

Obesity Management

A systematic review of drug absorption following bariatric surgery and its theoretical implications

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Summary

Demand for bariatric surgery has risen exponentially and bariatric patients often have multiple indications for post-operative pharmacotherapy. The purpose of this study was to systematically review the published literature examining the effect of bariatric surgery on drug absorption.

Studies were sought through searches of MEDLINE, EMBASE, the Cochrane Controlled Trials Registry and hand searches of reference lists. Two reviewers independently assessed studies for inclusion.

Twenty-six studies (15 case reports/case series evaluating 12 different agents and 11 non-randomized controlled studies examining 15 different agents) were found. Evidence for diminished drug absorption was found in 15/22 studies involving jejunoileal bypass, 1/3 studies of gastric bypass/gastroplasty and 0/1 studies examining biliopancreatic diversion. The effect of bariatric surgery on drug absorption appears drug-specific. Drugs that are intrinsically poorly absorbed, highly lipophilic and/or undergo enterohepatic recirculation exhibited the greatest potential for malabsorption. The most consistent evidence for diminished absorption was found for cyclosporine, thyroxine, phenytoin and rifampin.

Reduced drug absorption may occur post-bariatric surgery and this effect appears drug-specific. Individual dose-adjustment and therapeutic monitoring may be required. Rigorously conducted controlled studies are needed to evaluate the effect of modern bariatric procedures on drug absorption.

Keywords: Bariatric surgery, drug absorption, systematic review, therapeutic drug monitoring.

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Introduction

In the past decade, demand for bariatric surgery has increased exponentially in Canada (1), the United States (US) (2) and globally (3). An estimated 180 000 surgeries are performed annually in the US alone (4), and procedure types include purely restrictive (gastric banding, gastroplasty), restrictive with limitation of digestive capacity (sleeve gastrectomy), restrictive/malabsorptive (gastric bypass) and purely malabsorptive (biliopancreatic diversion, jejunoileal bypass). The latter two categories of procedures involve intestinal diversion. The most commonly performed procedure overall is Roux-en-Y gastric bypass (3,5).

Although the potential for malabsorptive procedures to cause nutritional deficiencies has been recently well documented (6), surprisingly little contemporary research has focused on the effect of bariatric surgery on drug absorption (7). Notably, the patient population receiving bariatric surgery is severely obese, with multiple medical comorbidities that often require multidrug treatment (8). Although many comorbidities improve post-operatively, most patients still remain clinically obese and regain weight over time, which may lead to the re-emergence of conditions previously in remission (9,10). Drug therapy is also commonly required to treat pain or other adverse effects of surgery, such as gastrointestinal reflux (11). Drug

malabsorption is a potential concern post-bariatric surgery, particularly after diversionary procedures, for several reasons. Nearly all oral agents are maximally absorbed in the small intestine, which is bypassed in several bariatric procedures. Delayed gastric emptying, diminished opportunity for mucosal exposure, and changes in drug dissolution and solubility resulting from alterations in intestinal pH are additional factors that may potentially impair drug absorption (7). A clear understanding of the effect of both historical and more contemporary bariatric procedures on drug absorption is paramount to ensure that drugs are optimally dosed and that the desired therapeutic effect is achieved. Therefore, we systematically reviewed the literature to identify and summarize the published literature examining this topic.

Methods

We searched the following electronic resources for studies examining the effects of bariatric surgery on drug absorption: The Cochrane Central Register of Controlled Trials and Database of Systematic Reviews (Third Quarter, 2008), MEDLINE (1966 to October, week 4, 2008) and EMBASE (1980 to week 43, 2008). Search terms included (but were not limited to) bariatric surgery, gastric bypass, jejunioileal bypass, gastric banding, vertical banded gastroplasty, biliopancreatic diversion, drug absorption and bioavailability. Reference lists of original studies and narrative reviews were also hand searched. Included studies were entered into PubMed and the 'related articles' link was also reviewed for additional articles. The search was limited to English language articles and is considered up-to-date as of October 20, 2008.

Human case reports, case series, cohort studies and randomized controlled trials that evaluated or described drug absorption in patients undergoing bariatric surgery were included. We excluded studies examining nutritional supplements such as vitamins and iron preparations. One reviewer (R. P.) reviewed all search results and excluded articles that were clearly not relevant. Two reviewers (R. P. and A. S.) then independently examined the remaining abstracts for potential inclusion. A Cohen's Kappa coefficient was calculated to assess inter-observer agreement for study inclusion. Disagreements were resolved by consensus.

One reviewer performed data extraction, which was independently checked by the second reviewer for accuracy. If studies reported results from multiple study designs, we preferentially extracted the most complete data from the highest type of study design. For case reports and case series, study results are presented in a descriptive fashion. For controlled studies, wherever possible, the mean area-under-the-concentration-time (AUC) curve drug levels were extracted and compared between groups. If both blood (serum or plasma) and urine levels were provided, we pref-

erentially extracted blood levels to minimize any potential confounding due to drug metabolism. If AUC levels were not reported, we abstracted per cent bioavailability instead. If studies using pre-post designs presented individual patient data, we calculated 95% confidence intervals for mean differences in drug levels between study groups using paired *t*-tests. Otherwise, unpaired *t*-tests were used to generate confidence limits and *P* values. If study sample sizes were prohibitively small (<5) and the Central Limit Theorem could not be invoked to utilize parametric tests of significance (12), data were presented in narrative fashion.

Results

Search results

Of the 68 initial citations identified by the electronic search, five were potentially relevant upon initial screening and were examined in further detail (Fig. 1). Of these, one met inclusion criteria. An additional 26 articles were identified via hand searches and through separate PubMed searches using the 'related articles' link of studies meeting inclusion criteria. Inter-observer agreement was 1.0 for study inclusion.

Study characteristics

Overall, 26 studies (15 case reports/case series evaluating 12 different agents and 11 non-randomized controlled studies evaluating 15 different agents) were found. Case

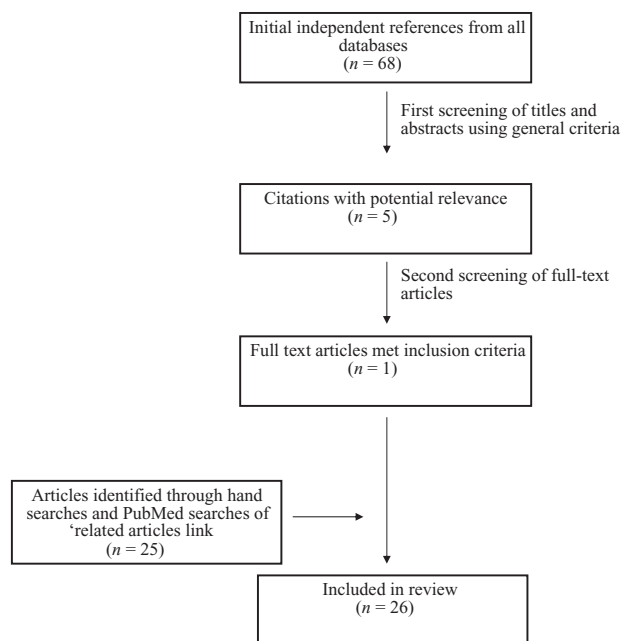


Figure 1 Flow diagram of study selection.

reports or case series examining phenytoin (2), ethosuximide, isoniazid (5), ethambutol (5), rifampin (3), amoxicillin, nitrofurantoin (as Macrochantin), cyclosporine (2), tacrolimus, thyroxine (2), ranitidine and haloperidol were identified (Table 1). Jejunioleal bypass was examined in 11 studies, gastric bypass in two and biliopancreatic diversion in one. Solid dosage forms were used in all studies except one, in which phenazone was administered as an oral solution (13).

Non-randomized controlled studies evaluating phenazone, acetaminophen, erythromycin, sulfisoxazole, ampicillin, penicillin, phenytoin, hydrochlorothiazide, digoxin (2), D-norgestrel, oestradiol, oestrone, norethisterone, L-norgestrel and propylthiouracil were identified (Table 2). Jejunioleal bypass was performed in 10 studies and the remaining study evaluated patients that had undergone gastric bypass or gastroplasty. Sample sizes ranged from 3 to 28 patients. Mean baseline weights were between 118 and 158 kg and patients were studied between 1.5 and 43 months post-operatively. Body mass index was not typically reported. Pre-post designs were used in six studies and comparisons of surgical cases with normal weight controls were performed in the remaining five.

Results of studies

Overall, evidence for a diminished magnitude of drug absorption was found in 15/22 studies involving jejunioleal bypass, 1/3 studies of gastric bypass/gastroplasty and 0/1 studies examining biliopancreatic diversion (Tables 1 and 2). Evidence for diminished absorption was present for anti-rejection drugs (cyclosporine and tacrolimus), thyroxine, phenytoin and rifampin in multiple reports. Single instances of diminished absorption of ethosuximide, amoxicillin, Macrochantin, tacrolimus, sulfisoxazole, pivampicillin and hydrochlorothiazide were reported. Conflicting evidence was present for ethambutol, digoxin and oral contraceptives. The data did not favour reduced absorption for isoniazid, ranitidine, haloperidol, phenazone, acetaminophen, erythromycin, penicillin or propylthiouracil.

Discussion

To summarize, the effect of bariatric surgery on drug absorption appears drug-specific. In some cases, substantial reductions in drug absorption may occur, which may be temporally associated with the need for dosage adjustment. There is a paucity of data examining modern procedures and further study is required to determine whether there are major differences among procedure types with respect to drug absorption. To our knowledge, this is the first published systemic review to examine this issue.

The major steps that must occur between the oral ingestion of a solid drug preparation and the entry of a drug into

the portal circulation are: drug disintegration/dissolution, transport through intestinal tract, mucosal exposure and transport across the intestinal epithelium. Additional factors that can reduce systemic drug exposure include first pass metabolism and reduced gastrointestinal blood flow – these latter factors are not considered in further detail here. The drug absorption process may be differentially altered according to the type of surgery performed and influenced by the underlying chemical properties of the drug ingested.

Procedures involving gastric restriction

Procedures involving gastric restriction alone (gastric banding, vertical banded gastroplasty) would be theoretically less likely to alter overall drug absorption compared with procedures involving intestinal diversion. Nevertheless, in the absence of definitive evidence demonstrating that absorption is unchanged in bariatric patients undergoing purely restrictive procedures, the following theoretical issues deserve consideration. These issues apply to all procedures involving some type of gastric restriction.

1. Drug disintegration is the first step required for drug absorption and is necessary in order for a drug to become soluble within the gastrointestinal milieu. This step, which may even vary considerably across different preparations of the same drug, is often the rate-limiting step in the absorption of most solid dosage forms (14). One factor that promotes drug disintegration is gastric mixing and this may be substantially reduced by such restrictive bariatric procedures as gastric banding, gastroplasty, gastric bypass, sleeve gastrectomy and some forms of biliopancreatic diversion. Administration of a drug as a liquid formulation or crushing/chewing solid formulations whenever possible would be expected to mitigate any diminished absorption that results from impaired drug disintegration. However, this is not always feasible and may alter desirable pharmacological properties of the drug.

2. Drug dissolution and solubility may be potentially altered in restrictive procedures that increase gastric pH in the newly created stomach. This may occur in gastric bypass or gastroplasty, in which the new gastric pouch is partitioned from acid-producing cells in the remaining stomach. Alternatively, sleeve gastrectomy and some forms of biliopancreatic diversion involve excision of the parts of the gastric fundus and body, the areas of the stomach that contain most of the acid-producing cells. Theoretically, according to the pH partition hypothesis, increasing gastric pH should increase the solubility of more basic drugs (become less ionized) and decrease the solubility of more acidic drugs (more ionized) (15). Increasing the pH may also reduce the disintegration of the solid dosage forms of some medications (16). It should be noted that changes in pH should primarily affect solubility within the stomach,

Table 1 Case reports and case series

Study	Surgery	Drug	Evidence favours decreased drug absorption?	Details
Anticonvulsants				
Peterson (26)	JIB	Phenytoin	Yes	A 43-year-old man with a seizure disorder. Post-JIB reversal, maintenance plasma phenytoin levels doubled.
Peterson and Zweig (27)	JIB	Phenytoin	Yes	A 42-year-old woman with a seizure disorder who experienced recurrent seizures 2–8 weeks post-JIB and required above average maintenance doses.
		Ethosuximide	Yes	
Antimicrobials				
Bruce and Wise (28)	JIB	Isoniazid	No	Four patients (24–40 years) who developed tuberculosis 6–10 months post-bariatric surgery successfully treated with multidrug regimens. Normal levels of isoniazid and ethambutol, but not rifampin, were documented.
		Ethambutol	No	
		Rifampin	Yes	
Polk <i>et al.</i> (29)	JIB	Isoniazid	No	A 36-year-old woman developed tuberculosis 4 years post-JIB. Successfully treated and achieved normal drug levels.
		Ethambutol	No	
Harris and Wasson (30)	JIB	Isoniazid	No	30-year-old and 42-year-old men who developed tuberculosis 2 and 10 months post-operatively. Both were successfully treated but evidence for low ethambutol and rifampin levels was found.
		Ethambutol	Yes	
		Rifampin	Yes	
Griffiths <i>et al.</i> (31)	JIB	Isoniazid	No	A 48-year-old woman developed tuberculosis 6 years post-JIB. Rifampin levels remained low, despite doubling of the usual dose to 1200 mg daily.
		Ethambutol	No	
		Rifampin	Yes	
Pickleman <i>et al.</i> (32)	JIB	Isoniazid	No	A 42-year-old woman developed tuberculosis within 1 year of JIB. Drug levels were reported as 'within normal range'.
		Ethambutol	No	
Magee <i>et al.</i> (33)	GB	Amoxicillin Nitrofurantoin (Macrochantin)	Yes Yes	A 29-year-old woman in 9-week gestation and 3 years post-GB developed a urinary tract infection. Required intravenous antibiotics after oral medication failed.
Immuno-suppressants				
Chenhshu <i>et al.</i> (34)	JIB	Cyclosporine microemulsion formulation	Yes	A 58-year-old woman 26 years post-JIB underwent liver transplant. Cyclosporine levels were over 50% lower than in liver transplant patients who did not have prior bariatric surgery.
Knight <i>et al.</i> (35)	JIB	Cyclosporine	Yes	A 41-year-old man with remote jejunoileal bypass developed idiopathic cardiomyopathy requiring cardiac transplantation. Post-transplant, absorption of cyclosporine was poor, with no enterohepatic recirculation. Absorption normalized post-JIB reversal.
Kelley <i>et al.</i> (36)	JIB	Tacrolimus	Yes	A 57-year-old woman who developed end-stage liver failure 20 years post-JIB requiring liver transplantation. Post-reversal of her JIB, maintenance tacrolimus dosage was halved.
Thyroid replacement				
Azizi <i>et al.</i> (37)	JIB	Thyroxine	Yes	A 38-year-old woman with hypothyroidism required thyroxine 0.2 mg daily preoperatively and 0.6 mg daily 2 years post-JIB to normalize TSH. After the JIB was reversed, 0.2 mg daily was required to normalize TSH.
Bevan and Munro (38)	JIB	Thyroxine	Yes	A 54-year-old man diagnosed with hypothyroidism 4 years post-JIB. Required thyroxine 0.5 mg daily (over threefold greater than normal average dose) to maintain normal thyroid function.
Other				
Adami <i>et al.</i> (39)	BPD	Ranitidine	No	Seven patients (mean age 32 years) 8–36 months post-BPD achieved therapeutic drug levels after administration of a single oral dose of 150 or 300 mg.
Fuller <i>et al.</i> (40)	GB	Haloperidol	No	A 51-year-old woman with schizophrenia controlled on haloperidol 20 mg daily. Although she required transient dosage doubling, normal serum levels were documented after her preoperative dose was resumed.

BPD, biliopancreatic diversion; GB, gastric bypass; JIB, jejunoileal bypass; TSH, thyroid stimulating hormone.

Table 2 Controlled comparisons

Study	Type of surgery	Mean preop wt (kg)	Mean time since operation (mo)	Design (n)	Drug and dose	Evidence favours decreased drug absorption?	Outcome and findings (SD)
Analgesics							
Andreasen <i>et al.</i> (13)	JIB	133	35	Surgical cases (17) Normal weight controls (11)	Phenazone 15 mg kg ⁻¹ single dose as oral solution	No	Urinary excretion of phenazone (mg 24 h ⁻¹): Cases 24.6 (8.4); controls 20.7 (14.1); difference 3.9; 95% CI -4.8 to 12.6; <i>P</i> = 0.37 Urinary excretion of 4-hydroxyphenazone (mg 24 h ⁻¹): Cases 299 (243); controls 228 (186); difference 371; 95% CI -106 to 248; <i>P</i> = 0.42
Terry <i>et al.</i> (41)	JIB	132	3	Pre-post surgery (3)	Acetaminophen 1.5 g single oral dose	No	Serum AUC (µg mL ⁻¹ ·h): Pre 43.0 (7.0); post 43.0 (14.9); difference 0; 95% CI -26 to 26; <i>P</i> = 1.0*
Antibiotics							
Prince <i>et al.</i> (42)	1 GB and 6 gastroplasties	158	1.5	Pre-post surgery (7)	Erythromycin base 250 mg single dose	No	Serum AUC 0–12 h (units mL ⁻¹ ·h) Pre 4.1 (0.8); post 2.7 (1.9); difference -1.3; 95% CI (-0.4 to 3.1); <i>P</i> = 0.11
Garrett <i>et al.</i> (43)	JIB	158	13	Pre-post surgery (3)	Sulfisoxazole 1 g single oral dose	Yes	No AUC levels provided. Mean bioavailability was reduced from 97% to 81%.
Kampmann <i>et al.</i> (44)	JIB	128	12	Pre-post surgery (6)	Ampicillin 500 mg single oral dose (given as pivampicillin 750 mg prodrug)	Yes	Bioavailability reduced from 109% to 41%. No significance testing performed because of small sample size.
Terry <i>et al.</i> (41)	JIB	132	3	Pre-post surgery (3)	Penicillin 1 g single oral dose	No	Serum AUC (units mL ⁻¹ ·h): Pre 17.1 (5.9); post 176.8 (98.1); difference 159.7; 95% CI 2.1 to 317.2; <i>P</i> = 0.048*
Anti-epileptics							
Kennedy and Wade (45)	JIB	121	7	Surgical cases (7) Normal weight controls (9)	Phenytoin 200 mg single oral dose	Yes	Plasma AUC 0–48 h (µg mL ⁻¹ ·h) Cases 34.4 (10.9); controls 108.3 (34.5); difference -73.9; 95% CI -44.7 to -103.1; <i>p</i> < 0.0001
Cardiovascular							
Backman <i>et al.</i> (46)	JIB	137	43	Surgical cases (4) Normal weight historical controls (8)	Hydrochlorothiazide 75 mg single oral dose	Yes	Plasma AUC 0–9 h (ng mL ⁻¹ ·h): Cases 889 (285); controls 1923 (295); difference -1034; 95% CI -635.5 to -1432.5; <i>P</i> = 0.0002*
Gerson <i>et al.</i> (47)	JIB	NR	14	Surgical cases (9) Normal weight controls (16)	Digoxin 0.5 mg single oral dose	Yes	Serum AUC (duration unspecified; ng mL ⁻¹ ·min): Cases 233 (93); controls 307 (66); difference -74.0; 95% CI -8.1 to -140.0; <i>p</i> < 0.03*
Marcus <i>et al.</i> (48)	JIB	145	2	Pre-post surgery (7)	Digoxin 1 mg loading dose then 0.5 mg daily × 8 days	No	Steady state serum AUC 0–24 h (ng mL ⁻¹ ·h): Pre 28.8 (6.5); post 25.7 (6.2); difference -3.1; 95% CI -2.7 to 8.8; <i>P</i> = 0.23*

Table 2 Continued

Study	Type of surgery	Mean preop wt (kg)	Mean time since operation (mo)	Design (n)	Drug and dose	Evidence favours decreased drug absorption?	Outcome and findings (SD)
Oral contraceptives							
Andersen <i>et al.</i> (49)	JIB	118	12	Pre-post surgery: 6 patients studied preop and 12 studied post-op	Single oral doses: D-norgestrel 125 µg Oestradiol 4 mg Oestrone 2 mg	No	Results displayed in graphical form only and not extractable. Figures demonstrate drug concentrations in bypassed patients were similar or higher than controls. No significant reduction in the absorption of any drug reported.
Victor <i>et al.</i> (50)	JIB	129	NR	Surgical cases (6) Normal weight controls (5)	Norethisterone 3 mg single oral dose L-norgestrel 0.25 mg single oral dose	Yes	Plasma AUC 0–24 h (ng mL ⁻¹ ·h): Cases 57.9 (8.7); controls 73.0 (5.5); difference –15.0; 95% CI –4.9 to –25.3; <i>P</i> = 0.009* Cases 21.6 (2.5); controls 38.7 (1.8); difference –17.0; 95% CI –14.1 to –20.1; <i>P</i> = 0.0001*
Thyroid blocker							
Kampmann <i>et al.</i> (44)	JIB	128	12	Pre-post surgery (8)	Propylthiouracil 400 mg single oral dose	No	Bioavailability increased from 78% to 85%

**P* value calculated using unpaired *t*-test. For pre-post designs, lack of individual patient data precluded calculation of paired *t*-test. AUC, area-under-the-curve; GB, gastric bypass; JIB, jejunoileal bypass; NR, not reported; SD, standard deviation.

which is not responsible for a large degree of drug absorption because of its relatively low surface area-to-volume ratio relative to the small intestine. If alterations in pH exert a clinically important effect on drug absorption post-bariatric surgery, this effect is likely drug-specific. Examples of drugs that depend upon an acidic environment for optimal dissolution include rifampin, digoxin and ketoconazole (16). Although drug dissolution has not been directly examined *in vivo* in a bariatric population, an *in vitro* analysis simulating dissolution post-gastric bypass found that 10 of 22 psychiatric medications exhibited significantly less dissolution and two exhibited significantly more dissolution in the post-gastric bypass environment compared with the control environment (17). Iron supplements, which were not studied in our review, are also optimally soluble within an acidic environment and the co-administration of ascorbic acid can increase iron absorption post-gastric bypass (18).

3. The effect of reduced gastric emptying, such as that which may occur following the ingestion of solids post-gastric bypass (19) and in the short-term but not long-term post-biliopancreatic diversion (20), is unclear. Pharmacokinetically, reduced gastric emptying would be expected to reduce the rate but not the overall magnitude of drug absorption – therefore, AUC levels should remain

unchanged. Studies examining the effect of non-bariatric procedures that limit gastric emptying on drug absorption have demonstrated a reduced rate of drug absorption with a variable effect on overall drug absorption (14).

Diversiory and malabsorptive procedures

Procedures that involve intestinal diversion clearly have the potential to reduce drug absorption, primarily because of alterations in solubility and reductions in intestinal length, intestinal transit and mucosal exposure. The following theoretical considerations apply:

1. Drugs with slow dissolution properties, particularly sustained release or enteric coated preparations, should be more likely to exhibit reduced absorption.
2. In addition, highly lipophilic drugs are more likely to be affected because they are often dependant upon the availability of bile acids to enhance solubility. Often, these agents also undergo enterohepatic recirculation. Bypass of the upper small intestine limits the mixing of such drugs with bile acids to the common (post-anastomotic) limbs of the distal small intestine. Jejunoileal bypass may also result in bile acid wasting. We found evidence for the reduced absorption of cyclosporine, phenytoin, rifampin, thyroxine

Table 3 Gastrointestinal absorptive characteristics of included drugs

Drug	Comment
Well absorbed	
Acetaminophen, antipyrine, digoxin, ethambutol, ethosuximide, erythromycin, hydrochlorothiazide, isoniazid, phenazone, propylthiouracil, sulfisoxazole	None
Amoxicillin and pivampicillin	Pivampicillin is a prodrug that is converted to ampicillin within intestinal epithelial cells.
Cyclosporine	Absorption limited by p-glycoprotein efflux pump as well as cytochrome P450 3A metabolism. Absorption is bile salt dependent as the drug is highly lipophilic with low aqueous solubility. Enterohepatic recirculation prolongs elimination time.
Nitrofurantoin (Macrochantin)	Macrochantin contains nitrofurantoin in a macrocrystalline form, which has a slower rate of dissolution and absorption.
Oral contraceptives	May undergo extensive first pass metabolism and enterohepatic recirculation.
Penicillin	Hydrolysis occurring within an acidic environment diminishes absorption.
Rifampin	Most soluble within an acidic environment. Undergoes enterohepatic recirculation.
Erratically absorbed	
Thyroxine	Acidic gastric environment appears important for maximal absorption. Undergoes enterohepatic recirculation.
Phenytoin	Absorption is dissolution rate-limited and may be slow and erratic. Undergoes enterohepatic recirculation.
Tacrolimus	Low bioavailability (20–30%) with incomplete and variable absorption due to high lipophilicity. Jejunum is the primary site of absorption.

and tacrolimus post-jejunoileal bypass. These agents are all lipophilic and all except tacrolimus undergo enterohepatic recirculation.

3. Bypass procedures that markedly reduce functional gastrointestinal length, such as jejunoileal bypass, gastric bypass and biliopancreatic diversion, reduce mucosal exposure to the greatest extent. It is unclear whether there is a difference in drug absorption between bypass of the proximal small intestine (gastric bypass) and the distal small intestine (jejunoileal bypass). Although the proximal small intestine has the largest overall surface area per unit length of the gastrointestinal tract, the intestinal transit time is slower in the longer distal small bowel (14). Consequently, most absorption takes place distally. In addition, previous studies have documented the phenomenon of 'intestinal adaptation' in short bowel states, whereby mucosal hypertrophy within the remaining intestine provides a compensatory increase in absorptive capacity over time (21). However, the extent to which this phenomenon affects drug absorption post-bariatric surgery is unknown.

4. Also unknown is the effect that bypassing specific portions of the small intestine has on the relative importance of drug metabolism and drug efflux within the intestinal wall. Because the influence of drug metabolism and efflux on drug absorption may substantially vary between drugs and across different parts of the intestine, different types of bypass may produce different alterations in drug absorption. For example, cyclosporine is a substrate for P-glycoprotein, a protein transporter and efflux pump

present within the intestinal wall that acts to diminish the absorption of many pharmaceuticals (22). The expression of P-glycoprotein increases as one moves from the proximal to the distal small intestine (23). Consequently, bypass of the proximal small intestine may increase the relative influence that P-glycoprotein plays in reducing the levels of drugs such as cyclosporine.

Table 3 provides an overall summary of the absorptive characteristics of the drugs included in this review and Fig. 2 summarizes how each step of drug absorption may theoretically be affected by each type of bariatric procedure. Overall, drugs that have the greatest potential for malabsorption, particularly with intestinal bypass procedures, include those that are intrinsically poorly absorbed and those that undergo enterohepatic recirculation. Drugs that have excellent intrinsic absorptive properties seem less likely to be affected. It is also important to note that malabsorption would be most clinically problematic for those agents that have a narrow therapeutic window, which includes most drugs that currently require therapeutic drug monitoring.

Limitations of this review include the potential for publication bias and the possibility that the search may have missed relevant studies. In addition, sample sizes were small and much of the available evidence is comprised of older case reports and case series, considered to be suboptimal study designs. Jejunileal bypass, the most frequently studied procedure, is rarely performed today because of

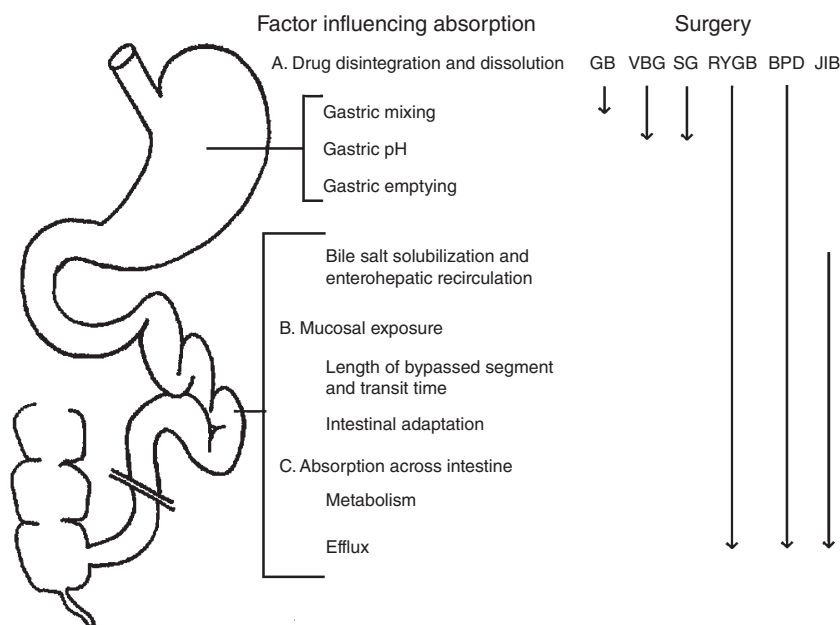


Figure 2 Summary of the theoretical effect of various bariatric procedures on factors influencing drug absorption. The major factors influencing drug absorption are depicted in the centre. For each factor, the major site involved is indicated (gastric vs. small intestine) on the left. The major types of bariatric surgery are listed on the right. The arrows summarize the potential spectrum of influence for each type of bariatric procedure. BPD, biliopancreatic diversion; GB, gastric bypass; JIB, jejunioleal bypass; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; VBG, vertical banded gastroplasty.

the potential for severe malabsorption and an overall unfavourable benefit/risk profile. This procedure leads to substantially different alterations in gastrointestinal anatomy than contemporary procedures such as gastric bypass and gastric banding. Consequently, while we were able to draw some general conclusions about the impact of bariatric surgery on drug absorption using jejunioleal bypass studies, there is clearly a need for a more rigorous evaluation of modern procedures to better inform policy and practice. Nevertheless, even though jejunioleal bypass is largely outdated, examining its effects still helps to provide a more complete understanding of the effect of bariatric procedures on drug absorption as a whole.

An additional limitation is that studies using normal weight controls, pre-post designs or reference drug levels derived largely from non-obese populations may not have properly accounted for the effect of obesity itself on drug levels. Although drug absorption *per se* does not appear to be substantially altered in obese patients (24), other pharmacokinetic parameters may change. The volume of distribution of lipophilic drugs may increase in obese patients; however, this would not be expected to substantially alter AUC levels. In contrast, increases or decreases in renal and/or hepatic clearance may decrease or increase, respectively, drug AUC levels (24). However, alterations in drug pharmacokinetics in the obese state are often drug-specific, are not easily predictable based upon the chemical properties of a given drug, and are poorly understood (24,25). In addition, there is also no dosing parameter (e.g. total body weight, lean body weight, body surface area) that can optimally control for body weight – even within drugs of the same class. Although an extensive

discussion of these issues is beyond the scope of this review, it is clear that future studies evaluating the effect of drug absorption post-bariatric surgery should attempt to correct for the effect of body weight on drug pharmacokinetics by using appropriate weight-matched controls as a comparison group. Failing this, adjusted dosing regimens based upon the known chemical nature of the drug and prior pharmacokinetic data (if available) or statistically controlling for weight differences between groups should be considered.

A number of important issues must be considered when designing future studies in this field:

1. There are few data examining modern procedures. Priority should be given to evaluating diversionary/malabsorptive types of procedures because the theoretical potential for altered drug absorption is clearly greater for these types of operations.
2. Standardized study protocols are essential. This not only refers to standardization of pharmacokinetic techniques, blood draws and study meals, but also to standardization of the selection of study subjects. Post-surgical patients should be at a baseline and stable volume status and should have experienced a routine post-operative course. The latter criterion provides reassurance that the surgery was successful and no major post-operative complications are present (e.g. persistent vomiting due to outlet stenosis). Because intestinal adaptation is a function of time, surgical patients should be studied at approximately the same time point in their post-operative course and this time point should be documented. Control patients should be age, sex and BMI-matched to ensure proper adjustment

for the potential effect of these parameters on drug absorption and pharmacokinetics.

3. Care must be taken to ensure that studies are adequately powered and, in addition to pharmacokinetic parameters, pertinent surrogate end points should be examined to confirm the clinical relevance of any observed changes in drug absorption.

From this systematic review of the published literature, we conclude that there is potential for reduced drug absorption post-bariatric surgery, particularly for drugs that have intrinsically poor absorptive characteristics, undergo enterohepatic recirculation and with narrow therapeutic windows. As, in theory, treatment failure may result, therapeutic drug monitoring is recommended on a case-by-case basis. Because surgery is commonly (and increasingly) performed and because bariatric patients often have multiple chronic comorbidities requiring long-term therapy, further procedure-specific and drug-specific studies are required to ensure that bariatric patients are receiving the intended benefits of drug therapy.

Conflict of interest statement

None.

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