Clinical Pharmacology & Toxicology Pearl of the Week

~ Impact of Roux-en-Y Gastric Bypass on Drug Pharmacokinetics and Pharmacodynamics ~

Case:

- A 52 y.o. female with obesity had a remote vertical banded gastroplasty converted to Roux-en-Y gastric bypass (RYGB) due to refractory acid reflux, nausea, and vomiting.
- Comorbidities include OSA, T2D (A1c 6.3% on metformin, sulfonylurea, insulin), hypertension (ARB), dyslipidemia (rosuvastatin), GERD (pantoprazole), anxiety/depression (fluoxetine, bupropion XR). Supplements include calcium carbonate and vitamin D.
- Post-operatively had symptomatic hypoglycemia prompting insulin reduction, later her SGLT2 inhibitor was held after euglycemic DKA, and lastly had VTE and started warfarin.
- Her family physician asks if medications now need to be adjusted with her altered anatomy.

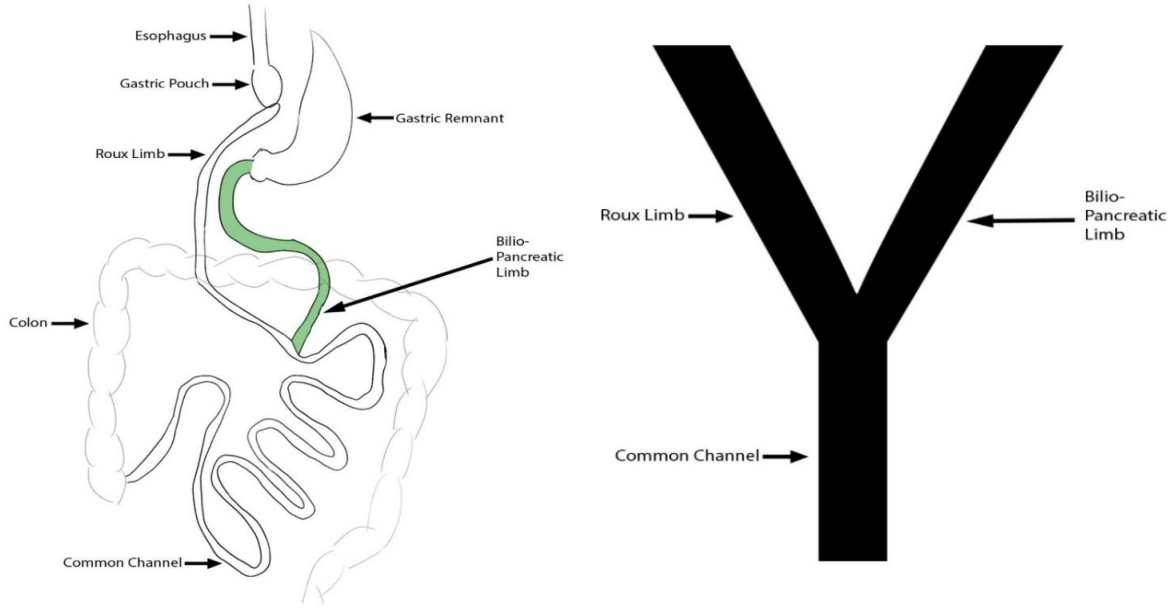
Background:

- An estimated one third of adult Canadians had obesity in 2022 and recent projections for the United States have estimated one half of adults will have obesity by 2030.
- Obesity and its well-known complications lead to significant morbidity and mortality with an estimated direct and indirect cost of $27.6 billion in 2023 in Canada (1% of our GDP).
- Surgical interventions including RYGB remain the most efficacious treatments for obesity although Canadian wait times are among the longest for surgically treatable conditions, averaging around 3 years or more pre-COVID. Incretin mimetics including glucagon-like peptide-1 (GLP-1) receptor agonists are revolutionizing the treatment landscape (Table 1).

Table 1. Efficacy and key considerations for select obesity interventions

Intervention Type	Avg. % Weight Loss	Key Considerations
Lifestyle	5–10%	Variable impact, needs sustained adherence
Pharmacologic	5–20%	Cost, side effects, requires chronic use
Tirzepatide (dual agonist)	~18%	Typical GLP / incretin adverse effects (mainly GI)
Semaglutide (GLP agonist)	~14%	Dose weekly, costly but cost-effective, retinopathy risk
Liraglutide (GLP agonist)	~5-8%	Dose daily, less costly
Naltrexone/bupropion	~5-8%	Opioid antagonism; GI distress, seizure, arrhythmia
Orlistat	~3-5%	Malabsorption, supplement vitamin D/E/A/K
Surgical	20-35%	- Outcomes influenced by centre expertise, volume - Surgical risk (leak, stenosis, marginal ulcers, VTE) - Malabsorption, requires vitamin/mineral supplement - Most durable
RYGB	~25-35%	
Sleeve gastrectomy	~20-30%	
Adjustable gastric banding	~15-20%	

Figure 1. Anatomy of the Roux-en-Y Gastric Bypass



Anatomic and physiologic changes of RYGB can affect drug absorption and metabolism, require titrating medications for comorbidities that improve with weight loss, and render unique considerations for the altered anatomy itself:

1. Loss of acidic environment needed for dissolution and absorption:
    a. *Note similarity to PPI effect, literature supports similar pharmacokinetic concerns*
    b. Examples:
        i. Calcium carbonate – rotate to calcium citrate (less pH dependent)
        ii. Iron – consider higher dose vs. polysaccharide form (less pH dependent)
        iii. Levothyroxine tab – may rotate to liquid form
        iv. Several azole antifungals – keto-, posa-, capsule itraconazole
        v. Certain kinase inhibitors – dasatinib for BCR/Abl in CML, gefitinib for EGFR mutated NSCLC, palbociclib for HR+ HER2- breast cancer
            - KI-PPI co-prescription linked to reduced survival for cancers listed

2. Loss of gastric fluid and transit time for dissolution and absorption:
    a. *Broadly relevant especially for enteric coated or sustained-release drugs*
    b. Examples:
        i. Psychiatric – duloxetine DR, bupropion SR/XL
        ii. Antihypertensives – nifedipine XL
        iii. Antiepileptics – carbamazepine XR, valproate ER, lamotrigine XR
        iv. Opioids - morphine ER, hydromorphone CR
        v. PPI – pantoprazole omeprazole etc. coated to pass inactivating gastric pH

3. Loss of bile acid lipid emulsification for absorption:
    a. Particularly important to solubility and absorption of lipophilic compounds
    b. Examples:
        i. Both warfarin, vitamin K (generally lower warfarin doses needed long-term)
        ii. Other fat-soluble vitamins D / E / A

iii. Calcineurin inhibitors (cyclosporine A, tacrolimus)
iv. Ezetimibe

4. Loss of absorptive area in the duodenum and proximal jejunum:
    a. *Broadly relevant for absorption of drugs, vitamins and minerals including the above*
    b. Examples:
        i. Most antihypertensives and other relevant drugs for obesity comorbidities
        ii. DOACs, hence typically avoided in favor of VKA, although apixaban has considerable absorption more distally in distal small bowel and colon
        iii. Multitude of water-soluble vitamins including vitamin B1 (thiamine)

5. Miscellaneous other potential pharmacokinetic changes can include:
    a. Bypassed carrier proteins (e.g. P-glycoprotein) affecting both drug efflux and influx
    b. Bypassed mucosal CYP metabolism counterbalanced by increased hepatic CYP metabolism following weight loss
    c. Increased bioavailability (rare) – e.g. metformin (not linked to lactic acidosis risk)
    d. Impaired vitamin B12 (cyanocobalamin) absorption due to reduced gastric intrinsic factor critical for terminal ileal absorption after pancreatic enzymes normally liberate cobalamin from salivary haptocorrin in the proximal small bowel

6. Weight loss following RYGB improves or induces remission for metabolic comorbidities:
    a. Half of patients discontinue antihyperglycemics (STAMPEDE) and antihypertensives (GATEWAY) if not reducing the number of agents needed in longitudinal follow-up

7. Unique considerations for RYGB anatomy
    a. Rapid transit into small bowel causes ethanol to be more rapidly absorbed and reaches higher peak concentrations, and non-absorbable sugar drug formulations may worsen dumping syndrome.
    b. Risk for marginal ulcers, particularly with irritants (e.g. NSAID, tobacco, alcohol), hence prophylactic PPI is usually prescribed for at least 90 days. GERD itself usually improves via multiple mechanisms and chronic PPI therapy merits reassessment.

Case Recommendations:

Applying the available data to the case at hand, the following was recommended:

1. Closely monitor for pharmacokinetic/dynamic changes after conversion to RYGB:
    - Type 2 diabetes: track point-of-care glycemia closely given she has already experienced hypoglycemia and may worsen with expected additional weight loss
        - Experts recommend large dose reductions if not discontinuing altogether:
            - Discontinue basal insulin < 30 units daily, reduce 50-80% if > 30 units, and utilize rapid-acting insulin until the new glycemic baseline is clarified
            - With A1c < 9% this patient can safely reduce to metformin monotherapy (note increased absorption after RYGB not seemingly clinically relevant)
    - HTN: similarly track BP, remain vigilant for overtreatment after additional weight loss
    - Dyslipidemia: adjust statin according to lipid panel and interval muscle symptoms
    - GERD: after minimum 90-day prophylactic PPI for marginal ulcer risk, reassess ongoing PPI prescription in likely situation that symptoms have improved

- Marginal ulcers: avoid potential irritants (NSAID, tobacco, alcohol, corticosteroids)
- Mood/anxiety: monitor for withdrawal syndrome or worsening mental health from likely reduced absorption of her fluoxetine and bupropion SR
- Nutritional: promote adherence to indicated multivitamin/mineral supplements
    - Including empiric switch to calcium citrate as per Canadian guidelines
- VTE: labile INR on warfarin to be monitored closely by anticoagulation clinic
- Counseling of increased ethanol toxicity risk with rapid transit and absorption

2. Drug absorption can be improved by rotating to faster release or liquid forms, crushing tablets, or opening capsules. This needs to be balanced with risk for adverse effects.
    a. E.g. risks of crushed bupropion SR (e.g. seizure, arrhythmia, GI distress) similar to IR formulation no longer marketed in Canada likely outweigh benefits if mental health is recently stable and without prior major safety concerns. If psychiatric symptoms worsen, SR tabs can be crushed and taken with water, max 150 mg/dose, 450 mg/d.
    b. If GERD persists, consider alternative PPI delivery e.g. crushed pantoprazole tablet, recognizing this might lead to some inactivation by residual acidic gastric fluid

References

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The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

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