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- Almost all weight loss medications reaching the market have been withdrawn due to increased cardiovascular risks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.

Obesity 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
Relative Risk of Morbidities from Obesity

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative Risk</th>
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</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Greatly increased (relative risk &gt;&gt;3)</td>
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<tr>
<td>Gall bladder disease</td>
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<tr>
<td>Hypertension</td>
<td>Slightly increased (relative risk 1-2)</td>
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<tr>
<td>Dyslipidemia</td>
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<tr>
<td>Insulin resistance</td>
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<tr>
<td>Breathlessness</td>
<td></td>
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<tr>
<td>Sleep apnea</td>
<td></td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>Greatly increased (relative risk &gt;&gt;3)</td>
</tr>
<tr>
<td>Osteoarthritis (knees)</td>
<td></td>
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<tr>
<td>Hyperuricemia and gout</td>
<td></td>
</tr>
<tr>
<td>Cancer, postmenopausal women, endometrial cancer, colon cancer</td>
<td>Greatly increased (relative risk &gt;&gt;3)</td>
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<tr>
<td>Reproductive hormone abnormalities</td>
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<tr>
<td>Polycystic ovary syndrome</td>
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<tr>
<td>Impaired fertility</td>
<td></td>
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<tr>
<td>Low back pain</td>
<td></td>
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<tr>
<td>Increased anesthetic risk</td>
<td></td>
</tr>
<tr>
<td>Fetal defects arising from maternal obesity</td>
<td>Slightly increased (relative risk 1-2)</td>
</tr>
</tbody>
</table>

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**
- Jejunostomal 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

Adjustable Gastric Banding

Vertical Banded Gastroplasty

**Sleeve Gastrectomy**

- **Restrictive**
- **Malabsorptive**

**Roux-en-Y Gastric Bypass**

- **Restrictive**
- **Malabsorptive**

**Efficacy for Weight Loss**

Mean percentage excess weight loss:
- 61.2% - All Patients
- 47.5% - Gastric Banding
- 61.6% - Gastric Bypass
- 68.2% - Gastroplasty

**Oral drug absorption is a prerequisite for pharmacological effects.**

**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

**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)
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


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

Drugs Transporters

<table>
<thead>
<tr>
<th>Transport Protein</th>
<th>Drug substrates</th>
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</thead>
<tbody>
<tr>
<td>PepT1</td>
<td>Beta lactam antibiotics, ACE inhibitors, antivirals</td>
</tr>
<tr>
<td>OATP2B1</td>
<td>DHEA, salicylate, valproate, pravastatin, atorvastatin, fexofenadine</td>
</tr>
<tr>
<td>PCFT</td>
<td>Folate, methotrexate, pemetrexed,</td>
</tr>
</tbody>
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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
  - Cpmax Goubled (p<0.01)
  - T_max 10 minutes vs. 45 minutes
- Results consistent with a previous, analogous trial


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.


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


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)
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


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


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.


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


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

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

5. Use medications that do not depend on food for bioavailability
6. Ask physician 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. 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