Review Article

Oral Contraceptives after Bariatric Surgery

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Key Words

Bariatric surgery · Oral bioavailability · Drugs · Contraception · Obesity

Abstract

Objective: Bariatric surgery offers a highly effective mode of treatment for obese patients. Some procedures such as bypass cause an alteration in normal gastrointestinal tract with possible consequences for the uptake of orally administered drugs. **Methods:** We assessed the literature to ascertain whether the use of oral drugs and especially oral contraceptives is effective and adequate after bariatric surgery. **Results:** The bioavailability of drugs could be affected by the solubility and pH of the modified medium after bariatric surgery and by the loss of gastrointestinal transporters. Bariatric surgery could potentially result in a transient change in the absorption of drugs such as analgesics, antibiotics, antiarrhythmics, anticoagulants, psychotropic, and oral contraceptive drugs. Effective contraception is especially critical in the postoperative period, and implants might be representing a safe contraceptive method in women undergoing bariatric surgery. **Conclusion:** Each drug will have to be evaluated with respect to its site of absorption and its mechanism of absorption, with special attention on parameters influencing the effectiveness of the absorption processes.

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Introduction

The prevalence of obesity doubled worldwide since 1980. In 2014, more than 1.9 billion adults were overweight [1]. Of these, more than 600 million were obese. Overall, approximately 13% of the world adult populations (11% of the men and 15% of the women) were obese in 2014 [1]. In the USA, it was estimated that 36% of the adult women were obese, with a BMI higher than 40 kg/m², and 6% of the pregnant women suffered from morbid obesity [2–4]. Moreover, the data of the National Health and Nutrition Examination Survey of 2007–

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2008 showed that 10.4% of the teenagers (12–19 years old) are seriously obese ($\text{BMI} \geq 35 \text{ kg/m}^2$) [5]. Epidemiological studies showed that obesity in pregnant women increased significantly the incidence of diabetes, fetal growth restriction, complications of childbirth, prematurity, stillborn babies, and some congenital malformations [6–9]. To reduce these co-morbidities and ensure a significant and sustainable weight loss, bariatric surgery has become one of the preferred procedures over the last years [10–12]. Between 1998 and 2006, the incidence of the bariatric surgery in the USA increased by 800% (20,000 procedures in 1998 vs. 200,000 procedures in 2006), with 83% women being in childbearing age [13, 14]. Bariatric surgery also improved menstrual disorders and fertility [14, 15]. The American College of Obstetrical and Gynecology (ACOG) and the French National Authority for Health (HAS) published guidelines for the postoperative management of these patients and recommended taking contraceptives during 12–24 months after the intervention [16, 17]. In France, the national surveys on obesity (ObEpi) published epidemiological data every 3 years [18]. In 2012, 32.3% of adults were in overweight ($25 < \text{BMI} < 30 \text{ kg/m}^2$) and 15% were obese ($\text{BMI} \geq 30 \text{ kg/m}^2$). The gold standard surgical weight loss technique is a combination of restrictive and malabsorptive procedures such as gastric bypass (RYGB) and biliopancreatic diversion (BPD) [19, 20]. The RYGB procedure reduces gastric capacity by 95% and bypasses the proximal small intestine [21]. Although RYGB was found to be the gold standard procedure, the most commonly performed procedure in many countries is currently the sleeve gastrectomy [22, 23]. Laparoscopic sleeve gastrectomy is a restrictive procedure that is characterized by the removal of most of the fundus of the stomach without alteration of intestinal absorption; it is considered to be relatively safe with low morbidity [24–26]. The changes of the gastrointestinal tract resulting from such interventions are supposed to also affect the absorption of orally administered drugs. There is a lack of published information regarding the medication used, particularly that of oral contraceptives. Therapeutic failure may occur in significant morbidity and unintended pregnancy. Practitioners involved on the aftercare of patients treated with restrictive and malabsorptive procedures should therefore propose medication alternatives for orally administered drugs. Until pharmacokinetic clinical studies are completed, clinicians should consider the physiochemical properties of drugs, such as the acid dissociation constant (pK_a) and the partition coefficient ($\log P$), as well as the localization of intestinal drug transporters.

Factors Affecting the Bioavailability of Drugs

Solubility and pH

The rate of dissolution and intrinsic permeability of a drug may be affected by changes in gastrointestinal pH [27]. The pH of gastrointestinal fluid has been shown to significantly affect the fraction of the dose absorbed of a drug [28, 29]. Typically, weak base drugs are better dissolved in gastric fluids than in the intestine, whereas weak acid drugs are at a minimum dissolved in the stomach and transported to the less acidic regions of the intestine [30]. The pH of gastric fluid is typically acidic ranging from 1 to 2 [31]. A reduction of gastric acid secretion in the stomach significantly impaired oral absorption of basic drugs that show low solubility at high pH due to incomplete dissolution [32, 33]. At physiological gastric pH, weak-base drugs are fully charged and have a high solubility in water, whereas weak-acid drugs are fully uncharged and then absorbed more rapidly from the stomach. Weak-base drugs are predominantly absorbed from the intestine because they are uncharged at the intestinal pH of 8. The uncharged substances can pass through the mucosal lining of the gastrointestinal tract [19]. The standard bariatric surgery bypass reduces the hydrochloric acid secretion in the stomach and can act on the charge of the drugs depending of their specific

acid dissociation constant (pKa) [34]. The pKa of a drug is a key physicochemical parameter influencing many biopharmaceutical characteristics. This dissociation constant helps in understanding the charge mode a drug will take across a range of pH. The pKa influences solubility and permeability, which directly affects absorption. If the pKa of a drug is close to the pH of the medium, the molecule is charged and its gastrointestinal diffusion is delayed. In summary, increasing gastric pH should decrease the solubility of basic drugs and increase the solubility of acidic drugs [35].

Gastrointestinal Transporters

The bypass procedure excludes parts of the intestine from absorption, thus decreasing the number of transporters. The organic anion transporter OATP1A2 is expressed on the duodenum and acts on the diffusion of thyroid hormones, steroid hormones, fluoroquinolones, or statines [36, 37]. The intestinal oligopeptide PEPT1 transporter interacts with some antibiotics such as beta-lactamines, the angiotensin converting enzyme inhibitors, the thrombin inhibitors, and some antineoplastics [38–41]. The P-glycoprotein (P-gp) plays an important role for the transport of drugs, particularly on the apical surface of the epithelial cells of the jejunum and colon. It also interacts moreover with the diffusion of digoxin, verapamil, diltiazem, and sotalol [42]. P-gp expression level is lowest in the duodenum and highest in the distal ileum and the colon [43]. Cytochromes P450, glucuronyltransferases, sulfotransferases and glutathione-S-transferases are the enzymes present at the enterocytes of the gastrointestinal tract. The cytochrome CYP3A4 is expressed along the entire small intestine, with slightly increased expression from the duodenum to the middle section of the jejunum and a gradually reduced expression in the distal jejunum and ileum [44]. The duodenum and proximal jejunum account for 20–40% of the total intestinal CYP3A4 activity. Its abundance after RYGB is estimated to decrease by 30% [45].

Bioavailability of Drugs after Bypass

Analgesics

The non-steroidal anti-inflammatory drugs (NSAIDs) have pKa in the range of 3–5 and thus are characterized by poor solubility in the stomach at typical gastric pH [46, 47]. These drugs are soluble in the intestine [46]. However, the modification of gastric pH by RYGB procedures increases the solubility of these drugs with a greater risk of ulcer. The use of paracetamol (pKa of 9.5) or tramadol (pKa 9.4) is regarded as an alternative for the use of NSAIDs in these patients [48, 49]. As paracetamol is mainly absorbed in the jejunum, this pathway is not affected by RYGB [48]. The plasma concentrations area under the plasma concentration time curves and urinary recovery were similar before and after bypass surgery, and the absorption pattern was essentially the same as in non-obese control subjects [48].

Antibiotics

Early pharmacokinetic research has shown that some fluoroquinolones are absorbed efficiently from the small intestine and transported by organic anion transporting polypeptides (OATPs) [50]. Colin et al. [51] investigated adequate moxifloxacin concentrations using a population pharmacokinetic analysis and pharmacokinetic-pharmacodynamic simulations in post-bariatric surgery patients. When considering the targets for suppression of bacterial resistance formation, even at minimal inhibition concentration values as low as 0.25 mg/l, standard moxifloxacin dosing does not attain adequate levels in this population. The authors emphasized the need for lean body mass individualized dosing of moxifloxacin. A case of malabsorption after oral administration of amoxicilline and nitrofurantoin exemplified this

dilemma of gastric bypass in a pregnant patient with urinary tract infection [52]. The urinary tract infection was ultimately resolved by intravenous ceftriaxone injections. A recent study characterized the pharmacokinetics of intravenous and oral linezolid before and 3 months after RYGB surgery [53]. The bioavailability of the drug was not impaired with a mean of 1.14 (0.816–1.47) before and 1.14 (1.01–1.26) after RYGB. The mean AUC with oral linezolid before RYGB was 41.6 mg.h/l compared with 98.9 mg.h/l after RYGB ($p < 0.001$). The serum exposure of the drug was more than 50% lower after bariatric surgery suggesting that dose modification may be needed.

Antiarrhythmics

Chan et al. [54] compared the pattern and magnitude of oral absorption of digoxin in obese patients before and after RYGB. The median time to peak concentration for digoxin decreased from 40 min at baseline to 30 and 20 min at 3 and 12 months after RYGB, respectively. The mean AUC for digoxin, heart rate, and electrocardiogram patterns were similar across the study phases.

Anticoagulants

A recent study quantified the change in weekly warfarin dose after RYGB in patients requiring long-term warfarin therapy [55]. In the bariatric surgery group, 74.1% of patients experienced a decrease that was 20% or more of the preoperative dose compared with 32.2% of control group patients. This study reported that bariatric surgery could result in a transient increase in warfarin sensitivity manifested clinically by the need for a significant reduction in the postoperative warfarin dose required to achieve therapeutic INR values. The suggested mechanism behind this observation was a more alkaline stomach pH value resulting in more unionized warfarin available for passive absorption [56].

Psychotropic Drugs

Many gastric bypass patients have psychiatric illnesses that are treated with medication preoperatively, but there are few data to guide psychiatric drug dosing postoperatively. Chan et al. [54] compared the pattern and magnitude of oral absorption of midazolam in obese patients before and after RYGB. The peak plasma concentration (C_{max}) of midazolam increased by 66% and 71% at 3 and 12 months after RYGB, respectively, whereas the median time to peak concentration was reduced by 50%. Midazolam is a CYP3A4 substrate with a high extraction rate which was further increased after RYGB. Seaman et al. [57] developed an in vitro drug dissolution model to approximate the gastrointestinal environment of the preoperative and post RYGB states. Psychiatric medication tablets were placed in the two environments, and the weights of the dissolved portions were compared. Within the antidepressant class, the dissolution of citalopram and venlafaxine did not differ between conditions but antidepressant medications such as amitriptyline, fluoxetine, paroxetine, and sertraline dissolved less in the RYGB model than in the control model. With respect to anxiolytics and sedatives (buspirone, diazepam, lorazepam, trazodone, zolpidem), there was no difference in the two environments. The dissolution of the antipsychotics haloperidol and oxcarbazepine also did not vary between conditions. The newer antipsychotics (clozapine, olanzapine, quetiapine, risperidone, and ziprasidone) had lesser dissolution in the RYGB condition. Summarizing these results, it could be noted that the solubility of psychiatric tablets is altered after gastric bypass, but to demonstrate a change in the bioavailability of these drugs a clinical trial with monitoring of serum drug level is required.

The European Association for the Study of Obesity (EASO), the International Association for the Study of Obesity (IASO), the International Society for the Perioperative Care of the Obese Patient (ISPCOP), the Society American Gastrointestinal Endoscopic Surgeons (SAGES),

the American College of Surgery (ACS), and the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) have endorsed clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient [58]. They recommended supplementation with multi-vitamins and oral calcium citrate for patients who had undergone RYGB and BPD. These practical guidelines do not give any recommendation as to how alter the choice or administration mode of these drugs after bariatric surgery.

Oral Contraception and Bariatric Surgery

In the normal population, oral contraceptives are dissolved in the stomach and transformed by bacterial enzymes and by enzymes in the intestinal mucosa. The metabolized and non-metabolized drugs are then absorbed through the intestinal mucosa and enter the portal vein blood [59]. The major estrogenic component of oral contraceptives, 17 α -ethinyloestradiol (EE₂), undergoes first-pass metabolism caused by gut wall sulfation at least 60% [60, 61]. Thus, absorption of oral contraceptives could be affected by malabsorptive and restrictive-malabsorptive bariatric procedures. Rapid weight loss in the months after bariatric surgery increases fertility while maternal and fetal risks from rapid weight loss remain elevated [62]. Consequently, effective contraception is critical in the postoperative period. Few data are published regarding the efficacy of oral contraception after bariatric surgery. A prospective study in 40 women (16–44 years) who underwent BPD evaluated the hormone status preoperatively and postoperatively after 2 and 7 days, 3 and 6 months, and 1 year [63]. The fertility and obstetric history was performed by sending a questionnaire at least 2 years after inclusion. From 9 patients using only an oral contraception, two patients developed an unintended pregnancy after BPD. Victor et al. [64] investigated the pharmacokinetics of two oral contraceptives (norethisterone (NET) 3 mg and levonorgestrel (LNG) 0.25 mg) in 7 obese women (20–44 years) after jejunioileal bypass. The surgical procedure withdrew 37 cm of jejunum and 12.5 cm of ileum in continuity. Plasma concentrations of the two gestagens in the operated women were compared to those of a reference group before as well as 1, 2, 4, 6, 8, and 24 h after ingestion of the tablet. The mean plasma levels of NET were lower in the operated patients at all times, except for the 24-hour samples, and those levels of LNG study, were significantly lower in the operated patients at 2, 4, and 6 h. The authors concluded that the risk for contraceptive failure with low-dose gestagen mini-pills is increased in patients operated with jejunioileal bypass. More recently, Ciangura et al. [66] reported three cases of young women with etonorgestrel (ENG) implant after RYGB surgery. An implant (Implanon, Organon, France) containing 68 mg of ENG had been inserted into inner side of the upper arm in anticipation of bariatric surgery. In two patients, the serum ENG concentrations remained higher than 150 pg/ml 6 months after surgery with an effective contraceptive effect. In one patient, ENG concentrations were low at 125 pg/ml at 9 months, corresponding to the lower range of ENG concentrations observed after 3 years of use in normal-weight women [66]. The authors suggested that ENG-releasing implants might represent a safe contraceptive method in women undergoing bariatric surgery.

Non-Oral Contraception

There is consensus that pregnancy should be avoided for 12–24 months after bariatric surgery [17]. In women undergoing bariatric surgery, the use of contraceptive implants seemed to outperform their oral application. The American Congress of Obstetricians and

Table 1. Partial recommendations for medical conditions added to the US medical eligibility criteria for contraceptive use [72]

Type of procedure	COC, P, R	POP	DMPA	Implant	LNG IUD	Cu IUD
Restrictive	1	1	1	1	1	1
Malabsorptive	COC: 2; P: 1	2	1	1	1	1

COC = Combined oral contraception; P = patch; R = ring; POP = progestin-only pills; DMPA: depot medroxyprogesterone acetate injection; LNG IUD = levonorgestrel intrauterine device; Cu IUD = copper-bearing intrauterine device; 1 = a condition for which there is no restriction for the use of contraceptive method; 2 = a condition for which the theoretical or proven risks usually outweigh the advantages of using the method.

Gynecologists encouraged considering long-acting reversible contraception methods such as intrauterine devices (IUDs) and contraceptive implants for preventing unintended pregnancy in adolescents [67]. At pre-bariatric visits patients should be informed about these aspects, and patients should be encouraged to make use of these devices. In terms of safety and efficacy, the LNG-releasing IUD appeared to have a favorable profile compared to alternatives [68]. The hormonal IUDs are highly efficacious, with less pregnancy rates than the copper IUDs [69]. However, discontinuation of treatment has been reported due to dysmenorrhea, pain, device expulsion, pelvic inflammatory disease, and infection [70, 71].

Discussion and Conclusion

It is important to keep in mind that there are only very little data in the scientific literature on the pharmacokinetics of drugs following bariatric surgery. Thus, each drug will have to be evaluated with respect to its site of absorption and its mechanism of absorption by means of certain enzymes or transporters, with special attention on parameters influencing the effectiveness of the absorption processes. The oral bioavailability of drugs after bariatric surgery should be examined for each drug separately. Considering the increase in the number of bariatric surgical interventions such as RYGB, the impact of these procedures on pharmacokinetics of drugs needs a thorough and detailed examination to guide therapeutic drug monitoring in obese patients after bariatric surgery. Especially, a potential impact of bariatric surgery on the efficacy of oral contraceptives is a matter of particular interest in order to effectively avoid unintended pregnancy over 12- to 24-month period post bariatric surgery. Bariatric surgery could potentially result in a transient change in drug absorption necessitating a change in the mode of contraception. Additional information on how bariatric surgery impacts drug pharmacokinetics and how this should affect clinical decisions is needed (table 1).

Disclosure Statement

The author has not declared any conflicts of interest.

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