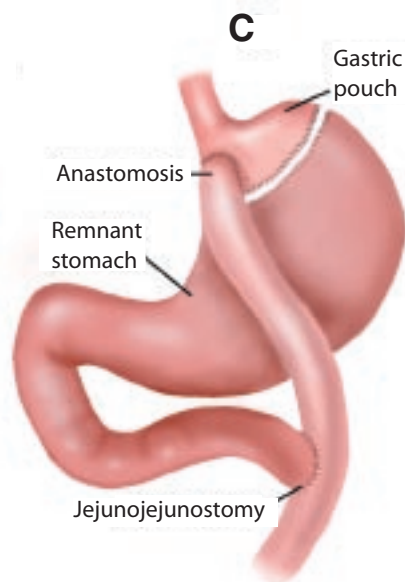


Figure 1C. Roux-en-Y gastric bypass. The small intestine is reconnected to bypass the duodenum, the jejunum, and all but the last 50–100 cm of the ileum. Illustration by Marie Dauenheimer, CMI. Adapted, with permission, from Medscape General Medicine. www.medscape.com/viewarticle/471952.



kaline environments are absorbed in the small intestine. In addition, some drugs depend on the enzymes in the small intestine to aid in their absorption. In patients who have had gastric bypass surgery, the small pouch located at the top of the stomach produces much less hydrochloric acid than the stomach previously did, possibly decreasing the absorption of medications dependent on acidic environments for solubility or absorption.

By bypassing major portions of the small intestine, Roux-en-Y bypass procedures drastically reduce the surface area for absorption. Villi and microvilli give the small intestine a much greater surface area than the large intestine.¹⁶ Thus, bypassing of the duodenum and jejunum represents a large loss of surface area for absorption. These changes may warrant manipulation in drug route or dose to ensure adequate delivery. Drugs with long absorptive phases that remain in the intestine for ex-

tended periods are likely to exhibit decreased bioavailability in patients who have undergone this procedure. Therefore, products with prolonged dissolution times, such as extended-release formulations, should be avoided in this population.

Considerations for nutrient replacement

Nutrient deficiencies in patients who have had restrictive procedures have been reported⁷; the exact prevalence is unknown. Because restrictive procedures retain the use of the entire gastrointestinal tract, nutrient deficiencies are less common than in patients who have had gastric bypass procedures. After gastric bypass procedures, patients are prone to deficiencies of the fat-soluble vitamins (A, D, E, and K) and calcium.^{7,8} In addition, these patients have an increased risk of developing anemia secondary to potentially inadequate amounts of iron, vitamin B₁₂, and folate. Because of these deficits, all patients should

receive a daily multivitamin and calcium supplementation indefinitely.^{7,8} In patients with anemia, additional supplementation with iron, vitamin B₁₂, and folate may be necessary. The specifics of these deficiencies have been discussed elsewhere.⁸

The partitioning of the stomach during bariatric surgery results in a dramatic decrease in the production of hydrochloric acid, affecting the absorption of calcium and iron. However, absorption can be increased by using different salt forms or manipulating gastric pH.^{7,8,17} Calcium carbonate depends on acid for its absorption; calcium citrate does not. One study comparing the bioavailability of both products in achlorhydric patients found the bioavailability of calcium carbonate and calcium citrate to be 4% and 45%, respectively.¹⁸ While calcium citrate is more expensive than calcium carbonate, it is logical to specifically recommend calcium supplementation with the citrate salt in this patient population.

Decreased calcium absorption can increase the risk of osteoporosis.¹⁹ While specific guidelines to monitor bone density do not exist for these patients, early bone densitometry testing would be prudent.

The duodenum is the primary site for absorption of iron and is bypassed in the Roux-en-Y procedure, creating the potential for nutrient deficiencies. To be absorbed, iron must be in the ferrous state (Fe^{2+}). However, most consumed iron is in the ferric form (Fe^{3+}) and reduced to the ferrous state in the acidic environment of the stomach. The ferrous form is then absorbed in the duodenum. In patients who have had gastric bypass surgery, iron salts can be combined with ascorbic acid (vitamin C) to acidify the stomach environment and facilitate absorption.^{17,20} There are commercially available products that combine these two nutrients.

Vitamin B_{12} absorption is dependent on the presence of intrinsic factor, which is produced in the parietal cells of the stomach. In addition, hydrochloric acid is necessary to cleave vitamin B_{12} from protein in the stomach. These variations can lead to deficiencies in patients after gastric bypass surgery.²¹ Monthly B_{12} injections are effective in this population; however, appropriate supplementation can also be achieved by using the oral formulation (1000 μg daily).²² This helps these patients avoid the inconvenience of frequent health care visits and the pain associated with injections.

Medication considerations

While very few specific recommendations on optimizing medication regimens exist for patients who have undergone bariatric surgery, some general guidelines can be formulated. The reduced size of the stomach after surgery can place patients at risk for adverse events associated with some medications. One case report described ulceration in a patient after gastric bypass and the use of

a nonsteroidal antiinflammatory drug.²³ Most bariatric surgery centers recommend that patients avoid the use of these agents indefinitely to avoid this potentially fatal complication.^{24,25} This complication theoretically extends to the salicylates. Given the lack of primary literature on this topic, the risks and benefits of daily aspirin therapy should be considered on an individual basis. Other options for oral pain medication include acetaminophen, opioids, and tramadol. The oral bisphosphonates are another class of medications that could present problems due to a reduced pouch size, which may increase the risk of gastrointestinal ulceration.²⁶ Since these patients can be at risk for osteoporosis because of decreased calcium absorption, other treatment options (e.g., calcitonin salmon nasal spray, synthetic parathyroid hormone [teriparatide], raloxifene [for women]) should be considered.

Reductions in drug absorption are more frequently encountered in patients who have had combination restrictive–malabsorptive procedures. Decreased intestinal length and surface area lead to the reduced absorption of extended-release drug preparations because these formulations are absorbed over 2–12 hours.²⁷ The reduction in functional intestine length makes it likely that extended-release preparations have passed through the gastrointestinal tract before absorption is complete. These same principles can also apply to delayed-release and enteric- or film-coated product formulations.²⁸ To overcome this problem, the immediate-release dosage forms should be substituted, which could require increased frequency of administration.

Other than extended-release preparations, changes in a patient's medication regimen are generally unnecessary unless patients have difficulties with decreased efficacy or increased adverse gastrointestinal effects. Consideration of the site of

absorption for specific medications can be helpful in determining whether reduced absorption is likely to occur (Table 1). Drugs that are rapidly and primarily absorbed in the stomach or duodenum are likely to exhibit decreased absorption in patients who have had combination restrictive–malabsorptive procedures. However, it is possible that compensatory absorption by other sites could mean that drugs are still adequately absorbed. Pharmacokinetic studies do not examine this particular effect, and it is generally unknown whether it will occur.

Because reduced drug absorption may result in decreased efficacy rather than toxicity, increased patient monitoring for therapeutic effects can help detect potential absorption problems. If appropriate doses appear to have little or no effect, the possibility of reduced drug absorption should be considered. A change to a liquid medication formulation could increase absorption by eliminating the need for drug dissolution. Other administration approaches, including subcutaneous, intravenous, rectal, vaginal, intranasal, and transdermal routes, should also be considered. However, it is important to consider the effect of obesity on drug absorption from subcutaneous or transdermal routes of administration. Increased monitoring is not effective in the management of potential reduced absorption of oral contraceptives. Obesity's link to infertility and the weight loss that occurs postsurgery could result in unwanted or unplanned pregnancy.²⁹ Therefore, nonhormonal, barrier contraception should be recommended for these patients.

Conclusion

Selection of appropriate nutrient salts can improve nutrient replacement in patients who have undergone bariatric surgery. Changes in dosage forms based on drug characteristics can improve bioavailability.

Table 1.
Selected Agents with Potential for Decreased Absorption in Patients Who Have Undergone Bariatric Surgery

Drug	Possible Site(s) of Absorption	Management
Enalapril	Hydrolyzed to active form, enalaprilat, in stomach; absorbed in small intestine ^a	May exhibit decreased activity; consider other angiotensin-converting-enzyme inhibitors
Ketoconazole	Likely absorbed in stomach because acidic medium required for absorption ^b	Absorption likely to be negligible; consider alternative agents ^c
Lamotrigine	Likely stomach and proximal small intestine due to rapid and complete absorption ^c	Monitor for and advise patients of decreased efficacy
Metformin	Slowly and incompletely absorbed in duodenum ^d	Increased monitoring of blood glucose; drug requirements can decrease as weight loss occurs
Metoprolol tartrate	Absorbed rapidly and completely, indicating stomach and duodenum ^e	Monitor blood pressure; medication requirements may decrease as weight loss occurs
Niacin	Primarily absorbed in duodenum ^f	Administer with low-fat snack to maximize absorption
Olanzapine	Stomach ^g	Monitor for decreased efficacy; switching to orally disintegrating tablet will not increase absorption (still absorbed in stomach)
Quetiapine fumarate	Exact location unknown, but likely stomach and duodenum due to rapid absorption ^h	Monitor for decreased efficacy
Ramipril	Unknown; decreased absorption documented in patients with steatorrhea and malabsorption ⁱ	Consider other agents; monitor blood pressure in the postoperative period; need for antihypertensives may decrease as weight loss occurs
Simvastatin	Absorption site unknown, but must be hydrolyzed to the active form in stomach ^j	Consider other agents; monitor serum lipids
Zolpidem	Absorbed rapidly and completely; absorption affected by food ^k	Absorption time may increase, resulting in delay to effect; take on an empty stomach

^aVasotec (enalapril) package insert. Morrisville, NC: Biovail Pharmaceuticals; 2002 Aug.

^bData on file. Janssen Pharmaceutica, Titusville, NJ.

^cLamictal (lamotrigine) package insert. Research Triangle Park, NC; GlaxoSmithKline; 2005 Aug.

^dVidon N, Chaussade S, Noel M et al. Metformin in the digestive tract. *Diabetes Res Clin Pract.* 1988; 4:223-9.

^eLopressor (metoprolol tartrate) package insert. Suffern, NY: Novartis; 2004 Nov.

^fData on file. Kos Pharmaceuticals, Cranbury, NJ; 2005 Aug.

^gData on file. Eli Lilly Pharmaceuticals, Indianapolis; 2005 Oct.

^hSeroquel (quetiapine fumarate) package insert. Wilmington, DE: AstraZeneca; 2005 Dec.

ⁱData on file. King Pharmaceuticals, Bristol, TN; 2004 Feb.

^jVickers S, Duncan CA, Chen IW et al. Metabolic disposition studies on simvastatin, a cholesterol lowering prodrug. *Drug Metab Dispos.* 1900; 18:138-45.

^kAmbien (zolpidem) package insert. New York: Sanofi-Synthelabo; 2004 Mar.

References

- Buchwald H, Avidor Y, Braunwald E et al. Bariatric surgery: a systematic review and meta-analysis. *JAMA.* 2004; 292:1724-37. [Erratum, *JAMA.* 2005; 293:1728.]
- Fussy SA. The skinny on gastric bypass: what pharmacists need to know. www.uspharmacist.com/index.asp?show=article&page=8_1438.htm (accessed 2006 Jun 29).
- National Heart, Lung, and Blood Institute. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report. www.nhlbi.nih.gov/guidelines/obesity/ob_gdlns.pdf (accessed 2006 Jun 29).
- Steinbrook R. Surgery for severe obesity. *N Engl J Med.* 2004; 350:1075-9.
- Zingmond DS, McGory ML, Ko CY. Hospitalization before and after gastric bypass surgery. *JAMA.* 2005; 294:1918-24.
- Livingston EH. Complications of bariatric surgery. *Surg Clin North Am.* 2005; 85:853-68.
- Brolin RE. Metabolic deficiencies and supplements following bariatric operations. In: Martin LF, ed. *Obesity surgery.* 1st ed. New York: McGraw-Hill; 2004:275-99.
- Ponsky TA, Brody F, Pucci E. Alterations in gastrointestinal physiology after Roux-En-Y gastric bypass. *J Am Coll Surg.* 2005; 201:125-31.
- Malone M. Altered drug disposition in obesity and after bariatric surgery. *Nutr Clin Pract.* 2003; 18:131-5.
- Kushner R. Managing the obese patient after bariatric surgery: a case report of severe malnutrition and review of the literature. *J Parenter Enteral Nutr.* 2000; 24: 126-32.
- Macgregor AM, Boggs L. Drug disposition in obesity and following bariatric surgery: a literature review. *Obes Surg.* 1996; 6:17-27.
- Heymol G. Clinical pharmacokinetics of drugs in obesity: an update. *Clin Pharmacokinet.* 1993; 25:103-14.
- Hydock CM. A brief overview of bariatric surgical procedures currently being used to treat the obese patient. *Crit Care Nurs Q.* 2005; 28:217-26.
- O'Brien PE, Brown WA, Dixon JB. Obesity, weight loss and bariatric surgery. *Med J Aust.* 2005; 183:310-4.

15. Benet LZ, Kroetz DL, Sheiner LB. Pharmacokinetics: the dynamics of drug absorption, distribution and elimination. In: Hardman JG, Limbird LE, eds. Goodman and Gilman's the pharmacological basis of therapeutics. 9th ed. New York: McGraw-Hill; 1996:3-27.
16. Rowland M, Tozer TN. Absorption. In: Clinical pharmacokinetics: concepts and applications. 3rd ed. Philadelphia: Lippincott, Williams, and Wilkins; 1995: 119-36.
17. Rhode BM, Shustik C, Christou NV et al. Iron absorption and therapy after gastric bypass. *Obes Surg.* 1999; 9:17-21.
18. Recker RR. Calcium absorption and achlorhydria. *N Engl J Med.* 1985; 313:70-3.
19. Nordin BE, O'Loughlin PD, Need AG et al. Radiocalcium absorption is reduced in postmenopausal women with vertebral and most types of peripheral fractures. *Osteoporos Int.* 2004; 15:27-31.
20. Harju E. Clinical pharmacokinetics of iron preparations. *Clin Pharmacokinet.* 1989; 17:69-89.
21. Behrns KE, Smith CD, Sarr MG. Prospective evaluation of gastric acid secretion and cobalamin absorption following gastric bypass for clinically severe obesity. *Dig Dis Sci.* 1994; 39:315-20.
22. Smith CD, Herkes SB, Behrns KE et al. Gastric acid secretion and vitamin B₁₂ absorption after vertical Roux-en-Y gastric bypass for morbid obesity. *Ann Surg.* 1993; 218:91-6.
23. Bielefeldt K. Not just an ulcer. Case-based learning in gastroenterology and hepatology: esophageal disorders. <http://web.archive.org/web/20040603153937/http://www.vh.org/adult/provider/internalmedicine/GICases/Esophageal/Ulcer/Ulcer.html> (accessed 2006 Mar 23).
24. Sapala JA, Wood MH, Sapala MA et al. Marginal ulcer after gastric bypass: a prospective 3-year study of 173 patients. *Obes Surg.* 1998; 8:505-16.25.
25. Northwest Center for Weight Management at St. Francis Hospital. Frequently asked questions. www.fhshealth.org/bariatric/faq.asp#meds (accessed 2005 Oct 11).
26. Fosamax (alendronate sodium) package insert. Whitehouse Station, NJ: Merck & Co. Inc.; 2005 Jul.
27. Franklin MR, Franz DN. Drug absorption, action, and disposition. In: Gennaro AR, ed. Remington: the science and practice of pharmacy. 20th ed. Baltimore: Lippincott, Williams, and Wilkins; 2000:1098-126.
28. Pinchiera JC, Prince RA, Mason EE. Effect of bariatric surgery on erythromycin absorption. *Am J Hosp Pharm.* 1981; 38: 232.
29. Raum WJ. Postoperative medical management of bariatric patients. In: Martin LF, ed. Obesity surgery. New York: McGraw-Hill; 2004:133-59.