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Oral drug dosing following bariatric surgery - General concepts and specific dosing advices

Jurjen Kingma[1], Desirée Burgers[1], Valerie Monpellier[2], Marinus Wiezer[1], Heleen Blussé van Oud-Alblas[1], Janelle Vaughns[3], Catherine Sherwin[4], and Catherijne Knibbe[1]

[1]Sint Antonius Hospital
[2]Nederlandse Obesitas Kliniek (Dutch Obesity Clinic)
[3]Children's National Health System
[4]Wright State University Boonshoft School of Medicine

December 17, 2020

Abstract

Bariatric or weight-loss surgery is a popular option for weight reduction. Depending on the surgical procedure, gastric changes like decreased transit time and volume and increased pH, decreased absorption surface in the small intestine, decreased exposure to bile acids and enterohepatic circulation, and decreased gastrointestinal transit time may be expected. In the years after bariatric surgery, patients will also substantially lose weight. As a result of these changes, the absorption, distribution, metabolism, and/or elimination of drugs may be altered. The purpose of this article is to report the general influence of bariatric surgery on oral drug absorption, and to provide guidance for dosing of commonly used or high-risk drugs in this special population. Upon oral drug administration, the time to maximum concentration is often earlier and this concentration may be higher with less consistent effects on trough concentrations and exposure. Additionally, prescription of liquid formulations to bariatric patients is supported by some reports, even though the high sugar load of these suspensions may be of concern. Studies on extended release medications result in an unaltered exposure for a substantial number of drugs. Also, studies evaluating the influence of timing after surgery show dynamic absorption profiles. Although for this group a specific advice can be proposed for many drugs, we conclude that there is insufficient evidence for general advices for oral drug therapy after bariatric surgery implying that a risk assessment on a case-by-case basis is required for each drug.

Introduction

Obesity (body mass index (BMI) above 30 kg/m^2) is currently one of the major health issues, with a worldwide prevalence of 13% [1]. Individuals with (morbid) obesity are exposed to an increased risk of cardiovascular disease, cancer, diabetes mellitus, hypertension, arthritis, sleep apnea, and other co-morbidities, at higher mortality rates [2,3].

For patients with morbid obesity (BMI above 40 kg/m^2) or obesity with a BMI above 35 kg/m^2 with one or more comorbidities like type 2 diabetes or hypertension, modification of the gastro intestinal (GI) tract by bariatric surgery is currently the most effective long term treatment [4–7]. Surgery results in weight loss up to 32 $\pm$ 8% after two years and has shown to lead to decreased incidence of diabetes, myocardial infarction, stroke, and cancer, and in a reduction in overall long-term mortality[4,8,9]. In addition, obesity has a negative impact on quality of life, which improves significantly after bariatric surgery[10].

Common techniques used in bariatric surgery includes, the sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB)[11]. The RYGB is associated with several anatomical and physiological changes. RYGB introduces a small gastric pouch, which results in an increased gastric pH [12,13]. The gastric pouch is connected to the lower part of the intestine, bypassing the small intestine and biliary limb. During the SG procedure, a

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small longitudinal stomach in created. For both types of surgery, these alterations in the GI tract are known to lead to nutritional deficiencies for which standardized nutritional supplementation is commonly advised [7]. Similarly, it can be anticipated that these changes may alter the absorption of drugs given orally.

Many patients who undergo bariatric surgery use one or more drugs to manage their co-morbid disease(s). Relevant drugs to these patients include cardiovascular (26%) and antidiabetic drugs (26%), analgesics (21%), anti-inflammatory and antirheumatic products (non-steroids) (10%), antidepressants (21%), thyroid therapeutics (12%) and drugs for obstructive airway disease (25%) [14].

In addition to the alterations in oral absorption due to modifications in the digestive tract there are also changes in distribution, metabolism and/or elimination of drugs as the result of substantial weight-loss associated with bariatric surgery [15,16]. The purpose of this article is to provide an overview of how bariatric surgery may influence the process of oral drug absorption and to give specific dosage advice for commonly used potent drugs in this special patient population.

Bariatric surgery and oral drug absorption

Theoretically, as a result of bariatric surgery, a number of alterations in the process of oral drug absorption may be expected which may alter the oral pharmacokinetic profiles of prescribed drugs. Table 1 summarizes these alterations, for which a distinction is made between changes occurring upon restrictive procedures, i.e. procedures leading to a limitation in the amount of food in the stomach such as adjustable gastric banding and gastroplasty, or to limited digestive capacity such as SG, versus combined restrictive/malabsorptive procedures that also cause malabsorption of nutrients, such as Roux-en-Y gastric bypass (RYGB). Whether or not these changes ultimately lead to altered pharmacokinetics of a specific drug will depend on individual drug properties. Here we discuss disintegration of the oral drug formulation, dissolution of the drug, gastrointestinal transit time and the role of bile acids as factors of interest for the absorption process of oral drugs.

Disintegration of the oral drug formulation

The first step in the absorption of solid formulations like tablets and capsules, is disintegration in the GI tract. Disintegration is affected by several variables, such as gastric volume and mixing, which can be both diminished after bariatric surgery [15,16]. Due to a reduced volume, it is often assumed that tablets, may not fully dissolve, resulting in altered exposure of the drug[17,18]. For this reason, administration of oral liquids is often proposed after bariatric surgery, even though hard evidence to support this statement is lacking. A disadvantage of liquid formulations like suspensions is that these formulations may contain sugars, which may, in large amounts, lead to the dumping syndrome[19].

Montanha et al. investigated the effect of RYGB on the bioavailability of amoxicillin tablets versus suspension [20]. A lower Area Under the Curve (AUC) for tablets (23.10 ± 7.41 mg.h/L) was found as compared to the suspension (27.59 ± 8.32 mg.h/L) , corresponding to a relative biological availability of 83%. The higher AUC of the suspension resulted from a higher Cmax (8.73 ± 3.26 vs 7.42 ± 2.99 mg/L) and lower Tmax compared to tablets (1.7 ± 0.86 vs 2 ± 0.76 hours). While no clinical outcome measures were reported, for both formulations, the time above the minimum inhibitory concentration (MIC) for pathogens with an MIC <4mg/l was attained, and therefore effectiveness seems to be guaranteed for both oral drug formulations.

Schulman et al. investigated the effect of RYGB surgery on Proton Pump Inhibitor (PPI) in Open Capsule (OC) versus Intact Capsule (IC) form[21]. They showed a significantly shorter healing time (median healing time of 91 days vs. 342 days) in the OC PPI group compared to the IC PPI group. There was, however, a significantly larger percentage of sucralfate use in the OC group and a larger non-significant percentage non-steroidal anti-inflammatory drug (NSAID) use in the IC group, which may have contributed to the reported difference in effect [21].

From these reports, it seems that suspensions may lead to a higher exposure but may not always be preferable because of sugar loads, and that open capsules may lead to more effective treatment than intact capsules after RYGB surgery. With increased exposure upon the use of the amoxicillin suspension, earlier and higher

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peak concentrations were observed. Such early and high peak concentrations may be undesirable for certain drugs like morphine, for which upon use of an oral solution yielded a three-fold increased Cmax, lower Tmax and increased AUC at six months after bariatric surgery [22]. Additionally, midazolam was reported to have an earlier and 1.5 fold higher peak concentration after oral administration [23].

Dissolution of the drug

After disintegration, a drug must become dissolved to be absorbed. This dissolution process is affected by several variables, such as gastric volume, gastric pH, and gastric transition time. After RYGB surgery, there is limited exposure to acid, which is in contrast with a SG procedure upon which the acid exposure time rises[12,13]. In any case, bariatric surgery patients are generally prescribed prophylactic PPIs to reduce the risk of gastro-intestinal complications after surgery, such as ulceration or gastro-intestinal bleeding during the first months after surgery[24,25]. Due to this rise in pH, the solubility of more basic drugs could decrease since they become less ionized, and the solubility of acidic drugs could increase since they become more ionized. Dissolution should, however, not be confused with absorption. Ionized drugs have good solubility and show generally lower absorption than unionized drugs, which are, in general less soluble. In healthy subjects, the stomach is capable of absorbing most acidic drugs and the very weakly basic drugs which are undissociated in the acidic gastric environment [26]. After surgery, the proposed rise in pH could lead to reduced absorption of these drugs in the stomach. This effect, however, should primarily affect the dissolution in the stomach, where usually only a small degree of drug absorption takes place, and the effect could, therefore, be small. In addition, there are other factors of relevance for dissolution other than altered pH, like gastric volume and transition time.

An example of a drug that is absorbed in the stomach is acetylsalicylic acid, which is unionized in the acidic environment of the stomach upon which it can be absorbed [26]. Theoretically, because of the higher pH, the absorption and exposure of acetylsalicylic acid (ASA) could be reduced in patients after bariatric surgery. Mitrov-Winkelmolen et al. studied the effect of RYGB on the pharmacokinetics of orally administrated ASA before and six weeks after RYGB surgery[27]. Instead of a lower AUC, they found a significant increase in AUC (14.1 vs. 11.4 mg h/l), an increased Cmax (4.6 vs. 3.5 mg/l) and a significantly decreased Tmax (0.7 vs. 1 hour) six weeks after RYGB surgery. According to the authors, the higher AUC and Cmax suggest that absorption of acetylsalicylic acid, even when occurring mainly in ionized form because of the elevated pH, can also take place in the jejunum where it may even exceed absorption in the stomach and duodenum. Regarding these results, it is unknown what the contribution of the higher pH and/or altered gastric emptying and transit time of the GI tract is, as all of these changes occur simultaneously after bariatric surgery.

The weak base posaconazole is another example of a drug where the absorption is related to the residence time in the acidic environment of the stomach. Several studies showed the dependence of posaconazole absorption on the pH, resulting in the avoidance of PPI in patients using posaconazole [28,29]. As in bariatric surgery patients, a higher pH and faster gastric emptying may be expected, Gesquiere et al. performed a single-dose pharmacokinetic study in 12 RYGB surgery patients before and 6-9 months after surgery. After surgery, the $AUC_{0-[?]}$ was significantly reduced (9.49 vs. 4.37 ug ml/h, $p<0.05$), which was explained by the low solubility of posaconazole, of which the absorption is very sensitive to intraluminal pH and residence time in the stomach [30]. As the decrease in AUC was more extensive than would be expected based on pH-related changes in absorption alone, the authors suggest that the reduced residence time after RYGB surgery contributes to their findings.

From these reports, it seems that the acidic drug acetylsalicylic acid is absorbed after RYGB surgery even when the pH in the stomach is decreased. However, the weak base posaconazole is, as expected, not absorbed, resulting in a lower $AUC_{0-[?]}$ in RYGB surgery patients.

Gastro-intestinal transit time

Besides the above-mentioned factors such as pH, gastric volume and gastric transition time, other factors like gastric emptying and gastro-intestinal transit time are relevant for absorption. After RYGB, a large proportion of the stomach and intestine is bypassed, which can result in altered gastro-intestinal transit

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time and gastric emptying time. Carswell et al. studied seven obese controls, six obese individuals undergoing adjustable gastric banding, seven subjects undergoing RYGB surgery, and five subjects undergoing biliopancreatic diversion with duodenal switch at 8 – 29 months post-surgery. The authors found no significant changes in gastro-intestinal transit time using a sulphasalazine/sulphapyridine test with sulphapyridine detected at 180 min in all four groups [31]. Dirksen et al. measured the transit time of water and solid nutrients through the stomach, small intestine and colon through scintigraphy in 17 RYGB subjects who were at least 12 months post-surgery and in nine non-obese control subjects. In this study, RYGB subjects had faster pouch emptying for water as well for solid nutrients but slower small intestinal transit time and similar colonic transit time in comparison to healthy controls [32]. Nguyen et al. studied the effect of RYGB on gastric emptying and cecal arrival time in ten RYGB subjects who underwent surgery at least 12 months earlier in comparison to healthy subjects [33]. Compared to the healthy controls, gastric emptying and cecal arrival time were substantially faster in RYGB patients. Moreover, gastric emptying was faster when subjects were in a sitting position and tended to be faster after 150 ml in comparison to the 50 ml administration. Lastly, Wang et al. showed rapid gastric emptying in seven patients who underwent RYGB one year after surgery[34], where the subjects were their own controls.

The results of these studies on gastric emptying and intestinal and colonic transit time show that gastric emptying is generally faster after bariatric surgery compared to healthy controls and that data on intestinal and colonic transit time is conflicting with more rapid and even slower small intestinal transit or cecal time reported in RYGB surgery patients.

Information on changes in the gastro-intestinal transit time as a result of bariatric surgery may also be deduced from results on studies evaluating the effect of bariatric surgery on the exposure of slow-release vs. immediate-release tablets. Yska et al. studied the effect of RYGB surgery on the exposure of metoprolol from immediate-release (IR) and controlled-release (CR) tablets in female patient volunteers one month before and six months after RYGB surgery[35]. The endpoint was the ratio of the metoprolol AUC_{after}/AUC_{before} surgery. For the IR tablets, no significant changes were observed, albeit with major intraindividual and interindividual variability in AUC (range ratio $AUC_{0–10\ hours\ after}/AUC_{0–10\ hours\ before}$: 0.74–1.98). For the CR tablets, a significantly lower AUC was observed after surgery (range ratio $AUC_{0–24\ hours\ after}/AUC_{0–24\ hours\ before}$: 0.43–0.77). Based on these results, the authors conclude that RYGB surgery may influence the bioavailability of metoprolol from an IR tablet and that after surgery, the dose of metoprolol CR tablets should be increased according to clinical response [35]. In contrast with these results, another study showed no significant effect on the AUC of metoprolol measured at 6 – 8 months after RYGB surgery in patients receiving oral metoprolol CR tablets [36]. Also, for IR tablets, no changes in exposure after surgery were found. Because of differences in the volume of water used to swallow the CR tablet influencing pouch emptying and differences between women and men (Yska et al. only included female volunteers) as explanations for the diverging results for CR tablets, it seems yet too early for conclusions on the use of metoprolol CR tablets after surgery.

For venlafaxine administered as CR capsules, Krieger et al. showed no effect on AUC of venlafaxine and its primary metabolite 3-4 months after RYGB [37]. Similarly, Hachon et al. investigated the effect of RYGB surgery on the pharmacokinetics of morphine CR tablets in RYGB patients (two years after surgery) and healthy controls. They found no significant changes in the AUC or other PK parameters between studied groups [38].

Based on the results of these studies on CR formulations, it seems that a priori, CR formulations may not need to be discouraged in patients after bariatric surgery.

Role of bile acids

After bariatric surgery, the influence of digestive content is also altered. Gastric acid secretion is significantly reduced following RYGB surgery, leading to an increase in pH in the stomach[12,13]. The altered GI tract may also lead to a delayed action of bile acids. Because bile salts do not reach the GI tract before the jejunum, contact between bile acids and a drug occurs later in comparison to normal subjects. A drug that has been demonstrated to be dependent on bile acids is fenofibrate. Gesquiere et al. performed a single-dose

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pharmacokinetic study in 12 RYGB surgery patients before and 6-9 months after surgery and surprisingly, the $AUC_{0-[?]}$, Cmax, and Tmax of fenofibrate were not altered[30]. The authors hypothesize that these results may be explained by higher fasting total serum bile acid concentration in patients after RYGB and by faster gastric emptying that might compensate for the delayed efflux of bile acids [30]. These study results suggest that the overall influence of altered timing of bile acids on oral drug absorption may be minor.

Overview of dosing information on commonly used and high-risk drugs after bariatric surgery

Here we provide an overview of the available literature on dosing of commonly used oral drugs in this special population (for summary see table 2).

Antibiotics

Obesity is a risk factor for infections, including surgical wound infections [39–41]. It has been shown, that the increased risk for surgical wound infections is probably due to the decreased penetration of the prophylactic antibiotic cefazolin into the subcutaneous tissue as a result of reduced blood flow to fatty tissue, as similar plasma concentrations but reduced subcutaneous tissue concentrations were found [42]. Similar reduced penetration into subcutaneous tissue and muscle was reported for ciprofloxacin [43]. With most studies evaluating concentrations in plasma, from these results it seems that potentially reduced perfusion into the target tissue should be considered when deciding what drug or dose to give after bariatric surgery.

Beta-lactam antibiotics (amoxicillin, penicillin and ampicillin)

To date, five studies have been published regarding the pharmacokinetics of oral beta-lactam antibiotics. Two studies, i.e. Terry et al. and Miskowiak et al., describe the pharmacokinetics of oral phenoxymethylpenicillin after gastroplasty and jejunoileal bypass, procedures that are to date not often applied any more[44,45]. Miskowiak et al. evaluated the effect of gastroplasty on the absorption of phenoxymethylpenicillin when given as a non-coated tablet or as an aqueous solution (one-week washout) in eight female bariatric surgery patients before and three months after gastroplasty surgery. In this study, no significant changes in plasma concentrations, Cmax, T1/2, Tmax and AUC were found before versus after surgery. [44]. There were also no significant differences in AUC between tablet and aqueous solution. Terry et al. studied the oral absorption of a single administration of 1 gram phenoxymethylpenicillin in three subjects before and three months after jejunoileal bypass and in five subjects three months after jejunoileal bypass [45]. In the group with AUC measurements before and after surgery, a substantially increased AUC after surgery (176.8 +- 98.1 vs. 17.1 +- 5.9 units/ml * hour) was demonstrated. However, in the group where AUC was only measured after surgery, the AUC was 46.2 +- 30.4 units/ml * hour, illustrating a large interindividual variability in the AUC after jejunoileal bypass surgery. Peak serum concentration also increased significantly. The authors explained the enhanced absorption of penicillin by the lack of degradation which generally occurs in acid gastric contents.

The pharmacokinetics of oral amoxicillin after RYGB surgery was studied by Rocha et al. and Montanha et al. [46,47]. Rocha et al. studied eight obese subjects receiving an amoxicillin 500mg capsule before and two months after RYGB surgery [47]. They found a large and significant rise in AUC (7.21 +- 5.13 vs. 2.03 +- 0.77 ug.h/ml) and Cmax (1.77 +- 1.19 vs. 0.62 +- 0.22) after surgery whereas Tmax and t1/2 were not significantly altered. All of these values were however substantially lower compared to non-obese subjects who had $AUC_{C0-tlast}$ values of 12.44 – 12.05 ug.h/ml and a Cmax ranging from 4.94 to 5.31 ug/ml.

As previously stated, Montanha et al. reported a higher AUC for amoxicillin suspension compared to amoxicillin tablets in 20 RYGB surgery patients [46]. This higher AUC was predominantly explained by the higher Cmax observed after the suspension. When comparing these results to amoxicillin absorption rates in non-bariatric and non-obese subjects, the total absorbed amount of amoxicillin appeared 40% lower the suspension group and 50% lower for the tablets. Even though no clinical outcome measures were reported, for both formulations, the time above the MIC for pathogens with a MIC <4mg/l was attained in the study of Montanha et al. Therefore, it seems that oral amoxicillin can be used in post RYGB surgery patients, despite the fact that the AUC is lower in comparison to normal weight subjects.

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Kampmann studied oral absorption of ampicillin in six patients with morbid obesity undergoing jejunoileostomy [48]. Before surgery and 1-2 weeks, 6 months and 12 months postoperatively, patients received 500 mg ampicillin intravenously and 700 mg of oral pivampicillin (the pivaloylmethylesther of ampicillin) on separate days. A significant decrease in bioavailability was reported at 1-2 weeks (65 +- 18%), 6 months (66 +- 36%) and at 12 months (41 +- 30 %) after surgery compared to preoperative bioavailability (109 +- 44 %). However, as the bioavailability in healthy normal-weight subjects was 50%, these lower values might not have implications for antibiotic therapy. The authors suggest that the impeded absorption compared to pre-surgery in morbidly obese patients which may have several explanations including: a change in bile acid metabolism; an increased number of enterobacteriae; premature splitting of the lipophilic part of pivampicillin; and/or an elevated mucosal enzyme level participating in the hydrolysis of pivampicillin [48]. No explanations were given for the higher bioavailability of pivampicillin in morbidly obese patients before surgery compared to healthy volunteers (109 vs 50%).

Macrolide antibiotics (azithromycin and erythromycin)

Two studies investigating macrolide antibiotics have been published.

Prince et al. studied seven patients with morbid obesity receiving a single dose of 250 mg erythromycin within three days before and six weeks after surgery (one gastric bypass, six gastroplasty)[49]. Mean weight-corrected AUC was reduced with 41% compared to pre-surgery values, with two patients having no detectable serum concentration after surgery. Mean peak concentration decreased from 1.04 to 0.5 ug/ml, and Tmax increased from 3.9 +- 1.5 to 6.7 +- 2.8 hours [49].

Padwall and colleagues studied azithromycin pharmacokinetics in 14 female RYGB surgery patients, and 14 BMI matched controls[50]. Subjects were administered two 250 mg azithromycin tablets at least three months after surgery. AUC was reduced in the RYGB subjects by 31%, Cmax and Tmax were not significantly altered[50].

Since both studies showed a reduction in exposure after surgery, it seems that the use of macrolide antibiotics should be discouraged after bariatric surgery.

Fluoroquinolone antibiotics (ciprofloxacin and moxifloxacin)

To date, there are two studies published investigating the effect of bariatric surgery on oral fluoroquinolone antibiotics.

De Smet and colleagues studied the oral bioavailability of moxifloxacin in 12 individuals after RYGB surgery [51]. Each subject received two single doses of 400 mg oral or intravenous moxifloxacin with a washout period of seven days at least six months after surgery. While mean oral bioavailability was 88%, oral and intravenous exposures were 50% higher than those described for subjects without gastric bypass [51]. The authors suggest that differences in percentage man/women or a higher enterohepatic recirculation of moxifloxacin after gastric bypass may contribute to this finding.

Rivas et al. evaluated the pharmacokinetic parameters of ciprofloxacin in 17 RYGB patients before, one month, and six months after surgery compared to 17 matched controls [52]. AUC was 9737.2 +- 2717.6 h.ng/ml in the control and 9141.3 +- 1774.0 h.ng/ml at baseline in the surgery group. One month after surgery, AUC decreased to 7581.4 +- 1511.1 h.ng/ml and returned to presurgical baseline values at 6 months after surgery (9067.6 +- 3880.2 h.ng/ml).

Failure of oral antibiotic therapy after bariatric surgery

Roy et al. investigated the association between the history of RYGB and increased treatment failure in patients who received oral antibiotics[53]. Treatment failure was defined as any prescription change that resulted in an increased daily dose, frequency or duration of current oral antibiotics, substitution or addition of another oral, intramuscular, or intravenous antibiotic for the same indication, any surgical intervention for current infection, emergency room or outpatient visit for current infection and hospitalization for current infection. In their study, 186 patients were included (58 RYGB patients and 128 controls). There was

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no significant difference in composite therapeutic failure rates by time since RYGB surgery (24.1%, n=14) compared to the control group (15.6% n=20). However, in the subgroup treated with fluoroquinolones (31.6 vs. 7.1 %, n= 6 and 2 respectively) and with sulfamethoxazole/trimethoprim (40 vs. 7.1%, n=4 and 2 respectively) more therapeutic failure rates were reported compared to controls.

Summarizing, for beta-lactam antibiotics, similar, increased or decreased exposure can be anticipated after surgery, however as concentrations seem overall high enough, these antibiotics can generally be applied. For macrolide antibiotics, a reduced exposure up to 30-40% after surgery has been reported and therefore the use of these antibiotics should be discouraged. While fluoroquinolones did show some reduction in exposure after surgery, the overall bioavailability seems adequate. In general, it seems that bariatric surgery patients treated with oral antibiotics should be monitored closely for therapy failure and side effects. When prescribing antibiotics to bariatric surgery patients, several factors should be considered including , the site and severity of infection, route of administration and potential toxicity.

Antihormones

Tamoxifen is widely used in the treatment of estrogen receptor-positive breast cancer and is known for its inter-individual variability in pharmacokinetics. Previously, a minimal concentration threshold of 5.9 mg/ml of the active metabolite (Z)-endoxifen for the recurrence of breast cancer has been identified [54]. Therefore, Therapeutic Drug Monitoring (TDM) has been recommended for tamoxifen to prevent under-treatment based on the (Z)-endoxifen concentration[55,56].

In patients after RYGB surgery, reduced absorption of tamoxifen has been described in three women after RYGB [57] with tamoxifen blood concentrations below the therapeutic level of 5.9 mg/ml. For one patient, the time between RYGB and measured tamoxifen concentration was described and was four years. Because of the established relation between (Z)-endoxifen and the recurrence of breast cancer, particularly for patients after bariatric surgery, it seems advisable to apply TDM of (Z)-endoxifen over time after bariatric surgery. The monitoring of side effects can be included in determining the effectiveness/absorption of the therapy, however, because hot flashes are not predictive for serum concentrations of tamoxifen and its metabolites [58], it can not replace TDM. To our best knowledge, there are no known data from other antihormones in patients with bariatric surgery. Tamoxifen seems to be the preferred antihormone therapy because of routine TDM.

Direct Acting Anticoagulants (DOACs)

In recent years, direct-acting anticoagulants (DOACs) have emerged as alternatives for vitamin K antagonists to be used for stroke prevention in atrial fibrillation and for the prevention and treatment of venous thromboembolism. Currently, four DOACs are available, of which apixaban, rivaroxaban, edoxaban are direct factor Xa inhibitors, and dabigatran is a direct thrombin inhibitor. In the general population, these drugs have a predictable pharmacokinetic profile, which enables fixed dosing without routine coagulation additional monitoring and consequently, DOACs may have a profound benefit over the vitamin K antagonists (VKAs)[59]. However, in patients undergoing bariatric surgery, these pharmacokinetic profiles may be aberrant. This may particularly apply to rivaroxaban of which oral absorption is linear until a dose of 15 mg, while in higher doses the bioavailability is reduced and becomes dependent on co-administration with food [59]. For rivaroxaban 20-mg tablets, AUC and Cmax were reported to increase by 39% and 76% when administered with food, respectively[60]. Also, dabigatran, which requires an acid environment for absorption for which tartaric acid is added to the tablet, the reduced volume for gastric acid secretion leading to a more alkaline pH in the gastric pouch, may be subject to altered absorption[61,62]. Since all DOACs are absorbed in the first part of the gastro-intestinal tract, surgery-related changes in the absorptive surface could alter the absorption of all these drugs[63].

Only limited information is available about the absorption of DOACs after bariatric surgery. Kroll et al. measured the rivaroxaban AUC after a single dose of 10 mg rivaroxaban in 12 patients with obesity one day before and three days after RYGB / SG surgery [64]. In this study, no significant changes in pharmacokinetic profile were reported. In an extension study, Kroll and colleagues investigated a single dose of oral rivaroxaban

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of 10 mg 6 to 8 months after SG or RYGB[65]. While the AUC and T1/2 were not significantly altered 6-8 months after surgery, Tmax was increased after RYGB and SG, and Cmax was lower and not altered in RYGB and SG patients, respectively[64,65]. Given the known nonlinear absorption of rivaroxaban, it is unknown whether these results can be extrapolated to 15 or 20 mg tablets.

Rottenstreich et al. matched 18 patients who underwent bariatric surgery (12 SG, four adjustable bands, and two RYGB) to 18 obese control subjects. They were receiving DOACs (9 apixaban 5 mg BID, 7 rivaroxaban 15 mg OD and 20 mg OD and 2 dabigatran 110 mg and 150 mg BID) for atrial fibrillation, pulmonary embolism or deep vein thrombosis. The median time elapsed from surgery until study inclusion was 4.9 years. Peak concentrations were within the normal range in all apixaban and dabigatran patients; however, five of the seven patients receiving rivaroxaban had significantly lower peak concentrations than the control group [66]. The authors conclude that all DOACs, particularly rivaroxaban, should be used cautiously after bariatric surgery if used at all given that VKAs can be easily monitored. In two case reports, thromboembolic events related to possible impaired dabigatran absorption have been published [67,68].

Based on the above reports, it seems that until more data on DOAC use is available, VKAs or low molecular weight heparins are to be preferred of DOACs. Measuring DOAC [69–71] or anti-Xa[72,73] concentrations has been suggested when applied in special patient groups, however as there is no hard evidence on the relation between peak, trough or AUC of these measures with outcome, it seems yet too early to use TDM as guidance for DOAC use in postbariatric surgery patients. In another special patient population (i.e. children), anti-Xa measurement for monitoring of the effect of rivaroxaban was regarded as inferior compared to measurement of rivaroxaban concentration. The reasons for this conclusion, is that the anti-Xa assay result may be falsely high or low because the assay can be influenced by pre-processing procedures (e.g., blood draw technique, extended time until measurement) [74].

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

The most common postoperative complications of bariatric surgery are related to the GI tract, such as bleeding and ulceration[75,76]. Depending on the definition, the reported incidence of ulceration ranges from 1 – 20%[75,77–84]. It is demonstrated that the use of NSAIDs is an independent risk factor for the development of ulcerations[85–87]. Although NSAIDs after bariatric surgery are often proclaimed to be life-long contraindicated[24,2524,25], NSAIDs are commonly used in bariatric surgery patients [86–88]. Studies show that the majority of the ulcerations occur within the first year after surgery[78,79,81], and therefore it can be speculated that the risk might thereafter be the same for bariatric surgery patients and other subjects. For now, it seems reasonable to conclude that NSAIDs are contraindicated in the first six months after bariatric surgery and that until there is more evidence, after these six months, the use of NSAIDS should be discouraged. There are no studies on the pharmacokinetics of NSAIDS before versus after bariatric surgery.

Oral contraceptives

Obesity is associated with infertility in women by various mechanisms[89], which seems to be (totally or partially) reversible after bariatric surgery [90]. As reproductive-aged women are advised to avoid pregnancy twelve to twenty-four months after bariatric surgery, contraceptives are recommended [91–93]. An anticipated reduction in absorption area, residence time and enterohepatic circulation after bariatric surgery may potentially decrease the reliability of oral contraceptives. There is however limited information on the use of oral contraceptives after bariatric surgery. Victor et al. showed that norethisterone and levonorgestrel levels were lower after jejunoileal bypass at 1-8 hours after ingestion even though at 24 hours, there was no difference [94]. Furthermore a reduced effect of oral contraceptives after biliopancreatic bypass was described[95]. Two of the nine patients who used oral contraceptives postoperatively were unexpectedly pregnant. These two patients suffered from chronic diarrhea. No unexpected pregnancies were reported among users of non-oral contraceptives [95]. Ciangura et al. showed reduced norgestrel levels six months after RYGB, however, these values were considered sufficiently high for a contraceptive effect [96].

In conclusion, the absorption of oral contraceptives may be reduced, particularly in the event of chronic diarrhea following restrictive and malabsorptive bariatric surgery. Oral contraceptives should be discouraged or

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alternative contraception should be used. Of note, Damhof et al. showed that 16% of the women undergoing bariatric surgery are using potentially unsafe contraception postoperatively warranting the attention of the health care professional for this problem[97].

Platelet aggregation inhibitors

Platelet aggregation inhibitors such as acetylsalicylic acid (ASA), clopidogrel, prasugrel, and ticagrelor are frequently prescribed for the prevention of (recurrent) thrombotic disease in high-risk patients. Clopidogrel and prasugrel, both thienopyridines, and ticagrelor, a cyclopentyltriazolopyrimidine, are oral $P2Y_{12}$ receptor antagonists. While clopidogrel and prasugrel both need metabolic activation, ticagrelor acts directly on the $P2Y_{12}$receptor. ASA, which is also a prodrug, exerts its effects by irreversible COX inhibition, which in turn leads to a reduction in the production of prostaglandin thromboxane A_2 and inhibition of platelet aggregation.

Several studies have shown that elevated bodyweight results in higher platelet reactivity, and therefore altered regimens for ASA[98–103] and clopidogrel [98,105–107]have been explored that might provide a more optimal platelet inhibition in obese patients. The relevance of the higher platelet reactivity in obese patients and its consequence for dosing of platelet inhitibitors is unknown.

To date, four studies have investigated the effect of bariatric surgery on the pharmacokinetic profile of platelet aggregation inhibitors. Three studies describe the effect on ASA [27,102,108]. The other study investigates the effect of surgery on the pharmacodynamics on ticagrelor [109].

As previously described, Mitrov-Winkelmolen et al. studied in an open-label longitudinal repeated-measure study the effect of RYGB on ASA pharmacokinetics. In their study, Tmax was shorter, and both Cmax and $AUC_{0\text{-}24}$ (14.1 and 11.4 mg/l respectively $p<0.001$) higher after surgery. Although statistically significant, the authors argue that there are no clinically relevant changes in ASA pharmacokinetics since the changes are still within the recommended dosing range for platelet aggregation inhibition[27].

Norgard and colleagues studied the effect of bariatric surgery on the aspirin-induced platelet inhibition and subsequent platelet aggregability [102]. Ten patients undergoing bariatric surgery (8 RYGB and 2 SG) were administrated two 7-day courses of ASA, before and three months after surgery. After the last dose, platelet reactivity expressed as aspirin reaction units (ARU) was tested and compared to data of normal-weighted subjects. They showed that before surgery, the platelet reactivity was significantly higher in patients with obesity compared to normal-weight subjects (469 +- 60 vs. 419 +- 52 ARU p=0.016) when using ASA. After surgery, the platelet reactivity was significantly reduced (432 +- 143 vs. 469 +- 60 ARU p=0.03), which was also seen in RYGB patients who did not use ASA (602 +- 59 vs. 531 +- 78 ARU p=0.035). This shows that the reduced reactivity after surgery compared to preoperative values may not be solely related to ASA[102].

The safety of low-dose ASA was studied by Kang and colleagues[108]. They followed a group of 1016 patients undergoing RYGB surgery, of whom 145 used ASA. The incidence of ulceration was not significantly different between the two treatment groups. Although it was a small study, the authors conclude that patients were not at increased bleeding risk when using low-dose ASA [108]. In contrast, Caruana et al. reported an overall rate of upper gastrointestinal bleeding of 4 of 11 bariatric surgery patients within 2-3.5 weeks after starting clopidogrel (25-234 days after surgery)[110]. As such, it seems that prophylactic PPIs are indicated for at least six months after bariatric surgery when platelet inhibitors are given.

Ma et al. measured the influence of ticagrelor on whole blood impedance platelet aggregability induced by adenosine in obese patients undergoing bariatric surgery and in healthy normal weighted control subjects[109]. The half-maximal inhibitory concentration (IC_{50}) value was 34.0 nM six weeks before bariatric surgery, which reduced to 23.1 nM 12 weeks after surgery whereas in controls, the IC_{50} level of ticagrelor was 14.5 nM. This suggests that bariatric surgery improves the ticagrelor pharmacodynamic response that was blunted by obesity, which is also showed in the study of Norgard described above [102].

In conclusion, although obese patients seem to differ from non-obese patients with respect to platelet activity, it seems that platelet aggregation inhibitors do exert an effect after bariatric surgery. However, it is difficult

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to distinguish between the influence of the reduction of obesity versus the effect of the platelet inhibitor. From the available results, it seems that there is no indication for dose adjustments of platelet inhibitors after bariatric surgery.

Proton Pump Inhibitors (PPIs)

According to many local protocols, PPIs are frequently prescribed after bariatric surgery for the prevention of ulceration, even though the duration of prophylactic PPI use seems to vary. In an internet-based survey among members of the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) on the management of anastomotic ulcers after RYGB surgery, 88% of the 189 participants reported the prescription of prophylactic medication of which 91% preferred proton pump inhibitors [111]. The prophylactic medication was prescribed for a period of one month in 25% of the cases, for a period of three months in 37% of the cases, for a period of six months in 28% of the cases, for more than six months in 4% of the cases and lifelong for 5% of the cases with a median of three months[111]. Even though the majority (˜75%) of ulceration appears to occur in the first year after surgery with the steepest increase in the first six months (˜60%)[78], the available literature regarding this subject is not conclusive on the duration of prophylaxis in this population[78–80,82,84,112].

Since the prescription and usage of PPIs is widespread, information on the absorption and dose is of relevance. Mitrov-winkelmolen et al. studied the pharmacokinetics of omeprazole in 34 patients with morbid obesity the months – two weeks before and more than six weeks after RYGB. Tmax after surgery was 0.9 h compared to 2.1h before surgery, Cmax was higher (958.6+-300.8 µg/l vs. (731.1±339.0 µg/l) and AUC_{0-12} was lower (2834.1±1560.4 vs. 3737.4±21932 µg h/l) after surgery [27]. Another study in 18 RYGB subjects one year after surgery also showed a reduced Tmax (0.75h vs. 4h) but no alterations in other PK parameters compared to matched controls [113]. This discrepancy might be explained by differences in study design (matched vs. repeated measure design) and/or large inter-individual variability in omeprazole PK. Also, the timing of the study in relation to surgery, can be relevant.

Another factor that might contribute to therapy failure of PPIs is the dissolution of the capsule, which was investigated by Schulman et al., reporting shorter healing time when the capsule was opened (as described under Disintegration of the oral drug formulation) [21]. Therefore, in case an inadequate response is observed, opening the PPI capsule can be advised provided that PPIs do not get in contact with acid to prevent degradation [114]. Therefore, PPI capsules can only be opened when this is allowed according to the SmPC.

Psychotropic drugs

Morbid obesity has been linked to different psychiatric disorders. Depression is the most common psychiatric disorder in the obese population with reported odds ratios (OR) ranging from 1.21 – 5.8 with a stronger association in women [115]. There is also a higher risk of anxiety disorders in the obese population (OR 1.27 – 1.40) [115]. The prescription of psychotropic drugs is, therefore, relatively common in the bariatric surgery population.

In an in-vitro model studying the dissolution of common psychotropic drugs, ten of 22 psychiatric drugs had a significantly lower dissolution fraction and two had significantly higher dissolution after RYGB compared to preoperatively [116].

Hamad et al. investigated the effect of RYGB on the pharmacokinetics of Serotonin Reuptake Inhibitors (SRI). Patients were taking venlafaxine (N=5), citalopram (N=2), escitalopram (N=2), sertraline (N=2), or duloxetine (N=1) [117]. AUC values decreased with 54% (36 – 80%) one month after surgery in comparison with pre-operative levels. In most patients AUC values returned to baseline or exceeded baseline at six months after surgery [117].

Marzinke et al. measured escitalopram plasma levels in four subjects two weeks before versus two and six weeks after RYGB. Two weeks after surgery, escitalopram plasma levels decreased by 4 – 71%. Samples collected six weeks after surgery showed a further decrease with 16 – 19% [118].

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Roerig et al. measured the AUC of duloxetine and sertraline in RYGB patients and matched controls [119,120]. For sertraline both the $AUC_{0\text{-}10,5}$ (124.4 +/- 55.5 ng-hr/ml vs 314.8 +/- 129.6 ng-hr/ml) and Cmax (19.0 +/- 7.8 ng/ml vs 48.7 +/- 19.1 ng/ml) were significantly lower 9-15 months after RYGB surgery[119]. For duloxetine, $AUC_{0\text{-}[?]}$ (646.74 +/- 79.7 vs 1119.91 +/- 593.40) and Tmax (2.2 +/- 0.86 vs 6.0 +/- 2.17) were significantly lower in the RYGB group 9 – 15 months after surgery [120].

These studies suggest that health care professionals should be aware of decreased serum concentrations when prescribing anti-depressants and anti-psychotics drugs to bariatric surgery patients, especially in the first few weeks and months after surgery [117–120]. Although no information was provided on the mental status of patients in the above mentioned reports, prescribers should, monitor patients for signs of therapy failure, particularly in the first year after bariatric surgery.

Vitamin K antagonists (VKAs)

VKAs such as acenocoumarol, fenprocoumon, and warfarin, inhibit the carboxylation of the vitamin K-dependent coagulation factors II, VII, IX, and X in the liver necessary for coagulation and thus indirectly inhibit the coagulation process. VKAs are used for the prophylaxis and treatment of VTE and stroke prevention in atrial fibrillation. As VKAs are absorbed in the proximal intestine, bariatric surgery could have an impact on the absorption of VKAs.

Several studies investigated the effect of bariatric surgery on the daily dose of warfarin

[121–124]. All studies demonstrated that the warfarin dose was significantly reduced after RYGB surgery, especially in the six month postoperatively. After the direct postoperative phase, the required dose tended to gradually go back up to pre-surgical levels at six months to one year after surgery [121–124]. It is not yet entirely clear why a lower dose is needed shortly after the operation. While it can be hypothesized that absorption may be increased because of crushing the tablets by patients directly after surgery, another explanation may lie in the changes that are associated with bariatric surgery that are to date not fully understood, such as metabolic changes [4]. Also changes in diet during the first months after surgery may play a role. Similar to the results of platelet aggregation inhibitors, it seems that bariatric surgery may improve the response on VKAs compared to obese subjects, especially in the first months after surgery [121,122]. It is known that compared to normal weight patients, obese patients require a higher average daily dose and also require more time to achieve therapeutic international normalized ratio (INR) [125]. While no studies have been conducted on acenocoumarol and fenprocoumon after bariatric surgery, it may seem that these results also apply to these drugs. Overall, more frequent monitoring of the INR seems appropriate in the first year after bariatric surgery.

Discussion

Because of the increasing number of bariatric surgery procedures that are performed to date, healthcare professionals will be increasingly confronted with the care of these patients. Since during this procedure, alterations to the gastro-intestinal tract are being made which results in substantial weight loss over time, changes in the absorption, distribution, metabolism and elimination of drugs can be expected, and special considerations, particularly regarding the dosing of oral drugs, may apply. In this overview, we report on the influence of bariatric surgery on the different steps of the process of oral drug absorption and give practical dosing considerations for several commonly used potent drugs for patients with a history of bariatric surgery based on a review of the available literature.

In general, the pharmacokinetic profile of orally administered drugs seems to change after bariatric surgery; the Tmax can be earlier and Cmax higher, with less consistent results on the AUC, which can be similar [37,38,46,64,65], lower[30,46,50,52,117,119] or higher[27,45,47] after surgery. Many reports compare the pharmacokinetics in patients after bariatric surgery to the pharmacokinetics before surgery, while some studies also consider the pharmacokinetics in non-obese individuals for comparison. The latter may particularly be of relevance for drugs for which altered pharmacokinetics in obese patients compared to non-obese patients have been reported, or when the pharmacodynamics are different in obese individuals as is the case for VKAs or

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platelet inhibitors. We note that even for similar drugs, different results may be observed, as shown for phenoxymethylpenicilin [44,45]. Also for controlled release formulations, conflicting results were obtained in different studies [35,36]. While these differences may result from large inter and intra-individual variability known in oral drug dosing, they may also result from different surgical techniques and formulations.

Another important issue to consider is that the shape of the pharmacokinetic profile of orally administered drugs may change substantially over time (for instance with psychotropic drugs). Although conclusions like earlier and higher concentration peaks seem applicable, general predictions on oral absorption after bariatric surgery are difficult to ascertain.

As such, advice regarding oral drug use after bariatric surgery should be given on a case by case basis.

Figure 1 shows some guidance about this issue. Firstly, available literature on the drug before and after surgery should be considered. Predictions based on drug properties such as the Log P or the location of absorption in the gastrointestinal tract are to be discouraged. For drugs where a direct effect can be measured (e.g. blood pressure, INR, blood glucose, T3, T4 and TSH), this can be monitored and the dose be adjusted accordingly. Another possibility is to measure serum concentrations of the specific drug through TDM. When measuring a trough concentration, the shape of the concentration-time curve may have changed after surgery. In such a case, a lower trough concentration may not be reflective of a lower AUC and therefore conclusions based on a trough sample alone may not be predictive of the ultimate effect of the drug. This phenomenon may be relevant for drugs that exert their pharmacodynamic effects based on the $AUC_{0\text{-}24h}$ (e.g., some antibiotics, DOACs, pain killers). For drugs dependent on time above a certain concentration such as antibiotics, these considerations are less relevant, as long as the peak concentration does not result in potential safety issues, as may be the case for oral morphine[22] or midazolam [23].

In addition, a risk assessment for the drug of interest can be made when prescribing oral drugs to post-bariatric surgery patients. During this assessment, the risk of reduced absorption and therapy failure and overdosing is weighed. If this risk is high (i.e. severe toxicity upon overdosing or increased morbidity and mortality upon underdosing), another therapy should be proposed. An example of such a drug are DOACs for which VKAs are a proposed alternative. For drugs which it is known that earlier and higher peaks may occur, for example, morphine and midazolam, adjusted doses or additional monitoring may be proposed. In this respect, also the type of surgery and period of time after bariatric surgery should be taken in to consideration.

Different surgical techniques may lead to differences in alterations in the GI-tract. The period of time after bariatric surgery is also relevant since there is evidence that pharmacokinetic changes might change over time (for example VKAs and psychotropic drugs). Here also the formulation needs to be considered, as studies on oral suspensions, open capsules and direct release and controlled release tablets have generally shown conflicting research (see table 3).

Conclusions

Bariatric surgery is increasingly employed for (morbid) obesity because it improves long-term morbidity and mortality. As a result of changes in the gastrointestinal tract that subsequently result in major weight loss, the pharmacokinetics of drugs in patients after bariatric surgery may be subject to alterations in the absorption, distribution, metabolism, and/or elimination. Due to an increased absorption rate after bariatric surgery, the time at maximum concentration is often earlier and the maximum concentration may be higher with less consistent effects on trough concentrations and exposure or area under the curve upon oral drug administration. We conclude that based on current literature an advice can be proposed in many cases but also that there is insufficient evidence for general dosing recommendations for oral drug therapy after bariatric surgery implying a risk assessment on a case by case basis.

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