Effects of surgical changes in digestive system on the pharmacokinetic behaviors of orally administered drugs

Abstract

Bariatric surgery is considered an appropriate method in cases of obesity, such as severe or comorbidities obesity. However, the number of patients requiring bariatric surgery is growing at a constant and rapid rate. Opposing to that, anatomical modifications of the gastrointestinal tract often led to a significant alteration in the pharmacokinetics of orally administered drugs in terms of absorption of drugs and the bioavailability of oral medications required after the surgery. The present study investigates the correlation between reduced body mass following bariatric surgery and the bioavailability of orally administered drugs. Therefore, it is required to warrant through clinical studies that help establish guidelines related to common oral drugs prescribed and monitor the medications that exhibit a small therapeutic window that should be assessed, excluding the clinical endpoint. Furthermore, the use of pharmacokinetic modeling based on a mechanical method to simulate the multivariate nature observed while changes occur during the exposure of drugs will help to serve as an essential tool to understand further the trends in oral exposure of drugs in postoperative cases develop practical clinical guidance.

Keywords*: Bariatric surgery, Bioavailability, GIT, Pharmacokinetic.*

INTRODUCTION

In the last few decades, a continually growing number of people with obesity have been observed worldwide up to a critical point when the WHO officials have declared that obesity is a global epidemic. Obesity is defined in terms of (ex - body mass index (BMI)); the BMI equals body weight (kg)/height (m^2). The classification of people with heavy weights is arbitrary classified based on BMI index as 'overweight' (BMI ≥ 25 and <30 kg/(m)2), 'obese' (with BMI ≥ 30 and <40 kg/(m)2) as well as ' comorbidities of obesity (BMI ≥ 40 kg/(m)2) [1]. Comorbidities of obesity are defined as the condition close to being obese while suffering from associated comorbid conditions. Obesity is found to be more prevalent in the United States and Europe as compared to other countries. Therefore, to manage obesity, behavioral modifications and the use of oral drugs are used. However, such type of treatments is found to have limited effects. Consequently, bariatric surgery is considered to be a long-term solution for obese people [2].

Bariatric surgery is considered the only treatment for patients suffering from comorbidities of obesity (i.e., with a BMI of > 40), which helps produce lifelong weight loss [3]. Various metabolic surgical methods are used, such as restrictive bariatric surgery (also known as gastric banding) and restrictive or malabsorptive (gastric bypass). Out of such procedures, the Roux-en-Y restrictive or malabsorptive bypass is the most common technique. The association of comorbidities of obesity is found to be with several comorbidities and decreased life expectancy. The patients who undergo bariatric surgery have to gain more weight due to the use of multidrug for several medical comorbidities. Bariatric surgery has the property of influencing the comorbidities incidence and oral drug pharmacokinetics. Therefore, to accomplish optimal effects, change in pharmacotherapy is practiced in patients. Hence, after bariatric surgery, the use of oral drugs and their dosage and other forms are changed as per the adverse effects of the drug and to accomplish the optimal therapeutic effect. Alternate surgical procedures affect drug absorption factors, such as disintegrating and dissolving the drug and the absorption of drugs in the intestine; hence, the drug pharmacokinetics might change after the bariatric surgery in a patient. Such altered changes are due to the alterations in gastric mixing, emptying, and pH, which affect the absorption of oral drug formulations in solid form such as coated and release preparations in control form [4].

Types of Bariatric Surgery:

According to WHO statistics, higher than 1.9 billion people are found to be suffering from obesity. In 2014, the data revealed that about 13% of the world population is obese (11% are men, and 15% are women) [5]. The data also depicts that around 36 percent of obese women are present in the United States with a BMI greater than 40 kg/m^2, while 6 percent of morbidly obese women [6]. Furthermore, the comprehensive epidemiological data depicts that women above 20 years are obese, while males account for about 32.2 %. However, in France, the epidemiological data reveals that 32.3 percent of adults are overweight [7]. In the UK, the country reported the highest rate of obesity compared to other countries, *i.e.*, 24% of males and 25% of females in the age groups above 16 years as obese. Furthermore, bariatric surgery is found to be successful in treating comorbidities of obesity [8].

Various methods of bariatric surgery are present in healthcare, such as the adjustable gastric band (*i.e.*, AGBD), sleeve gastrectomy (also known as SG), biliopancreatic diversion (*i.e.*, BPD), and Roux-en-Y gastric bypass (*i.e.*, RYGB) [9]. Several other procedures are found to have been suppressed due to the adverse conditions produced during their use, including the jejunoileal bypass (JIB) procedure. However, the primary treatment for obesity and comorbidities of obesity is weight loss, and a slight decrease in weight can provide benefits related to various cardiometabolic risk factors. The treatment and management of obesity can be done with the help of calorie restriction, physical activity, pharmacotherapy, and bariatric surgery [10].

There are three most common types of bariatric surgeries, namely, gastric banding, the surgery is performed by implantation of an adjustable ring that helps in constriction of the stomach upper portion; sleeve gastrectomy, the surgery involves the use of a longitudinal resection which is in stomach greater curvature; and the Roux-en-Y gastric bypass (i.e., RYGB), in this surgery a small functional stomach pocket is created, and a bypass is done for most of the parts of the stomach, duodenum, and jejunum through directing contents inside the intestine from these regions towards an anastomosis along the lower part of the small intestine. All three surgeries have a common restrictive effect on the stomach, while in RYGB, an additional malabsorptive element also contributes to losing weight [11].

Pharmacokinetics of Drugs

The initial process in drug absorption is disintegration, which is the drug mixing in the stomach for drug dissolution. This process will be affected by bariatric surgery, subsequently, drug absorption since there is a reduction in the stomach. Therefore, patients have been advised for more chewing to compensate for the loss of disintegration that promotes absorption.

A previous study conducted post-gastric bypass found that ten of twenty-two psychiatric medications showed a reduction in the dissolution process [12,13]. In addition, the enterically coated drug absorption will be affected due to the impairment of the gastric emptying process. Moreover, hydrophobic drugs such as griseofulvin, wetted and solubilized by bile salts in the stomach, will reduce their absorption after surgery. Besides, the Bypassing effect of bariatric surgery may cause fluctuation in drug absorption as in cyclosporine.

Bioavailability

However, in malabsorption, certain drugs have poor bioavailability because of the reduced rate of dissolution. Similarly, the absorption of the lipophilic drug is altered by the low solubilized form of bile salt, and enterohepatic recirculation as the bariatric surgery causes a reduction in functional GI length, reducing the absorption of drug; however, it can be balanced by the adaptation of the intestine and mucosal hypertrophy to increase the capacity of drug absorption. Furthermore, bariatric surgery does affect drug pharmacokinetics, but only some clinical data is available [14].

Bariatric surgery is found to impose different types of physiological alterations that affect the oral drug bioavailability, which depends on the drug fraction absorbed in the intestine's gut wall, out of which some fraction escapes the metabolism of the wall. Some fraction of it escapes the hepatic metabolism. The fraction that escapes the metabolism of the wall and the drug fraction which is absorbed in the gut wall is highly influenced by the specific properties of the oral drugs, i.e., permeability and solubility, as well as the physiology of the GI tract, including the overall gastric emptying time, pH, transit time of the small intestine, metabolizing enzymes of the drug and the gastrointestinal efflux transporters. The emptying time is considered a rate-limiting step in medicines with high permeability and solubility because the drug absorption from the stomach is of a low level. The pH of the GI tract also affects drug dissolution in the case of drugs that are of permeability limited. The transit time of the small intestine influence the absorption of drugs that have low solubility [15].

The gut metabolism helps in the regulation of oral drug bioavailability as well as different xenobiotics, which is an essential determinant of the substrate drug metabolism. The drug-metabolizing enzyme, such as CYP3A4, is found in abundance in the gastrointestinal tract, followed by CYP2C9/19 in terms of their appearance order in GI. However, the presence of CYP3A4 and CYP3A5 is observed in the GI tract, while the expression of CYP3A4 is more along the jejunum, which tends to decrease along.

Ileum. The gastrointestinal transporters might have powerful effects on the absorption of oral drugs and the metabolism extent towards the gut with the help of active substrate efflux [16].

Oral Bioavailability Depends on Several Factors:

1. **Solubility and pH:**

   Any change in GI pH tends to affect the dissolution rate as well as intrinsic drug permeability. Therefore, the GI pH affects the absorbed dose fraction of the oral drug. However, medications with a weak base have high solubility in gastric fluids compared to the intestine. However, the medications with weak acid have low solubility in the stomach from which they are transported towards the less acidic intestine parts. However, the pH of GI fluid is acidic, which ranges from 1-2, and a slight decrease in the secretion of acid inside the stomach affects the oral drug absorption as they are less soluble at high pH because of the incomplete dissolution process [17]. As a result, the drugs with a weak base get full of charge and are highly soluble in water at physiological gastric pH. In contrast, oral medications with weak acid remain free from charge and are absorbed efficiently from the stomach.

   Further, it is well known that the orally administered drugs, which are weakly basic exist as free form and thus absorbed at intestinal pH. The standard bariatric surgery bypass helps decrease the HCl secretion inside the stomach. It has its activity on the charge carried by drugs based on the drugs' specific acid dissociation constant (pKa) [34]. The specific dissociation constant of a drug is an essential physicochemical parameter that influences several biopharmaceutical features. It helps to understand the mode of charge a drug will get at different pH range. The pKa also has powerful effects on the solubility and permeability of the drugs that, in turn, affect oral drug absorption. The increase in gastric pH reduces the solubility of basic drugs while increasing the solubility of acidic medications [18,19].

2. Gastrointestinal Transporters:

The bypass process tends to prevent intestine parts from absorbing, which helps decrease the transporters in GI. OATP1A2 is an organic anion transporter that shows its expression inside the duodenum and helps in diffusing hormones such as thyroid and steroid, fluoroquinolones, and statins. However, PEPT1 is an intestinal oligopeptide transporter that interacts with antibiotics, namely, beta-lactamines, some inhibitors, and some antineoplastic. The P-gp (also known as P-glycoprotein) helps in drug transportation, specifically on the epithelial cells of the jejunum and colon apical surface. P-gp is highly expressed in the ileum and colon and regulates digoxin, verapamil, and sotalol diffusion. CYP3A4 is a cytochrome that shows its expression inside the small intestine and duodenum. The total activity of CYP3A4 is expressed highly in duodenum and jejunum proximal end up to 25 – 45%. However, its overall abundance decreases after the RYGB surgery, up to 30 percent [20].

The Oral Bioavailability of Drugs Following Bariatric Surgery

Analgesics

The pKa of NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) range from 3-5 and have low solubility at normal gastric pH [20]. However, the drugs are highly soluble inside the intestine. The RYGB surgery modifies the gastric pH and tends to increase the drug solubility and a high ulcer risk. However, some alternative forms are used in place of NSAIDs, such as paracetamol (with a pKa of 9.5) and tramadol (with a pKa 9.4) in such patients. The alternates are used as they are absorbed inside the jejunum, which is not affected by the RYGB surgery [21,22].

Antibiotics

Several pharmacokinetics types of research have proven that several fluoroquinolones are easily absorbed inside the small intestine. From there, they are transported with the help of an organic anion transporting polypeptides (known as OATPs). In addition, a study emphasized the requirement for a lean body mass along with a single dose of moxifloxacin. Further, a reduced serum level of intravenous linezolid has been reported in a patient when administered after three months of bariatric surgery [23,24].

Anticoagulants

Bariatric surgery increases the sensitivity of warfarin when observed clinically through the requirement for a decrease in the warfarin dose postoperative to achieve optimal therapeutic effects or values. The mechanism behind such an observation is due to high alkalinity inside the

stomach, which increases the unionized form of warfarin, which will be absorbed through a passive process [2].

Psychotropic Drugs

The solubility of psychotropic drugs is altered after the surgery or gastric bypass; however, to understand the change in the bioavailability of oral medications, a clinical trial and the process to monitor the level of serum drugs is essential. It is recommended to provide the patients with multi-vitamins and oral calcium citrate that have gone through bariatric surgery [2].

Nutraceuticals:

Restrictive procedures are accompanied by nutrient deficiency and, to a lesser degree, compared to a patient who undergoes gastric bypass [25,26]. Gastric bypass surgery is associated with hypovitaminosis of fat-soluble vitamins (A, D, E, and K), Calcium, Vitamin B_{12}, Folic acid, and iron [27,28]. Therefore, the following recommendation for those patients are:

While Calcium carbonate absorption relies on acidic pH, calcium citrate does not. One of the studies in the field displays patients with achlorhydria; the bioavailability of calcium carbonate and calcium citrate were 4% and 45%, respectively. So, a calcium citrate supplement is a recommended rationale for those patients [29].

The Roux-en-Y procedure is accompanied by iron deficiency due to the absence of the duodenum as a primary site for iron absorption, manifested by iron deficiency anemia [30], and it will be corrected by intravenous (IV) administration [31]. However, adopting the IV approach as replacement therapy is impractical due to poor patient compliance. Therefore, it is highly recommended to use ascorbic acid with oral iron form as an acidifying agent to promote the formation of Fe^{+2} rather than Fe^{+3} (Fe^{+2} is the main absorbable form) [32,33]

Vitamin B12 depends on two factors: Intrinsic factor and Calcium. Intrinsic factors are released by parietal cells, and they will be diminished in bypass surgery. Although much evidence suggested that parenteral administration will correct it, parenteral administration is preferable only in acute cases and will be effective in the first two weeks. So, it is wise to adopt the methylated form of orally administered vitamin B12 (oral methylcarbylamine) as it enters passively without Calcium and/or intrinsic factor [34–36].

Malabsorption:

The procedures of bariatric surgical procedures are characterized as restrictive (based on physiological reduction in dietary intake) and malabsorptive in terms of the property of

decreasing the ability of the GI tract for the absorption of nutrients. Restrictive procedures include AGBD and SG, which tend to reduce the gastric capacity of the GI tract up to 15 ml to 20 ml and 60 ml to 80 ml [37]. The malabsorptive procedure, including JIB, causes bypass up to 91-95 percent of the small intestine, which retains the duodenum, jejunum, and ileum towards the terminal end. BPD-DS is also a malabsorptive procedure that causes a reduction in the gastric volume (i.e., up to 120–175 ml). It causes bypass in the small intestine, with the help of a formation of a biliopancreatic canal that transports the bile towards the ileum distal end. The RYGB technique works in a combination of restrictive and malabsorptive procedures, which leads to 16-30 ml of restriction of the stomach and causes the bypass of the small intestine towards the proximal end [10]

The oral drugs with the highest potential for malabsorption, specifically with the process of bypass inside the intestines, consist of those with low absorption and undergo enterohepatic recirculation. However, the bioavailability of oral medications is affected by the excellent intrinsic absorptive property of a drug—Metformin, a drug with high solubility and whose permeability is limited to the basic compound. The drug is uptake by an organic cation transporter inside the intestine, which results in the absorption, which is dependent on the dose, although and is excreted via the kidney. Thus, increasing postoperative bioavailability because of the alterations in the transit of the small intestine, decreased gastric emptying time, and the overall motility of the small intestine, leading to high-rate exposure towards the transporters such as enterocytic influx. Various surgical implications on the physiology of the gastrointestinal tract led to variable trends in the exposure of drugs post-surgery along with bariatric surgery.

Similarly, atorvastatin acid results in an increase in AUC after bariatric surgery. However, it has been discussed that the overall outcome of the common oral drug bioavailability in bariatric surgery is still unknown. Hence, oral drugs such as immunosuppressants and central nervous system active drugs that exhibit a small therapeutic range and display low measurable clinical endpoints will need a better monitoring method [11].

Pharmacomicrobiomics

The gut microbiota is many beneficial or harmless microorganisms that occupy the intestinal, reaching more than 1000 strains. They play essential roles in the human body in different aspects; for example, they protect competing with enteropathogenic organisms, stimulate the immune system, particularly in early childhood, and contribute to harvesting nutrients and

energy from food [38,39]. In addition, antibiotics consumption throughout life, breastfeeding time, and delivery type affect gut microbiota [40].

Gut microbiota profiles differ among obese and lean individuals, which can play an essential role in extracting and consuming energy or extracting and depositing energy in fat [41]. Also, the gut microbiota is considered a metabolic organ due to its role in human health, illnesses, and treatment. For instance, gut microbiota shows remarkable effects on drug metabolism either by activating or inactivating the pharmacological property of many drugs. Therefore a new term, "pharmacomicrobiomics," was claimed to indicate the influence of gut microbiota on pharmacokinetics and pharmacodynamics [42]. Furthermore, the effect of microbiota on pharmacokinetics can be achieved through different ways (i) producing microbial enzymes that transform drug molecules, (ii) manufacturing microbial metabolites to interfere with drug metabolism, (iii) modifying enzymes in host liver or intestine tissues [43–45].

However, several previous years have conducted several investigations to study the impact of gut microbiota on drug metabolisms; only about 40 drugs have been reported to be affected. In addition, the complications of gut microbiota and its connection with host metabolism make the particular roles and mechanisms of gut microbial modulation on drug metabolism still largely unexplored [43].

Several studies have shown that Bariatric surgery impacts the gut microbiota via making remarkable functional changes of the gastrointestinal tract, including altered bile acid flow, pH, hormones secretions, and gut motility [39],e.g., *Lactobacillus* and *Bifidobacterium* found to be decreased after RYGB surgery. At the same time, *Bacteroides*, *Alistipes*, and *Escherichia* were increased [40]. Therefore, Bariatric surgery can cause gut dysbiosis, which consequently can impact pharmacokinetics and pharmacodynamics.

CONCLUSION

It is to note that only a few clinical data are available on the pharmacokinetics and oral drug bioavailability following bariatric surgery. Therefore, every drug needs to be evaluated in terms of its absorption site and overall with the help of enzymes or GI transporters. Specific attention should be given to the factors that influence the effectiveness of the drug bioavailability. The oral drug bioavailability following bariatric surgery needs to be examined for every drug individually. However, keeping in mind the increase in bariatric surgical interventions (RYGB), the impact of such surgeries on drug pharmacokinetics is required to have a detailed examination

that will help guide the monitoring of the therapeutic drugs in patients suffering from obesity following bariatric surgery. Bariatric surgery results in the change of absorption of drugs and hence the bioavailability of drugs. Therefore, there is a need to have additional information on the impact of bariatric surgery on drug pharmacokinetics and oral drug availability and its role in clinical decisions.

Malabsorptive procedures should be given priority as they have theoretical potential in case of alterations in drug absorption. Standardization of the procedures of drug pharmacokinetic techniques, study subject's selection is required. The patients who have experienced the post-surgical routine will help to provide reassurance regarding bariatric surgery and the associated complications. Therapeutic drug monitoring is also recommended, and procedure-specific and study-specific to drug bioavailability are needed to ensure that the bariatric patients receive the related benefits of drug therapy.

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