Medications to Avoid After Bariatric Surgery

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Goals

- Goal 1: To provide an introduction of the physical changes that occur to the gastrointestinal tract after bariatric surgery.
- Goal 2: To describe the ways drug absorption is affected after bariatric surgery
- Goal 3: To provide recommendations for medication management based on theoretical and evidence-based medicine in patients after bariatric surgery

Introduction

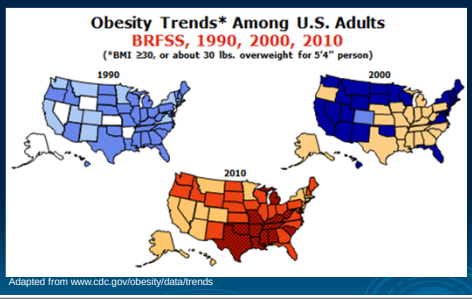
- Bariatric surgery has become the preferred therapy for severely obese patients who are refractory to traditional medical therapy.
- Traditional medical therapy is largely behavioral modification therapy +/- medications.
- Almost all weight loss medications reaching the market have been withdrawn due to increased cardiovascular risks

Obesity is epidemic

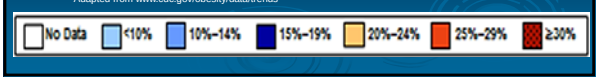
- Obesity affects over 300 million individuals worldwide.
- Over the past 20 years, the subgroup of obese considered 'severe' has nearly quadrupled throughout Northern America and Europe.
- In 2008, medical costs associated with obesity were estimated at $147 billion; the medical costs paid by third-party payors for people who are obese were $1,429 higher than those of normal weight.

Hossain P, Kawar B, El Nahas M. Obesity and diabetes in the developing world . N Engl J Med 2007; 356:213–215.
Centers for Disease Control and Prevention (CDC). Behavioral Risk Factor Surveillance System Survey Data. Atlanta, Georgia: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2008.

Obesity Trends



Adapted from www.cdc.gov/obesity/data/trends



Consequences of Obesity

Obesity is associated with extensive morbidity and premature mortality.

- Type 2 Diabetes
- Dyslipidemia
- Hypertension
- Obstructive sleep apnea
- Heart Disease
- Stroke
- Asthma
- Weight-bearing degenerative problems
- Depression
- Cancer

http://amyinohio.com/2008/09/

Relative Risk of Morbidities from Obesity

Greatly increased (relative risk >>3)	Moderately increased (relative risk 2-3)	Slightly increased (relative risk 1-2)
Diabetes	Coronary heart disease	Cancer postmenopausal women, endometrial cancer, colon cancer)
Gall bladder disease	Osteoarthritis (knees)	Reproductive hormone abnormalities
Hypertension	Hyperuricemia and gout	Polycystic ovary syndrome
Dyslipidemia		Impaired fertility
Insulin resistance		Low back pain
Breathlessness		Increased anesthetic risk
Sleep apnea		Fetal defects arising from maternal obesity

Bariatric Surgery

National Institute of Health recommendations for patients over age of 18:

Body Mass Index (BMI) greater than 40

Body Mass Index (BMI) greater than 35 + significant comorbidities

Types of Bariatric Surgery

Purely Restrictive
- Vertical-banded gastroplasty
- Adjustable gastric banding

Restrictive > Malabsorptive
- Roux-en-Y gastric bypass (RYGB)

Malabsorptive > Restrictive
- Biliopancreatic diversion

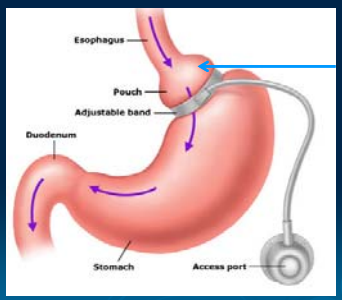
Purely Malabsorptive
- Jejunoilieal bypass
- Jejunocolonic bypass

Demand

- In 2008, over 350,000 procedures performed globally
- Most popular worldwide
  1. Adjustable gastric banding (AGB; 42%)
  2. Roux-en-Y gastric bypass (RYGB; 39%)
  3. Sleeve gastrectomy (SG; 5%) (14).
- Most popular in United States: Roux-en-Y

Buchwald H, Oien DM. Metabolic/bariatric surgery Worldwide 2008. *Obes Surg 2009;* ***19: 1605–1611.***

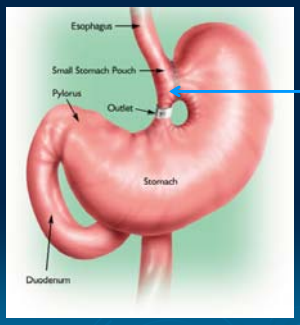
Adjustable Gastric Banding



Restrictive

http://www.ebariatricsurgery.com/adjustablegastricbanding.html

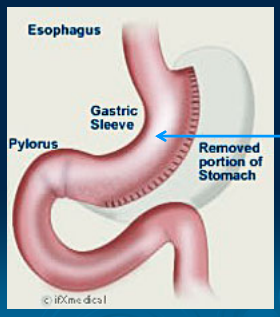
Vertical Banded Gastroplasty



Restrictive

http://ozobesitysurgery-info.webstarts.com/surgical_procedures.html

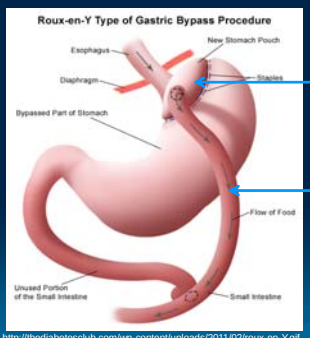
Sleeve Gastrectomy



Restrictive & Malabsorptive

gastricbypassfacts.com

Roux-en-Y Gastric Bypass



Restrictive

Malabsorptive

http://thediabetesclub.com/wp-content/uploads/2011/02/roux-en-Y.gif

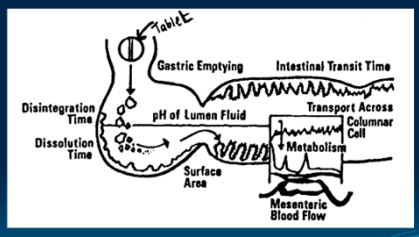
Efficacy for Weight Loss

Mean percentage excess weight loss:

- 61.2% - All Patients
- 47.5% - Gastric Banding
- 61.6% - Gastric Bypass
- 68.2% - Gastroplasty

Buchwald H, et al. Bariatric surgery: A systematic review and meta-analysis. *JAMA* 2004;14:1724-37.

Oral drug absorption is a prerequisite for pharmacological effects.



Passage of drug, administered via a tablet dosage form, through the gastrointestinal tract and the factors that contribute to the variability in drug absorption

Jambhekar Sunil, Clinical Pharmacokinetics Chapter 2, LECOM Bradenton 2008.

Drug Absorption

1. Disintegration
2. Dissolution
3. Gastric emptying
4. Intestinal transit time
5. Blood flow to gastrointestinal tract
6. Metabolism of drug within gastrointestinal tract

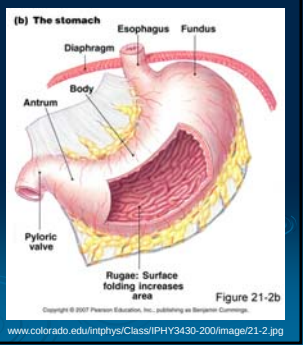
→ 1. pH of lumen fluid
2. Surface area

Miller AD, Smith KM. Medication and nutrient administration considerations after bariatric surgery. *Am J Health—Syst Pharm* 2006;63:1852-57.

Disintegration & Dissolution

Stomach

- Main role is to mix, reduce, & dissolve ingested food/drugs for delivery to the small intestine
- Not a major site of drug absorption except weak acidic drugs (aspirin)



www.colorado.edu/intphys/Class/IPHY3430-200/image/21-2.jpg

Post-Bariatric Surgery

Stomach

- Surface area reduced
  - Impaired drug disintegration/dissolution
- Loss of gastric acid production
  - Increased pH of stomach

Medications dependent on acidic pH for bioavailability:

1. Itraconazole
2. Ketoconazole
3. Atorvastatin

Chan LN. Drug therapy-related issues in patients who received bariatric surgery (Part I) *Pract Gastroenter* 2010;86:24-32.

pH-Partition Theory of Drug Absorption

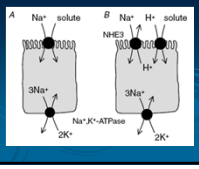
- The rate & extent of drug absorption (bioavailability) is dependent *only* on:

1. Drug pKa
2. pH at site of absorption
3. Partition co-efficient

- Weak acidic drugs are unionized/more lipophilic in stomach→ site of absorption
- Weak basic drugs are unionized/more lipophilic in small intestine→ site of absorption

Small Intestine

- Most important site of drug absorption in the body
- Villi & micro-villi (caves) = Huge surface area
- Presence of numerous drug influx and efflux pumps along lining of the small intestine
- Most recognizable, P-glycoprotein



Drug Transporters

Transport Protein	Drug substrates
PepT1	Beta lactam antibiotics, ACE inhibitors, antivirals
OATP2B1	DHEA, salicylate, valproate, pravastatin, atorvastatin, fexofenadine
PCFT	Folate, methotrexate, pemetrexed,

Post-Bariatric Surgery

- Roux-en-Y gastric bypass reduces small intestine length which dramatically reduces overall surface area
- Length reduction highly variable
- Drug transporter distribution heterogeneous and so drug absorption not predictable
- Complex pharmacodynamics

Clinical Translation

- Paucity of clinical studies comparing the pharmacokinetics/dynamics of medications pre- and post-bariatric surgery.
- Most clinical data was obtained from outdated bypass procedures
- Reduction of small intestine length and/or stomach size not consistently reported
- Lack of comparators in trials & case reports makes data interpretation difficult

Evidence-Based Medicine

Trial Design

- Comparison of acetaminophen pharmacokinetics/dynamics in subjects before, at 3 months, and 1 year after surgery
- Oral, liquid acetaminophen
- Post-surgery
  - Cp_{max} doubled ($p<0.01$)
  - T_{max} 10 minutes vs. 45 minutes
- Results consistent with a previous, analogous trial

Chan LN, Lin YS, Horn JR et al. The effect of proximal roux-en-Y gastric bypass surgery on upper gastrointestinal transit time: a pilot study. [Abstract]. *J Parentr Ent Nutr* 2010;34(2).

Clinical Translation

- Nutrient deficiencies
  - Most studied
  - Endocrine Society published guidelines in 2010 on the Nutritional Management of the Post-Bariatric Surgery Patient
- Medication pharmacokinetic data
  - Case studies
  - *In vitro* testing
  - Theoretical

Vitamin Supplementation

- Daily multivitamin and calcium supplementation with added vitamin D for all weight-loss surgery patients.
- Calcium citrate preferred
  - Salt is better absorbed in the absence of gastric acid production.

Saltzman E, Anderson W, Apovian CM, et al. Criteria for patient selection and multidisciplinary evaluation and treatment of the weight loss surgery patient. Obes Res 2005;13:234–243.

Osteoporosis

- Well documented, especially in women
- Several studies have documented the high incidence of secondary hypoparathyroidism (30-60%) at one year
- Medications contributing to hypocalcemia:

1. Loop diuretics
2. Carbamazepine
3. Oxcarbazepine

Larrad-Jiménez A, Díaz-Guerra CS, de Cuadros Borrajo P, et al. Short-, mid-and long-term results of L arrad biliopancreatic diversion. *Obes Surg* 2007;17:202–210.

Bisphosphonates

- Increased risk of esophagitis with adjustable gastric band
- Potentiates risk of developing malabsorptive hypocalcemia
- However, extensive weight loss leads to bone demineralization
- Risk vs. benefit
- Recommend once yearly IV zoledronic acid to minimize risk of esophagitis

NSAIDs

- Chronic use of NSAIDs increases risk of gastric ulcers
- 11-fold increased risk of ulcers with chronic NSAID use after bariatric surgery
- Recommendation: avoid use
  - topical alternatives (diclofenac gel, capsaicin, menthol, camphor)
  - Switch to another class of medications (tramadol)

Chan LN, Lin YS, Horn JR et al. The effect of proximal roux-en-Y gastric bypass surgery on upper gastrointestinal transit time: a pilot study. [Abstract]. J Parentr Ent Nutr 2010;34(2).

Gout

- Both surgery and weight loss after bariatric surgery increase risk of acute gout attacks
- Prophylactic gout therapies should be initiated prior to surgery to minimize risk
- Avoid medications known to precipitate gout
- Consider use of colchicine over NSAIDs for acute gout attacks

Friedman JE, Dallal RM, Lord JL. Gouty attacks occur frequently in postoperative gastric bypass patients. Surg Obes Relat 2008;Dis 4:11–13.

Warfarin

- Very close INR monitoring suggested in patients after bariatric surgery
- Unknown if warfarin bioavailability affected
- Vitamin K intake unpredictable
  - Diet restrictions post-operatively
  - Unstable diet
  - Change in eating habits
- Consider low-molecular weight heparins, which have established safety and efficacy in this population

Chan LN, Lin YS, Horn JR et al. The effect of proximal roux-en-Y gastric bypass surgery on upper gastrointestinal transit time: a pilot study. [Abstract]. J Parentr Ent Nutr 2010;34(2).

Case

- A 50-year-old, 250 lb woman suffered idiopathic proximal right popliteal and calf deep vein thrombosis (DVT) 3 years previously. Her warfarin has been managed successfully by a centralized pharmacist-run anticoagulation service, and she has easily achieved and maintained her target international normalized ratio range between 2.0 and 3.0. She has had no bleeding or thrombotic complications. The surgeon calls to notify you the patient will undergo RYGB surgery in two weeks. As a pharmacist, what will you recommend?

Warfarin

- One case report of warfarin resistance following RYGB.
- Chronic atrial fibrillation patient previously therapeutic (INR 2-3) on 5 mg warfarin daily required doses up to 20 mg/day after surgery in order to maintain INR goal.

Sobieraj DM, Wang F, Kirton OC. Warfarin resistance after total gastrectomy and Roux-en-Y esophagojejunostomy. *Pharmacotherapy* 2008; 28:1537-41.

Tamoxifen

- Three case reports documenting subtherapeutic tamoxifen levels in patients after RYGB.
- Therapeutic range 95-520 ng/ml
- Recommend steady-state tamoxifen levels or use of intravenous chemotherapy agents, when appropriate

Wills SM, Zekman R, Bestul D. Tamoxifen malabsorption after roux-en-Y gastric bypass surgery: a case series and review of the literature. *Pharmacotherapy* 2010;30(2):217.

Contraception

- Women of child-bearing age are advised to avoid pregnancy for up to 2 years post-surgery
- Evidence limited
- Efficacy of contraception medication has not been established
- Recommendation: IV, transdermal, intrauterine, or barrier contraceptive methods that do not rely on gut absorption

Paulen ME, Zapata LB, Cansino C, et al. Contraceptive use among women with a history of bariatric surgery: a systematic review. *Contraception* 2010;82(1):86-94.

Summary

In lack of evidence-based medicine to support safety & efficacy of a given medication, the pharmacist should:

1. Suggest an alternative dosage form that does not depend on gut absorption
2. Recommend liquid dosage forms whenever possible to avoid problems associated with drug disintegration and dissolution
3. Remember pharmacokinetics/dynamics of drug absorption
4. Use therapeutic drug monitoring to evaluate efficacy

Summary

5. Use medications that do not depend on food for bioavailability
6. Ask physican and/or patient for surgical details in order to make educated conclusions as to the degree of restriction and/or malabsorption
7. Remember that older studies are mostly based on outdated surgical procedures causing extensive malabsorption and should be interpreted with caution

True or False?

- True/False. A patient who has received a Roux-en-Y bypass procedure will have decreased surface area of the small intestine?
- Answer: True

- True/False. Calcium carbonate is the best choice for calcium supplementation in a patient after bariatric surgery.
- Answer: False, calcium citrate

True or False?

- True or False. Ketoconazole is a medication that relies on an acidic medium for absorption and so will have increased drug absorption necessitating dose reduction following bariatric surgery.
- Answer: False, decreased drug absorption possibly necessitating dose increase