Clinical Update: February 2023

IMPACTS OF BARIATRIC SURGERY

Bariatric Surgeries[1,2,6]

- Restrictive procedures
  - Sleeve gastrectomy
  - Gastric banding
  - Vertical banded gastroplasty
- Malabsorptive procedures – new pathways created
  - Roux-en-Y gastric bypass (RYGBP) = "gastric bypass surgery"
  - Single anastomosis gastric bypass
  - Biliopancreatic diversion and duodenal switch
  - Jejunoileal bypass

Restrictive procedures are aimed at altering the stomach to both reduce caloric intake and limit gastric volume to cause satiety. Malabsorptive procedures are different than restrictive procedures because the intestinal tract is altered to reduce intestinal mucosal area and to decrease nutrient absorption. These procedures also include limiting stomach size. For example, RYGBP restricts food intake by removing 45 cm of small intestine and connecting a new ~30 mL pouch directly to the lower intestine. This connection from pouch to intestine is 1 cm in diameter. RYGBP is one of the most frequently preformed bariatric surgeries in the United States.

General Effects of Bariatric Surgery on Medications

Pharmacokinetic changes are often underrecognized and must be considered following bariatric surgery. These may include significant changes to sites of absorption and/or metabolism.[3,4] Disintegration and dissolution of medications primarily occurs in the stomach followed by absorption in the intestines. Both are impacted following bariatric surgery from the decreased surface area in the small bowel.[3] Pre-systemic intestinal and hepatic metabolism (first pass metabolism) are bypassed in RYGBP which leads to higher oral bioavailability of medications. The predominant enzymes responsible for metabolism are cytochrome P450. CYP3A4 is the most abundant subfamily widely expressed in the duodenum and proximal jejunum and accounts for 80% of the total cytochrome P450 concentration in the proximal small intestine.[4] The impacts of the major presence of CYP3A4 may be significant as 50% of drugs are metabolized by this enzyme.

Post-operative Recommendations[5]

Immediately after surgery, it is recommended to restrict medication size for 2-6 weeks (note this may vary depending on procedure and surgeon preference; therefore, ask patient about specific instructions). To reduce medication size, most tablets must be crushed or converted to liquid formulations. Patients are encouraged to increase fluid intake following these procedures as well. Progression of calorie intake is slow as most patients do not reach 1500 kcal/day until 6 months following surgery.

Alcohol[6]

Patients who undergo RYGBP may be at an increased risk of developing alcohol use disorder (AUD). Substances which reach peak concentrations more rapidly are associated with a higher addictive potential. There is a reduced first-pass metabolism of alcohol due to reduced gastric alcohol dehydrogenase. Steffen et al. 2013 reported 0.3 g/kg of alcohol per actual body weight led to a mean blood alcohol content (BAC) of 43.4 $\pm$ 10.2 mg/dL one minute

post-drink, and a mean BAC of 86.8 ± 34.5 mg/dL (over the legal driving limit) two minutes post-drink. Patients who have undergone bariatric surgery should routinely be assessed for AUD.

Lithium[7-11]

Lithium, an FDA approved treatment of bipolar disorder, has a narrow therapeutic index and is a high risk for toxicity. [7] Musfeldt et al. 2016 reported lithium toxicity post RYGBP following conversion to liquid formulation. A pre-surgery level 0.61 mEq/L and a post-surgery level 1.51 mEq/L lead to symptoms of toxicity and the need for the dose to be reduced from 1200 mg/day to 600 mg/day, which resulted in a level of 0.54 mEq/L. [9-11] Alam et al. 2016 documented toxicity following sleeve gastrectomy that resulted in a level of 2.7 mEq/L, which ultimately lead to the patient needing emergent hemodialysis.[10] Jamison et al. 2020 case report showed toxicity following sleeve gastrectomy with baseline levels 0.62 mEq/L to post surgery levels of 1.63 mEq/L. The dose was reduced from 600mg/day to 300mg/day. Recommendations were to monitor lithium levels every 2-4 weeks until weight loss was stable or if symptoms of toxicity were present.[11]

Antidepressants[12]

Many antidepressants are absorbed in the duodenum and ileum which result in reduction of blood concentrations following bariatric surgery. Reports related specifically to duloxetine, sertraline, and escitalopram have shown decreased area under the curve (AUC) following RYGBP. Marzinke et al. 2015 reported escitalopram had 33% plasma concentration reduction 2 weeks following surgery with an additional 16-19% reduction at 6 weeks.

Ziprasidone[13,14]

Nepal et al. 2015 reported the first case of primary mania following bariatric surgery. Patient underwent RYGBP and developed mania 2 months following surgery. The patient was started on ziprasidone 80 mg/day which was then increased to 160 mg/day. The patient stabilized 7 days following hospitalization for treatment of mania. At a 3-month follow up appointment the patient had complete resolution of symptoms. Ziprasidone requires 500 calorie meals with each dose to be adequately absorbed, and RYGBP patients do not consume this type of caloric intake until 3-4 months post-op. It is crucial to understand the food requirements when dosing ziprasidone to avoid results similar to this clinical presentation.

Buprenorphine[15]

Krabseth et al. 2020 assessed the pharmacokinetics of buprenorphine after a 45-year-old patient underwent sleeve gastrectomy. The patient had a BMI of 23.8 kg/m^2 12 months post-surgery, compared to a BMI of 42.0 kg/m^2 at the time of referral. The patient's exposure of buprenorphine, which was expressed by an AUC, decreased by 43% and 42% which was measured at 1 month and 12 months respectively post sleeve gastrectomy. This change in concentration may be due to decreased oral pH seen post bariatric surgery, which may affect absorption of the patient's sublingual buprenorphine. The authors recommend monitoring for patients undergoing these types of surgeries for symptoms of abstinence.

Morphine[16,17,18]

Hachon et al. 2017 assessed the plasma levels of sustained release morphine and related metabolites in 12 patients that underwent RYGBP and compared these levels to 12 control subjects via LC/MS/MS. The patients that had undergone RYGBP 6 years prior (3.8-9.9) had a median BMI loss of 13.5 (7.4–20.5) kg/m^2 and a weight loss of 35.6 (19.1–56.1) kg. There were not statistically significant findings comparing the pharmacokinetics of the RYGBP group to the control groups, and no specific dose adjustment for morphine sustained release is necessary. The authors did point out that the RYGBP patients had increased drowsiness comparatively. Another study, Lloret-Linares et al 2017, evaluated the effect of morbid obesity on morphine glucuronidation. This study found that a

significant BMI decrease post-RYGBP resulted in increased Cmax ($p< 0.001$) and AUC ($p=0.001$) among 30 patients at 6 months post-op. These authors encourage morphine dose reduction for patients who are chronically receiving immediate-release oral morphine and who will be undergoing RYGBP.

Oxycodone[19]

Ladebo et al. 2021 evaluated the impact of RYGBP on oxycodone controlled-release and liquid formulations, showed a 14.4% higher bioavailability for post-RYGBP patients when compared to healthy volunteers ($P<0.001$). Additionally, post-RYGBP patients experienced a shorter absorption lag time of 11.5 minutes when compared to 14 minutes in health volunteers ($P<0.001$). It should be noted that there were no differences in reported side effects between both groups.

Methadone[20]

Strømmen et al. 2016 evaluated the pharmacokinetics of methadone in a patient post sleeve gastrectomy. The authors documented a decrease in T_{max} and an increase in the patient's exposure to methadone following the sleeve gastrectomy. The patient's methadone serum concentrations were followed for 7 months post-op and a 3-fold increase in AUC from baseline (14,368 nmol/L*h) to 7 months (44,983 nmol/L*h) was observed. This significant increase in AUC is likely due to the large increase in the bioavailability of methadone.

Summary

Bariatric surgery alters normal physiology of the gastrointestinal tract which may impact the period of detection of certain medications/substances in definitive testing leading to unexpected results. Medication pharmacology differs and patients may require a change in their medication management to overcome the factors related to their surgery. Clinicians must be cautious of changes in medication effects post bariatric surgery, which should encourage clinical monitoring. The clinical team at Aegis offers a role in helping clients understand the metabolic processes to provide safer medication management in addition to interpreting unexpected results.

NOTICE: The information above is intended as a resource for health care providers. Providers should use their independent medical judgment based on the clinical needs of the patient when making determinations of who to test, what medications to test, testing frequency, and the type of testing to conduct.

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